SBFTE

56 Anos

1966 - 2022

54th Brazilian Congress of Pharmacology and Experimental Therapeutics

PROGRAM AND ABSTRACTS

OCTOBER 18 to 21, 2022

ONLINE EVENT

Welcome Letter

Dear fellow SBFTE Members, Colleagues, and Friends,

I am happy to welcome you to the 54th Brazilian Congress of Pharmacology and Experimental Therapeutics. This annual strategic meeting has been organised by the Brazilian Society of Pharmacology and Experimental Therapeutics (SBFTE) since 1967. SBFTE is a highly consolidated scientific society in national research, development, and innovation. Throughout its 55 years, our society has held annual events in which pharmacology and experimental therapeutics come together on a wide range of topics, high scientific standards, and international coverage. The current meeting will not be different for sure. It is true that due to the pandemic, we will not be able to meet in person to celebrate our achievements and the latest developments in the field. Although we will miss the face-to-face warming approach, I am confident there are many remarkable things to look forward to in our online meeting.

The scientific organising committee, headed by Professor Rui Prediger (UFSC), has worked hard to provide inspiring and thought-stimulating keynote presentations, symposiums and round tables exploring the latest advances in pharmacology research and education, attached with new therapeutic perspectives. “Directing Cellular Metabolism in Diseases of Ageing” is the theme chosen for this meeting, a sensitive subject covering a substantial part of the scientific program. The congress will assemble national and international leaders at the frontier of pharmacological and biomedical knowledge, addressing the most recent advances and progress in critical areas of pharmacology, such as inflammation and pain, cardiovascular pharmacology, neuropharmacology, and natural products. Fourteen poster discussion sessions and three courses will address educational, scientific dissemination and the popularisation of pharmacology, encouraging the maximum possible formal and informal interaction among all participants.

The Rocha e Silva Memorial Lecture, one of the most significant accomplishments of the annual Society’s meetings, will bring a presentation by Professor Juan Saavedra (Georgetown University, USA). Numerous pharmacologists in Brazil and abroad benefit from microbiochemical methods he developed to study neurotransmitters in the brain, blood, and many other tissues. Another highlight of the SBFTE yearly meeting is the José Ribeiro do Valle (JRV) Award Symposium, which is a fantastic opportunity to congratulate the five young pharmacologists selected for the Award 2022. It is a great initiative that motivates early-career scientists interested in developing the skills necessary for a fruitful pharmacological career. I also encourage you to visit the Rocha e Silva and Sergio Ferreira tribute rooms. In these spaces, you will find homage videos of these two great scientists specially developed for the current event. Rocha e Silva and Sergio Ferreira have left an incredible and inspiring legacy in the field of Pharmacology in Brazil and abroad. In this edition, we also will pay tribute to Professor Alexandre Pinto Corrado, a founder and former president of SBFTE. At 94 years old, he still regularly attends the Department of Pharmacology of the Faculty of Medicine of Ribeirão Preto, USP, where he built an inspiring career as a docent and investigator.

Meetings do not just happen. There are many people I would like to thank who have brought this one to life. The 2022 SBFTE congress committed a significant group of people who either helped to set up the scientific program or to do the rigorous refereeing process of the abstract submitted to communications. Many thanks to our invited speakers, session chairs, and those who have been involved in our homage actions. I also should like to thank the JRV Award Committee, composed of Profs Thereza C.B. Fidalgo, João Batista Calixto, and Juan Saavedra. I want to thank our partner Biolab for supporting the JRV Award, our sponsors, Aché and Alesco, and the National Council for Scientific and Technological Development (CNPq) for its financial support, despite the significant budget cuts imposed on it. Finally, on behalf of the SBFTE Directory board, my special thanks to Sandra H. R da Cruz (SBFTE Executive Secretary), responsible for this book and many other instrumental contributions, as well as the SBFTE Communication team and Nui Eventos for the fantastic job done in this event.

I wish you an exciting and fruitful experience at the 54th Brazilian Congress of Pharmacology and Experimental Therapeutics.

Marco Aurélio Martins
President of SBFTE

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Useful Information

E-Posters

E-Poster presenters must attend the Room Session scheduled (Oct 19th and 20th from 16h45 to 19h within 20 min in advance) when posters will be viewed by Poster Evaluators.

The Sessions Program is available here.

Certificates

The Certificates will be sent by e-mail from Softaliza Ciente Studio within 7 days after the event.

Courses

The course certification will be given for the participants with at least 2 classes attendance within at least 30 min.

Abstracts

Abstracts presented at the poster session will be available at SBFTE website (http://www.sbfte.org.br).

Rocha e Silva Memorial Lecture

Invited Speakers History

1984 *The role of endothelial cells and relaxation of vascular smooth muscle by acetilcoline and bradikinin*. Robert Furchgott (04/07)

1987 *Caracterização do fator de relaxamento arterial*. Salvador Moncada

1989 *Asma*: *uma doença inflamatória*. Boris Vargaftig

1991 *A morada Perigosa*: *morte e a vida da Leishmania nos fagolisossomas*. Michel Rabinovich

1993 *Structure*, *dynamics, and functions of atrial natriuretic factor receptor*. Tomas Maack

1995 *Receptores para Bradicinina*. Domenico Regoli

1997 *Disfunções na produção de fatores vasoativos em doenças cardiovasculares* Paul Vanhoutte

1999 *Purinergic signaling* Geoffrey Burnstock

2001 *Mecanismos celulares da Asma Brônquica*. Bernardo Boris Vargaftig

2003 *Pharmacology adventures down a long and winding Road*. John Wallace (University of Calgary)

2005 *Inflammation*: *my wanderings along Mauricio Rocha e Silva's trail*. Roderick John Flower (University of London, England)

2007 *Can we develop anti-inflammatory drugs for infectious diseases*? Mauro Martins Teixeira (UFMG)

2009 *Understanding peripheral analgesics*. Sérgio Henrique Ferreira (USP)

2011 *Bradykinin revisited 62 years after its discovery*. João Batista Calixto (UFSC)

2012 *Discovery of nitric oxide and cyclic GMP in cell signaling and their role in drug development*. Ferid Murad (Nobel Prize Laureate, George Washington University, USA)

2014 *Resolution pharmacology*: *A new approach to anti-inflammatory therapy*. Mauro Perretti (The William Harvey Research Institute, UK)

2016 *The joy of discovery*: *My life in Pharmacology*. Salvador Moncada (University of Manchester, UK)

2018 Functional *selectivity and spatio-temporal propagation of GPCR signaling*; *from structural determinants to better drugs*. Michel Bouvier (University of Montreal, Canada)

2021 *6-NitroDopamine, the New kidDo in town*. Gilberto de Nucci (Unicamp)

Keynote Speakers

Mauricio Rocha e Silva Lecture

Juan M. Saavedra, MD is Adjunct Professor at the Dept of Pharmacology and Physiology, Georgetown University Medical Center. Dr. Saavedra graduated from Medical School in 1965 and obtained his board certification in Psychiatry in 1970, from Buenos Aires University, Argentina. In 1971 he joined the Section on Pharmacology at the National Institute of Mental Health in Bethesda, Maryland as a Visiting Fellow. Under the supervision of Julius Axelrod, PhD, 1970 Nobel Prize winner in Medicine, Dr. Saavedra developed novel biochemical micromethods to study neurotransmitters in the brain, and was awarded tenure at NIH with a Civil Service Excepted Appointment in 1975. 1971-1989: International Fellow, Visiting Scientist, Medical Officer, Section on Pharmacology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA. From 1989 to 2013 Dr. Saavedra was Chief of the Section on Pharmacology at the National Institute of Mental Health Intramural Program. At the NIH, Dr. Saavedra's research interests included molecular and physiological aspects of endocrine and cardiovascular regulation, and more recently mechanisms of neuroprotection in stroke, Alzheimer's disease, mood disorders and Traumatic Brain Injury. The main objective of the research was to find novel therapies for inflammatory, degenerative, mood and traumatic disorders of the brain. In September 2013 Dr. Saavedra transitioned from NIH to Georgetown University, where he joined the Dept of Pharmacology and Physiology. In his new laboratory, Dr. Saavedra continues his work to advance his more recent finding, the observation that a novel class of compounds, the sartans, previously used for the treatment of cardiovascular and metabolic disorders, are potent neuroprotective agents and may be of significant therapeutic relevance for the treatment of neurodegenerative, mood and traumatic brain disorders. Dr. Saavedra has been Editor of Cellular and Molecular Neurobiology since 1983. Peer-reviewed publications (1966-present): about 500. From these, 40 publications with Brazilian co-authors. Trained 45 postdoctoral Fellows from 14 different countries, including Brazil (Fernando M.A. Correa, Ana Maria de Oliveira, Gilberto L. Sanvitto).

Keynote Speaker – Closing lecture

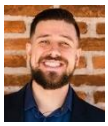
Gregg L. Semenza received his A.B. from Harvard University. He earned M.D. and Ph.D. degrees from the University of Pennsylvania, completed residency training in pediatrics at Duke University Medical Center, and postdoctoral training in medical genetics at Johns Hopkins. Dr. Semenza joined the Johns Hopkins School of Medicine faculty in 1990 where he is currently a professor of genetic medicine, pediatrics, radiation oncology, and molecular radiation sciences, biological chemistry, medicine, and oncology, besides serving as the director of the vascular program at the Institute for Cell Engineering. One of today's preeminent researchers on the molecular mechanisms of oxygen regulation, Dr. Semenza has led the field in uncovering how cells adapt to changing oxygen levels. He is best known for his ground-breaking discovery of the HIF-1 (hypoxia-inducible factor 1) protein, which controls changes in gene expression in response to changes in oxygen availability. The discovery of HIF-1 has far-reaching implications for understanding and treating conditions, such as cancer and ischemic cardiovascular disease, in which hypoxia plays an important role in disease pathogenesis. His lab's research has been published in more than 400 research articles and book chapters, which have been cited more than 150,000 times. Dr. Semenza is a fellow of the American College of Medical Genetics, the Association of American Physicians, the National Academy of Sciences, and the National Academy of Medicine of the United States. He has been recognized with numerous other awards from different international institutions. For his groundbreaking research, he was awarded the Nobel Prize in Physiology or Medicine in 2019 with William G. Kaelin, Jr. of the Dana-Farber Cancer Institute, and Peter J. Ratcliffe of Oxford University.

José Ribeiro do Valle Award

José Ribeiro do Valle Award – First Place Winner History

1998: Maria Martha Campos (UFSC; Adviser: João Batista Calixto)
1999: José Eduardo da Silva Santos (UFSC; Adviser: Jamil Assreuy)
2000: Ana Paula V. Dantas (USP-SP; Adviser: Maria Helena Catelli de Carvalho)
2001: Liliam Fernandes (USP-SP; Adviser: Maria Helena Catelli de Carvalho)
2002: Isaias Gleizer (USP-SP; Adviser: Cristoforo Scavone)
2003: Juliano Ferreira (UFSC; Adviser: João Batista Calixto)
2004: João Alfredo de Moraes (UERJ; Adviser: Thereza Christina Barja-Fidalgo)
2005: Tiago Chiavegatti (Unifesp-EPM; Adviser: Rosely O. Godinho)
2006: Ana Letícia G. Cabral Maragno (USP-RP; Adviser: Marcelo Damário Gomes)
2007: Maria Fernanda de Paula Werner (UFSC; Adviser: Giles A. Rae)
2008: Ana Luiza Andrade de Paula Lopes (Unifesp-EPM; Adviser: Rosely O. Godinho)
2009: Silvio Manfredo Vieira (USP-RP; Adviser: Fernando de Q. Cunha)
2010: Vanessa Olzon Zambelli (Instituto Butantan; Adviser: Yara Cury)
2011: Tatiana Paula Teixeira Ferreira (Fiocruz; Adviser: Patrícia Machado Rodrigues e Silva)
2012: Maíra Assunção Bicca (UFSC; Adviser: João Batista Calixto)
2013: Jaqueline Raymondi Silva (USP-RP; Adviser: Fernando de Q. Cunha)
2014: Jhimmy Talbot (USP-RP; Adviser: Fernando de Q. Cunha)
2015: Daniele Maria Ferreira (UFPR; Adviser: Maria Fernanda de Paula Werner)
2016: Gabriela S Kinker (USP, Adviser: Pedro Augusto Carlos Magno Fernandes)
2017: Fernando Olinto Carreño (UFRGS, Adviser: Teresa C. Dalla Costa)
2018: Bruna da Silva Soley (UFPR, Adviser: Daniela de Almeida Cabrini)
2019: Douglas da Silva Prado (USP-RP) Adviser: José Carlos Alves Filho
2021: Rianne Remus Pulcinelli (UFRGS) Adviser: Rosane Gomez

José Ribeiro do Valle Award – 2022 Finalists



Tiago H Zaninelli
BSc in Biological Sciences (UEL) (2010 -2016)
MSc in Experimental Pathology (UEL) (2016-2018)
PhD in Experimental Pathology (UEL)
Adviser: Waldiceu Aparecido Verri Junior (UEL)

Diulle Spat Peres
BSc in Biomedicine (UFN) (2013-2017)
MSc in Pharmacology (UFSM) (2018 – 2020)
PhD in Pharmacology (UFSM) (2018 – 2020)
Adviser: Gabriela Trevisan dos Santos

Aurilene Gomes Cajado
BsC in Biology (UVA) (2009-2012)
MSc in Biotechnology (UFC) (2013-2015)
PhD in Pharmacology (UFC)
Adiviser: Roberto C. P. Lima Júnior (UFC)

Fabio Bonifacio de Andrade
BSc in Biomedicine (Unifil) (2014 – 2017)
MSc in Experimental Pathology (UEL) 2018 – 2020
PhD in Biological Sciences (Pharmacology) (USP-RP)
Adviser: Thiago M. Cunha (USP-RP)

Viviano G. de Oliveira Neves
BSc in Pharmacy (UFOP) (2012-2016)
MSc in Biological Sciences (UFOP) (2017-2019)
PhD in Biological Sciences (USP-RP)
Adviser: Michele Mazzaron de Castro (USP-RP)

About SBFTE Jovem

SBFTE Jovem, founded in 2013, is the Young Committee of the Brazilian Society of Pharmacology and Experimental Therapeutics (SBFTE), comprised of young Pharmacologist's members of the society. Our mission, working in association with the SBFTE Board of Directors, is to create a permanent political-scientific forum dedicated to undergraduate and graduate students, postdoctoral fellows, as well as young investigators and Junior faculty members. We aim to discuss pharmacology-related scientific topics in order to promote the early-career investigators development and to stimulate the participation, insertion and collaboration of our members into SBFTE activities.

This year, SBFTE Young Committee will sponsor two crucial events during the 54th Brazilian Congress of Pharmacology and Experimental Therapeutics: The Roundtable Beyond the Academy and Meet the Professor Activity. The former is proposed as an open discussion about innovation, new challenges in science, how to engage into industry/pharma-carriers, or any other relevant opportunities beyond scholar-driven carriers to early-career scientists, scheduled to happen on November 20th, 2022 from 10h15 to 12h15 (BRT). The latter is proposed as a safe space for undergrads and grad-students to talk with established Professors about career challenges, project ideas, scientific questions, and experiences to be shared aiming to encourage early-career scientists to pursue their goals. This event is scheduled to happen on October 19th, 2022, from 12h20 to 13h20 (BRT). Last but not least, in its second edition, the Cultural Competition for Scientific Dissemination of SBFTE Jovem is the attempt of this Committee to contribute with science dissemination by stimulating students to produce informative videos about pharmacology using audiovisual aids, layman's terms, metaphors, and creativity. Videos have been analyzed by pharmacology professors/experts and elected by popular vote on social media. The winners will be announced at the 2022 Congress Closing Session.

SBFTE Young Committee
Jamylle Nunes de Sousa Ferro (UFAL, Coordinator
Guilherme Carneiro Montes (UERJ)
João Agostinho Machado Neto (USP-SP)
Maíra Assunção Bicca (Johns Hopkins University, USA)
Weverton Castro Coelho Silva (Unicamp)

Scientific Program at a Glance

	18/10/22 (Tuesday)	19/10/22 (Wednesday)	20/10/22 (Thursday)	21/10/22 (Friday)
08h00	Courses	Courses	Courses	
09h00	Meeting of SBFTE Directory Board and Deliberative Council			
09h05		Lectures	Lectures	Lectures
10h05		Coffee-break	Coffee-break	
10h10				Symposia
10h15		Symposia/Oral Communication	Symposia/Oral Communication	
12h00	Lunch			Lunch
12h20		Lunch Meet the Professor	Lunch SBFTE Assembly	
13h00				Symposia/Oral Communication
13h25		Lectures	Lectures	
13h30	Meeting of SBFTE Permanent Forum of Postgraduation in Pharmacology			
14h30		Symposia/Oral communication	Symposia	
15h05	Roundtable			
15h10				Closing lecture
16h15				Closing Session
16h35		Coffee-break	Coffee-break	
16h45		E-Poster Session 1	E-Poster Session 2	
17h00	Opening Session			
17h35	Opening Lecture			

Scientific Program

18/10/22 (Tuesday)

08h00-09h00 **Courses**

Campeche Room

Pharmacological Treatments Based on Scientific Evidence (**Tratamentos Farmacológicos Baseados em Evidências Científicas**)

Chair: Rosane Gomez (UFRGS)

- Class 1: *Clinical study design and how they support the pharmacological treatment*. (*Diferentes tipos de estudos clínicos e como eles auxiliam na escolha do tratamento farmacológico*)
  Rosane Gomez (UFRGS)

Joaquina Room

Digital Games as Tools for Scientific Divulgation (**Jogos Digitais como Ferramentas para Divulgação Científica**)

Chair: François G. Noël (UFRJ)

- Class 1: *Digital games for scientific divulgation and citizen science* (*Jogos digitais para divulgação científica e ciência cidadã*)
  Tadeu Moreira de Classe (Unirio)

Jurerê Room

Population Pharmacokinetics Analysis (**Análise Farmacocinética Populacional**)

Chair: Bibiana Verlindo de Araujo (UFRGS)

- Class 1: *Basic concepts in population pharmacokinetics* (*Conceitos básicos de farmacocinética populacional*)
  Bibiana Verlindo de Araujo (UFRGS)

09h00-11h00 **Meeting of SBFTE Directory Board and Deliberative Council** (Council and Directory Board Members only) (Google Meet)

12h00-13h30 **Lunch**

13h30-15h00 **Meeting of SBFTE Permanent Forum of Postgraduation in Pharmacology** (Google Meet)

15h05-16h15 **Roundtable**

Campeche Room

Equity, Diversity and Inclusion in Postgraduation Courses and Impact Science (**Equidade, Diversidade e Inclusão na Pós-Graduação e na Ciência de Impacto**)

Chair: Carolina Demarchi Munhoz (USP-SP, Coordinator SBFTE Permanent Forum of Postgraduation in Pharmacology)

- *Scientists Women Yesterday and Today*: *The History Showing the Importance of Diversity in the Knowledge* (*Mulheres Cientistas Ontem e Hoje*: *A História Mostrando a Importância da Diversidade no Conhecimento*)
  Vanderlan da Silva Bolzani (Unesp-Araraquara)
- Débora Foguel (UFRJ)
- *Towards SDG number 5*: *Gender Equality and Women´s Empowerment*
  Helena B. Nader (Unifesp-EPM, President Brazilian Academy of Sciences)

17h00-17h30 **Opening Session**

Campeche Room

17h35-18h35 **Opening Lecture**

Campeche Room

Rocha e Silva Memorial Lecture

Neuroprotective Mechanisms of Angiotensin II Receptor Blockers

Juan M. Saavedra (Georgetown University, USA)

Chair: Marco Aurélio Martins (Fiocruz)

Presented by Fernando Morgan de Aguiar Correa (USP-RP)

19/10/22 (Wednesday)

08h00-09h00 **Courses**

Campeche Room

Pharmacological Treatments Based on Scientific Evidence (**Tratamentos Farmacológicos Baseados em Evidências Científicas**)

Chair: Rosane Gomez (UFRGS)

- Class 2: *Search for scientific evidence in databases and check the quality of studies and scientific journals*. (*Busca de evidência científica em base de dados e qualidade dos estudos e revistas científicas*)
  Adriane Ribeiro Rosa (UFRGS)

Joaquina Room

Digital Games as tools for Scientific Divulgation (**Jogos Digitais como Ferramentas para Divulgação Científica**)

Chair: François G. Noël (UFRJ)

- Class 2: *DiscoveRx, a digital game for scientific divulgation of the drug discovery and development process* (*DiscoveRx, um jogo digital para divulgação científica do processo de descoberta e desenvolvimento de fármacos*)
  François G. Noël (UFRJ)

Jurerê Room

Population Pharmacokinetics Analysis (**Análise Farmacocinética Populacional**)

Chair: Bibiana Verlindo de Araujo (UFRGS)

- Class 2: *Pharmacometrics applied to Real-World data analysis* (*Farmacometria aplicada à análise de dados do Mundo Real*)
  Fernando Olinto Carreño (GSK, USA)

09h05-10h05 **Lectures**

Campeche Room

Registered Reports: A Vaccine against Bias in Research and Publishing

Chris Chambers (Cardiff University, UK)
Presented by Cilene Lino de Oliveira (UFSC)

Joaquina Room

Emerging Opportunities and Challenges for Drug Discovery and Healthcare Innovations in an Academic Setting

Chris Thiemermann (Queen Mary University of London, UK)
Presented by Regina de Sordi (UFSC)

10h05-10h15 **Coffee-break**

10h15-12h15 **Symposia/Oral Communication**

Campeche Room

Towards Novel Approaches to Study, Understand, and Treat Pain

Chair: Maíra Assunção Bicca (Johns Hopkins University, USA)

- *Screening for nociceptor-selective silencers as novel analgesics*
  Clifford J. Woolf (Harvard University, USA)
- *Interruptions of sleep — A new pain biomarker*
  Alban Latremoliere (Johns Hopkins University, USA)
- *Cell metabolism on chemotherapy-induced neuropathic pain*
  Thiago M. Cunha (USP-RP)
- *Oral* Communication 1: 05.007 *Effects of 4'-metoxichalcone in chemotherapy-induced neuropathic pain*.
  Evelynn Dalila do Nascimento Melo[1], Botinhão MC[1], Marchon ISS[1], Cavararo AR[1], Ramos IFO[1], Rocha Reis JV[1], Souza ROMA[2], Leal ICR[2], Raimundo JM[1], Bonavita AGC[1], Muzitano MF[1], Mendonça HR[1], Carmo PL[1]
  [1]UFRJ-Macaé, [2]UFRJ-Rio de Janeiro

Joaquina Room

Publishing in the Open Science Era

Chair: Cilene Lino de Oliveira (UFSC)

- *Why does science need immediate and substantial reform*?
  William Ngiam (University of Chicago, USA)
- *What are preprints and why we should post preprints*?
  Gillian Currie (University of Edinburgh, UK)
- *Introducing the Peer Community in Registered Reports*
  Chris Chambers (Cardiff University, UK)
- *Publishing Pharmacology in the Open Science era*
  Cilene Lino de Oliveira (UFSC)

Jurerê Room

Brain Disorders Associated with Chronic Diseases: Are Inflammatory Processes a Key Issue?

Chair: Janaina Menezes Zanoveli (UFPR)

- *Two birds one stone*: *The neuroprotective effect of anti-inflammatory drugs on Parkinson disease*
  Elaine Aparecida Del Bel Belluz Guimarães (USP-RP)
- *Cognitive dysfunction following viral infections*: *neuroinflammation as a therapeutic target*
  Giselle Fazzioni Passos (UFRJ)
- *Alzheimer's disease and depression*: *What is the role of neuroinflammation*?
  Josiane Budni (Unesc)
- *Impact of type-1 Diabetes* mellitus *on the development of anxiety and depression*: *would neuroinflammation be a key factor*?
  Janaina Menezes Zanoveli (UFPR)

12h20-13h20 **Lunch**

12h20-13h20 **Meet the Professor** (Google Meet)
(Chair: Sbfte Jovem Committee)

- Alexander Bishop (University of Texas Health at San Antonio, USA)
- Alyssa Panitch (University of California, USA)
- Chris Chambers (Cardiff University, UK)
- Giles Alexander Rae (UFSC)
- Michael Caterina (Johns Hopkins University School of Medicine, USA)
- Silvia Regina Rogatto (University of Southern Denmark, Denmark)

13h25-14h25 **Lectures**

Campeche Room

Identification of Oligopeptidases and Intracellular Peptides Key Function in Cell Metabolism

Emer Suavinho Ferro (USP-SP)
Presented by Regina P. Markus (USP-SP)

Joaquina Room

Seeing Alzheimer's through a Different Lens: How Retina Cells can shed light on the Physiological Role of AD-related Toxins?

William L. Klein (Northwestern University, USA)
Presented by: Maíra Assunção Bicca (Johns Hopkins University)

14h30-16h30 **Symposia/Oral communication**

Campeche Room

Sperm Cell Signaling: Therapeutic Opportunities for Male Infertility Treatment and Contraception

Chair: Erick José Ramo da Silva (Unesp-Botucatu)

- *Effect of mitochondrial uncouplers on human sperm motility*
  Polina Lishko (University of California, Berkley, USA)
- *Understanding the molecular mechanisms responsible for age-dependent decline in spermatozoa quality*
  Margarida Fardilha (University of Aveiro, Portugal)
- *CRISP proteins as novel targets for male fertility regulation*

Patricia S. Cuasnicú (IBYME-Conicet, Argentina)

- Oral Communication 1: 06.002 *Aging as an important contributor factor for decreased semen quality in Hypertensive Rats*: *A role for enhanced testis vasomotricity*.
  Nicolle Rakanidis Machado[1], Miyazaki MA[2], Belardin LB[2], Colli LG[1], Bertolla RP[2], Rodrigues SF[1] [1]ICB-USP – Farmacology; [2]USP – Urology
- Oral Communication 2: 07.009 *b1- and b1/b2-adrenergic receptor antagonists block 6-nitrodopamine-induced contractions on the rat isolated epididymal vas deferens*.
  Amanda Consulin Amorim, Lima Silva AT, Britto-Júnior J, Campitelli RR, Fregonesi A, Mónica FZ, Antunes E, De Nucci, G FCM-Unicamp

Joaquina Room

Pharmacological Opportunities in the Tumor Microenvironment

Chair: Alfeu Zanotto Filho (UFSC)

- *Delineating the role of BRCA1 in the mammary gland and the therapeutic strategies it reveals*
  Alexander J. R. Bishop (UT Health San Antonio, Texas, USA)
- *Adenosinergic signaling as a key component of cancer-related immunosuppression*
  Elizandra Braganhol (UFSCPA)
- *Targeting mutant p53 protein gain-of-function in cancer*: *role of cytokines and tumor microenvironment*
  Alfeu Zanotto Filho (UFSC)
- *Oral* Communication 1: 10.011 *Antileukemic potential of EMT to eliminate leukemic stem cells from acute myeloid leukemia in an in vitro and* in vivo *model*.
  Suellen Rocha Silva[1], Dias IRSB[2], Costa RGA[1], Rodrigues ACCB[2], Oliveira MS[2], Bezerra DP[2] [1]UFBA, [2]IGM-Fiocruz-BA
- Oral Communication 2: 10.012 *NRF2 pathway activation and tumor recurrence correlate with thioredoxin reductase-1 up-regulation in non-small cell lung cancer*.
  Marina Delgobo[1], Gonçalves[2] RM, , Delazeri MA[3], Falchetti M[1], Zandoná S[3], Neves RN[1], Almeida K[1], Fagundes AC[1], Fracasso JI[4], Macêdo GB[4], Priori L[4], Gelain DP[5], Forcelini CM[3], Moreira JCF[5], Zanotto-Filho A[1] [1]UFSC, [2]UFRJ, [3]UPF, [4]HSVP, [5]UFRGS

Jurerê Room

Metabolic Diseases and Inflammation: Impacts on Co-morbidities

Chair: Vinicius de Frias Carvalho (Fiocruz)

- *Enteric glia regulate intestinal neuroinflammation and neuroplasticity following inflammation*
  Brian D. Gulbransen (Michigan State University, USA)
- *Metabolic syndrome and neuroinflammation*: *A role for TLR4*?
  Hugo Caire Castro Faria Neto (Fiocruz)
- *High fat diet rapidly impacts the hippocampal function*: *microglia activation and blood brain dysfunction as trigging events*
  Andreza Fabro de Bem (UnB)
- Oral Communication 1: 04.025 *Glucagon is involved with increased susceptibility to sepsis in murine model of diabetes through down regulation of neutrophil migration*.
  Daniella Bianchi Reis Insuela[1], Ferrero MR[1], Albuquerque CFG[1,2], Chaves AS[1], Silva AYO[1], Faria-Neto HCC[1], Simões Rafael L[3], Barja-Fidalgo[3] Silva PMR[1], Martins MA[1], Silva AR[1], Carvalho VF [1]IOC-Fiocruz, [2]Unirio, [3]UERJ
- Oral Communication 2: 04.019 *Glucocorticoid-Induced Leucine Zipper Alleviates Lung Inflammation and Enhances Bacterial Clearance during Pneumococcal Pneumonia*.
  Antônio Felipe Silva Carvalho[1], Souza JAM[1], Grossi LC, Zaidan I[1], Oliveira LC, Vago JP[2], Cardoso C[1], Santos Souza GV[1], Queiroz-Junior CM[1], Morand EF[3], Bruscoli S[4], Riccardi C[4], Teixeira MM[1], Tavares LP[5], Sousa LP[1] [1]UFMG, [2]Radboud University Medical Center, [3]Monash University, [4]University of Perugia, [5]Harvard Medical School

16h35-16h45 **Coffee-break**

16h45-19h00 **E-Poster Session 1**

Room 01:

01. Cellular and Molecular Pharmacology (01.001 a 01.007, 01.009-01.012)

Room 02:

02. Neuropharmacology (02.001 a 02.003)

03. Psychopharmacology (03.001 a 03.006)

Room 03:

04. Inflammation and Immunopharmacology (04.001 a 04.004)
05. Pain and Nociception Pharmacology (05.001 a 05.004)

Room 04:

04. Inflammation and Immunopharmacology (04.014 a 04.019, 04.021 a 04.023)

Room 05:

05. Pain and Nociception Pharmacology (05.005 a 05.007, 05.009 a 05.013, 05.015)

Room 06:

06. Cardiovascular and Renal Pharmacology (06.008 a 06.013)

Room 07:

07. Endocrine, Reproductive and Urinary Pharmacology (07.001 a 07.009)

Room 08:

08. Respiratory and Gastrointestinal Pharmacology (08.001 a 08.012)

Room 09:

09. Natural Products and Toxinology (09.001 a 09.009)

Room 10:

09. Natural Products and Toxinology (09.017 a 09.025, 09.027)

Room 11:

10. Cancer Pharmacology (10.001 a 10.007)

Room 12:

11. Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Toxicology (11.001 a 11.008)

Room 13:

12. Drug Discovery and Development (12.003)
14. Pharmacology: Other (14.005 a 14.008)

20/10/22 (Thursday)

08h00-09h00 **Courses**

Campeche Room

Pharmacological Treatments Based on Scientific Evidence (**Tratamentos Farmacológicos Baseados em Evidências Científicas**)

Chair: Rosane Gomez (UFRGS)

- Class 3: *A critical analysis of the scientific evidence that supports the best pharmacological treatment*. (*Análise crítica das evidências científicas que suportem o melhor tratamento farmacológico*.)
  Adriane Ribeiro Rosa (UFRGS)

Joaquina Room

Digital Games as tools for Scientific Divulgation (**Jogos Digitais como Ferramentas para Divulgação Científica**)

Chair: François G. Noël (UFRJ)

- Class 3: *Educational games for scientific literacy*: *the case of the game Immuno Rush* (*Jogos educacionais para letramento científico*: *o caso do game Immuno Rush*)
  Luiz Osório Silveira Leiria (USP-RP)

Jurerê Room

Population Pharmacokinetics Analysis (**Análise Farmacocinética Populacional**)

Chair: Bibiana Verlindo de Araujo (UFRGS)

- Class 3: *Applications of POPPK on precision dosing* (*Aplicações de POPPK em dose de precisão*)
  Manuel Ibarra (University of the Republic, Uruguay)

09h05-10h05 **Lectures**

Campeche Room

Germline Variants Associated with Cancer Risk and Actionable Drug Targets

Silvia Regina Rogatto (University of Southern Denmark, Denmark)
Presented by Roberto César Pereira Lima Júnior (UFC)

Joaquina Room

Cellular and Molecular Mechanisms of Cutaneous Pain Sensation

Michael Caterina (Johns Hopkins University, USA)
Presented by: Maíra Assunção Bicca (Johns Hopkins University)

10h05-10h15 **Coffee-break**

10h15-12h15 **Symposia/Oral Communication**

Campeche Room

Role of Inflammatory proteins in Vascular Dysfunction

Chair: Carlos Renato Tirapelli (USP-RP)

- Resolution *of inflammation as a novel approach for vascular damage in hypertension*
  Ana Maria Briones (UAM, Spain)
- *Role of HIV-derived viral proteins in the development of endothelial dysfunction and hypertension*
  Eric J. Belin de Chantemèle (Augusta University, USA)
- *CCL5/CCR5 interaction on the vascular diseases*
  Thiago Bruder do Nascimento (University of Pittsburgh, USA)
- Oral Communication 1: 01.010 *Endothelial P2Y2 receptors signaling in primed cells contribute to leukocyte adhesion during chronic inflammation*.
  Nathália Ferreira de Oliveira, Tamura AS, Mainieri NS, Coutinho-Silva R, Savio LEB, Silva CLM UFRJ
- Oral Communication 2: 06.022 *Sarcoplasmic Reticulum Calcium ATPase* (*SERCA*) *proteolysis by Matrix Metalloproteinase-2 results in hypertension-induced morphofunctional vascular alterations*.
  Marcela Maria Blascke de Mello, Neves VGO, Pernomian L, Parente JM, Rocha EV, Silva PHL, Castro MM FMRP-USP

Joaquina Room

Novel Pharmacological Approaches for the Treatment and/or Prevention of Schizophrenia

Chair: Felipe Villela Gomes (USP-RP)

- *Peripubertal intervention as a preventive measure for the transition to a schizophrenia phenotype in developmental disruption models of the disorder*
  Anthony A. Grace (University of Pittsburgh, USA)
- *Studying adolescent stress in the search for new drugs to treat schizophrenia*
  Felipe Villela Gomes (USP-RP)
- *MMP9/RAGE mechanism as a promising target for early intervention in early psychosis patients*: *a translational study*
  Daniella Dwir (University of Lausanne, Switzerland)
- *Challenges in Drug Development for Psychiatry*
  Patricio O'Donnell (Sage Therapeutics, USA)

Jurerê Room

Beyond the Academy (Além da Academia)

Chair: Jamylle Nunes de Sousa Ferro (SBFTE Jovem, UFAL)

- *The Blue Ocean of Life Sciences – From professional carrier to market potential for Brazil* (*O oceano azul de Ciências da Vida- Da trajetória ao potencial de mercado para o Brasil*)
  Claudia Emanuele Carvalho Sousa (Merck)
- *There is life beyond the Academy* (*Há vida além da academia*!)
  Angela Alice Amadeu Megale (IBu)
- *Consolidated Academic Career*? *There are no Barriers to the Pursuit of new Dreams*!!! (*Carreira Acadêmica Consolidada*? *Não há Barreiras para a Busca de Novos Sonhos*!!!
  Rafael Cypriano Dutra (UFSC)

12h20-13h20 **Lunch** / SBFTE Assembly (Google Meet)

13h25-14h25 **Lectures**

Campeche Room

Can we recover aging-related steroidogenic dysfunction?

Vassilios Papadopoulos (University of South California, USA)
Presented by Maria Christina W. de Avellar (Unifesp-EPM)

Joaquina Room

Hormesis Based Biological Effects of Low Levels of Chemicals and Radiation

Edward J. Calabrese (University of Massachusetts Amherst, USA)
Presented by Elisa Mitiko Kawamoto (USP-SP)

14h30-16h30 **Symposia**

Campeche Room

José Ribeiro do Valle Award

Chair: Marco Aurélio Martins (Fiocruz)

Tiago H Zaninelli

- 05.014 *Resolvin D1 Disrupts CGRP-Dependent neuroimmune communication unveiling a hitherto unknown gouty arthritis mechanism and therapeutic target*. Zaninelli TH[1], Fattori V[2], Saraiva-Santos T[1], Badaro-Garcia S[1], Staurengo-Ferrari L[1], Artero NA[1], Ferraz CR[1], Bertozzi MM[1], Rasquel-Oliveira F[1], Amaral FA[3], Teixeira MM[3], Borghi SM[1], Rogers MS[2], Casagrande R[1], Verri Jr WA[1] [1]UEL, Lab of Pain, Inflammation, Neuropathy, and Cancer, Dept of Pathology, Centre of Biological Sciences, Londrina, Brazil, [2]Boston Children's Hospital, Harvard Medical School, Vascular Biology Program, Dept of Surgery, Boston, USA, [3]UFMG, Dept of Biochemistry and Immunology, Biological Sciences Institute, Federal University of Minas Gerais, Belo Horizonte, Brazil

Diulle Spat Peres

- 02.011 *TRPA1 channel involvement in depression- and anxiety-like behaviors in a progressive multiple sclerosis model in mice*. Peres DS[1], Theisen MC[1], Pessano Fialho MF[2], Dalenogare DP[1], Rodrigues P[1], Kudsi SQ[1], Bernardes LB[1], Ruviaro da Silva NA[1], Lückemeyer DD[3], Antoniazzi CTD[1], Santos GT[1] [1]UFSM, Santa Maria, Brazil, [2]UFSM, Toxicological Biochemistry, Santa Maria, Brazil, [3]UFSC, Florianopolis, Brazil

Aurilene Gomes Cajado

- 04.020 *Blockade of PI3K-y attenuates chemotherapy-associated intestinal mucositis without compromising the anticancer effect of irinotecan*. Cajado AG[1], Rangel GFP[1], Quintela LCS[1], Quispe CC[1], Padilla Paguada AL[1], Ferreira KQ[1], Ferreira LMM[1], Dias Florêncio KG[1], Pereira AF[1], Nunes Alves APN[1], Alencar NMN[1], Hirsch E[2], Wong DVT[1], Lima-Junior RCP[1] [1]UFC [2]Università di Torino

Fabio Bonifacio de Andrade

- 05.008 *Role of the cytoplasmic DNA sensor, STING, on the development of neuropathic pain induced by cisplatin*. Andrade FB[1], Lee SH[2], Cunha FQ[1], Alves Filho JC[1], Berta T[2], Cunha TM[1] [1]FMRP-USP, Center for Research in Inflammatory Diseases, Dept of Pharmacology, Ribeirão Preto, Brazil, [2]University of Cincinnati Medical Center, Pain Research Center, Dept of Anesthesiology, Cincinnati, EUA

Viviano Gomes de Oliveira Neves

- 01.008 *Matrix Metalloproteinase* (*MMP*)*-2 proteolyzes Type I Collagen* (*COL-1*) *and contributes to focal adhesion kinase* (*FAK*) *activation and vascular smooth muscle cells proliferation in aorta of Acute Hypertensive Rats*. Neves VGO, Blascke de Mello MMB, Rodrigues D, Rocha EV, Parente JM, Tostes RC, Castro MM FMRP-USP, Dept Pharmacology, Ribeirão Preto, Brazil. Neves VGO, Blascke de Mello MMB, Rodrigues D, Rocha EV, Parente JM, Tostes RC, Castro MM FMRP-USP, Dept Pharmacology, Ribeirão Preto, Brazil

16h35-16h45 **Coffee-break**

16h45-19h00 **E-Poster Session 2**

Room 14:
02. Neuropharmacology (02.005 a 02.010, 02.012 a 02.013)

Room 15:
03. Psychopharmacology (03.007 a 03.013)

Room 16:
04. Inflammation and Immunopharmacology (04.006 a 04.013)

Room 17:
04. Inflammation and Immunopharmacology (04.024 a 04.028)
05. Pain and Nociception Pharmacology (05.016 a 05.018)

Room 18:
06. Cardiovascular and Renal Pharmacology (06.001 a 06.007)

Room 19:
06. Cardiovascular and Renal Pharmacology (06.014 a 06.024)

Room 20:
07. Endocrine, Reproductive and Urinary Pharmacology (07.010 a 07.017)

Room 21:
08. Respiratory and Gastrointestinal Pharmacology (08.013 a 08.022)

Room 22:
09. Natural Products and Toxinology (09.010 a 09.016)

Room 23:
09. Natural Products and Toxinology (09.026, 09.028 a 09.036)

Room 24:
10. Cancer Pharmacology (10.008-10.013)

Room 25:
12. Drug Discovery and Development (12.001 a 12.002)
13. Pharmacology Education and Technology (13.001 a 13.003)
14. Pharmacology: Other (14.001 a 14.004)

19h15-20h15 **SBFTE Jovem Assembly** (Google Meet)

21/10/22 (Friday)

08h00-09h00 **Meeting of the North-Northeast and Central West Region Pharmacology Network** (Google Meet)

09h05-10h05 **Lectures**

Campeche Room

Prediction of the Fate of Drugs in the CNS in Health and Disease by the Leiden CNS PBPK Model
Elizabeth de Lange (Leiden University, The Netherlands)
Presented by Teresa Dalla Costa (UFRGS)

Joaquina Room

Enzyme inhibitors: Foes and Friends?
Gokhan Zengin (Selcuk University, Turkey)
Presented by Lucindo Quintans Júnior (UFS)

10h10-11h10 **Symposia**

Campeche Room

UFSC Graduate Program in Pharmacology 30th Anniversary: Insights from Former SBFTE Presidents
Chair: Rui Daniel Prediger (UFSC)

- *My memories of 4 Years as President of the Brazilian Society of Pharmacology and Experimental Therapeutics*
  João Batista Calixto (CIEnP)
- *Recollections on our adventures to put UFSC's Pharmacology Department and Graduate Studies Program on the National map*
  Giles Alexander Rae (UFSC)
- *A Journey in Science*
  Jamil Assreuy (UFSC)

12h00-13h00 **Lunch**

13h00-15h00 **Symposia/Oral Communication**

Campeche Room

New Trends in Pharmacology Research and Teaching at the Graduate Level
Chair: Soraia K P Costa / Luciana B. Lopes (USP-SP)

- *Development of nano-based drug delivery systems to improve tissue healing*
  Alyssa Panitch (University of California, Davis, USA)
- *Understanding the skin barrier*
  Jack L. Arbiser (Emory University, USA)
- *The BPS eLearning platform and our new Experimental design resources*
  Lee Page (British Pharmacological Society, UK)
- Oral Communication 1: 06.017 *6-Nitrodopamine is a major modulator of heart chronotropism*.
  José Britto-Júnior[1], Taranto M[1], Campos R[2], Mónica FZ[1], Antunes E[1], De Nucci G[1] [1]UNICAMP, [2]UECE
- Oral Communication 2: 14.007 *Nebivolol mitigates endothelial dysfunction in a model of preeclampsia*.
  Thainá Omia Bueno Pereira, Matheus MB, , Nunes PR, Rocha ALV, Sandrim VC UNESP-Botucatu

Joaquina Room

Novel Insights in Psychopharmacology: A Tribute to Prof. Reinaldo Takahashi
Chair: Rui Daniel Prediger (UFSC)

- *The* "stress side" *of addiction*: *beyond reward*
  Leandro Franco Vendruscolo (NIDA-NIH, USA)
- *Phytocannabinoids to the treatment of addictive behaviors*: *Preclinical evidence*
  Cristiane Ribeiro de Carvalho (UFSC)
- *Helping to build the Brazilian* cannabis *market* "from scratch": *where science and entrepreneurship meets*
  Fabrício Alano Pamplona (Entourage Phytolab)
- *Insights on Parkinson's disease research*: *from olfactory vector hypothesis to neuroprotection challenges*
  Rui Daniel Prediger (UFSC)

Jurerê Room

Pharmacological and Non-Pharmacological Approaches for Modulating Aging, Age-Related Diseases, and Longevity

Chair: Ionara Rodrigues Siqueira (UFRGS)

- *Role of genistein in Alzheimer's disease therapeutics*: *from molecular mechanisms to clinical trials*
  Jose Viña (Valencia University, Spain)
- *Potential involvement of extracellular vesicles as mediators in the aging process*: *impact of exercise*
  Ionara R Siqueira (UFRGS)
- *Gut microbiome-brain interactions in Parkinson's disease*
  Livia Hecke Morais (California Institute of Technology, USA)
- Oral Communication 1: 02.010 *Involvement of neuroinflammation in the effect of Vitamin D and Donepezil in adult and aged ovariectomized rats*.
  Eduarda Behenck Medeiros, Gabriel JRM, Santos MLC, Lídio AV, Boaventura A, Ceolin de Jesus L, Santos LM, Bobinski F, Budni J Unesc
- Oral Communication 2: 06.020 *Effects of* Euterpe oleracea Mart. (açaí) *Seed Extract* (*ASE*) *in mitochondrial biogenesis and oxidative stress in brown adipose tissue of High-Fat-Fed C57Bl/6 mice*.
  Dafne Lopes Beserra Silva, Santos IB, Romão MH, Menezes MP, Oliveira BC, Ognibene DT, Bem GF, Costa CA, Resende AC UERJ

15h10-16h10 Closing lecture

Campeche Room

Hypoxia-Inducible Factors in Physiology and Medicine

Gregg L. Semenza (Johns Hopkins University, USA, 2019 Nobel Prize in Physiology or Medicine)
Presented by: Thiago M. Cunha (USP-RP)

16h15-17h00 Closing Session

Campeche Room

Awards and Prize Announcements
Closing Ceremony

E-Poster Session 1

19/10/2022 (Wednesday)

Room 1:

01. Cellular and Molecular Pharmacology

01.001 **Endothelium-Dopamine is a Major Vascular Mediator**. Campitelli RR[1], Britto-Júnior J[1], Souza VB[1], Schenka AA[1], Mónica FZ[1], Antunes E[1], De Nucci G[1,2,3] [1]FCM-Unicamp, Dept Pharmacology, Campinas, Brazil, [2]ICB-USP, Dept of Pharmacology, São Paulo, Brazil. [3]Univ Brasil, Fernandópolis, Brazil

01.002 **Mesenteric Endothelial Oxidative Stress and Antioxidant Profile during Schistosomiasis**. Monteiro MMLV[1], Valença SS[2], Silva CLM[1]. [1]ICB-UFRJ, Lab Farmacologia e Bioquímica Molecular, Rio de Janeiro, Brazil, [2]ICB-UFRJ, Lab de Biologia Redox, Rio de Janeiro, Brazil

01.003 **Evaluation of Gene Expression in the Thymus, a Mouse Model of Accelerated Aging Induced by D-galactose**. Nascimento LMM, Santos MRS, Silva ELES, Mendonça BS, Porto FL, Reis MDS UFAL, Lab Biologia Celular

01.004 **V-type Allosteric Enhancement of Jack Bean Urease by Thiourea**? Silva, MRS, Freiria AJI, Penha NC, Santos Filho PR, Silva JMSF, Kiguti LRA, Unifal, Alfenas, Brazil

01.005 **A Computational Study of the Sperm-Associated Protein EPPIN: Insights on its Structure and Druggable Properties for Male Contraceptive Development**. Santos NCM, Rosa LR, Borges RJ, Fontes MRM, Silva EJR, Gomes AAS IBB-Unesp-Botucatu, Dept of Biophysics & Pharmacology, Botucatu, Brazil

01.006 **Evaluation of Cytotoxic Activity and Phytochemical Screening of Extract and Fractions from the Bark of Plant** *Diplotropis racemosa* **Hoene (from Woody Residue)**. Mota JA[1], Pereira JVM[1], Manso MP[1], Guimarães AC[2], Araújo IM[2]; **Gomes SLF[2]; Sampaio TA[2]**; Veiga Junior V[3], Guimarães CJ[1], Pessoa C[1] , [1]NPDM-UFC – Experimental Oncology, [2]Q-BIOMA-UFAM – Chemistry, [3]Military Engineering Institute

01.007 *In vitro* **Aging Affects Epithelial Renal Cells Phenotype and Pharmacological Response to Bufalin**. Barros GMOB, Araújo LS, Morais JA, Almeida e Silva AC, Quintas LM ICB-UFRJ, Rio de Janeiro, Brazil

01.009 **Uvaol Inhibits TGF-β-Induced Epithelium-Mesenchymal Transition in Human Alveolar Epithelial Cells**. Tenório-Gonçalves LP[1 2 3], Xavier FHC[2 3], Wagner MSW[4], Savino W[2 3], Bonomo A[2 3], Barreto E[1 3 1]UFAL, Cell Biology Laboratory, Institute of Health and Biological Sciences, Maceió, Brazil, [2]IOC-Fiocruz, Lab on Thymus Research, Rio de Janeiro, Brazil, [3]National Institute of Science and Technology on Neuroimmunomodulation, [4]INCa, Cell Structure and Dynamics Rio de Janeiro, Brazil

01.010 **Endothelial P2Y2 Receptors Signaling in Primed Cells Contribute to Leukocyte Adhesion during Chronic Inflammation**. Oliveira NF[1], Tamura AS[2], Mainieri NS[1], Savio LEB[2], Coutinho-Silva R[2], Silva CLM[1] [1]ICB-UFRJ, [2]IBCCF-UFRJ, Rio de Janeiro Brazil

01.011 **Cellular distribution of the male contraceptive target EPPIN and its co-localization with binding partners in mouse spermatozoa during capacitation**. Mariana NAP, Santos NCM, Santos GVM, Andrade AD, Kushima H, Silva EJR IBB-Unesp-Botucatu, Botucatu, Brazil

01.012 **The Omega-3 Lipid 12-Hydroxyeicosapentaenoic Acid (12-HEPE) Exerts Cardiometabolic Effects through Partial Agonism of Thromboxane Receptor (TP)**. Gonçalves TT[1,2,3], Pereira da Silva MH[2,3], Passos ASC[2,3], Alves JM[2,3], Oliveira AA[5], Alnouri W[4], Offermanns S[4], Leiria LOS[2,3] [1]FCM-Unicamp, Dept Pharmacology, Campinas Brazil, [2]FMRP-USP, Dept Pharmacology, Ribeirão Preto, Brazil, [3]FMRP-USP, Center for Research in Inflammatory Diseases, Ribeirão Preto, Brazil, [4]Max Planck Institute for Heart and Lung Research, Dept Pharmacology, Germany, [5]CNPEM, Brazilian Biosciences National Laboratory, Campinas, Brazil

Room 2:

02. Neuropharmacology

02.001 **Protein Kinase M Zeta Maintains Remote Contextual Fear Memory by Inhibiting GluA2-Dependent AMPA Receptor Endocytosis in the Prelimbic Cortex**. Fujita GVR[1], Marcondes LA[1,2] , Myskiw JC[2], Nachtigall EG[1], Narvaes RF[3], Izquierdo I[4], Furini[1] CRG[1] Fujita GVR1, Marcondes LA1,2, Myskiw JC2, Nachtigall EG1, Narvaes RF1,3, Izquierdo I4, Furini CRG1. [1]PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, [2]UFRGS, Porto Alegre, Brazil, [3]Tufts University, Boston, USA, [4]PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil

02.002 **Involvement of Medial Prefrontal Cortex Canonical Wnt/β-catenin and Non-Canonical Wnt/Ca2+ Signaling Pathways in Contextual Fear Memory in Male Rats**. Dalferth TF1, Narvaes RF1, 2, Nachtigall EG1, Marcondes LA1, 3, Izquierdo I4, Myskiw JC3, Furini CRG1 1PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, 2UFRGS, Porto Alegre, Brazil, 3Tufts University, Boston, USA, 4PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil

02.003 **Systemic Inflammation and Oxidative Stress in Parkinson's Disease Patients may be Associated with Blood Biomarkers**. Santos BN[1], Maes M[2], Bonifácio KL[2], Matsumoto AK[2], Brinholi FF[2], Melo LB[2], Moreira EG[2], , Barbosa DS, Farias CC[1] [1]IFES, Vila Velha, Coordination of Biomedicine, Brazil; [2]UEL, Graduation Program in Health Sciences, Londrina, Brazil

03. Psychopharmacology

03.001 **Lower Antidepressant Response to Fluoxetine is Associated with Anxiety-Like Behavior, Hippocampal Oxidative imbalance, and increase on Peripheral IL-17 and IFN-γ Levels**. Piton E[1], Pereira GC[2], Santos BM[2], Bochi GV[2,3] [1]UFSM, Graduating in Pharmacy, Santa Maria, Brazil, [2]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2,3]UFSM, Dpt of Physiology and Pharmacology, Santa Maria, Brazil

03.002 **Experimental Evaluation of Delayed Behavioral Changes Associated with Depression in Mice Infected with *Plasmodium berghei* ANKA, Pharmacologically Treated And Cured**. Pires BB[1], Medeiros JGC[1,2], Noleto TG[2], Passos TG[2], Oliveira JPM[1,2], Dias QM[1,2] [1]UniSL-Afya [2]Fiocruz-RO, Lab de Neuro e Imunofarmacologia

03.003 **Alcohol Binge Drinking and Taurine are not Associated with Anxiety-Like Behaviors in Adolescent Rats**. Sant'Ana BH[1], Zilli GAL[1], Bastiani CS[1], Pulcinelli RR[1], Izolan LR[2], Gomez R[1,2] [1]UFRGS – PPG Farmacologia e Terapêutica, [2]UFRGS– PPG Neurociências

03.004 **Maternal Deprivation Induces Long-term Anxious-like Behavior and Exacerbates Lipopolysaccharide-Induced Microglia Activation in the Dentate Gyrus**. Oliveira CA, Gaspar DM, Chaves Filho AJM, Sousa RC, Cunha NL, Jucá PM, FM-UFC – Neuropharmacology Lab, Drug Research, and Development Center, Department of Physiology and Pharmacology, Fortaleza, Brazil

03.005 **Assessment of Anxiety Level and Locomotor Ability in Experimental Malaria Recurrence in Pharmacologically treated Mice Infected by *Plasmodium berghei* ANKA**. Medeiros JGC[1,2], Pires BB[1,2], Oliveira JPM[2], Nôleto TG[1], Passos TG[1], Dias QM[1,2] [1]NIMFAR-Fiocruz-RO [2]Afya-UniSL

03.006 **Two Weeks of Strength Training Fails to Decrease Voluntary Alcohol Consumption but Decreases Anxiety-Like Behaviors in Alcohol Withdrawal Rats**. Bastiani CS[1], Pulcinelli RR[1], Izolan LR[2], Silva J[2], Zilli GAL, Sant'Ana BH, Gomez R[1,2] [1]UFRGS – PPG Farmacologia e Terapêutica, Porto Alegre, Brasil, [2]UFRGS – PPG Neurociências, Porto Alegre, Brasil

Room 3:

04. Inflammation and Immunopharmacology

04.001 **Evaluation of Camphor Hidrazones Derivatives as Inhibitors of Myeloperoxidase and Acetylcholinesterase Enzymes**. Frias B[1], Souza MVN[2], Silva LL[3] [1]UFRJ-Macaé Integrated Laboratory for Research in Natural and Bioactive Products, Macaé, Brazil, [2]Fiocruz, Rio de Janeiro, Brazil, [3]FF-UFRJ, Health Sciences, Rio de Janeiro, Brazil

04.002 **Low Birth Weight Induced by Maternal Malnutrition Impair Phagocytic and Microbicidal Activity of Alveolar Macrophages and Increases Susceptibility to Infections**. Negreiros NGS[1], Azevedo GA[1], Gil NL[1], Lippi BK[1], Landgraf MA[2] Landgraf RG[1] [1]Unifesp, Ciências Farmacêuticas, Diadema, Brazil [2]UniP-Rangel

04.003 **Anti-Inflammatory Effect of Cannabidiol (CBD) in Human HMC3 Microglia: Contribution of Pro-Autophagic Mechanisms**. Sousa RC[1], Chaves Filho AJM[1], Jucá PM[1], Oliveira CA[1], Gaspar DM[1], Joca SRL[2], [1]UFC, Drug Research and Development, [2]Aarhus University-Denmark – Biomedicine

04.004 **Inhibition of Myeloperoxidase Chlorinating Activity by Propolis Samples from Rio das Ostras-RJ, Brazil**. Condack CPM, Silva LL, Raimundo JM, Barth T, Muzitano MF, Teixeira FM, Nascimento JCM UFRJ-Macaé, Integrated Laboratory of Research in Bioactive Products, Macaé, Brazil

05. Pain and Nociception Pharmacology

05.001 **Effective, long-Lasting and Safe Multimodal Analgesia Produced by a Novel Anesthetic/Analgesic Drug Protocol in Mice**. Hoepers JVA, Godoi MM, Ferreira J UFSC, Dpt of Pharmacology, Florianópolis, Brazil

05.002 **Antinociceptive and Antiedematogenic Effect of α-Bisabolol in Mice**. Bernardes LB, Viero FT, Rodrigues P, Santos GT UFSM, PPG in Pharmacology, Santa Maria, Brazil

05.003 **Nonclinical Investigation of the Analgesic Efficacy of Topical Acid Dibucaine in a Mice Model of Painful HIV-Sensory Neuropathy**. Bittencourt MCS[1], Schran RG[2], Silva AM[2], Ferreira MA[2], Ferreira[2] J [1]UFSC, Undergraduate student in Pharmacy, Florianópolis, Brazil, [2]UFSC, PPG Pharmacology, Florianópolis, Brazil

05.004 **Chronic Effect of Gold Nanoparticles in a Preclinical Model of Complex Regional Pain Syndrome (CRPS)**. Nascimento MAS[1], Oliveira HC[2] Teixeira KJJS[2], Borgmann G[3], Plautz K[3], Delmônego L[3], Gastaldi AB[3], Delwing-de Lima D[3], Dal Magro DD[4] [1]UNIVILLE Joinville, Dpt of Pharmacy, Brazil, [2]UNIVILLE, Dpt of Medicine, Joinville, Brazil, [3]UNIVILLE, PPG em Health and Environment ,Joinville, Brazil [4]FURB, Dpt of Natural Sciences, Blumenau, Brazil

Room 4:

04. Inflammation and Immunopharmacology

04.014 **Metformin Reverses the Pro-Inflammatory Effects and Oxidative Stress Markers of Methylglyoxal in Ovalbumin-Induced Mouse Airway Inflammation**. Medeiros ML, Oliveira AL, Antunes E FCM-Unicamp, Dept Pharmacology, Campinas, Brazil

04.015 **IGF-1 Increases Survival of CD4+ Lineage in a 2D Model of Thymocyte/Thymic Stromal Cell co-Culture**. Porto FL, Vieira LFA, Lins MP, Smaniotto S, Reis MDS UFAL, Laboratory of Cell Biology, Institute of Biological and Health Sciences, Maceió, Brazil

04.016 **Mouse Model of Oleic Acid-Induced Acute Respiratory Distress Syndrome**. Almeida MAP[1,2,6], Rodrigues SO[1,2,5], Castro-Faria-Neto HC[1,3,4], Silva AR[1,3], Gonçalves-de-Albuquerque CF.[1,2,4,5,6] [1]Fiocruz, Lab de Imunofarmacologia,[2]IB-Unirio, Depto de Bioquímica, Lab de Imunofarmacologia, [3]IOC-Fiocruz, PPG Biologia Celular e Molecular, [4]Unirio, PPG Biologia Molecular e Celular, [5]UFF, PPG Ciências e Biotecnologia, [6]UFF, PPG Neurociências

04.017 **Evaluation of the Effect of Hyperglycemia on the Autophagy Pathway in Macrophages from Diabetic Mice**. Sousa ESA, Queiroz LAD, Pantoja KC, Barros RS, Martins JO FCF-USP, Lab of Immunoendocrinology, Dept of Clinical and Toxicological Analyses, São Paulo, Brazil

04.018 **Regulation of the mTOR receptor by rapamycin in Accelerated Senescence Mice: The Role of Autophagy in the Aging Process**. Queiroz LAD[1], Barros RS[1], Assis JB[2], Pantoja KC[1], Sá-Nunes A[2], Rodrigues SFP3, Martins JO[1] [1]FCF-USP, Lab of Immunoendocrinology, Dept of Clinical and Toxicological Analyses, São Paulo, Brazil, [2]ICB-USP, Lab of Experimental Immunology, Dept of Immunology, Sao Paulo, Brazil, [3]ICB-USP, Lab of Vascular Nanopharmacology, Dept of Pharmacology, Sao Paulo, Brazil

04.019 **Glucocorticoid-Induced Leucine Zipper Alleviates Lung Inflammation and Enhances Bacterial Clearance during Pneumococcal Pneumonia**. Carvalho AFS[1], Souza JAM[1], Grossi LC[1], Zaidan I[1], Oliveira LC[1], Cardoso C[1], Santos Souza GV[1], Vago JP[5], Queiroz-Junior CM[2], Morand EF[3], Bruscoli S[4], Riccardi C[4], Teixeira MM[1,2], Tavares LP[6], Sousa LP[1,2] [1]FF-UFMG, Signaling in Inflammation Laboratory, Depto de Análises Clínicas e Toxicológicas, [2]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [3]Monash University, Rheumatology Group, Centre for Inflammatory Diseases, School of Clinical Sciences at Monash Health, Melbourne, Australia, [4]University of Perugia, Dept of Medicine and Surgery, Section of Pharmacology, Perugia, Italy, [5]Radboud University Medical Center, Dept of Rheumatology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands, [6]Brigham and Women's Hospital and Harvard Medical School, Dept of Medicine

04.021 **Plasmin Modulates the Inflammatory Response in Experimental Pneumococcal Pneumonia**. Cardoso C[1,2], Montuori-Andrade, ACM[1,2], Carvalho AFS[1], Zaidan I[1], Ferreira LCG[1,2], Lara ES[1,2], Souza JAM[1], Teixeira MM3, Braga FC[4], Tavares LP[5], Sousa LP[1,2,3] [1]FF-UFMG, Signaling in Inflammation Laboratory, Depto de Análises Clínicas e Toxicológicas, [2]FF-UFMG, PPG Ciências Farmacêuticas, [3]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [4]FF-UFMG, Lab de Fitoquímica e Biologia Farmacêutica, Faculdade de Farmácia, Universidade Federal de Minas Gerais, [5]Harvard Medical School – Pulmonary and Critical Care Medicine

04.022 **Angiotensin-(1-7)/MasR Axis Promotes Migration of Monocytes/Macrophages with a Regulatory Phenotype to Perform Phagocytosis and Efferocytosis**. Zaidan I[1], Tavares LP[2], Sugimoto MA[3], Lima KM[1], Negreiros-Lima GL[1], Teixeira LCR[1], Miranda, TC[1], Valiate, BVS[2], Cramer A[1], Vago JP[4], Campolina-Silva G[1], Souza JAM[1], Grossi LC[1], Pinho V[1], Campagnole-Santos MJ[1], Santos, RAS[1], Teixeira MM[1], Sousa LP [1]UFMG, [2]Harvard Medical School – Pulmonary and Critical Care Medicine, [3]University College London, [4]Radboud University Medical Center

04.023 **Evaluation of the Anti-Inflammatory Potential of** *Allophylus edulis* **(A.St.-Hil., Cambess. & A. Juss.) Radlk. Leaves**. Santos SM[1], Marangoni JA[1], Oliveira Junior PC[2], Souza MF[1], Narcizo LL[3], Gonçalves L[1], Vieira AR[1], Santos JM[1], Borges JAT[1], Silva ME[1], Passos BP[3], Formagio ASN[13]. [1]UFGD, PPG Health Sciences, Dourados, Brazil; [2]UFGD, PPG Biotechnology and Biodiversity (Rede Pró-Centro Oeste), Dourados, Brazil; [3]UFGD, PPG Biodiversity and Environment, Dourados, Brazil

Room 5:

05. Pain and Nociception Pharmacology

05.005 **Characterization of Nociception and Inflammation Observed in a Traumatic Muscle Injury Model in Rats**. Kudsi SQ[1], Antoniazzi CTD[3], Camponogara C[2], Marchesan S[2], Santos GT[1] [1]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2]UFSM, PPG Biochemistry Toxicology, Santa Maria, Brazil, [3]Dublin City University, International Centre for Neurotherapeutics, Dublin, Ireland

05.006 **Antinociceptive Potential of Isopulegol in a Model of Subacute Oncological Pain**. Dias WA[1], Pimentel VD[1], Sales SCS[1], Acha BT[1], Ferreira PMP[2], Almeida FRC[1] [1]UFPI, Lab of Pain Pharmacology, Medicinal Plants Research Center, Teresina, Brazil, [2]UFPI, Lab in Experimental Cancerology, Dept of Biophysics and Physiology, Teresina, Brazil

05.007 **Effects of 4'-metoxichalcone in chemotherapy-induced neuropathic pain**. Melo EDN[1], Botinhão MC[1], Marchon ISS[1], Cavararo AR[1], Ramos IFO[1], Rocha Reis JV[1], Souza ROMA[2], Leal ICR[2], Raimundo JM[1], Bonavita AGC[1], Mendonça HR[1], Muzitano MF[1], Carmo PL[1] [1]UFRJ-Macaé, Bioactive Products Laboratory, Macaé, Brazil, [2]UFRJ, Rio de Janeiro, Brazil

05.009 **Occlusal Trauma Promotes Orofacial Pain and Masticatory Muscle Damage by Inducing Caspase-1 Activation and Reducing Anti-Oxidative Enzymes**. Oliveira JP[1], Santos LGK[1], Teixeira SA[1], Contin I[2], Oliveira MA[1], Muscará MN[1], Costa SKP[1] [1]ICB-USP Dept of Pharmacology, São Paulo, Brazil; [2]FO-USP, Dept of Prosthesis, São Paulo, Brazil

05.010 **Participation of CB2 Receptors in the Antinociceptive Effect of β-Caryophyllene in Oxaliplatin-Induced Neuropathy in Tumor-Bearing Mice Model**. Agnes JP[1], Delgobo M[1], Lima KA[1], Schran RG[2], Ferreira MA[2],

Ferreira J[2], Zanotto-Filho A[1] [1]UFSC, PPG em Farmacologia, Lab de Farmacologia e Bioquímica do Câncer, , Depto de Farmacologia, Florianópolis, Brasil, [2]UFSC, PPG em Farmacologia, Lab de Farmacologia Experimental, Depto de Farmacologia, Florianópolis, Brasil

05.011 **Effect of *Plasmodium berghei* Infection and Chloroquine Treatment on Ehrlich Tumor-Induced Inflammatory and Nociceptive Response in Mice**. Aguiar MFR[1,2], Dias QM[1], Guterres MM[1], Passos TG[1], Noleto TG[1], Benarrosh EM[1], Verri Junior WA[3], , [1]Fiocruz-RO, Lab de Neuro e Imunofarmacologia, [2]UNIR, [3]UEL

05.012 **CGRP, Interleukin 6 and Tumor Necrosis Factor Induced by Stress in Mice Causes Migraine-Like Behaviors with Sexual Dimorphism**. Viero F[1], Rodrigues P[1], Frare JM[1], Silva NA[1], Nassini R[2], Geppetti P[2], Pereira GC[1], Bocchi G[1], Santos GT[1] [1]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2]University of Florence, Dept of Health Science, Clinical Pharmacology and Oncology, Florence, Italy

05.013 **Advanced Oxidation Protein Products (AOPPs) Role on Nociceptive Behavior in a Mice Model of Progressive Experimental Autoimmune Encephalomyelitis (P-EAE)**. Rodrigues P[1], Vieiro FT[1], Peres DS[1], Frare JM[1], Stein CS[2], Brum ES[3], Moresco RN[2], Oliveira SM[3], Bochi G, Santos GT[1,3] [1]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2]UFSM, PPG in Pharmaceutical Sciences, Santa Maria, Brazil, [3]Graduated Program in Biological Sciences, Toxicological Biochemistry, Santa Maria, Brazil

05.015 **Can 6-Nitrodopamine (6-ND) be the Mediating Mechanism Involved in Pain Relief by Antidepressant Drugs?** Dallazen JL[1], Santos LG[1], Britto-Júnior J[2], Campos R[3,4], Muscará MN[1], Antunes E[2], De Nucci G[1,2], Costa SKP[1] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil [3]UFC, Drug Research and Development Center, Clinical Pharmacology Unit, Fortaleza, Brazil, [4]ISCB-UECE, Fortaleza, Brazil

Room 6:
06. Cardiovascular and Renal Pharmacology

06.008 **Apocynin Treatment Restores the Caveola Function in Endothelial Cells from Spontaneously Hypertensive Rats**. Silva MSQ[1], Graton ME[1,2] Silva CA[1] [1]FO-Unesp-Araçatuba, PPG Multicêntrico em Ciências Fisiológicas, [2]University of Alberta

06.009 **Effects of Treatment with Sodium Nitrite on Hypertension and Endothelium Dysfunction Caused by Reducing Uteroplacental Perfusion Pressure Method in Rats**. Martins LZ, Silva MLS, Rodrigues SD, Dias Junior CAC IBB-Unesp-Botucatu, Dept of Pharmacology, Botucatu, Brazil

06.010 **Isoflurane Anesthesia Reveals Protective Effects against Endothelium Dysfunction and Hypertension in Pregnant Rats**. Rodrigues SD, Silva MLS, Martins LZ, Dias Junior CAC IBB-Unesp-Botucatu, Dept of Pharmacology, Botucatu, Brazil

06.011 **The Effect of Antidepressants on Blood Pressure of Male and Female Rats: a Systematic Review and Meta-Analysis**. Santos TM, Martins TMS, Lino de Oliveira C, Linder AE UFSC – PPG in Pharmacology, Florianópolis, Brazil

06.012 **Anti-Inflammatory and Cardioprotective Effect of Alpha-Bisabolol in the Doxorubicin-induced Experimental Cardiotoxicity**. Padilla Paguada AL, Silva RL, Quispe CC, Silva JMR, Mendoza MFM, França JC, Alcântara LG, Alves SG, Silva LGF, Camelo TS, Santos AA, Siqueira RJB, Wong DVT, Lima-Júnior RCP UFC

06.013 **Antioxidant Treatment with Resveratrol during Gestational and Lactation Phase Reduces MMP-2 Activity and Arterial Hypertension in Adult Offspring**. Gomes BQ, Rocha EV, Blascke de Mello MM, Assis VO, Pernomian L, Castro MM. FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

Room 7:
07. Endocrine, Reproductive and Urinary Pharmacology

07.001 **Changes in Estrous Cyclicity and Libido on Females Rats Exposed to Aripiprazole**. Angelo ABS[1], Silva AGG[1,2], Moura MJN[1,2], Pereira AKH[1], Felix RGS[1], Santos CCA[1], Pereira MLS[1], Silva ALS[1], Freire LHF[1], Rozza AL[3], Borges CS[1,2] [1]CCBS-UFERSA, Lab of Tissue Biology and Developmental Toxicology, Mossoró, Brazil, [2]UERN,

Multicenter Graduate Program in Biochemistry and Molecular Biology, Mossoró, Brazil, [3]IBB-Unesp, Dept Structural and Functional Biology, Botucatu, Brazil

07.002 **Estrous Cycle and Gonadal Histology of Female Rats Chronically Submitted to Different Diets and Exercise Protocols**. Pereira AKH[1], Gomes FTS[2], Santos CCA[1], Felix RGS[1], Angelo ABS[1], Moura MJN[1,3], Silva AGG[1,3], Fonseca IAT[2], Borges CS[1,3] [1]CCBS-UFERSA, Lab of Tissue Biology and Developmental Toxicology, Mossoró, Brazil, [2]CCBS-UFERSA, Multicenter Graduate Program in Physiological Sciences (PPGMCF), Mossoró, Brazil, [3]UERN, Multicenter Graduate Program in Biochemistry and Molecular Biology, Mossoró, Brazil

07.003 **Three Months Exposure to Different Lipidic Diets and Physical Exercises: A Look at the Female Reproductive System**. Santos CCA[1], Gomes FTS[2], Pereira AKH[1], Felix RGS[1], Angelo ABS[1], Moura MJN[2], Silva AGG[2], Fonseca IAT[2], Borges CS[1] [1]UFERSA, [2]UERN

07.004 **Spirulina platensis Supplementation Prevents Histomorphometric Changes in the Adrenal Gland of Wistar Rats submitted to Progressive Strength Training**. Francelino DMC, Ferreira PB, Barros BC, Diniz AFA, Lacerda Júnior FF, Alves AF, Silva BA UFPB

07.005 **Targeting NOX2 Ameliorates Cyclophosphamide-Induced Bladder Injury Via Attenuation of Urothelial Barrier Dysfunction**. Garcia MO[1,2], Piccoli BS[1,2], Passos GR[2], Monica FZ[2], Antunes E[2], Oliveira MG[2] [1]PUCamp, Campinas, Brazil, [2]FCM-Unicamp, Dept of Translation Medicine (Pharmacology area), Campinas, Brazil

07.006 **Impairment of Male Reproductive System after Subchronic Exposure to Aripiprazole**. Felix RGS[1], Santos CCA[1], Pereira AKH[1], Angelo ABS[1], Pereira MLS[1], Moura MJN[1,2], Silva AGG[1,2], Rozza AL[3], Borges CS[1,2] [1]CCBS-UFERSA, Lab of Tissue Biology and Developmental Toxicology, Mossoró, Brazil, [2]UERN, Multicenter Graduate Program in Biochemistry and Molecular Biology, Mossoró, Brazil, [3]IBB-Unesp, Dept Structural and Functional Biology, Botucatu, Brazil

07.007 **Analysis of Phenotypic and Metabolic Changes in Neurolysin (Nln-/-) Knockout Animals in a Diet-Induced Obesity Model**. Caprioli B, Gewehr MCF, Eichler RA, Ferro ES USP

07.008 **The Non-Selective Inhibitors for the Multidrug Resistance Proteins, MK571 and Probenecid Potentiated the Relaxation Induced by cAMP- and cGMP-Increasing Substances in Isolated Bladder from Healthy Pig**. Gomes ET, Passos GR, Britto-Junior J, Antunes E, Mónica FZ Unicamp, Dpt of Pharmacology, Campinas, Brazil

07.009 **b1- and b1/b2-Adrenergic Receptor Antagonists Block 6-Nitrodopamine-Induced Contractions on the Rat Isolated Epididymal Vas Deferens**. Amorim AC, Lima Silva AT, Britto-Júnior J, Campitelli RR, Fregonesi A, Mónica FZ, Antunes E, De Nucci, G FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil

Room 8:

08. Respiratory and Gastrointestinal Pharmacology

08.001 **Can Gastric Healing be Altered in Obese Animals? Evaluation of the Antiulcerogenic Effect of Citral in Mice Fed with High-Fat Diet**. Dario FL, Ohara R, Rocha LRM, Hiruma Lima CA IBB-Unesp-Botucatu, Dpt of Structural and Functional Biology (Physiology), Botucatu, Brazil

08.002 **Evaluation of the Involvement of Prostaglandins in the Gastroprotective Effect of the Hydroethanolic Extract of the Stem Barks of *Ximenia americana* L. – EIPGEHESBXA**. Silva AB[1], Pessoa RT[1], Santos LYS[1], Alcântara IS[1], Costa RHS[1], Silva TM[1], Muniz DF[2], Oliveira MRC[3], Martins AOBPB[1], Menezes IRA[1], [1]URCA, [2]UFPE, [3]UECE

08.003 **Food Supplementation with *Spirulina platensis* Prevents Damage to Ileal Contractile Reactivity by Modulating NO and COX Pathways in Rats Fed a Hypercaloric Diet**. Freire B, Diniz AFA, Francelino DMC, Barros BC, Lacerda Júnior FF, Souza PPS, Ferreira PB, Silva BA UFPB

08.004 **Gastroprotective Effect of the Hydroethanolic Extract of the Stem Barks of *Ximenia americana* L. on the Involvement of α2-adrenergic Receptors – GEHESBXAIAR**. Silva ES[1], Pessoa RT[1], Santos LYS[1], Alcântara IS[1], Silva TM[1], Costa RHS[1], Oliveira MRC[2], Muniz DF[3], Martins AOBPB[1], Menezes IRA[1] [1]URCA, [2]UECE, [3]UFPE

08.005 **Antidiarrheal Activity and Effects on Gastrointestinal Motility of Carveol in animal models**. França JS[1], Pessôa MLS, Alves VP[1], Pessôa MLS[2], Alves Júnior EB[2], Araruna MEC[2], Pessoa MMB[2], Batista LM[2] [1]UFPB, Graduate Student in Pharmaceutical Sciences, João Pessoa, Brazil, [2]UFPB, PPG in Natural and Synthetic Bioactive Products, Health Sciences Center, João Pessoa, Brazil

08.006 **Study of the Gastroprotective Activity of the Juice and Hydroethanolic Extract of the Fruit Peels of** *Plinia peruviana* (**Poir**.) **Govaerts** (**Myrtaceae**) **on the Involvement of Nitric Oxide Action – EAGSEHCFPPPGMEAON**. Silva TM, Alcântara IS[1], Pessoa RT[1], Santos LYS[1], Costa RHS[1], Martins AOBPB[1], Menezes IRA[1], Wanderley AG[2] [1]Urca, [2]Unifesp, São Paulo, Dpt of Pharmaceutical Sciences, Brazil

08.007 **Evaluation of Antidiarrheal Activity, Effects on Motility and Mechanism of Action of Estragole in Animal Models**. Alves VP, Silva LMO, Pessoa MMB, Pessôa MLS, Alves Júnior EB, Araruna MEC, Batista LM, França JS UFPB

08.008 **The Gastroprotective Effect of the Cashew Bark Aqueous Extract** (*Anacardium occidentale* L). Pereira YLG[1], Mello VJ[2], Diniz LA[1], Hamoy M[2], Paz APS[2], Souza KR[2] [1]UFPA, Faculty of Medicine, Belém, Brazil, [2]UFPA, Institute of Biological Sciences, Belém, Brazil

08.009 **Impact of Cyclic AMP Efflux Induced by Phosphodiesterase Inhibitors and β2 Adrenoceptor Agonists on Airway Smooth Muscle Relaxation**. Satori NA, Pacini ESA, Godinho RO Unifesp-EPM, Div of Cellular Pharmacology, Dept of Pharmacology, São Paulo, Brazil

08.011 **p-Cymene Displays Antimicrobial and Antidiarrheal Activity due to Antimotility and Antisecretory Mechanism in Experimental Models**. Pessoa MMB, Pessôa MLS, Alves Júnior EB, Araruna MEC, Serafim CAL, Barros MEFX, Formiga RO, Sobral MV, Silva MS, Souza ML, Diniz Neto H, Lima EO, Batista LM UFPB, UEPB

08.012 **Farnesol Presents Low Toxicity and Gastroprotective Activity in Mouse Animal Models**. Pessôa MLS, Pessoa MMB, Araruna MEC, Alves Júnior EB, Alves VP, Batista LM UFPB Depto de Ciências Farmacêuticas, João Pessoa, Brasil

Room 9:

09. Natural Products and Toxinology

09.001 **Inhibition of** *Aedes aegypti* **Larvae Angiotensin Converting Enzymes** (**ACE 1/ACE 2**) **Homologues by** *Cecropia glazioui* **Sneth Extracts. A Potential Non-Toxic Insecticide**. Pederiva VP, Tanae MM, Myamoto DT, Lapa AJ EPM-Unifesp, Dpt of Pharmacology, São Paulo, Brazil

09.002 **Inhibitory Effect of Methyl Cinnamate on TGF-β-Induced Epithelial to Mesenchymal Transition in Alveolar Epithelial Cells**. Ferreira E, Barros ABB, Silva JP, Carmo JOS, Barreto EO UFAL, Lab de Biologia Celular

09.003 *Crotalus durissus terrificus* **and** *Crotalus durissus collilineatus* **Snake Venoms Coagulotoxic Profile**. Padueli LD[1,2], Galizio NC[1], Vidueiros JP[1], Tanaka-Azevedo AM[1], Zani KM[1] [1]Instituto Butantan, Lab de Herpetologia, São Paulo, Brasil, [2]FCF-USP, São Paulo, Brasil

09.005 *Hibiscus sabdariffa* **Improves Murinometric Parameters in a Model Obesity-Exacerbated Asthma in Wistar Rats**. Martins AMO[2], Ferreira SRD[1], Pessoa RF, Figueiredo IAD[1], Vasconcelos LHC, Cavalcante FA, UFPB

09.006 **Histological and Immunohistochemical Analysis of Skin Wound Healing Influenced by the Topical Application of Brazilian Red Propolis Hydroalcoholic Extract**. Conceição M[1], Gushiken LFS[3], Aldana-Mejía JA[2], Tanimoto MH[2], Ferreira MVS[1], Miyashita MN[1], Bastos JK[2], Beserra FP[1,2], Pellizzon CH[1] [1]IBB-Unesp, Botucatu, São Paulo, Brazil, [2]FCFRP-USP, Ribeirão Preto, Brazil, [3]Unicamp, Campinas, Brazil

09.007 **Characterization of the Tocolytic Mechanism of Action of the Ethanolic Extract of** *Varronia dardani* (**Taroda**) **J.S. Leaves in Rats**. Fernandes JM, Figueiredo IAD, Ferreira SRD, Pessoa RF, Veloso CAG, Costa VCO, Silva MS, Cavalcante FA UFPB

09.008 **Cardiotoxic Action of** *Micrurus dumerilii carinicauda* **and** *Micrurus corallinus* **(Elapidae) Venoms and Neutralization by Brazilian Coral snake Antivenom and Selective Phospholipase A2 Inhibitor**. Gaspar MZ[1], Yabunaka AC[1], Silva-Carvalho R[1], Nascimento CU[4], Brinholi RB[4], Silva EO[2], Gerez JR[3], , Silva Júnior NJ[5] , Hyslop S[6], Pacagnelli FL[4], Floriano RS[1] [1]Unoeste, PPG in Health Sciences, Lab of Toxinology and Cardiovascular Research, [2]Unoeste, Lab of Pathological Anatomy, Veterinary Hospital, [3]UEL, Dpt of Histology, [4]Unoeste, PPG in Health Sciences, Lab of Cardiac Structural and Functional Assessment, [5]PUC Goiás PPG in Environmental Sciences and Health, [6]FCM-Unicamp, Section of Pharmacology, Dpt of Translational Medicine,

09.009 **The Amazonian Fruit Tucumã** (*Astrocaryum aculeatum*) **modulates the genotoxicity associated with superoxide, hydrogen peroxide, nitric oxide imbalance in human fibroblasts**. Bonotto N[1], Azzolin VF[2], Ribeiro Filho E[2], Azzolin VF[2], Duarte MMF[3], Duarte T[1], Pellenz NLK[1], Ribeiro EAM[2], Cruz IBM[1], Barbisan F[1,4] [1]UFSM, Biogenomics Lab, Dept of Morphology, Santa Maria, Brazil, [2]FUnATI, Manaus, Brasil, [3]ULBRA, Torres, Brazil, [4]UFSM, Department of Pathology, Santa Maria, Brazil

Room 10:

09. Natural Products and Toxinology

09.017 **Cytotoxic evaluation of the hydroalcoholic extract from stem bark of** *Hymenaea courbaril* **L. in RAW264.7, L929 and MRC-5 cells**. Lobo LAC[1], Ethur EM[2], Silva FC[3], Pereira P[1], Goettert MI[2] [1]UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, [2]Univates, Cell Culture Laboratory, PPG in Biotechnology [3]UniSL, Lab of Phytochemical Analysis, Ji-Paraná, Rondônia

09.018 **Hepatoprotective Effect of Piperine in Acetaminophen-induced Liver Injury in Mice**. Coelho AM, Queiroz IF, Souza MO, Lima WG, Costa DC UFOP

09.019 **Toxicological and Antioxidant Evaluation of Geniposide in the** *Caenorhabditis elegans* **Model**. Uczay M[1], Santos PA[1], Poser G[2], Vendrúsculo MH[2], Pereira P[1] [1]ICBS-UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, Porto Alegre, Brazil, [2]FacFar-UFRGS, Lab of Pharmacognosy, Porto Alegre, Brazil

09.020 **Investigation of Proliferative Potential of Monoterpene Citral in Lineage of Intestinal Cells Caco-2**. Fagundes FL[1], Zarricueta ML[1], Caxali GH[2], Aal MCE[2], Delella FK[2], Hiruma-Lima CA[1] [1]Unesp-Botucatu, Lab of Biological Assays with Natural Products, Dept of Structural and Functional Biology, Sector of Physiology, [2]Unesp-Botucatu, Lab of Studies of Extracellular Matrix, Dept of Structural and Functional Biology, Sector of Morphology

09.021 **Survival Rates and Antioxidant Activity Evaluation of the Aqueous Extract of** *Achyrocline satureioides* **in the** *Caenorhabditis elegans* **Model**. Santos PA[1], Uczay M[1], Lobo LAC[1], Brittes RM[2], Siqueira IR[1], Pereira P[1] [1]ICBS-UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, Porto Alegre, Brazil, [1]ICBS-UFRGS, Lab of Microbiology and Parasitology, Porto Alegre, Brazil,

09.022 **Gastroprotective Effect of** *Lonchocarpus sericeus* **on Ethanol-induced Gastric Lesion in Mice: Role of Prostaglandins and Nitric Oxide**. Freire GP[1], Almeida Filho LCP[2], Nunes PIG[1], Portela BYM[1], Lima RP[1], Carvalho AFFU[2], Santos FA[1] [1]UFC, Dept of Physiology and Pharmacology, Fortaleza, Brazil, [2]UFC, Dept of Biochemistry, Fortaleza, Brazil

09.023 **Ethanolic Extract of** *Varronia dardani* **(Taroda) J.S. Leaves Inhibits Writhing in a Primary Dysmenorrhea Mice Model**. Figueiredo IAD, Ferreira SRD Pessoa RF- Veloso CAG, Costa VCO, Silva MS, Cavalcante FA UFPB

09.024 **Protective Effect of Chalcone 2-Hydroxy-3,4,6-Trimetoxyacetophenone (HTMCX) on Ketamine-Induced Cytotoxicity in Renal Tubular Cells**. Alencar MMC[1,3], Magalhães EP[2,3], Almeida IM[3], Ali A[1,3], Bezerra de Menezes RRPP[2,3], Sampaio TL[1,3], Martins AMC[1,3] [1]UFC, PPG in Pharmacology, Fortaleza, Brazil, [2]UFC, PPG n Pharmaceutical Sciences, Fortaleza, Brazil, [3]UFC, Dept of Clinical and Toxicological Analysis, Fortaleza, Brazil

09.025 **Inhibition of the AGE/RAGE Pathway in an Experimental Model of Non-Alcoholic Fatty Liver Disease: A Focus on Anti-Inflammatory and Antioxidant Mechanisms**. Silvares RR, Araujo BP, Lima LN, Rodrigues KL, Pereira ENGS, Silva VVD, Daliry A IOC-Fiocruz, Lab of Cardiovascular Investigation, Rio de Janeiro, Brazil

09.027 *Spirulina platensis* Prevents the Increase in IL-1β levels and Improves the Antioxidant Capacity of the Ileum of Obese Rats Fed a Hypercaloric Diet. Diniz AFA, Claudino BFO, Francelino DMC, Barros BC, Lacerda Júnior FF, Ferreira PB, Alves AF, Silva BA UFPB

Room 11:

10. Cancer Pharmacology

10.001 Peri/Epicellular Protein Disulfide Isomerase (pecPDI) inhibition decreases Migration and Colony Formation and Sensitizes Melanoma cells to B-RAF Inhibitors. Mota AN, Lopes LR, Machado Neto JA ICB-USP, Pharmacology Dept, São Paulo, Brazil

10.002 The Aqueous Extract Obtained from *Abelmoschus esculentus* (L.) Moench. has an Antitumor Effect in the Ascitic Ehrlich Tumor Model (EAC). Silva ELES, Souza TPM[1], Carmo JOS[1,], Almeida JH[1], Silva JYR[2], Alves Júnior S[2], Ferro JNS[1] [1]UFAL, [2]UFPE

10.003 Establishment of Patient Tumor Cell Lines and Prediction of Growth Profiles and Responsiveness to New Treatments Derived from *Phoneutria nigriventer* Venom (PnV). Silva MVR[1], Santos NB[2], Rocha-e-Silva TAA[3], Sutti R[4], Vitorino-Araújo JL[4], Sciani JM[5], Verinaud L[2], Carneiro CRD[2] [1]FCF-Unicamp, Campinas, São Paulo, Brasil, [2]IB-UNICAMP, Campinas, São Paulo, Brasil, [3]Albert Einstein Israeli Faculty of Health Sciences, São Paulo, SP, Brasil, [4]FCMSCSP, São Paulo, SP, Brasil, [5]LMP-USF, Bragança Paulista, SP, Brasil

10.004 Bioguided Study of Cytotoxicity and Phytochemical Screening of Extract and Fractions from the Bark of *Gamela laurel* (*Sextonia rubra* (Mez) van der Werff) from Logging Residue. Pereira JVM[1], Mota JA[1], Manso MP[1]., Sales SLA[1], Costa PMS[1], Flores SLG[1], Araújo IM[2], Alves TS[2], Veiga Junior V[3], Guimarães AC[2], Guimarães CJ[1], Pessoa C [1] [1]LOE-NPDM-UFC, [2]Q-BIOMA-UFAM, [3]Military Engineering Institute

10.005 Cannabidiol Protects Myoblasts and their Differentiation into Myotubes from the Cytotoxic Effects of Cisplatin while Decreasing the Viability of MCF7 Tumor Cells. Santos MRM, Zamarioli LS, Pereira THR, Guariglia L, Smaili SS, Pereira GJS, Trindade CB Unifesp-EPM, Dept de Farmacologia, São Paulo, Brasil

10.006 Evaluation of the Antineoplastic Effects of Polysaccharides Extracted from Tucum-do-Cerrado Fruits (*Bactris setosa* Mart) in Mice. Oliveira KM, Radulski DR, Faria BC, Galindo CM, Pereira GS, Stipp MC, Cordeiro LMC, Acco A UFPR, Department of Pharmacology, Curitiba, Brazil

10.007 Palladium (II) Complexes Containing Orthometallated Oximes are Cytotoxic to Resistant Human Osteosarcoma Cells by Inducing Apoptosis and Lysosomal Membrane Permeabilization. Pereira THR[1], Santos MRM[1], Zamarioli LS[1], Justo GZ[1], Moura TR[2], Pereira GJS[1], Godoy Netto AV, Trindade CB[1] [1]Unifesp, [2]Unesp

Room 12:

11. Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Toxicology

11.001 Physiologically Based Pharmacokinetic Modeling (PBPK) to Predict the Pharmacokinetics of Hydroxychloroquine Enantiomers According to Gene Polymorphisms of CYP2D6 and CYP2C8. Ribeiro GSG[1], Moraes NV[2] [1]Unesp-Araraquara, Ararquara, Brazil São Paulo State University, Araraquara, Brazil, [2]University of Florida, Center for Pharmacometrics & Systems Pharmacology, USA

11.003 Population Pharmacokinetics of Intravenous Busulfan in Brazilian Pediatric Patients. Olivo LB[1], Zuckermann J[3], Pinhati AV[2,3], Correa GG[2], Daudt LE[4], Dalla Costa TCT[1], Araújo BV[1,2] [1]UFRGS, PPG Pharmaceutical Sciences; Porto Alegre; Brazil, [2]UFRGS, PPG Medical Sciences, Porto Alegre, Brazil, [3]HCPA-UFRGS, Pharmacy Service, Porto Alegre, Brazil, [4]HCPA-UFRGS, Hematology Service, Porto Alegre, Brazil

11.004 Pharmacogenetic Testing-Guided Treatment for Oncology: An Overview of Reviews. Lara DV[1], Melo DO[2], Kawakami DY, Gonçalves TS[1], Santos PCJL[1] [1]Unifesp-EPM, Dpt of Pharmacology, São Paulo, Brazil, [2]ICAQF-Unifesp-Diadema, Dpt of Pharmaceutical Sciences, Diadema, Brazil

11.005 Are Ciprofloxacin Plasma Concentrations Influenced by Different Gram-Negative Bacteria Infection? Lock GA[1], Dias BB[1], Helfer VE[1], Barreto F[2], Araújo BV[1,], Dalla Costa T[1] [1]UFRGS, PPG Pharmaceutical Sciences, Pharmacokinetics and PK/PD Modeling Lab, [2]LFDA-RS

11.006 **Hepatic CYP3A4 Activity in Obese and Post-Bariatric Patients: An Exploratory Analysis Using Midazolam Single Time Point Concentration**. Medeiros JIM[1], Yamamoto PA[2], Santos BM[1], Salgado Junior W[3], Santos JS[3], Kemp R[3], Sankarankutty AK[3], Vozmediano V[4], Cristofoletti R[4], Moraes NV[4] [1]Unesp-Araraquara, Dept of Drugs and Medicines, Araraquara, Brazil, [2]FMRP-USP, Ribeirao Preto, Brazil, [3]FMRP-USP, Ribeirao Preto, Brazil, [4]University of Florida, Center for Pharmacometrics & Systems Pharmacology, Orlando, USA

11.007 **Interferon-Beta Injection in Multiple Sclerosis Patients Related to the Induction of Headache and Flu-Like Pain Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Pereira LG, Rodrigues P, Frare JM, Ramanzini LG, Viero FT, Santos GT UFSM, Depto de Fisiologia e Farmacologia, Santa Maria, Brasil

11.008 **Praziquantel and *Moringa oleifera* Extracts Combination: Bioavailability in Rats and Cysticidal Activity in a Murine Model**. Castro N[1,2], González Esquivel DF[1], Palomares Alonso F[1], Rojas Tomé IS[1], Vidal-Cantú GC[3], González Hernández I[1], Jung H[1,2] [1]MVS, Inst Nacional de Neurología y Neurocirugía, Cidade do México, México, [2]UNAM, Facultad de Química, [3]CDMX, Dpt de Farmacobiología, Centro de Investigación y de Estudios Avanzados, Cidade do México, México

Room 13:

12. Drug Discovery and Development

12.003 **Drug-Target Kinetics in Drug Discovery: Using of K+-pNPPase Activity to Characterize the Kinetics of Cardiotonic Steroids on Na+/K+-ATPase in a Cheap Way**. Azalim P[1], Liu X[2], Silva SC[3], Barbosa LA[3], O'Doherty GA[2], Quintas LEM[1], Noël FG[1] [1]ICB-UFRJ, Lab de Farmacologia Bioquímica e Molecular, Rio de Janeiro, Brazil, [2]Northeastern University, Dpt of Chemistry and Chemical Biology, Boston, USA, [3]UFSJ, Lab de Bioquímica Celular, Divinópolis, Brasil

14. Pharmacology: Other

14.005 **ATB346, a Hybrid H_2S Donor, Enhances Time for Blood Vessel Occlusion in Brain of Mice**. Dias KT, Muscara MN, Rodrigues SFP ICB-USP, Dept of Pharmacology

14.006 **Maternal Microbiota or Early Life Microbiota Dysbiosis Induces Neurodevelopmental and Behavioral Impairments Associated with Psychiatric Disorders**. Hassib L[1], Campos AC[2], Ferreira FR[3], [1]FMRP-USP, Dept of Mental Health, Ribeirão Preto, Brazil; [2]FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil, [2]Fiocruz

14.007 **Nebivolol Mitigates Endothelial Dysfunction in a Model of Preeclampsia**. Bueno Pereira TO, Bertozzi-Matheus M, Nunes PR, Rocha ALV, Sandrim VC IBB-Unesp-Botucatu, Dept of Biophysics and Pharmacology, Botucatu, Brazil

14.008 **Cardiac Alterations in Hepatic Steatosis: Role of the Age-Rage Pathway**. Rodrigues KL[1], Silva VVD[1], Pereira ENGS[1], Silvares RR[1], Linhares DOC[1], Flores EEI[1], Araujo BP[1], Ramos IP[2], Daliry A[1] [1]IOC-Fiocruz, Lab of Cardiovascular Investigation, Rio de Janeiro, RJ, Brazil, [2]UFRJ, National Center of Structural Biology and Bio-imaging, Rio de Janeiro, Brazil

E-Poster Session 2:

20/10/2022 (Thursday)

Room 14:

02. Neuropharmacology

02.005 **Selective CD36 Receptor Ablation in Olfactory Sensory Neurons Impacts Gene Expression in the Olfactory Epithelium**. Petrucci TVB[1], Pinheiro ES[1], Gonçalves GA[1], Malnic B[2], Febbraio M[3], Festuccia WTL[2], Glezer I[1], [1]Unifesp, Dpt of Biochemistry, São Paulo, Brazil, [2]USP, Dpt of Biochemistry and Biophysics, São Paulo, Brazil [3]University of Alberta, Dpt of Dentistry, Alberta, Canada

02.006 **Beneficial Effect of the Specialized Pro-Resolution Mediator Protectin DX Over Mechanical Allodynia and Depressive-Like Behavior in an Animal Model of Type-1 Diabetes Mellitus**. Waltrick APF[1], Verri Junior WA[2], Cunha JM[1], Zanoveli JM[1] [1]UFPR, Neuropsychopharmacology Lab, Dept of Pharmacology, Londrina, Brazil, [2] UEL, Pain, Inflammation, Neuropathy and Cancer Lab, Dept of Pathological Sciences, Londrina, Brazil

02.007 **Low Doses of Rotenone Promote Changes in Mitochondrial Membrane Polarization without Cell Death**. Siena A[1], Silva LFS[1], Silva Júnior PI[2], Scavone C[1], Rosenstock TR[1] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]Butantan Institute, São Paulo, Brazil

02.008 **NADPH Oxidase Contributes to Medullary Respiratory Neurodegeneration and Respiratory Pattern Dysfunction in 6-OHDA Animal Model of Parkinson's Disease**. Medeiros POS, Nascimento ALF, Pedrão LFAT, Takakura AC, Falquetto B USP

02.009 **GL-II-73, A Positive Allosteric Modulator of Alpha 5 Subunit-Containing GABAA Receptors, Improves Cognitive Deficits in Female Senescence-Accelerated Prone 8 (SAMP8) Mice**. Silva T[1], Colodete DAE[1], Guimarães FS[1], Sharmin D[2], Cook J[2], Gomes FV[1] [1]FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil; [2]University of Wisconsin, Dept of Chemistry, Milwaukee, USA

02.010 **Involvement of Neuroinflammation in the Effect of Vitamin D and Donepezil in Adult and Aged Ovariectomized Rats**. Medeiros EB, Gabriel JRM, Santos MLC, Lídio AV, Boaventura A, Ceolin de Jesus L, Santos LM, Bobinski F, Budni J Unesc

02.012 **The Role of Carbonic Anhydrases in Extinction of Contextual Fear Memory**. Nachtigall EG[1,2], Schmidt SD[2,3,4], Costa A[5], Rani B4, Passani MB[4], Carta F[4], Nocentini A[4], Myskiw JC[2,5], Furini CRG[1,2], Supuran CT[5], Izquierdo I[2], Blandina P[4], and Provensi G[4] [1]PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil; [2]PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, [3]Western University, London, Canada, [4]University of Florence, Florence, Italy, [5]UFRGS Psychobiology and Neurocomputation Lab, Dept of Biophysics, Institute of Biosciences, Porto Alegre, Brazil

02.013 **Melatonin Reduces β-Amyloid Accumulation and Improves Short-Term Memory in Streptozotocin-Induced Sporadic Alzheimer's Disease Model**. Andrade MK[1], Souza LC[1], Azevedo EM[2], Bail EL[2], Zanata SM[3], Andreatini R[1], Vital MABF[1] UFPR, [1]UFPR, Dept of Pharmacology, Curitiba, Brazil, [2]UFPR, Dept of Physiology, Curitiba, Brazil, [3]UFPR, Dept of Basic Pathology, Curitiba, Brazil,

Room 15:

03. Psychopharmacology

03.007 **Evaluation of Angiotensin I – Converting Enzyme (ACE) Activity in a Transgenic Animal Model of Schizophrenia (SCZ)**. Santiago TC[1], Nani JVS[1,2], Cruz FC[1], Hayashi MAF[1,2] [1]Unifesp-EPM, Dept. Pharmacology, São Paulo, Brazil, [2]Instituto Nacional de Medicina Translacional (INCT-TM, CNPq/FAPESP/CAPES), Ribeirão Preto, Brasil

03.008 **The Anticompulsive-like Effect of Memantine Seems not to Depend on Sex of Mice**. Macedo BL, Veloso MF, Dias IB, Ayub JGM, Beijamini V UFES, Dept of Pharmaceutical Sciences, PPG Health Sciences Center, Vitória, Brazil

03.009 **Glutamatergic Signaling within the Dorsal Hippocampus Modulates the Effects of Delta-9 Tetrahydrocannabinol in Fear Memory Labilization and Reconsolidation**. Raymundi AM, Sohn JMB, Salemme BW, Stern CAJ UFPR, UFPR, Dpt of Pharmacology, Curitiba, Brazil

03.010 **Taurine Reduces Serum Corticosterone of Highly Alcohol-Consuming Rats**. Pulcinelli RR[1], Izolan LR[2], Zilli GAL[1], Sant'Ana BH[1], Bastiani CS[1], Gomez R[1,2] [1]UFRGS, PPG Farmacologia e Terapêutica, Porto Alegre, Brazil, [2]UFRGS, PPG Neurociências, Porto Alegre, Brazil

03.011 **Pre-Treatment with Ethanol inhibits the Expression of Conditioned Place Preference to Ketamine in Mice: The Role of Neurotrophin Receptors and Caspase-3 Activity**. Contó MB, Camarini R ICB-USP, Dept of Pharmacology, Brazil

03.012 **Involvement of Adenosinergic Receptors in the Antidepressant-Like Effects of Cannabidiol in Mice**. Sales A, Alves da Silveira JR, Ferreira BF, Guimarães FS FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

03.013 **PPARgamma agonist pioglitazone reduces microglial activation induced by two hit model: possible implications for schizophrenia**. Sonego AB[1,2], Prado DS[3], Uliana DL[2] , Cunha TM[1], Grace AA[2], Resstel LB[1] [1]FMRP-USP – Pharmacology, [2]University of Pittsburgh – Neuroscience, [3]University of Pittsburgh – Immunology

Room 16:

04. Inflammation and Immunopharmacology

04.006 **Contribution of Obese Adipose Tissue to Cellular Regression of Mature Osteoblast Phenotype**. Forte YS[1], Renovato-Martins M[2], Barja Fidalgo TC[1] [1]UERJ, Dpt of Cell Biology, Rio de Janeiro, Brazil [2]UFF, Dpt of Molecular Cellular Biology, Rio de Janeiro, Brazil

04.007 **Evaluation the Impact of Autophagy on the Regulation of the Senescent Phenotype of Prone and Resistant Mice to Accelerated Senescence**. Barros R, Queiroz LAD, Pantoja KC, Sousa ESA, Martins JO FCF-USP, Immunoendocrinology Laboratory; São Paulo, Brazil

04.009 **Study of the Annexin A1/FPR2 Pathway in the Context of Experimental Bacterial Pneumonia**. Lara ES[1,2], Carvalho AFS[1,2], Montuori-Andrade ACM[1], Cardoso C[1], Zaidan I[1], Grossi L[1], Teixeira MM[3], Costa VV[3], Tavares LP[4], Sousa LP[1,2,3] [1]FF-UFMG, Signaling in Inflammation Laboratory, Dpto Análises Clínicas e Toxicológicas, [2]FF-UFMG, PPG Análises Clínicas e Toxicológicas, [3]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [4]Brigham and Women's Hospital and Harvard Medical School, Pulmonary and Critical Care Medicine Division, Dept of Medicine

04.010 **Therapeutic Treatment with Gold Nanoparticles (AuNPS) Reduces Lung Fibrosis Target by Bleomycin in Mice**. Ferreira GG, Abreu FVG, Fernandes AJ, Pires ALA, Arantes ACS, Sá YAPJ, Ribeiro NBS, Martins MA, Silva PMR Fiocruz

04.011 **GILZ Modulates the Recruitment of Mononuclear Cells Endowed with a Resolving Phenotype and Plays a Relevant Role During *Escherichia coli* Infection**. Grossi L[1], Zaidan I[1], Souza JAM[1], Matoso AC[1], Carvalho AFS[1], Cardoso C[1], Morand EF[2], Riccardi C[3], Bruscoli E[3], Teixeira MM[4], Tavares LP[5], Vago JP[6], Sousa LP[1] [1]FF-UFMG, Lab of Inflammation and Neoplasms Signaling, Dept of Clinical and Toxicological Analysis, Brazil, [2]Monash University, Rheumatology Group, Centre for Inflammatory Diseases, School of Clinical Sciences at Monash Health, Melbourne, Australia, [3]University of Perugia, Dept of Medicine and Surgey, Section of Pharmacology, Perugia, Italy, [4]ICB-UFMG, Drug Research and Development Center, Dept of Biochemistry and Immunology, Brazil, [5]Brigham and Women's Hospital and Harvard Medical School Dept of Medicine, [6]Radboud University Medical Center Dept of Rheumatology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands

04.012 **Vinorelbine Induces Extravasation Injury Accompanied by Neutrophil Accumulation in a Resident Cell-Independent Mechanism**. Quintela LCS[1], Cajado AG[2], Holanda GS[2], Gama LC[2], Santos ABM[2], Rodrigues MAP[2], Freitas GL[1], Teles ACF[2], Gadelha EC[2], Rodrigues TS[2], Sousa LSP[2], Wong DVT[2], Lima-Júnior RCP[2] [1]FM-UFC, PPG in Pathology, Dept of Pathology and Forensic Medicine, Fortaleza, Brazil [2]FM-UFC, Drug Research and Development Center, Dept of Physiology and Pharmacology, Fortaleza, Brazil

04.013 **Evaluation of Anti-Inflammatory Activities of New Heterocyclic Derivatives Analogues of Chalcones**. Botinhão MC[1], Araújo MH[1], Cavararo AR[1], Alves TS[1], Melo EDN[1], Rodrigues CR[2], Gomes AO[1], Muzitano MF[1], Carmo PL[1] [1]UFRJ-Macaé, Macaé, Brazil;[2]UFRJ, Rio de Janeiro, Brazil

Room 17:

04. Inflammation and Immunopharmacology

04.024 **Suppression by Quercetin of the Early Phase of Silicosis in Swiss-Webster Mice**. Abreu FVG, Ferreira TPT, Arantes ACS, Martins MA, Martins PMRS Fiocruz

04.025 **Glucagon is Involved with Increased Susceptibility to Sepsis in Murine Model of Diabetes Through Down Regulation of Neutrophil Migration**. Insuela DBR[1], Ferrero MR[1], Gonçalves-de-Albuquerque CF[2,3], Chaves AS[1], Silva AYO[2], Faria-Neto HCC[2], Simões RL[4], Barja-Fidalgo TC[4] Martins PMRS[1], Martins MA[1], Silva AR[2], Carvalho VF[1] [1]IOC-Fiocruz – Lab Inflammation, Rio de Janeiro, Brazil, [2]IOC-Fiocruz – Lab Immunopharmacology, Rio de Janeiro, Brazil, [3]Unirio – Lab Immunopharmacology, Biomedical Institute, Rio de Janeiro, Brazil, [4]UERJ – Lab of Cellular and Molecular Pharmacology, Biology Institute, Rio de Janeiro, Brazil

04.026 **Evaluation of GILZ Protein as Potential Therapeutic Alternative in the Coronavirus-Induced Infection**. Montuori-Andrade ACM[1], Souza JAM[1], Carvalho AFS[1], Grossi LC[1], Zaidan I[1], Oliveira LC[2], Cardoso C[1], Tavares LP[3], Morand EF[4], Bruscoli S[5] Riccardi C[5], Teixeira MM[2], Sousa LP[1] [1]FF-UFMG – Análises Clínicas e Toxicológicas, Belo Horizonte, Brazil, [2]ICB-UFMG – Bioquímica e Imunologia, Belo Horizonte, Brasil, [3]Harvard Medical School – Pulmonary and Critical Care Medicine, [4]Monash University, Melbourne, Australia, [5]University of Perugia – Section of Pharmacology, Perugia, Italy

04.027 **Development of a Murine Model to Study the SARS-CoV-2 Spike Protein S1 Subunit-Induced Inflammation and Endocrine Dysfunctions in K18-hACE2 Transgenic Mice**. Ferreira TPT, Brasiel PG, Chaves AS, Cotias AC, Arantes ACS, Martins PMRS, Carvalho VF, Martins MA Fiocruz

04.028 **Impact of Long-Term of Standard and High Fat Diet on Selected Obesity Parameters and Respiratory Mechanics in Phenotypically Selected Mice for Minimal or Maximal Acute Inflammatory Reaction**. Tino De Franco M[1], Massa S[1], Moriya HT2, Antonio NS[1], Oliveira MA3, Tavares-de-Lima W3, Ribeiro OG[1], Trezena AG[1] [1]Instituto Butantan, Lab de Imunogenética, [2]USP – Escola Politécnica, Lab de Engenharia Biomédica, [3]ICB-USP, Dept Farmacologia

05. Pain and Nociception Pharmacology

05.016 **Study of the Mechanisms Involved on the Analgesic Effect of *Vitex polygama* Extract in Vincristine-Induced Neuropathic Pain**. Ramos IF, Mello C, Melo EDN, Santos IS, Carmo PL, Muzitano MF, Bonavita AGC UFRJ

05.017 **Sub-Doses of Aspirin-Triggered Lipoxin A4 Attenuate Mechanical Allodynia and Dampen Anxious-Like Behavior Associated with Experimental Diabetes**. Ferreira MV[1], Jesus CHA[1], Bonfim JC[1], Liebl B[1], Oliveira G[1], Verri Júnior W[2], Zanoveli JM[1], Cunha JM[1]. [1]UFPR, Dept of Pharmacology, Biological Science Sector, Paraná, Brazil, [2]UEL, Dept of Pathology, Center of Biological Sciences, Londrina, Brazil

05.018 **Effects of 4-Dimethylaminochalcone on Vincristine-Induced Neuropathic Pain in Mice**. Melo EDN, Santos IS, Rocha Reis JV, Souza ROMA[2], Leal ICR[2], Muzitano MF[1], Bonavita AGC[1], Raimundo JM[1] Carmo PL[1] [1]UFRJ-Macaé, [2]UFRJ-Rio de Janeiro

Room 18:

06. Cardiovascular and Renal Pharmacology

06.001 **Perivascular Adipose Tissue Phenotype and Thoracic Aortic Stiffness in an Aging Murine Model**. Diccini I, Marques BVD, Akamine EH USP São Paulo, Dpt of Pharmacology, São Paulo, Brazil

06.002 **Aging as an Important Contributor Factor for Decreased Semen Quality in Hypertensive Rats: A Role for Enhanced Testis Vasomotricity**. Machado NR[1], Miyazaki MA[2], Colli LG[1], Bertolla RP[2], Belardin LB[2], Rodrigues SFP[1] [1]ICB-USP, Dept of Pharmacology, [2]Unifesp, Dept of Surgery, Division of Urology

06.003 **Study of the Effect of FoxO1 O-GlcNAcylation on Vascular Endothelial Function**. Pedersoli C[1], Silva Neto JA[1], Duarte DA[1], Gonçalves DAP[2], Silva NLE[1], Silva JF[3], Bressan AFM[1], Kettelhut IC[1], Navegantes LC[1], Carneiro FS[1], Tostes RC[1] [1]FMRP-USP, [2]UFMG, [3]University of Arizona

06.004 **Antioxidant Effect of Quercetin Reduces Oxidative Stress and the Activity of Matrix Metalloproteinase (MMP)-2 in the Heart of Renovascular Hypertensive Rats**. Rocha EV, Falchetti F, Pernomian L, Blascke de Mello MMB, Parente JM, Nogueira RC, Sanches-Lopes JM, Tanus-Santos JE, Castro MM FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

06.005 **Cardiovascular Repercussions in Virgin and Pregnant Female Rats First-generation Offspring of Mothers with Induced Gestational Hypertension**. Bozoni FT, Santos NCM, Souza-Paula E, Mariana NAP, Rocha ALV, Silva EJR, Dias-Junior CA IBB-Unesp-Botucatu

06.006 **Cardiovascular Effects of** *Alpinia zerumbet* **Leaves Extract in Spontaneously Hypertensive Rats**. Santos GP, Menezes MP, Oliveira BC, Cavalheira MA, Silva DLB, Bem GF, Costa CA, Resende, AC, Ognibene DT IB-UERJ, Dept of Pharmacology, Rio de Janeiro, Brazil

06.007 **Evaluation of Vascular Adverse Effects of Intrauterine and Lactational Exposure to Cyantraniliprole**. Morimoto KY, Boese CM, Moura KF, Gonçalves CO, Rodrigues KFS, Verlingue TZ, Rodrigues MD, Menezes ACF, Fernandes GSA, Ceravolo GS UEL, Dpt of Physiology Sciences, Londrina, Brazil

Room 19:

06. Cardiovascular and Renal Pharmacology

06.014 Characterization of Abnormalities in *Corpora cavernosa* from Hypertensive Rats. Silva LB[1], Jesus RLC[1], Araújo FA[1,2], Silva DF[1,2] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Salvador, BA, Brazil, [2]IGM-Fiocruz, Salvador, BA, Brazil

06.015 Impact on Stomach pH of Sodium Nitrite on Gestational Hypertension Caused by the Reduced of Uteroplacental Perfusion Pressure Model in Rats. Silva MLS, Martins LZ, Rodrigues SD, Dias-Junior CA IBB-Unesp-Botucatu, Dpt of Pharmacology, Botucatu, Brazil

06.016 Effects of Ouabain Administration and High-Salt Diet in Wistar Rats. Feijó PRO[1], Panice MS[1], Morcillo LSL[2], Quintas LEM[1] ICB-UFRJ, Lab of Molecular and Biochemical Pharmacology, Lab of Renal Pharmacology

06.017 6-Nitrodopamine is a Major Modulator of Heart Chronotropism. Britto-Júnior J[1], Oliveira MG[1], Campos R[2], Mónica FZ[1], Antunes E[1], De Nucci G[1] [1]FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil, [2]ISCB-UECE, Fortaleza, Brazil

06.018 The Role of Renin Angiotensin System and Reactive Oxygen Species in Aortic Endothelial Dysfunction caused by Childhood Obesity in Female Rats. Moura KF, Jezuino JS, Boese CM, Gonçalves CO, Uchoa ET, Ceravolo GS UEL

06.019 Antithrombotic Effect of the Polysaccharide Extract from the Stem Barks of Libidibia ferrea Associated with the Anticoagulant Rivaroxaban After Oral Treatment in Rat. Gadelha CJMU[1], Morais EB[1], Lessa RA[2], Silva ALM, Nobre ES[2], Assreuy AMS[1], Pereira MG[2] [1]ISCB-UECE, Fortaleza, Brazil, [2]FECLESC-UECE, College of Education, Science and Letters of Central Sertão, Quixadá, Brazil

06.020 Effects of *Euterpe oleracea* Mart. (açaí) Seed Extract (ASE) in Mitochondrial Biogenesis and Oxidative Stress in Brown Adipose Tissue of High-Fat-Fed C57Bl/6 Mice. Silva DLB, Santos IB, Romão MH, Menezes MP, Oliveira BC, Ognibene DT, Bem GF, Costa CA, Resende AC UERJ, Dpt of Pharmacology, Rio de Janeiro, Brazil

06.021 Pharmacological Inhibition of FAK-Pyk2 Pathway Protects Against the Hyper-Inflammatory State in Sepsis and Prolongs Mice Survival. Alves GF[1,2], Aimaretti E[3], Einaudi G[4], Mastrocola R[3], Oliveira JG[2], Collotta D[1], Porchietto E[4] , Aragno M[3], Cifani C[4], Sordi R[2], Thiemermann C[5], Fernandes D[2], Collino M[6] [1]University of Turin, Dept of Drug Science and Technology, Turin, Italy, [2]UFSC, Dept of Pharmacology, Florianópolis, Brazil, [3]University of Turin, Dept of Clinical and Biological Sciences, Turin, Italy, [4]University of Camerino, Pharmacology

Unit, School of Pharmacy, Camerino, Italy, [5]Queen Mary University of London, Centre for Translational Medicine and Therapeutics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom, [6]University of Turin, Dept of Neurosciences (Rita Levi Montalcini), Turin, Italy

06.022 Sarcoplasmic Reticulum Calcium ATPase (SERCA) Proteolysis by Matrix Metalloproteinase-2 Results in Hypertension-induced Morphofunctional Vascular Alterations. Mello MMB, Neves VGO, Pernomian L, Parente JM, Rocha EV, Silva PHL, Castro MM FMRP-USP, Dpt of Pharmacology, Ribeirão Preto, Brazil

06.023 7-Hydroxycoumarin Induces Hypotension and Vasorelaxation in SHR Rats: A Promising Molecule for the Treatment of Hypertension. Silva ILP[1,2], Jesus RLC[1,2], Brito DS[1], Lima GBC[1], Silva LB[1], Araújo FA, Moraes RA, Alves QL, Silva DF [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Health Sciences Institute, Salvador, Brazil; [2]FF-UFBA PPG in Pharmaceutical Sciences, Salvador, Brazil

06.024 NONO2P, NO Donor, Induces Vascular Tolerance Involving Endothelium-Derived Prostanoids. Moraes RA[1], Araujo FA[1,2], Brito DS[1,3], Lima GBC[1,3], Sá DS[4], Silva CDS[4], Rocha ZN[3], Silva DF[1,2,3] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Bioregulation Department, Salvador, Brazil, [2] FIOCRUZ, Gonçalo Moniz Institute, Salvador, Brazil, [3]UFBA, Salvador, Brazil, [4]IFBA, Salvador, Brazil

Room 20:

07. Endocrine, Reproductive and Urinary Pharmacology

07.010 Role of Advanced Glycation End-Products (AGE) in Bladder Dysfunction in ob/ob Mouse Model of Type 2 Diabetes. Oliveira AL, Medeiros ML, Ghezzi AC , Mello GC, Monica FZ, Antunes E FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil

07.011 Alpha1-Adrenergic Antagonists Block 6-Nitrodopamine Contractions on the Rat Epididymal Vas Deferens. Silva Lima AT, Britto-Júnior J, Fregonesi A,, Mónica FZ, Antunes E, De Nucci G Unicamp

07.012 *Spirulina platensis* Prevents Uterine Morphological Changes Promoted by Strength Training and Inhibits NADPH Oxidase. Barros BC, Lacerda Júnior FF, Diniz AFA, Souza PPS, Alves AF, Ferreira PB, Silva BA UFPB

07.013 Braylin Favors Penile Erection in a Model of the Hypertension-Associated Erectile Dysfunction. Araújo FA[1,2], Jesus RLC[1,3], Moraes RA[1,2], Silva LB[1,3], Lima GBC[1], Brito DS[1], Campos L[4], Santos V[4], Azeredo FJ[4], Costa RS[5], Souza OP[5], Velozo ES[5], Silva DF[1,2,3] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Health Sciences Institute, Salvador, Brazil,[2]IGM-Fiocruz PPG in Biotechnology in Health and Investigative Medicine, Salvador, Brazil, [3]FF-UFBA PPG in Pharmaceutical Sciences, Salvador, Brazil, [4]UFBA, Lab of Pharmacokinetics and Pharmacometry, Salvador, Brazil, [5]UFBA, Lab of Research in Medical Matter, Salvador, Brazil

07.014 The Impact of Gender Differences on the Anti-Inflammatory and Analgesic Effects of Hydrogen Sulfide in a Model of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). Kiataki LGS[1], Teixeira SA[1], Oliveira MG[2], Dallazen JL[1], Oliveira JP[1], Whiteman M[3], Muscará MN[1], Mónica FZ[2], Antunes E[2], Costa SKP[1] [1]USP, Dpt of Pharmacology, São Paulo Brazil, [2]Unicamp, Dept of Pharmacology, Brazil [3]University of Exeter, England

07.015 MK571, A Multidrug Resistance Proteins Inhibitor, Restored the Erectile Function of Obese Mice Through cGMP Accumulation. Oliveira MG[1]., Passos GR., Gomes ET, Leonardi GR, Zapparoli A, Antunes E., Monica FZ FCM-Unicamp, Dpt of Translation Medicine (Pharmacology area), Campinas, Brazil

07.016 *Spirulina platensis* Supplementation Prevents Histomorphometric Changes in the Uterus of Wistar Rats Submitted to Progressive Strength Training. Ferreira PB, Lacerda Júnior FF, Souza PPS, Barros BC, Diniz AFA, Alves AF, Silva AS, Silva BA UFPB

07.017 Lipopolysaccharide and Lipoteichoic Acid Differentially Regulate Toll-like Receptor Signaling Pathway-Associated Genes in the Mouse Epididymis. Silva EJR[1], Kushima H[1], Avellar MCW[2], Pleuger C[3], Andrade AD[1] [1]IBB-Unesp-Botucatu, Dpt of Biophysics and Pharmacology, Botucatu, Brazil, [2]Unifesp-EPM, Dpt of Pharmacology, São Paulo, Brazil, [3]Justus-Liebig-University Giessen, Institute of Anatomy and Cell Biology and Hessian Centre of Reproductive Medicine, Giessen, Germany

Room 21:

08. Respiratory and Gastrointestinal Pharmacology

08.013 **Estragole Prevents Duodenal Ulcer and Improves Gastric Healing with Involvement of Antioxidant and Immunomodulatory Pathways in Animal Models**. Alves Júnior EB[1], Serafim CAL[1], Araruna MEC[1], Pessôa MLS[1], Pessoa MMB[1], França JS[1], Araujo AA[2], Batista LM[1] [1]UFPB, [1]UFRN

08.014 **The Local Anaesthetic Derivative JME-209 Improves Steroid Resistance in Distinct Murine Models of Lung Airway Diseases: Impact on Oxidative Stress**. Gomes: HS[1], Coutinho DS[1], - Cotias AC[1], Costa JCS[2], Carvalho VF[1], Martins PMRS, Martins MA[1] [1]IOC-Fiocruz – Lab Immunopharmacology, Rio de Janeiro, Brazil, [2] IOC-Fiocruz – Production and Innovation in Health

08.015 **(-)-Fenchone Prevents Cysteamine-Induced Duodenal Ulcers and Accelerates Healing of Gastric Ulcers in Rats Via Antioxidant and Immunomodulatory Mechanisms**. Araruna MEC[1], Alves Júnior EB[1], Serafim CAL[1], Pessôa MLS, Pessoa MMB[1], Alves VP[1], Araújo AA[2], L Batista LM [1]UFPB, [2]UFRN

08.016 *Cissampelos sympodialis* **Extract Attenuates Cigarette Smoke-Induced Acute Lung Injury in Mice**. Queiroz Neto RF[1], , Oliveira-Melo P[2], Barbosa-Filho JM[3], Silva FAC[1], Manzuti GM[2], Santos CCA[1], Silva AGG, Moura MJN[1], Silva GM[1], Borges CS[1], Kennedy-Feitosa E[1], Oliveira MF [1]UFERSA [2]InCor-HC-USP, [3]UFPB

08.017 **Supplementation with *Spirulina platensis* Prevents Changes in Intestinal Contractile Reactivity by Inhibiting ROCK and Increasing SOD In Rats Fed a Hypercaloric Diet**. Ravilly RAA, Diniz AFA[1], **Claudino BFO**[1], Francelino DMC[1], Barros BC, Lacerda Júnior FF[2], Ferreira PB, Silva BA [1]UFPB, [2]UFPE

08.018 **Mechanism of Action of *Hibiscus sabdariffa* Reversing Functional Alterations in the Trachea of Wistar Rats with Obesity-Exacerbated Asthma** Ferreira SRD[1], Pessoa RF[1], Figueiredo IAD[1], Martins AMO[2], Vasconcelos LHC[3], Cavalcante FA[3] [1]UFPB-PPgPNSB João Pessoa, Brazil, [2]UFPB-PIBIC João Pessoa, Brazil, [3]UFPB, Dpt of Physiology and Pathology, João Pessoa, Brazil

08.019 **Extracellular Cyclic AMP Induces Airway Smooth Contraction Through Mast Cell Degranulation in Ovalbumin-Sensitized Rat**. Pacini ESA, Tavares-de-Lima W[2], Godinho RO[1] [1]Unifesp-EPM, Dept of Pharmacology, São Paulo, Brazil, [2]ICB-USP Dept of Pharmacology, São Paulo, Brazil

08.020 **Nanoemulsion Containing Pequi Oil Improves Lipopolysaccharide-Induced Lung Inflammation in Mice**. Coutinho DS[1], Pires J[2], Gomes HS[1], Pohlmann AR[3], Guterres SS[4], Martins PMRS, Martins MA[1], Ferrarini SR[2], Bernardi A[1] [1]IOC-Fiocruz, Lab Immunopharmacology, Rio de Janeiro, Brazil, [2]ICS-UFMT, Sinop, Brazil, [3]UFRGS, Dpt of Organic Chemistry, Porto Alegre, Brazil, [4]UFRGS, PPG Pharmaceutical Sciences, Porto Alegre, Brazil

08.021 **Respiratory Parameters and Respiratory Mechanics in Senescence Mice Model**. Oliveira MA[1], Lino Alvarado AE[3], Maia OAC[2], Moreira TS[2], Tavares-de-Lima W[1], Moriya HT[3] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]ICB-USP, Dept of Physiology, São Paulo, Brazil, [3]USP, Lab of Biomedical Engineering, Escola Politécnica, São Paulo, Brazil

08.022 **Use of Phytotherapy with Anti-Inflammatory and Antioxidant Potential in Celiac Patients**. Marques CRS[1], Saboia KA[1], Costa LA[2], Milhome Y[1], Borges AG[1] [1]Centro Universitário Estácio do Ceará, [2]ICC-Hospital Haroldo Juaçaba, Fortaleza, Brazil

Room 22:

09. Natural Products and Toxinology

09.010 **Limonene Acts on Cell Differentiation Through Modulation of Adipogenic Factors in 3T3-L1 Cells**. Assunção R[1], Pinto TS[2], Emilio-Silva MT[1], Andrade AFC[2], Zambuzzi WF[2], Hiruma Lima CA[1], [1]IBB-Unesp-Botucatu, Dept of Structural and Functional Biology (Physiology), Botucatu, SP, [2]IBB-Unesp-Botucatu, Dept of Chemical and Biological Sciences, Botucatu, Brazil

09.011 **Glycosylated Chrysin Protects Against the Neurotoxicity Induced by 3-Nitropropionic Acid in Swiss Male Mice**. Pereira RM[1], Oliveira PY[1], Campos HM[1], Menegatti R[2], Ghedini PC[1] [1]ICB-UFG, Dpt of Pharmacology, [2]FF-UFG

09.012 Glycosylated Chrysin protects Against Aluminum-Induced Neurotoxicity. Okoh VI[1], Ferreira P[1], Pereira RM[1], Campos HM[1], Menegatti R[2], Ghedini PC[1] ICB-UFG, Dpt of Pharmacology, Goiânia, Brasil, [2]FF-UFG, Goiânia, Brasil

09.013 *In vitro* and *In Silico* Studies of the Vasorelaxant Mechanism of Action of Synthetic Amide (E)-N-(4-Methoxyphenethyil)-3-(Thiophen-2-yl)Acrylamide in Rat Aorta. Cavalcanti-Silva ARLF, Pessoa RF, Moura TMCF, Fernandes JM, Figueiredo IAD, Ferreira SRD, Sousa NF, Scotti L, Silva LAA, Rodrigues LC, Cavalcante FA UFPB

09.014 Gastroprotective Effect of *Egletes viscosa* Chemotype a Infusion on Ethanol-Induced Gastric Lesions in Mice. Portela BYM[1], Nunes PIG[2], Freire GP[2], Lima RP[1], Viana AFSC[1], Carvalho KR[3], Canuto KM[3], Santos FA[1,2] [1]UFC, PPG Pharmacology, Fortaleza, Brazil, [2]UFC, PPG Medical Sciences, Fortaleza, Brazil, [2]Embrapa Tropical Agroindustry

09.015 Influence of Phospholipase A2 on the Neuromuscular Blockade Caused by Coral Snake (Elapidae) Venoms in Mouse Phrenic Nerve-Diaphragm Preparations *In Vitro*. Couceiro FYG[1], Demico PJ[1], Diamante CF[1], Dias SR[1] , Silva Júnior NJ[2], Grego KF[3], Sant'Anna SS[3], Zani KM[3], Hyslop S[4], Floriano RS[1] [1]Unoeste, PPG em Ciências da Saúde, Lab de Toxinologia e Estudos Cardiovasculares, Presidente Prudente, Brazil, [2]PUC Goiás, PPG em Ciências Ambientais e Saúde, Goiânia, Brazil, [3]IBu, Lab Herpetologia, São Paulo, Brazil, [4]FCM-Unicamp, Seção de Farmacologia, Dept de Medicina Translacional, Campinas, Brazil

09.016 *Rhinella schneideri* (*Rhinella diptycha*) Skin Secretion Bioprospection: New Tools for Neurodegenerative Diseases Treatment. Caires GA[1], Pimenta DC[2], Sciani JM[3], Búfalo MC[4], DeOcesano C[4], Kerkis I[1], Vigerelli H[1] [1]IBu Lab de Genética, São Paulo, Brasil, [2]IBu, Lab de Bioquímica, São Paulo, Brasil, [3]UFS, Lab Multidisciplinar de Pesquisa, Bragança Paulista, Brasil, [4]IBu, Centre of Excellence in New Target Discovery, São Paulo, Brasil

Room 23:

09. Natural Products and Toxinology

09.026 Analysis of the Healing Potential of *Montrichardia linifera in vitro*. Bastos AC[1], Gomes MF[1], Amarante CB[2], Pinheiro WBS[1], Botelho AS[1], Khayat AS[1], Yamada ES[1], Bastos GNT[1] [1]UFPA, [2]Museu Paraense Emílio Goeldi

09.028 Liver Histopathology of Silver Catfish Infected by *Aeromonas hydrophila* and Treated with Extract of *Hesperozygis ringens* (Benth.) Epling. Rosa IA[1], Bandeira Junior G[1], Bianchini AE[1], Pereira da Silva HN[1], Ferrari FT[2], Costa ST[3], Baldisserotto B[1], Heinzmann BM[1,2] [1]UFSM, Department of Physiology and Pharmacology, Santa Maria, Brazil, [2]UFSM, Department of Industrial Pharmacy, Santa Maria, Brazil, [3]UFSM, Dept of Morphology, Santa Maria, Brazil

09.029 Comparative Compositional and Functional Activities of *Lachesis muta* Venom from Adult and Juvenile Individuals. Galizio N[1], Torres-Bonilla KA[2], Varón JCG[2], Moraes-Santos LS[3]., Yabunaka AC[3], Silva Júnior NJ[4], Hyslop S[2], Tanaka-Azevedo AM[1], Floriano RS[1], Floriano RS[3] [1]Ibu, Lab of Herpetology, Instituto Butantan, Sao Paulo, SP, Brazil, [2]FCM-Unicamp, Section of Pharmacology, Dpt of Translational Medicine, Campinas, Brazil, [3]PPG in Biotechnology, University of Sao Paulo, Sao Paulo, SP, Brazil, [3]Unoeste, PPG in Health Sciences, Lab of Toxinology and Cardiovascular Research, Presidente Prudente, Brazil, [4]PUC Goiás PPG in Environmental Sciences and Health, Goiânia, Brazil

09.030 Antinociceptive Activity of Aqueous Extract of *Bauhinia pulchella* Benth in Mice. Nunes PIG[1], Estevão VA[1], Maurício MTA[1], Lima RP[1], Portela BYM[1], Freire GP, Carvalho AA[2], Chaves MH[3], Santos FA[1] [1]FM-UFC, [2]IFPI, Piripiri, Brazil, UFPI, Chemistry Department, Teresina, Brazil

09.031 Taraxasterol Acetate, Isolated from *Eupatorium balotteifolium*, Improves Glucose Uptake by Increasing Membrane GLUT4 Expression in TNFα-Induced 3T3-L1 Cells. Lima RP[1], Oliveira FTB[2], Freire GP[2], Portela BYM[1], Nunes PIG[2], Albuquerque MRJR[3], Pessoa ODL[3], Santos FA[1] [1]UFC, PPG Pharmacology, Fortaleza, Brazil, [2]UFC, PPG Medical Science, Fortaleza, Brazil; [3]UFC, PPG Chemistry, Fortaleza, Brasil

09.032 **Coumestrol: A Promising Molecule for Wound Healing**. Bianchi SE, Bassani VL UFRGS, PPG em Ciências Farmacêuticas, Porto Alegre, Brazil

09.033 **Caspase-1 and Cathepsin B Inhibitors from Marine Animals, as Modulators of Neuroinflammation in Alzheimer's Disease**. Moreno RI[1,2], Zambelli VO[3], Picolo G[3], Cury Y[3], Morandini AC[4,5], Marques AC[4], Sciani JM[1] [1]USF, Lab Multidisciplinar de Pesquisa, Bragança Paulista, Brazil, [2]UNIFAG, Bragança Paulista, Brazil, [3]IBu, Lab Dor e Sinalização, São Paulo, Brazil, [3]IB-USP, Dept de Zoologia, Centro de Biologia Marinha, São Sebastião, Brazil, [4]IB-USP, Dept de Zoologia, São Paulo, Brazil

09.034 **Evaluation of the Effects of *Marrubium vulgare* L. Infusion on Zootechnical Performance Parameters and Blood Metabolomics in Weaned Piglets**. Schlemper V[1], Tizziani T[2], Sandjo LP[2] [1]UFFS, Veterinary Medicine Course, Realeza, Brazil, [2]UFSC, Departament of Chemistry, Florianópolis, Brazil

09.035 **Nociceptive Evaluation of the Lyophilized Extract of *Lupinus mutabilis* Sweet (TARWI) in Experimental Animals**. Gamarra F[1], Salazar-Granara A[1], Martínez Herrera J[2], Jurado RB[3] [1]Universidad de San Martín de Porres, Facultad de Medicina Humana, [2]Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias, [3]Universidad de la Laguna, San Cristóbal de La Laguna, Tenerife, España

09.036 **Antinociceptive Effect of Ethanol Extract of *Nephelium lappaceum* L. Fruit Peel Involves Opioid Receptors, Nitric Oxide and ATP-Sensitive Potassium Channels**. Oliveira AS[1], Biano LS[1], Palmeira DN[1], Kohlhoff M[2], Sousa JAC[3], Brandão GC[3], Oliveira e Silva AM[1], Grespan R[1], Camargo E[1] [1]UFS, [2]Fiocruz, [3]UFOP

Room 24:

10. Cancer Pharmacology

10.008 **Evaluation of the Antitumor Activity of the Constituents of *Sinningia reitzii* on Solid Ehrlich Tumor Model in Mice**. Radulski DR, Pereira GS, Acco A UFPR

10.009 **Cellular and Molecular Effects of Eribulin in Pre-clinical Models of Hematological Malignancies**. Vicari HP, Lima K, Costa-Lotufo LV, Machado-Neto JA ICB-USP, Dpt of Pharmacology, São Paulo, Brazil

10.010 *In vitro* **Evaluation of Cytotoxic Activity of *Tithonia diversifolia* (td) in HCT-116 a Colorectal Carcinoma Lineage**. Madrid MFM, Hernández ENM, Mota JA, Rocha DD, Moraes Filho MO, Pessoa CO UFC, PPG of Physiology and Pharmacology, Fortaleza, Brazil

10.011 **Antileukemic Potential of EMT to Eliminate Leukemic Stem Cells from Acute Myeloid Leukemia in an *in vitro* and *in vivo* Model**. Silva SLR[1], Costa RGA[1], Dias IRSB[2], Rodrigues ACCB[2], Oliveira MS[2], Bezerra DP[2] [1]FF-UFBA, Salvador, Brazil, [2]IGM-Fiocruz-BA, Salvador, Brazil

10.012 **NRF2 Pathway Activation and Tumor Recurrence Correlate with Thioredoxin Reductase-1 up-Regulation in Non-Small Cell Lung Cancer**. Delgobo M[1], Gonçalves RM[1], Delazeri MA[2], Falchetti M[1], Zandoná S[2], Neves RN[1], Almeida K[1], Fagundes AC[1], Gelain DP[3], Fracasso JI[2], Macêdo GB[2], Priori L[2], Forcelini CM[2], Moreira JCF[3], Zanotto-Filho A[1] [1]UFSC, Dpt of Pharmacology, Florianópolis, Brazil. [2]UPF, Dpt of Medicine, Passo Fundo, Brazil. [3]UFRGS, Dpt of Biochemistry, Porto Alegre, Brazil

10.013 **Protective Effect of Ethanolic Extract of *Chuquiraga spinosa* Less (huamanpinta) and *Senecio rhizomatus* Rusby (Llancahuasi) on Prostatic Neoplasia Induced with Testosterone, NMU and Cyproterone in Rats**. Arroyo Acevedo JLA[1,2], Rojas-Armas JP[1,2], Justil-Guerrero HJ[2], Calva-Torres JW[3], Cieza-Macedo EC[2], Condorhuamán-Figueroa YM[4], García-Bustamante CO[2], Villena-Tejada M[5], Chavez-Asmat RJ[6], Herrera-Calderón O[7], Chamba-Granda DF[7] [1]Universidad Nacional Mayor de San Marcos – Clinical Research Institute School of Medicine "San Fernando", Lima, Perú, [2]Universidad Nacional Mayor de San Marcos, Lab of Pharmacology, Lima, Perú, [3]Chemistry Dept, Universidad Técnica Particular de Loja, Loja, Ecuador, [4]Universidad Nacional Mayor de San Marcos, Research Institute of Pharmaceutical Sciences and Natural Resources, Lima, Perú, [5]Universidad Nacional de San Antonio Abad del Cusco., Academic Dpt of Pharmacy, Faculty of Health Sciences, Cusco, Perú, [6]Universidad Nacional Mayor de San Marcos, Association for the Development of Student Research in Health Sciences, Faculty of Medicine, Lima, Perú, [7]Universidad Nacional Mayor de San Marcos, Faculty of Pharmacy and Biochemistry

Room 25:

12. Drug Discovery and Development

12.001 **New Perspectives for Melanoma and Fungal Infections Treatment: Development of Polymeric Nanoparticles for Seriniquinone Delivery**. Miguel RA[1], Hirata AS[1], Barroso VM[1], Furtado LC[1], Ishida K[2], Costa-Lotufo LV[1], Lopes LB[1] [1]ICB-USP, Dpt of Pharmacology, São Paulo, Brazil, [2]ICB-USP, Dpt of Microbiology, São Paulo, Brazil

12.002 **Wound Healing Potential of Mitochondria-Targeted Hydrogen Sulfide (H_2S) Donors: ROLE of hyperglycemia**. Gois GA, Amorim LA, Cerqueira ARA, Oliveira JP, Teixeira SA, Muscará MN, Costa SKP ICB-USP

13. Pharmacology Education and Technology

13.001 **Interactions Between Drugs and Food/Nutrients: Report of this Practice of Extension Education in the Context of Remote Teaching**. Montes GC[1], Campos WVA[2], Rossi BA[2], Barbosa CD[2], Ferreira CCD[2], Carmo PL[2] [1]UERJ, Rio de Janeiro, Brazil, [2]UFRJ-Macaé, Macaé, Brazil

13.002 **Undergraduate Medical Students Perception of Team-Based Learning in the Study of Antibiotics Pharmacology**. Morais SA, Cabral MCB, Coelho AM, Januário MJB, Bessa MMM, Lima LAR, Oliveira FFB FAP, Medicina, Araripina, Brazil

13.003 **Team Basic Learning (TBL) as Collaborative Learning Tool for the Study of Pharmacology of Antibiotics**. Coelho AM, Januário MJB, Cabral MCB, , Morais SA, Bessa MMM, Lima LAR, Oliveira FFB FAP, Medicina, Araripina, Brazil

14. Pharmacology: Other

14.001 **Development and Evaluation of the Bioadhesive Properties of Chitosan and Hyaluronic Acid Polyelectrolyte Nanoparticles**. Hirokawa CM[1,2], Passos JS[2], Lopes LB[2] ICB-USP, Dpt of Pharmacology, São Paulo, Brazil [1]FCF-USP, São Paulo, Brazil, 2 ICB-USP, Dpt of Pharmacology, São Paulo, Brazil

14.002 **Transgenic Effect on the Composition of Nutrients from Corn: GMO Vigilance**. Vital AJL[1], Castro LGG[2], Ribeiro AF[1], Barros BAF[1] [1]PUC-MG, [2]UFMG

14.003 **Drug-Drug Interactions in Patients on Covid-19 During the First Wave in Brazil**. Santos JR, Razera A, Marques ACR, Carraro E Unicentro, Dpt of Pharmacy, Guarapuava, Brazil

14.004 **Pathophysiological Mechanism of Primary Dysmenorrhea involves Enlargement of the Uterine Myometrium and Oxidative Stress**. Souza PPS, Lacerda Júnior FF, Barros BC, Almeida Filho EJB, Ferreira PB, Silva AS, Silva BA UFPB

Lectures Abstracts

Courses

Course Pharmacological Treatments based on Scientific Evidence (Tratamentos Farmacológicos Baseados em Evidências Científicas). Adriane Ribeiro Rosa e Rosane Gomez (UFRGS)

Clinical trials are a source of information on the efficacy and safety of drugs. Despite being peer-reviewed before publication, many studies are not conducted with scientific rigor, presenting methodological and/or interpretation errors. The selection of the best treatment based on this clinical evidence depends on the training of the healthcare team. In this course, we intend to present the study designs most frequently used for decision making, as well as indicate databases for the selection of reliable articles and discuss some important research metrics such as h index, impact factor, and others. We also intend to show some instruments for the critical analysis of scientific articles and decision-making. It is aimed at undergraduate and graduate students with an interest in the field of clinical pharmacology.

Digital Games as Tools for Scientific Divulgation (Jogos Digitais como Ferramentas para Divulgação Científica)

Digital Games for Scientific Divulgation and Citizen Science (Jogos Digitais para Divulgação Científica e Ciência Cidadã). Tadeu Moreira de Classe, Graduate Program on Informatics (PPGI), Federal University of State of Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil

The game industry moves an astronomical amount of money annually. It is the field that attracts the newest customers, passing classical markets such as music and movies. Due to that, new companies must arise, and they bring innovation to engage their clients. In this context, considering the vital game feature of engaging people, fields such as health, education, and science, for instance, are looking for how to think and apply these games that enable players to solve problems and learn with them. These games are knowns as Games with a Purpose (GWAP). They are games whose primary goal is not entertainment but, to make players understand game messages and learn with them. These games can show the players situations of complex scientific experiments in a ludic manner, making their comprehension of the scientific context easy. Therefore, when we think about these games, we think about how they could clarify science and be used as scientific divulgation tools. On the other hand, from the player's perspective, when we think about citizen science, we can glimpse some games in which players contribute to the science. They do not need to consider complex theories, rigid methodologies, or scientific experiments steps. They just play.

DiscoveRx, a Digital Game for Scientific Divulgation of the Drug Discovery and Development Process. François Noël, Institute of Biomedical Sciences, Universidade Federal do Rio de Janeiro, Brazil.

The use of games as a strategy for educational purpose is an important current trend that has been used widely but not for the Drug Discovery and Development (DDD) process. To fill this gap, we first created SCREENER, a hybrid of board and card games designed for students enrolled in postgraduate programs in pharmacology and related areas such as medicinal chemistry and pharmacy. This game, developed by a multidisciplinary team at our university, is being distributed by the Brazilian Society of Pharmacology and Experimental Therapeutics (SBFTE) who supported the initiative. As there is also a need for scientific divulgation targeting young people, we decided to develop a game on the same topic but designed to be attractive for digital native people so that a digital game for use in cell phones appeared as an obvious choice. We will present here the game DiscoveRx, addressed to a lay public mainly targeting children and adolescents to illustrate how new medicines are discovered and developed. Our strategy was to build up seven sequential games each corresponding to one of the seven stages of the DDD process described in SCREENER. While 29 tasks had to be performed in SCREENER, we selected here one task for each stage based on its importance and feasibility for introducing diversity in the game dynamics. As for many digital games, the player can either chose the *Campaign* mode or play specific games in the *Arcade* mode, where its ability will be challenged as the difficulty increases according to the level. The idea is to provide an attractive and pleasant game that could illustrate in a simple way the long and difficult multi-step process necessary to put a new medicine on the market, from *in vitro* hit selection to phase 3 clinical trial. In order to ensure the possibility of additional information for adolescents or even adults, “Know more” buttons have been added in each mini game. The game will be uploaded at the Google play platform for easy and free access, launching initially the first three mini-games, and thereafter the following ones, one at a time. Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil.

Population Pharmacokinetics Analysis (Análise Farmacocinética Populacional)

Applications of POPPK on Precision Dosing (Aplicações de POPPK em Dose de Precisão). Manuel Ibarra, Associate Professor – Dept of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República (UDELAR), Uruguay

The goal of a pharmacological treatment is to attain a beneficial clinical response in the patient receiving it. Pharmacotherapeutic decisions should maximize the probability of achieving the desired drug action (i.e., efficacy) and minimize the chances of adverse events (i.e., safety) at the individual level. Accomplishing this in different patients within a given population can be extremely difficult due to the variability in the dose-exposure-response relationship. The pharmaceutical characteristics of the drug product, the administration conditions, the treatment adherence, and the patient characteristics have a significant impact on the treatment outcome, conveying into a complex system that must be rationally approached. Precision dosing can be defined as the individualization of drug treatment regimens based on patient characteristics known to alter drug pharmacokinetics and pharmacodynamics. Pharmacometric models can predict the time course of drug concentrations, effects, and disease based on individual characteristics and hence support the a priori definition of the pharmacotherapeutic regimen more likely to achieve the desired clinical response in each patient. Furthermore, observations made in a given patient after treatment instauration can be considered by these models to tailor the dose regimen supporting the "adaptive dosing" strategy. Pharmacometrics can additionally support other precision medicine strategies such as patient stratification to guide medical diagnosis and drug selection. The application of pharmacometric models in precision dosing has led to the model-informed precision dosing (MIPD) paradigm, which comprehends the use of mathematical modeling approaches in combination with individually measured patient characteristics and disease characteristics to inform clinical decisions aimed to give the right drug, in the right dose, to the right patient, at the right time. In a broad sense, MIPD can be viewed as the natural evolution of therapeutic drug monitoring through the incorporation of pharmacometric principles. This talk will cover essential concepts and practical issues related to the application of pharmacometric models in MIPD.

Lectures

Neuroprotective Mechanisms of Angiotensin II Receptor Blockers. Juan M. Saavedra, MD., Dept of Pharmacology and Physiology, Georgetown University Medical Center

Angiotensin Receptor Blockers (ARBs) are safe compounds commonly used for the treatment of high blood pressure because they control and reduce the pro-hypertensive effects of excessive Angiotensin II production and Angiotensin II AT1 receptor (AT1R) overstimulation. In the brain, AT1R are localized in cerebrovascular endothelial cells and the circumventricular organs, while no Angiotensin II is produced in the brain parenchyma. By regulating the brain circulation, AT1R activity participates in multiple brain functions, including the control of the autonomic and hormonal systems, behavior, and cognition. Increased AT1R expression and overstimulation, damages the cerebral vasculature and is an important injury factor in aging and several neuropsychiatric ailments, including neurodegenerative disorders such as Parkinson's and Alzheimer's disease, stroke, and stress related conditions. Gene Set Enrichment Analysis and Gene Ontology analysis reveal, in brain cell cultures, that ARBs normalize the expression of hundreds of genes involved in neurodegenerative, metabolic, and inflammatory disorders. Conversely, ARBs increase the expression of multiple genes involved in neuroprotective mechanisms. This explains that ARB treatment reduces common injury mechanisms affecting the brain, decreasing excessive inflammation, protecting the cerebral vasculature, the cerebrovascular endothelium, and the blood-brain barrier, and preserving mitochondrial function and brain oxygenation. Of significant and current interest is the effect of ARBs on SARS-CoV-2 infection. ARBs reduce COVID-19 comorbidities and risk factors such as hypertension and diabetes, exert anti-aging effects, reduce the COVID-19 cytokine storm and viral load, protect the cerebrovascular endothelium and the blood-brain barrier, and decrease the prothrombotic state, and in neuronal cultures they normalize the expression of hundreds of genes upregulated in SARS-CoV-2 infection. Many recent clinical trials suggest that ARB therapy may be beneficial in COVID-19 patients. While the potential indications for ARB treatment continue to expand, future controlled studies are necessary to establish the scope of ARB therapy in medical conditions.

Registered Reports: A Vaccine against Bias in Research and Publishing. Chris Chambers (Cardiff University, UK)

Registered Reports are a form of preregistered empirical publication that aims to eradicate publication bias and reporting bias (e.g., selective reporting of statistically significant results and hindsight bias), by performing peer review *before* research commences. Publishability is then decided by the importance of the research question and quality of the methodology, and never based on the results. In this talk I will introduce the concept of Registered Reports and provide an update on its progress, including adoption by more than 300

journals, and early evidence of positive impacts on the field. I will also discuss "Registered Reports 2.0" in which the format is transcending journals altogether. In 2021 we created the *Peer Community in Registered Reports* (PCI RR): a free, non-commercial platform that coordinates the peer-reviews of RR preprints (https://rr.peercommunityin.org/about/about). Once the submissions are accepted following peer review (or, in PCI terms, "recommended"), the revised manuscript is posted at the server where the preprint is hosted, and the peer reviews and recommendation of the preprint are posted at the PCI RR website. PCI RR is also joined by a growing fleet of "PCI RR-friendly" journals that accept the recommendations of PCI RR without further peer review (https://rr.peercommunityin.org/about/pci_rr_friendly_journals), giving the authors the power to choose which journal, if any, will publish their manuscript. By reclaiming control of the peer review process from publishers, PCI RR offers a promising avenue for ensuring that Registered Reports are made as open, accessible, and rigorous as possible, while also moving toward a future in which journals themselves become obsolete.

Emerging Opportunities and Challenges for Drug Discovery and Healthcare Innovations in an Academic Setting
Christoph Thiemermann, William Harvey Research Institute, Bart's and the London School of Medicine & Dentistry, Queen Mary University of London, UK

In this talk, I will share my views and reflections on some Emerging Opportunities and Challenges for Drug Discovery and Healthcare Innovations with a particular focus on Drug Discovery and Translation in an Academic Setting. The latter is more likely achievable by using existing medicines for a new disease indication; a strategy known as repurposing. Examples of the repurposing of drugs for other indications include sepsis including COVID-19, trauma and metabolic diseases associated with chronic, low-grade inflammation (type 2 diabetes mellitus, NASH, chronic kidney disease). Severe injuries account for 9% of all deaths worldwide. Although guidelines for the early management of trauma and blood loss have decreased the rates of early deaths, post-injury multiple organ failure (MOF) is still associated with significant morbidity and mortality. To date, there are no specific pharmacological interventions used clinically to prevent MOF following/associated with Trauma/COVID/Sepsis. This talk summarises our preclinical targets and efficacy studies, explains the regulatory steps that are necessary for clinical translation, and provides examples of the translation of a preclinical discoveries to a phase II clinical trials in patients with trauma-hemorrhage and COVID-19. In the sections below, I summarise 2 examples of anti-inflammatory strategies can can be deployed in acute (sepsis/COVID/trauma) and chronic conditions with systemic inflammation and organ injury and dysfunction: *Host-defense/antimicrobial peptides* (*AMPs*): Host-defense/antimicrobial peptides form part of the innate immune system of insects, plants, and vertebrates by defending the host against invading microorganisms. The most extensively studied host-defense/ antimicrobial peptide in humans is the cathelicidin-derived peptide LL-37. Plasma LL-37 was 12-fold higher in patients with trauma/HS compared to healthy volunteers. HS rats treated with Pep19-4LF [66 (n = 8) or 333 µg/kg · h (n = 8)] for 4 hours following resuscitation had a higher mean arterial pressure and less organ injury / dysfunction. Similarly, synthetic AMPs also reduce the liver inflammation, lipid deposition (NASH), dyslipidaemia and other metabolic alterations associated with experimental diabetes. Although a complete preclinical package of Pep19-4LF is available, translation to a clinical trial is hampered by the lack of phase 1 clinical data with this peptide. *Artesunate*: Artesunate is a safe, low-cost drug, which has been used by thousands of patients with malaria without serious adverse effects. Male Wistar rats were submitted to HS. Mean arterial pressure was reduced to 30 mmHg for 90 min, followed by 4-h resuscitation. Rats were treated with artesunate (2.4 or 4.8 mg/kg i.v.) or vehicle upon resuscitation. Artesunate attenuated the organ injury/dysfunction associated with HS by a mechanism that involves the activation of the Akt-endothelial nitric oxide synthase survival pathway, and the inhibition of nuclear factor kappa B. In April 2017, we have started the recruitment for a phase II placebo-controlled randomized clinical trial designed to evaluate the effects of GMP-artesunate (2.4 or 4.8 mg/kg i.v.) in 105 patients with trauma and severe hemorrhage.

Identification of Oligopeptidases and Intracellular Peptides Key Function in Cell Metabolism. Emer S. Ferro, PhD. Biomedical Science Institute, University of São Paulo, Brazil

A brief historical perspective of *oligopeptidases* application to identify and characterize a new class of biological active molecules coined *intracellular peptides* will be presented. About seven decades ago, pharmacologist Maurício Oscar da Rocha e Silva, MD, PhD (Ribeirão Preto Faculty of Medicine of the University of São Paulo), in collaboration with physiologist Wilson Teixeira Beraldo, MD, PhD (Federal University of Minas Gerais) and hematologist Gastão Rosenfeld, MD, PhD (Butantan Institute), observed that *Bothrops jararaca* venom reacted with human plasma releasing a substance of protein nature they named as *bradykinin*. Nowadays, more than 22,000 scientific articles related to bradykinin can be found searching PubMed; a great scientific recognition of bradykinin biological significance. Two decades after bradykinin was identified,

pharmacologists Antônio Carlos Martins de Camargo, MD, PhD, and Frederico Graef, MD, PhD, who were trained at the Ribeirão Preto Faculty of Medicine of the University of São Paulo by Professor Maurício Oscar Rocha e Silva, described for the first-time the existence of bradykinin-degrading peptidases in mammalian central nervous system. Due to their substrate-size restriction for peptides containing from 8-12 amino acids, these bradykinin-degrading peptidases were later characterized as "oligopeptidases" by biochemical Eduardo Brandt de Oliveira, PhD, at that time a biomedicine student from Professor Antônio Carlos Martins de Camargo, at the Ribeirão Preto Faculty of Medicine of the University of São Paulo. Five decades after bradykinin was identified, in 2003, biologist Vanessa Rioli, PhD, at that time a graduate student from my laboratory, produced recombinant catalytically inactive mutants of oligopeptidases thimet oligopeptidase (THOP1) and neurolysin (Nln), which were used to identify a large group of novel biologically active peptides coined *"intracellular peptides"* (fragments of intracellular proteins produced by the ubiquitin-proteasome system). The phenotype of C57BL6 mice strains with deletion of genes encoding either oligopeptidase THOP1 or Nln have been characterized at our laboratory. THOP1 knockout, for example, makes mice resistant to diet-induced obesity that in parallel alters the content of intracellular peptides, microRNAs and gene expression in the adipose tissue. The Nln knockout, on the other hand, makes C57BL6 mice more sensitive to insulin-induced glucose uptake, whereas more susceptible to diet-induced obesity. In conclusion, we intend to strengthen the importance of long-term investments in science and technology to the advancement of science. Research supported by FAPESP, CNPq and CAPES.

Germline Variants Associated with Cancer Risk and Actionable Drug Targets. Silvia Regina Rogatto, Dept of Clinical Genetics, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, and Danish Colorectal Cancer Center South, DK

Germline pathogenic variants in specific genes have been described as associated with several hereditary cancer predisposition syndromes. For example, the relation between *RB1* and retinoblastoma, *TP53* and Li Fraumeni syndrome, *BRCA1/ BRCA2*, and breast and ovarian cancer syndrome is well established. Germline testing is also helpful in distinguishing some conditions, such as neurofibromatosis type 1 (NF1) and constitutional mismatch repair deficiency, which has clinical and therapeutic relevance and critical differences in these conditions. Moreover, the knowledge of specific mutations has therapeutic implications, such as *BRCA1*, *BRCA2*, and mismatch repair genes (*MLH1, MSH2, MSH6*, and *PMS2*). Next-generation sequencing in cancer patients has increased the burden of germline variants associated with cancer risk and those with known pharmacogenetic consequences. We will report germline variants in two groups of early-onset cancer patients (head and neck and rectal cancer) who presented an increased worldwide incidence during the last decade. Our findings revealed the presence of variants in cancer predisposition genes that potentially contribute to an increased risk of developing the disease at a young age. We also reported a set of druggable alterations with clinical relevance as potential predictive biomarkers. Financial support: Region of Southern Denmark Research Fund, Denmark and National Institute of Science and Technology in Oncogenomics (FAPESP #2008/57887–9 and CNPq #573589/08-9), Brazil.

Cellular and Molecular Mechanisms of Cutaneous Pain Sensation. Michael Caterina (Johns Hopkins University, USA)

Pathological skin pain can arise from many different hereditary and acquired conditions. This diversity of etiologies is mirrored by a diversity of underlying cellular and molecular pain mechanisms, some of which are shared among painful conditions, and other that are idiosynchratic. Mouse models of cutaneous pain offer an opportunity to dissect these diverse mechanisms and thus to identify pathological and pathophysiological processes that could be targeted in humans suffering from cutaneous pain. I will describe recent findings from our laboratory that have emerged from the study of mouse models of a family of painful hereditary skin diseases known as palmoplantar keratodermas. In addition, I will describe our recent findings related to neuroanatomical plasticity in the setting of traumatic peripheral nerve injury.

Can We Recover Aging-Related Steroidogenic Dysfunction? Vassilios Papadopoulos, Dept of Pharmacology & Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA 90089, USA

The progressive decline of testosterone (T) with aging results in 20-50% of men over 60 with significantly reduced T levels. Age-related decline in T is characterized by symptoms including mood changes, fatigue, depression, decreased lean body mass, reduced bone mineral density, increased visceral fat, metabolic syndrome, cardiovascular disease, decreased libido, and erectile dysfunction.

T is synthesized by testicular Leydig cells (LCs) under the control of the pituitary luteinizing hormone that regulates the formation of an organelle communication network, mediated by protein-protein interactions, that drives the delivery of cholesterol into mitochondria, the rate-limiting step in steroidogenesis. The

supramolecular complex of organelle/cytosolic and mitochondrial proteins is called Steroidogenic InteracTomE (SITE). SITE is involved in targeting cholesterol to CYP11A1 in the mitochondria, the first enzyme of the steroidogenic cascade. We hypothesized that aging is associated with LC-specific changes in interorganelle trafficking, redox balance, and protein-protein interactions at the SITE, likely affected by age-dependent changes that lead to reduced cholesterol transfer to CYP11A1 and reduced T production in aging LCs. T replacement therapy (TRT) is used clinically to restore T levels. However, there are limitations to using TRT, making it desirable to develop additional strategies for increasing T. A promising approach would be to develop the means to increase T production by the hypofunctional Leydig cells. The role of numerous SITE proteins has been investigated to identify therapeutic targets. Genetic or pharmacological approaches revealed that although many SITE proteins are critical for steroid formation, their presence in other steroidogenic tissues is a barrier to the safe and efficacious treatment of testosterone deficiency. The sole exception has been blocking the 14-3-3ε-VDAC1 interaction using VDAC1-designed peptides. The identified lead peptide rescued intratesticular and serum T formation in hypogonadal male rats, representing a novel first-in-class biologic that rescues T formation in rats without affecting adrenal or brain steroid formation.

Hormesis Based Biological Effects of Low Levels of Chemicals and Radiation. Edward J. Calabrese, Ph.D.; School of Public Health and health Sciences; Dept of Environmental Health Sciences; Morrill I, N344; University of Massachusetts (USA); Amherst MA 01003;

There is much debate over the fundamental shape of the dose response curve in the low dose zone, particularly in the fields of toxicology and risk assessment. The defaults, principally accepted dose response models in major texts in these areas and in governmental regulatory activities, are a threshold model for non-carcinogens and a linear model for most carcinogens. We have argued that in properly designed studies the U-shaped hormetic response predominates and is more fundamental. In this presentation, a broad range of basic issues associated with the acceptance of hormetic dose responses as central to toxicology, pharmacology, and their application to risk assessment and medicine will be discussed. Funding: Research supported by Air Force Office of Scientific Research

Prediction of the Fate of Drugs in the CNS in Health and Disease by the Leiden CNS PBPK Model. Elizabeth CM de Lange, Predictive Pharmacology, Leiden University, The Netherlands)

We have previously developed the comprehensive physiologically-based LeiCNS-PK3.0 model that demonstrated to adequately predict the unbound pharmacokinetics (PK) of multiple small drugs in healthy rat and human brain extracellular fluid and lumbar cerebrospinal fluid (CSF) within the two-fold error limit. The LeiCNS-PK3.0 model accounts for small drug physicochemical properties (lipophilicity, charge, and molecular weight), and physiological CNS properties (blood-brain barrier (BBB), blood-CSF barrier (BCSFB), brain extracellular and intracellular fluid, lateral ventricle, third & fourth ventricle, cisterna magna, and subarachnoid space), on the basis of size, surface area, pH, and flows. This model is used to predict drug transport across the BBB and BCSFB; extra- and intracellular brain and CSF compartments drug distribution and non-specific brain tissue binding. The LeiCNS-PK3.0 model can be used to predict the unbound PK profiles at CNS target sites for small molecule CNS drugs and off-target sites for non-CNS drugs, that can be linked to CNS drug effects as well as side effects and toxicities. In addition, the mechanistic structure of the model allows translation of PK predictions across species as well as between the different CNS physiological states, i.e. healthy, diseased, maturing, etc. In this presentation the development of the LeiCNS-PK3.0 model and its applications in health and disease will be presented for discussion.

Symposia

Towards Novel Approaches to Study, Understand, and Treat Pain

Screening for Nociceptor-Selective Silencers as Novel Analgesics. Clifford J Woolf, Boston Children's Hospital and Harvard Medical School

The traditional approach to drug discovery is identification of a target, screening for compounds that only act on the target and then evaluating drug-like properties, efficacy and safety. This approach is based on the premise that engagement with a single target is sufficient to produce the desired effect. However, this may not be correct in many instances and contributes to the high failure rate of many new drugs. We are engaged in the discovery of novel non-opioid analgesics and one of our strategies is to find compounds that selectively silence only nociceptors, the sensory neurons that trigger pain, without or reduced activity on other excitable cells. This will likely require activity on multiple targets, and we have developed human stem cell derived phenotypic excitability assays to do this, looking for compounds that silence human nociceptors without affecting cortical and motor neurons or cardiomyocytes (Jayakar et al, 2021). This constitutes a novel approach to drug discovery. Jayakar S, Shim J, Jo S, Bean BP, Singeç I, Woolf CJ. Developing nociceptor-

selective treatments for acute and chronic pain. Sci Transl Med. 2021 Nov 10;13(619): eabj9837. Supported by DARPA.

Publishing in the Open Science Era

Why Does Science Need Immediate and Substantial Reform? William Ngiam, Dept of Psychology, University of Chicago, USA

In this talk, I will provide an overview of some of the issues that have led to science's current reproducibility crisis. Firstly, the proportion of papers finding positive evidence for their hypotheses has ballooned to implausible levels. Secondly, there are too few attempts to reproduce results from published studies, and these efforts are usually impossible to conduct from the details of the research paper alone. The few largescale replication efforts have demonstrated a low replicability rate across science. Thirdly, the current peer review process is not adequately upholding rigorous scientific standards, having downstream effects that waste significant time and money. I'll briefly mention further ways that the current scientific publishing ecosystem is broken, and highlight the critical efforts to modernize scientific products and processes, and to increase transparency in science. My message is simple – the structures and processes of science require immediate and substantial reform. **Financial Support:** National Institutes of Health – Grant Number 5R01MH087214 awarded to Edward Awh and Edward Vogel.

What are Preprints and why We Should Post Preprints? Gillian Currie (University of Edinburgh, UK)

Evidence is incremental, and new research findings need to be shared to allow others to build on these findings. Delays in the dissemination of research findings cause delays in scientific progress. Publishing scientific findings in academic journals is a lengthy process. A pilot study indicated that the median time from approval of an *in vivo* animal study at the University of Edinburgh to submission of the studies' findings to a journal was 756 days [IQR 587-877] and the median time from approval of a study to publication was 987 days [IQR 795-1203]. For these studies, a median of 235 days [IQR 169-348] of this time to publication was taken up at the journal i.e. the time from submission to a journal to final publication. Preprints offer an opportunity to accelerate the dissemination of research findings. Preprints are a version of a scholarly article, at a stage that is ready to submit for publication or is awaiting publication, shared with a public audience. Preprints are submitted to a preprint repository- an online service that allows authors to post their preprints to share openly e.g. bioRxiv is a repository for the life sciences. Most preprint repositories make preprints freely available and open access for no charge. Posting preprints has many benefits for authors including accelerating dissemination of academic findings, facilitating open access, increasing visibility and facilitating collaborations. Preprint repositories are becoming the new location to discover new research and are useful for receiving comments and feedback- leading to higher quality manuscripts. However, research findings published as preprints should be interpreted with care- these manuscripts have not yet been externally peer reviewed. As more funders and journals now require or encourage preprints- preprints are here to stay. In this presentation, I will describe a research improvement project that we are implementing at the University of Edinburgh to increase the use of preprints.

Introducing the Peer Community in Registered Reports. Chris Chambers (Cardiff University, UK)

Registered Reports are a form of empirical publication, offered by over 300 journals, in which study proposals are peer reviewed and pre-accepted before research is undertaken. By deciding which articles are published based on the question, theory, and methods, Registered Reports offer a remedy for a range of reporting and publication biases. As part of this symposium, I will introduce a new platform for supporting Registered Reports called the *Peer Community in Registered Reports* (PCI RR). PCI RR is a non-profit, non-commercial platform that coordinates the peer-reviews of RR preprints (https://rr.peercommunityin.org/about/about). Once the submissions are accepted following peer review (or, in PCI terms, "recommended"), the revised manuscript is posted at the preprint server where the preprint is hosted, and the peer reviews and recommendation of the preprint are posted at the PCI website. PCI RR is also joined by a growing fleet of "PCI RR-friendly" journals that agree to endorse the recommendations of PCI RR without further review. (https://rr.peercommunityin.org/about/pci_rr_friendly_journals), giving the authors the power to choose which journal, if any, will publish their manuscript. By reclaiming control of the peer review process from publishers, PCI RR (and the wider suite of PCIs in different fields) offer a promising avenue for ensuring that Registered Reports are made as open, accessible, and rigorous as possible, while also moving toward a future in which journals themselves become obsolete. **Background**: https://blogs.sussex.ac.uk/psychology/2021/07/26/registered-reports-free-forauthors-and-readers/

Publishing Pharmacology in the Open Science Era. Cilene Lino de Oliveira (UFSC).

This symposium aim to discuss the advantages and challenges to implement open access to scientific knowledge, especially in the field of Pharmacology. Worldwide scientists, scientific societies, research funding organizations and governments are investing resources to disseminate scientific knowledge to society [1][2] [3]. According to the UNESCO recommendations [1], the values of open science are quality and integrity, collective benefit, equity and fairness, diversity and inclusiveness. The principles, among others, include FAIR (**F**indability, **A**ccessibility, **I**nteroperability, and **R**euse of digital assets), [4]. Open scientific knowledge includes open access to scientific publications, which requires infrastructures, engagement of societal actors and open dialogue with other knowledge systems. The challenges to implement open access to scientific knowledge are vast, varies geographically and across disciplines. Panel members with expertise in open science in the fields of psychology (Prof Chris Chambers), meta-research (Dr Gillian Currie), neuroscience (Dr Plinio Casarotto) and pharmacology (Prof Cilene Lino) may bring to pharmacologists insights on how to publish in the open science era. We hope that, this round table will help us to answer questions like these: How are pharmacologists dealing with open access challenges? What are the barriers to implement open access to pharmacological knowledge? Are barriers to pharmacologists geographically specific? [1] UNESCO Recommendation on Open Science: https://en.unesco.org/science-sustainable-future/open-science/recommendation, [2] Plan S: https://www.coalition-s.org/about/, [3] Lattes data: https://lattesdata.cnpq.br/dvn/about/, [4] Fair principles: https://www.go-fair.org/fair-principles/

Brain Disorders Associated with Chronic Diseases: Are Inflammatory Processes a Key Issue?

Two Birds One Stone: The Neuroprotective Effect of Anti-Inflammatory Drugs on Parkinson Disease. Elaine Aparecida Del Bel Belluz Guimarães (USP-RP)

Pharmacologic manipulation of neuroinflammation has been proven to be a promising strategy to alleviate L-DOPA-induced dyskinesia (LID). Recently, our group has demonstrated drugs with anti-inflammatory properties re responsible for alleviating LID in hemiparkinsonian mice and in rat. Here we addressed the hypothesis that L-DOPA-induced dyskinesia (LID) could be reversed by sub-antibiotic doses of the antibiotic doxycycline (Doxy), i.e., doses that present anti-inflammatory actions without acting on bacterial structure. To this aim, we used 6-OHDA-lesioned C57BL/6 hemiparkinsonian mice that present a partial lesion of the nigrostriatal pathway and treated them with L-DOPA (L-DOPA 25 mg/kg + benserazide 10 mg/kg i.p. for 21 days). These animals developed severe axial, limb and orofacial abnormal involuntary movements (AIMs). Following this period, the animals were exposed to doxy (20 or 40 mg/kg s.c.) 30 minutes prior to L-DOPA for 5 days. Sub-chronic treatment with Doxy (20 and 40 mg/kg s.c.) in dyskinetic mice presented a significant effect on reducing the already stablished L-DOPA-induced AIMs without affecting the locomotor activity improved by L-DOPA, as demonstrated by total distance travelled and average speed. Doxy at 40 mg/kg had a more robust effect over AIMs compared to Doxy 20 mg/kg, as in day 5 of treatment, it reduced AIMs by 65%, 20% more than Doxy 20 mg/kg. However, since doxy 20 mg/kg (the lower dose without antibiotic activity) caused a significant decrease of LID, we chose this dose for molecular analysis. After the confirmation of LID attenuation, we performed immunohistochemistry for the glial markers COX-2-immunoreactive cells and ELISA for cytokines TNF-α, IL-1β and IL-6 and for COX-2 metabolite PGE2 in the lesioned dorsal striatum of hemiparkinsonian mice. Molecular analysis revealed that LID decrease was accompanied by the reduction of COX-2 expression and decrease of the cytokines TNF-α and IL-1β and COX-2 metabolite PGE2 in the dorsal striatum of dyskinetic mice. Overall, we conclude that sub-antibiotic doses of doxy are responsible for anti-inflammatory actions that are mandatory for LID attenuation and might

Cognitive Dysfunction Following Viral Infections: Neuroinflammation as a Therapeutic Target. Passos GF[1]; Fontes-Dantas FL[1,2]; Fernandes GG[1]; Araújo SB[1]; De Lima EV[1]; Antonio LS[1]; Araújo HM[1]; Colodeti LC[1]; Romão L[3]; Savio L.E.B.[4]; da Costa R.[1]; Clarke JR[3]; Da Poian AT[5], Alves-Leon SV[1,3]; Figueiredo CP[1]. [1] UFRJ; [2] UERJ; [3] UNIRIO.

Long-lasting cognitive deficits that persist even after the virus has been cleared are among the most debilitating consequences of some viral infections. Persistent cognitive symptoms have been frequently reported following COVID-19, but the underlying mechanisms remain elusive. To address this gap, we infused the spike protein of SARS-CoV-2 into the lateral ventricle of mice in order to establish a model to understand the role of this protein in late cognitive impairment after viral infection. Spike induces no acute effects on animal behavior, but causes late memory impairment, thus recapitulating COVID-19 clinical outcomes. Hippocampal neuroinflammation, synapse loss, and microglial engulfment of presynaptic terminals were detected at later time points after spike infusion. We also found an upregulation of complement system protein (C1q) in the hippocampus, and showed that its blockage prevented memory impairment. Accordingly, TLR4 was found to be upregulated in the hippocampus of mice, and blockage of the receptor rescues memory deficits. We also demonstrated that TLR4 activation is implicated in the increase of serum neurofilament light

chain (NfL) levels induced by spike infusion, a putative biomarker of neurodegeneration and cognitive decline predictor. Similarly, we found extensive synaptic loss and memory dysfunction following infection with the re-emerging arbovirus chikungunya, a phenomenon largely dependent on glial activation and neuroinflammatory responses. Our findings point out neuroinflammation as the chief mediator of cognitive dysfunction following viral infections, and can pave the way to therapeutic strategies. Financial Support: FAPERJ, CAPES, CNPq

Alzheimer's Disease and Depression: What is the Role of Neuroinflammation? Josiane Budni (Programa de Pós-graduação em Ciências da Saúde (PPGCS), UNESC)

Major depression is a prevalent illness that increases the risk of several neurological conditions, including Alzheimer's disease (AD), a neurodegenerative disease characterized by severe cognitive impairment. AD and depression are among the world's most significant public health concerns. The pathophysiological process of both AD and depression involves neuroinflammation. Studies show that stress in the prenatal period can lead to epigenetic changes in fetal microglia. In turn, it can increase susceptibility to neurodegenerative diseases such as AD in adulthood. Therefore, it is possible that proinflammatory cytokines and microglial activation drive brain pathology leading to depression and mild cognitive impairment, which may progress to dementia. Increased activation of microglia and astrocytes, production of proinflammatory cytokines, and reduction of anti-inflammatory molecules are common pathways impaired in dementia and depression. Therefore, we will discuss the role of neuroinflammation in AD and depression to understand this relationship and contribute to new therapeutic strategies. Financial support: UNESC; CNPq; CAPES; FAPESC.

Impact of Type-1 Diabetes mellitus on the Development of Anxiety and Depression: Would Neuroinflammation be a Key Factor? Janaina Menezes Zanoveli (Depto de Farmacologia, UFPR);

Type-1 diabetes *mellitus* (T1DM), which often occurs in childhood, despite having a lower prevalence compared to type 2, is not preventable and requires self-care and attention from the patient throughout his life to avoid several complications or the severity of those complications. Among these, we highlight complications of the Central Nervous System, such as Anxiety and Depression, which have been associated to brain injury evidenced through experimental, clinical, neuroimaging and neuropathological studies. Considering that neuroinflammation has been evidenced in both T1DM and Depression/Anxiety, this presentation will discuss the bidirectional relationship between peripheral and central inflammation, the integrity of the blood-brain barrier and the consequences of the chronicity of this inflammation (even in low-grade) on emotional responses. Furthermore, if neuroinflammation is a key factor in this T1DM and Depression/Anxiety relationship, what would be the rationale for promising more effective treatments? Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnologico.

Sperm Cell Signaling: Therapeutic Opportunities for Male Infertility Treatment and Contraception

Effect of Mitochondrial Uncouplers on Human Sperm Motility. Will M. Skinner[1], Natalie True Petersen[2], Bret Unger[3], Shaogeng Tang[4,5], Emiliano Tabarsi[2,6], Julianna Lamm[2,7], Liza Jalalian[8], James Smith[8], Ambre M. Bertholet[9,10], Ke Xu[3,11,12], Yuriy Kirichok[9], Polina V. Lishko[2,13,*]. [1] Endocrinology Graduate Group, University of California, Berkeley, Berkeley, CA, 94720, [2] Dept of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA, 94720, [3] Dept of Chemistry, University of California, Berkeley, Berkeley, CA, 94720, [4] Dept of Biochemistry, Stanford University School of Medicine, Stanford, CA, 94305, [5] Sarafan ChEM-H, Stanford University, Stanford, CA, 94305, [6] Keck School of Medicine, University of Southern California, Los Angeles, CA, 90033 (Current Affiliation), [7] Dewpoint Therapeutics, Boston, MA, 02210 (Current Affiliation), [8] Dept of Urology, University of California, San Francisco, San Francisco, California, 94158, [9] Dept of Physiology, University of California San Francisco, San Francisco, CA, 94158, [10] Dept of Physiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, 90095 (Current affiliation), [11] California Institute for Quantitative Biosciences, University of California, Berkeley, CA, 94720, [12] Chan Zuckerberg Biohub, San Francisco, CA, 94158, [13] Center for Reproductive Longevity and Equality, Buck Institute for Research on Aging, Novato, CA, 94945, *Corresponding Author: Polina V. Lishko

Sperm motility is necessary for successful fertilization, but there remains controversy about whether human sperm motility is primarily powered by glycolysis or oxidative phosphorylation. To evaluate the plausibility of reducing human sperm mitochondrial ATP production as an avenue for contraceptive development, we treated human sperm with small-molecule mitochondrial uncouplers, which reduce mitochondrial membrane potential by inducing passive proton flow, and evaluated the effects on a variety of physiological processes that are critical for fertilization. We also sought to clarify the subcellular localization of Adenosine Nucleotide Translocator 4 (ANT4), a gamete-specific protein that has been suggested as a contraceptive target. We determined that ANT4 is mitochondrially localized, that induced mitochondrial uncoupling can be partially mediated by the ANT family, and that several small molecule uncouplers significantly decreased sperm

progressive motility. However, these uncouplers did not reduce sperm ATP content or impair other physiological processes, implying that human sperm can rely on glycolysis for ATP production in the absence of functional mitochondria. Thus, since certain mitochondrial uncouplers impair motility through ATP-independent mechanisms, they could be useful ingredients in on-demand, vaginally-applied contraceptives. However, systemically delivered contraceptives that target sperm mitochondria to reduce their ATP production would need to be paired with sperm-specific glycolysis inhibitors. Current support: NIH/NIA R03 AG-7-755-01 (multi-PI: Lishko, Garrison) and Pew Charitable Trusts

Understanding the Molecular Mechanisms Responsible for Age-Dependent Decline in Spermatozoa Quality. Joana Santiago[1], Joana Vieira Silva[1], Manuel A S Santos[1], Margarida Fardilha[1] [1]Institute of Biomedicine – iBiMED, Dept of Medical Sciences, University of Aveiro

Male fertility is strongly affected by environment and lifestyle. Advanced paternal age has been linked with changes in testicular structure and function, impaired semen parameters and DNA integrity, lower pregnancy rates and decline in offspring fitness. The sperm quality decline with ageing has also been associated with an increase in oxidative stress. However, the molecular mechanisms responsible for age-dependent decline in sperm quality are not fully understood. As such I will present the work that is being performed in our lab aimed to study the ageing-related alterations in human signaling pathways, sperm protein and small RNA content possibly responsible for the age-associated decline in male fertility. To that end we first evaluated the impact of ageing on human spermatozoa signaling pathways, including the mitogen-activated protein kinases (MAPKs), the mechanistic target of rapamycin (mTOR), and the apoptosis signaling pathways. Given the heterogeneous nature of the ejaculate in terms of sperm integrity/functionality, two distinct spermatozoa populations were analyzed: total spermatozoa fractions and highly motile/viable fractions. Additionally, we determined whether age thresholds for the signaling proteins examined existed. An interaction network of the sperm proteins associated with male age was constructed and analyzed. Second, we analyzed the proteome of 19 normozoospermic human sperm samples divided into four groups according to men's age was evaluated by quantitative proteomic analysis. The small RNA content of 16 human sperm samples was investigated using small RNA sequencing. Our data showed no correlation between paternal age (mean age 35.2 ± 6.32 years) and the seminal parameters examined. Proteomic analysis revealed 46 differentially expressed proteins (DEPs) between groups. Gene ontology analysis of all deregulated sperm proteins shown that response to unfolded protein, positive regulation of mitochondrion organization and apoptotic process, negative regulation of phosphoprotein phosphatase activity, and spermatogenesis are common biological processes affected. Transcriptomic analysis identified 5 differentially expressed miRNAs (DEMs) between groups. The DEPs, DEMs and signaling pathways here identified could help to elucidate and/or became potential diagnostic markers for age-associated decline in human sperm quality.

CRISP proteins as novel targets for male fertility regulation. Patricia S. Cuasnicú (IBYME-Conicet, Argentina)

There is a need to develop new family planning methods that meet the different needs and preferences of people. Whereas women have several options, men only have condoms, indicating the need to develop new male contraceptive methods that promote the participation of men in family planning. In this regard, the epididymis is an excellent contraceptive target since it is not involved in sperm or hormone production but specifically in the acquisition of sperm fertilizing ability during maturation. Based on this, one of the main objectives of our group has been to investigate the relevance of epididymal proteins for fertility and their potential use for non-hormonal male contraception. Our studies were carried out using the CRISP (Cysteine-Rich Secretory Proteins) family of proteins as experimental model. Results showed that epididymal protein CRISP1 is a clear mediator of the fertilization process, participating in different stages of gamete interaction through complementary sites in the oocyte. Furthermore, immunization experiments with CRISP1 revealed that this protein is capable of producing an immune response and a significant decrease in male fertility, representing a strong proof of concept in favor of CRISP1 as a contraceptive candidate. Despite these observations, the knockout (KO) animal for epididymal CRISP1 generated in our laboratory was fertile, suggesting the existence of compensatory mechanisms between family members. Subsequent results showed that a double KO (DKO) animal lacking both epididymal CRISP1 and CRISP4 simultaneously, exhibited a significant decrease in male fertility, confirming the relevance of CRISP for male fertility and the existence of functional compensation between homologous proteins. In addition to its role in gamete interaction, CRISP1 also exhibits the ability to inhibit CatSper, the main sperm calcium channel essential for male fertility, constituting the first natural regulator of CatSper. In view of this, our laboratory is currently investigating different immunological and pharmacological approaches to block the role of CRISP1 and CRISP4 in gamete interaction and CatSper regulation. We believe these studies will contribute not only to the development of

new and better male contraceptive methods but also to a better understanding, diagnosis and treatment of human infertility.

Pharmacological Opportunities in the Tumor Microenvironment

Delineating the Role of BRCA1 in the Mammary Gland and the Therapeutic Strategies It Reveals. Nicholas Bassani[a], Alfeu Zanotto-Filho[a,b] and Alexander J. Bishop[a] [a] Greehey Children's Cancer Research Institute, Dept of Cell Systems and Anatomy, UT Health San Antonio, San Antonio, Texas, 78339, USA [b] Lab de Farmacologia e Bioquímica do Câncer, Depto de Farmacologia, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, 88040-900, Brazil

BRCA1 is a ubiquitously expressed gene with patients who carry a BRCA1 mutation predisposed to develop triple negative breast cancer. On a molecular level, BRCA1 is best understood to promote repair of DNA double strand breaks by homologous recombination (HR). HR is a repair process utilized by all proliferating cells, which adds to the confusion as to why BRCA1 mutation would lead to a particular predisposition to breast cancer. Indication is for a specific role for BRCA1 in the mammary gland. Interestingly, conditional loss of BRCA1 in mice leads to an altered distribution of cell types in the mammary gland during pregnancy with increased luminal progenitors and reduced epithelial cell markers. As a consequence of the reduced lobular-alveolar development and ductal structure formation BRCA1 deficient glands produce less milk, something also observed in BRCA1 patients. Importantly, BRCA1 is involved in numerous complexes with different protein partners related to different functions. Considering this, we explored another BRCA1 protein partner, NRF2. NRF2 protein levels are tightly regulated by KEAP1, which binds the DLG and ETGE motifs within NRF2, targeting NRF2 for degradation. Interestingly, BRCA1 also binds the ETGE motif, helping augment NRF2 stability and transcriptional activity; in the absence of BRCA1, NRF2 transcriptional responses are muted. Importantly, NRF2 interacts with the BRCT repeats of BRCA1, potentially competing with BRCA1 interactions that promote HR activity. We therefore set out to explore NRF2 and BRCA1 in the normal mammary gland, to determine the functional relationship between these proteins in that context, and whether these interactions can be utilized therapeutically to promote an effective HR defect to increase PARP1 inhibitor sensitivity. Financial Support: Basser Foundation Grant to AJB and BCRP Postdoctoral Fellowship Award [CDMRP; W81XWH-14-1-0026] to AZF.

Adenosinergic signaling as a key component of cancer-related immunosuppression. **Elizandra Braganhol, PhD - Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA**.

Glioblastomas (GBs) are brain tumors extremely aggressive and devastating. CD73 is the limiting enzyme in the production of adenosine in the extracellular space and it is overexpressed by tumor cells. Adenosine mediates a variety of effects that promote tumor growth, angiogenesis, metastasis, escape from immune surveillance, and chemoresistance. Therefore, CD73 blockage could be a strategy to prevent adenosine-mediated protumor actions. Here, we validated the CD73 as a therapeutic target for GBs. Initially, downregulation of CD73 expression and activity decreased GB cell migration, invasion, chemoresistance, and proliferation. In addition, CD73 knockdown impaired *in vivo* GB progression by reducing tumor size by 40-45%. After proving the potential of CD73 as a target, a nanotechnological approach was developed aiming CD73-siRNA nasal delivery (NE-CD73 siRNA). *In vitro* studies have demonstrated that the NECD73 siRNA was efficiently internalized by GB cells, resulting in decreased AMPase activity and cell viability. Following nasal administration, the complexes were detected in the brain and selectively reduced *in vivo* tumor size by 60%. The formulation had no synergistic or additive effect when administered in combination with the standard gold agent temozolomide, but it is important to note that it had a superior effect when compared to the classic chemotherapeutic agent. In addition, the CD73 blockade was effective in controlling infiltration of classic inhibitory immune cells involved in GB progression, including macrophages and T lymphocytes. In conclusion, this investigation demonstrates the potentialities of nasaladministered NE-CD73 siRNA as an innovative strategy for GB therapy. Financial support: FAPERGS, Capes, CNPq

Targeting Mutant p53 Protein Gain-of-Function in Cancer: Role of Cytokines and Tumor Microenvironment. Raquel Nascimento das Neves, Alfeu Zanotto-Filho_Dept of Pharmacology, Universidade Federal de Santa Catarina, Florianopolis, SC, Brazil.

TP53 is the most frequently mutated gene in most types of human cancer. In particular, triple-negative breast cancer (TNBC) shows TP53 mutation in approximately 80% of patients. Unlike hormone-dependent breast cancers, TNBC currently lack an approved highly effective targeted therapy. Notably, most TNBC acquires TP53 mutations, which, in addition to the loss of canonical p53 functions, can result in gain-of-function (GOF), activating different cellular mechanisms involved in cancer progression. Here, we show that mutant p53 promotes malignant phenotypes in TNBC cells, in particular their inflammatory profile. Small interfering RNA-

mediated depletion of mutant p53 had minor impact on the cell viability, while it impaired cell invasion and migration of MDA-MB231 and Hs578t cells. RNA sequencing and protein analysis by ELISA and immunoblot in MDA-MB231 cells revealed that mutant p53 knockdown decreases expression of several constitutively expressed pro-inflammatory cytokines such as IL8, IL6 and CXCL2, with none effect upon DNA damage response gene sets (NRF2 and Endoplasmic reticulum stress) or genes typically regulated by wild-type p53. RNA sequencing also indicated genes known to be involved in breast cancer cells malignance, such as COX-2 and MMP1, which were not affected by p53 knockdown but were regulated by constitutively active ERK1/2 MAPK pathway in TNBC. Combined mutant p53 knockdown with ERK1/2 pathway inhibitors (UO126, sorafenib) caused a more pronounced IL8 and IL6 depletion when compared to either p53 knockdown or UO126/sorafenib alone, whereas MMP1 and PGE2 levels were only dependent upon MEK/ERK1/2. Mutant p53 GOF and ERK1/2 also exert an upstream control of NFkappaB and AP-1 transcription factors, both associated with expression of secretome genes. Moreover, concomitant inhibition of mutant p53 and MEK/ERK1/2 reduces cell proliferation, invasion, and migration, indicating that mutant p53 cooperates with ERK1/2 signaling pathway to promote secretome production and malignant phenotypes in TNBC cell models. Funding: DOD-CDMRP Breast Cancer Research Program (W81XWH-14-1-0026), FAPESC (2021TR000310).

Metabolic Diseases and Inflammation: Impacts on Co-morbidities

Enteric Glia Regulate Intestinal Neuroinflammation and Neuroplasticity Following Inflammation. Brian D. Gulbransen, PhD, Michigan State University, Dept of Physiology, Neuroscience Program, East Lansing, MI, USA
Enteric glia are a unique type of peripheral glia that accompany enteric neuron cell bodies and nerve fibers in the digestive tract. Enteric glia fulfil diverse functions related to maintaining homeostasis in the enteric nervous system (ENS) which include supporting neuronal function and survival, regulating immune cell phenotype, and influencing epithelial function. In health, bi-directional communication between enteric neurons and glia functions to refine enteric motor neurocircuits. Enteric glia sense neurotransmitters and exhibit activity in the form of intracellular calcium responses. Subpopulations of enteric glia are associated with specific neural pathways in the ENS and exhibit circuit-specific responses. Glial activity encoded by calcium responses evokes transmitter release through glial membrane channels composed of connexin-43. Gliotransmitters affect activity in specific neural circuits and set the tone of neurotransmission in the ENS. In disease, enteric glia sense and produce mediators of inflammation and play a key role in driving neuroinflammation in the ENS. Glial activation during acute inflammatory responses leads to enteric neurodegeneration and contributes to long-lasting hypersensitivity in enteric and sensory neurons that innervate the intestine. Enteric glia also interact with cells of the innate and adaptive branches of the immune system which influence inflammatory and defensive responses of the intestine. Together, multiple lines of evidence show that enteric glia play an important role in regulating intestinal motor function and inflammatory processes in the intestine. These roles highlight enteric glia as a pivotal cells type in processes related to gastrointestinal motility disorders, disorders of gut-brain interaction, and gastrointestinal inflammation. Financial Support: BDG receives support from grants R01DK103723 and R01DK120862 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and grant P01HL152951 from the National Heart, Lung, and Blood Institute.

Metabolic syndrome and neuroinflammation: A role for TLR4? Nathalie Obadia, Vanessa Estato e Hugo C. Castro Faria Neto (Fiocruz)
Background: Metabolic syndrome (MS) is defined as a low-grade proinflammatory state in which abnormal metabolic and cardiovascular factors increase the risk of developing cardiovascular disease and neuroinflammation. Events, such as the accumulation of visceral adipose tissue, increased plasma concentrations of free fatty acids, tissue hypoxia, and sympathetic hyperactivity in MS may contribute to the direct or indirect activation of Toll-like receptors (TLRs), specifically TLR4, which is thought to be a major component of this syndrome. Activation of the innate immune response via TLR4 may contribute to this state of chronic inflammation and may be related to the neuroinflammation and neurodegeneration observed in MS. In this study, we investigated the role of TLR4 in the brain microcirculation and in the cognitive performance of high-fat diet (HFD)-induced MS mice. Methods: Wild-type (C3H/He) and TLR4 mutant (C3H/HeJ) mice were maintained under a normal diet (ND) or a HFD for 24 weeks. Intravital video-microscopy was used to investigate the functional capillary density, endothelial function, and endothelial-leukocyte interactions in the brain microcirculation. Plasma concentrations of monocyte chemoattractant protein-1 (MCP-1), adipokines and metabolic hormones were measured with a multiplex immunoassay. Brain postsynaptic density protein-95 and synaptophysin were evaluated by western blotting; astrocytic coverage of the vessels, microglial activation and structural capillary density were evaluated by immunohistochemistry.

Results: The HFD-induced MS model leads to metabolic, hemodynamic, and microcirculatory alterations, as evidenced by capillary rarefaction, increased rolling and leukocyte adhesion in postcapillary venules, endothelial dysfunction, and less coverage of astrocytes in the vessels, which are directly related to cognitive decline and neuroinflammation. The same model of MS reproduced in mice deficient for TLR4 because of a genetic mutation does not generate such changes. Furthermore, the comparison of wild-type mice fed a HFD and a normolipid diet revealed differences in inflammation in the cerebral microcirculation, possibly related to lower TLR4 activation. Conclusions: Our results demonstrate that TLR4 is involved in the microvascular dysfunction and neuroinflammation associated with HFD-induced MS and possibly has a causal role in the development of cognitive decline.

Role of Inflammatory proteins in Vascular Dysfunction

Resolution of Inflammation as a Novel Approach for Vascular Damage in Hypertension. Ana Maria Briones, Universidad Autónoma de Madrid, Instituto de Investigación Hospital La Paz, Ciber Cardiovascular

Inflammation is a typical feature of many cardiovascular diseases such as atherosclerosis, aneurysms, obesity or hypertension. In hypertension, excessive inflammation from innate and adaptative immune systems associated with elevated levels of local and circulating proinflammatory cytokines and oxidative stress, plays a key role in endothelial dysfunction, vascular remodeling and augmented vascular stiffness associated to this pathology. Excessive inflammation can result from elevated cytokines production, but unresolved or inefficient resolution of inflammation might also contribute to the augmented inflammatory milieu found in the vasculature in different cardiovascular diseases. Resolution of inflammation is mediated by a family of specialized pro-resolving mediators (lipoxins, resolvins, protectins, maresins), that limit immune cell infiltration and initiate tissue repair mechanisms. In my talk, I will show our latest advances on the potential beneficial effects of boosting resolution of inflammation as a new therapeutic approach for the treatment of hypertension and its associated vascular alterations. Funding: PID2020-116498RB-I00, MSCA-ITN-EJD GA 954798

Role of HIV-Derived Viral Proteins in the Development of Endothelial Dysfunction and Hypertension. Eric J. Belin de Chantemèle (Augusta University, USA)

Thanks to the onset of combination antiretroviral therapy (cART), patients living with HIV (PLWH) live longer but experience accelerated rates of hypertension. However, the etiology and individual contributions of repressed viral infection and cART to HIV-associated hypertension remains illdefined. Despite cART treatment, PLWH exhibit detectable circulating levels of viral proteins leading us to hypothesize that HIV-associated hypertension is immune regulated and exhibits sex differences. To examine the individual contribution of repressed viral infection, we took advantage of a transgenic model (Tg26) to investigate the contribution of HIV viral proteins to chronic inflammation and hypertension. A preliminary cytokine panel looking at 15 different cytokines found an increase in TNFα in male mice ($P<0.05$). Blood pressure (BP) measurements via radiotelemetry revealed increased mean arterial pressure (MAP: male: WT=112.3±1.3 vs Tg26=121.9±4.0 mmHg/ female: WT=110.6±3.01/ Tg26=120.3±6.9 mmHg) and heart rate ($P<0.05$) with preservation of diurnal variation in both sexes. Treatment with the TNFα inhibitor, etanercept, restored BP in Tg26 males only, reflecting the cytokine panel. Further investigation into vascular reactivity revealed endothelium-dependent dysfunction in both conduit and resistance vessels ($P<0.05$) with no impairment in vascular contractility in either sex. To test the contribution of immune cell derived viral proteins to cardiovascular disease, WT and Tg26 mice were submitted to bone marrow transplant (BMT) and vascular reactivity was assessed in resistance and conduit vessels. Tg26->WT BMT impaired endothelial relaxation ($p<0.05$), while WT->Tg26 BMT remarkably reversed the phenotype, suggesting a clear role of BM derived immune cells in the observed endothelial dysfunction. Investigation of immune cell subtypes led us to co-culture WT thoracic aortas in media of Tg26 Tcells, the primary target of HIV, for 16 hours which impaired endothelial relaxation when compared to aortas incubated in WT media. A cytokine panel of the media revealed a modest increase in TNFα levels ($P=0.16$) suggesting Tcells are a contributor to both impaired endothelium and increased TNFα. Further investigation into the source of endothelial dysfunction led us to investigate oxidative stress and the contribution of NADPH oxidases (NOX) and found only an increase in NOX1 expression in male ($P<0.05$) mice and a trend in females ($P=0.06$) when compared with NOX2 and NOX4. Additionally, an increase in NOX1 expression was found in Tg26->WT BMT in males ($P=0.06$) and females ($P<0.05$) which was restored to WT levels in WT->Tg26 BMT male mice. Inhibition of NOX1 utilizing the selective NOX1 inhibitor, GKT771, restored endothelial relaxation in Tg26->WT BMT in both vessel types and sexes showing a clear role of NOX1 in the observed endothelial impairment. Collectively, these data indicate that HIV-related hypertension involves

immune regulated NOX1-dependent endothelial dysfunction in both sexes but TNFα-dependent mechanisms in males only providing evidence of sex specific mechanisms.

CCL5/CCR5 Interaction on the Vascular Diseases. Thiago Bruder do Nascimento, Dept of Pediatrics and Vascular Medicine Institute (VMI) at University of Pittsburgh

Chemokines are small chemotactic cytokines that assist leukocytes locate specific targets by binding to receptors positioned at the target cell surface. Compelling evidence places chemokines and their receptors as key regulators of several cardiovascular diseases. Among the chemokine family, chemokine (C-C motif) receptor 5 (CCR5) and its main ligand (C-C motif) ligand 5 (CCL5 or RANTES) have been abundantly studied in infectious diseases due to their participation as co-receptors for pathogens in immune cells, however compelling evidence suggests that CCR5 have a particular role on the genesis and progression of cardiovascular disease. We recently demonstrated that NADPH oxidase 1 (Nox1)-derived reactive oxygen species (ROS) regulate CCR5 expression in a mouse model of acquired lipodystrophy, which in turn, modulates the endothelial function and vascular inflammation. Particularly for this symposium, we will present our more recent findings where we are describing a positive feedback between CCL5/CCR5, and Nox1-derived ROS, which can contribute to vascular damage. We basically found that CCL5 binds to CCR5 in vascular smooth muscle cells (VSMC) activating Nox1 and leading to VSMC proliferation and migration and vascular remodeling. For this study, we treated Rat Aortic Vascular Smooth Muscle Cells (RASMC) with recombinant CCL5 (rCCL5) and observed that CCL5 increases Nox1 expression and activity, which are blocked by antagonizing the CCR5 with maraviroc. Furthermore, we found that Nox1 inhibition blunts CCL5-induced RASMC proliferation and migration, as well as NFkB and ERk1/2 activation. Finally, we observed that treatment with maraviroc *in vivo* attenuates carotid ligation-induced vascular injury. Summarizing, our data indicate that CCL5 activates Nox1 in the vasculature, leading to vascular injury likely via NFkB and Erk1/2. Herein, we place CCR5 antagonists and/or Nox1 inhibitors as preeminent antiproliferative compounds to reduce the cardiovascular risk associated with medical procedures and vascular diseases associated with vascular hyperproliferation. Funding: NHLBI-(R00HL14013903), AHA-(CDA857268), VMI, and University of Pittsburgh Medical Center

Novel Pharmacological Approaches for the Treatment and/or Prevention of Schizophrenia

Peripubertal intervention as a preventive measure for the transition to a schizophrenia phenotype in developmental disruption models of the disorder. Anthony A. Grace, Felipe V. Gomes, Daniela L. Uliana, Xiyu Zhu. Departments of Neuroscience, Psychiatry and Psychology, University of Pittsburgh Pittsburgh, PA 15217 USA

Gestational treatment of pregnant rats with the developmental mitotoxin methylazoxymethanol acetate (MAM) yields offspring that, as adults, display disruptions in sensory gating, executive function, and affect along with hippocampal hyperactivity, parvalbumin neuron loss, and an overactive dopamine system, consistent with schizophrenia in humans. Patients at risk for schizophrenia that show increased anxiety in the premorbid state are more likely to transition to schizophrenia later in life. In our studies, we found that MAM-treated rats exhibit increased anxiety, increased response to stressors, and basolateral amygdala hyperactivity during the prepubertal period prior to the emergence of dopamine hyperactivity. If stress plays a role in the developmental etiology of schizophrenia, treating stress early may prevent the transition to psychosis in adults. Treating the anxiety for 10 days prepubertally with either the antianxiety agent diazepam or pomaglumetad, or with 20 days of environmental enrichment, circumvents the transition to a psychosis-like state as adults. If prepubertal stress plays a role in the emergence of pathology in the adult, this suggests that environmental stressors prepubertally should elicit the same pathology. Indeed, combined footshock and restraint stress 10 days prepubertally yielded the same pathology in adults as MAM treatment. In addition, lesion of the prelimbic prefrontal cortical regulation of the amygdala stress response in normal rats caused footshock alone to produce the adult pathology. These data suggest that predisposition to schizophrenia is due to responsivity to prepubertal stress-induced hippocampal damage, and that substantial stress, such as childhood trauma, would cause individuals to be more susceptible to the emergence of schizophrenia. Supported by USPHS MH57440. AAG received funds from the following organizations: Lundbeck, Pfizer, Otsuka, Asubio, Autofony, Janssen, Alkermes, SynAgile, Merck and Newron.

Studying adolescent stress in the search for new drugs to treat schizophrenia. Felipe V. Gomes[1], Andreza M. Cavichioli[1], Thamyris Santos-Silva[1], Francisco S. Guimarães[1], Anthony A. Grace[2] [1]Dept of Pharmacology, Ribeirao Preto Medical School, University of Sao Paulo, Brazil, [2]Departments of Neuroscience, Psychiatry and Psychology, University of Pittsburgh, USA

Stress during adolescence acts as a major risk factor for the development of psychiatric disorders later in life, including schizophrenia. We previously found that adolescent stress caused, in adulthood, behavioral changes,

hippocampal hyperactivity, and dopamine system activity overdrive consistent with schizophrenia. All these changes were associated with a functional loss of parvalbumin interneurons in the ventral hippocampus which leads to a dysregulation of the excitatory-inhibitory (E/I) balance. Therefore, drugs targeting the modulation of the (E/I) have the potential to attenuate schizophrenia-related changes. We found that levetiracetam, an antiepileptic drug, that is posited to ameliorate deficits in the E/I balance by regulating the release of neurotransmitters, including glutamate, via the inhibition of SV2A and modulating the activity of parvalbumin interneurons via Kv3.1 channels, attenuated schizophrenia-related changes caused by adolescent stress. Also, redox dysregulation is proposed as a common mechanism associated with the functional loss of parvalbumin interneurons in schizophrenia. We found that adolescent increases the levels of oxidative stress markers in the ventral hippocampus along with mitochondrial dysfunction. We will present findings indicating that targeting redox dysregulation after stress may attenuate deficits in parvalbumin interneurons and, consequently, the emergence of schizophrenia-related changes. Overall, in this talk, we will discuss potential targets to prevent the emergence of schizophrenia or treat it when the pathology is already established by using a rodent model based on adolescent stress exposure. Supported by FAPESP (18/17597-3; 20/04241-6), CNPq (303137/2021-5), and CAPES.

MMP9/RAGE Mechanism as a Promising Target for Early Intervention in Early Psychosis Patients: A Translational Study. Daniella Dwir[1], Jan-Harry Cabungcal[1], Lijing Xin[2], Basilio Giangreco[1], Enea Parietti[1], Martine Cleusix[1,3], Raoul Jenni[1,3], Paul Klauser[1,3], Philippe Conus[3], Michel Cuénod[1], Pascal Steullet[1], Kim Q. Do[1] [1]Center for Psychiatric Neuroscience, Dept of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland, [2]Animal Imaging and Technology Core (AIT), Center for Biomedical Imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [3]Service of General Psychiatry, Dept of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland.

A hallmark of schizophrenia (SZ) is a dysfunction of parvalbumin-expressing fast-spiking interneurons (PVI), which are essential for neuronal synchrony during sensory/cognitive processing. Oxidative stress (OxS) and inflammation during early brain development, as observed in SZ, lead to impaired cortical circuitry, specifically the PVI and the perineuronal nets (PNN). In a translational approach both in an animal model and in early psychosis patients (EPP), we aimed (1) to identify a precise mechanism, leading to PVI/PNN impairments, and (2) to interfere with the proposed mechanism by using the antioxidant N-acetyl-cysteine (NAC) and environmental enrichment (EE) to rescue PVI maturation. This study was conducted on a transgenic mouse model of GSH deficit (GCLM KO) with SZ related phenotype and on EPP from a well-characterized cohort. Mice were treated with a dopamine reuptake inhibitor (GBR), to mimic a social stress and induce an additional oxidative challenge, at postnatal day (P)10-20, followed by NAC/EE during juvenile/adolescent period. EPP were enrolled in a double-blind, randomized, placebo-controlled clinical trial of NAC supplementation for 6-months. We identified during peripubertal stage of GCLM KO a vicious cycle of processes involving activation of MMP9 by OxS, leading to RAGE shedding, which maintain neuroinflammation and OxS, inducing long-term impairment of PVI. These long-lasting effects were completely reversed by the NAC/EE. This recovery is mediated by NAC, via the inhibition of OxS-induced MMP9/RAGE, as it interrupts the deleterious feedforward mechanism, allowing PVI/PNN maturation. The decreased fast-rhythmic oscillations, reflecting PVI neuronal synchronization, in the GCLM KO were recovered by NAC/EE. 6-month NAC treatment decreased RAGE shedding in EPP plasma, in association with increased prefrontal GABA, improvement of cognition/clinical symptoms, suggesting similar neuroprotective mechanisms. MMP9/RAGE pathway represents a key regulatory mechanism by which OxS interacts with neuroinflammation. The long-lasting effects on PVI/PNN can be reversed by a combined NAC/EE. In analogy, patients carrying genetic risks to redox dysregulation potentially vulnerable to early-life insults could benefit from a combined pharmacological and psycho-social therapy. Our findings highlight the MMP9/RAGE pathway as a promising target for novel drug development in psychiatry. Financial support: This work was supported by the National Center of Competence in Research (NCCR): The Synaptic Bases of Mental Diseases (SYNAPSY) (n°51AU40_125759). Daniella Dwir is supported by the “Adrian et Simone Frutiger” foundation.

UFSC Graduate Program in Pharmacology 30th Anniversary: Insights from Former SBFTE Presidents

Recollections on our adventures to put UFSC’s Pharmacology Department and Graduate Studies Program on the National map. Giles Alexander Rae, retired Professor of the Dept of Pharmacology, CCB, Universidade Federal de Santa Catarina, Florianopolis, SC, Brazil.

This presentation intends to provide insights into how a very small group of young pharmacologists came together in the mid-to-late70’s, at the UFSC in Florianopolis, to actively engage in building an eclectic productive Pharmacological research group. The story will include the difficulties and challenges we had to

overcome to reach the criteria for approval from CAPES to initiate our Graduate Studies Program in late 1992, how it evolved to initiate Doctorate Studies in 1997, and also how it became one of the top programs in Brazilian Pharmacology. Since the early days, the team of researchers expanded considerably, the scientific output as reflected by its publications even more so, and the number of graduate students of the program over the last 30 years has surpassed the 200 mark. In the process, the group contributes significantly to strengthening the Brazilian Society of Pharmacology and Experimental Therapeutics, with three of us, myself included, taking on the responsibility of presiding over the society for several years. Looking back on this collective experience is not only gratifying to me, but also puts into perspective how Pharmacology has changed over the last several decades of my lifetime as a pharmacologist, and hints on the many challenges facing the future of Pharmacology at UFSC, in Brazil and globally.

A Journey in Science. Jamil Assreuy (UFSC)
In this brief talk, I will present some relevant turning points that led me to work in science and specifically in Pharmacology, the importance of the Graduate Program in Pharmacology in shaping my career and the privilege of being a President of SBFTE. In addition, I will comment briefly on the importance of Science and Education as tools for enlightenment and development.

New Trends in Pharmacology Research and Teaching at the Graduate Level

The BPS eLearning Platform and our New Experimental Design Resources. Prof Clare Stanford (Pharmacologist, HonFBPhS) University College London. Dr Simon Bate (Statistician) Author of InVivoStat and The design and statistical analysis of animal experimental. Dr Jude Hall (Educationalist, FBPhS) Kings College London. Lee Page (Project Manager) British Pharmacological Society.
In 2017, the British Pharmacological Society launched a curriculum for the use of research animals, this provided a set of core and experiential learning outcomes relevant to undergraduates and taught masters on any bioscience degree programme. This curriculum provides a framework for local institutions to design their own programmes. We are aware that bioscience degree programmes align to local strengths. Therefore, the aim of this eLearning project is to invest in a series of freely available online resources to support bioscience students/educators on the topic of experimental design and statistical analysis. These resources can be used by any learner and will contribute to a higher degree of consistency in experience on the topic of experimental design. The aim is to offer blended learning tools that will complement teaching in the classroom without excessively increasing student/educator time burden. *Financial support*: Staff time and the animation video production for this eLearning resource was charitably funded by the British Pharmacological Society.

Novel Insights in Psychopharmacology: A Tribute to Prof. Reinaldo Takahashi

The young pharmacologist Reinaldo Naoto Takahashi came from São Paulo State together with some colleagues in the mid-to-late70's, at the UFSC in Florianopolis, to actively engage in building a productive Pharmacological research group. Over the last 30 years, Professor Takahashi contributed in the academic formation of more than one hundred of students (scientific initiation, master, PhD and pos-doc). The Takahashi research group provided pioneering scientific contributions in diverse fields of Psychopharmacology area, including insights about the neurobiology and pharmacological targets for the treatment of drug addiction, psychiatric disorders and neurodegenerative diseases. Therefore, this online symposium is a tribute to Professor Reinaldo Takahashi with the aim to highlight some scientific contributions of Lab of Psychopharmacology UFSC focusing on the role of stress on drug addiction, the pharmacological properties of cannabinoids and early events on Parkinson's disease. Translational implications will also be discussed.
The "Stress Side" of addiction: beyond reward Leandro Franco Vendruscolo Neurobiology of Addiction Section, Integrative Neuroscience Research Branch, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD, USA
Substance use disorder is a major public health issue worldwide. Initially, the drug may be consumed for its rewarding effects (i.e., drug intake for pleasure). However, as drug addiction progresses, stress systems become sensitized, and this sensitization mediates negative emotional states during drug withdrawal. We hypothesize that negative emotional states drive compulsive drug taking and seeking via negative reinforcement (i.e., drug intake for stress relief). In this presentation, hormonal and neurotransmitter systems that are dysregulated in drug dependence will be discussed, with an emphasis on the "stress side" of addiction. Translational implications will also be discussed.

Phytocannabinoids to the Treatment of addictive Behaviors: Preclinical Evidence. Cristiane Ribeiro de Carvalho (UFSC)

Previous studies from Takahashi's lab provide preclinical insights of phytocannabinoid on disrupting maladaptive drug memories, which may trigger a relapse. Since cannabidiol, a non-psychotomimetic constituent of Cannabis impairs the reconsolidation of associative drug memories in rats. Compulsive behavior is also a critical component of addictive behaviors and plays a crucial role in the physiopathology of some eating disorders. β-caryophyllene, a cannabinoid receptor CB2 agonist, decreases the incentive salience performance ("wanting") for palatable food and attenuates chocolate-induced place preference in mice. These findings suggest that phytocannabinoids have a potential therapeutic value in disrupting the long-lasting memories that can trigger drug relapse and may be helpful to treat compulsive eating disorders.

Helping to Build the Brazilian Cannabis Market "from Scratch": Where Science and Entrepreneurship Meets. Fabrício Alano Pamplona (Entourage Phytolab)

When someone leaves academia, the feeling is somewhere between "awe and fear": there is so much out there VS. what do I do now? Truth is that academia never leaves you and scientific skills often translate to other contexts, and one suddenly realizes that all scientific training was not in vain. Here I'll tell a story on how being a scientist helped me to engage into the first steps in the private sector and entrepreneurship. Ultimately, the scientist-entrepreneur is a duality of my career where the skillset blends into unique abilities to create businesses out of challenging scientific questions turned into real world solutions. I'll exemplify the topic using my experience as former Director of Entourage Phytolab, a pioneer startup in the field of Cannabis-based medicine in Brazil.

Insights on Parkinson's Disease Research: From Olfactory Vector Hypothesis to Neuroprotection Challenges. Rui Daniel Prediger (UFSC)

Parkinson's disease (PD), the second most common neurodegenerative disease, is a multisystem disorder clinically diagnosed by the motor symptoms related to dopaminergic neurodegeneration in the nigrostriatal pathway. However, nowadays PD is no longer considered a pure motor and dopaminergic disease. The presence of smell loss and the pathological involvement of olfactory pathways and different brain areas in the early stages of PD are in accord with the tenants of the olfactory vector hypothesis. According to it, the nose has a propitious anatomy for the transfer of environmental xenobiotics (viruses, toxins, agricultural chemicals and metals) into the brain, subsequently inducing damage to central brain structures associated with PD. In presentation, we provide an overview of the main behavioral and neurochemical findings provided by the Experimental Lab of Neurodegenerative Diseases (LEXDON, UFSC) over the last 15 years using preclinical models of PD in which toxicants have been introduced into the nose. These results indicate the intranasal administration of different xenobiotics (mainly the neurotoxin MPTP) as a valuable approach to understand PD pathogenesis and the development of translational research looking for the development of new treatments for PD.

Pharmacological and Non-Pharmacological Approaches for Modulating Aging, Age-Related Diseases, and Longevity

Role of Genistein in Alzheimer's Disease Therapeutics: From Molecular Mechanisms to Clinical Trials. Jose Vina and Consuelo Borrás, Dpt. Physiology. Fac. Medicine. University of Valencia, Valencia. Spain

In Alzheimer's disease therapeutics, brain damage, start well before the onset of clinical symptoms. The lag period may be one or even two decades. On the other hand, Alzheimer's pathology is so serious that it involves not only one mechanism, but a series of molecular mechanisms leading to amyloid-β accumulation and tau hyperphosphorylation. Attempts to treat Alzheimer's by delaying the onset of dementia, i.e. changing the course of the disease, must be multimodal, because the pathogenetic mechanisms leading to the disease are also multimodal. Treatment of this disease which must be performed over the course of decades must be practically devoid of side effects. For instance, intravenous drugs may not be indicated as they are non-convenient for the patients. In the past two decades, we have analysed the characteristics of oxidative stress associated with Alzheimer's disease and found that these changes in redox signalling contribute to link amyloid-β pathology with tau hyperphosphorylation. Some time ago we realised that genistein, a soya isoflavone that binds to PPAR-γ, activates a production of ApoE, which in turn clears amyloid-β from brain. We tested this hypothesis in an animal model, i.e. the APP-PS1 and observed that genistein very significantly lowers the amount of amyloid-β in brain, decreases brain inflammation associated with Alzheimer's and improves cognition in animal tests. Now we report the results of a pilot clinical trial that show that genistein is effective in delaying the transition of minimal cognitive impairment patients to dementia. The mechanisms for these results will be discussed.

Potential Involvement of Extracellular Vesicles as Mediators in the Aging Process: Impact of Exercise. Ionara R Siqueira (UFRGS)

Exercise has been recognized as an effective preventive and therapeutic approach for several diseases, including on those age-related. It has been highlighted the relationship between extracellular vesicles and particles cargo changes on both physiopathological functions in aging process and exercise-induced benefits, as well. Our group described that circulating adipocytes-derived extracellular vesicles and particles cargo possess a potential involvement with the aging process, as a whole-body phenomenon, spreading spread pro-senescence molecules to recipient cells. In the opposite way, exercise seems to be able to alter circulating extracellular vesicles and particles cargo, evaluated in human experimentation and animal models, being a potential mechanism of spreading molecules involved with beneficial effects.

Gut microbiome-brain interactions in Parkinson's disease. Livia Hecke Morais[1] and Sarkis K. Mazmanian[1]
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Gut microbiome-brain interactions have been implicated in a wide range of neurological conditions, including Parkinson's disease (PD). Motor dysfunction in PD is primarily associated with the selective dysfunction and loss of nigrostriatal dopaminergic neurons, potentially due to their relatively high energetic demand in comparison to other neurons. Defects in mitochondrial function may underlie vulnerability to neurodegeneration through impaired cellular respiration and accumulation of oxygen reactive species. While the etiology of PD us incompletely understood, most cases are believed to have a strong environmental contribution. The gut microbiome is altered in PD stool samples compared to household or population controls. Accordingly, our group has previously demonstrated that the gut microbiome exacerbates motor deficits, promotes neuroinflammation and α-synuclein (αSyn) brain pathology in mice. Various metabolites produced by gut bacteria have the potential to modulate host metabolism, but a link between the microbiome and brain mitochondrial function remains unknown. Using α-syn overexpressing (ASO), we investigated the influence of the microbiome on mitochondrial function and motor performance. Herein, we reveal that the presence of a microbiome alters mitochondrial morphology and mitochondrial complex I and II respiration in the mouse brain. Furthermore, striatal gene and protein expression patterns suggest a role for the microbiome in regulating mitochondrial protein metabolism and oxidative stress. Motor testing of mice with or without microbiomes uncovered associations with striatal oxidative stress and enhanced progression of PD-like symptoms. These data demonstrate that the microbiome influences mitochondrial functions in the brain of αSyn overexpressing mice, and suggest gut microbial deviations in humans may be environmental risks for PD.
Funding sources: American Parkinson's Disease Association, Michael J. Fox Foundation, The *Aligning* Science Across Parkinson's (*ASAP*), National Institutes of Health, and the Dept of Defense

Roundtables

Equity, Diversity and Inclusion in Postgraduation Courses and Impact Science (**Equidade, Diversidade e Inclusão na Pós-Graduação e na Ciência de Impacto**)

Towards SDG Number 5: Gender Equality and Women´s Empowerment. Helena B. Nader. Academia Brasileira de Ciências. Escola Paulista de Medicina, Universidade Federal de São Paulo

As stated by United Nations Sustainable Development Goals (https://www.un.org/sustainabledevelopment/gender-equality/) "Gender equality is not only a fundamental human right, but a necessary foundation for a peaceful, prosperous and sustainable world". In this round-table discussion we are going to focus on Brazil´s women and girls' positions in politics, management, and science. We need to acknowledge that some progress has been achieved. More girls are nowadays going to school, more women are in positions of leadership, but discrimination against women is still increasing and laws in favor of women´s right are being questioned by segments of our society and some political parties. Women represent the majority in higher education and graduate programs, nevertheless they still are outnumbered by men when taking into consideration higher positions. Women encounter challenges in all professions, but specially in scientific careers. In most countries, women must deal with male-dominated institutional cultures, family responsibilities, and as pointed out by several papers and reports, biases in research allocation, outcome of peer review, citations. These and other topics are going to be discussed.

Beyond the Academy (**Além da Academia**)

The Blue Ocean of Life Sciences – From Professional Carrier to Market Potential for Brazil (O Oceano Azul de Ciências da Vida- Da Trajetória ao Potencial de mercado para o Brasil). Claudia Emanuele Carvalho de Sousa Bióloga, Mestrado e Doutorado em Fisiologia, Merck SA

The Life Sciences industry comprises companies, businesses and research institutions dedicated to improving life and can be divided into different segments, pharmaceuticals, biotechnology, medical technologies, nutraceuticals, cosmeceuticals, food processing (Delloite, 2014). There is a common denominator of "Life Science": trade between companies that provide reagents, equipment, devices, services, and technologies that accelerate and facilitate the development of research, production of medicines in different laboratories (Lohr and Kemler, 2021). Different from what is common sense, specializing, following the different and long steps of a postgraduate course, living experiences outside the country in Research Institutions is crucial for preparing and an open door to most relevant companies in the sector. Whether for the technical area directly in R&D laboratories or commercial area, such as scientific support or sales, Brazilian companies have ambitions and innovation challenges that demands expert professionals capable of guiding growth.The blue ocean of possibilities is indeed real when we see the capacity and investments that Brazil has received for Innovation in Biotechnology, the new sustainability trends such as clean meat, cell therapy and 3D printing, the emerging market for Cannabis and the pandemics impulse has facilitated the adoption of new processes originally used to streamline vaccines and therapeutics. Additionally, it matters to mention that Brazil is supposed to be on the top 5 list of the raking in Pharmaceutical of Biggest Market (IQVIA, 2021). The outstanding growth is going to drive important demanding from suppliers, and certainly for scientists from all kinds of fields in Life Science.

There is life beyond the Academy (Há vida além da academia!) Angela Alice Amadeu Megale, Institution: Instituto Butantan / Fundação Butantan

In the last decades, the number of Masters and Doctors formed in Brazil, especially in the areas of health & life sciences, has grown exponentially. While this is a real progress of national high education and science, in parallel, these very specialized professionals face with scarce opportunity in the Academies due to the increase of competition and the lack of investments in public Universities and Research Centers. With the Covid-19 pandemic, the contribution of several expert health science professionals was crucial to the successful of research and the fast development of vaccines and drugs that saved countless lives. These professionals contributed since the basic and applied research to the availability of drugs and vaccines in many ways in industries. In this period was evidenced the needs of specialists in health science not only in the Academy, but in several areas of expertise. In this sense, I will talk about my carrier in the Academy and how I joined into the industry of immunobiologicals, with the aim to show that is possible to contribute with public health and science beyond the Academy. During my master's degree in Immunology at the Institute of Biomedical Science of the University of Sao Paulo (ICB/USP) in partnership with Butantan Institute, I worked with the production and characterization of monospecific antibodies against synthetic peptides outlined on specific regions of NaPi-IIb protein, a potential ovarian cancer biomarker. In my PhD., also at ICB/USP and Butantan, I studied the inflammatory profile related to the *Bitis arietans* snake envenomation and the role of lipid mediators in this process. Critical thinking and technical knowledge obtained during master's and doctoral degrees were essential for my contribution to the Biological Quality Control of Butantan Foundation in developing of methodologies related to the validation and approvement of vaccines against Covid-19 - CoronaVac and ButanVac.

Consolidated Academic Career? There are no Barriers to the Pursuit of New Dreams!!! (Carreira Acadêmica Consolidada? Não há Barreiras para a Busca de Novos Sonhos!!!)

Rafael Cypriano Dutra (UFSC)

Every change deals damage! However, being willing to change means that we are willing to grow and live new experiences personal or professional, and above all, to follow in the pursuit of your dreams - and I repeat, it will not be an easy journey, but I can guarantee that it will be very rewarding, exciting and full of energy. Thinking about completely changing your life (and your entire family), work, country, language and culture, away from friends and family and, mainly, from all your comfort zone after 10 years as Associate Professor at the sixth best Federal University in Brazil and with a well-established professional career - it's an almost unthinkable decision for most people - but it wasn't for me. In this symposium, I will talk about my history, and how I made the decision to switch from a stable professional career as Professor at the University to a new position in the multinational pharmaceutical industry.

Abstracts

01. Cellular and Molecular Pharmacology

01.001 **Endothelium-Dopamine is a Major Vascular Mediator**. Campitelli RR[1], Britto-Júnior J[1], Souza VB[1], Schenka AA[1], Mónica FZ[1], Antunes E[1], De Nucci G[1,2,3] [1]FCM-Unicamp, Dept Pharmacology, Campinas, Brazil, [2]ICB-USP, Dept of Pharmacology, São Paulo, Brazil. [3]Univ Brasil, Fernandópolis, Brazil

Previous studies with umbilical cord vessels (HUCV) and snake's aorta revealed endothelium dependent EFS-induced contractions in both of them. Aiming to determine the mediator(s)'s nature responsible for this HUCV contractions, human umbilical artery (HUA) and human umbilical vein (HUV) were dissected in rings, with and without endothelium, which were placed in organ bath with Krebs-Henseleit's solution, constant heating and oxygenation (95% O2, 5% CO2). By LC-MS-MS, dopamine, adrenaline, and noradrenaline basal releasing was measured, and cumulative concentration response curves with dopamine were performed, in the absence and presence of dopamine antagonists and L-NAME. Furthermore, EFS trials were performed in the presence and absence of L-NAME, the dopamine antagonists SCH-23390 and haloperidol, the α-adrenergic blockers prazosin and idazoxan. By fluorescence in situ hybridization and immunohistochemistry, tyrosine hydroxylase (TH) and dopa-decarboxylase (DDC) presence in the tissues were investigated. The protocol was approved by the Ethics Committee of the Institute of Biomedical Sciences of the University of São Paulo - ICB/USP (protocol number 3. 165. 417) and followed the principles outlined in the Declaration of Helsinki. The results from LC-MS-MS revealed the necessity of the HUA and HUV's intact endothelium to the basal release of dopamine. In addition, immunohistochemistry showed that in both HUA and HUV, TH and DDC were identified only in the endothelium. In terms of tissue contraction, dopamine only induced it in the in the HUA in presence of L-NAME, while in the HUV, dopamine contraction was potentialized by L-NAME. Also, L-NAME potentialized in both HUA and HUV the EFS-induced contractions, whereas it was inhibited by haloperidol (D2-like antagonist). Contractions of HUA and HUV were not affected by the α-adrenergic antagonists prazosin and idazoxan and the D1-like receptor antagonist SCH-23390. In conclusion, the main modulator of HUCV reactivity *in vitro* is an endothelium-derived dopamine. The authors thanks CAPES and FAPESP.

01.002 **Mesenteric Endothelial Oxidative Stress and Antioxidant Profile during Schistosomiasis**. Monteiro MMLV[1], Valença SS[2], Silva CLM[1]. [1]ICB-UFRJ, Lab Farmacologia e Bioquímica Molecular, Rio de Janeiro, Brazil, [2]ICB-UFRJ, Lab de Biologia Redox, Rio de Janeiro, Brazil

Introduction: Schistosomiasis is a neglected tropical disease caused by Schistosoma affecting more than 200 million people worldwide. Intravascular worms establish a chronic infection triggering host immune responses and mesenteric endothelial cells acquire a pro-inflammatory phenotype (Oliveira et al., 2011, Plos One, 6:e23547). The endothelial oxidative balance plays a pivotal role during inflammation; a stress caused by an imbalance of reactive oxygen species (ROS) could lead to an endothelial dysfunction and NO reduction. Therefore, in the present study, mice mesenteric endothelial cells (MEC) infected with Schistosoma mansoni were evaluated ROS formation, lipid peroxidation and major antioxidant enzymes expression. **Methods:** CEUA A01/22-A01-21-A01-19-048-16. Swiss mice (newborn) were percutaneously infected with approximated 80 cercarie obtained from FIOCRUZ. Control and S. mansoni-infected male mice (60-90 days old) were anesthetized and euthanized, mesenteric vessels were removed, minced and plated with DMEM enriched with 20% fetal bovine serum, 1% antibiotics at 37°C, 5% CO 2 until confluence. Ex-vivo MEC phenotypic characterization was performed by flow cytometry for PECAM-1 (CD31). ROS levels (manly superoxide anion) were evaluated by nitrotetrazolium (NBT) adapted from Choi et al., 2006 (J. Immunoassay Immunochem, 27:31). Lipid peroxidation rate as malondialdehyde (MDA) used a TBARs assay kit (Cayman). Total protein extracts were harvested from CEM and the antioxidant enzymes expression were analyzed by Western blotting for superoxide dismutase (SOD1), glutathione peroxidase (GPx1), catalase (CAT), nuclear factor erythroid 2- related factor 2 (Nrf2), oxidative stress marker nitrotyrosine (PNK) and β-actin. NO production was evaluated by fluorimetric assay using DAF-FM. All assays used confluent MEC (1 st passage). Statistical analysis was performed by using Student's t test expressed as means ± SEM and $P < 0.05$ was considered significant. **Results:** MEC from both groups showed immunoreactivity to CD31+ (>97%). MEC from the infected group produced twice ROS levels as compared to

control (0. 06 ± 0. 005 a. u vs. 0. 028 ± 0. 005 a. u., n= 5 ***P<0. 001). Moreover, the same pattern was observed in TBARS levels (7. 1 ± 0. 5; vs. 3. 7 ± 0. 51 µmol/mg protein, n=3, P<0.05). NO production in response to 1 µM bradykinin was reduced in the infected group (P <0.05). Antioxidant enzymes expressions did not change between groups as well as the nuclear factor Nrf2. PNK is an indirect marker of nitrosylation caused by peroxynitrite (ONOO -) formed in a spontaneous reaction between superoxide anion (O 2 . -) and nitric oxide (NO). However, despite the increased levels of superoxide anion in the infected group, we observed a reduced PNK level (1. 44 ± 0.13 a. u.) in relation to control (1. 84 ± 0.05 a. u., n=3, *P<0.05). The smallest production of ONOO - in S. mansoni-infected mice could result from the reduced NO production in this group. **Conclusion:** The redox balance in mesenteric endothelial cells during schistosomiasis leads to an increased oxidative stress with no regulation of antioxidant system. The increased superoxide anion production and lipid peroxidation, hallmarks of endothelial dysfunction, may contribute to mesenteric inflammation observed in schistosomiasis. **Financial Support:** CNPq

01.003 **Evaluation of Gene Expression in the Thymus, a Mouse Model of Accelerated Aging Induced by D-galactose**. Nascimento LMM, Santos MRS, Silva ELES, Mendonça BS, Porto FL, Reis MDS UFAL, Lab Biologia Celular

Introduction: Thymus involution is considered one of the main factors contributing to the age loss of immune function. This process is characterized by the accumulation of senescent thymic epithelial cells and the development of an inflammatory environment with high levels of oxidative stress. (BUDAMAGUNTA, Aging. 13:15, 2021). The present study aimed to evaluate the gene expression of senescent markers in the thymus of aging model mice induced by D-galactose (D-gal). **Methods:** Male C57BL/6 mice were subcutaneously injected with 200 mg/kg of D-gal or saline (control) for 45 days. Twenty-four hours after the last treatment, animals were euthanized, and thymus was collected and immersed in Trizol for extraction of the ribonucleic acid (RNA) and synthesis of complementary deoxyribonucleic acid (cDNA). The real-time quantitative polymerase chain reaction (qPCR) was performed in the QuantiStudio 5 Real-Time PCR System (Applied Biosystems) using specific oligonucleotides for the target genes: catalase (Cat), cyclin-dependent kinase inhibitor 1 (P21), tumour necrosis factor (Tnf) and the endogenous gene beta-actin (Actb). All the animal care and research protocols were approved by the Ethical Committee in Use of Animal Experimentation of the Federal University of Alagoas (CEUA/UFAL) nº 19/2019. The GraphPad Prism software was used for statistical analysis and graphing, and the results are showed as mean ± standard error of the relative gene expression of each group and statistically evaluated using Student's t test, with a significance level selected for p<0.05. **Results:** There was a significant decrease in the expression of the Cat gene in the thymus of the animals treated with D-gal (0,01525 ± 0,003825, p=0,0471) when compared to the control group (0,03209 ± 0,005145, p=0,0471). Also, it was observed a significant increase in the expression of the P21 gene in the organ of animals after treatment with D-gal (1,689 ± 0,1325, p=0,0466) related to the non-treated animals (0,893 ± 0,107, p=0,0466). These results are in line with previous report, where it is shown that genomic instability of T cells associated with ageing can occur due to oxidative stress and reduced activity of repair enzymes such as catalase. Furthermore, premature ageing of T cells has been causally linked to the upregulation of the P21 gene, one of the main markers of senescence (MITTELBRUNN, Nat Immunol. 22(6):687, 2021). The expression of the Tnf gene did not change when comparing the control (0,001084 ± 0,0002692, p=0,7026) and treated (0,000934 ± 0,0002535, p=0,7026) groups, and this result may be related to the treatment time or the concentration of D-galactose, opening another line that may be explored in further evaluations. **Conclusion:** Chronic exposure to D-gal at a concentration of 200 mg/kg for 45 days can promote cellular senescence in the thymus of mice, with the elevation of P21 and reduction of the Cat gene expression.

01.004 **V-type Allosteric Enhancement of Jack Bean Urease by Thiourea**? Silva, MRS, Freiria AJI, Penha NC, Santos Filho PR, Silva JMSF, Kiguti LRA, Unifal, Alfenas, Brazil

Introduction: Urease, an Ni2+-dependent metalloenzyme, catalyzes urea hydrolysis to carbon dioxide and ammonia (NH3) and is the target of drug development campaigns aiming enzyme inhibitors of agricultural and medical importance. Thiourea (TU), an urea-like compound is classically viewed as an urease inhibitor and a prolific scaffold in the search of new multipurpose anti-urease drugs. Accordingly, a plethora of TU-derived

urease orthosteric/allosteric inhibitors were already described. Here we report preliminary experimental evidence suggesting that TU can also act as a V-type allosteric enhancer of Jack bean urease (JBU). **Methods:** NH3 production was evaluated by the indophenol blue method (Wheatherburn MW, Anal. Chem., 39:971, 1967). All incubations and reactions were carried out in triplicate wells of 96 well-plates at 37ºC in 20 mM phosphate buffer (PB) added of 1 mM EDTA, pH 7. 0. "Single point studies": 3. 5 mU of JBU (Type III urease, Sigma Co.) were incubated with vehicle (PB) or different concentrations of TU (0.1 uM-1 mM) or the orthosteric inhibitor boric acid (BA, 1 uM-10 mM) for 30 minutes. Following the vehicle/drug incubation period, 4 mM urea was added to each well and the reaction allowed to proceed for 30 minutes. NH3 production in the presence of TU and BA was evaluated and compared to that of PB-treated wells. "Saturation curve studies": 3. 0 mU of JBU were incubated with PB or TU (3. 0, 30 or 100 uM) for 30 minutes at 37ºC. Then, different concentrations of urea (1. 0 - 32 mM) were added and the reaction allowed to proceed for 30 minutes. All absorbance data were corrected for spontaneous and putative JBU-induced hydrolysis of TU to NH3. Data were analyzed in GraphPad Prism 5 software and derived parameters ("single point studies": pIC50 for BA and pEC50 for TU; "saturation studies": Km and Vmax values derived from Michaelis-Menten kinetics) averaged and presented as mean ± standard error of mean (sem) of n independent experiments. Absorbance raw values for Vmax calculation are expressed in arbitrary absorbance units. Statistical analysis: ANOVA+Newman-Keuls test; values of $p<0.05$ were considered statistically significant. ResultsSingle point studies: BA inhibited NH3 production by JBU (pIC50 = 3. 87 ± 0.17, maximal inhibition = 100%; n = 7). TU increased NH3 production by JBU in the 0. 3-100 uM range (maximal increase in ammonia production: 62. 62 ± 4. 35% at 100 uM TU; pEC50 = 6. 66 ±0. 45, n = 7) while inhibiting NH3 production at 300 uM (-15. 56% vs maximal NH3 production in the presence of 100 uM TU) and 1 mM (-64,57% vs maximal NH3 production in the presence of 100 uM TU). Saturation studies: TU 30 and 100 uM increased the Vmax of JBU by ~70% (Vmax Control: 1. 20 ± 0. 20; +TU 3. 0 uM: 1. 50 ± 0.18; +TU 30 uM: 2. 02 ± 0.12*#; +TU 100 uM: 2. 08 ± 0.13*#; n = 5, *$p<0.05$ vs Control, #$p<0.05$ vs +TU 3. 0 uM) with no effect on urea Km (Control: 3. 34±1. 85, +TU 3. 0 uM: 2. 34 ± 1. 03, +TU 30 uM: 2. 49 ± 0. 56, +TU 100 uM: 2. 92 ± 0. 65; n = 5, $p>0.05$ for all comparisons). **Conclusion:** Experimental evidence suggests TU can act as a V-type allosteric enhancer of JBU. To our knowledge, this is the first description of positive V-type modulation of JBU. Detailed investigation on the mechanistic basis of TU-induced positive allosteric modulation of JBU is underway. **Financial Support:** CAPES (#001, NCP)

01.005 **A Computational Study of the Sperm-Associated Protein EPPIN: Insights on its Structure and Druggable Properties for Male Contraceptive Development**. Santos NCM, Rosa LR, Borges RJ, Fontes MRM, Silva EJR, Gomes AAS IBB-Unesp-Botucatu, Dept of Biophysics & Pharmacology, Botucatu, Brazil

Introduction: The Epididymal Protease Inhibitor (EPPIN) is a drug target for male contraception due to its crucial role in sperm motility. It presents an N-terminal WFDC (whey-acidic protein four-disulfide core) domain and a C-terminal Kunitz-type protease inhibitor domain. On the sperm surface, EPPIN acts as a hub for a protein-protein network that contains the seminal plasma protein semenogelin-1 (SEMG1) as an interacting partner. EPPIN/SEMG1 interaction leads to transient inhibition of sperm motility after ejaculation. Characterization of EPPIN/SEMG1 binding led to the development of small-organic compounds such as the triazine ring derivative EP055. Nevertheless, little is known about the structural aspects of the EPPIN binding to its endogenous (SEMG1) and exogenous (EP055) ligands. Herein, we investigate the key interactions taking place in EPPIN binding to SEMG1 and EP055 using in silico structural analysis. **Methods:** We generated a full-length EPPIN (P22-P133; UniProtKB: O95925) using Modeller, which the best model was submitted to molecular dynamics simulations (MDS; 500 ns) (GROMACS). The most stable conformations were submitted to molecular docking (Patchdock and Autodock4) to obtain initial conformations of EPPIN in complex to the SEMG1E229-Q247 (E2Q) peptide and EP055, respectively. The best complexes were submitted to another step of MDS to determine the main contribution of EPPIN residues in the interaction with these ligands. **Results:** We observed conformational changes of EPPIN related to domain-domain interaction, which were validated by normal mode analysis. A closed EPPIN state was determined as the most stable conformation from MDS with SASA (Solvent-Accessible Surface Area) value reduced from 1. 78 to 1. 42 nm2, which presented a binding pocket formed by both WFDC and Kunitz domains. According to molecular docking, this binding pocket accommodated E2Q peptide and EP055 with free energy values of -7. 98 and -6. 59 kcal/mol, respectively. Further, MDS accommodated both molecules

presenting RMSD (Root-Mean-Square Deviation) values of 7. 8±1. 7 and 6. 5±1. 1Å, respectively. We identified EPPIN F63 and K68 residues in the WFDC domain, and N113 and N114 in the Kunitz domain, with contact percentages >94% and >97%, respectively. A hinge segment (D71-D75) connecting these domains is essential for stabilizing ligands in the binding pocket, highlighting the D71 residue with permanent contact with both ligands. Moreover, we observed a high percentage of contacts of hydrophobic residues (P22, L24, L28, F29, F123, and P133; >80%) and hydrophilic residues (R52, K97, K98, N100, and K130; >90%), indicating that they play a role in EPPIN's anchoring to the plasma membrane, leaving the binding pocket exposed to the solvent. **Conclusions:** Our findings suggest that EPPIN protease inhibitor domains and its hinge region contain residues forming a stable orthosteric binding pocket on the sperm surface, accommodating endogenous and exogenous ligands, thus contributing to the rational design of a novel generation of EPPIN ligands. Altogether, our study provides novel insights on EPPIN as a male contraceptive drug target. **Financial Support**ed: PIBIC/UNESP, FAPESP, CAPES, and CNPq. This study did not require Ethics Approval.

01.006 **Evaluation of Cytotoxic Activity and Phytochemical Screening of Extract and Fractions from the Bark of Plant** *Diplotropis racemosa* **Hoene** (**from Woody Residue**). Mota JA[1], Pereira JVM[1], Manso MP[1], Guimarães AC[2], Araújo IM[2]; Gomes SLF[2]; Sampaio TA[2]; Veiga Junior V[3], Guimarães CJ[1], Pessoa C[1] , [1]NPDM-UFC – Experimental Oncology, [2]Q-BIOMA-UFAM – Chemistry, [3]Military Engineering Institute

Cancer occupies the second place among the diseases with the highest cause of mortality in the world and there is a growing need for the search for new therapeutic possibilities. Therefore, the screening of new chemical classes with cytotoxic potential from plant extracts becomes an important preliminary step to be investigated for the selection of substances with anticancer potential. The plant *Diplotropis racemosa* (Hoehne), the popular common name sucupira preta, is a species widely distributed throughout Brazil. *D*. *racemosa*, has two relevant synonyms: basionym *Bowdichia racemosa* Hoehne which is a homotypic synonym of *Staminodianthus racemosus* (Hoehne). It has applications for timber purposes and in folk medicine as a cicatrizant, anti-ulcerative, antidiabetic and for the treatment of rheumatism. The objective of this work was to analyze the phytochemical aspect and cytotoxic potential of extracts and fractions from Black Sucupira under the codes LSP (hydroalcoholic extract), LSP02 (chloroformic fraction), LSP03 (ethyl acetate fraction), LSP04 (butanolic fraction) and LSP05 (hydroalcoholic residue). The peels were extracted with 70% ethanol under reflux for 72 hours. The crude extract (LSP-39. 11g) was partitioned with hexane (LSP01-0. 23g), chloroform (LSP02-2. 29g), ethyl acetate (LSP03-1. 51g) and butanol (LSP04-8. 40g), (LSP05-hydroalcoholic residue-26. 66g), generating five fractions. Phytochemical evaluation by tube reaction assays indicated the presence of unchain pentacyclic triterpenoids, condensed tannins, flavones, flavonoids and xanthones in the crude extract (LSP). The unchain pentacyclic triterpenoids were detected in the fractions LSP01, LSP02 and LSP03. Condensed tannins, flavones, flavonoids, xanthones and saponins were detected in fractions LSP03, LSP04 and LSP05. The alkaloids were detected only in fractions LSP04 and LSP05. For the evaluation of cytotoxic potential, the samples were submitted to Single Concentration Evaluation (SCA), followed by the determination of the Inhibitory Concentration (IC50), in the following tumor lines: SNB-19 (glioblastoma), HCT-116 (colon carcinoma), PC3 (prostate carcinoma) and HL-60 (Promyelocytic). The method was based on the MTT(3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2-H-bromide tetrazolium) assay. Of the samples submitted to SCA, only fractions LSP02 and LSP03, showed inhibitory capacity above 60%, with values between 84 to 90% for LSP02 and 66 to 90% for LSP03. The determination of IC50 in PC3, SNB19, HCT116 and HL60 strains corresponded, respectively, to 18. 72; 42. 0; 36. 29; 27. 14 µg/mL for LSP02 and 54. 83; 92. 18; 51. 93; 53. 82 µg/mLfor LSP03. Therefore, the cytotoxic activities presented may be related to the terpenoid and phenolic constituents present in fractions LSP02 and LSP03. This evaluation demonstrates the potential of apolar and medium polarity sucupira preta extracts for the bioguided isolation of active compounds.

01.007 *In vitro* **Aging Affects Epithelial Renal Cells Phenotype and Pharmacological Response to Bufalin**. Barros GMOB, Araújo LS, Morais JA, Almeida e Silva AC, Quintas LM ICB-UFRJ, Rio de Janeiro, Brazil

Introduction: Cell aging is characterized by loss of adaptation and failure to re-enter the cell cycle in response to mitogenic stimulation. The cardiotonic steroid bufalin selectively binds to and may evoke Na+/K+-ATPase (NKA) signal transduction. We have shown that bufalin induces epithelial-mesenchymal transition (EMT) in cultured

LLC-PK1 cells of high passages (P>80), with no effect in low passages (P<40). Accordingly, this work aims to investigate the phenotypical differences between these two cell populations and their respective pharmacological responses to bufalin. **Methods:** P>80 and P<40 LLC-PK1 cells (porcine proximal renal tubule) were cultured in 12-well plates (5,000 cells/well) and the cell proliferation rate was evaluated by Trypan blue-free cells counting up to 72 hours in a Neubauer chamber. Cell viability was evaluated through the MTT test (1,000 cells/well). Cell migration/motility was evaluated by the wound healing method. The biochemical and molecular investigation assessed NKA activity has been studied with the colorimetric Fiske and Subbarow method, and the protein expression levels of NKA-α1 isoform, ERK1/2, AKT, GSK3 and adhesion molecules as β-catenin and E-cadherin were measured by western blot. To evaluate the effect of caveolar derangement, cells were FBS-deprived and after 24 hours they were pre-treated with 10 uM methyl-β-cyclodextrin (MβCD) for 30 min. Afterwards, MβCD was washed out and cells were treated with bufalin for 48 hours. Statistics was performed by using one-way analysis of variance (ANOVA) or student's t test with a significance level of $p<0.05$, followed by a Sidak posttest. Data were expressed as means ± SEM. **Results:** Compared to P<40, P>80 cell number and viability was 70% and 50% higher after 72 h, respectively ($p<0.05$, n=5-6). The migration rate was 2. 6 and 2. 2-fold greater than P<40 after 24 and 48 h, respectively ($p<0.05$, n=10). NKA activity (in µmol Pi/mg/h: 7. 4 ± 1. 2 P<40 vs 6. 7 ± 1. 3 P>80; n=11) and α1 expression were similar between both groups. ERK1/2 was 2. 2-fold more active ($p<0.05$, n=4) and total AKT was 2-fold higher in P>80 ($p<0.05$, n=5) without changes in GSK3β expression. The expression of adhesion protein β-catenin is comparable between the two groups while E-cadherin expression was very high (8. 4-fold) in P>80 ($p<0.05$, n=5). The MβCD treatment resulted in a reduction in the EMT-associated morphological profile that bufalin induces in P>80 cells. **Conclusion:** Our results indicate the LLC-PK1 in the different passages *in vitro* present different phenotypes and the response to bufalin of P>80 cells should be through signaling NKA located in caveolae. Increased proliferative capacity, viability and motility of P>80 cells may be related to MAP kinase activity. In contrast to P<40, P>80 cells were sensitive to the EMT-like phenomenon induced by bufalin, but no alteration in NKA activity and expression was detected. **Financial Support:** PIBIC/UFRJ, CAPES, FAPERJ e CNPq.

01.008 **Matrix Metalloproteinase (MMP)-2 Proteolyzes Type I Collagen (COL-1) and Contributes to Focal Adhesion Kinase (FAK) Activation and Vascular Smooth Muscle Cells Proliferation in Aorta of Acute Hypertensive Rats**. Neves VGO, Blascke de Mello MMB, Rodrigues D, Rocha EV, Parente JM, Tostes RC, Castro MM FMRP-USP, Dept Pharmacology, Ribeirão Preto, Brazil

Introduction: Increased expression and activity of MMP-2 contribute to accentuated vascular smooth muscle cells (VSMC) proliferation in early hypertension. MMP-2 also proteolyzes many proteins of the extracellular matrix of VSMC, including type 1 collagen (COL-1). The cleaved products from COL-1 may activate the focal adhesion kinases (FAK) that trigger the migration and proliferation signal in VSMCs. We hypothesized that increased activity of MMP-2 proteolyzes COL-1 in aortas of hypertensive rats, and then, it induces FAK phosphorylation through integrin receptors and leads to increased VSMC proliferation in hypertrophic arterial remodeling. **Methods:** Male Sprague-Dawley rats were submitted to renovascular hypertension by two kidney-one clip (2K-1C) model and treated with doxycycline (Doxy, 30 mg/kg/day) by gavage from the third to seventh-day post-surgery. Control rats were submitted to sham surgery (CEUA-USP 165/2019). Systolic blood pressure (SBP; tail-cuff plethysmography) was daily measured and aortas were processed for gel and in situ zymography, MMP-2, pFAK/FAK, integrin (α2, αV, β1 e β3) and COL-1 levels by Western blot, hydroxyproline assay, morphological analysis by hematoxylin and eosin and picrosirius red, Ki-67 immunofluorescence. *In vitro* assay was performed in A7R5 SMCs in DMEM containing glucose, pyruvate and inactivated fetal bovine serum. Cells were stimulated with COL-1 (25 µg/cm2) and treated with the MMP inhibitors (Doxy (40 µg/mL) and ARP-100 (100 µM), and with the FAK inhibitor PND 1186 (2. 5 µM) for 24 hours at 37°C. After incubation, cells were lysed and evaluated for pFAK/FAK; the supernatant was used to analyze COL-1 by Western blot and MMP-2 by gel zymography. Statistical analysis was done by two-way ANOVA followed by Tukey post-test (animal protocol) and t-Test Unpaired Welch's Corrections (Cell culture), accepted $p<0.05$. **Results:** The 2K-1C rats developed elevated SBP in the first week (144 mmHg ± 3. 4 vs. Sham $p<0.001$) as well as increased the expression and activity of MMP-2 in the aortas ($p<0.01$ vs. Sham). Treatment with Doxy reduced both MMP activity and expression in

hypertensive rats (p<0.05). Doxy also prevented the potential proteolysis of COL-1 in the aortas of 2K-1C rats (p<0.05). In contrast, it seems that occurs a potential deposition of total collagen fibers in the aortas of 2K-1C to try to compensate the proteolysis (p=0.058 vs Sham). In aortas of 2K-1C it was observed increased pFAK/FAK (p<0. 001 vs Sham) and increased VSMC proliferation (p<0.05 vs Sham), although the levels of β3 integrin decreased (p<0. 01 vs. Sham) and αV, α2, and β1 did not change. Doxy reduced FAK activation (p<0.05), higher VSMC proliferation (p<0.05) and β3 integrin reduction (p<0.05 vs 2K-1C). Hypertension and higher VSMC proliferation contributed to the hypertrophic vascular remodeling as seen by increased cross-sectional area and media/lumen ratio (p<0.05 vs sham). In the cell culture, MMP-2 was able to proteolyze COL-1, an effect reversed by ARP-100 or Doxy (p<0.05). Furthermore, COL-1 activated pFAK/FAK pathway (p<0.05 Vs Control) and the inhibitors of MMP-2 and FAK reduced this effect (p<0.05). **Conclusion:** Increase in MMP-2 expression and activity may be associated with COL-1 cleavage which activates FAK and induces VSMC proliferation and hypertrophic remodeling in the initial phase of hypertension; and data suggest that MMP inhibitors could improve arterial remodeling in hypertensive patients. **Financial Support:** CAPES/ FAPESP/ CNPQ/ FAEPA.

01.009 **Uvaol Inhibits TGF-β-Induced Epithelium-Mesenchymal Transition in Human Alveolar Epithelial Cells**. Tenório-Gonçalves LP[1 2 3], Xavier FHC[2 3], Wagner MSW[4], Savino W[2 3], Bonomo A[2 3], Barreto E[1 3 1]UFAL, Cell Biology Laboratory, Institute of Health and Biological Sciences, Maceió, Brazil, [2]IOC-Fiocruz, Lab on Thymus Research, Rio de Janeiro, Brazil, [3]National Institute of Science and Technology on Neuroimmunomodulation, [4]INCa, Cell Structure and Dynamics Rio de Janeiro, Brazil

Introduction: Epithelial-mesenchymal transition (EMT) has been reported to be a possible mechanism for development of pulmonary fibrosis, which is mediated by transforming growth factor β (TGF-β). Therefore, targeting EMT may represent a novel opportunity to fibrosis treatment and drug development. Uvaol (Urs-12-ene-3,28-diol), one of the pentacyclic triterpenoids found in various medicinal plants and fruits, possessed some beneficial effects under pathological conditions, including lung inflammation. However, the effect of uvaol upon the EMT remains unknown. The present study aimed to investigate the effects of uvaol on TGF-β-induced EMT in human alveolar epithelial cells. **Methods:** Human alveolar epithelial A549 cells were treated with TGF-β (10 ng/mL), uvaol (5 ng/mL), or both TGF-β/MC, and EMT was identified by morphological changes and expression of marker proteins after 48h. Cell morphology was observed under a conventional and confocal microscopy. The expression of mesenchymal markers (N-caderin e vimetin) was assessed by western blotting, while expression of extracellular matrix receptors (integrins α5β1 and α6β1) was analyzed by flow cytometry. Scratch assay was used to assess cellular migration ability. Cell viability was detected by flow cytometry using BD Horizon Fixable Viability reagents. Statistical significance between groups was determined by ANOVA followed by Tukey's test (p<0.05). **Results:** Stimulation of A549 cells with TGF-β induced morphological change from a cobblestone-like shape to a fibroblast-like appearance with loss of cell-to-cell junctions, increased formation of stress fibers, associated with an increase of mesenchymal cell markers N-cadherin and vimentin. In addition, in A549 cells under TGF-β1 stimulation there was an increased the expression of integrin-type receptors α5β1 and α6β1, and also a significant increase in the cell migration. The uvaol treatment in A549 cells stimulated with TGF-β for 48h restored epithelial cell morphology, decreased the production of N-cadherin and vimentin, reduced the expression of integrin-type receptors, as well as attenuated migration without affecting cell viability. **Conclusion:** These results suggest that uvaol might be a potential drug candidate for therapies targeting TGF-β-induced EMT. Keywords: Uvaol; epithelial-mesenchymal transition; cell motility, extracellular matrix. **Financial Support:** CNPq, Fiocruz, Faperj, INCT-NIM and FOCEM/-Mercosul

01.010 **Endothelial P2Y2 Receptors Signaling in Primed Cells Contribute to Leukocyte Adhesion during Chronic Inflammation**. Oliveira NF[1], Tamura AS[2], Mainieri NS[1], Savio LEB[2], Coutinho-Silva R[2], Silva CLM[1 1]ICB-UFRJ, [2]IBCCF-UFRJ, Rio de Janeiro Brazil

Introduction: The metabotropic P2Y2 receptor (P2Y2R) has been studied in some vascular injury models through ATP or UTP activation (Burnstock G., Front. Pharmacol. (8):661, 2017). The endothelial damage caused by chronic inflammatory vascular disease during schistosomiasis is flagged through molecular pattern receptors such as TLR4 promoting endothelial dysfunction and ATP release which modulates host immune responses (Liu C., Stem Cell Res. Ther. (11):217, 2020). However, the purinergic P2Y2R role during chronic inflammation

associated with schistosomiasis is unknown. Therefore, our aim was to investigate the role of endothelial P2Y2R in leukocyte adhesion during schistosomal inflammation in mice. **Methods:** Newborn (~10 days old) male Swiss mice were infected with *S. mansoni* cercariae (CEUA A01/22-048-16). Primary cultures of endothelial cells (EC) were obtained from control and infected mice (50-70 days p. i.) kept in DMEM 20% FSB and plated to leukocyte adhesion or WB assays. Mononuclear cells were isolated using the Ficoll gradient. Confluent EC was stimulated with UTP for 5h, in the absence or presence of the pre-treatment (added 30 min before) and then co-incubated with mononuclear cells for 30 min. Cells were washed and the number of adherent cells was determined using optical microscopy (400x magnification). **Results:** UTP (1–300 μM) increased leukocyte adhesion to EC in a concentration-dependent manner with the maximal effect observed at 100 μM in both groups. In the control group, the EC treatment with UTP 100 μM increased leukocyte adhesion from 2. 6 ± 0. 3 to 6. 5 ± 0. 3 cells/field ($P < 0.001$), but the effect was higher in the infected group (7. 4 ± 0. 6 to 12. 4 ± 0. 6 cells/field, n = 36 replicates from 5-6 individual experiments, $P < 0.001$). The P2Y2R antagonist suramin 50 μM blocked the agonist effect, while ectonucleotidases inhibitor (ARL67156, 100 μM) did not alter the UTP effect. Both data suggest a P2Y2R-mediated effect. WB data showed similar levels of protein expression P2Y2R. In both groups, phospholipase C inhibition (U73122, 1 μM), intracellular Ca2+ chelation (BAPTA-AM, 3 μM), and SrC inhibition (SU6656, 5 μM) impaired the agonist effect. However, in the infected group, both U73122 and BAPTA not only blocked the UTP (100 μM) effect but also decreased the basal leukocyte adhesion suggesting that the EC has a pro-adhesive phenotype ($P < 0.001$). Interestingly, in the infected group, the co-activation of P2Y2R and P2X7R by UTP (100 μM) plus ATP (500 μM), respectively, stimulated mononuclear cell adhesion to EC monolayer over the UTP condition alone, which was not observed in the control group. Moreover, preliminary results showed a higher IL-1β soluble from EC-infected supernatant compared with control. We hypothesized that the P2Y2R-P2X7R signaling crosstalk could be involved with chronic findings during schistosomiasis, with a putative role of inflammasome activation. **Conclusion:** The mesenteric endothelial P2Y2R increases leukocyte adhesion. However, the downstream endothelial Ca2+ signaling is enhanced during schistosomiasis. These data unveil the role of endothelial P2Y2R signaling in mesenteric inflammation during schistosomiasis. Acknowledgments: CNPq, CAPES.

01.011 **Cellular distribution of the male contraceptive target EPPIN and its co-localization with binding partners in mouse spermatozoa during capacitation**. Mariani NAP, Santos NCM, Santos GVM, Andrade AD, Kushima H, Silva EJR IBB-Unesp-Botucatu, Botucatu, Brazil

Introduction: Epididymal Protease Inhibitor (EPPIN) is a sperm-associated target for male contraception due to its crucial role in regulating sperm motility after ejaculation and druggable properties. The relevance of EPPIN for reproduction has been demonstrated by its role as a docking site for the seminal plasma protein semenogelin-1 (SEMG1) on the human sperm surface, which temporarily inhibits sperm motility and promotes sperm survival in the uterus. Our previous study expanded the EPPIN protein-protein interaction profile by demonstrating its co-immunoprecipitation with other sperm-specific proteins, glyceraldehyde 3-phosphate dehydrogenase (GAPDHS) and A-kinase anchor protein 4 (AKAP4), in addition to SEMG1 in mouse spermatozoa. Owing to the essential roles of SEMG1, GAPDHS, and AKAP4 for sperm function, we hypothesize that EPPIN acts as a central node in a sperm protein network crucial for reproduction. Here, we investigated the EPPIN protein-protein interaction network in spermatozoa during their journey to fertilization by evaluating its stability and co-localization with SEMG1, GAPDHS, and AKAP4 in mouse spermatozoa isolated from different sites of the female reproductive tract. **Methods:** Male Swiss mice were mated with females previously submitted to hormonal treatment to induce estrous. After confirmation of mating by the presence of the copulatory plug, we isolated mouse spermatozoa from the vagina, and proximal (near the cervix) and distal (near the oviduct) uterus. The sperm smears were processed for immunofluorescence assays using specific antibodies to evaluate the co-localization of EPPIN with SEMG1, GAPDHS, and AKAP4. The colocalization was evaluated qualitatively by fluorescence microscopy according to the immunodistribution pattern of the proteins in spermatozoa. **Results:** We found that EPPIN is immunolocalized in the head and flagellum of spermatozoa collected from all regions of the female reproductive tract. EPPIN co-localized with SEMG1, GAPDHS, and AKAP4 in spermatozoa isolated all regions of the female reproductive tract, albeit with differences in the co-immunolocalization pattern. EPPIN co-localized with SEMG1 in the sperm head (acrosome and post-acrosomal regions) and midpiece and principal

piece of the flagellum. Conversely, EPPIN co-localized with GAPDHS only in the principal piece and with AKAP4 in the midpiece and principal piece of the flagellum. We further observed a co-localization between EPPIN and AKAP4 in the acrosome of some, but not all, spermatozoa. **Conclusion:** Our findings show that EPPIN remains bound to sperm surface during all steps of their journey to the site of fertilization, suggesting it could play roles in other aspects of sperm function beyond motility. The co-localization of EPPIN and its binding partners SEMG1, GAPDHS, and AKAP4 indicate a dynamic EPPIN protein network in ejaculated spermatozoa undergoing the last maturation steps for fertilization. The relative stability of EPPIN in spermatozoa transiting in the female reproductive tract supports the viability of an EPPIN-based male contraceptive. Altogether, our study contributes to understanding the roles of EPPIN in reproduction, which may facilitate its development as a male contraceptive candidate. **Financial Support:** PIBIC/UNESP; CAPES and FAPESP (2021/04746-3; 2020/04841-3). Ethics committee protocol numbers: 5402261121; 5219150420.

01.012 **The Omega-3 Lipid 12-Hydroxyeicosapentaenoic Acid (12-HEPE) Exerts Cardiometabolic Effects through Partial Agonism of Thromboxane Receptor (TP)**. Gonçalves TT[1,2,3], Pereira da Silva MH[2,3], Passos ASC[2,3], Alves JM[2,3], Oliveira AA[5], Alnouri W[4], Offermanns S[4], Leiria LOS[2,3] [1]FCM-Unicamp, Dept Pharmacology, Campinas Brazil, [2]FMRP-USP, Dept Pharmacology, Ribeirão Preto, Brazil, [3]FMRP-USP, Center for Research in Inflammatory Diseases, Ribeirão Preto, Brazil, [4] Max Planck Institute for Heart and Lung Research, Dept Pharmacology, Germany, [5]CNPEM, Brazilian Biosciences National Laboratory, Campinas, Brazil

Introduction: It is known that lipids released by brown adipose tissue (BAT) during cold exposure can exert beneficial effects on glucose and lipoprotein homeostasis. Recently, Leiria et al. demonstrated that the 12-LOX biosynthetic pathway is activated in BAT in response to cold or beta-adrenergic stimulation, generating lipid mediators such as 12-hydroxyeicosapentaenoic acid (12-HEPE). 12-HEPE was shown to improve glucose tolerance and insulin sensitivity through the stimulation of a G-protein coupled receptor (GPCR). However, the receptor to which 12(S)-HEPE binds to in order to exerts its functions remains unknown. Thus, in this study we aimed to identify and characterize the 12-HEPE targeted GPCR. **Methods:** The screening of 70 non-olfactory GPCR candidates was performed on HEK293 cells stimulated or not with 12-HEPE (5µM). Receptors were individually expressed in HEK293 cells, and its activation was measured by dynamic mass redistribution (DRM) assay. Following the identification of the potential receptor, we validated the result by monitoring intracellular Ca2+ levels through a concentration-response curve to 12-HEPE in HEK293 cells. We performed in silico docking experiments to predict the binding model of 12-HEPE to the identified receptor. The receptor was prepared following OPLS3 force field refinement parameters, energy minimization, hydrogen addition, complementation of side chains and unmodeled loops. A 20 Å box was generated so that the ligands U46619 (TP agonist), Ramatroban (receptor antagonist) and 12-HEPE could bind freely. To study the biological effects resultant from this ligand-receptor interaction, thoracic aorta artery rings were isolated from 12-week-old male C57BL6/J and its contractile responses were monitored through a myograph, in response to cumulative doses ranging from 100pM to 3uM of 12-HEPE. **Results:** Through the DRM screening, we found that thromboxane receptor (TP) exhibited the strongest interaction with 12(S)HEPE (5uM). To validate the screening results, we incubated HEK293 cells with 12-HEPE or U46619 and quantified intracellular calcium mobilization. Our data demonstrate that 12-HEPE is a partial agonist of TP, with an EC50 of 314nM vs 7. 2nM of U46619. Through the docking experiment, we found that the induced fit score (IDF) or redocking (GlideScore) values for the compounds were quite similar (U46619 [IDF -574. 49/GlideScore -18. 39], Ramatroban [IDF - 573. 80/GlideScore -16. 88] and 12-HEPE [IDF -571. 70/GlideScore -14. 59]). Since the values indicate that the more negative the value presented, the greater the “affinity” for the site, one can infer that 12-HEPE binds with a slightly lower affinity than the positive controls. Of note, 12-HEPE and U46619 interacts with TP receptor in a similar fashion. Furthermore, incubation of the thoracic aorta artery with 12-HEPE produced dose-dependent increases in arterial constriction, with this effect being completely prevented by the TP antagonist, Seratrodast (1uM). **Conclusions:** Our results suggest that 12-HEPE is an endogenous partial agonist of TP receptor and such an interaction is required for this lipids’ biological effects. Importantly, the vasoconstriction effect exerted by the cold-induced lipokyne 12-HEPE might be an important physiological adaptation to avoid body temperature loss under cold exposure, thereby allowing for an appropriate thermogenesis. **Financial Support:** FAPESP, CNPq. License number of ethics committee: CEUA 158/2020.

02. Neuropharmacology

02.001 **Protein Kinase M Zeta Maintains Remote Contextual Fear Memory by Inhibiting GluA2-Dependent AMPA Receptor Endocytosis in the Prelimbic Cortex**. Fujita GVR[1], Marcondes LA[1,2], Myskiw JC[2], Nachtigall EG[1], Narvaes RF[3], Izquierdo I[4], Furini[1] CRG[1] Fujita GVR1, Marcondes LA1,2, Myskiw JC2, Nachtigall EG1, Narvaes RF1,3, Izquierdo I4, Furini CRG1. [1]PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, [2]UFRGS, Porto Alegre, Brazil, [3]Tufts University, Boston, USA, [4]PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil

Introduction: Fear memories allow animals to recognize and adequately respond to dangerous situations. The prelimbic cortex (PrL) is a crucial node in the circuitry that encodes contextual fear memory, and its activity is central for fear memory expression over time. However, while PrL has been implicated in contextual fear memory storage, the molecular mechanisms underlying its maintenance remain unclear. Protein kinase M zeta (PKMzeta) is a persistently active enzyme, which has been shown to maintain many forms of memories by inhibiting the endocytosis of GluA2-containing AMPA receptors. Therefore, we hypothesized that the action of PKMzeta on AMPARs containing GluA2 is one mechanism responsible for the maintenance of contextual fear memory in PrL. **Methods:** To test this hypothesis, we used 119 male Wistar rats (300–330g) housed 4 to a cage, maintained underr a 12:12-hour light/dark cycle (lights on 7 a. m.) and allowed access to food and water ad libitum. Animals were anesthetized and submitted to stereotaxic surgery to implant bilateral stainless steel 22-gauge guide cannulae aimed 1. 0 mm above the PrL. After recovery, we trained the animals in a contextual fear conditioning paradigm (CFC; Training session: 2 min habituation, followed by 3 footshocks of 0. 7 mA/2 sec at a 30s interval) and administered intra-PrL infusions of the PKMzeta inhibitor ZIP (10 nmol/side), the GluA2-dependent endocytosis inhibitor GluA23Y (100 pmol /side) or the inactive peptide GluA23Y(s) (100 pmol/side), either 2 or 20 days after conditioning, and long-term memory retention was assessed twenty-four hours later, wherein the animals were placed in the same apparatus for a 3min retention test without footshocks. Control groups received sterile saline (Vehicle). The time animals spent freezing was measured during the first 2min of the training session and during the 3min of the retention test. Data were analyzed using two-way ANOVA followed by Bonferroni's test and expressed as mean ± S. E. M. A p value < 0.05 was considered statistically significant. **Results:** We found that acute inhibition of GluA2-dependent AMPAR endocytosis in the PrL does not affect recent or remote contextual fear memory maintenance (recent: Veh 47. 57±5. 85, GluA23Y 38. 27±6. 49, GluA23Y(s) 47. 18±8. 95; remote: Veh 38. 85±7. 53, GluA23Y 33. 00±5. 42, GluA23Y(s) 36. 53±5. 94). Also, PKMzeta inhibition in the PrL does not impair the maintenance of recent contextual fear memory (Veh 63. 00±6. 06, ZIP 57. 44±8. 91). However, we found that inhibition of PrL PKMzeta at a remote time point disrupts contextual fear memory maintenance, and that blocking GluA2-dependent removal of AMPARs prevents this impairment (Veh 45. 75±11. 12, ZIP 15. 48±2. 81, GluA23Y+ZIP 50. 35±5. 87, GluA23Y(s)+ZIP 20.18±4. 52; $p<0.0001$ ZIP vs. Veh; $p<0.0001$ ZIP+GluA23Y vs. ZIP and GluA23Y(s)+ZIP). Our results confirm the central role of PrL in fear memory and identify PKMzeta-induced inhibition of GluA2-containing AMPAR endocytosis as a key mechanism governing remote contextual fear memory maintenance. **Conclusion:** In summary, our study confirms the PrL as a cardinal site for remote fear memory storage and identifies PKMzeta driven inhibition of GluA2-containing AMPAR endocytosis as a molecular mechanism underlying the persistence of the remote contextual fear memory trace in this region. These findings may help to understand the differential contribution of the prelimbic cortex to fear memories over time and also to elucidate the molecular underpinnings of memory persistence. Approval CEUA/PUCRS: 9421. **Financial Support:** CAPES e CNPq.

02.002 **Involvement of Medial Prefrontal Cortex Canonical Wnt/β-catenin and Non-Canonical Wnt/Ca^{2+} Signaling Pathways in Contextual Fear Memory in Male Rats**. Dalferth TF[1], Narvaes RF[1, 2], Nachtigall EG[1], Marcondes LA[1, 3], Izquierdo I[4], Myskiw JC[3], Furini CRG[1] [1]PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, [2]UFRGS, Porto Alegre, Brazil, [3]Tufts University, Boston, USA, [4]PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil

Introduction: Wnt proteins activate different signaling pathways, such as the canonical Wnt/β-catenin signaling pathway and non-canonical β-catenin-independent signaling pathway and have been related to several functions in central nervous system, including learning and memory. However, whether these signaling

pathways are required in the medial prefrontal cortex (mPFC) for fear memory acquisition, consolidation and retrieval remains unclear. So, here we investigated the requirement of canonical Wnt/β-catenin and non-canonical Wnt/Ca^{2+} signaling pathways on the acquisition, consolidation and retrieval of short- and long-term contextual fear conditioning (CFC) memory. **Methods:** For this, male adult Wistar rats were submitted to stereotaxic surgery to implant bilateral infusion cannulae into the mPFC. After recovery, animals were submitted to a CFC paradigm (Tr: Training session - 2 min habituation, followed by 3 footshocks of 0. 5 mA/2 sec at a 30 s interval). One hour later (short-term memory, STM) or 24h later (long-term memory, LTM), the animals were placed in the same apparatus for a 3 min retention test without footshocks. The time the animals spent freezing was measured during the first 2 min of the Tr session and during the 3 min of the retention test. The administration of canonical Wnt/β-catenin and non-canonical Wnt/Ca^{2+} signaling pathways inhibitors, DKK1 (100 ng per side) and SFRP1 (125ng per side), respectively, into the mPFC occurred at different moments to evaluate STM and LTM acquisition, consolidation and retrieval of CFC memory. Control groups received sterile saline (Vehicle - Veh). To assess whether drug administration altered the animals general behavior, locomotor and exploratory activities were evaluated using the open field (OF) task and the anxiety state was evaluated using the elevated plus-maze (EPM). Data of CFC paradigm were analyzed using two-way ANOVA followed by Bonferroni's test. OF and EPM data were analyzed using one-way ANOVA followed by Bonferroni's test. $p < 0.05$ was considered statistically significant. **Results:** To evaluate CFC memory acquisition, DKK1 or SFRP infusions were performed 15 min before the CFC Tr and animals were tested 1h (STM) or 24h (LTM) later. To evaluate CFC memory consolidation, DKK1 or SFRP infusions were performed immediately after the CFC Tr and animals were tested 1h or 24h later. In both cases, the animals that received drugs exhibited similar levels of freezing like those of the Veh group during STM and LTM retention test, indicating that DKK1 and SFRP did not affect the acquisition and consolidation of STM and LTM of CFC. However, when infusion occurred 15 min before the retention test for STM or 15 min before the retention test for LTM, the animals that received DKK1 or SFRP exhibited lower levels of freezing during the STM and LTM retention test when compared to the Veh groups, demonstrating that DKK1 and SFRP impaired the retrieval of both STM and LTM of CFC. In locomotor and exploratory activities or anxiety behavior, the drugs had no effect on the total number of entries and the percentage of time spent in the open arms during EPM or, the number of crossings and rearings during the OF. **Conclusion:** The results observed here shed light on the mechanistic process of fear memory, demonstrating that both canonical Wnt/β-catenin and non-canonical Wnt/Ca^{2+} signaling pathways are necessary in the mPFC to the STM and LTM retrieval but not to the acquisition and consolidation of CFC STM and LTM. Approval CEUA/PUCRS: 8366. **Financial Support:** CAPES e CNPq

02.003 **Systemic Inflammation and Oxidative Stress in Parkinson's Disease Patients may be Associated with Blood Biomarkers**. Santos BN[1], Maes M[2], Bonifácio KL[2], Matsumoto AK[2], Brinholi FF[2], Melo LB[2], Moreira EG[2],, Barbosa DS, Farias CC[1] [1]IFES, Vila Velha, Coordination of Biomedicine, Brazil; [2]UEL, Graduation Program in Health Sciences, Londrina, Brazil

Introduction: Parkinson's disease (PD) is the second most important neurodegenerative disease and still remains without no confiable test for diagnosis and prognosis. Therefore, studies investigate some possibilities for PD blood biomarkers associated with oxidative stress and immune-inflammatory pathways. Oxidative stress is closely related with lipid oxidation which releases some secondary products such as malondialdehyde (MDA). Besides that, the enzyme paraoxonase 1 (PON1), which is anchored in high-density lipoproteins (HDL), composes the antioxidant system of the human body. Besides that, studies have identified a state of systemic inflammation in PD patients associated with the increase of inflammatory interleukins in peripheral blood. So, this study was to evaluate these molecules as potential blood biomarkers in PD. **Methods:** 56 patients with PD in stages 1-3 of the Hoehn and Yahr Scale were recruited from the neurology ambulatory at Clinical Hospital, UEL, as well as 56 healthy individuals. PD patients were being treated with levodopa and carbidopa (n=13), levodopa and benserazide (n=37), pramipexole (n=30), amantadine (n=12), biperiden (n=7) and/or entacapone (n=5). MDA in plasma was quantified by high-performance liquid chromatography (HPLC) and total serum activity of PON1 by UV spectrophotometer. Interleukin 6 (IL-6) and soluble interleukin 6 receptor (sIL-6R) were quantified by ELISA. For statistical analyses we use ANOVAs to check the difference between study groups and multivariate GLM analyses, employed to examine the multivariate effects of diagnosis on biomarkers. All tests were p-value of

0.05 for statistical significance. **Results:** we found significant multivariate effects of diagnosis (df=5/70, p=<0,001), tobacco use (df=5/70, p=0,004) and sex (df=5/70, p=0,005) as explanatory variables on PON1, MDA, IL-6, sIL-6R and IL-6 x sIL-6R (a surrogate index for IL-6 trans-signaling). Tests for between-subject effects showed significant associations between diagnosis and MDA (F=103. 93, df=1/74, p=<0. 001) and IL-6 (F=5,02, df=1/74, p=0,028) while the sIL-6R (df=1/74, p=<0,001) and IL-6 x sIL-6R (df=1/74, p=0,017) were associated with tobacco use. There was a trend toward lowered PON1 values in PD as compared to controls (F=3. 91, df=1/74, p=0.052). The estimated marginal mean (SE) values of the significant biomarkers was: in controls, MDA was 166. 4 (5. 01) uM/mg pt, IL-6 was 3. 46 (0. 55) pg/mL and PON1 was 227. 0 (12. 2) U/mL and, in PD MDA was 211. 3 (4. 1) uM/mg pt, IL-6 was 4. 39 (0. 44) pg/mL and PON1 was 198. 8 (9. 7) U/mL. Thus MDA and Il-6 was significantly higher while PON1 was significantly lower in PD than in controls. Forced entry of other possible independent variables showed that these variables were not significant and did not change the impact of diagnosis on the biomarkers, including use of medicactions such as levodopa (F=2. 08, df=5/69, p=0. 078), amantadine (F=0. 93, df=5/69, p=0. 470), pramipexole (F=1. 64, df=5/69, p=0.162), biperiden (F=0. 22, df=5/69, p=0. 954), entacapone (F=1. 07, df=5/69, p=0. 383) and levodopa + benserazide (F=1. 08, df=5/69, p=0. 377). **Conclusion:** The major finding in this study is the significant association between PD diagnosis and biomarkers linked to oxidative-stress and immune-inflammatory pathways. Besides that, the study indicates a state of systemic inflammation and oxidative stress in patients with PD.

02.006 **Beneficial Effect of the Specialized Pro-Resolution Mediator Protectin DX Over Mechanical Allodynia and Depressive-Like Behavior in an Animal Model of Type-1 Diabetes Mellitus**. Waltrick APF[1], Verri Junior WA[2], Cunha JM[1], Zanoveli JM[1] [1]UFPR, Neuropsychopharmacology Lab, Dept of Pharmacology, Londrina, Brazil, [2] UEL, Pain, Inflammation, Neuropathy and Cancer Lab, Dept of Pathological Sciences, Londrina, Brazil

Type-1 diabetes *mellitus* (T1DM) is a chronic and metabolic disease in which hyperglycemia is the main characteristic. Hyperglycemia leads to an increase in oxidative stress and, consequently, to chronic inflammation. These changes are related to different comorbidities associated with T1DM, such as diabetic neuropathy and depression. It is also quite common for patients to develop the diabetic neuropathic pain in which the patient presents mechanical allodynia, i. e. there is a decrease in pain threshold. The treatment of these comorbidities related to T1DM is a great challenge since most diabetic patients are refractory and/or resistant to currently used treatments. Since inflammation is an important feature of T1DM and that pro-resolving lipid mediators can exert restorative actions on inflammatory processes, this study aimed to evaluate the therapeutic potential of the pro-resolving lipid mediator protectin DX (PDX) in an animal model of T1DM that presents depressive-like behavior and mechanical allodynia. For that, two different experiments were carried out. In both experiments, the induction of T1DM (streptozotocin, 60 mg/kg; or citrate vehicle to control group; i. p) occurred on day 0 of the experimental protocol. Then, male *Wistar* rats received 6 injections of PDX (0, 1, 3 and 10 ng/animal i. p, 200 µl; n = 8 animals/group) performed on days 14, 15, 18, 21, 24 and 27 after the experimental induction of T1DM. In experiment 1, in which mechanical allodynia was evaluated, the animals underwent the basal electronic Von Frey test (VFT) one day before T1DM induction, and then from day 14 (before and after the PDX injections) to day 27 of the protocol. In experiment 2, in which we evaluated locomotor/exploratory activity and depressive-like behavior, the animals underwent the same procedure of induction of T1DM and treatment with PDX (n = 8 animals/group). On day 27 of the protocol, a pretest session of the modified forced swimming test (mFST) was performed. On day 28 of the protocol, the open field test (OFT) was performed followed by mFST. In both experiments, the parameters of weight gain and blood glucose were evaluated. All protocols were approved by the UFPR Ethics Committee for the Use of Animals (CEUA/UFPR; #1108). Values were expressed as meand as mean±SEM. In experiment 1, we can observe a decrease in the mechanical threshold in the VFT from the 14th day onwards in the animals with induced T1DM [(g) 52. 9±0. 3 vs 40. 5±0. 6]. In turn, 3 and 10 ng/animal doses of PDX were efficient improving mechanical allodynia of animals with induced T1DM from day 16 to 26 in a consistent way [(g) 37. 7±1. 6 vs 42. 4±0. 4 and 44. 9±0. 8, respectively] ($p<0.05$). In experiment 2, PDX treatment did not alter locomotor activity [(frequency) 35. 5±2. 5 vs 37. 8±2. 8] ($p>0.05$), but doses of 3 and 10 ng/animal of PDX altered exploratory activity by increasing rearing frequency [7. 6±1. 5 vs 13. 8±1. 5 and 16. 7±1. 7, respectively]. Regarding the mFST test, all doses of PDX were able to induce an antidepressant-like effect, by decreasing immobility frequency [54. 5±0. 8 vs 38. 2±2. 4] ($p<0.05$). Treatment

with PDX also improved parameters related to the diabetic condition by increasing the weight gain [(g) -13. 5±7. 7 vs 23. 2±7. 7] and decreasing hyperglycemia [(mg/dL) 548. 3±16. 1 vs 470. 5±16. 7] ($p<0.05$). Our findings indicate that PDX presents a therapeutic potential in relieving neuropathic pain and depressive behavior associated with T1DM, and in improving the diabetic condition. Financial Support: Fundação Araucária/CNPq – PRONEX 02/2016, protocol 46843

02.007 **Low Doses of Rotenone Promote Changes in Mitochondrial Membrane Polarization without Cell Death**. Siena A[1], Silva LFS[1], Silva Júnior PI[2], Scavone C[1], Rosenstock TR[1] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]Butantan Institute, São Paulo, Brazil

Administration of mitochondrial complex I inhibitor, Rotenone (Rot 0.1mg/kg), during neurodevelopment, can lead to behavioral deficits in adulthood related to schizophrenia-like phenotype in addition to alterations in synaptic proteins (Siena et al., 2021; Varga et al., 2021). However, the exact cellular mechanism that culminated in this network disruption is not yet elucidated. Then, this work aims to analyze the neuronal alterations promoted by Rot in cortical primary neurons and mitochondrial function. Firstly, we determined the dose that reached the cortex of the animals treated with Rot during the neonatal period (Siena et al., 2021) by high-performance liquid chromatography (HPLC). The neuronal primary culture was produced using 19 days old embryos obtained from female adult Wistar. We evaluate the cellular viability of the Rot doses by reduction of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT); the mitochondrial membrane potential by Tetramethylrhodamine (TMRE) fluorescent dye; and the intracellular calcium levels by Fluo-4 fluorescent dye. The results were analyzed by ANOVA One Way with Bonferroni posthoc. We discovered, by HPLC, that with 7 days of treatment with Rot 0.1mg/kg (schizophrenia-like animal model), 1. 325nM of Rot reached the cortex of the animals (n=3). Then, we used this dose (and a range of Rot doses varying from 0.1nM to 10nM) to treat the primary neuron culture for 24h and 48h. We verified that the cellular viability was not different between Rot treated groups (0.1nM, 0. 5nM, 1. 325nM, 5nM or 10nM) for the period of 24h (p=0. 86) and 48h (p=0. 91), in relation to control group. Regarding mitochondrial function, we found that mitochondria were hyperpolarized in the group treated with Rot 1. 325nM for 24h in relation to the control group (n=3; p=0. 0252). However, the calcium levels were unaltered in the groups treated with Rot (0.1nM, 0. 5nM, 1. 325nM, 5nM, and 10nM) (n=3) for 24h (p= 0. 9) or 48h (p=0. 43), in relation to the control group. Our results indicate that Rot induces mitochondrial membrane hyperpolarization without cellular death. The study was approved by the Animal Research Ethical Committee (4482061120), and it was supported by FAPESP (2015/02041-1; 2021/03021-5). **References:** Siena et al., Mol Neurobiol. 58(7):3015, 2021Varga et al., Psychopharmacology (Berl) 238(9):2569, 2021

02.008 **NADPH Oxidase Contributes to Medullary Respiratory Neurodegeneration and Respiratory Pattern Dysfunction in 6-OHDA Animal Model of Parkinson's Disease**. Medeiros POS, Nascimento ALF, Pedrão LFAT, Takakura AC, Falquetto B USP

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the Substantia Nigra (SNpc). There are several motor and non-motor symptoms, such as respiratory problems. It's also known that oxidative stress is directly related to the neurodegeneration in respiratory regions such as nucleus of solitary tract (NTS), retrotrapezoid nucleus (RTN), preBotzinger complex (preBotC) and rostral ventral respiratory group (rVRG). In 6-hydroxydopamine (6-OHDA) animal PD model, it causes high loss in respiratory function, which may be due to increased enzymatic activity of NADPH Oxidase (NOX). Our aim was to evaluate the effects of the NOX non-specific inhibitor, apocynin (APO), preventing the neurodegeneration of respiratory nuclei and the respiratory deficits in 6-OHDA animals. **Methods:** 6-OHDA (24mg/ml) or vehicle was injected into caudate putamen (CPu) to induce PD model in male Wistar rats (weight: 200-300g, age: 3 months) (n= 100). Dihydroethidium (DHE) analysis for superoxide anion expression in respiratory nuclei (NTS, RTN, PreBotC and rVRG), to measure the oxidative stress, was performed 20 and 40 days after PD induction (n=15). 30 days after brain injections the same assay was done with APO treatment for 10 days (started 20 days after brain injections), (n=26). To evaluate breathing function and neurodegeneration, another experimental group (n=59) was treated with APO for 20 days after 20 days of brain injections. The animal's body weight and water intake were measured every 3-4 days during treatment. On the 35th day, the

animals were submitted to the rotarod motor test and on the 40th day to the whole-body plethysmography, perfusion. Brain dissection was done to perform immunohistochemistry (IHC) to evaluate Phox2b and NK-1R in respiratory nuclei. All animals were submitted to IHC to tyrosine hydroxylase (TH) to evaluate SNpc degeneration. 1- or 2-way ANOVA followed by Bonferroni's was applied with $p < 0.05$. **Results:** 6-OHDA reduced TH+ neurons in SNpc, presented motor dysfunction and APO treatment did not reverse it, as expected, confirming the PD model. DHE analysis didn't show differences at 20 and 40 days after 6-OHDA injections, but at 30 days was an increase in oxidative stress in all respiratory nuclei prevented with APO. rVRG and the preBötC NK1 receptor and the Phox2b marker of the NTS and RTN were reduced in 6-OHDA animals prevented with APO. At normoxia and hypercapnia, 6-OHDA animals showed reduced respiratory frequency and ventilation with changes in inspiratory time and expiratory time that was prevented with APO. **Conclusion:** The respiratory impairments and the neurodegeneration of respiratory neurons observed in the PD 6-OHDA animal model are preceded by superoxide production, possible by NADPH oxidase. **Financial Support:** FAPESP 2019/00065-1 and CNPq/PIBIC 2020. CEUA: 2740200319

02.009 **GL-II-73, A Positive Allosteric Modulator of Alpha 5 Subunit-Containing GABAA Receptors, Improves Cognitive Deficits in Female Senescence-Accelerated Prone 8 (SAMP8) Mice**. Silva T[1], Colodete DAE[1], Guimarães FS[1], Sharmin D[2], Cook J[2], Gomes FV[1] [1]FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil; [2]University of Wisconsin, Dept of Chemistry, Milwaukee, USA

Introduction: Progressive decline in cognitive function is one of the most important manifestations related to aging, especially in Alzheimer's disease (AD). AD is an irreversible neurodegenerative condition with no currently effective therapeutic options. The senescence-accelerated prone 8 (SAMP8) mice and its respective control (senescence-accelerated mouse resistant, SAMR1) have been used to the study of cognitive decline related to aging and AD and new pharmacological approaches to improve cognitive function, since SAMP8 display early phenotype of accelerated aging with learning and memory impairments. Alpha 5 subunit-containing GABAA receptors (α5-GABAAR), expressed mainly in the hippocampus, have been proposed as a potential target to treat aging-related cognitive deficits due to its key role in cognition and memory without the typical side effect of benzodiazepines. Here, we evaluated the effects of GL-II-73 (GL, 10 mg/kg, i. p), a positive allosteric modulator of α5-GABAAR, and Diazepam (DZP, 10 mg/kg, i. p) on cognitive function in females SAMP8 and SAMR1 mice. **Methods:** Female SAMP8 with 6 months (SAMP8-6m) or 9 months old (SAMP8-9m) and SAMR1 9 months old (SAMR1-9m) were subjected to the novelty object recognition (NOR) task to evaluate effect of GL or DZP (n=8-9/group) on cognitive function. Animals were subject to 2 trials separated by 1 hour. During the first trial (acquisition), mice were allowed to explore two identical objects for 5 min in a circular arena. Immediately after the aquisition, animals were injected with GL, DZP or vehicle. In the second trial (retention trial), one of the objects was replaced by a unknow object and animals were placed back in the arena for 5 min. Recognition memory was assessed using the discrimination index, corresponding to the difference between the time exploring the novel and the familiar object, corrected for the total time exploring both objects. All experiments were approved by the Institution's Ethical Committee (CEUA #70/2020). Data were presented as the mean ± the standard error of the mean (SEM). All the data were subjected to tests to verify the homogeneity of variances (Bartlett's test) and if they followed a normal distribution (Shapiro–Wilk test). Those that met these parameters were subjected to parametric analysis (2-way ANOVA followed by the Tukey's post-test). **Results:** SAMP8-9m showed cognitive deficits in the NOR test compared to SAMP8-6m and SAMR1-9m (SAMP8-9m + Veh: -0. 20 ± 0. 08; SAMP8-6m + Veh: 0. 44 ± 0. 09; SAMR1-9m + Veh: 0. 44 ± 0.1; $p < 0.05$; n=11-8/group). GL reversed the cognitive deficits in SAMP8-9m, without inducing changes in SAMP8-6m and SAMR1-9m (SAMP8-9m + GL: 0. 23 ± 0.05; SAMP8-6m+GL: 0. 36 ± 0. 07; SAMR1-9m + GL: 0. 53 ± 0. 06; $p < 0.05$; n=11-8/group). On the contrary, DZP did not attenuate cognitive disruption in SAMP8-9m (SAMP8-9m + Veh: 0. 06 ± 0. 08; SAMP8-9m + DZP: -0. 06 ± 0.14; $p < 0.05$; n=6-8/group). Instead, DZP caused SAMR1-9m to show decreased cognitive performance (SAMR1-9m + Veh: 0. 43 ± 0. 07; SAMR1-9m 0. 09 ± 0. 08; $p < 0.05$; n=6-8/group). **Conclusion:** GL, a positive allosteric modulator of α5-GABAAR, reversed the cognition performance of SAMP8 animals. This study opens new perspective to evaluate the GL as potential pharmacological approach to improve cognition in aging-related disorders, such as AD. **Financial Support:** FAPESP, CAPES and CNPq.

02.010 **Involvement of Neuroinflammation in the Effect of Vitamin D and Donepezil in Adult and Aged Ovariectomized Rats**. Medeiros EB, Gabriel JRM, Santos MLC, Lídio AV, Boaventura A, Ceolin de Jesus L, Santos LM, Bobinski F, Budni J Unesc

Aging is a natural, irreversible process that can be successful or pathological, resulting in chronic degenerative diseases such as Alzheimer's disease. Menopause leads to low estrogen and may induce to dementia. Aging is related to low levels of vitamin D and, when supplemented, has a neuroprotective and neuromodulatory effect. Therefore, this study aims to evaluate the involvement of neuroinflammation in adult and aged ovariectomized rats treated with vitamin D3 alone or associated with donepezil. 2- and 4-month-old Wistar female rats were subjected to ovariectomy (OVX). Those animals were treated for 1 or 8 months after the surgery. The animals were divided into 7 experimental groups (1 - Sham + water; 2 - OVX + water; 3 - OVX+ Vitamin D 42 IU/kg; 4 - OVX+ Vitamin D 420 IU/kg; 5 - OVX+ Donepezil 1mg/kg; 6 - OVX+ Vitamin D 420 IU/kg + Donepezil 1mg/kg; 7 - OVX+ Vitamin D 420 IU/kg + Donepezil 1mg/kg). Treatment with vitamin D (42 or 420 IU/kg orally) and/or donepezil (1 mg/kg orally) lasted 21 days. On the 22nd day of the protocol, 24 hours after the last administration, the animals were euthanized and were dissected the structures of the frontal cortex and hippocampus to analyze the levels of cytokines such as interleukin 10 (IL-10), IL-1 β, and tumor necrosis factor α (TNF- α) by enzyme immunoassay test. The local ethics committee (Ethics Committee on Animal Use - CEUA of the Universidade do Extremo Sul Catarinense) approved this study protocol 123/2019. The study used around 3-6 animals in each group. The results were expressed as the mean+SEM. The enzyme immunoassay data were analyzed by one-way ANOVA followed by Duncan's post hoc test, when appropriated. The results were significant when $p<0.05$. The results showed that 60 days-old rats and 1 month of OVX showed an increase in IL-1β e TNF-α levels in the frontal cortex and hippocampus, and there was a reversal when treated with Vitamin D 420 IU /Kg and associations. The 60 days-old rats and 8 months of OVX showed increased IL-1β levels in the frontal cortex and hippocampus. All treatments could reverse this effect, except the vitamin D 420 IU/kg. In this protocol, TNF-α levels did not show any significant change. However, there was only an increase in IL-10 levels in the frontal cortex, which was reversed by treatment with vitamin D 420 IU/kg, vitamin D 42 IU/kg and vitamin D 42 IU/kg + Donepezil. On the other hand, 120 days-old rats subjected to OVX for 1 month showed an increase in IL-1β levels only in the frontal cortex, but with the treatment of vitamin D 420UI/Kg it was possible to reverse this effect. The OVX induced neuroinflammation and the treatment with vitamin D alone or associated with donepezil had beneficial effect.

02.011 **TRPA1 Channel Involvement in Depression- and Anxiety-Like Behaviors in a Progressive Multiple Sclerosis Model in Mice**. Peres DS[1], Theisen MC[1], Pessano Fialho MF[2], Dalenogare DP[1], Rodrigues P[1], Kudsi SQ[1], Bernardes LB[1], Ruviaro da Silva NA[1], Lückemeyer DD[3], Antoniazzi CTD[1], Santos GT[1] [1]UFSM, Santa Maria, Brazil, [2]UFSM, Toxicological Biochemistry, Santa Maria, Brazil, [3]UFSC, Florianopolis, Brazil

Progressive multiple sclerosis (PMS) is an autoimmune and chronic neurological disease of the central nervous system (CNS) and is associated with the development of depression and anxiety, but the available treatments are still unsatisfactory (ACHARJEE, Brain Behav Immun, 2013). The transient receptor ankyrin 1 (TRPA1) is a cation channel activated by reactive compounds, and it has been shown that blocking this receptor can reduce depressive- and anxious-like behaviors in naive mice. Thus, we investigated the role of TRPA1 in depressive- and anxious-like behaviors in a mouse model of PMS. Adult C57BL/6 female mice (CEUA nº: 8592031218) were induced with the PMS-EAE model using MOG35–55 and CFA (200 µg, 5 mg/ml, s. c.) administered to both flanks (100 µl). Mice also received pertussis toxin in PBS (30 ng/µl) intraperitoneally (i. p.) on day 0 and day 2. Control animals received only corresponding doses of CFA (RITTER, Mol Neurobiol, 2020). Nine days after PMS-EAE induction, 1 hour after drug treatments, behavioral tests (tail suspension and elevated plus maze test) were performed to verify the effects of sertraline (positive control) (PANG, Hum. Mol. Genet, 2009), selective TRPA1 antagonist (A-967. 079), and antioxidants (α-lipoic and apocynin) (RITTER, Mol Neurobiol, 2020). The prefrontal cortex and hippocampus were collected to evaluate biochemical and inflammatory markers. The activity of NADPH oxidase and SOD enzymes in the pré-frontal cortex and hippocampus were evaluated as described before (ANTONIAZZI, Int. J. Cancer, 2018). The activity of NADPH oxidase was observed in samples using an appropriate assay kit (CY0100, cytochrome c reductase, NADPH Sigma-Aldrich, Milan, Italy), and it was expressed as U/mL/mg of protein. To determine the SOD activity, after homogenization, the samples were incubated with

sodium carbonate buffer (Na2CO3) (50 mM, pH 10. 2) at 30 ◦C. The reaction was started by adding adrenaline (60 mM, pH 2. 0), and the reactive mixture was protected from light during the reaction time. The SOD activity was determined spectrophotometrically at 480 nm in kinetic mode for 2 min. The values of SOD activity were described as U/mL of the sample (TREVISAN, Brain, 2016). RNA from the prefrontal cortex and hippocampus was isolated using the ReliaPrep™ RNA Tissue Mini-Prep System (Promega) based on the manufacturer's protocol, which included DNAse treatment, and quantified using a Nanodrop ND-1000. Quantification of specific products was done using GoTaq® qPCR Master Mix (Promega), in StepOne™ equipment (Applied Biosystems). Primer specificity in all samples was confirmed by single peak performances of PCR products in melt curve analysis (LIVAK, Methods, 2001). The induction of PMS-EAE did not cause locomotor changes, but it triggered depressive- and anxious-like behaviors in the tail suspension and elevated plus maze tests, which were reversed by treatments with sertraline, A-967079, α-lipoic acid, or apocynin. Furthermore, PMS-EAE increased NADPH oxidase and superoxide dismutase activities and in the levels of endogenous TRPA1 agonists (hydrogen peroxide and 4-hydroxynonenal). Neuroinflammatory markers (Aif1, Gfap, Il-1β, Il-17, and Tnf-α) were increased in the hippocampus of mice. This model did not alter TRPA1 RNA expression levels in the hippocampus, but decreased TRPA1 levels in the prefrontal cortex. TRPA1 plays a key role in depression- and anxiety-like behaviors in a PMS-EAE model. Thus, it could be a possible pharmacological target for treating depressive and anxious symptoms in PMS. Financial CNPQ and CAPES.

02.012 **The Role of Carbonic Anhydrases in Extinction of Contextual Fear Memory**. Nachtigall EG[1,2], Schmidt SD[2,3,4], Costa A[5], Rani B4, Passani MB[4], Carta F[4], Nocentini A[4], Myskiw JC[2,5], Furini CRG[1,2], Supuran CT[5], Izquierdo I[2], Blandina P[4], and Provensi G[4] [1]PUCRS, Lab of Cognition and Memory Neurobiology, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil; [2]PUCRS, Memory Center, Brain Institute of Rio Grande do Sul, Porto Alegre, Brazil, [3]Western University, London, Canada, [4]University of Florence, Florence, Italy, [5]UFRGS Psychobiology and Neurocomputation Lab, Dept of Biophysics, Institute of Biosciences, Porto Alegre, Brazil

Introduction: Carbonic anhydrases (CAs) are metalloenzymes present in mammals with 16 isoforms that differ in terms of catalytic activity as well as cellular and tissue distribution. CAs are involved in various physiological processes, including learning and memory. Here we report that the integrity of CA activity in the brain is necessary for the consolidation of extinction of fear memory. **Methods:** Adult male Wistar rats were submitted to contextual fear conditioning (CFC). The training session consisted of 2 min habituation followed of three electrical footshocks (0. 5 mA, 2 s) at 30-s intervals (day 1). On Day 2, animals returned to CFC apparatus for a 15- or 30-min extinction session (Ext), without footshock. Immediately after Ext sessions vehicle (Veh - saline solution 0. 9%), CA activator (D-phenylalanine, D-phen), or CA inhibitors (acetazolamide, ACTZ or 1-N-(4-sulfamoylphenyl-ethyl)-2,4,6-trimethylpyridinium perchlorate, C18) were administered either systemically (i. p.) or locally into selected brain regions through cannulae stereotaxically implanted bilaterally. After 24 h (day 3), animals were submitted to a 3-min retention test. The time the animals spent freezing was measured during the first 2 min of training session, during the Ext session and during the retention test. Data were analyzed using two-way ANOVA followed by Bonferroni's test. For all groups data are expressed as mean ± SEM. **Results:** We found that systemic administration of ACTZ (10 or 30 mg/kg), a CA inhibitor, immediately after a 30-min extinction session dose-dependently impaired the consolidation of fear extinction memory, whereas C18 (30 mg/kg), a membrane-impermeable CA inhibitor that is unable to reach the brain tissue, had no effect. n = 6-10 per group. $P < 0.001$, ACTZ 30 mg/kg vs. Veh, ACTZ 10 mg/kg, and C18 30 mg/kg in the retention test. To evaluate a potentiating effect, a weaker extinction protocol was induced by shortening the Ext session to 15 min. When administered immediately after the 15-min Ext session, D-phen (300 mg/kg), a CA activator, enhanced the consolidation of extinction memory. Simultaneous administration of ACTZ fully prevented the promnesic effect of D-phen. n = 8-9 per group. $P < 0.05$, $P < 0.01$, D-phen vs. Veh and D-phen + ACTZ in the retention test. Furthermore, when administered locally into the ventromedial prefrontal cortex, basolateral amygdala or hippocampal CA1 region, after a 30-min extinction session, the CA inhibitor ACTZ (10 nmol/side) impaired the consolidation of extinction memory. However, this effect was not observed when ACTZ was infused into the substantia nigra pars compacta. n = 8 to 13 per group. $P < 0.0001$ Veh vs. ACTZ in the retention test. Additionally, to evaluate a potentiating effect, a 15-min Ext session was performed and D-phen (50 nmol/side) was infused into the ventromedial prefrontal cortex, basolateral amygdala or hippocampal CA1 region wherein was able to

potentiate the consolidation of extinction memory. This effect was not observed when D-phen was infused into the substantia nigra pars compacta. For all regions, data are P < 0. 01 or P < 0. 0001, Veh vs. D-phen in the retention test. n = 8 to 13 per group. **Conclusion:** These findings reveal that the engagement of CAs in some brain regions is essential for providing the brain with the necessary resilience to ensure the consolidation of extinction of emotionally salient events. Authorization of Italian Ministry of Health: nº649/2017. **Financial Support:** Italian Ministry of Education, Universities and Research; CNPq and CAPES.

02.013 **Melatonin Reduces β-Amyloid Accumulation and Improves Short-Term Memory in Streptozotocin-Induced Sporadic Alzheimer's Disease Model**. Andrade MK[1], Souza LC[1], Azevedo EM[2], Bail EL[2], Zanata SM[3], Andreatini R[1], Vital MABF[1] UFPR, [1]UFPR, Dept of Pharmacology, Curitiba, Brazil, [2]UFPR, Dept of Physiology, Curitiba, Brazil, [3]UFPR, Dept of Basic Pathology, Curitiba, Brazil,

Melatonin is a hormone secreted by the pineal gland, it can be associated with circadian rhythms, aging and neuroprotection. Melatonin levels are decreased in sporadic Alzheimer's disease (sAD) patients, which suggests a relationship between the melatonergic system and sAD. Melatonin may reduce inflammation, oxidative stress, TAU protein hyperphosphorylation, and the formation of β-amyloid (Aβ) aggregates. Therefore, the objective of this work was to investigate the impact of treatment with 10 mg/kg of melatonin (i. p) in the animal model of sAD induced by the intracerebroventricular (ICV) infusion of 3 mg/kg of streptozotocin (STZ). ICV-STZ causes changes in the brain of rats similar to those found in patients with sAD. These changes include; progressive memory decline, the formation of neurofibrillary tangles, senile plaques, disturbances in glucose metabolism, insulin resistance and even reactive astrogliosis characterized by the upregulation of glucose levels and glial fibrillary acidic protein (GFAP). The results show that ICV-STZ caused short-term spatial memory impairment in rats after 30 days of STZ infusion without locomotor impairment which was evaluated on day 27 post-injury. Furthermore, we observed that a prolonged 30-day treatment with melatonin can improve the cognitive impairment of animals in the Y-maze test, but not in the object location test. Finally, we demonstrated that animals receiving ICV-STZ have high levels of Aβ and GFAP in the hippocampus and that treatment with melatonin reduces Aβ levels but does not reduce GFAP levels, concluding that melatonin may be useful to control the progression of amyloid pathology in the brain.

03. Psychopharmacology

03.001 **Lower Antidepressant Response to Fluoxetine is Associated with Anxiety-Like Behavior, Hippocampal Oxidative imbalance, and increase on Peripheral IL-17 and IFN-γ Levels**. Piton E[1], Pereira GC[2], Santos BM[2], Bochi GV[2,3] [1]UFSM, Graduating in Pharmacy, Santa Maria, Brazil, [2]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2,3]UFSM, Dpt of Physiology and Pharmacology, Santa Maria, Brazil

Major depressive disorder (MDD) is a mood disorder characterized by its chronic and recurrent nature, in addition to high rates of refractoriness to treatment. Treatment-resistant depression is defined as a subset of MDD, characterized by refractoriness to traditional or first-line treatment options, considered to be failure to respond to two or more antidepressants. Thus, the aim of this study was to investigate the effect of fluoxetine treatment on depressive-like behavior and oxidative and inflammatory parameters in mice submitted to chronic administration of corticosterone (AC). Forty-three Swiss male mice (20-30 g, at 6-8 weeks) approved by the UFSM Animal Care and Use Committee (Process number 7698200617/2017) were used. The animals were initially segregated into 3 groups: vehicle (VEH), corticosterone (CORT) and corticosterone + fluoxetine (CORT+FLU). Subcutaneous AC (20 mg/kg/day) or vehicle was performed for 21 days and oral treatment with fluoxetine (10 mg/kg/day) for 14 days, started on the 7th day of corticosterone administration. After 24 hours of the last administration, the animals were submitted the following behavioral tests: Open Field Test (OFT), Elevated Plus Maze Test (EPMT), Tail Suspension Test (TST) and Forced Swimming Test (FST), followed by euthanasia to remove brain structures and blood. After evaluating the immobility time in the TST (F3,31 = 21. 7, p < 0. 0001), the animals CORT+FLU group were subdivided into two groups: antidepressant responders (good response to antidepressant, GRA, less immobility. GRA 41. 1 ± 8. 8 vs. CORT 126. 4 ± 5. 4, p < 0. 0001) and non-responders (resistance to antidepressant, AR, greater immobility. AR 111. 0 ± 14. 7 vs. GRA 41. 1 ± 8. 8, p < 0. 0001). Furthermore, the animals of the CORT group presented longer immobility time than the VEH group, indicating depressive-like behavior (CORT 126. 4 ± 5. 4 vs. VEH 75. 8 ± 4. 4, p < 0. 001). In the FST (F3,29 = 17. 1,

p < 0. 0001), the animals of the CORT group showed a tendency towards greater immobility when compared to the VEH group (CORT 107. 0 ± 10. 6 vs. VEH 71. 8 ± 6. 4, p = 0.0536), while the GRA and AR groups had reduced immobility when compared to the CORT group (p < 0. 0001). In the EPMT, the GRA group spent more time in the open arms (F3,30 = 7. 6, p < 0. 001; GRA 71. 2 ± 6. 6 vs. CORT 32. 5 ± 9. 0, p = 0. 0059; GRA 71. 2 ± 6. 6 vs. AR 38. 3 ± 7. 0, p = 0. 0416) and less time in the closed arms (F3,31 = 6. 7, p = 0. 0013; GRA 152. 0 ± 7. 83 vs. CORT 208. 1 ± 11. 6, p = 0. 0025; GRA 152. 0 ± 7. 83 vs. AR 203. 7 ± 10.1, p = 0. 0121) when compared to the CORT and AR groups, suggesting that both showed greater anxiety-like behavior. In the OFT, there were no significant differences in locomotor and exploratory activity of the animals (crossing p = 0. 0896, rearing p = 0.1221). Regarding *in vitro* analyses, the AR group exhibited increased levels of hydrogen peroxide (H2O2) in hippocampus when compared with GRA (t(13) = 2. 191, p = 0. 0473) and decreased activity of the catalase enzyme in the hippocampus compared to the GRA (t(13) = 2. 325, p = 0. 0369), as well as increased serum levels of IL-17 (t(7) = 2. 835, p = 0. 0252) and IFN-γ (t(9) = 2. 726, p = 0. 0234). It can be suggested that the impaired response to fluoxetine treatment of the animals in the AR group is evidenced by anxiety-like behavior, accompanied by a hippocampal redox imbalance, combined with increased levels of peripheral IL-17 and INF-γ. **Financial Support:** CAPES and CNPq.

03.002 **Experimental Evaluation of Delayed Behavioral Changes Associated with Depression in Mice Infected with *Plasmodium berghei* ANKA, Pharmacologically Treated And Cured**. Pires BB[1], Medeiros JGC[1,2], Noleto TG[2], Passos TG[2], Oliveira JPM[1,2], Dias QM[1,2] [1]UniSL-Afya [2]Fiocruz-RO, Lab de Neuro e Imunofarmacologia

Introduction: Evidence shows that patients who had malaria and were effectively treated with antimalarials may develop neuropsychiatric changes within days or weeks after effective cure. Among the main neuropsychiatric alterations observed are confusion, convulsion, speech alterations, and tremor. However, there is no evidence that malaria can trigger long-term psychiatric disorders like depression. Therefore, the present study aimed to assess whether *Plasmodium*-infected mice that were effectively treated with antimalarials developed long-term behavioral changes associated with the development of depressive disorders in the forced swim test. Method: In the study, C57BL/6 adult male mice were infected with 10^6 red blood cells parasitized by *Plasmodium berghei* of the ANKA strain and treated with chloroquine (25 mg/kg) and primaquine (0. 72 mg/kg) for seven days. The animals were infected on day 0 of the experimental protocol, and the infection was monitored by analyzing parasitemia on the 5th, 13th, and 19th days post-infection. From the 6th to the 12th day post-infection, the animals were treated with the antimalarial combination chloroquine plus primaquine. On the 18th day post-infection, the forced swimming test evaluated behavioral manifestations associated with depression. The forced swim test is an experimental model widely used to assess stress-related changes (behavioral despair). **Results:** The results show that the infected animals developed *Plasmodium* infection, as verified by verifying parasitic blood forms typical of the parasite. Antimalarial treatment with chloroquine + primaquine proved effective, as evidenced by the absence of post-treatment parasitic forms. In the forced swimming test, performed on the 18th day post-infection, it was observed that the experimental animals treated with antimalarials, uninfected and infected by *Plasmodium*, showed no significant change in swimming time or immobility time as compared to control. **Conclusion:** These results indicate that the treatment with antimalarials in uninfected animals and those infected by *Plasmodium* did not show behavioral changes suggestive of the development of depression post-infection. **Financial Support:** Programa de Excelência em Pesquisa da Fiocruz Rondônia – PROEP. Animal Research Ethics Committee: license number 08/2021. **Reference**: SLATTERY DA et al. Nature protocols. 7(6): 1009-1014, 2012; DE SOUSA LP, et al. Parasit Vectors. 11(1):191, 2018; ROMAN GC; SENANAYAKE N. Arq. Neuro-Psiquiat. 50(1):3-9, 1992.

03.003 **Alcohol Binge Drinking and Taurine are not Associated with Anxiety-Like Behaviors in Adolescent Rats**. Sant'Ana BH[1], Zilli GAL[1], Bastiani CS[1], Pulcinelli RR[1], Izolan LR[2], Gomez R[1,2] [1]UFRGS – PPG Farmacologia e Terapêutica, [2]UFRGS– PPG Neurociências

Introduction: Episodic consumption of an excessive amount of alcohol in a short period (binge drinking - BD) is a harmful risk behavior associated with serious injuries and diseases. In adolescents, BD has been associated with disruption of the brain frontal connectivity maturation and predisposes to alcohol use disorder in adulthood. Energy drinks contain taurine, a semi-essential amino acid with osmoregulatory and anti-

inflammatory properties. In the brain, taurine acts as a positive modulator of GABAergic and a negative modulator of glutamatergic systems. Combined alcohol and energy drink consumption is four times more likely to binge drink at high intensity. However, taurine effects on BD behavior have not yet been explored. Thus, we aimed to evaluate the effect of different regimes of taurine treatment on the anxiety-like behavior of adolescent rats exposed to the BD model. **Methods:** Adolescent (PND35) male Wistar rats (n=48) were exposed to 4 cycles of BD, with free access to bottles containing alcohol solution (20%), 2 h/day, for 3 days, followed by 4 days of withdrawal. They were divided into 4 groups according to saline or taurine (100 mg/kg) i. p. administration: 1) S – saline; 2) T – taurine; 3) TD – taurine only during BD; and 4) TA – taurine only during withdrawal. Groups TD and TA received saline on the other days. On day 24 (PN60), 18 h from the last BD session, rats were exposed to the light-dark box for 5 min. **Results:** Results showed that either different regimes of taurine administration or BD did not show anxiogenic or anxiolytic-like effects. Only rats from the TD group decreased their risk assessment behavior (P = 0. 049). **Conclusion:** We conclude that withdrawal from BD is not associated with anxiogenic-like behavior in adolescent rats, suggesting that this pattern of consumption does not produce anxiety or that adolescents are more resilient to alcohol episodic consumption effects. However, we found that combined use of alcohol and taurine during BD increased rats' impulsivity, related to lower time evaluating risk in the TD group. **Financial Support:** CNPq, CAPES, Propesq-UFRGSApproval by Animal Research Ethical Committee: CEUA-UFRGS # 41136

03.004 **Maternal Deprivation Induces Long-term Anxious-like Behavior and Exacerbates Lipopolysaccharide-Induced Microglia Activation in the Dentate Gyrus**. Oliveira CA, Gaspar DM, Chaves Filho AJM, Sousa RC, Cunha NL, Jucá PM, FM-UFC – Neuropharmacology Lab, Drug Research, and Development Center, Department of Physiology and Pharmacology, Fortaleza, Brazil

Early life stress (ELS) has been very related to the development of depression in adulthood. In this study, we hypothesized that ELS induced by maternal deprivation (MD) will promote age-progressive abnormal anxiety behavior and hippocampal microglia activation in mice. Therefore, we aimed to determine the behavioral and microglia morphology changes in adult and aged mice submitted to maternal deprivation early in life, with and without a systemic immune challenge with lipopolysaccharide (LPS). Then, the animals were separated from their mothers for 1 hour for a total period of 13 days from postnatal day (PND) 1 to PND13. At the PND60 and PND180, motherly-deprived (MD+) and control (MD-) groups were exposed to an intraperitoneal LPS injection (0. 5 mg/kg) or saline and, 24-hours later, they were submitted to behavioral tests: the open field (OFT) and the light/dark box test (LDB). The dentate gyrus was chosen for the counting analysis of different microglia phenotypes (ameboid, intermediary, bipolar and ramified). For behavioral analysis, it was used an N of 10 animals/group, and for microscopy analysis, an N of 4 animals/group with at least 3 images of randomly selected site/animal. In the OFT, we did not observe any significant difference between the tested groups. Otherwise, in LDB we observed a significant increase in the latency time(s) in the group MD+ /aged/LPS compared to MD+/aged/SAL (MD: -79,24; CI of diff, -147,2 to -11,25. P=0,0119), to MD+/adult/LPS (MD:-77,38, CI of diff: -145,4 to - 9,377, P= 0,0153) and to MD-/adult/SAL (-MD: 84,18, CI of diff: -152,2 to -16,19, P = 0,006). In a similar-way, both aged MD+ groups (MD+/aged/SAL and MD+/aged/LPS) showed a significant increase in the time spent in the dark box compared to their respective non-deprived groups: MD-/aged/SAL (MD:-105,6, CI of diff: 204,8 to -6,492, P=0,0290) and MD-/aged/LPS (MD: -114,7; CI of diff: -207,7 to -21,58, P=0,0064). Moreover, in the morphometric analysis of microglia, a non-significant tendency to increase the number of ameboid microglia was evident in the aged LPS-challenged groups: MD-/aged/LPS (MD: - 4,333, CI of diff: -9,790 to 1,123, P=0,1797) and MD+/aged/LPS (MD: -4,000, CI of diff: - 9,456 to 1,456, P= 0,2518) compared to MD-/adult/LPS and MD+/adult/LPS. Regarding ramified microglia, we observed a significant decrease in this microglia phenotype in both aged LPS-challenged groups: MD-/aged/LPS (MD:24,00, CI of diff: 7,187 to 40,81, P=0,0029 and MD+/aged/LPS (MD: 25,67, CI of diff: 8,854 to 42,48, P=0,0015) compared to MD-/adult/SAL one. Additionally, a significant decrease in ramified microglia was evident in the group MD+/adult/LPS compared to MD-/adult/SAL (MD: 21,00, CI of diff: 4,187 to37,81, P=0,0095). In Conclusion: these results indicate that MD induced an anxious-like behavior mainly in aged animals, and potentiated the anxiogenic-like effect of LPS in senescence. Also, regarding microglia morphology, LPS challenge promoted a tendency to exacerbate microglia activation (ameboid cell) in aged animals, while MD reduced homeostatic ramified microglia in both ages. These results

indicate MD as ELS affects the long-term anxiety-like behavior of mice and promoted age-progressive microglia morphological changes toward a microglia ameboid phenotype in aged mice. This study was approved by the Ethics Committee on Animal Use of the Federal University of Ceará through protocol 37/2016, obeying the technical and ethical principles of the Brazilian College of Animal Experimentation. Keywords: Maternal deprivation, Microglia, Anxiety.

03.005 **Assessment of Anxiety Level and Locomotor Ability in Experimental Malaria Recurrence in Pharmacologically treated Mice Infected by *Plasmodium berghei* ANKA**. Medeiros JGC[1,2], Pires BB[1,2], Oliveira JPM[2], Nôleto TG[1], Passos TG[1], Dias QM[1,2] [1]NIMFAR-Fiocruz-RO [2]Afya-UniSL

Introduction: Malaria is a severe infectious disease caused by the protozoan of the *Plasmodium* genus. This disease is pharmacologically treatable with antimalarial drugs such as chloroquine in combination with primaquine. Evidence indicates that *Plasmodium* infection and antimalarial drugs can generate neuropsychiatric alterations, such as changes in the level of anxiety and locomotor activity. These manifestations can be observed during the malaria infection and reinforced during the antimalarials during treatment. Although pharmacological treatment of malaria is effective in curing the disease in most cases, there are reports of therapeutic failure that led to disease recurrence. The effect of malaria recurrence on anxiety and locomotor capacity was not reported. In this sense, the present study evaluated the changes in anxiety level and locomotor capacity in mice that developed malaria recurrence after effective treatment with antimalarials. **Methods:** The experimental malaria was induced by intraperitoneal injection of *Plasmodium berghei* ANKA in adult male C57BL/6 mice. The antimalarial used was chloroquine plus primaquine injected by intraperitoneal route for seven consecutive days. For the accomplishment of the study, the animals were infected with *Plasmodium*, and the infection was followed by the analysis of the parasitemia on the 5th, 13th, 18th, 23rd, and 29th days post-infection. From the 6th to the 12th day post-infection, the animals are treated with the antimalarial combination chloroquine plus primaquine. **Results:** On the 15th-day post-treatment with antimalarials (28th day post-infection), the behavioral manifestations associated with anxiety and the motor displayed in the elevated plus-maze test are evaluated. Preliminary results show that infected animals developed *Plasmodium* infection, as evidenced by observing parasitic blood forms typical of the parasite. Antimalarial treatment with chloroquine plus primaquine proved effective, as evidenced by the absence of parasitic forms on the 1st and 6th day after treatment, corresponding to the 13th and 18th day post-infection. Recurrence of infection was confirmed by analysis of parasitemia from the 11th post-treatment day, which persisted until the 17th post-treatment day, corresponding to the 23rd and 29th post-infection days. The 29th-day parasitemia was significantly higher than the 5th-day post-infection parasitemia. In the elevated plus-maze test, performed on the 28th day post-infection (18th-day post-treatment), we observed that the experimental animals treated with antimalarials, both uninfected and infected by *Plasmodium*, did not show a significant change in the number of entries in the arms open arms, time spent in the open arms and time spent in the central quadrant. **Conclusion:** These results indicate that the treatment with antimalarials in uninfected animals and those infected by *Plasmodium* did not present significant changes in the anxiety level. It was also observed that animals infected with *Plasmodium* and that had post-treatment recurrence showed a significant reduction in the number of crossings in the central quadrant, in the total number of entrances in the arms, and the total number of crossed areas plus elevation. **Financial Support:** Programa de Excelência em Pesquisa da Fiocruz Rondônia – PROEP. Animal Research Ethics Committee: license number 08/2021.

03.006 **Two Weeks of Strength Training Fails to Decrease Voluntary Alcohol Consumption but Decreases Anxiety-Like Behaviors in Alcohol Withdrawal Rats**. Bastiani CS[1], Pulcinelli RR[1], Izolan LR[2], Silva J[2], Zilli GAL, Sant'Ana BH, Gomez R[1,2] [1]UFRGS – PPG Farmacologia e Terapêutica, Porto Alegre, Brasil, [2]UFRGS – PPG Neurociências, Porto Alegre, Brasil

Introduction: Alcohol use disorder (AUD) is a serious public health problem with few therapeutic alternatives available. Although physical exercise is a safe and effective form of prevention and therapeutic resource for several health problems, little is known about the benefits of exercise for individuals with AUD. The possible effects of an intervention with physical strength training on alcohol consumption behavior have not yet been investigated in preclinical studies of alcoholism. The aim of this study was to evaluate the effect of strength training on behavioral changes resulted by alcohol chronic consumption and withdrawal in rats. **Methods:** Male

adult Wistar rats (n=96) were divided into 6 groups: Sedentary Control (CS), Trained Control (CT), Abstinent Sedentary (WS), Abstinent Trained (WT), Alcohol Sedentary (AS), and Alcohol Trained (AT). Two-bottle choice model of voluntary alcohol intake was used to induce alcohol dependence for 28 days. Then, the animals were strength trained by vertical climbing for 2 weeks. Voluntary alcohol consumption and anxiety-like behaviors in the light/dark task were evaluated. **Results:** Strength training did not significantly alter the alcohol voluntary intake or alcohol preference in chronic alcohol-treated rats (AT group). Conversely to our expectations, rats from the AT group showed anxiety-like behavior after the intervention with physical exercise. However, strength training prevented anxiety-like behaviors of the alcohol abstinent rats (WT group). **Conclusion:** Strength training intervention prevents the anxiety-like effect produced by alcohol withdrawal, possibly related to its anti-inflammatory and neuroprotective effects. We suggest that strength training may be beneficial as an adjuvant therapy to abstinent alcohol-dependent individuals, possibly preventing relapse by reducing the withdrawal-associated anxiogenic effect. **Financial Support:** CNPq, CAPES, Propesq-UFRGSApproval by Animal Research Ethical Committee: CEUA-UFRGS # 36723

03.007 **Evaluation of Angiotensin I – Converting Enzyme (ACE) Activity in a Transgenic Animal Model of Schizophrenia (SCZ)**. Santiago TC[1], Nani JVS[1,2], Cruz FC[1], Hayashi MAF[1,2] [1]Unifesp-EPM, Dept. Pharmacology, São Paulo, Brazil, [2]Instituto Nacional de Medicina Translacional (INCT-TM, CNPq/FAPESP/CAPES), Ribeirão Preto, Brasil

Introduction: Schizophrenia (SCZ) is a serious mental disorder whose symptoms are classified as positive (such as hallucinations and delusions), negative (such as anhedonia and decreased social interaction), and cognitive (learning and memory deficits). The diagnosis of MDs is mainly based on clinical interviews, therefore, still lacking of molecular methods or biomarkers to support the differential diagnosis of several MDs sharing similar symptoms. SCZ has no cure and the currently treatment employs typical and/or atypical antipsychotics drugs that act as antagonists of dopaminergic and serotoninergic system. Our group has investigated the role of oligopeptidases in the pathophysiology of SCZ, and their use as potential biomarkers to support the diagnosis and/or to follow-up the disease progression was recently proposed. The oligopeptidase angiotensin I - converting enzyme (ACE) has been associated with cognitive dysfunction in SCZ patients, and our group has demonstrated that those patients have higher ACE activity when compared to healthy controls. Disrupted-in-Schizophrenia 1 (DISC1) gene was initially identified as a susceptibility risk factor for SCZ, however, the protein product of this gene is now investigated due to its possible association with dopamine signaling impairments. Aiming to evaluate if higher ACE activity observed in SCZ patients is related to dysfunctional proteostasis of DISC1, a transgenic animal model overexpressing the full-length human DISC1 (tgDISC1) showing aberrant neurodevelopment and amphetamine-supersensitivity due to DISC1 aggregates, was used to evaluate ACE activity in blood samples, after a chronic treatment with the atypical antipsychotic clozapine. **Methods:** Male Sprague-Dawley rats (5-month-old) wild-type control (WT) and tgDISC1 were separated into 4 groups: groups 1 and 2 (WT and tgDISC1, respectively) received saline vehicle by intraperitoneal (i. p.) route for 30 days, while groups 3 and 4 (WT and tgDISC1, respectively) were daily treated with the atypical antipsychotic clozapine (2. 5 mg/kg, i. p.) for 30 days (N = 8/group). ACE activity was determined by monitoring the hydrolysis of the FRET substrate (Abz -FRK(Dnp)P-OH). Data were analyzed by two-way ANOVA test, considering the strain and the treatment as independent variables. The distributions were checked by Shapiro-wilk normality test and homogeneity of variances by Levenne's test. The values were considered significantly different for $p \leq 0.05$. **Results:** ACE activity (mean ± standard deviation) in tgDISC1 (3. 25 ± 0. 31) and WT (3. 66 ± 1. 06) groups did not show significant differences (strain effect: F (1,25) = 0. 8, p = 0. 366). On the other hand, after 30 days of daily treatment with clozapine, a significant increase in ACE activity was observed in both WT (5. 98 ± 2. 34) and tgDISC1 (5. 44 ± 1. 34) animals (treatment effect: F (1,25) = 19. 03, p = 0. 01). **Conclusion:** The present results, showing increased ACE activity after a long-term treatment with an atypical antipsychotic, corroborate with the hypothesis of the interaction of ACE with the dopaminergic system, since the antagonism of dopaminergic system by the antipsychotic clozapine increased the ACE activity. However, the DISC1 protein misassembly, which was demonstrated to alter dopamine homeostasis, does not seem to influence the ACE activity changes in response to the treatment with clozapine. The Ethical Committee of the Federal University of São Paulo

(UNIFESP/EPM), under CEUA nº 8047260421 (id 011221), approved this study. **Financial Support:** FAPESP, CNPq and CAPES.

03.008 **The Anticompulsive-like Effect of Memantine Seems not to Depend on Sex of Mice**. Macedo BL, Veloso MF, Dias IB, Ayub JGM, Beijamini V UFES, Dept of Pharmaceutical Sciences, PPG Health Sciences Center, Vitória, Brazil

The Anticompulsive-like Effect of Memantine Seems Not to Depend on Sex of Mice Macedo BL[a], Veloso MF[b], Dias IB[b], Ayub JGM[a], Beijamini V[b a a]Pharmaceutical Sciences Graduate Program, Health Sciences Center, Federal University of Espírito Santo, Vitória, ES, Brazil [b a]Dept of Pharmaceutical Sciences, Health Sciences Center, Federal University of Espírito Santo, Vitória, ES, Brazil ***Introduction***: The selective serotonin reuptake inhibitors (SSRI) are the first-line drugs for treatment of obsessive-compulsive disorder (OCD). Nevertheless, up to 40-60 % of patients do not respond properly to the SSRI. For this reason, new drugs are under evaluation. Some clinical and preclinical studies showed that memantine, a non-competitive NMDA receptor antagonist, induces anti-compulsive effects [1, 2, 3]. However, none of them reported or investigated if there are sex differences. Additionally, female mice seem to be more sensitive to the behavioral effects of ketamine, another NMDA antagonist. This study aimed to examine whether sex influences the effect of acute administration of memantine in male and female mice tested in the marble-burying test (MBT), an animal test for screening of anti-compulsive-like effect. We hypothesized that female mice would respond to memantine at lower doses than male mice. **Methods:** Both male and female adult Swiss mice (8-10 weeks old) were used. The animals were maintained in the same temperature-controlled room (± 22°C) under a 12h light-dark cycle (lights on at 6:30 a. m.), and the bedding was changed three times a week. The experiment evaluated the effects of memantine (3 and 10 mg/kg i. p.) in mice submitted to Open Field Test (OFT) and the MBT at 30 and 35 min, respectively, after drug administration. Fluoxetine 10 mg/kg was used as positive control and saline was administered to the control group. An experimenter blinded to treatment groups evaluated the number of marbles buried in the MBT. The total distance traveled in the OFT was measured by Anymaze software. Data were represented as mean + standard error of mean and analyzed by two-way ANOVA followed by Tukey post hoc when appropriated. Our protocol was accepted by the Committee for the Ethical Use of Animals in Scientific Research (CEUA-UFES nº 16/2018). Every effort was made to minimize the animals suffering. **Results:** Memantine 10 mg/kg (male n=12, 4. 6 ± 1. 1; female n=10, 2. 2 ± 0. 8), but not 3 mg/kg (male n=12, 5. 2 ± 1. 1; female n= 12, 5. 1 ± 1. 2), decreased the number of marbles buried in the MBT (treatment effect, F2,69=8. 6, p< 0. 001, p<0,001 from Tukey compared to the control group (male n=12, 8. 2 ± 1. 1; female n=12, 7. 1 ± 1. 1) without changing locomotor activity (treatment effect, F2,69= 0. 997, p=0. 375). No differences between sexes were observed in the number of marbles buried (sex effect, F1,69=115, p= 0.115; no interaction between treatment and sex) and in the locomotor activity (sex effect, F1,69=0.113, p=0. 738, no interaction between treatment and sex). **Conclusion:** Our results reproduced the anti-compulsive-like effect of memantine in male mice. Our data also suggest that memantine induced an anti-compulsive-like effect in female Swiss mice and showed no influence of sex in this effect. **Financial Support:** Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Universidade Federal do Espírito Santo (UFES). **References**: [1] EGASHIRA, N. EURO. J. PHARMA., 586, 164, 2008. [2] MODARRESI, M. PHARMA., 51, 263, 2018. [3] GHALEIHA, A. J. PSY. RES., 47,175, 2013.

03.009 **Glutamatergic Signaling within the Dorsal Hippocampus Modulates the Effects of Delta-9 Tetrahydrocannabinol in Fear Memory Labilization and Reconsolidation**. Raymundi AM, Sohn JMB, Salemme BW, Stern CAJ UFPR, UFPR, Dpt of Pharmacology, Curitiba, Brazil

Introduction: Upon retrieval fear memory may become labile and undergoes reconsolidation, which has great potential in the treatment of posttraumatic stress disorder (PTSD). GluN2B- and GluN2A-NMDA receptors seem to be necessary for labilization and reconsolidation, respectively, as well as cannabinoid type-1 receptors (CB1) of the dorsal hippocampus (DH). Cannabis compounds such as delta-9-tetrahydrocannabinol (THC), a partial agonist of CB1, have been suggested as a treatment for PTSD. Since CB1 activation may change the expression of GluN2B- and GluN2A-NMDA, we hypothesized that THC would affect memory labilization by changing the expression of GluN2B- and/or GluN2A-NMDA receptors in the DH. The objective was to investigate the effects of THC on fear memory labilization and consequently, reconsolidation. **Methods:** Fear-conditioned male Wistar rats (n=8-11/group) were exposed to a short retrieval to induce labilization/reconsolidation. 20 min before they

received THC (0. 002 or 0. 3 mg/kg) or vehicle (VEH) i. p. and immediately after retrieval, VEH or anisomycin (ANI, protein synthesis inhibitor; 50 µg/0. 5 µl/side) into the DH. In experiment 2, 20min before retrieval, rats received VEH or THC 0. 3 i. p. and VEH, PEAQX (GluN2A-NMDA receptor antagonist; 0. 5 ng/0. 5 µl/side), or ifenprodil (IFE; GluN2B-NMDA receptor antagonist; 0. 5 ng/0. 5 µl/side) into the DH. Immediately after retrieval, they received VEH or ANI. In experiment 3, 20min before retrieval, rats received VEH or THC 0. 002 i. p. and VEH, PEAQX, or IFE into the DH. After 1 and 7 days, rats were exposed again to the context to Test A1 and Test A2 to evaluate the treatment effects. The DH of rats treated with THC (0. 002 or 0. 3 mg/kg) or vehicle (VEH) i. p. 20min before retrieval were removed immediately after retrieval or Test A1 and the expression of GluN2A and GluN2B were analyzed by western blot. Results were expressed as mean±SEM and analyzed by Repeated-measures ANOVA followed by Newman-Keuls. CEUA authorization number 1247. **Results:** The ANI infusion into the DH of VEH-pretreated rats or the pretreatment with THC 0. 002 significantly reduced freezing behavior during Test A1 (32. 4±5. 6 and 42. 6±6. 0) and Test A2 (23. 7±5. 1 and 23. 7±5. 2) compared to controls (Test A1: 74. 1±4. 7; Test A2: 52. 4±8. 1), suggesting an impairment in memory reconsolidation. However, the pretreatment with THC 0. 3 abolished the ANI-induced effect (Test A1: 68. 5±6. 1; Test A2: 45. 0±6. 5) suggesting an impairment in memory labilization [F(4,88)=4. 47; p=0. 002]. The blockade of GluN2B, but not GluN2A, prevented the reconsolidation impairing effects on Test A1 of THC 0. 002 (74. 3±5. 4) [F(2,46)=3. 66; p=0. 03] and ANI (60. 6±5. 5) [F(2,54)=4. 45; p=0. 02]. However, the blockade of GluN2B, but not GluN2A, restored the ANI effect in THC 0. 3-pretreated rats (16. 4±3. 9) [F(2,56)=9. 28; p=0. 001]. The treatment with THC 0. 3 before memory retrieval significantly decreased the expression of GluN2A (33. 9 ± 6. 6) [F(3,20)=3. 31; p=0. 04] and the GluN2A/GluN2B ratio (42. 1±9. 6) [F(3,19)=3. 16; p=0. 04] in the DH compared to controls (100.1±30. 8 and 119. 8±33. 2) after Test A1, without changing GluN2B expression. No significant changes were observed after retrieval. **Conclusion:** A low dose of THC did not affect fear memory labilization and disrupted reconsolidation, whereas the highest dose impaired memory labilization. These effects depended on hippocampal GluN2B-NMDA receptors, suggesting that activation of CB1 receptors modulates the contribution of NMDA receptors in memory labilization and reconsolidation. **Financial Support:** CAPES and CNPq.

03.010 **Taurine Reduces Serum Corticosterone of Highly Alcohol-Consuming Rats**. Pulcinelli RR[1], Izolan LR[2], Zilli GAL[1], Sant'Ana BH[1], Bastiani CS[1], Gomez R[1,2] [1]UFRGS, PPG Farmacologia e Terapêutica, Porto Alegre, Brazil, [2]UFRGS, PPG Neurociências, Porto Alegre, Brazil

Introduction: Alcohol regulates the hypothalamic-pituitary-adrenal (HPA) axis, serum corticosterone (CORT) release, and stress-related responses. Taurine is an abundant amino acid in the CNS that show antioxidant, anti-inflammatory, and neuromodulatory properties. Taurine administration prevents alcohol-induced neurotoxicity, oxidative stress, and withdrawal behavioral signs in rats. We previously showed that chronic taurine increases voluntary alcohol intake and produces anxiolytic-like behaviors in alcohol-dependent rats (Pulcinelli RR et al., Alcohol, vol. 88, pg. 55, 2020). In the present study, we evaluated the correlation between alcohol consumption and serum CORT levels of rats. **Methods:** Adult male Wistar rats (~280 g) were exposed to a two-bottle choice voluntary intake model. The Alcohol group received a bottle containing 20% alcohol and another with 0. 08% saccharin (vehicle) solution, and the Control group received two bottles containing vehicle solution, 24 h per day, for 5 weeks. After 3 weeks, rats were subdivided into 4 groups (n=12/group) to receive 100 mg/kg taurine (TAU) or saline (SAL) intraperitoneally once a day for 2 weeks. On day 36, 24 h after the last taurine administration, the rats' trunk blood was collected, centrifuged, and serum was stored at –80°C. Serum CORT levels were determined by ELISA and correlated with the average daily alcohol consumption. **Results:** Two-way ANOVA showed a significant main effect of the condition, indicating that both Alcohol groups reduced CORT compared to the Control groups (P=0. 027). Moreover, chronic taurine selectively reduced CORT in the Alcohol/TAU group (Pinteraction=0. 030). Pearson test indicated an inverse correlation between CORT and the average daily alcohol consumption after the beginning of taurine treatment (r= –0. 580; P=0. 012). **Conclusion:** Higher alcohol consumption is associated with lower serum CORT levels, indicating a blunted HPA axis signaling underlying alcohol dependence. Taurine treatment selectively produces even lower CORT levels in rats with increased alcohol consumption. It is suggested that taurine may act synergistically with alcohol, enhancing its stress relief and anxiolysis effects and, hence, motivating excessive drinking. Thus, taurine treatment may possibly be beneficial in previously detoxified alcohol-dependent individuals, relieving stress responses associated with withdrawal, and decreasing the risk of relapse. **Financial Support:** CNPq, CAPES, Propesq-UFRGSApproval by Animal Research Ethical Committee: CEUA-UFRGS #32850

03.011 **Pre-Treatment with Ethanol inhibits the Expression of Conditioned Place Preference to Ketamine in Mice: The Role of Neurotrophin Receptors and Caspase-3 Activity**. Contó MB, Camarini R ICB-USP, Dept of Pharmacology, Brazil

Introduction: There is a high incidence of comorbidity between depression and alcohol use disorder. Recently, ketamine was approved as antidepressant treatment, although it is also used as a recreational drug. In this study, we investigated behavioral and biochemical interactions between ketamine and ethanol. The conditioned place preference (CPP) model was used to study the rewarding properties of ketamine and the influence of ethanol pre-treatment on ketamine's rewarding effect. We also investigated alterations in the expression of the neurotrophin receptors tyrosine kinase B (TrkB) and p75NTR, which play an important role in reward pathway plasticity and in the pathophysiology of depression. In addition, both the receptors regulate, in opposite directions, caspase-3 activity, a cell apoptosis biomarker. Aims Verify if ethanol pre-treatment induces alteration in the rewarding effect of ketamine, evaluated by the CPP model. Investigate, in the hippocampus, possible differences in the protein expression of the receptors p75NTR and TrkB as well as in the caspase-3 activity. **Methods:** Adult male Swiss mice, 80 days old, were housed in standard polycarbonate boxes, 5 mice/cage, food and water ad libitum. The protocol of CPP to ketamine (30 and 50 mg/kg, i. p.) consisted of habituation (H1), conditioning (D2-D9) and test (D10). Mice were treated with ketamine and ethanol or ketamine and saline on alternate days. The ketamine doses (30 or 50 mg/kg) were administered on days D2, D4, D6 and D8, alternating with ethanol or saline injections, which were administered on days D1, D3, D5 and D7 (24 hours before ketamine doses). Different groups of mice were treated with the same treatments and were euthanized twenty-four hours after the last injection. The hippocampus was dissected for biochemical analysis. The study was approved by the Ethics Committee of Animal Use of the Institute of Biomedical Sciences-USP (Protocol 132/2016). **Results**: Ketamine induced CPP at both doses. Ethanol pre-treatment did not alter CPP to 30 mg/kg ketamine (Bonferroni test: time spent in ketamine-paired compartment significantly different from time spent on saline-paired

compartment-, $p < 0.05$) but prevented CPP to 50 mg/kg ketamine (time spent in ketamine-paired compartment was similar from time spent in saline-paired compartment $p > 0.05$). The expression of TrkB was significantly decreased in Saline–Ketamine (50 mg/kg) ($U = 7$; $Z = 2.0000$; $p < 0.05$) and Ethanol–Ketamine (50 mg/kg) mice ($U = 0$; $Z = 2.8419$; $p < 0.01$), compared to Saline–Saline counterparts. Significant differences were also found between Saline–Ethanol mice compared to Ethanol–Ketamine (50 mg/kg) mice ($U = 0$; $Z = 2.6111$; $p < 0.01$). Kruskal-Wallis did not detect significant differences among the groups in the caspase-3 activity. **Conclusion:** Our results demonstrated that ethanol (1.8 g/kg) pre-treatment does not affect CPP to 30 mg/kg of ketamine but inhibits the expression of CPP to 50 mg/kg of ketamine. An interaction between ethanol and ketamine-50 mg/kg decreased the levels of the receptors TrkB and p75NTR in the hippocampus. No differences were found in caspase-3 activity. Considering the role of the receptors TrkB and p75NTR in neural plasticity of spatial memory consolidation, it is possible that a deficit in the hippocampal functionality might had impaired the ability of the animal to consolidate the association between ketamine effects and the drug-paired compartment. **Financial Support:** Capes, FAPESP (2018/05038-0)

03.012 **Involvement of Adenosinergic Receptors in the Antidepressant-Like Effects of Cannabidiol in Mice**. Sales A, Alves da Silveira JR, Ferreira BF, Guimarães FS FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

Introduction: Cannabidiol (CBD), a non-psychoactive cannabinoid, has shown potential therapeutic in psychiatric disorders. Preclinical studies suggest diverse effects of CBD including antipsychotic-, anxiolytic- and antidepressant-related behaviors in animals. However, the precise molecular mechanisms involved in such effects are not yet completely understood. Adenosinergic signaling has been associated with stress and depression. Furthermore, CBD inhibits adenosine reuptake in vitro. However, the involvement of adenosinergic receptors in antidepressant responses induced by CBD remains unexplored. Therefore, this work investigated if the antagonism of adenosinergic receptors (AR; A1 and A2a) are involved in the CBD effects in mice exposed to the forced swimming test (FST). **Methods:** Male and female Swiss mice received intraperitoneal (i. p.) injection of CBD (5, 10 and 30 mg/kg), caffeine (non-selective AR antagonist; 2.5, 5 and 10 mg/kg), SCH-58261(A1 antagonist; 0.5 and 1 mg/kg), CPT (A2a antagonist; 0.1, 0.5, 1 and 10 mg/kg) or vehicle (10 ml/kg), and 30 minutes after they were submitted to the open field test (OFT; 6 minutes). Immediately after, the animals were submitted to the FST (6 minutes). Additionally, mice received injection (i. p.; ineffective doses) of caffeine (2.5 mg/kg), SCH-58261 (1 mg/kg), CPT (1 mg/kg) or vehicle (10ml/kg) followed, 10 minutes after, by injection (i. p.; effective or ineffective doses) of CBD (10 and 30 mg/kg) or vehicle (10 ml/kg). 30 minutes after the animals were submitted to the OFT (6 minutes) and FST (6 minutes). Data were analyzed by 1-way ANOVA followed by Dunnett´s post-hoc tests. **Results:** The administration of caffeine (ineffective dose) did not block the CBD (effective dose) effect in the FST mice ($F3,48 = 3.867$; $p< 0.05$; n = 12-13/group). However, the association in subeffective doses of CBD and SCH-58261 ($F3,28 = 8.871$; $p < 0.05$; n = 8/group), or CBD and CPT ($F3,26 = 5.088$; $p < 0.05$; n = 6-8/group) decreased immobility time in the FST. None of the treatments induced locomotor effects (CBD/caffeine: $F3,48 = 1.374$; $p > 0.05$; n =12-13/group;CBD/SCH-58261: $F3,28 = 2.928$; $p > 0.05$; n = 8/group; CBD/CPT: $F3,26 = 1.779$; $p > 0.05$; n = 6-8/group). **Conclusion:** 1. CBD induces an antidepressant-like effect in female and male mice submitted to the FST; 2. Adenosine receptors (A1 and A2a) are not necessary for antidepressant-like effects induced by CBD; 3. The combination of CBD and antagonist of adenosine receptors (A1 and A2a) in innefective doses induce antidepressant-like effects in the FST. **Financial Support:** CAPES, CNPq and FAPESP. CEUA number: 187/2019.

03.013 **PPARgamma agonist pioglitazone reduces microglial activation induced by two hit model: possible implications for schizophrenia**. Sonego AB[1,2], Prado DS[3], Uliana DL[2], Cunha TM[1], Grace AA[2], Resstel LB[1] [1]FMRP-USP – Pharmacology, [2]University of Pittsburgh – Neuroscience, [3]University of Pittsburgh – Immunology

Introduction: Schizophrenia is a complex psychiatric disorder, with genetic and environmental factors influencing its development (1). Among the environmental insults, maternal infection (2) and stress exposure (3), especially during childhood and adolescence, have been implicated as risk factors for this disorder. Both insults induce an exacerbated inflammatory response (2,4), which could mediate disturbance of neurodevelopmental processes and, ultimately, malfunctioning of neural systems observed in schizophrenia (5). Thus, anti-inflammatory drugs may potentially be used to treat this disorder. In this study, we evaluate if the

combination of maternal immune activation (MIA) and adolescent stress could induce behavioral alterations in adult offspring. Moreover, we investigate if pioglitazone (PIO), an anti-inflammatory drug by activating PPARgamma receptors (6), could reduce the microglial activation by two-hit model. **Methods:** Pregnant Sprague-Dawley rats were injected with saline or poly (I:C) (0. 5mg/kg; ip) on GD17. From PD31 to PD40, a group of animals was submitted to a daily stressor (footshock) while another group remained undisturbed in their home cage. At adulthood, the offspring were evaluated in the social interaction (SI) and novel object recognition (NOR) tests, as well as amphetamine-induced locomotor activity. On the other hand, C57Bl6 pregnant mice received saline or poly (I:C) (1mg/kg; ip) on GD17. On PD0, the microglial culture was prepared. After 14 days, the cells were pretreated with PIO (10mM) and, 4h later, they were stimulated by LPS (1ng/mL). After, 6 or 24h of stimulation, proinflammatory mediators were measured by qPCR and ELISA, as well as phagocytosis test was performed by flow cytometry. **Results:** Both males and females from poly (I:C) and stress group showed a reduction of social preference and discrimination index in the IS and NOR tests, respectively, compared to the other groups (SNK test, $p<0.05$). However, there was no difference in the amphetamine-induced locomotor activity (SNK test, $p>0.05$). Poly (I:C) microglial cells stimulated with LPS increased mRNA expression of proinflammatory mediators, such as cytokines, iNOS and Iba-1 (SNK test, $p<0.05$), and PIO reduced them (SNK test, $p<0.05$). These effects were also observed in the supernatant after 24h of LPS stimulation (SNK test, $p<0.05$). On the other hand, CX3CR1 and PPARgamma expression was decreased by LPS (SNK test, $p<0.05$). Microglial cells from poly (I:C) offspring showed a decrease of phagocytic activity compared to saline cells (SNK test, $p<0.05$). LPS, in turn, reduced the phagocytosis in both saline and poly (I:C) cells (SNK test, $p<0.05$) and PIO did not change these effects (SNK test, $p>0.05$). **Conclusions:** MIA is acting as primer, increasing the sensitivity of microglia to second stimulus, which could lead to behavioral alterations in the adult offspring. Pioglitazone, in turn, seems to reduce the microglial activation induced by two-hit model, suggesting a possible effect on the behavioral alterations induced by the combination of MIA and adolescent stress. **References:** (1) KAHN, R. S. Nat. Rev. Dis. Prim., v. 1, p. 1, 2015. (2) SCOLA, G. Neuroscience, v. 346, p. 403, 2017. (3) GOMES, F. V. Schizophr. Res., v. 213, p. 107, 2019. (4) GRIPO, A. J. Mod. Trend Pharmacopsychiatry, v. 28, p. 20, 2013. (5) ALLSWEDE, D. M. Dev. Psychopathol., v. 30, p. 1157, 2018. (6) DAYNES, R. A. Nat. Rev. Immunol., v. 2, p. 748, 2002. **Financial Support:** FAPESP, CNPq and CAPES Number process of ethical committee: 067/2019; 21028730

04. Inflammation and Immunopharmacology

04.001 **Evaluation of Camphor Hidrazones Derivatives as Inhibitors of Myeloperoxidase and Acetylcholinesterase Enzymes**. Frias B[1], Souza MVN[2], Silva LL[3] [1]UFRJ-Macaé Integrated Laboratory for Research in Natural and Bioactive Products, Macaé, Brazil, [2]Fiocruz, Rio de Janeiro, Brazil, [3]FF-UFRJ, Health Sciences, Rio de Janeiro, Brazil

Introduction: Acetylcholinesterase (AChE) plays an important role in the pathogenesis of neurodegenerative diseases by influencing the inflammatory response, apoptosis, oxidative stress and aggregation of pathological proteins. There is a search for new compounds that can prevent the occurrence of neurodegenerative diseases and slow down their course [1]. Another enzyme that has emerged as a possible therapeutic target for the treatment of neurodegenerative diseases (NDD) is myeloperoxidase (MPO) which is secreted by neutrophils and macrophages. MPO and its oxidative products react with various lipids, proteins, and nucleic acids causing some detrimental effects in tissues that are usually associated with ongoing inflammatory [2]. In this context, dual AChE/MPO inhibitors represent a suitable starting point to anti-neurodegenerative drug development [3] and hydrazones have been described as inhibitors of both AChE and MPO [4,5,6]. Goal:To evaluate a hydrazonic camphor serie with seventeen derivatives looking for multitarget inhibitors for NDD treatment. Method: AChE inhibitory activity was evaluated by Ellman's colorimetric method. Assay was performed using 96-well plates at a final volume of 250 µL. Camphor derivatives were evaluated at 50 µM in 250 µL of sodium phosphate buffer (0.1 M, pH 8), containing 0. 25 U/mL AChE, and 3 mM DTNB (5,5-dithiobis-2-nitrobenzoic acid). After 30 min under agitation, the reaction was started with the addition of 1,5 mM AChI (acetylthiocholine iodide). Absorbance was measured at 412 nm for 10 min. Rivastigmine was used as a reference standard (positive control) [5]. MPO activity was determined by hypochlorous acid production by the rat bone marrow extract. Assay was performed using 96-well plates, at a final volume of 125 µL containing sodium phosphate buffer (0.

02 M, pH 7,4), MPO, 100 mM taurine, 100 mM NaCl, and an excess of TNB. After 20 min under agitation reaction was started by adding 50 µM H2O2 the absorbance was measured at 412 nm [7]. For the Cl-tau scavenger activity evaluation the same reaction medium was used, only replacing H2O2 (MPO substrate) with the product of the reaction of HOCl with taurine (Cl-tau). The free radical-scavenging activity of camphor derivatives was measured using the DPPH method. A 0. 2 mM solution of DPPH in methanol was prepared and mixed to 0. 4 mM derivative methanolic solution at proportion 1:1. After 30 min under agitation in the dark the absorbance at 517 nm was measured [8]. All experiments were performed in triplicate with at least 3 independent assays. For statistical analysis and regressions, the GraphPad Prism software version 5. 0 was used. **Results:** The derivatives were not able to significantly inhibit AChE activity at a concentration of 50 µM. Although some derivatives significantly reduced MPO HOCl production: PASALR 29 (36 ± 4. 3), 30 (47. 1 ± 4), 32 (33. 6 ± 4. 5), 39 (37. 6 ± 6. 5), 40 (27. 2 ± 5. 1), 41 (55. 5 ± 4. 7), 42 (64. 4 ± 2. 9), 45 (40.1 ± 5. 7) and 47 (31. 4 ± 5. 2) at 100µM. In addition, these MPO inhibitors don't showed cl-taurine scavenger at 100µM. Concentration-response curves were made for PASALR 41 and 42 that presented IC50 values 90. 6 (95. 8 to 124. 7) and 43. 3 (35 to 53. 5), respectively. On the other hand, some derivatives showed radical DPPH scavenging activity: 30 (108. 8 ± 8. 4), 41 (6. 8 ± 1. 8) and 42 (103. 6 ± 7. 6). **Conclusion:** Among PASALR derivatives studied, none inhibited AChE, but 41 and 42 were the most active MPO inhibitors and 42 was still a DPPH scavenger, suggesting differences in their mechanism of inhibition. **Financial Support:** FAPERJ.

04.002 **Low Birth Weight Induced by Maternal Malnutrition Impair Phagocytic and Microbicidal Activity of Alveolar Macrophages and Increases Susceptibility to Infections**. Negreiros NGS[1], Azevedo GA[1], Gil NL[1], Lippi BK[1], Landgraf MA[2] Landgraf RG[1] [1]Unifesp, Ciências Farmacêuticas, Diadema, Brazil [2]UniP-Rangel **Introduction:** Maternal food restriction during pregnancy induces morphological and metabolic fetal adaptations and predisposes to metabolic diseases including diabetes and hypertension, in offspring. Metabolic disturbances can also be induced by the imbalance of pro and anti-inflammatory factors, as observed in sepsis. In previous studies, our group demonstrated that food restriction during pregnancy resulted in low birth weight, hypocellularity in bone marrow and peripheral blood, reduction in leukocyte migration, and a defective inflammatory response in Wistar rats at 12 weeks. The aim of this study was to evaluate the phagocytic and microbicidal capacity of macrophages of maternal malnutrition during the pregnancy, in adult offspring. **Methods:** Timed mating was carried out in age-matched (12- to 16-wk-old) female and male Wistar rats. Day 1 of the pregnancy was defined as the day on which spermatozoa were detected in the vaginal smear. After confirmation that mating had occurred, female rats were randomly divided into 2 groups: nourished - diet and water ad libitum; malnourished - 50% food restriction and water ad libitum. At 12 weeks of age, male offspring rats from both groups were To assess phagocytic activity of alveolar macrophages, these cells were incubated with Saccharomyces cerevisiae, in a 4:1 ratio. To evaluated microbicidal activity was count of colony forming units (CFU) these cells with Saccharomyces cerevisiae. **Results:** Malnutrition during gestation caused a drop in fetal birth weight (LBW) compared with offspring from control group (normal body weight at birth-NBW. LBW group showed defective phagocytic activity because the number of yeasts phagocytosed by alveolar macrophages is lower than NBW group. Evaluated microbicidal activity, the count of colony forming units (CFU) was significantly higher in LBW when compared to NBW group. **Conclusion:** Low birth weight induced by maternal malnutrition during pregnancy prejudices phagocytic and microbicidal activity of alveolar macrophages and could compromises immune response and increases susceptibility to infections. **Financial Support:** FAPESP (2019/05242-9, 2020/16020-4), CNPq and CAPES – Finance Code 001 Animal Research Ethical Committee: CEP/UNIFESP nº 2849110517

04.003 **Anti-Inflammatory Effect of Cannabidiol (CBD) in Human HMC3 Microglia: Contribution of Pro-Autophagic Mechanisms**. Sousa RC[1], Chaves Filho AJM[1], Jucá PM[1], Oliveira CA[1], Gaspar DM[1], Joca SRL[2] - sjoca@biomed.au.dk, [1]UFC – Drug Research and Development, [2]Aarhus University-Denmark – Biomedicine
Psychiatric disorders, mainly mood disorders, are one of the leading causes of disability worldwide. The costs in the world economy for depression and anxiety reach $1 trillion per year (WHO, Geneva, 2018). In these conditions, it has been observed that the microglia present an overexpression of a pro-inflammatory phenotype with the production of pro-inflammatory cytokines and concomitantly a decrease in their phagocytic and autophagic capacity, failing to promote autoregulation. Cannabidiol (CBD) is a non-psychotic compound derived

from the Cannabis sativa which has been a target for the treatment for several neuropsychiatric disorders. Recent studies have highlighted the potential anti-inflammatory and microglia suppressant-effect of CBD in animal models. However, little is known about the underlying mechanisms for this effect. Based on this, this study aims to evaluate the anti-inflammatory action of cannabidiol (CBD) in human microglial cells, and its modulatory effect on autophagy to the emergence of CBD immunoregulatory profile. To do this, human microglia cell lineage HMC3 was challenged with lipopolysaccharide (LPS) (1 µg/ml) and exposed to cannabidiol (1, 10 or 100 µM): simultaneously (pre-treatment) or 24 hours after immune challenge (post-treatment). After 24 hours of CBD exposure, samples were collected and methyl-tetrazolium (MTT) cell viability, arginase enzyme activity, IL-6, IL-4, TNFα, nitrite (NO) were determined. Acridine orange acidic vesicles(AVOS) flow-cytometry protocol for the measuring of late autophagy was also performed. In line with this, the CBD-treated groups demonstrated increased level of arginase activity and IL-4, as well as reduced the levels of TNFα and IL-6 compared to LPS-treated group. CBD also upregulated AVOS+ cells compared to LPS-treated group mainly in post-treatment protocol. Taken together, our results demonstrated the promising anti-inflammatory action of CBD in human microglia as well as the up-regulation of autophagic flux by this drug as potential mechanism for the latter effect. Our findings strengthened the body of evidence for CBD therapeutic usage for neuroinflammatory disorders. The present study was conducted according to the best practices for cell culture experiments. Since it was performed in immortalized lineage cells, it was not required ethics council approval for human or animal experiments. We also thank to the Financial Support from the Brazilian Institutions the Higher Education Improvement Coordination (CAPES), the Cearense Foundation of and Technological Support (FUNCAP) and the National Council for Scientific and Technological Development (CNPq). Keywords: Neuroinflammation, Cannabidiol, Autophagy, Microglia

04.004 Inhibition of Myeloperoxidase Chlorinating Activity by Propolis Samples from Rio das Ostras-RJ, Brazil. Condack CPM, Silva LL, Raimundo JM, Barth T, Muzitano MF, Teixeira FM, Nascimento JCM UFRJ-Macaé, Integrated Laboratory of Research in Bioactive Products, Macaé, Brazil

Introduction: Myeloperoxidase (MPO) is an enzyme that generates oxidant species in an exaggerated and uncontrolled manner after cell migration to the site of inflammation can amplify and result in tissue damage [1]. MPO has been considered as an important therapeutic target in inflammatory conditions, such as neurodegenerative and cardiovascular diseases [1, 2]. Propolis is a natural resinous mixture produced by honeybees from substances collected from parts of plants, buds, and exudates. Several compounds have been identified in propolis such as, phenolic compounds, aromatic acids and waxes. Currently propolis is used as an anti-bacterial, anti-inflammatory, anti-oxidant, etc [3]. Furthermore, MPO inhibition has been described for some propolis [4]. Goal: To evaluate the antioxidant profile of ethanolic extracts of 4 varieties of propolis from Rio das Ostras-RJ (P1-4) measuring the ability of extracts to inhibit HOCl production by MPO and sequester reactive species. Methods: For the inhibition of MPO activity the HOCl production was measured using rat bone marrow extract. In 96-well microplates in a final volume of 125 µL, propolis extracts were evaluated in the range of 3. 125 to 200 µg/mL in a reaction medium containing sodium phosphate buffer (0. 02 M, pH 7. 4), MPO, 100 mM taurine, 100 mM NaCl and an excess of TNB. After 20 minutes under stirring, the reaction was started by adding 50 µM of H2O2, the bleaching was measured at 412 nm by 10 min [5]. To evaluate the Cl-Tau scavenger activity, the same medium was used, substituting H2O2 for chlorotaurine (Cl-tau) to start the reaction. To evaluate the antioxidant activity, the method based on 1,1-diphenyl-2-picrylhydrazyl (DPPH•) free radical scavenging was used. A 0. 26 mM solution of DPPH in methanol was prepared and mixed with the samples at different concentrations (25 to 400 µg/mL) in methanol in a 3:1 ratio. After 30 minutes of stirring in the dark, the plate was read, measuring the absorbance at 517 nm [6]. All experiments were performed in triplicate with at least 3 independent assays. For statistical analysis and regressions, version 5. 0 of the GraphPad Prism software was used. Results: All propolis extracts were able to inhibit MPO activity at screening concentration. The Concentration-activity showed that P2 is more potent than P3 (15. 5 ± 2 e 32. 1 ± 4. 5 µg/mL, respectively). The samples P1 and P4 were not different from each other or from the others (24. 5 ± 3. 3 e 26. 2 ± 4. 1 µg/mL, respectively). Extracts were screened for their Cl-tau scavenging capacity and were inactive (P1 78. 2 ± 7. 7 %, P2 84. 4 ± 4. 8 %, P3 91. 3 ± 6. 6 %, and P4 84. 3 ± 11. 3 %) when compared to vehicle (89. 1 ± 4. 7 %). On the other hand, the extracts showed DPPH scavenging activity. P3 and P4 extracts showed the highest DPPH

scavenging capacities (IC50 values µg/mL: 15. 5 ± 1. 2 and 14. 5 ± 1. 3, respectively) than P1 and P2 (IC50 values µg/mL: 23 ± 1. 6 and 23. 1 ± 1. 2, respectively). These results show that the extracts effectively inhibited MPO, not directly interfering with Cl-tau concentrations, but through an interaction of one or more constituents with the enzyme. In addition, they demonstrated the ability to scavenge radical species liksuch as DPPH. **Conclusion:** Here it was demonstrated an antioxidant effect of propolis samples from Rio das Ostras, through the scavenging of radical species and also the inhibition of HOCl production by MPO. Thus, propolis produced in the region can be sources of antioxidative and MPO inhibitor substances with potential anti-inflammatory activity. **Financial Support:** PIBIC – CNPq.

04.006 **Contribution of Obese Adipose Tissue to Cellular Regression of Mature Osteoblast Phenotype**. Forte YS[1], Renovato-Martins M[2], Barja Fidalgo TC[1] [1]UERJ, Dpt of Cell Biology, Rio de Janeiro, Brazil [2]UFF, Dpt of Molecular Cellular Biology, Rio de Janeiro, Brazil

Introduction: Obesity is a worldwide disease characterized by an increase in adipose tissue (AT) accumulation, which leads to harmful consequences to health1. In obese subjects, imune cells in the adipose tissue (AT) shift towards a pro-inflammatory phenotype contributing to AT inflammation2. Inflammatory mediators released systemically by obese AT, can affect functionality of other tissues, including bones. The constant renewing of bones relays on the osteoblasts, bone forming cells and the osteoclasts, resorption cells. A balanced activity between these cells is crucial for healthy bone remodeling (BR). Thus, the imbalance between bone resorption and formation leads to bone loss3. Data on the effects of obesity on BR are still conflicting, showing overweight as an osteoprotective factor, while the pro-inflammatory molecules from obese AT inhibiting osteoblasts and stimulating osteoclasts4. AIMS: In this study, we investigated the effect of conditioned medium obtained from subcutaneous AT (SAT) depots from obese and eutrophic subjects on osteoblast differentiation and activity. **Methods:** SAT samples were collected from obese or eutrophic patients undergoing bariatric or plastic surgery (CAAE 36880914. 0. 0000. 5259). SAT was cut into small fragments and incubated for 24 hours in culture medium to obtain the CM. The osteoblast lineage SAOS-2 was incubated with 20% (v/v) of eutrophic AT-CM (ECM) or obese AT-CM (OCM). Cell proliferation evaluated by MTT assay, after 48 hours treatment; Extracellular matrix calcification cells analyzed using Alizarin Red staining, after 10 days treatment of cells with ECM or OCM, in the presence of osteogenic differentiation medium; The expression of osteogenic markers and activation of the Wnt/B-Catenin pathway, accessed by western blott, in cells treated with the CMs for 7 days and for 5 hours, respectively; Cell morphology evaluated by light microscopy after 3 days of treatment. **Results:** OCM induced an increase in cell proliferation and triggered spindle-shaped morphology in osteoblasts, while control cells remained with cuboid morphology. Alizarin staining showed that both ECM and OCM induced a reduction in calcification, but the inhibition was more potent in OCM. OCM reduced the expression of collagen I and alkaline phosphatase in treated cells. OCM and ECM did not change expression in nuclear B-catenin. **Conclusion:** Soluble factors released by obese AT induce a regression of mature osteoblast phenotype toward an osteoprogenitor-like phenotype. Funding Support: FAPERJ, CAPES and CNPQ. **References:** 1 WHO – World health organization, 2016. 2 STOLARCZYC, Emilie. Current Opinion in Pharmacol., v. 37, 35, 2017. 3 KIM, Jung-Min. Cells, V. 9, 2073, 2020. 4 GKASTARIS, Konstantinos. J Musculoskelet neuronal interact., v. 20, 372, 2020. **Acknowledgments**: Thanks to Doctor Christina Fidalgo and Doctor Mariana Renovato, to SBFTE organization, and to FAPERJ, CAPES and CNPQ for financial support.

04.007 **Evaluation the Impact of Autophagy on the Regulation of the Senescent Phenotype of Prone and Resistant Mice to Accelerated Senescence**. Barros R, Queiroz LAD, Pantoja KC, Sousa ESA, Martins JO FCF-USP, Immunoendocrinology Laboratory; São Paulo, Brazil

Introduction: Autophagy is a conserved cellular process and an essential metabolic pathway for the maintenance of cellular homeostasis, which plays an active role in the control of protein and organelle biosynthesis. This pathway is regulated naturally by the nutrient-sensing receptor known as mechanistic target of rapamycin (mTOR) or chemically by the drug rapamycin (RAPA), which has a direct relationship with cellular homeostasis and maintenance of the senescent and immunosenescent phenotypes. This project seeks Investigate the relationship between autophagy, induced by mTOR inhibition by RAPA, in the regulation of immunosenescence in Senescence-Accelerated Mouse Prone 8 (SAM-P8) and Senescence-Accelerated Mouse Resistant 1 (SAM-R1). **Methods:** The animals SAM-P8 and SAM-R1 mice (12 weeks old) were divided into two groups: SAM-P8 and

SAM-R1 treated with rapamycin (0. 78 mg/kg of RAPA diluted in 150 uL of filtered water) and SAM-P8 and SAM-R1 control group (treated with 150 uL of filtered water), both groups treated by gavage procedure, once every 5 days for two months (CEUA/FCF/USP nº. 632/21). During and after treatment, the body weight, leukogram and hematometric indices (RBC, HGB, HCT, MCV, MHC and MCHC) were evaluated. After the euthanasia procedure, the detection of the cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α were measured in the serum, bone marrow, thymus and spleen samples. **Results:** The body weight of the SAM-P8 and SAM-R1 animals treated with RAPA showed no changes when compared to their respective control groups. In the blood count analyses, the treated groups showed no hematological changes that could be caused by rapamycin. IL1-β was detected in all spleen samples of the four groups analyzed, IL-6 showed higher expression in SAM-R1 samples compared to SAM-P8 samples, and the cytokine TNF-α showed higher expression in SAMP-8 samples, except in the spleen, where expression was similar in SAM-R1 and SAM-P8 animals. **Conclusion:** The treatment with RAPA did not induce changes in the evolution of the body weight and hematological parameters. Although these are preliminary data, we analyzed that the secretion of IL-6 and TNF-α could be correlated with the regulation of immunosenescence in SAM-P8 and SAM-R1 mice. However, the analysis of other markers related to immunosenescence is essential, such as the induction and inhibition of proteins of the autophagic signaling pathway, assessment of gene expression, and the increase and decrease of populations and subpopulations of immune system cells. **Financial Support:** CNPq (310993/2020-2); FAPESP (2020/03175-0; 2021/00310-6).

04.009 **Study of the Annexin A1/FPR2 Pathway in the Context of Experimental Bacterial Pneumonia**. Lara ES[1,2], Carvalho AFS[1,2], Montuori-Andrade ACM[1], Cardoso C[1], Zaidan I[1], Grossi L[1], Teixeira MM[3], Costa VV[3], Tavares LP[4], Sousa LP[1,2,3] [1]FF-UFMG, Signaling in Inflammation Laboratory, Dpto Análises Clínicas e Toxicológicas, [2]FF-UFMG, PPG Análises Clínicas e Toxicológicas, [3]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [4]Brigham and Women's Hospital and Harvard Medical School, Pulmonary and Critical Care Medicine Division, Dept of Medicine

Introduction: Pneumonia represents one of the main causes of morbidity and mortality worldwide and results of the lower respiratory tract infection caused by microorganisms, such as viruses, fungi, and mainly by Gram-positive or Gram-negative bacteria. The inflammation of the lung parenchyma triggered during infection is essential and must be spatial and temporally orchestrated by cells and mediators of the innate immunity, aiming to eliminate the infectious stimuli and restore tissue homeostasis protecting the host from infection-evoked damage. Conversely, an inefficient engagement of the resolution program during lung infection leads to exacerbated inflammation, causing intense pulmonary damage/dysfunction and bacterial dissemination, and increasing pneumonia severity. We have demonstrated that the proresolving pathway engaged by Annexin A1 (AnxA1)/FPR2 controls the inflammatory response and bacterial dissemination in experimental pneumonia induced by pneumococcus (a Gram-positive bacteria), and treatment of mice using the AnxA1 peptidomimetic Ac2-26, afford protection during pneumococcal pneumonia (Machado M. G. et al, 2019). Herein, we have evaluated the role of the axis triggered by the protein AnxA1 and its receptor FPR2 during pneumonia induced by the Gram-negative bacteria Escherichia coli. **Methods:** For that, wild type mice and those deficient for AnxA1 (AnxA1 knockout in BALB/c background) or FPR2/3 (FPR2/3 Knockout in C57BL/6 background) were intranasally infected with 2 x 10(6) CFU of E. coli (ATCC 25922). Mice were euthanized 24 h post-infection and bronchoalveolar lavage (BAL) was collected to analyze leukocyte infiltration, cytokine and protein levels, and bacterial loads. All procedures described here were approved by the Ethics Committee of the Universidade Federal de Minas Gerais (CEUA, protocol number: 262/2018). ResultsMice deficient in AnxA1 or FPR2/3 showed a more pronounced inflammatory response, characterized by increased neutrophilic infiltration and lower numbers of macrophages associated with higher bacterial counts in the airways. There were also high levels of pro-inflammatory cytokines and protein (an indirect measurement of edema) in AnxA1 knockout and compared to their respective WT controls. **Conclusion:** The data obtained so far suggest an inflammatory response of higher intensity in mice deficient in AnxA1/FPR2 axis, evidencing the importance of this pathway on modulation of inflammation. Studies using the AnxA1-mimetic peptide Ac2-26 will be carried out to verify the effectiveness of this treatment in pneumonia induced by Gram-negative bacteria. ReferencesMACHADO, M. G. et al., The

Annexin A1/FPR2 pathway controls the inflammatory response and bacterial dissemination in experimental pneumococcal pneumonia. FASEB JOURNAL, v. 1, p. 1-16, 2019. **Financial Support:** FAPEMIG, Capes and CNPq.

04.010 **Therapeutic Treatment with Gold Nanoparticles (AuNPS) Reduces Lung Fibrosis Target by Bleomycin in Mice**. Ferreira GG, Abreu FVG, Fernandes AJ, Pires ALA, Arantes ACS, Sá YAPJ, Ribeiro NBS, Martins MA, Silva PMR Fiocruz

Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease, characterized by inflammatory cell infiltration, hyperplasia of alveolar epithelial cells and fibroblasts, extracellular matrix deposition, and scarring, representing a challenge for health services due to the nonexistence of effective antifibrotic therapy. Evidence exists that gold nanoparticles (AuNPs) have a marked anti-inflammatory activity, which indicates them as a potential therapeutic option for lung disorders. AIM: This study was undertaken to investigate the effect of aerosolization of AuNPs on bleomycin-challenged mice, a widely used experimental model that resembles IPF. **Methods:** Anesthetized female C57/BL6 mice were challenged by oropharyngeal aspiration with a single dose of bleomycin (0,06 U/ 40 µL sterile 0. 9% saline/animal). Controls received the same volume of saline alone. AuNPs (0.05 - 1. 5 µg/mL) were aerosolized every two days, from day 14 to 20 post-bleomycin, and the analyzes were performed 1 day after the last administration. The following parameters were analyzed: i) lung function (resistance and elastance) and airway hyper-reactivity to methacholine (3 - 81 mg/mL) measured by whole-body invasive plethysmography (Finepointe, Buxco System); ii) morphological and morphometric analysis by histological techniques with Hematoxylin-Eosin and Gomori Trichrome stain; and iii) quantification of collagen by Sircol assay. All experimental procedures were approved by the Committee on Use of Laboratory Animals of Oswaldo Cruz Foundation (license LW001/19). **Results:** Mice challenged with bleomycin exhibited an increase in airway resistance and elastance to methacholine aerosolization, showing a clear condition of airway hyper-reactivity. Lung collagen content was determined and revealed that bleomycin-induced about a twofold increase as compared with controls, at 21 days. The extent of fibrosis was also assessed histologically and lungs from bleomycin-challenged mice showed a marked increase in the number of interstitial cells, some with a fibroblastic phenotype, as well as a considerable increase in the amount of extracellular matrix, mainly collagen. Therapeutical administration of AuNPs to bleomycin-challenged mice restored normal lung function and attenuated fibrosis as attested by a reduction in collagen deposition. AuNPs had no effect on basal lung function and collagen levels in saline-treated mice, **Conclusion:** Our findings show that aerosolized AuNPs in mice stimulated with bleomycin resulted in amelioration of lung function and suppression of fibrosis, suggesting that they may warrant further consideration in the treatment of fibrotic lung diseases. **Financial Support:** FIOCRUZ, FAPERJ, CNPq (Brazil).

04.011 **GILZ Modulates the Recruitment of Mononuclear Cells Endowed with a Resolving Phenotype and Plays a Relevant Role During *Escherichia coli* Infection**. Grossi L[1], Zaidan I[1], Souza JAM[1], Matoso AC[1], Carvalho AFS[1], Cardoso C[1], Morand EF[2], Riccardi C[3], Bruscoli E[3], Teixeira MM[4], Tavares LP[5], Vago JP[6], Sousa LP[1] [1]FF-UFMG, Lab of Inflammation and Neoplasms Signaling, Dept of Clinical and Toxicological Analysis, Brazil, [2]Monash University, Rheumatology Group, Centre for Inflammatory Diseases, School of Clinical Sciences at Monash Health, Melbourne, Australia, [3]University of Perugia, Dept of Medicine and Surgey, Section of Pharmacology, Perugia, Italy, [4]ICB-UFMG, Drug Research and Development Center, Dept of Biochemistry and Immunology, Brazil, [5]Brigham and Women's Hospital and Harvard Medical School Dept of Medicine, [6]Radboud University Medical Center Dept of Rheumatology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands

Macrophages are critical cells on resolution of inflammation, contributing to the elimination of pathogens and apoptotic cells and paving the way to the tissue homeostasis. Studies of GILZ (Glucocorticoid Induced Leucine Zipper) in different models of inflammation have shown its anti-inflammatory and proresolving actions, by inducing neutrophil apoptosis and reprogramming macrophages toward resolving phenotypes and increasing efferocytosis. Here, we have investigated the role of GILZ in a key event of inflammation resolution named nonphlogistic recruitment of mononuclear cells. Wild Type (WT) and GILZ-deficient mice (GILZ-/-) were submitted to self-resolving inflammatory model, in which migration of the mononuclear cells is a hallmark of the resolving phase. Animal experiments were approved by the Ethics Committee of the Universidade Federal de Minas Gerais (CEUA, protocol number: 183/2017). To assess GILZ-induced migration, WT mice received an intrapleural injection of PBS, TAT or TAT-GILZ (a cell permeable GILZ-fusion protein) and were euthanized at

different time points post injection. Pleural lavage samples were used for morphological cell count, leukocyte phenotyping by flow cytometry, cytokine/chemokine and protein measurements. In a self-resolving peritonitis model, WT and GILZ-/-mice were inoculated intraperitoneally with 1x106 CFU of E. coli and were euthanized at different times post-infection. Peritoneal exudates were harvested for morphological count of leukocytes, determination of apoptosis and efferocytosis, cytokine/chemokine measurements, bacterial loads and leukocyte phenotyping by flow cytometry. *In vitro* chemotaxis assays and bacterial phagocytosis were also performed. Our data demonstrate that TAT-GILZ induces chemotaxis of RAW macrophages and the injection of TAT-GILZ into the pleura of WT mice induce a time-dependent influx of leukocytes, which was mainly composed by mononuclear cells, without significant changes in neutrophils. TAT-GILZ-induced migration was accompanied by increased CCL2, IL-10 and TGF-β levels and was composed by macrophages of resolving phenotype, presenting higher expression of CD206 and YM1 markers. During the resolving phase of E. coli-induced peritonitis, which the cellularity is composed mainly by mononuclear cells, lower numbers of these cells alongside lower levels CCL2 were found in the peritoneal cavity of GILZ-/- mice, as compared to WT. Furthermore, we found higher bacterial loads, lower percentage of apoptotic neutrophils and efferocytosis and lower numbers of proresolving macrophages in GILZ-/- mice, when compared to WT. *In vitro* bacterial phagocytosis assays, using bone marrow-derived macrophages (BMDMs), showed that pre-treatment with TAT-GILZ increases this effector function of macrophage. Conversely, phagocytic capacity from peritoneal cells and BMDMs from GILZ-/- animals was lower than those of cells from WT mice, and this function was rescued by treatment with TAT-GILZ. In summary, GILZ induces CCL2-dependent mononuclear cells recruitment and macrophage polarization for a resolving/regulatory phenotype, characterized by up-regulation of IL-10, TGF-β, CD206 and YM1. Furthermore, in the context of E. coli infection, TAT-GILZ promoted increased phagocytosis and bacterial clearance. **Financial Support:** Capes and CNPq.

04.012 **Vinorelbine Induces Extravasation Injury Accompanied by Neutrophil Accumulation in a Resident Cell-Independent Mechanism**. Quintela LCS[1], Cajado AG[2], Holanda GS[2], Gama LC[2], Santos ABM[2], Rodrigues MAP[2], Freitas GL[1], Teles ACF[2], Gadelha EC[2], Rodrigues TS[2], Sousa LSP[2], Wong DVT[2], Lima-Júnior RCP[2] [1]FM-UFC, PPG in Pathology, Dept of Pathology and Forensic Medicine, Fortaleza, Brazil [2]FM-UFC, Drug Research and Development Center, Dept of Physiology and Pharmacology, Fortaleza, Brazil

Introduction: Extravasation injury is a term that describes the manifestations of tissue damage resulting from the accidental leakage of a drug into the subcutaneous space during intravenous infusions. It is an oncologic emergency since it courses with tissue necrosis and severe pain. Vinca alkaloids and their derivatives, such as vinorelbine, are among the most prominent vesicant anticancer drugs. We aimed to delineate an experimental model of vinorelbine-induced extravasation injury and test resident cells' role in the lesion's mechanism. **Methods:** Male Wistar rats were divided into groups (n=6/group). Anesthetized animals received an intradermal injection of vinorelbine (0. 03, 0.1, 0. 3, or 1 mg/100 uL) or saline solution (control group). The animals were euthanized after 2, 4, 8, or 16 h post-chemotherapy injection. We analyzed the skin samples using Evan's blue extravasation method to determine cutaneous vascular permeability. The dye (25 mg/kg, i. v.) was administered 1 h before animal euthanasia. The experiment was repeated following the same time course for the myeloperoxidase (MPO) assay. In another experimental setting, the animals were divided into two groups: 1) rats with peritoneal cavities carrying normal resident cell population (sham group), and 2) animals perfused with saline solution (30 mL) for the depletion of resident cells in the peritoneal cavity (washed group). These groups received saline (1 mL/cavity, i. p.), vinorelbine (1 mg/mL/cavity, i. p.), or vinorelbine + dexamethasone (3 mg/kg, s. c.) 30 min after cell depletion. The peritoneal exudate was harvested 4 h post-chemotherapy exposure to measure the number of migrated neutrophils. One- or Two-way ANOVA followed by the Bonferroni test was used for the statistical analysis. The differences between the groups were accepted when $P<0.05$. Ethics committee approval: CEUA 4753300919. **Results:** The highest tested vinorelbine concentration (1 mg/100 uL) caused a time-dependent cutaneous vascular permeability verified by the tissue accumulation of Evan's Blue. Pronounced edema was verified 16 hours after chemotherapy exposure compared with the saline group ($P<0.05$). The increase in the MPO activity accompanied the edematogenic response. Remarkably, vinorelbine failed to induce signs of inflammation at 2-, 4-, or 8 hours post-drug injection. We depleted the mononuclear cell population in the rats' peritoneal cavity to test whether the chemotherapy induces neutrophil migration by

a resident cell-dependent mechanism. Notably, vinorelbine's capacity to induce the accumulation of neutrophils was magnified in the washed cavity. Additionally, dexamethasone significantly prevented neutrophil migration ($P<0.05$). It indicates that vinorelbine induces neutrophil chemotaxis in a resident cell-independent mechanism. **Conclusion:** We delineated a new animal model of vinorelbine-induced extravasation injury. The chemotherapeutic induces neutrophil accumulation during tissue lesion independently of resident cells stimulation. **Financial Support:** CNPq, Capes, and Funcap.

04.013 **Evaluation of Anti-Inflammatory Activities of New Heterocyclic Derivatives Analogues of Chalcones**. Botinhão MC[1], Araújo MH[1], Cavararo AR[1], Alves TS[1], Melo EDN[1], Rodrigues CR[2], Gomes AO[1], Muzitano MF[1], Carmo PL[1] [1]UFRJ-Macaé, Macaé, Brazil;[2]UFRJ, Rio de Janeiro, Brazil

Introduction: The pharmacological therapies currently used for the treatment of pain and inflammation can cause several adverse effects1,2. For a long time, few innovative pharmacological therapies were introduced on the market and this situation stimulates the search for new molecules that are potentially effective in the treatment of these processes. In this context of drug development, chalcones appear as sources of new bioactive products, due to their simple structure and a variety of pharmacological properties, including anti-inflammatory and analgesic actions3,4,5. Thus, the objective of this study is to evaluate the anti-inflammatory effects of new heterocyclic derivatives synthetic analogues of chalcones. Methodology: Through *in vitro* experiments, six chalcones (MEO-2, MEO-5, MEO-6, MEO-7, MEO-8, MEO-9) were evaluated for their immunomodulatory activity by lipopolysaccharide (LPS)-activated RAW 264. 7 macrophages (MO). The cells were plated in the 96-well microplate and incubated overnight at 37 °C with a 5% CO2. After this period, MO cultures were stimulated with LPS and treated with chalcones in three concentrations: 6. 25, 25 and 100 µg/ml. After 24 h, the culture supernatant was collected to evaluate the ability to inhibit nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) production and measure cytotoxicity by MTT. **Results:** In the *in vitro* experiment, with the exception of MEO-6 at 6. 25 µg/mL, all chalcones were able to inhibit NO production by macrophages, when compared to (LPS)-stimulated macrophages. Regarding cytotoxicity, when compared to (LPS)-stimulated macrophages (viability control), MEO-6 and MEO-7 (at all concentrations), MEO-8 and MEO-9 at 25 and 100 µg/mL were cytotoxic. The chalcones MEO-2 and MEO-5, although it showed a cytotoxic effect in the highest concentration (100 µg/mL), these compounds at 25 µg/mL maintained an inhibition of NO production of 67. 4% and 60. 6%, respectively, without a significant cytotoxic effect. No significant inhibition of TNF-α production was observed for all tested chalcones. **Conclusion:** These results showed that MEO-2 and MEO-5 were the most potent chalcones to modulating NO production and will be tested in protocols to evaluate antinociceptive and anti-inflammatory in vivo activities. **References:** [1] SILVA M. M., et al. Rev. Cad. Med., v. 2, p. 90, 2019. [2] LISTOS J., et al. Int. J. Mol. Sci., 20, 1, 2019. [3] CORRÊA R., et al. Arch Pharm, 334, 332, 2001. [4] MOHAMED A. S., et al. Eur. J. Pharm, 647, 103, 2010. [5]. SAMBASEVAM Y., et al. Eur J Pharmacol, 796,32, 2017.

04.014 **Metformin Reverses the Pro-Inflammatory Effects and Oxidative Stress Markers of Methylglyoxal in Ovalbumin-Induced Mouse Airway Inflammation**. Medeiros ML, Oliveira AL, Antunes E FCM-Unicamp, Dept Pharmacology, Campinas, Brazil

Aims: Methylglyoxal (MGO) is a highly reactive dicarbonyl species associated with diabetes and other diseases (1). MGO is a major precursor of the advanced glycation end-products (AGEs), which interacts with its receptor RAGE, triggering multiple intracellular signaling pathways, including increased production of pro-inflammatory mediators and reactive oxygen species (ROS) (2). Prolonged intake of MGO significantly potentiates both acute lung injury and allergic airways inflammation in mice (3). In the LPS-induced lung inflammation, oral treatment with the anti-hyperglycemic drug metformin significantly reduced the exacerbation by MGO of the airway inflammation, strongly suggesting that metformin acts by scavenging MGO from blood circulation (4). A previous study showed that metformin reduces the eosinophilic inflammation and Th2 markers in lungs of high-fat diet fed hyperglycemic mice (5). Here, we hypothesized that beneficial effects of metformin in mouse allergic lung inflammation take place partly due to MGO inactivation. Therefore, this study was carried out to evaluate the effect of metformin on the potentiation by MGO of ovalbumin (OVA)-induced mouse airways inflammation. **Methods:** The study was approved by the Animal Use Ethics Committee (CEUA-UNICAMP; pro Number 5200-1/2019). C57BL/6 male mice received or not 0. 5% MGO in the drinking water for 12 weeks. Metformin was given in the last two weeks of MGO treatment (300 mg/kg, gavage). Mice were sensitized twice with OVA (100

µg, s. c), and two weeks later they were challenged intranasally with OVA (10 µg) twice a day. Bronchoalveolar lavage fluid (BAL) and lung tissues were collected to quantify the airway cell infiltration and levels of cytokines and reactive-oxygen species (ROS), as well as the mRNA expressions of NADPH oxidase isoforms. **Results:** Serum MGO concentration achieved after 12-week intake (20. 6 ± 1. 3 µg/ml) was higher than untreated mice (2. 2 ± 0.14 µg/ml; P<0.05), which was significantly reduced by metformin treatment (3. 5 ± 0. 64 µg/ml; P<0.05). In OVA-challenged mice, MGO treatment significantly increased the total number of inflammatory cells and eosinophils (3. 38 ± 0.17 and 2. 83 ± 0. 21 × 106/BAL) compared with control animals (1. 52 ± 0. 21 and 1. 42 ± 0. 27 ×106/BAL; P<0.05). The levels of the Th2 cytokines IL-4 e IL-5 in BAL were also significantly increased by MGO treatment (239. 3 ± 23. 80 and 193. 0 ± 17. 69 pg/ml) compared with control animals (159. 9 ± 10. 69 and 107. 2 ± 17. 33 pg/ml; P<0.05). In lung tissue of MGO-treated mice the levels of NOX-2, NOX-4 and ROS increased by 100%, 100% and 80% (P<0.05). In MGO-treated mice, metformin treatment normalized the OVA-induced eosinophilic inflammation and the levels of IL-4, IL-5, NOX-2, NOX-4 and ROS. **Conclusion:** Metformin reduces the OVA-induced airways inflammation and oxidative stress markers in response to prolonged MGO intake, which may be due to direct MGO scavenging. References1. Schalkwijk C. G, et al. Physiol. Rev, (100): 407-461; 20202. Checa J and Aran J. M. . J Inflamm Res,13:1057-1073; 2020 3. Medeiros ML, et al. Int Immunopharmacol. 81:106254; 20204. Medeiros ML, et al. J Inflamm Res. 2;14:6477-6489; 20215. Calixto MC et al. PLOS ONE, (10):1-13; 2013FINANCIAL BY: CAPES 88882. 435314/2019-01

04.015 **IGF-1 Increases Survival of CD4+ Lineage in a 2D Model of Thymocyte/Thymic Stromal Cell co-Culture**. Porto FL, Vieira LFA, Lins MP, Smaniotto S, Reis MDS UFAL, Laboratory of Cell Biology, Institute of Biological and Health Sciences, Maceió, Brazil

IGF-1 increases survival of CD4+ lineage in a 2D model of thymocyte/thymic stromal cell co-cultureaFelipe Lima Porto, aLarissa Fernanda de Araújo Vieira, abMarvin Paulo Lins, abSalete Smaniotto, abMaria Danielma dos Santos ReisaLab of Cell Biology, Institute of Biological and Health Sciences, Federal University of Alagoas, Maceió, Brazil; Brazilian National Institute of Science and Technology on Neuroimmunomodulation (INCT-NIM), Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil. Insulin-like growth factor-1 (IGF-1), in addition to its classic effects on cell proliferation and organism growth, has pleiotropic actions on the immune system, particularly on the thymus. Thus, the objective of this study was to evaluate the influence of IGF-1 on molecules involved in the differentiation of T lymphocytes *in vitro* using a co-culture system with thymic stromal cells obtained from C57BL/6 mice. The thymic stroma obtained has contained thymic epithelial cells, macrophages, dendritic cells, fibroblasts, and preserved the expression of the major histocompatibility complex (MHC) molecules. Fresh thymocytes were added to these cultures and the co-culture were treated daily with IGF-1 (100 ng/mL) for 3 days. In this scheme, the viability of the thymocytes were about 70%, either in the control (non-treated cells) and in the IGF-1- treated cultures. It was found that IGF-1 was able to increase the percentage of thymocytes from the CD4 + single-positive (SP) subpopulation. This result was accompanied by an increase in the MHC II expression on thymic stromal cells and na augment on the interleukin-7 receptor (CD127) on the surface of the CD4SP thymocytes after treatment with IGF-1. Finally, IGF-1 treatment increased the expression of the ThPOK encoding gene Zbtb7b, which is involved in the differentiation of CD4SP thymocytes. Our study demonstrates the participation of IGF-1 in the thymocyte/thymic stroma interactions, especially in the commitment to the CD4+ lineage in the thymus. The authors thank Juliane Pereira for handling in the cytometer and data acquisition. **Financial Support:** CNPq (Nº. 408677/2016-3) and FAPEAL (Nº. 60030 001260/2017). All animal experimentation was carried out in accordance with institutional guidelines and ethics of the Federal University of Alagoas and was approved by the Ethical Committee in Use of Animal Experimentation (CEUA no 47/2016).

04.016 **Mouse Model of Oleic Acid-Induced Acute Respiratory Distress Syndrome**. Almeida MAP[1,2,6], Rodrigues SO[1,2,5], Castro-Faria-Neto HC[1,3,4], Silva AR[1,3], Gonçalves-de-Albuquerque CF.[1,2,4,5,6] [1]Fiocruz, Lab de Imunofarmacologia,[2]IB-Unirio, Depto de Bioquímica, Lab de Imunofarmacologia, [3]IOC-Fiocruz, PPG Biologia Celular e Molecular, [4]Unirio, PPG Biologia Molecular e Celular, [5]UFF, PPG Ciências e Biotecnologia, [6]UFF, PPG Neurociências

Introduction: The acute respiratory distress syndrome (ARDS) is a pulmonary inflammation that leads to an acute respiratory failure and hypoxemia, diffuse bilateral alveolar damage and edema \[1, 2]. ARDS development is risk-associated with direct or indirect factors \[3]. These conditions cause the release of PAMP's and DAMP's, inducing a proinflammatory state \[4]. Preclinical studies in animal models help understand the pathology and are essential for new ARDS treatments research. **Methods:** The procedures used in this study were approved by the Ethics Committee on the Use of Animals of the Oswaldo Cruz Foundation (CEUA licenses n° 002-08, 36/10 and 054/2015). Male swiss webster mice weighing between 20-30g were anesthetized and an incision was made at the thyroid level to expose the trachea. Animals were instillated with 25 mM sodium oleate (OA) or 50 µL of sterile saline. Euthanization occured 24h after instillation. Bronchoaveolar lavage fluild (BALF) and lungs were collected for analyses. **Results:** Sodium oleate injection increased total leukocytes in BALF. Higher levels of IL-6, IL-1β, and TNF-α in the BALF were observed after 24h of OA intratracheal instillation \[5]. Total protein in BALF, showed OA administration increased edema. OA enhanced lipid bodies formation and Prostsglandin E2 (PGE2) production \[5] after 24 h. OA instillation also induced tissue disruption, hemorrhage, and leukocyte infiltration. **Conclusion:** In this work we have shown that sodium oleate instilaltion can properly induce severe lung damage in mice. It is worth noting that patients with ARDS have higher plasmatic OA concentration \[6]. Also, we published a correlation between OA/albumin disbalance and higher death risk in patients with leptospirosis \[7]. Our model provides great reproducibility of ARDS using oleic acid in its salt form. Thus, decreasing the toxic effects of OA, avoiding emboli formation and pH fluctuation in blood. \[6]. Acknowledgments:** **This research was funded by the Instituto Oswaldo Cruz, Fundação Oswaldo Cruz (FIOCRUZ), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) Grant 001, Programa de Biotecnologia da Universidade Federal Fluminense (UFF), Universidade Federal do Estado do Rio de Janeiro (UNIRIO), Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). **References:** 1. Force*, T. A. D. T., Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA, 2012. 307(23): p. 2526-2533. 2. Hewitt,R. J. and C. M. Lloyd, Regulation of immune responses by the airway epithelial cell landscape. Nat Rev Immu, 2021. 21(6):p. 347-362. 3. D'Alessio, F. R., Mouse Models of Acute Lung Injury and ARDS. **Methods:** Mol Biol, 2018. 1809: p. 341-350. 4. Millar, F. R., et al., The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities. Thorax, 2016. 71(5): p. 462. 5. Gonçalves-de-Albuquerque,C. F., et al., Oleic acid induces lung injury in mice through activation of the ERK pathway. Mediators Inflamm, 2012. 2012:p. 956509. 6. Gonçalves-de-Albuquerque,C. F., et al., Oleic acid inhibits lung Na/K-ATPase in mice and induces injury with lipid body formation in leukocytes and eicosanoid production. J Inflamm (Lond), 2013. 10(1):p. 34. 7. Martins, C. A., et al., The relationship of oleic acid/albumin molar ratio and clinical outcomes in leptospirosis. Heliyon, 2021. 7(3): p. e06420.

04.017 **Evaluation of the Effect of Hyperglycemia on the Autophagy Pathway in Macrophages from Diabetic Mice**. Sousa ESA, Queiroz LAD, Pantoja KC, Barros RS, Martins JO FCF-USP, Lab of Immunoendocrinology, Dept of Clinical and Toxicological Analyses, São Paulo, Brazil

Introduction: Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. Type 1 DM (DM1) destroys pancreatic beta cells, which most often consists of an autoimmune process, promoting an insulin deficiency. The hyperglycemic state resulting from the lack of insulin leads to an impaired immune system. Thus, the aim of this study is to evluate the autophagy process and the lipopolysaccharide-induced response (LPS) in bone marrow-derived macrophages (BMDM) of diabetic (D-BMDM) and non-diabetic (ND-BMDM) animals. **Methods:** For this, we used BMDM from diabetic and non-diabetic C57BL/6 mice. DM1 was induced by alloxan (60mg/kg, i. v.) [CEUA/FCF/USP nº570/2018]. BMDM were cultured in normal glucose concentration (5. 5 mM) and a high glucose concentration (25 mM) medium, and were stimulated or not with LPS at a concentration of 100 ng/mL and Nigericin at a concentration of 20 µM, at times 30 minutes; 2; 4; 6; 24 hours. The autophagy activation pathway was evaluated by dosing the autophagic proteins LC3b and Beclin-1 by the Western Blotting technique in 24 hours. The cytokines IL-6, IL-1β, TNF-α and IL-10 were measured by enzyme-linked immunosorbent assay (ELISA) at all times. **Results:** In our studies, we identified changes in the levels of pro-inflammatory cytokines IL-6, IL-1β and TNF-α, where ND-BMDM and D-BMDM showed an increase in the secretion of these cytokines when stimulated by LPS + Nigericin. No significant changes were observed in

IL-10 levels. In addition, changes were observed in the autophagy pathway, where the increase in the autophagic protein LC3b and Beclin-1 occurred by ND-BMDM in hyperglycemic medium, without LPS stimulation. Macrophages from diabetic animals in hyperglycemic medium with stimulation showed a reduction on the expression of LC3b, suggesting an impaired autophagic process in these cells. **Conclusion:** Alterations in autophagic proteins expression may directly interfere in the inflammatory response of diabetic subjects. The results obtained allow us to suggest that hyperglycemia stimulates the inflammatory state and impairs the autophagy pathway in macrophages stimulated by LPS, playing an important role in the inflammatory response of diabetic individuals.

04.018 **Regulation of the mTOR receptor by rapamycin in Accelerated Senescence Mice: The Role of Autophagy in the Aging Process**. Queiroz LAD[1], Barros RS[1], Assis JB[2], Pantoja KC[1], Sá-Nunes A[2], Rodrigues SFP3, Martins JO[1] [1]FCF-USP, Lab of Immunoendocrinology, Dept of Clinical and Toxicological Analyses, São Paulo, Brazil, [2]ICB-USP, Lab of Experimental Immunology, Dept of Immunology, Sao Paulo, Brazil, [3]ICB-USP, Lab of Vascular Nanopharmacology, Dept of Pharmacology, Sao Paulo, Brazi

Introduction: Aging is a natural and multifactorial process. In this context, autophagy, a process of degradation of intracellular content, naturally regulated by the nutrient receptor sensor mammalian target of rapamycin (mTOR) or chemically by the drug rapamycin (RAPA), has a direct relationship with cell homeostasis and maintenance of the senescent phenotype. This project seeks Investigate and identify which changes in glucose metabolism are caused by RAPA-stimulated autophagy, and how this impacts the expression of the senescent phenotype in cells of the immune system and in tissues and organs of high metabolic activity, in Senescence-Accelerated Mouse Prone 8 (SAM-P8) and Senescence-Accelerated-Resistant 1 Mouse (SAM-R1). **Methods:** animals SAM-P8 and SAM-R1 was treated with 0. 78 mg/kg of RAPA diluted in filtered water and administered once at five days by gavagem [CEUA/FCF/USP nº 619] during two months,with the control group of both strains being treated in the same way with only the vehicle solution. We evaluated the variance of the following parameters: (a) Weigh; (b) Glycemia; (c) Sensitivity for glucose and insulin in vivo; (d) Profile of cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, in the muscle, pancreas and liver homogenate **Results:** both SAM-P8 and SAM-R1 animals treated with RAPA showed no change in their weight, as well as in their glucose levels, or insulin or glucose sensitivity when compared to the control group; Control SAM-P8 animals showed a higher concentration of IL-6 and TNF-a in their muscle and liver tissue when compared to animals in the SAM-R1 groups. **CONCLUSION:** S: These findings suggest that the protocol chose to treat the animals did not induce changes in the glucose homeostasis, or in the profile of inflammatory cytokines, with the SAM-P8 mice be more propense to an inflammatory profile. **Financial Support:** CNPq (310993/2020-2); FAPESP (2020/03175-0; 2020/05439-4).

04.019 **Glucocorticoid-Induced Leucine Zipper Alleviates Lung Inflammation and Enhances Bacterial Clearance during Pneumococcal Pneumonia**. Carvalho AFS[1], Souza JAM[1], Grossi LC[1], Zaidan I[1], Oliveira LC[1], Cardoso C[1], Santos Souza GV[1], Vago JP[5], Queiroz-Junior CM[2], Morand EF[3], Bruscoli S[4], Riccardi C[4], Teixeira MM[1,2], Tavares LP[6], Sousa LP[1,2] [1]FF-UFMG, Signaling in Inflammation Laboratory, Depto de Análises Clínicas e Toxicológicas, [2]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [3]Monash University, Rheumatology Group, Centre for Inflammatory Diseases, School of Clinical Sciences at Monash Health, Melbourne, Australia, [4]University of Perugia, Dept of Medicine and Surgery, Section of Pharmacology, Perugia, Italy, [5]Radboud University Medical Center, Dept of Rheumatology, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands, [6]Brigham and Women's Hospital and Harvard Medical School, Dept of Medicine

Introduction: Pneumonia is a leading cause of morbidity and mortality worldwide. While inflammation is a host protective response that ensures bacterial clearance, a finely regulated response is necessary to prevent bystander tissue damage. Glucocorticoid (GC)-induced leucine zipper (GILZ) is a GC-induced protein with anti-inflammatory and proresolving bioactions, yet the therapeutical role of GILZ in infectious diseases remains unexplored. Herein, we investigate the role and effects of GILZ during ALI induced by LPS and Streptococcus pneumoniae infection. **Methods:** Mice were anesthetized and ALI was induced by instillation of LPS (1 µg - 500 endotoxin unit) or Streptococcus pneumoniae (105 CFU), intranasally in 40 µL. Control mice received saline (mock infection). The models of acute lung injury (ALI) were performed using wild-tipe male BALB/c or C57BL/6,

and GILZ-/- mice (C57BL/6 background). Twelve hours post infection or LPS instillation, mice were treated with 200 µL of TAT-GILZ (0. 2 mg/kg, i. p.), a cell-permeable GILZ fusion protein, or empty TAT (0.1 mg/kg, i. p.). Twenty-four hours post-LPS instillation or pneumococcus infection, the bronchoalveolar lavagem (BAL) was harvested for analysis of inflammatory parameters: differential leukocyte count; TNF-α, IL-6, CXCL1 and CXCL2 evaluation by ELISA; and total protein quantification by Bradford assay. The Left lungs were submitted to histopathological analysis to evaluate lung damage. To analyze survival rates, mice were treated at 12, 24 and 48 h after S. pneumoniae infection and were monitored by 10 days. **Results:** GILZ-/- presented more severe ALI, characterized by increased inflammation, decreased macrophage efferocytosis and pronounced lung damage. In keep with that, pulmonary inflammation, and damage were attenuated in WT mice treated with TAT-GILZ. During pneumococcal pneumonia, TAT-GILZ reduced neutrophilic inflammation and prevented the associated lung damage. There was also enhanced macrophage efferocytosis and bacterial clearance in TAT-GILZ-treated mice. Mechanistically, TAT-GILZ enhanced macrophage phagocytosis of pneumococcus, which was lower in GILZ-/- macrophages. Noteworthy, early treatment with TAT-GILZ rescued 30% of S. pneumoniae-infected mice from lethal pneumonia. **Conclusion:** Altogether, we present evidence that TAT-GILZ enhances host resilience and resistance to pneumococcal pneumonia by controlling pulmonary inflammation and bacterial loads leading to decreased lethality. Exploiting GILZ pathways holds promise for the treatment of severe respiratory infections. **Financial Support:** This work was supported by the National Institute of Science and Technology in Dengue and host-microbial interactions, a programme grant (465425/2014-3) from Fundação do Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG, Brazil) APQ-03221-18, Coordenação de Apoio ao Ensino de Pessoal de Nivel Superior (CAPES, Brazil) 23038. 003950/2020-16, and Conselho Nacional de Ensino e Pesquisa (CNPq, Brazil) PQ-306789/2018/3. Institutional Review Board Statement: Experiments had prior approval from the Animal Ethics Committee of Universidade Federal de Minas Gerais - UFMG (CEUA, protocol number 162/2020, approval date: 14 September 2020.

04.020 **Blockade of PI3K-γ Attenuates Chemotherapy-Associated Intestinal Mucositis without Compromising the Anticancer Effect of Irinotecan**. Cajado AG[1], Rangel GFP[1], Quintela LCS[1], Quispe CC[1], Padilla Paguada AL[1], Ferreira KQ[1], Ferreira LMM[1], Dias Florêncio KG[1], Pereira AF[1], Nunes Alves APN[1], Alencar NMN[1], Hirsch E[2], Wong DVT[1], Lima-Junior RCP[1] [1]UFC [2]Università di Torino

Introduction: Mucositis is a common toxicity of irinotecan-based colorectal cancer treatment. Such adverse effect can lead to sepsis and increased risk of patient death. The role of the phosphoinositide 3-kinases (PI3K) family of enzymes has been investigated in cancer and inflammatory diseases. Notably, PI3K-γ is mainly expressed in leukocytes, but its expression by other cells increases upon stress. The efficacy of PI3Kγ inhibition on modulating inflammatory conditions led us to speculate whether PI3K-γ would be a suitable target in chemotherapy-associated intestinal mucositis. We also tested a potential antitumor synergy between PI3K inhibition and irinotecan. **Methods:** C57BL/6 male mice (20-22g, n=6–9/group) received an i. p. injection of vehicle, irinotecan (120 mg/Kg, one injection/day/four days) alone or combined with AS-605240 (a selective PI3K-γ inhibitor, 10 mg/kg, p. o.). On day seven post-first dose of irinotecan, we determined the diarrhea severity and body mass variation. After animal euthanasia, we harvested the small intestine to measure the morphometry, oxidative stress, and inflammatory parameters. We detected the malondialdehyde (MDA), glutathione (NP-SH), myeloperoxidase (MPO), cytokine levels (IL1-β and IL-6), gene expression of toll-like receptors (2, 4, and 9), and immunofluorescence for F4/80, FOXP3 and p-AKT. We also tested whether AS-605240 would affect the antitumor effect of SN-38 (the active metabolite of irinotecan). Then, we run the cell viability (2 x 10ˆ4 cells of Mc-38, n=3 per group) and sulforhodamine B (SRB) assays. In the in vivo antitumor effect, the mice were inoculated with Mc-38 cells (1x10ˆ6 cells) in the axillary region. We treated the mice for seven days with AS-605240, irinotecan, or their combination post-tumor establishment. One-way ANOVA followed by the Bonferroni test was used to determine the statistical differences between the groups ($P<0.05$). Ethics committee approval: CEUA N°5132240718. Results. Irinotecan-associated body mass loss (21. 61% vs. vehicle group) was unaffected ($P>0.05$) by AS-605240 (19. 30%). Conversely, PI3K-γ inhibition partially attenuated the intestinal injury, as detected by the milder diarrhea scores [1 (1-2)] and improved villus/crypt ratio versus the irinotecan group (diarrhea: 2[1-3], $P<0.05$). PI3K-γ inhibition modulated the inflammatory response by reducing neutrophil accumulation, the expression of Tlr2, Tlr4, and Tlr9, and the levels of IL-1 and

IL-6. The fluorescence for the macrophage marker (F4/80), regulatory T cell transcription factor (FOXP3), and p-AKT were found to increase in the irinotecan group (P<0.05 vs. vehicle). Conversely, the PI3K-γ inhibition reduced the expression of these markers (P<0.05 vs. irinotecan). Remarkably, irinotecan increased the production of MDA and reduced the NP-SH levels. In contrast, the inhibition of PI3K-γ reduced the oxidative stress response, demonstrated by the reduced production of MDA and increased NP-SH (P<0.05 vs. irinotecan). The *in vitro* assays revealed that AS-605240 showed concentration-dependent cytotoxicity without affecting the SN-38 cell growth inhibition. Furthermore, PI3K-γ inhibition and irinotecan treatment reduced the tumor weight in mice, but their combination did not potentiate the tumor growth inhibition. **Conclusion:** PI3K-γ inhibition reduces chemotherapy-associated intestinal mucositis without compromising the anticancer effect of irinotecan. **Financial Support:** CNPq, Capes, and Funcap.

04.021 **Plasmin Modulates the Inflammatory Response in Experimental Pneumococcal Pneumonia**. Cardoso C[1,2], Montuori-Andrade, ACM[1,2], Carvalho AFS[1], Zaidan I[1], Ferreira LCG[1,2], Lara ES[1,2], Souza JAM[1], Teixeira MM3, Braga FC[4], Tavares LP[5], Sousa LP[1,2,3] [1]FF-UFMG, Signaling in Inflammation Laboratory, Depto de Análises Clínicas e Toxicológicas, [2]FF-UFMG, PPG Ciências Farmacêuticas, [3]ICB-UFMG, Centro de Pesquisa e Desenvolvimento de Fármacos, Depto de Bioquímica e Imunologia, [4]FF-UFMG, Lab de Fitoquímica e Biologia Farmacêutica, Faculdade de Farmácia, Universidade Federal de Minas Gerais, [5]Harvard Medical School – Pulmonary and Critical Care Medicine

Although plasmin is best known by its action on dissolution of the fibrin clots, recent studies highlight the role of plasminogen/plasmin system in other physiological functions, such as cell migration, tissue repair and inflammation. By using self-resolving models of inflammation have shown that Plg/Pla modulate key steps of inflammation resolution, such as neutrophil apoptosis, efferocytosis, and macrophage reprogramming toward resolving phenotypes (Sugimoto, M. A. et al., 2017; Vago, J. P. et al., 2019); yet their effect on infectious disease remains unexplored. Here, we have investigated the effect of plasmin on inflammatory response in airways and lungs induced by intranasal infection with Streptococcus pneumoniae. Experimental model was carried out with male BALB/c mice. All procedures described here were approved by the Ethics Committee of the Universidade Federal de Minas Gerais (CEUA, protocol number: 3/2019). Two different protocols were applied. Mice were intranasally infected with 105 CFU of S. pneumoniae (ATCC 6303 serotype 3) and then treated, 12 h later, with Plasmin (10 µg per animal, i. p.) or saline. At 24 h (short protocol) or 48 h (long protocol) after infection, mice were euthanized and broncoalveolar lavage (BAL) was collected to analyze inflammatory parameters (leukocyte infiltration and cytokine measurement) and bacterial loads. Lungs were collected and assayed for myeloperoxidase as indirect measurement of neutrophilic infiltration. Short treatment protocol of pneumococcal pneumonia with plasmin significantly decreased the numbers of neutrophils and increased the numbers of macrophages and efferocytosis counts, without changing bacterial counts, total protein and cytokine profile in the airways. Interestingly, plasmin decreases lung neutrophilic infiltration. The longer treatment of pneumococcal pneumonia with plasmin, decreased neutrophil numbers and increase macrophage numbers accompanied by increased efferocytosis counts in the airways. Moreover, Plasmin was able to decrease TNF and IL-6 levels in BAL and neutrophilic infiltration in the lungs. The data gathered so far suggest that Plasmin modulates neutrophilic inflammation in airways and lungs and reduces the release of pro-inflammatory mediators, deserving efforts to continues the characterization of such an effect. **References:** Sugimoto, M. A. et al. Plasmin and plasminogen induce macrophage reprogramming and regulate key steps of inflammation resolution via annexin A1. Blood. May 25; 129(21): 2896; 2017. Vago, J. P. et al. Plasminogen and the Plasminogen Receptor, Plg-RKT, Regulate Macrophage Phenotypic, and Functional Changes. Front Immunol. Jun 28; 10:1458; 2019. **Financial Support:** Capes and CNPq.

04.022 **Angiotensin-(1-7)/MasR Axis Promotes Migration of Monocytes/Macrophages with a Regulatory Phenotype to Perform Phagocytosis and Efferocytosis**. Zaidan I[1], Tavares LP[2], Sugimoto MA[3], Lima KM[1], Negreiros-Lima GL[1], Teixeira LCR[1], Miranda, TC[1], Valiate, BVS[2], Cramer A[1], Vago JP[4], Campolina-Silva G[1], Souza JAM[1], Grossi LC[1], Pinho V[1], Campagnole-Santos MJ[1], Santos, RAS[1], Teixeira MM[1], Sousa LP [1]UFMG, [2]Harvard Medical School – Pulmonary and Critical Care Medicine, [3]University College London, [4]Radboud University Medical Center

Abstract: nonphlogistic migration of macrophages contributes to the clearance of pathogens and apoptotic cells, critical steps for the resolution of inflammation and return to homeostasis. Angiotensin-(1-7) [Ang-(1-7)] is an heptapeptide of the Renin-Angiotensin system that acts through Mas receptor (MasR). Ang-(1-7) has recently emerged as a novel pro-resolving mediator, yet Ang-(1-7) resolution mechanisms are not fully determined. Herein, Ang-(1-7) stimulated migration of human and murine monocytes/macrophages in a MasR, CCR2 and MEK/ERK1/2-dependent manner. Pleural injection of Ang-(1-7) promoted nonphlogistic mononuclear cell influx alongside increased levels of CCL2, IL-10 and macrophage polarization towards a regulatory phenotype. Ang-(1-7) induction of CCL2 and mononuclear cell migration was also dependent on MasR and MEK/ERK. Noteworthy, MasR was upregulated during resolution phase of inflammation and their pharmacological inhibition or genetic deficiency impaired mononuclear cell recruitment during self-resolving models of LPS pleurisy and E. coli peritonitis. Inhibition/absence of MasR was associated with reduced CCL2 levels, impaired phagocytosis of bacteria, efferocytosis and delayed resolution of inflammation. In summary, we have uncovered a novel pro-resolving feature of Ang-(1-7), namely the recruitment of mononuclear cells favoring efferocytosis, phagocytosis and resolution of inflammation. Mechanistically, cell migration was dependent on MasR, CCR2 and the MEK/ERK pathway. Study approval: Experiments had prior approval from the Animal Ethics Committee of Universidade Federal de Minas Gerais - UFMG (CEUA, protocol number: 295/2018) and Research Ethics Committee of UFMG, for human cell studies (COEP, protocol number 0319. 0. 203. 000-11). Acknowledgments: This work was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG, Brazil), Pró-Reitoria de Pesquisa da Universidade Federal de Minas Gerais-PRPq, Brazil, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

04.023 **Evaluation of the Anti-Inflammatory Potential of** *Allophylus edulis* (**A.St.-Hil., Cambess. & A. Juss.**) **Radlk. Leaves**. Santos SM[1], Marangoni JA[1], Oliveira Junior PC[2], Souza MF[1], Narcizo LL[3], Gonçalves L[1], Vieira AR[1], Santos JM[1], Borges JAT[1], Silva ME[1], Passos BP[3], Formagio ASN[13]. [1]UFGD, PPG Health Sciences, Dourados, Brazil; [2]UFGD, PPG Biotechnology and Biodiversity (Rede Pró-Centro Oeste), Dourados, Brazil; [3]UFGD, PPG Biodiversity and Environment, Dourados, Brazil

Introduction: Allophylus edulis (A. St. -Hil., Cambess. & A. Juss.) Radlk. is a tree native to South America and popularly known by the name Vacum (Köhler et al., 2013). The leaves are used in folk medicine to treat Inflammation and sore throats (Körbes, 1995). Biological activities reported antioxidant (Tirloni et al., 2015), hepatoprotective (Hoffmann-Bohm et al., 1991), and negative ionotropic potential (Matsunaga et al., 1997) activity. Essential oils in turn are described as having anti-inflammatory, antioxidant and antimycobacterial activity (Trevizan et al., 2016; Piekarski-Barchik et al., 2021; Santos et al., 2021). Considering the use in folk medicine, this study aimed to evaluate the anti-inflammatory potential of the hydromethanolic fraction of the methanolic extract and the aqueous extract of A. edulis leaves. **Methods:** Allophylus edulis leaves were collected in the city of Dourados/MS (SisGen-A51F665). To obtain the hydromethanolic fraction, leaves were subjected to maceration with metanol. After partitioning the crude extract using solvents in increasing order of polarity, the hydromethanolic fraction was submitted to rotaevaporation. The aqueous extract was obtained from fresh leaves by the infusion process followed by lyophilization. The evaluation of the anti-inflammatory capacity was performed by the carrageenan-induced pleurisy test, according to Vinegar et al. (1973), in the doses of 3 mg/kg of A. edulis hydromethanolic fraction and A. edulis aqueous extract (3 and 30 and 100 mg/kg). Protein dosage was performed using the Bradford kit. Differences between groups were analyzed by ANOVA followed by Newman-Keuls post-test. ResultsThe partitioning of the methanolic extract of the dry leaves produced a yield of 7%, while the aqueous extract produced a yield of 3. 5%. The anti-inflammatory evaluation performed by the carrageenan-induced pleurisy test decreased leukocyte migration by 53% in the group tested with 3 mg/kg of the hydromethanolic fraction of A. edulis. The doses of 3, 30 and 100 mg/kg of the aqueous extract of the leaves presented 45%, 52% and 33% of decreased leukocyte migration, respectively. The positive control group Dexamethaxone, in turn, showed 79% inhibition of leukocyte migration. Likewise, the protein dosage test revealed that the lowest values were found at doses of 3 mg/kg of the hydromethanolic fraction and 3. 30 mg/kg of the aqueous extract. **Conclusion:** Considering the analysis of leukocyte migration and protein dosage, it is possible to state that the hydromethanolic fraction of the methanolic extract and the aqueous extract of A.

edulis leaves have anti-inflammatory potential, corroborating the popular use of this species. **Financial Support**Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (CAPES) - Finance Code 001. Ethics committee approvalCEUA/UFGD Protocol nº 05/2021. ReferencesHoffmann-Bohm, K. et al. Planta Med. 58, 544, 1992. Köhler, M. et al.,Cartilha das frutas nativas de Porto Alegre, 2013. Körbes, V. C. Plantas medicinais. 48. ed., 1995. 188p. Matsunaga, K. et al. Nat. Med. 51, 478–481, 1997. Piekarski-Barchik et al. Chem. Biodivers, 2021. Santos, S. M. et al. J. Ethnopharmacol. 267, 113495. 2021. Tirloni, A. S. C. African J. Pharm. Pharmacol. 9, 353, 2015Trevizan, L. N. F. et al. J. Ethnopharmacol. 192, 510, 2016. Vinegar, J. F. et al. Exp. Biol. Med., 143 pp. 711, 1973. Acknowledgments The authors express their gratitude to the Federal University of Grande Dourados and CAPES for **Financial Support**.

04.024 **Suppression by Quercetin of the Early Phase of Silicosis in Swiss-Webster Mice**. Abreu FVG, Ferreira TPT, Arantes ACS, Martins MA, Martins PMRS Fiocruz

Introduction: Silicosis is a chronic and irreversible lung disease, characterized by an early inflammatory phase characterized by leukocyte infiltration, oxidative damage, and fibrosis. Quercetin is a flavonoid present in several plants including fruits, vegetables, and some grains, showing anti-inflammatory and antioxidant activities. Objective: This study was undertaken to investigate the potential effect of quercetin on the early phase of experimental silicosis in mice. **Methods:** Male Swiss-Webster mice were anesthetized with isoflurane, and then instilled with crystalline silica (10 mg; particle size 0. 5 – 10 µm) by intranasal via. Treatment with quercetin (10 mg/kg, p. o.) was performed daily, from day 1 to 7 pos-silica and analyses were performed 1 day after the last administration. The parameters evaluated included: i) pulmonary function (resistance and elastance) and airway hyper-reactivity to methacholine (whole body invasive plethysmography; ii) leukocyte infiltration in the bronchoalveolar lavage (BAL); iii) morphology and morphometry analyses of lung tissue; iv) quantification of inflammatory mediators cytokines/chemokines by ELISA and markers of oxidative stress by biochemistry. All experimental procedures were performed according to the guidelines of the Committee on Use of Laboratory Animals of the Oswaldo Cruz Foundation (LW57-14/L001-19). **Results:** We showed that silicotic mice exhibited increased lung resistance and elastance, as well as airways hyper-reactivity to methacholine. In parallel, we detected leukocyte infiltration in the BAL, mainly of neutrophils, in a direct correlation with increased levels of myeloperoxidase (MPO) in the lung tissue. Levels of the inflammatory cytokine IL-1β and of the CXC chemokines CXCL-1/KC and CXCL-2/MIP-2) were augmented in the lung tissue. The activity of the antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD) was altered and levels of reactive oxygen species (ROS) and malondialdehyde (MDA) were increased. Collagen deposition and granulomas were also detected in the silicotic lungs. Oral treatment with quercetin reduced leukocyte infiltration in the BAL and in lung tissue as well as collagen deposition and cytokine/chemokine generation in silicotic mice. Quercetin also reduced ROS and MDA levels and restored CAT and SOD activities in silicotic lungs. **Conclusion:** Altogether, our findings show that the administration of quercetin, at the early phase of silicosis in mice, suppressed the inflammatory component and restored the lung function, supporting the idea that its anti-inflammatory and antioxidant properties of quercetin may be useful in the treatment of the acute phase of some restrictive diseases such as silicosis. **Financial Support:** FIOCRUZ, FAPERJ, CNPq (Brazil).

04.025 **Glucagon is Involved with Increased Susceptibility to Sepsis in Murine Model of Diabetes Through Down Regulation of Neutrophil Migration**. Insuela DBR[1], Ferrero MR[1], Gonçalves-de-Albuquerque CF[2,3], Chaves AS[1], Silva AYO[2], Faria-Neto HCC[2], Simões RL[4], Barja-Fidalgo TC[4] Martins PMRS[1], Martins MA[1], Silva AR[2], Carvalho VF[1] [1]IOC-Fiocruz – Lab Inflammation, Rio de Janeiro, Brazil, [2]IOC-Fiocruz – Lab Immunopharmacology, Rio de Janeiro, Brazil, [3]Unirio – Lab Immunopharmacology, Biomedical Institute, Rio de Janeiro, Brazil, [4]UERJ – Lab of Cellular and Molecular Pharmacology, Biology Institute, Rio de Janeiro, Brazil

Introduction: Diabetes mellitus (DM) is one of the main diseases related to the development and worsening of sepsis, however, the mechanisms responsible for this are not yet understood. DM patients show an increase in concentrations of the hormone glucagon (GLU). The same is observed in severe sepsis. In addition, we observed that GLU exerts anti-inflammatory effects. Thus, we hypothesized that DM-triggered hyperglucagonemia may reduce migration of neutrophils, increasing sepsis susceptibility. **Methods:** The animals were obtained from Oswaldo Cruz Foundation breeding colony and used in accordance with the guidelines of the Ethic Committee on Use of Laboratory Animals of the Oswaldo Cruz Foundation, Licenses L–027/2016 and LW36/10. DM was

induced in male Swiss-Webster mice by i. v. of alloxan, and 21 days later, sepsis was established by cecum ligation and puncture (CLP). The DM-mice were treated with GLU receptor (GcgR) antagonist (0. 3 or 1 mg/kg, i. p.) 24h and 1h before CLP, and we evaluated neutrophil and colony-forming units (CFU) numbers in the peritoneal cavity 3h after CLP. In addition, non-DM animals were treated with GLU (1 µg/Kg, i. p.) 1h before administration with CXCL1/KC (200 ng/Cavity, i. p.), and analysis of neutrophil migration to the peritoneal cavity was performed 3h after stimulation. The action of GLU on the chemotaxis of murine polymorphonuclear cells (PMNs) *in vitro* was tested using transwell plates. Levels of actin polymerization in PMNs stimulated with CXCL1/KC *in vitro* were analyzed by fluorescence microscopy, and ROS production was measured through chemiluminescence after stimulation with zymosan A in vitro. The expression of total PKA and phospho-PKA in PMNs after GLU treatment *in vitro* was evaluated by western blot. **Results:** GcgR antagonist recovered neutrophil migration and decreased the number of CFU in the peritoneal cavity of DM-mice after CLP, increasing the survival rate, but with no effect on cytokine levels in the peritoneum. GLU inhibited CXCL1/KC-induced neutrophil migration into the peritoneal cavity of non-DM mice (1. 38 x 106 ± 0. 23; 9. 11 x 106 ± 1. 59; 4. 02 x 106 ± 0. 89 neutrophils in peritoneum of saline, CXCL1/KC and CXCL1/KC plus GLU, respectively; mean ± SEM; n = 5; $p<0.05$), and also inhibited the chemotaxis of PMNs stimulated with CXCL1/KC, PAF or fMLP in vitro. This effect of GLU on chemotaxis was abolished by pretreatment of PMNs with the GcgR antagonist, adenylyl cyclase or PKA inhibitors in vitro. Furthermore, GLU increased PKA phosphorylation in PMNs in vitro. GLU was able to inhibit CXCL1/KC-induced actin polymerization in PMNs in vitro. Although GLU inhibited the chemotaxis of PMNs in vitro, it did not alter the expression of CD11a and CD11b on the surface of these cells. Finally, GLU inhibited ROS production induced by zymosan A in PMNs in vitro. **Conclusion:** GLU can be important to failure of neutrophil recruitment and increased susceptibility to sepsis observed in DM mice in a mechanism associated with activation of cAMP-PKA signaling pathway (Insuela DBR et al., Front. Immunol. 12. 2021). **Financial Support:** CNPq, INCT-NIM, FAPERJ and Programa INOVA FIOCRUZ. Keywords: cAMP, Diabetes, Glucagon, Neutrophil, Sepsis.

04.026 **Evaluation of GILZ Protein as Potential Therapeutic Alternative in the Coronavirus-Induced Infection**. Montuori-Andrade ACM[1], Souza JAM[1], Carvalho AFS[1], Grossi LC[1], Zaidan I[1], Oliveira LC[2], Cardoso C[1], Tavares LP[3], Morand EF[4], Bruscoli S[5] Riccardi C[5], Teixeira MM[2], Sousa LP[1] [1]FF-UFMG – Análises Clínicas e Toxicológicas, Belo Horizonte, Brazil, [2]ICB-UFMG – Bioquímica e Imunologia, Belo Horizonte, Brasil, [3]Harvard Medical School – Pulmonary and Critical Care Medicine, [4]Monash University, Melbourne, Australia, [5]University of Perugia – Section of Pharmacology, Perugia, Italy

Introduction: SARS-CoV-2 infection is associated with an intense and persistent pro-inflammatory response, which can be controlled, at least in part, by glucocorticoids. Studies have shown that glucocorticoic-induced leucine ziper (GILZ) is a key component that control the immune response and is an important mediator of inflammation resolution, including infectious diseases, by using preclinical models of infection. Therefore, the aim of this work was to evaluate the therapeutic effect of TAT-GILZ (a cell permeable GILZ-fusion protein) on the susceptibility of C57BL/6 mice (CEUA 260/2020) to severe acute respiratory syndrome (SARS) induced by intranasal inoculation of the betacoronavirus MHV-3, a murine model that recaptulate many aspects of the respiratory disease and systemic alterations seen in patients with moderate or severe COVID-19. **Methods:** Mice were infected intranasally with 103 PFU (for inflammation experiments) or 102 PFU (for lethality experiments) and then treated intraperitoneally at different times after infection with vehicle or with equimolar doses of TAT (2 . 5 µg per animal) or TAT-GILZ (5 µg per animal). Resouts: Our results showed that TAT-GILZ rescued 60% of MHV-infected mice from lethality in addition to protection against weight loss associated with disease. To evaluate the inflammatory parameters and viral load in tissues, animals were euthanized on the third or fifth day. On the third day of infection, TAT-GILZ treated mice showed decreased influx of cells to the alveoli, characterized mainly by reduction of macrophages and lymphocytes in bronchoalveolar lavage (BAL), also accompanied by decreasing amounts of extravasated protein in BAL. There were a trend to decrease neutrophils in the lungs (evaluated by MPO), and an increase in IL-10 levels. Experiments carried out with a delayed treatment with TAT-GILZ showed similar effect on the leukocytes in the alveoli and decreased levels of IL-6 in lungs on the fifth day after infection. Regarding systemic response parameters, MHV-3 infection cause lymphopenia and thrombocytopenia characteristics of the SARS-CoV-2 infection. The treatment of MHV-infected mice with TAT-GILZ was able to partially rescue these blood parameters and to increase the numbers

of leukocytes and platelets. Despite modulating the inflammatory response, TAT-GILZ did not interfere with viral replication in the lungs, liver and BAL on third and fifth days pos infection. **Conclusion:** The effects of GILZ observed in this work suggest a potential protective effect against coronavirus infections and stimulate to investigate further the mechanisms behind the protection to the virus-induced lethality. Acknowledgment: CAPES, CNPQ

04.027 **Development of a Murine Model to Study the SARS-CoV-2 Spike Protein S1 Subunit-Induced Inflammation and Endocrine Dysfunctions in K18-hACE2 Transgenic Mice**. Ferreira TPT, Brasiel PG, Chaves AS, Cotias AC, Arantes ACS, Martins PMRS, Carvalho VF, Martins MA Fiocruz

Introduction: Coronavirus disease 2019 (Covid-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reached pandemic proportions and enormous socioeconomic issues. Although the world scientific community has promptly responded to the challenge posed by pandemic, with the development of effective vaccines and some drugs in record time, the concomitant threat of emergent variants continues to impose the study of new therapies. SARS-CoV-2 infects cells through the interaction of its spike protein with angiotensin-converting enzyme 2 (ACE2) and activation by proteases. The SARS-CoV-2 Spike Protein S1 subunit (S1PS) facilitates ACE2-mediated virus attachment while the S2 subunit promotes membrane fusion. The clinical cases of severe Covid-19 are characterized by a cytokine storm with their coagulation changes that can lead to tissue damage, especially in the lungs, and death. The pre-existing endocrine and metabolic disorders, including diabetes and obesity, may be risk factors for the worse clinical progression of Covid-19. In addition, ACE2 and transmembrane serine protease 2 (TMPRSS2) are expressed in several endocrine tissues, such as the hypothalamus, pituitary, thyroid, adrenal, gonads, and pancreatic islets, and some studies have shown that endocrine organs can be infected by SARS-CoV-2. In this study, we evaluate the effect of S1PS stimulation on lung inflammation and its effects on metabolic hormones in K18-hACE2 transgenic mice. **Methods:** Male K18-hACE2 transgenic mice were oropharyngeally instilled with S1SP (400 μg/Kg). After 72 hours, the following analyses were performed: i) leucocyte evaluation in bronchoalveolar lavage fluid (BALF) and blood; ii) cytokine/chemokine and thrombin-antithrombin complexes quantification in the lung and plasma, respectively, by ELISA; iii) metabolic hormones dosage in plasma by Milliplex kit. **Results:** We showed that S1PS-induced an accumulation of mononuclear cells and neutrophils in the BALF, however, its only increased neutrophils in the peripheral blood. Furthermore, S1PS evoked a rise in the KC and MCP-1 levels in lung tissue, without modifying the content of TNF-α and IL-6. On the other hand, stimulation with S1PS led to a reduction in the circulating levels of glucagon and resistin, and a tendency to decrease the levels of insulin and leptin. Finally, we did not observe any alteration in the thrombin-antithrombin complexes formation in the plasma of mice stimulated with S1PS compared to control mice. **Conclusions:** Our results show that S1PS provocation promotes airway and lung inflammation, in parallel to reduction in metabolic hormone levels in the plasma of K18-hACE2 transgenic mice. We suggest that this mouse model is a useful system for studying the inflammatory response and endocrine dysfunctions similar to those observed in Covid-19 and for screening new adjuvant therapeutic strategies for treatment of Covid-19, under class 1 biosafety level conditions. Furthermore, the model may be useful for a better understanding of long-term complications of Covid-19 that are related to endocrine disorders observed in the Covid-19 patients. **Financial Support:** FIOCRUZ, CNPq, FAPERJ. The license number of the ethics committee: (CEUA license number – L-008/2021).

04.028 **Impact of Long-Term of Standard and High Fat Diet on Selected Obesity Parameters and Respiratory Mechanics in Phenotypically Selected Mice for Minimal or Maximal Acute Inflammatory Reaction**. Tino De Franco M[1], Massa S[1], Moriya HT2, Antonio NS[1], Oliveira MA3, Tavares-de-Lima W3, Ribeiro OG[1], Trezena AG[1] [1]Instituto Butantan, Lab de Imunogenética, [2]USP – Escola Politécnica, Lab de Engenharia Biomédica, [3]ICB-USP, Dept Farmacologia

Introduction: Obesity is a public health concern and induces a systemic chronic low-grade inflammatory condition involving the release of a wide spectrum of cytokines. In addition, obesity exerts a pivotal role on lung homeostasis, modifying respiratory mechanics. Two strains of well-established mice selected for high (AIRmax) or low (AIRmin) acute inflammatory reactivity (Ibañez, OM et al, Eur. J. Immunol., 22, 2555, 1992) were used here to characterize the repercussions of long-term standard (SD) and high-fat diet (HFD) on obesity and respiratory mechanics profiles. **Methods:** Male and female mice of the AIRmax and AIRmin lines were submitted

to SD or HFD for 26 weeks (CEUAIB: 3268080319). Body weight and consumption were quantified weekly. At the end of the period, weight gain, gonadal, and retroperitoneal fat were determined. Respiratory mechanics was quantified by recording the changes of airway resistance (Raw) and parenchymal resistance (G) induced by methacholine (MCh) using the FlexiVent system. **Results:** Male HFD-AIRmax mice significantly increased the weight (55. 0 ± 3. 74g) as compared to male and female HFD-AIRmin (35±2. 9g; 41±1. 7g, respectively), whereas the fed consumption did not differ between the studied groups. Male HFD-AIRmax showed a more intense increase in weight gain than male SD-AIRmax mice (36. 3±1,67g). In contrast, an increased perigonadal fat accumulation was found in female HFD-AIRmin (3. 0±0. 09g) and female HFD-AIRmax (4. 5±0. 58g) compared to male HFD-AIRmin (1. 7±0. 58g) and male HFD-AIRmax (1. 8±0.16g). Although male and female AIRmin mice submitted to SD HFD have revealed less weight gain, these mice were more responsive to MCh, showing increased Raw and G values. **Conclusions:** Our data suggest that the genetic background of AIRmin and AIRmax could be related to obesity and respiratory mechanics profile. These mice could be a suitable model to evaluate the interaction of inflammatory genetic profile with the repercussions of obesity. **Financial Support:** Fundação Butantan

05. Pain and Nociception Pharmacology

05.001 **Effective, long-Lasting and Safe Multimodal Analgesia Produced by a Novel Anesthetic/Analgesic Drug Protocol in Mice**. Hoepers JVA, Godoi MM, Ferreira J UFSC, Dpt of Pharmacology, Florianópolis, Brazil

Introduction: A review on anesthesia and analgesia protocols after invasive procedures in laboratory animals revealed that many published studies do not include pain relief (Jirkof P. Lab Anim. 2017;46:123), apart current legislation recommending the use of analgesic drugs (systemic opioids plus NSAIDs) by at least 3 days after invasive procedures. The pain management, as well as any untreated pain, has the potential to affect scientific results, thereby hampering the reproducibility of experiments). Here, we investigate the efficacy, the duration and the safety of the analgesia produced in mice by a novel combination of anesthetic/analgesic drugs available in the Brazilian market. **Methods:** Male and female C57BL/6-UFSC mice (N=4-5, 20-25 g) were used. Before the drug administration, we detected baseline values of withdrawal latency to heat (to detect antinociception), facial expressions (to detect sickness), water and food consumption, body wight or nidification (to detect animal well-being). To mimic a sham invasive procedure, mice were pre-treated with morphine (3 mg/kg, subcutaneously), followed by a general anesthesia with isoflurane (5%). After induction, the mice dorsal region was shaved, 0,02mL of lidocaine (0. 2%) was infiltrated subcutaneously in a small area, 1 cm2 of buprenorphine patch (5 ug/hour) was applied 1 cm from the infiltrated area and was covered with transparent dressing. Moreover, mice were subcutaneously treated with carprofen (5 mg/kg). Surgical plane anesthesia was maintained by 15 to 30 minutes. From 1 to 14 days after this protocol, we detected again analgesia, sickness and well-being. **Results:** The baseline values of nociception (5. 1±1. 1 and 7. 7±1. 1 seconds of latency), sickness (0±0 and 0±0 grimace scores) and well-being (3. 5±0. 5 and 3. 8±0. 2 nidification scores) were similar between male and female mice. None of the nine treated animals died until 14 days after the treatment. Compared to baseline values, we detected a significant analgesic-like effect of the treatment from 1 to 3 days after the sham procedure in male mice (32±4 % maximal possible effect, 1 day after), with a trend to significance in female mice at 1 and 2 days (35±9 %, p = 0. 2481). The treatment did not induce sickness behaviors in male or female mice (grimace scores were not different from zero in any time analyzed). However, anesthetic/analgesic drug treatment caused a significant reduction in body weights from 1 to 2 days after procedure both in male and female mice (-7±1 and -5±1 % of variation from the baseline weight after 2 days, respectively). The water or food consumption was not altered by treatment in any time analyzed in male and female mice (1. 5±1. 5 and -1. 0±0. 3 ml or -0. 2±0. 6 and -0. 4±0. 7 g from the baseline consumption after 1 day, respectively). **Conclusion:** To the best of our knowledge, our results demonstrate for the first time that the multimodal treatment with systemic short- (morphine) and long-acting (buprenorphine) opioids plus long-acting NSAID (carprofen), combined with local anesthetic infiltration (lidocaine), produced an effective, long-lasting (up to 3 days) and safe (minimally impacting well-being) analgesic-like (antinociceptive) effect in isoflurane anesthetized mice, in males. Studies are ongoing to validate the effectiveness and the safeness of our protocol in mice submitted to invasive procedures (such as

surgery and burn injuries). Acknowledgments: This study was approved by the CEUA-UFSC number: 4926230522. **Financial Support** for this project was provided by INCT-INOVAMED, BioCelltis Biotech and CNPq.

05.002 **Antinociceptive and Antiedematogenic Effect of α-Bisabolol in Mice**. Bernardes LB, Viero FT, Rodrigues P, Santos GT UFSM, PPG in Pharmacology, Santa Maria, Brazil

Introduction: Pain is considered an unpleasant sensation, and its perception differs among individuals, and its mechanism is poorly elucidated. In addition, the therapies available for pain control often do not have complete relief or have several contraindications. Thus, it is necessary to search for new therapeutic alternatives to reduce pain. In this sense, the compound α-bisabolol (BISA), a terpene found in native plants of Brazil, such as chamomile and sage, has already demonstrated antinociceptive, anxiolytic and anti-inflammatory effects. Still, its mechanism of action has not yet been elucidated. Thus, the aim of this study was to verify the lower dose of BISA that has an antinociceptive effect in mice after intraplantar AITC injection. **Methods:** The study used adult male mice C57BL/6 (CEUA UFSM #6302200821) divided into groups with n samples of 8 animals. Initially, a dose curve of the compound was performed using doses of 10, 30, 50 and 100 mg/kg orally, which was performed for the evaluation of mechanical nociception, cold allodynia, spontaneous pain and edema of the paw caused by intraplantar injection of allyl isothiocyanate (AITC) 0.05 mg/mL. Thus, the animals were pre-treated with oral BISA at the pre-established doses 1 hour before the intraplantar injection of AITC (20 µl). After administration, spontaneous nociception behaviour was observed for 5 minutes and edema after 15 minutes of AITC injection. Then, a mechanical nociception test was performed using the Von Frey test, and cold allodynia, measured by the acetone test, in the period of 0. 5, 1, 2, 3 and 4 hours after administration of AITC. The results were expressed as the mean, and standard deviation of the mean and statistically analyzed by a one-way variance test (ANOVA), followed by the Bonferroni post-test. Differences between groups were considered significant when P values were lower than 0.05 ($P<0.05$) through GraphPad Prism 9. 0. **Results:** The data obtained showed that the BISA doses of 50 and 100 mg/Kg compared to the vehicle group reduced spontaneous nociception and paw edema ($p=0.015$ and $p=0.0038$, respectively). However, doses 10 and 30 mg/Kg did not show significant results when compared to control ($p = 0.28$ and $p = 0.12$) respectively). In addition, when mechanical allodynia and cold were evaluated, both doses of 50 mg/kg and 100 mg/kg of BISA were shown to reduce nociception and cold allodynia when compared to the vehicle group ($p=0.0014$). However, the doses of 10 and 30 mg/kg did not show significant results **Conclusion:** Thus, we conclude that the lowest dose capable of reducing all nociceptive parameters investigated in this study was the dose of 50 mg/kg. From this experiment, more studies will be needed to verify the mechanism of action of the antinociceptive mechanism of BISA. Fellowships from the Conselho Nacional de Desenvolvimento Científico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

05.003 **Nonclinical Investigation of the Analgesic Efficacy of Topical Acid Dibucaine in a Mice Model of Painful HIV-Sensory Neuropathy**. Bittencourt MCS[1], Schran RG[2], Silva AM[2], Ferreira MA[2], Ferreira[2] J [1]UFSC, Undergraduate student in Pharmacy, Florianópolis, Brazil, [2]UFSC, PPG Pharmacology, Florianópolis, Brazil

Introduction: Pain is pharmacoresistant and a major source of morbidity in people living with HIV which present sensory neuropathy (HIV-SN) (Egan, Curr Pain Headache Rep. 2021;25:55). Topical capsaicin (8%) is the only effective treatment available for SN-HIV, apart producing skin irritation after application. Capsaicin acts by stimulating TRPV1 receptors and activating calpain proteolytic enzymes, leading to a defunctionalization of TRPV1 positive neurons and inducing long-lasting analgesia. Since i) protons are agonists of TRPV1 receptors, ii) local anesthetics permeates TRPV1 pore to selectively act on TRPV1 positive neurons and; iii) the local anesthetic dibucaine is not only a sodium channel blocker, but also a calpain activator; we hypothesize that the topical treatment with an acid cream of dibucaine could produce analgesic-like effect in a mice model of painful HIV-SN. **Methods:** Male C57BL/6-UFSC mice (N= 4-6, 20-25 g) were submitted to a model of HIV-SN induced by repeated administration of intrathecal HIV envelope protein gp120 (100 ng/site, once a day, every 3 days, 3 times) plus intravenous antiretroviral drug d4T (50 mg/kg, once a day, every 4 days, twice). Acid cream (pH 4,0) without or with dibucaine were administered topically in the hind-paws of mice 0. l% (once a day, seven times) 15 days after gp120+d4T treatment stated. We detected paw withdrawal thresholds (PWTs) and affective motivational behaviors (AMBs) after von Frey filaments application in the hind-paw. PWTs were determined by using the up-and-down method and AMBs were detected by scoring the behaviors (0-normal paw, 1-sideways

paw, 2-raised paw and 3-licking, shaking or biting the paw (Corder, Nat Med. 2017;23:164). PWTs and AMBs were detected before and 15 days after gp120+d4T as well as 7 days after topical treatment started. **Results:** Animals treated with gp120+d4T had a reduction of PWTs (mechanical hyperalgesia) and an increase of AMBs (thresholds of 0. 488±0. 071 or 0. 024±0. 007 g and scores of 1. 2±0. 5 or 7. 8±2. 1, before or 15 days after treatment). The topical treatment with acid dibucaine cream significantly reduced the mechanical hyperalgesia (thresholds of 0. 268±0. 027 and 0. 036±0. 015 g, for dibucaine and vehicle groups), but did not alter AMBs (scores of 7. 6±2. 1 and 4. 8±1. 5 g, for dibucaine and vehicle groups). **Conclusion:** Our results demonstrate that topical application of an acid dibucaine cream was able to reduce the sensory, but the affective component of the nociception in a mice model of HIV-SN. Studies are ongoing to improve the efficacy of the dibucaine cream (e. g., increasing dose and time of treatment) in our model. Acknowledgments: This study was approved by the CEUA-UFSC number PP00872. **Financial Support** for this project was provided by INCT-INOVAMED and CNPq.

05.004 **Chronic Effect of Gold Nanoparticles in a Preclinical Model of Complex Regional Pain Syndrome (CRPS).**
Nascimento MAS[1], Oliveira HC[2] Teixeira KJJS[2], Borgmann G[3], Plautz K[3], Delmônego L[3], Gastaldi AB[3], Delwing-de Lima D[3], Dal Magro DD[4] [1]UNIVILLE Joinville, Dpt of Pharmacy, Brazil, [2]UNIVILLE, Dpt of Medicine, Joinville, Brazil, [3]UNIVILLE, PPG em Health and Environment ,Joinville, Brazil [4]FURB, Dpt of Natural Sciences, Blumenau, Brazil
Introduction: The pathogenesis of pain is related to several mechanisms, including inflammatory processes, which culminate in the generation of free radicals and consequently in oxidative stress [1]. From the population affected by chronic pain, 50 to 60% are partially or totally disabled, compromising their quality of life [2]. Gold nanoparticles (AuNPs) have been suggested in the management of pain associated with inflammation or neuropathy, such as Complex Regional Pain Syndrome Type I (CRPS-I), due to their antioxidant and anti-inflammatory capabilities. This study aimed to evaluate the chronic effect of AuNPs on oxidative stress and pain in a model of CRPS-I in blood and sciatic nerve of 60-day-old male mice. **Methods:** Animals were anesthetized intraperitoneally (i. p.) and an elastic tourniquet was inserted and maintained around the left hind paw for 120 minutes. Mechanical threshold measurements were performed using the Von Frey test and thermal threshold to cold (20 µL of acetone placed on the animals' paw). The animals received i. p. administration of AuNPs (2. 5, 7. 0 and 22. 0 mg/L), vehicle or TRPA1 receptor antagonist (HC030031) 300 mg/kg/10mL, according to the group analyzed on days 1, 2, 3 and 4. Measurements were performed before and on days 1, 5, 9, 12, and 17 after ischemia. On the 17th day, the animals were euthanized by decapitation, blood was collected, and the sciatic nerve was separated for analysis of the level of thiobarbituric acid reactive substances (TBA-RS), total sulfhydryl content, and catalase enzyme activity (CAT) [3, 4, 5]. Data were collected and statistically analyzed by one-way and two-way ANOVA, followed by Duncan's and Bonferroni's post hoc test, respectively, when indicated ($p<0.05$). **Results:** The AuNP of 2. 5 mg/L showed mechanical antiallodynic effect on days 1 and 5 and thermal on days 1, 5 and 9. The AuNPs of 7. 0 and 22. 0 mg/L showed significant mechanical and thermal antiallodynic effect from day 1 to day 17. The CRPS model promoted significant elevation of TBA-RS in sciatic nerve and plasma, which was prevented by AuNPs of 7. 0 and 22. 0 mg/L; significant decrease of sulfhydryl in plasma, which was reversed by AuNPs of 22. 0 mg/L and elevation of catalase (CAT), which was significantly attenuated by AuNPs of 7. 0 and 22. 0 mg/L. Regarding toxicity, in short term treatment, they do not promote hepato or nephrotoxicity. **Conclusion:** Oxidative stress was not circumscribed to the injured nerve only. The results indicate involvement of oxidative stress in the installation and maintenance of CRPS and AuNPs show promise for mechanical and thermal anti-allodynia results in the three concentrations, besides presenting antioxidant activity. Support: FAP (Fundo de Apoio à Pesquisa da Univille). **References:** [1] Sasaki A, J Pharmacol Exp Ther. 351, 568, 2014. [2] Oliveira RM, Rev. dor. 14, 39, 2013. [3] Ohkawa H, Anal Biochem. 95, 351, 1979. [4] Aksenov MY, Neurosci Lett. 302, 141, 2001. [5] Aebi H, **Methods:** Enzymol. 105, 121, 1984. License number of ethics committee: CEUA/Univille Nº004/1118.

05.005 **Characterization of Nociception and Inflammation Observed in a Traumatic Muscle Injury Model in Rats.**
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Muscle pain is the most prevalent type of pain in the world, but treatment remains ineffective. Thus, it is relevant to develop trustable animal models to understand the involved pain mechanisms. Therefore, this study

characterised the inflammation in a traumatic muscle injury model in rats. A single blunt trauma impact on the right gastrocnemius muscle of male Wistar rats (250–350 g; protocol number #6579280218) was used as model for muscle pain. Animals were divided into four groups (sham/no treatment; sham/diclofenac 1%; injury/no treatment; injury/diclofenac 1%) and the topical treatment with a cream containing 1% monosodium diclofenac (applied at 2, 6,12, 24, and 46 h after muscle injury; 200 mg/muscle). Nociception (mechanical and cold allodynia, or nociceptive score) were evaluated at 26 and 48 h after injury. Also, inflammatory and oxidative parameters were evaluated in gastrocnemius muscle and the creatine kinase (CK) activity and lactate/glucose levels in rat's serum and plasma, respectively. Muscle injury caused mechanical and cold allodynia and increased nociceptive scores. This model also increased the inflammatory cells infiltration (seen by myeloperoxidase and N-acetyl-β-D-glucosaminidase activities and histological procedure), nitric oxide, interleukin (IL)-1β, IL-6, and dichlorofluorescein fluorescence in muscle samples; and CK activity and lactate/glucose ratio. The treatment with 1% monosodium diclofenac reduced inflammatory cells infiltration, dichlorofluorescein fluorescence, and lactate/glucose levels. Thus, we characterised the traumatic muscle injury as a reproducible model of muscle pain, which makes it possible to evaluate promising antinociceptive and anti-inflammatory therapies

05.006 **Antinociceptive Potential of Isopulegol in a Model of Subacute Oncological Pain**. Dias WA[1], Pimentel VD[1], Sales SCS[1], Acha BT[1], Ferreira PMP[2], Almeida FRC[1] [1]UFPI, Lab of Pain Pharmacology, Medicinal Plants Research Center, Teresina, Brazil, [2]UFPI, Lab in Experimental Cancerology, Dept of Biophysics and Physiology, Teresina, Brazil

Introduction: Cancer pain is not a diagnosis and it is not a syndrome, in fact, it is pain resulting from the sum, synergism or combination of several causes. Fifty per cent of cancer patients and up to 90% of advanced cancer patients have this pain. Its treatment is through several pharmacological agents, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TADs) and others. In this scenario, the inclusion of new pharmaceutical agents becomes increasingly necessary, such as natural substances, including Isopulegol (ISO), a secondary metabolite of essential oils, which has important biological activities such as anti-inflammatory, antinociceptive and others. Given the facts, the objective of this study was to investigate a possible antinociceptive effect of ISO in an animal model of subacute cancer pain, in addition to in silico evaluations of possible pharmacological targets. **Methods:** Female Swiss mice weighing between 25 and 35 g were used and the experiments were previously approved by the Ethics Committee on the Use of Animals (CEUA / UFPI nº 146/16). For induction of hypernociception, 2. 5 million sarcoma cells were inoculated into the right paw of mice, and mechanical allodynia was assessed with von Frey filaments, in subacute treatment of 30 days?? evaluation. Furthermore, the animals were divided into 6 groups: sham (normal animals), vehicle (0. 9% NaCl with 2% Tween 80), positive antinociceptive control (pregabalin 10 mg/kg po), and 3 doses of ISO (12. 5, 25 and 50 mg/kg po). The in silico evaluation was performed using the ACD/ChemSketch software version 14. 0 and the PreADMET online server for the test. **Results:** The reduction in subacute hypernociception was evidenced by comparing the means of the groups in the Von Frey test from the first day of evaluation, where the evaluation took place for 30 days. First day: (sham =8. 00 ± 0. 32; ISO 12. 5mg = 3. 00 ± 0. 38; ISO 25mg = 4. 00 ± 0. 43; ISO 50mg = 6. 00 ± 0. 42; pregabalin 10mg = 5. 00 ± 0. 37 and vehicle = 0. 67 ± 0. 45) (* $p < 0.05$). Last day of evaluation (sham = 9. 00 ± 0. 37; ISO 12. 5mg = 3. 00 ± 0. 42; ISO 25mg = 4. 00 ± 0. 44; ISO 50mg = 6. 00 ± 0. 45; pregabalin 10mg = 4. 00 ± 0. 38 and vehicle = 067 ± 0. 32) (* $p < 0.05$). ISO improved locomotion of animals in the open field when compared to negative and positive controls. Regarding the in silico tests, the ISO was performed on the opioid receptors, since morphine was one of the positive controls, and it presented the same result in the kappa receptor, in addition to a significant result in the Mu and Delta receptors. ISO was also coupled to pregabalin receptors, another positive control, and showed more affinity for these receptors than pregabalin. ISO also showed greater affinity for GABA receptors than pregabalin. **Conclusion:** ISO has a potential antinociceptive effect in cancer pain model, supposedly by opioid action and by mechanisms similar to pregabalin, mainly by inhibiting glutamate. Keywords: Isopulegol, natural substances, 180 sarcoma.

05.007 **Effects of 4'-metoxichalcone in chemotherapy-induced neuropathic pain**. Melo EDN[1], Botinhão MC[1], Marchon ISS[1], Cavararo AR[1], Ramos IFO[1], Rocha Reis JV[1], Souza ROMA[2], Leal ICR[2], Raimundo JM[1], Bonavita AGC[1],

Mendonça HR[1], Muzitano MF[1], Carmo PL[1] [1]UFRJ-Macaé, Bioactive Products Laboratory, Macaé, Brazil, [2]UFRJ, Rio de Janeiro, Brazil

Introduction: Neuropathic pain (NP) affects approximately 3-17% of the general population and the main pharmacological classes still be ineffective for their treatment [1]. In this context, natural or synthetic chalcones become good study targets, since of their ability to inhibit pro-inflammatory pathways, in addition to antinociceptive and anti-inflammatory activities in NP models [2]. In previous studies carried out by our research group, the anti-inflammatory activity *in vitro* [3] and the anti-inflammatory and antinociceptive activity in vivo of the 4'-methoxyhalcone (LC24) was confirmed. Therefore, the objective of this work was to evaluate the effects of LC24 in a vincristine-induced neuropathic pain (VINP) model. **Methods:** Male Swiss mice (25-30 g, n= 8-10) received intraperitoneally (I. P.) vincristine sulfate (0.1 mg/kg) once a daily for 14 consecutive days. After NP induction, the animals received the treatment via I. P. with LC24 (60 mg/kg) or pregabalin (10 mg/kg) for 14 consecutive days. Assessments of mechanical allodynia by the Von Frey test and thermal hyperalgesia by the hot plate test were performed before induction of NP, on the 14th day after VCR and during an assessment of the acute (1, 3, 5 and 24 h after the first administration of chalcone or pregabalin) and subchronic effects (3rd, 7th and 14th days of treatment). **Results:** 1) Von Frey test: After the 14th day of I. P administration of VCR, the animals showed nocifensive behavior confirming mechanical allodynia, after stimulation with 0. 2 gf and 2. 0 gf filaments, increasing the percentage of removal of paw from 2. 5 ± 1. 6% to 51. 2 ± 7. 7% ($P<0.05$), and from 32. 5 ± 4. 1 to 87. 5 ± 3. 7% ($P<0.05$), respectively. In the acute evaluation, through the stimulus performed with the 0. 2 gf filament, LC24 reduced the paw withdrawal from 51. 2 ± 7. 7 to 21. 2 ± 2. 9 % ($P<0.05$) at 24h after its first administration. When the stimulus was caused with the 2. 0 gf filament, the paw withdrawal reduced from all times tested (1, 3, 5 and 24 h), from 87. 5 ± 3. 7% to 72. 5 ± 3. 1; 62. 5 ± 3. 7; 70. 0 ± 3. 8; and 57. 5 ± 5. 3% ($P<0.05$), respectively. In the subchronic evaluation, LC24 reduced the percentage of paw withdrawal with the filament by 0. 2 gf on all days tested (3rd, 7th and 14th days), from 51. 3 ± 7. 7% to 16. 2 ± 5. 0; 6. 2 ± 4. 2 and 5. 0 ± 2. 7% ($P<0.05$), respectively; the same being observed when the stimulus was performed with the 2. 0 gf filament, reducing from 87. 5 ± 3. 7% to 40. 0 ± 6. 0; 18. 7 ± 4. 8 and 10. 0 ± 3. 3% ($P<0.05$), respectively. 2) Hot plate test: After the 14th day of I. P administration of VCR, all animals showed a significant reduction in the permanence time on the hot plate, from 9. 5 ± 0. 8 s to 3. 7 ± 0. 4 s ($P<0.05$), indicating the presence of thermal hyperalgesia. However, in the acute (up to 24 h) and subchronic (3rd, 7th and 14th days) evaluations, LC24 at dose of 60 mg/kg was not able to increase the animals' permanence time on the hot plate. **Conclusion:** The chalcone LC24 reverse the allodynia mechanical of VINP, and has pharmacological potential for its treatment. **Financial Support:** CAPES. Approval of the CEUA protocol MAC044. **References:** [1] MITSIKOSTAS, D. -D. et al. Cureus, 14, e22419, 2022; [2] CAVALLI, E. et al. Int J Imunopathol Pharmacol, 33, 205873841983838, 2019; [3] VENTURA, T. L. B. V. et al. Molecules, 20, 8072, 2015.

05.008 **Role of the Cytoplasmic DNA Sensor, STING, on the Development of Neuropathic Pain Induced by Cisplatin**. Andrade FB[1], Lee SH[2], Cunha FQ[1], Alves Filho JC[1], Berta T[2], Cunha TM[1] [1]FMRP-USP, Center for Research in Inflammatory Diseases, Dept of Pharmacology, Ribeirão Preto, Brazil, [2]University of Cincinnati Medical Center, Pain Research Center, Dept of Anesthesiology, Cincinnati, EUA

Introduction: Cisplatin-induced neuropathic pain (CINP) is a common and serious side effect experienced by cancer patients receiving this drug. This condition can impact quality of life and persist even after the treatment is over. Current therapies for CINP are ineffective. In this context, the search for molecular targets amenable to pharmacological intervention is necessary. Emerging evidences demonstrate involvement of mitochondrial dysfunction in CINP development. We therefore hypothesized that cisplatin-induced mitochondrial damage causes escape of mitochondrial DNA into the cytosol of nociceptors, which then triggers activation of the stimulator of interferon genes (STING). Finally, these mechanisms might be involved in the development of CINP. **Methods:** For CINP model, mice received three intraperitoneal (i. p.) injections of cisplatin on consecutive days (2 mg/kg/day, total cumulative dose of 6 mg/kg). To evaluate mechanical hypersensitivity, the Von Frey filament test (VFFT) was performed to determine paw withdrawal threshold and frequency of responses to application of 0. 02 g and 0.16 g filaments. The expression of STING and cytokines in dorsal root ganglia (DRG), sciatic nerve and spinal cord were evaluated by qPCR, using the cycle/threshold comparative method. Flow cytometry analysis of the DRG and sciatic nerve was performed using a FACS Verse instrument. This project was approved

by the Ethics in Animal Research Committee of the Ribeirao Preto Medical School (Process number 1027/2021). **Results:** To investigate if STING plays a role in CINP, C57/BL6 wild-type (WT) and STING GT/GT (STING knockout) mice were treated with cisplatin and submitted to VFFT. Remarkably, mechanical hypersensitivity was attenuated in mice lacking STING, starting on day 3 and lasting up to day 10 from cisplatin treatment. Pharmacological treatment of WT mice with a STING antagonist (C176 100 µg/100 µl, i. p.) attenuated mechanical hypersensitivity, starting on day 3 and lasting up to day 7. Intraplantar injection of a STING agonist (CAY10748 20 µg/20 µl,) induced mechanical hypersensitivity in WT mice after 60 minutes. To evaluate STING expression in portions of the somatosensory system, we collected DRG, sciatic nerve and spinal cord samples from cisplatin-treated WT mice and submitted them to qPCR analysis. Our data revealed increased expression of STING in sciatic nerve 4 and 8 days from cisplatin treatment, and of cytokines IL-6, TNF-alpha, and IFN-beta 4 days after cisplatin. IL-6 expression was also increased in DRG at the same time point. To verify the relevance of these cytokines for CINP development, we induced CINP in IFNAR-KO and IL-6-KO mice and submitted them to VFFT. Our data revealed that neuropathic pain development was dependent on IL-6 synthesis, starting on day 3 and lasting up to day 10. Flow cytometry analysis ruled out leukocyte infiltration into DRG and sciatic nerve 4 days from cisplatin treatment. Our previous data showed STING expression on primary sensory neurons (nociceptors). We then generated conditional knockout mice lacking STING in Nav1. 8+ nociceptors (cKO). When injected with cisplatin and submitted to VFFT, cKO mice displayed attenuated mechanical hypersensitivity starting at day 1 and lasting up to day 10. **Conclusion:** Our findings reveal a crucial role of STING expressed in nociceptors for the development of CINP, and suggest that inhibition of STING signaling might constitute an interesting approach to prevent CINP development.

05.009 **Occlusal Trauma Promotes Orofacial Pain and Masticatory Muscle Damage by Inducing Caspase-1 Activation and Reducing Anti-Oxidative Enzymes**. Oliveira JP[1], Santos LGK[1], Teixeira SA[1], Contin I[2], Oliveira MA[1], Muscará MN[1], Costa SKP[1] [1]ICB-USP Dept of Pharmacology, São Paulo, Brazil; [2]FO-USP, Dept of Prosthesis, São Paulo, Brazil

Introduction: Orofacial pain is usually associated with inflammatory conditions of orofacial tissues caused by many factors, such as trauma occlusal (Alamir et al, 2019). We previously showed a standardization of rodent occlusion model (Oliveira et al., SBFTe 2021) and the potential protective role of H2S, an endogenous transmitter involved in inflammation and pain protection (Costa et al., 2020). This study aimed to determine whether occlusal trauma in our model contributes to the masticatory muscle damage and orofacial pain by inducing caspase-1 activation, oxidative stress or changes in the endogenous production of H2S and its related-producing enzymes cystathionine β-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST) expression. **Methods:** Universal crowns of 1mm thickness were made in correspondent right lower molar teeth (1º to 3º molars) by using photopolymerizable micro-hybrid composite resin. Under anesthesia, male Wistar rats (60 days) received resin crown in molar teeth, after preparation of dentary units with acid etching with 37% phosphoric acid and photoactivated dentin adhesive. Crowns were installed in molars with aid of flow resin and photoactivated bonding, remaining on the occlusal surface for 1, 3 or 7 days. Sham rats were kept with oral cavity open for 5 minutes. Orofacial mechanical hyperalgesia was performed by electronic Von Frey. Following euthanasia, mandibles were removed for dental radiography, masseter muscle and trigeminal ganglia were collected for H2S endogenous production via lead acetate assay and stress oxidative markers 3-nitrotyrosine (3-NT) and 4-hydroxinonenal (4-HNE) by SLOT blot assay, respectively. Expression of GFAP, a marker of glia cells, and H2S-producing enzymes CBS and 3-MST was carried out via Western blotting. Caspase-1 and SOD-1 expression were assessed in glioma C6 (astrocytes), neuro-2a (neuron) and BV-2 (microglia) lineages stimulated with LPS (0. 4 to 1 µM) and ATP (2. 5 to 5 mM) for 6 h (5% CO2, 37°C) by W. blotting. Mean ± SEM (n= 6 rats or 3 independents cell culture). Significance level ($p<0.05$). **Results:** Significant inflammatory process in the gum and masseter muscle was revealed after 24 h induction of occlusal trauma ($p<0.05$ vs sham on 1, 3 and 7 th). Inflammation was progressively intensified until the 7th day evaluated, which was paralleled by orofacial hyperalgesia, bone reabsorption and reduction of periodontal support in teeth submitted to bonding crowns ($p<0.05$ vs sham). On day 7th, reduced expression of 4-HNE ($p<0.05$ vs sham), and unchanged 3-NT expression were observed in comparison with control rats. Increased expression of GFAP was observed in trigeminal ganglia ($p<0.05$ vs sham), in addition to increased expression of CBS, but not 3-MST, on day 7th. No changes in H2S

production were observed in the masseter muscle. In all cell lineages, the LPS and ATP stimulation led to increased caspase-1 expression and promoted a reduced SOD-1 expression ($p<0.05$ vs vehicle). **Conclusion:** Occlusal trauma led to a marked inflammatory process in the masticatory muscle that is associated with orofacial hyperalgesia, bone reabsorption and reduced tooth periodontal support, and these are correlated with reduced antioxidant activity and upregulation of CBS, GFAP and caspase-1 expression without changes in local H2S production. **References:** Alamir et al. (2019) 20(10): 1138-1140 Costa et al. (2020) 33(14):1003-1009 License number of ethics committee: CEUA-ICB/USP, Protocol nº 2055050819. **Financial Support:** CAPES and CNPq (n° 142342/2020-3).

05.010 **Participation of CB2 Receptors in the Antinociceptive Effect of β-Caryophyllene in Oxaliplatin-Induced Neuropathy in Tumor-Bearing Mice Model**. Agnes JP[1], Delgobo M[1], Lima KA[1], Schran RG[2], Ferreira MA[2], Ferreira J[2], Zanotto-Filho A[1] [1]UFSC, PPG em Farmacologia, Lab de Farmacologia e Bioquímica do Câncer, , Depto de Farmacologia, Florianópolis, Brasil, [2]UFSC, PPG em Farmacologia, Lab de Farmacologia Experimental, Depto de Farmacologia, Florianópolis, Brasil

Introduction: One of the challenges in cancer patient management is the treatment of pain. Some chemotherapeutics such as platinum derivatives induce marked neuropathy. The symptoms of chemotherapy-induced neuropathy (CIN) can significantly affect the patient's quality of life of the patient in chemotherapy, hence demanding changes in the chemotherapy protocol to minimize. However, this alteration of protocol may favor the emergence of chemoresistant tumor cells, reducing the chance of success of antitumor therapy. CIN is pharmaco-resistant, such that few drugs have a satisfactory analgesic effect that significantly reduces the symptoms experienced during neuropathy. It is known that neuroinflammation is a crucial factor for the development of chemotherapy-induced nociceptive changes, and anti-inflammatory strategies that can be used in the long term can reduce chemotherapy-induced nociceptive changes. In this sense, the use of agonists of CB2 receptors (RCB2) can perform this role, since RCB2 are expressed in active inflammatory cells, where their activation reduces the release of inflammatory mediators and consequently neuroinflammation. Thus, we hypothesized that the use of RCB2 agonists may reduce neuroinflammation and consequently the symptoms of CIN. In this work, we evaluated the effects of the CB2R agonist β-caryophyllene (BCP) on nociceptive behavior in a model of oxaliplatin-induced neuropathy and on the kinetics of tumor growth in a model of mammary adenocarcinoma and melanoma. **Methods:** Female Swiss mice were used in the nociception experiments; experimental protocols were approved by CEUA-UFSC (1670201021). For neuropathy induction, 5 mg/kg oxaliplatin (OXA) was injected i. p. every 48 hours for 14 days. BCP was administered by gavage at different doses (10 to 100 mg/kg/day) concomitantly with OXA treatment or in protocol after the establishment of the CIN of phenotype. To assess the participation of CB2R in the antinociceptive responses to BCP, the CB2 antagonist SR144528 (1mg/kg) was administered concomitantly with BCP. Mechanical nociception was assessed using the Von Frey filament test and the cold plate test to assess thermal nociception. To assess the effects of BCP on tumor growth, we implanted Ehrlich adenocarcinoma cells in the paramammary tissue; for the melanoma model, B16F10 cells were implanted in the lumbar region of C57Bl/6 mice. **Results:** We observed that treatment with BCP was efficient in attenuating nociceptive responses to mechanical and thermal/cold stimuli in mice treated with OXA. When evaluating the effect of BCP in mice with established neuropathy, we observed that BCP was effective in attenuating mechanical and cold nociception. The CB2R antagonist was able to inhibit the BCP effect in mechanical but not cold thermal nociception. Regarding tumor volume, in the adenocarcinoma model, we did not observe differences between the groups treated with BCP and OXA when compared to animals treated only with OXA, and in the melanoma model, BCP significantly reduced the volume of tumors. **Conclusions:** So far, we can infer that BCP is effective in reducing hypernociceptive behaviors in mice treated with OXA in both concomitants and established CIN protocols. The CB2R antagonist reversed the mechanical hyperalgesia induced by OXA. Regarding tumor development, BCP does not alter the antitumor efficacy of OXA in the model used here and has a potential antitumor effect against melanoma. We thank the funding agencies CNPq and CAPES for supporting this work; and the LAMEB-UFSC for technical support.

05.011 **Effect of *Plasmodium berghei* Infection and Chloroquine Treatment on Ehrlich Tumor-Induced Inflammatory and Nociceptive Response in Mice**. Aguiar MFR[1,2], Dias QM[1], Guterres MM[1], Passos TG[1], Noleto TG[1], Benarrosh EM[1], Verri Junior WA[3], , [1]Fiocruz-RO, Lab de Neuro e Imunofarmacologia, [2]UNIR, [3]UEL

Introduction: Malaria and Cancer are highly prevalent diseases, being significant causes of death, thus configuring an immense public health challenge in Brazil. Evidence shows that malaria can influence the development and survival of different types of tumors. Furthermore, despite the known antitumor activity of antimalarial drugs *in vitro* experiments, little is known about the effect of these drugs when administered in vivo, especially in association with *Plasmodium berghei* infection in experimental malaria. Thus, the present study aimed to evaluate the effect of experimental malaria and chloroquine treatment on the nociceptive response triggered by Ehrlich tumor cells after its intraplantar administration in mice. **Methods:** Male BALB/c mice previously infected with *Plasmodium berghei* 10^7 red cells parasitized intraperitoneal injecting and injected with Ehrlich tumor $1x10^6$ cells in the right paw. Subsequently, the animals were treated with chloroquine according to the regimens recommended by the World Health Organization daily orally for 3 days: 8. 6 mg/Kg or 260 µg/mL/30g (1st day), 6. 45 mg/Kg or 190 µg/mL/30g(2nd and 3rd day). Parasitemia was measured before and after treatment (7th and 10th experimental day). At the end of the treatments, the animals were submitted to experimental tests to evaluate the evolution of edema, nociceptive threshold against mechanical and thermal stimuli (von Frey test and hot plate test), and serological quantification of inflammatory cytokines (IL-1 beta and TNF-alpha). **Results:** The results show that the blood parasitemia of animals infected by *Plasmodium* and not treated with chloroquine is significantly increased, both on the 7th and 10th day post-infection. In animals treated with chloroquine, blood parasitemia on the 10th day post-infection was reversed and reduced mechanical nociceptive responses, proving the effectiveness of treatment. The tumor did not interfere with the development of *Plasmodium* infection or the ability of chloroquine to reduce infection. Chloroquine treatment in uninfected animals increased the mechanical, but not thermal, nociceptive response. The Ehrlich tumor cells triggered paw edema and provoked pain in response to both mechanical and thermal stimuli. Animals with Ehrlich tumor, infected by *Plasmodium*, not treated with chloroquine, there was no significant change in the mechanical and thermal nociceptive response. In animals with tumor, infected by *Plasmodium* and treated with chloroquine, a significant reduction in mechanical nociceptive responses was observed. The results show that the growth of the paw tumor did not cause a significant increase in the plasma levels of IL-beta and TNF-alpha. In animals only treated with chloroquine, increase in serum chloroquine levels of IL-1-beta, but not TNF-alpha, was observed. The presence of Ehrlich tumor increased serum levels of IL-1beta in chloroquine-only or infected-only animals. In animals infected and then treated with chloroquine, serum levels of IL-1beta and TNF-alpha were significantly higher in the presence of Ehrlich tumor **Conclusion:** Understanding the inflammatory and nociceptive response in the interaction between tumors, infection and antimalarial treatment is complex and requires further studies for a better understanding. **Financial Support:** Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação Rondônia de Amparo ao Desenvolvimento das Ações Científicas e Tecnológicas e à Pesquisa do Estado de Rondônia (FAPERO). Approval by animal research ethical committees: licence number 2017/02.

05.012 **CGRP, Interleukin 6 and Tumor Necrosis Factor Induced by Stress in Mice Causes Migraine-Like Behaviors with Sexual Dimorphism**. Viero F[1], Rodrigues P[1], Frare JM[1], Silva NA[1], Nassini R[2], Geppetti P[2], Pereira GC[1], Bocchi G[1], Santos GT[1] [1]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2]University of Florence, Dept of Health Science, Clinical Pharmacology and Oncology, Florence, Italy

Introduction: Migraine represents one of the major causes of disability worldwide and is more prevalent in women. Stress is a frequently reported trigger in migraine patients, such as sound stress, but the underlying mechanisms are not fully understood. Thus, the aim of the study was to characterize the model of migraine-like behavior after the induction of unpredictable sound stress in male and female mice and evaluated the effect of a calcitonin gene-related peptide (CGRP) antagonist, as well as detected the plasmatic levels of pro-inflammatory cytokines and CGRP. **Methods:** Male and female adult C57BL/6 mice (20–30 g) were used. The protocols employed in our study were approved by Committee for Animal Care of the Federal University of Santa Maria (UFSM; #9818180820). The mice were exposed to unpredictable sound stress for 3 days along 30 minutes. Non-stressed animals were placed in the sound chamber but without exposure to the sound stimulus. The treatment

group was composed of BIBN4096BS (olcegepant) (i. p., 100 mg/kg) or its vehicle. Grimace scale, periorbital, hind paw thresholds to von Frey filaments and open field were recorded. After, post-stress induction the behavioral experiments were evaluated on days 1, 3, 7, 10, and 14 days. Subsequently, on the nociceptive peak after stress induction (7 days) the treatment protocol with CGRP antagonist or the different plasma analyses, such as corticosterone, CGRP assay ad cytokines levels were performed. Statistical analyses were performed using Graph Pad Prism 9. 0 software. **Results** In the first, was determined the development of nociception post stress in the 1, 3, 7, 10, and 14 days and addressed whether there would be a sexually dimorphic effect. We observed in this stress model, that on day 1 after stress induction there was an enhancement in the plasma corticosterone level, but not after 7 days of stress exposure (data not shown), as described before for this model using rats. Male and female mice showed hind paw mechanical allodynia in the 3-, 7-, and 10-days post stress induction. Mice returned to baseline withdrawal thresholds in 14 days post stress induction. Mainly, after 7 days of the last stress session mice developed hind paw, periorbital mechanical allodynia, grimacing pain behavior. These nociceptive and behavioral alterations detected in this model were shown mostly in female stressed mice. To hind paw behavior, stress females demonstrated 17% mostly allodynia than males. Similarly,in periorbital mechanical allodynia (21%), grimacing pain behavior (82%). In addition, we demonstrated an increase in levels of IL-6 and TNF-α and CGRP levels in stressed mice plasma, with female with higher levels when compared to male mice. Nevertheless, there was no difference in the plasmatic levels of IFN-γ, IL-2, IL-4, IL-10 and IL-17 between groups. Besides, 7th-day post-stress nociception, these behaviors were consistently abolished by CGRP receptor antagonist olcegepant (BIBN4096BS, 100mg/kg by intraperitoneal route) until 3 h after treatment in stressed mice. **Conclusion:** Our data showed that unpredictable sound stress model in mice causes periorbital/hind paw mechanical allodynia, and grimacing pain behavior with sexual dimorphism, similar to occurs in the clinic. Therefore, these data support the use of this stress priming model to the study of the mechanisms by which stress contributes to migraine-related pain. Fellowships from the Conselho Nacional de Desenvolvimento Cientíifico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

05.013 **Advanced Oxidation Protein Products (AOPPs) Role on Nociceptive Behavior in a Mice Model of Progressive Experimental Autoimmune Encephalomyelitis (P-EAE)**. Rodrigues P[1], Vieiro FT[1], Peres DS[1], Frare JM[1], Stein CS[2], Brum ES[3], Moresco RN[2], Oliveira SM[3], Bochi G, Santos GT[1,3] [1]UFSM, PPG Pharmacology, Santa Maria, Brazil, [2]UFSM, PPG in Pharmaceutical Sciences, Santa Maria, Brazil, [3]Graduated Program in Biological Sciences, Toxicological Biochemistry, Santa Maria, Brazil

Introduction: Progressive multiple sclerosis (PMS) is a chronic autoimmune demyelinating neurological disease associated with the development of pain. Reactive oxygen species are involved in PMS development (MILLER, Clin Biochem, 45, 26, 2012). Thus, there is a need to identify a biological marker related to PMS neurodegeneration. In this context, the oxidative stress marker advanced oxidative protein products (AOPPs) stand out since it is increased in MS patients with increased disability (RODRIGUES, Mol. Neurobiol, 58, 5724, 2021). Thus, the present study aims to evaluate the AOPPs role in nociceptive behaviour in a model of progressive experimental autoimmune encephalomyelitis (P-EAE). **Methods:** Adult C57BL/6 female mice (CEUA nº: 9746010620) were induced with the P-EAE model using MOG35–55 and CFA (200 µg, 5 mg/ml, s. c.) administered to both flanks (100 µl). The animals also received two doses of pertussis toxin (300 ng, i. p.), one at the time of induction and another at 48 h. Control animals received only the CFA dose and two toxin applications (RITTER, Mol Neurobiol, 2020). The animals were evaluated for the clinical score, weight and strength of plantar pressure, rotarod test, and mechanical and cold allodynia before induction (baseline) and on days 7, 10, and 14. Also, on the 13 days post-induction, the animals' nest building was evaluated. On the 14-day post-induction, the animals were euthanized and the samples of prefrontal cortex and spinal cord were removed to measure the levels of AOPPs and the activity of NADPH oxidase (Nox) and myeloperoxidase (MPO) enzymes. Parametric data were analyzed by t test, two-way-ANOVA, posthoc or Bonferroni, and the non-parametric data were analyzed by Mann-Whitney or Kruskal-Wallis test. **Results:** The clinical score increased 14 days (mean 0. 9) post-induction in the P-EAE animals compared to control (mean 0. 0, Kruskal-Wallis test), without changes in weight and mobility. The paw strength decreases 10 days (mean 71. 7) post-induction in the P-EAE animals compared to control (mean 90. 5, two-way-ANOVA). Similarly, the mechanical allodynia threshold reduced from 7 (mean 1. 0) to 14 days (mean 0. 2, two-way-ANOVA) in the P-EAE animals compared to control (mean 1. 5),

indicating a nociceptive peak. Also, cold allodynia increased 10 days (mean 5. 7) post-induction in the P-EAE animals compared to control (mean 3. 6, Kruskal-Wallis test). In the nest building score in the P-EAE animals were reduced (mean 3. 2) compared to control (mean 4. 5, Mann-Whitney test), indicative of spontaneous nociception. Representative images show the impaired nest-building of P-EAE and the typical nest-building behavior in the control group. Finally, the AOPPs levels and the NADPH oxidase and MPO activity were increased in P-EAE mice in the spinal cord (AOPP mean 1. 9; MPO mean 0. 6; NADPH mean 0. 004) and prefrontal cortex (AOPP mean 5. 6; MPO mean 2. 5; NADPH mean 0. 001) compared to control (AOPP mean 1. 2 and 2. 5; MPO mean 0. 2 and 1. 6; NADPH mean 0. 0006 and 0. 0003, t test). **Conclusion:** Thus, at the nociceptive peak there was an increase in AOPPs levels in central nervous system structures of the EAE-P model. Therefore, this biomarker could be involved in the neuropathic-like pain behavior development of P-EAE. Hence, compounds that modulated AOPPs formation pathway could represent a therapeutic complement for MS patients. **Financial Support:** FAPERGS, CNPq, and Capes.

05.014 **Resolvin D1 Disrupts CGRP-Dependent Neuroimmune Communication unveiling a Hitherto Unknown Gouty Arthritis Mechanism and Therapeutic Target**. Zaninelli TH[1], Fattori V[2], Saraiva-Santos T[1], Badaro-Garcia S[1], Staurengo-Ferrari L[1], Artero NA[1], Ferraz CR[1], Bertozzi MM[1], Rasquel-Oliveira F[1], Amaral FA[3], Teixeira MM[3], Borghi SM[1], Rogers MS[2], Casagrande R[1], Verri Jr WA[1] [1]UEL, Lab of Pain, Inflammation, Neuropathy, and Cancer, Dept of Pathology, Centre of Biological Sciences, Londrina, Brazil, [2]Boston Children's Hospital, Harvard Medical School, Vascular Biology Program, Dept of Surgery, Boston, USA, [3]UFMG, Dept of Biochemistry and Immunology, Biological Sciences Institute, Federal University of Minas Gerais, Belo Horizonte, Brazil

Introduction: Gouty arthritis is an intermittent disease characterized by an intense inflammatory response to monosodium urate crystals (MSU), which induces joint damage, and movement limitation, and increases the probability of recurrent acute flares. The intense and debilitating pain during gout episodes is the main reason for patients to seek medical care. Current gout arthritis therapies produce non-satisfactory analgesic effects. Therefore, novel analgesic drugs are still needed for gout treatment. Resolvin D1 (RvD1) is a specialized pro-resolving mediator derived from the omega-3 metabolite, docosahexaenoic acid (DHA). RvD1 is an endogenous molecule that was demonstrated to have anti-inflammatory and analgesic properties in inflammatory and neuropathic contexts. We evaluated the effects and mechanisms of action of RvD1 in an experimental mouse model of gouty arthritis. This aim was not pursued in the literature yet. **Methods:** Male swiss and LysM-eGFP C57BL/6 mice were used in this study. All experimental procedures were approved by the State University of Londrina ethics committee (CEUA-UEL, process number 22186. 2016. 37). Mice were treated with RvD1 (intrathecally or intraperitoneally) before or after intra-articular stimulation with MSU crystals. Mechanical hyperalgesia was assessed using an electronic von Frey aesthesiometer and weight distribution in the rear limbs using the static weight-bearing apparatus. Leukocyte recruitment was determined by knee joint wash cell counting and immunofluorescence. IL-1β production was measured by ELISA in vivo and in vitro. Phosphorylated NF-kB and apoptosis-associated speck-like protein containing CARD (ASC), and CGRP were detected by immunofluorescence. The mRNA expression was determined by RT-qPCR. CGRP release was determined by EIA and immunofluorescence. Bone marrow-derived macrophages (BMDM) MSU crystal phagocytosis was evaluated by confocal microscopy. **Results:** RvD1 treatment, by intraperitoneal (i. p.) and intrathecal (i. t.) routes, inhibited MSU-induced mechanical hyperalgesia in a dose- and time-dependent (up to 70%) manner, and restored weight distribution in the rear limbs. RvD1 treatment reduced leukocyte recruitment (i. p. 65%, i. t. 79%) and IL-1β production (i. p. 79%, i. t. 76%) in the knee joint. In vitro, RvD1 decreases macrophage activation by reducing NF-kB phosphorylation (74%), ASC expression (97%), and IL-1β maturation (40%). Intrathecal RvD1 reduced the activation of peptidergic neurons (CGRP+, 62%) and macrophages as well as silenced nociceptor to macrophage communication and macrophage function by reducing calcitonin gene-related peptide (CGRP) release (*in vitro* 82%, in vivo 99%). CGRP stimulated MSU phagocytosis (93%) and IL-1β production (82%) by macrophages. RvD1 treatment down-modulated this phenomenon (92% and 51%, respectively) directly by acting on macrophages, and indirectly by inhibiting CGRP release and CGRP-dependent activation of macrophages. **Conclusions:** We unveil that RvD1 disrupts nociceptor neuron and macrophage activation, and their CGRP-dependent neuroimmune communication. These previously unknown mechanisms of RvD1 and gout pathology offer novel treatment approaches since they differ from the current gout arthritis therapies. Funding:

PRONEX (SETI/Araucária Foundation, MCTI/CNPq, and Paraná State Government, agreement 014/2017, protocol 46. 843); (MCTI/FINEP/CT-INFRA-PROINFRA, Brazil, grant agreements 01. 12. 0294. 00 and 01. 13. 0049. 00); Grants from The J. Willard and Alice S. Marriott Foundation and Marriott Daughters Foundation; CAPES and CNPq.

05.015 **Can 6-Nitrodopamine (6-ND) be the Mediating Mechanism Involved in Pain Relief by Antidepressant Drugs**? Dallazen JL[1], Santos LG[1], Britto-Júnior J[2], Campos R[3,4], Muscará MN[1], Antunes E[2], De Nucci G[1,2], Costa SKP[1] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil [3]UFC, Drug Research and Development Center, Clinical Pharmacology Unit, Fortaleza, Brazil, [4]ISCB-UECE, Fortaleza, Brazil

Tricyclic antidepressants (TCA), mainly amitriptyline (AMT), have been widely used for chronic and neuropathic pain treatments. However, the mechanisms underlying their analgesic effects remain unclear and are mostly attributed to their central action and descending pathways. 6-Nitrodopamine (6-ND) is drawing attention as a novel endogenous mediator, and, peripherally, TCA act as selective antagonists of 6-ND receptors. Despite the efforts to describe and understand the central mechanisms of TCA-induced pain relief, the peripheral analgesia and antinociception promote by them are still poorly investigated. Thus, this study aimed to investigate the local effect promoted by intraplantar injection of 6-ND on nociceptive thresholds and behaviors, and the effect of AMT pretreatment on these parameters. The experiments were conducted using male BALB/c mice (~25 g, CEUA-ICB/USP:1804010721). The basal release of 6-ND from samples of hind paw skin and muscle, sciatic nerve, and spinal cord (L4-L5) placed in Krebs-Henseleit's solution were measured by LC-MS-MS. Mice received via intraplantar (i. pl; 20 µL) route vehicle (VEH: sterile 0. 9% saline), or 6-ND (150 fmol-150 nmol), and the nociceptive thresholds (mechanical: von Frey test; and thermal: hot plate at 52±0.1ºC), paw edema (plethysmometer), and licking behavior were evaluated prior to (basal), and at 1, 2, 3, and 24 h after injection. To assess if the effects of 6-ND on mechanical threshold and paw volume can be potentiated by inflammatory mediators (at doses insufficient to induce allodynia and edema alone), 6-ND (150 fmol) was co-administered (20 µL, i. pl.) with PGE2 (0. 01 nmol) or BK (30 nmol). To detect participation of a TCA-sensitive mechanism on 6-ND-induced mechanical allodynia and licking behavior, mice were pretreated with VEH (20 µL, i. pl.) or AMT (30, 100, and 300 nmol), 15 min before the VEH (20 µL, i. pl.) or 6-ND (150 nmol, i. pl.) administration in the same hind paw. Mechanical threshold was evaluated prior to and at 0. 25, 0. 5, 1, 2, and 3h after second injection. In parallel, the 6-ND-induced licking behavior was evaluated for 30 min after its injection. 6-ND was not detected in tissues, probably due to limitations in sensitivity of the quantification method (>0.1 ng/mL). 6-ND at 15 and 150 nmol induced mechanical allodynia from 0. 25 h to 2 h after i. pl., decreasing the mechanical threshold by 59. 0%, and 70. 7%, respectively, and evoked 111. 2±41. 9 s and 105. 8±26. 4 s of licking behavior, respectively, compared to vehicle group (VEH: 1. 7±0.1 g/h; 13. 4±2. 0 s). On the other hand, 6-ND failed to change thermal latency. At low doses, 6-ND (0. 0015, 0. 0150 and 0.15 nmol) induced short-lasting (0. 5 to 2 h) paw edema in mice, and its co-injection (150 fmol) with PGE2 (0. 01 nmol) or BK (30 pmol) potentiated edema and mechanical allodynia for up 2 to 3 h, respectively. Prior i. pl. treatment with AMT (100 and 300 nmol) significantly reduced the mechanical allodynia induced by 6-ND (150 nmol) compared to VEH treated groups (VEH+6-ND: 0. 2±0. 04 g/h; and VEH+VEH: 1. 9±0.1 g/h), by 24. 5% and 90. 4%, respectively. Likewise, local AMT pretreatment (300 nmol) abolished the 6-ND-induced licking behavior. Tricyclic antidepressant AMT inhibited 6-ND-induced mechanical allodynia and referred pain. The findings indicate that 6-ND may function as a neurotransmitter in the sensory pathway and is involved in the mechanism of peripheral analgesia promoted by AMT. FAPESP (2019/16805-4), CAPES (001), CNPq (142343/2020-0;312514/2019-0). Keywords: nitrocatecholamine, 6-nitrodopamine, nociception, amitriptyline

05.016 **Study of the Mechanisms Involved on the Analgesic Effect of *Vitex polygama* Extract in Vincristine-Induced Neuropathic Pain**. Ramos IF, Mello C, Melo EDN, Santos IS, Carmo PL, Muzitano MF, Bonavita AGC UFRJ

Neuropathic pain is a public health problem and pharmacological treatments are inefficient or with several side effects. Our previous work showed that *Vitex polygama* extract (VPE) was able to reduce both inflammatory and neuropathic pain. In the present work we studied the possible mechanism of action of VPE. Neuropathic pain was induced in Swiss mice (30-35g) by intraperitoneal injection (ip.) of vincristine (0,1 mg/kg QD) for 10 days and thermal hyperalgesia and mechanical allodynia was attested by the hot plate test and von Frey test

respectively. VPE were injected (30 mg/kg ip.) 1h before the nociception evaluation. Saline (0,9% NaCl) or morphine (10 mg/kg) were used as negative and positive controls, respectively. To evaluate the possible mechanism of action animals were treated ip. with the classical opioid receptor antagonist (Naloxone, 1 mg/kg), or the muscarinic receptor antagonist (Atropine, 2mg/kg), or the nitric oxide synthase inhibitor (L-Name, 30mg/kg) 1 hour before VPE. All experiments were approved by the UFRJ Animal Care and Use Committee under protocol #MAC051. Vincristine induced pain in animals as observed by the decrease of hind paw raise latency (5. 03 ± 0. 25 s) when compared with saline treated group (11. 95 ± 1. 11 s) on the hot plate test. When animals treated with VPE was observed an analgesic effect. For purposes of effect comparison treatment with 30 mg/kg of VPE produced a latency of 10. 6 ±1. 3 s compared with the 8. 75 ± 1. 11s of morphine, 1 hour after treatments. The pharmacological treatments significantly affected the analgesic effect of VPE showing latency times of 3. 75 ± 0. 95s for atropine, 8. 0 ± 1. 89s for naloxone and 6. 5 ± 2. 65s for L-NAME. Similar data were observed in the von Frey test. These data indicate that opioid receptors, muscarinic receptors, and nitric oxide have a paper for the effects of VPE. Thus, we concluded that VPE anti-nociception effect on vincristine-induced neuropathic pain act by a multiple mechanism of action. **Financial Support:** FAPERJ.

05.017 **Sub-Doses of Aspirin-Triggered Lipoxin A4 Attenuate Mechanical Allodynia and Dampen Anxious-Like Behavior Associated with Experimental Diabetes**. Ferreira MV[1], Jesus CHA[1], Bonfim JC[1], Liebl B[1], Oliveira G[1], Verri Júnior W[2], Zanoveli JM[1], Cunha JM[1]. [1]UFPR, Dept of Pharmacology, Biological Science Sector, Paraná, Brazil, [2]UEL, Dept of Pathology, Center of Biological Sciences, Londrina, Brazil

Introduction: Neuropathy is the most common complication of diabetes and in its painful form, can manifest itself as spontaneous pain, hyperalgesia, and/or allodynia. In addition, diabetes may still be associated with a higher prevalence of psychiatric disorders such as depression and anxiety. Pharmacological approaches to managing these complications are not satisfactory, which poses a clinical challenge. These comorbidities might share common pathophysiological mechanisms, in that neuroinflammation seems to play an important role. In this sense, aspirin-triggered lipoxin A4 (ATL), an important specialized pro-resolving mediator, has been demonstrated to inhibit inflammatory pain and mechanical allodynia in models of mechanically-induced neuropathic pain. Therefore, little is known about the effect of ATL on neuropathic pain, anxiety, or depressive-like behaviors associated with experimental diabetes, which was the aim of this study. **Methods:** Experimental diabetes was induced by a single injection of streptozotocin (STZ; 60mg/kg; i. p) in male Wistar rats (weighing 180-220g). Seven experimental groups were conducted in parallel: normoglycemic treated with vehicle (NGL-VEH), diabetic treated with VEH (DBT-VEH) and DBT treated with ATL at different doses (0. 3, 1, 3, 10, or 30 ng/rat; i. p.) starting 14 days after STZ and lasting until the 30th. Mechanical allodynia was assessed by electronic Von Frey test (VFT) and was performed one day before STZ injection (baseline), and again from the 14th to the 27th day after STZ. The open-field test (OF), the elevated plus-maze (EPM), and the modified forced swimming test (MSFT) were conducted 28, 29, or 30 days after STZ, respectively. All protocols were approved by Institutional Ethics on Animal Experimentation (CEUA-BIO-UFPR #1418). **Results:** When compared to NGL-VEH rats, DBT-VEH animals developed: 1) a significant reduction of the mechanical threshold on the VFT, starting on the 14th day after diabetes induction, peaking at the 27th day; 2) a significant reduction in the number of crossings and the time spent on the central square of the OFT (29% and 80%, respectively); 3) a significant reduction in the time and entries on open arms in the EPM test (66% and 71%, respectively); 4) a significant increase in immobility time (25%), and also a significant reduction on swimming mean counts (83%) in MFST. Treatment with ATL at doses of 1, 3, 10, or 30 ng, but not at 0. 3 ng, significantly reverses the mechanical allodynia of the DBT rats (18, 16, 12, 21%, respectively). Treatment with ATL does not change the number of total crossings in the OFT but significantly increased the number of crossings and the time spent on the central square of the OFT of the DBT rats (at doses of 1 or 10 ng, 80 and 80%, respectively). In the EPM test, ATL (at the dose of 10 ng) was able to increase entries (50%) and time (60%) on open arms. ATL was not able to reduce immobility time nor increase climbing or swimming mean counts on the MFST. **Conclusion:** Our data indicate, for the first time in the literature, the potential of ATL in attenuating mechanical allodynia and anxious-like behavior associated with experimental diabetes. Further experiments are still needed to understand the mechanisms related to the antinociceptive and anxiolytic-like effects of ATL in this experimental model. **Financial Support:** CAPES (Finance Code 001), Pronex (Contract 014/2017.; Protocol 46843. 484. 37488. 23052016).

05.018 **Effects of 4-Dimethylaminochalcone on Vincristine-Induced Neuropathic Pain in Mice**. Melo EDN, Santos IS, Rocha Reis JV, Souza ROMA[2], Leal ICR[2], Muzitano MF[1], Bonavita AGC[1], Raimundo JM[1] Carmo PL[1] [1]UFRJ-Macaé, [2]UFRJ-Rio de Janeiro

Introduction: Chalcones are substances of medicinal interest since they show a broad spectrum of biological activities. The objective of this study was to evaluate the effect of a 4-dimethylaminochalcone (LC4) on neuropathic pain (NP) induced by vincristine (VCR). **Methods:** NP was induced in male Swiss mice (25-30 g; n= 8-12 per group) by intraperitoneal administration of VCR (0.1 mg/kg; once a day) for 14 consecutive days. After that, the animals were treated for 14 days with DMSO, LC4 (10 or 30 mg/kg) or pregabalin (10 mg/kg; positive control). The hot plate test was performed to evaluate thermal hyperalgesia, where mice were individually placed on a hot plate (mod. EFF-361, Insight, Brazil) with the temperature adjusted to 52. 0 ± 0. 5 ºC. The latency to the nociceptive behavior, licking and lifting the paw, in response to the heat stimulus was recorded. The von Frey filaments test was used to evaluate mechanical allodynia. Filaments weighing 0. 2g or 2. 0g were applied 5 times vertically to the right hind paw and the percentages of paw withdrawal responses were determined. Mice were evaluated at both tests before NP induction, on the 14th day after VCR administration and during acute (1, 3, 5, and 24 h after first administration of DMSO, LC4 or pregabalin) and sub chronic (3rd, 7th and 14th days of treatment) evaluations. All protocols were approved by the Animals Ethics Committee of UFRJ/Macaé (MAC044). **Results:** VCR-induced NP was confirmed by the development of thermal hyperalgesia and mechanical allodynia. LC4, 10 mg/kg, significantly increased mice permanence time on the plate at 1, 3, 5 and 24 h from 4. 4 ± 0. 3 s (VCR) to 6. 3 ± 0. 6 s (P<0.05), 7. 4 ± 0. 6 s (P<0.05), 9. 5 ± 0. 7 s (P<0.05) and 7. 0 ± 1. 0 s (P<0.05), respectively. At 30 mg/kg, LC4 increased permanence time at 3, 5 and 24 h from 4. 3 ± 0. 3 s (VCR) to 12. 0 ± 0. 4 s (P<0.05), 11. 5 ± 0. 6 s (P<0.05) and 11. 5 ± 0. 5 s (P<0.05), respectively. During the sub chronic evaluation, thermal hyperalgesia was reversed only at the dose of 30 mg/kg. At the 3rd, 7th and 14th days, the permanence time on the hot plate was increased to 10. 8 ± 0. 5 s (P<0.05), 10. 9 ± 0. 5 s (P<0.05) and 11. 0 ± 0. 5 s (P<0.05), respectively. Percentages of paw withdrawal responses to mechanical stimulation with the filament of 0. 2 g were reduced from 100 % to 70. 0 ± 6. 5 % (P<0.05), 72. 5 ± 6. 5% (P<0.05) and 45. 0 ± 3. 3% (P<0.05) at 3, 5 and 24 h after 30 mg/kg LC4 administration. With the 2. 0 g filament, LC4 was effective only at 24 h after administration. During the sub chronic evaluation, LC4, 30 mg/kg, reversed mechanical allodynia in response to both filaments. For example, with the 2. 0 g filament, the percentages of paw withdrawal responses were reduced from 100% to 65. 0 ± 5. 0 % (P<0.05), 12. 5 ± 3. 7 % (P<0.05) and 15. 0 ± 3. 3 % (P<0.05) on the 3rd, 7th and 14th days, respectively. **Conclusion:** LC4 was able to reverse both thermal hyperalgesia and mechanical allodynia in mice with VCR-induced NP, indicating the pharmacological potential of this substance. **Financial Support:** FAPERJ.

06. Cardiovascular and Renal Pharmacology

06.001 **Perivascular Adipose Tissue Phenotype and Thoracic Aortic Stiffness in an Aging Murine Model**. Diccini I, Marques BVD, Akamine EH USP São Paulo, Dpt of Pharmacology, São Paulo, Brazil

Introduction: The increase in life expectancy resulting from greater possibilities of therapeutic and preventive treatments favored an increase in the longevity of the world population. However, aging favors the development of cardiovascular diseases, because, among the various factors, we have an increase in arterial stiffness. This event occurs mainly due to the degradation of elastin fibers, collagen accumulation and chronic inflammation of the arterial wall. Associated with this phenomenon, a phenotypic change in vascular smooth muscle cells (VSMCs) characterized by a secretory and proliferative profile is also observed. Perivascular adipose tissue (PVAT) influences the vasculature, and a change in its phenotype can have a negative impact. The aim of the present project is to evaluate the role of the PVAT phenotype in the secretory profile of VSMCs and whether a change in the PVAT phenotype is associated with increased thoracic aortic (TA) stiffness in SAMP-8 mice, a murine model of accelerated aging. **Methods:** 3-month-old (3-mo) and 8-month-old (8-mo) male SAMP-8 mice were used. PVAT dissecated from TA and PVAT-denuded TA were used for: histological analysis of PVAT, reverse transcriptase - quantitative polymerase chain reaction for analysis of TGF-beta mRNA expression in TA, western blot for the analysis of elastin, collagen 1/3 and alpha-actinin protein expression in TA, and tension curves for

the analysis of the mechanical properties of TA. The results are presented as mean ± SEM. N represents the number of animals evaluated in each group. **Results:** The area occupied by white adipocytes in relation to the total area of PVAT was similar in the animals of both ages (3-mo: 27. 3±3. 6; 8-mo: 36. 1±7. 3; n=5), but the area varied from 17% to 35% in 3-mo SAMP-8 and from 17% to 55% in 8-mo SAMP-8. The expression of alpha-actinin protein (a marker of the contractile phenotype of VSMCs) was reduced (3-mo: 100. 0±1. 9 A. U.; 8-mo: 112. 1±2. 4 A. U.; $p<0.05$; n=5), whereas the expression of TGF-beta mRNA (a mediator of arterial stiffness) was increased (3-mo: 1. 0±0.1 A. U.; 8-mo: 1. 9±0.1 A. U.; $p<0.05$; n=6) in the TA of 8-mo SAMP-8 when compared to 3-mo SAMP-8. The results obtained showed an unexpected increase in the expression of the elastin protein (3-mo: 100. 0±1. 9 A. U.; 8-mo: 112. 1±2. 4 A. U.; $p<0.05$; n=6), without a change in collagen 1/3 (3-mo: 100. 0±1. 9 A. U.; 8-mo: 91. 5±2. 1 A. U.; n=6), in the TA of 8-mo SAMP-8 when compared to 3-mo SAMP-8. At the same stretch level, TA of 8-mo SAMP-8 developed higher tension than younger animals (point before the mechanical failure was observed - 3-mo: 44. 5±5. 1 mN/mm; 8-mo: 63. 5±4. 2 mN/mm; $p<0.05$; n=3). **Conclusion:** Until the moment, our results show that VSMCs of the TA have a more secretory profile and TA is stiffener in 8-mo SAMP-8. However, data on the expression of elastin and collagen, which are the components that determine arterial stiffness, are contradictory and fragmentation of elastin should be evaluated. Moreover, the TA PVAT phenotype should be further characterized by the expression of the specific markers; likewise, a direct effect of PVAT from older mice on VSMC phenotype and elastin and collagen expression should also be evaluated. Ethical committee: CEUA 4063121120 **Financial Support:** FAPESP, CAPES (Brazil)

06.002 **Aging as an Important Contributor Factor for Decreased Semen Quality in Hypertensive Rats: A Role for Enhanced Testis Vasomotricity**. Machado NR[1], Miyazaki MA[2], Colli LG[1,] Bertolla RP[2], , Belardin LB[2], Rodrigues SFP[1] [1]ICB-USP, Dept of Pharmacology, [2]Unifesp, Dept of Surgery, Division of Urology

Aging as an Important Contributor Factor for Decreased Semen Quality in Hypertensive Rats: A Role for Enhanced Testis Vasomotricity. Nicolle R. Machado1, Mika A. Miyazaki2, Larissa B. Belardin2, Lucas G. Colli1, Ricardo P. Bertolla2, Stephen F. Rodrigues1. 1. Dept of Pharmacology, Institute of Biomedical Sciences, University of São Paulo; 2. Dept of Surgery, Division of Urology, Universidade Federal de São Paulo. **Introduction:** Hypertension is a multifactorial chronic disease that is present in about one out of four adults in Brazil, and men are often more affected than woman – at least until menopause, when prevalence is similar. Several organs are compromised by hypertension, including heart, brain, eyes, and kidneys. More recently, studies have reported the male reproductive system as a marker of men's health, since it can be impaired by different diseases, including hypertension. In fact, we demonstrated lower semen quality and enhanced vasomotricity in testis of spontaneously hypertensive rats (SHR) compared with their normotensive counterparts. Those results were demonstrated in adult rats, thus nothing is known about the influence of combined hypertension and aging on semen quality. Therefore, in this study, we aimed to verify the role of aging on semen quality and testis microcirculation in SHR. Additionally, we verified the role of both the AT1 angiotensin II receptor and the alpha1-adrenergic receptor on those parameters by using the antihypertensive drugs losartan or prazosin. **METHODS:** SHR and Wistar normotensive rats at three different ages were used: eight- to ten-week-old (youngers), twenty- to twenty-four-week-old (adults), and sixty- to sixty-six-week old (middle-aged) (CEUA protocol #8026181120). Losartan (15 mg/kg/day) or prazosin (1 mg/kg/day) was given by gavage or in the drinking water, respectively, to adult and middle-aged SHR for 15 days. Tap water with no drug was given to a group of SHR that served as control. RESULTS. Blood pressure (BP) was higher in SHR in all ages, but less in the youngers (by 140 mmHg, youngers, 180 mmHg, adults, and 170 mmHg, middle-aged). Both losartan and prazosin reduced BP to similar levels in adults and middle-aged SHR (20% reduction) ($P < 0.05$). Leukocyte adhesion and ROS generation was not different in the testicular microcirculation of SHR and Wistar rats ($P > 0.05$). On the other hand, while no change in testis vasomotricity was demonstrated in young SHR, increased vasomotricity was observed in adult SHR (by 30%), and a dramatic increase (around 300%) in middle-aged SHR compared to their Wistar counterparts. Changes in vasomotricity were not noticed in SHR previously treated with losartan but remained elevated after prasozin. Regarding semen parameters, young SHR showed only reduced sperm concentration; lower sperm motility was observed in adult SHR, and middle-aged SHR presented reduced sperm concentration, motility, altered sperm mitochondrial activity, and a higher number of sperm with damaged acrosomes compared to their age-matched controls. **CONCLUSION:** Aging is an important contributor for decreased semen

quality observed in hypertensive rats, which occurs in parallel with an AT1R-mediated enhanced vasomotricity seen in testes blood vessels. Funding support: FAPESP (#2021/07212-7; #2020/12616-0), and CAPES (finance code 001).

06.003 **Study of the Effect of FoxO1 O-GlcNAcylation on Vascular Endothelial Function**. Pedersoli C[1], Silva Neto JA[1], Duarte DA[1], Gonçalves DAP[2], Silva NLE[1], Silva JF[3], Bressan AFM[1], Kettelhut IC[1], Navegantes LC[1], Carneiro FS[1], Tostes RC[1] [1]FMRP-USP, [2]UFMG, [3]University of Arizona

Introduction: FoxO1 is an intracellular transcriptional factor related to insulin/glucose signaling. FoxO1 is regulated by the hexosamine biosynthesis pathway, where a moiety of N-acetyl-glucosamine (GlcNAc) is attached to intracellular and nuclear proteins generating a post-translational modification called O-GlcNAcylation (O-GlcNAc). This process is increased in cells from humans and experimental models of diabetes mellitus. Increased O-GlcNAc leads to changes in location, structure, traffic and function of proteins, including the FoxO1 molecule. This posttranslational modification is catalyzed by two enzymes: OGT that attaches, and OGA that removes the O-GlcNAc modification. Thiamet-G is a pharmacological tool used to artificially increase O-GlcNAc in animals and cells by OGA inhibition. In the vasculature, increased O-GlcNAc content impairs the function of proteins such as eNOS, impairing endothelial function. Likewise, the overactivation of the transcription factor FoxO1 contributes to oxidative stress and reduces nitric oxide (NO) bioavailability in the endothelial cell, processes that lead to blood vessel damage. Hypothesis: We investigated whether the O-GlcNAc modification of FoxO1 changes its activity leading to endothelial dysfunction. **Methods:** A human endothelial cell line (HUVEC) was used to evaluate the levels of O-GlcNAcylation after treatment with Thiamet-G. O-GlcNAc-modified proteins and the production of oxidants were determined by immunoblot; calcium transients induced by a calcium ionophore were determined using the cell permeant FLUO-4 probe, and intracellular NO production using DAF-2-FM in flow cytometry assays. Experiments were performed in the presence of vehicle or AS1842856, a FoxO1 inhibitor. HEK293T cells were transfected with Foxo1-Rluc, a FoxO1 construct that allows the detection of FoxO1 translocation; and the content of O-GlcNAcylated-FoxO1 was determined by immunoprecipitation. Concentration-response curves for acetylcholine (ACh) were performed in aortic rings of db/db mice, which are spontaneously diabetic and their respective controls (db/+). The efficacy (Emax) and potency (pEC50) of this vasorelaxant agonist were determined. **Results:** Thiamet-G increased the content of O-GlcNAcylated proteins in both cell lines, increasing the migratory activity of FoxO1 to the nucleus. The generation of oxidant species was increased in cells with high O-GlcNAc content and the calcium ionophore-induced calcium signal was lower in thiamet-G-treated cells. Isolated aortic rings of the db/+ mice showed a relaxation of 71. 87±5% of the initial tone, while the aortas of the db/db relaxed 66. 9±8% (p=0. 6; n=4) in response to ACh. ACh potency (pD2) was decreased in the db/db group [6. 3 ± 0. 2 in the db/+ group vs. 5. 3±0. 6 in the db/db group ($p<0.05$; n=4)], i. e. isolated aortic rings of db/db mice, which are spontaneously diabetic and have a higher content of O-GlcNAcylated proteins, showed reduced reactivity to ACh when compared to control aortas. **Conclusion:** High levels of O-GlcNAc-modified proteins increase FoxO1 activity in HUVEC and HEK293T. O-GlcNAcylation of FoxO1 leads to increased production of oxidants and decreased calcium signaling. These phenomena, considered deleterious for endothelial cells, allow us to infer that overactivation of FoxO1 is present in conditions linked to high O-GlcNAc protein levels, such as in arteries from diabetic animals, and may represent a mechanism for vascular injury in this disease. **Financial Support:** FAPESP (2021/04378-4). Animal research ethical committees: CEUA FMRP-USP 072/2020

06.004 **Antioxidant Effect of Quercetin Reduces Oxidative Stress and the Activity of Matrix Metalloproteinase (MMP)-2 in the Heart of Renovascular Hypertensive Rats**. Rocha EV, Falchetti F, Pernomian L, Blascke de Mello MMB, Parente JM, Nogueira RC, Sanches-Lopes JM, Tanus-Santos JE, Castro MM FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

Arterial hypertension is a chronic inflammatory disease and an important risk factor for the development of heart failure. Matrix metalloproteinase (MMP)-2 is a protease that acts on tissue remodeling at both extra and intracellular levels and its activation can be regulated by inflammatory factors and oxidative stress. Increased oxidative stress and MMP-2 activity were associated with cardiac hypertrophy in rats with renovascular hypertension. Quercetin is an important natural antioxidant that ameliorates hypertrophic vascular remodeling of hypertension, and also cardiac dysfunction in several models of cardiovascular diseases. We hypothesized

that quercetin decreases oxidative stress, inflammation and the activity of MMP-2 in the heart of hypertensive rats, which may improve cardiac remodeling and function. Method: Male Sprague-Dawley rats were submitted to renovascular hypertension by two kidney-one clip (2K-1C) model and treated with quercetin (10 mg/kg/day) by gavage for eight weeks. Control rats were submitted to sham surgery (CEUA-USP 090/2020). Systolic blood pressure (SBP) was weekly measured by tail-cuff plethysmography. Cardiac function was evaluated by Langendorff and hearts were processed for in situ zymography, DHE and lucigenin analyses, morphological analysis by hematoxylin and eosin and Elisa for tumor necrose factor (TNF)-α. Statistical analysis was done by two-way ANOVA followed by Tukey post-test with $p<0.05$. **Results:** 2K-1C rats presented increased SBP vs. Sham groups and quercetin did not reduce it ($n=5-7$; $p<0.05$). However, treatment with quercetin decreased both oxidative stress ($n=5$; $p<0,05$ vs Sham groups) and the gelatinolytic activity of MMP-2 in the left ventricles of hypertensive rats ($n=7-5$; $p<0.05$ vs. Sham groups). It seems that TNF-α is increased in the hearts of hypertensive rats and treatment with quercetin decreased it. At this moment, quercetin did not improve hypertension-induced cardiac contractile dysfunction, although coronary perfusion pressure appears to ameliorate in the 2K-1C ($n=5-10$). **Conclusions:** Chronic treatment with quercetin decreases the activity of MMP-2 and oxidative stress in the left ventricles of hypertensive rats although it did not ameliorate yet hypertension-induced cardiac remodeling and dysfunction. Perhaps more time is needed for the treatment starts to ameliorate the functional parameters of the heart during hypertension. **Financial Support:** FAPESP, CNPq, CAPES.

06.005 **Cardiovascular Repercussions in Virgin and Pregnant Female Rats First-generation Offspring of Mothers with Induced Gestational Hypertension**. Bozoni FT, Santos NCM, Souza-Paula E, Mariana NAP, Rocha ALV, Silva EJR, Dias-Junior CA IBB-Unesp-Botucatu

Introduction: Preeclampsia is a hypertensive pregnancy disorder characterized by systolic and diastolic blood pressure commonly greater than 140/90 mmHg and usually manifesting after the 20th week of pregnancy (YU et al., Med., v. 98, p. 1, 2019). Studies suggest an increase in oxidative stress in pre-eclampsia and in antiangiogenic factors with a concomitant reduction in vasodilator mediators and deficient placentation, which are accompanied by endothelial dysfunction and increased peripheral vascular resistance (GUERBY et al., Red. Bio., v. 22, p. 20, 2019). The placental commitment caused by decreased elasticity of the vessels impacting the blood flow to the fetus and possibly causes placental hypoperfusion (HERREIRA-GARCIA et al., Cur. Hyp. Rep., v. 16, p. 475, 2014). We hypothesized that there are harmful cardiovascular repercussions to the offspring of mothers with gestational hypertension, during adulthood and during pregnancy. **Methods:** The descendant female rats were distributed in 4 groups: G1: virgin offspring of normotensive mothers (VN), G2: Virgin offspring of hipertensive mothers (VH), G3: Pregnant offspring of normotensive mothers (PN), G4: Pregnant offspring of hipertensive mothers (PH). We investigated the impact of gestational hypertension on the cardiovascular system of offspring, examining hemodynamic, biochemical and vascular reactivity parameters. At 90 days of life, groups 1 and 2 were euthanized and on the 20th day of pregnancy, groups 3 and 4 were euthanized. **Results:** The virgin offspring presented systolic and diastolic arterial hypertension in the young phase (60 days of life). The pregnant offspring had systolic arterial hypertension in early pregnancy (7th day). Both pregnant offspring and virgin offspring of hypertensive mothers were more responsive to phenylephrine, and the maximum effect of phenylephrine was significantly greater in pregnant offspring of hypertensive mothers compared to pregnant offspring of normotensive mothers, in rings with endothelium. The vascular sensitivity to nitric oxide (NO) also seems to be compromised in vessels from the offspring of hypertensive mothers. The synthesis of plasma NO was shown to be deficient in the pregnancy of the offspring of hypertensive mothers and DAF-FM probe assay suggesting us that maternal hypertension causes a lower bioavailability of substrate for NO formation, both in pregnant and virgin offspring. In a complementary way, the production of vasodilator hydrogen sulfide (H2S) during the pregnancy of the offspring of hypertensive mothers was also statistically impaired. **Conclusion:** We suggest that the experimental model of gestational hypertension generates some negative impacts on virgin first-generation offspring and on their pregnancy in factors such as hemodinamic parameters, vascular reactivity and bioavailability os vasodilators. Moreover, the use of animals was previously approved by the ethics committee of the Institute of Biosciences, Sao Paulo State University, Botucatu, Brazil, with protocol number: 7056090420. **Financial Support:** PIBIC/UNESP and FAPESP.

06.006 **Cardiovascular Effects of *Alpinia zerumbet* Leaves Extract in Spontaneously Hypertensive Rats**. Santos GP, Menezes MP, Oliveira BC, Cavalheira MA, Silva DLB, Bem GF, Costa CA, Resende, AC, Ognibene DT IB-UERJ, Dept of Pharmacology, Rio de Janeiro, Brazil

Introduction: The *Alpinia zerumbet* is a plant native to West Asia and also abundant on the Brazilian coast, where it is commonly known as Colônia. This plant is widely used in folk medicine as an antihypertensive, diuretic, and anxiolytic. This study aimed to investigate the effects of the hydroalcoholic extract obtained from Colônia leaves (AZE) on hypertension, vascular dysfunction, and remodeling in spontaneously hypertensive rats (SHR). Besides that, we studied the oxidative status and AT1 receptor levels. **Methods:** SHR and Wistar-Kyoto male rats, 90 days old, treated or not with AZE (50mg/kg/day in drinking water) for six weeks, were used in this study. Blood pressure (BP) was assessed once a week by tail plethysmography. At the end of treatment, the animals were anesthetized with thiopental (70mg/kg i. p.); blood was collected through abdominal aorta puncture; the thoracic aorta was isolated for morphological analysis and immunostaining of 8-isoprostane, a marker of oxidative damage, and AT1 receptors; and the mesenteric arterial bed (MAB) was isolated and coupled to an organ perfusion system for the assessment of responsiveness to vasoconstrictor and vasodilator agents. Protein carbonylation levels as well as catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) enzymatic activities were evaluated in plasma samples by spectrophotometry (Animal Research Ethical Committee: CEUA-IBRAG-UERJ/052/2016). **Results:** AZE was able to normalize the BP in SHR ($p<0,05$). Although the treatment did not improve the MAB vascular dysfunction in this model, it was able to reverse the vascular remodeling in the aorta. Besides that, AZE treatment improved CAT and GPx activities and decreased protein carbonylation in plasma samples, as well as reduced 8-isoprostane and AT1 receptors immunostaining in the aorta, even though it did not improve SOD activity ($p<0,05$). **Conclusion:** The results suggest that AZE reverses hypertension and thoracic aorta remodeling in SHR, which was associated with lower oxidative stress and AT1 receptors. However, AZE treatment for six weeks did not improve vascular dysfunction in this model. **Financial Support:** FAPERJ and CNPq.

06.007 **Evaluation of Vascular Adverse Effects of Intrauterine and Lactational Exposure to Cyantraniliprole**. Morimoto KY, Boese CM, Moura KF, Gonçalves CO, Rodrigues KFS, Verlingue TZ, Rodrigues MD, Menezes ACF, Fernandes GSA, Ceravolo GS UEL, Dpt of Physiology Sciences, Londrina, Brazi

Cyantraniliprole (CYA) is a commercial insecticide that targets insect ryanodine receptor and can be used to control a wide range of agricultural pests. Also, CYA is described with relatively low toxicity for non-target species, such as mammals. However, it was recently described that intrauterine a lactational exposure to this insecticide causes unfavorable outcomes for the reproductive system of exposed rodent. Despite this information, there are no studies evaluating the effects of intrauterine and lactational exposure to this xenobiotic on the vascular system of exposed offspring. Thus, the present study aimed to evaluate in the offspring the vascular outcome of maternal administration of cyantraniliprole through gestation and lactation. For this, female Wistar rats were treated with cyantraniliprole (CYA group, 10mg/Kg/day, gavage) or vehicle (CTR group, vehicle by gavage) from the gestational day five until the day of offspring´s weaning. The pesticide dose chosen is the lowest toxic dose described in the registration leaflet in the Ministério da Agricultura e Planejamento - Brazil. In the post-natal day (PND) 55 (n=6/group) and 90 (n=6/group), the *in vitro* thoracic aorta reactivity to phenylephrine (phenyl), acetylcholine (ACh) and sodium nitroprusside (SNP) was evaluated in male offspring. The maximum response (Rmax) was calculated and used to compare the response between groups. The Rmax to phenyl was expressed in gram and to the vasodilators as % of relaxation). The data was analyzed by ANOVA (two-ways and Tukey's) or T-test; the results expressed as mean ± s. e. m., differences when $p<0.05$. (CEUA N°20/2020). The aortic response to phenyl in the presence (E+) or absence (E-) of endothelium was similar between groups rats in the PND55 (CTR E+: 2,28±0,12 vs CYA E+: 2,39±0,18; CTR E-: 4,04±0,15 vs CYA E-: 3,66±0,28) and PND90 (CTR E+: 2,28±0,12 vs CYA E+: 2,17±0,11; CTR E-: 3,19±0,13 vs CYA E-: 3,15±0,17). The Rmax to ACh was not different between groups at PND55 (CTR: 91,79±2,37 vs CYA: 89,98±1,86) and PND90 (CTR: 90,84±1,05 vs CYA: 90,92±1,10). The Rmax to SNP was also similar between the groups. These results demonstrated that the exposure to CYA during gestational and lactational development did not cause deleterious outcomes to vascular response of exposed offspring. However, before classify CYA as a safe pesticide

more studies with different doses are needed. **Financial Support:** CAPES, PIBIC, Fundação Araucária (grant: 215/2022-PBA).

06.008 **Apocynin Treatment Restores the Caveola Function in Endothelial Cells from Spontaneously Hypertensive Rats**. Silva MSQ[1], Graton ME[1,2] Silva CA[1] [1]FO-Unesp-Araçatuba, PPG Multicêntrico em Ciências Fisiológicas, [2]University of Alberta

Introduction: The endothelial nitric oxide synthases (eNOS) are anchored to caveolae on endothelial cells. A reduced number of caveolae was observed in aortas and mesenteric arteries from spontaneously hypertensive rats (SHR). This alteration is associated with endothelium dysfunction and hypertension. Apocynin treatment reduces systolic blood pressure in SHR. We hypothesize that apocynin prevents endothelial dysfunction by altering the role of caveolae in eNOS activity in SHR aorta. **Methods:** The Animal Research Ethics Committee of the School of Dentistry of Araçatuba, UNESP, approved all the procedures used in this study (Process CEUA FOA 2022-0097). Aortas from Wistar rats and SHR, untreated or treated with Apocynin (30mg/Kg, p. o, from 4th to 10th week of life) were incubated with methyl-β-cyclodextrin (dextrin, 10mmol/L), which disrupts caveolae by depleting cholesterol. Concentration-response curves to acetylcholine (ACh) or A23187, a calcium ionophore, were analyzed in the presence or absence of dextrin and compared between groups. **Results:** Our results demonstrated that chronic treatment with Apocynin prevents hypertension in SHR but it did not alter systolic blood pressure (SBP) in Wistar rats. Dextrin impairs endothelial function in both groups, but this effect is greater in SHR aortas than in normotensive Wistar rat aortas. Interestingly, Apocynin treatment prevented the effect of dextrin in aortas from SHR, but not in Wistar aortas. **Conclusion:** Our results suggest that Apocynin treatment reduced hypertension in SHR by a mechanism that prevents caveolae disruption in blood vessels and improves eNOS activity and NO production. **Financial Support:** CAPES (code 001), FAPESP (2016/22180-9, 2017/18436-0, 2019/13751-0).

06.009 **Effects of Treatment with Sodium Nitrite on Hypertension and Endothelium Dysfunction Caused by Reducing Uteroplacental Perfusion Pressure Method in Rats**. Martins LZ, Silva MLS, Rodrigues SD, Dias Junior CAC IBB-Unesp-Botucatu, Dept of Pharmacology, Botucatu, Brazil

Introduction: Preeclampsia (PE) is a pregnancy complication whose pathogenesis is still unclear, but it is characterized by an increase in maternal blood pressure. Some theories suggest that in cases of PE, trophoblastic invasion, and formation of blood vessels at the maternal-fetal interface is compromised, decreasing the passage of placental blood flow causing hypoxia and ischemia, raising blood pressure. Recently, it has been suggested that some endogenous mediators may be related to the pathogenesis of gestational hypertension, such as deficits in the bioavailability of nitric oxide (NO). The experimental model of induction of gestational hypertension and PE known as Reducing Uteroplacental Perfusion Pressure (RUPP) has been shown to be one of the best to demonstrate most of the responses observed in human PE. **Methods:** On the 14th day of gestation, the rats in the hypertensive groups were anesthetized with isoflurane (1. 5-2%) and, later, a midline incision was made to implant a 0. 203mm silver clip in the lower abdominal aorta and two other clips. 0.100mm silver pieces (each) were implanted in the right and left branches of each ovarian artery. The animals were divided into groups treated by gavage with 0. 9% saline or treated with 15mg/kg/day sodium nitrite. NORM-PREG group: pregnant rats that received saline solution. NORM-PREG+N group: pregnant rats that received sodium nitrite by gavage from the 14th gestational day until the end. RUPP group: pregnant rats submitted to the RUPP model on the 14th day of gestation that received saline solution. RUPP+N group: pregnant rats submitted to the RUPP model on the 14th day of gestation and receiving nitrite from the 14th gestational day. During the 11th, 13th and 21st, Systolic Blood Pressure (SBP) was measured. In the first 2 days, by the method of plethysmography of solution and in the last day by vascular catheterization through surgical isolation of the carotid artery. Thoracic arteries were dissected into 3 to 4 mm segments. The rings placed in Krebs-Henseleit nutrient solution and suspended between two wires, one close to the support and the other connected to an isometric force transducer. The nutrient solution was adjusted to pH 7. 4 and maintained at 37°C in the presence of a carbogen mixture (95% O2 and 5% CO2). Changes in aortic tension were recorded using isometric force transducers. **Results:** Increases in SBP were observed in the RUPP group compared to the NORM-PREG group (103. 5±6. 8 vs. 72. 5±1. 5) and an improvement was observed in the RUPP+N group (86±3. 9) at day 21. In the KCl-induced contraction, we observed greater contraction in the RUPP when compared to the NORM-PREG group (0. 94±0.19 vs. 0. 67±0.16)

and less contraction in the RUPP+N group (0. 42± 0,12). Increases in contraction of the α-adrenergic receptor agonist phenylephrine were observed in the RUPP group (0. 82±0. 20 vs. 0. 73±0. 20g) and an improvement in the contraction of RUPP+N (0. 57±0. 16g). We compared relaxation responses to acetylcholine and found that endothelium-dependent vasodilation was significantly impaired in RUPP rats (66. 8±9. 4 vs. 51. 5±12. 7g) as well as responses to sodium nitroprusside (50 . 8±14. 7 vs. 62. 8±14. 9g). **Conclusion:** Thus, RUPP-induced hypertension in pregnant rats has similar characteristics to preeclampsia in women and which are attenuated by nitrite treatment, being the way to advance further studies to understand its mechanisms, investigating the role of endothelium-dependent mediators that may contribute to better treatment alternatives. Ethics Committee: IBB/UNESP 7946200721.

06.010 **Isoflurane Anesthesia Reveals Protective Effects against Endothelium Dysfunction and Hypertension in Pregnant Rats**. Rodrigues SD, Silva MLS, Martins LZ, Dias Junior CAC IBB-Unesp-Botucatu, Dept of Pharmacology, Botucatu, Brazil

Introduction: Despite major advances in the diagnosis and treatment of hypertensive diseases during pregnancy, such conditions still have their pathophysiology undefined and are still among the causes of greater maternal and perinatal morbidity and mortality worldwide. Preeclampsia (PE) is associated to generalized vasoconstriction, endothelial dysfunction, and also reduced nitric oxide (NO), an important cardiovascular homeostatic regulator. Studies suggest that maternal-fetal exposure to anesthetics can trigger undesirable hemodynamic changes, which makes it even more critical in cases of PE, raising the need for adequate planning and anesthetic procedures. Isoflurane is an inhalational anesthetic widely used in clinical routine, due to its rapid induction and easy recovery, in addition to being cardioprotective. Anesthesia with isoflurane in pregnant women with PE can influence the bioavailability of NO, restoring the endothelial function of the vessels and, consequently, influencing vascular reactivity. **Methods:** Female Wistar rats (24) were randomly assigned to 4 groups: normotensive pregnant rats (Preg), isoflurane anesthetized normotensive pregnant rats (Preg + Iso), hypertensive pregnant rats (Htn Preg) and isoflurane anesthetized hypertensive pregnant rats (Htn Preg + Iso). Gestational hypertension was induced using the DOCA-salt model, with 12. 5 mg of DOCA intraperitoneally on the 1st day of gestation and 6. 25 mg of DOCA on the 7th and 14th of gestation. In addition, tap water was replaced for 0. 9% saline solution throughout pregnancy. On the 20th day of gestation, rats were anesthetized with isoflurane at a rate of 1. 5% to 2% for 150 minutes, and had the hemodynamic parameters monitored. After euthanasia, the rats had their thoracic artery excised and divided into 4mm segments with endothelium and segments with mechanically removed endothelium. Artery segments were kept in a bath with Krebs solution at 95% O2 and 5% CO2, and controlled temperature, and had their isometric contraction and relaxation evaluated through vascular function recordings using transducers. **Results:** For the induction and maintenance of anesthesia, there was no statistical difference between the Preg + Iso and the Htn Preg + Iso groups. Decreased fetal weight was observed in the Htn Preg group (2. 8 ± 0. 8 g) when compared with the other groups. In vessels with intact endothelium, Phe (phenylephrine) caused greater concentration-dependent contraction in the Htn Preg group compared with Htn Preg +Iso (1. 15 ± 0. 79 g vs 0. 90 ± 0. 63 g respectively). Phe contraction in arteries without endothelium of the respective groups also showed a statistical difference (1. 57 ± 0. 98 g vs 0. 96 ± 0. 66 g). Relaxation induced by Ach (acetylcholine) was impaired in the Htn Preg group by approximately 25% relaxation vs 40% relaxation in the Htn Preg + Iso group. In the relaxation of vessels pre-contracted with Phe to sodium nitropussiate (SNP), the Htn Preg group had lower sensitivity to the exogenous NO donor. **Conclusion:** The similarity of hemodynamic parameters during anesthetic maintenance between the group of normotensive pregnant rats and the group with comorbidity suggests that isoflurane may be an anesthetic agent of choice in critical cases such as PE. Furthermore, the lower contraction and greater relaxation of the vessels of the Htn Preg+Iso group indicates a possible endothelial restoration by the anesthetic agent, reducing the vascular hyperreactivity caused by hypertension. Ethics Committee: IBB/UNESP 9543200721. **Financial Support:** FAPESP, 2021/03792-1.

06.011 **The Effect of Antidepressants on Blood Pressure of Male and Female Rats: a Systematic Review and Meta-Analysis**. Santos TM, Martins TMS, Lino de Oliveira C, Linder AE UFSC – PPG in Pharmacology, Florianópolis, Brazil

Antidepressants (ADTs) modulate different physiological responses beyond the central nervous system such as the cardiovascular system through different mechanisms of actions. However, isolated studies do not seem to allow clear. **Conclusions:** regarding the effect of these drugs on rat blood pressure. There is evidence that male and female rats respond differently to antidepressants in some behavioral tests. Based on these data, we aimed to test the hypothesis that sexually dimorphic responses are also found in the effects of antidepressants on rat blood pressure. A systematic review and meta-analysis were conducted according to a pre-established protocol (PROSPERO, ID=CRD42021277987) to answer these questions transparently. Initially, searches were performed on variations of terms related to population (rats), intervention (antidepressant), and outcome (blood pressure) in Medline (via Pubmed), SCOPUS, and EMBASE databases. All publications (n=2144) returned from searches were exported to EndNote X9 for duplicate exclusion (n=436) and selection using inclusion/exclusion criteria. Those that did not meet the selection criteria (see protocol) were excluded (n=1412). A total of 44 publications in any language that described the pressor effects of animals treated with ADTs were included. A single reviewer performed the selection and data extraction to evaluate external validity (experimental qualities), internal validity (risk of bias, RoB-Syrcle tool), and meta-analysis (random-effects model). Most studies included in the library used males (70. 45 %, n=31), followed by females (15. 9 %, n=7) and no-specified sex (13. 63 %, n=6). The predominant class of antidepressants was the selective serotonin reuptake inhibitors (37. 5 %, n=18). The overall risk of biases was unclear for all publications included in the library. A total of 30 publications (with 59 studies and 872 animals) that measured mean arterial pressure (MAP) were included in the analysis. Based on the random-effects model, the estimate shows a decrease in MAP in rats treated with ATDs, but the effect size was very low, non-statistically significant and with high inconsistency (Hedges' g= -0. 06; 95% CI[-0. 40; 0. 27]; I^2 = 74. 6 %, Z = -0. 39, p=0. 70). When separated by sex, males presented a decrease in MAP, and the effect size was very low and non-statistically significant, with high inconsistency (Hedges' g = -0.13; 95% CI[-0. 58; 0. 32]; I^2 = 79. 56 %, k=40), females presented a increase in MAP, with a very low and non-statistically significant effect size, and low inconsistency (Hedges' g = 0.12; 95% CI[-0. 29; 0. 53]; I^2 = 49. 05 %, k=17), and those with non-specified sex presented a moderate non-statistically significant decrease in MAP and high inconsistency (Hedges' g = -0. 74; 95 % CI[-2. 55; 1. 07]; I^2 = 76. 73 %, k=2). Egger's regression test (p=0. 34) and Trim-and-fill result (no missing studies) did not indicate asymmetry of the funnel plot. These results indicate an unknown internal validity in the publications of this literature, which may be related to failures in the reporting of the design, conduct and analysis of reviews in basic science. In addition, further studies would be valuable to support a hypothesis about the non-effect of ADTs on blood pressure.

06.012 **Anti-Inflammatory and Cardioprotective Effect of Alpha-Bisabolol in the Doxorubicin-induced Experimental Cardiotoxicity**. Padilla Paguada AL, Silva RL, Quispe CC, Silva JMR, Mendoza MFM, França JC, Alcântara LG, Alves SG, Silva LGF, Camelo TS, Santos AA, Siqueira RJB, Wong DVT, Lima-Júnior RCP UFC **Introduction:** Cardiotoxicity is a side effect resulting from the treatment of cancer patients with anthracyclines. Doxorubicin is one of the most frequently drugs used for the management of several types of cancer in adults and pediatrics, including breast cancer, the most prevalent in women. Unfortunately, despite its effectiveness, the clinical significance of incorporating doxorubicin in cancer therapy is undermined by its toxicities. It is usually manifested as cardiotoxicity up to years after discontinuation of treatment. It is then especially important in cardio-oncology research to identify therapies to delay or prevent the occurrence of doxorubicin-related cardiovascular complications. Alpha-bisabolol is a sesquiterpene alcohol with an important anti-inflammatory action described. The present study aimed to investigate the role of alpha-bisabolol on doxorubicin-induced cardiotoxicity. **Methods:** C57BL/6 male mice (25-25g) were divided into groups (n=6/group) and injected with vehicle (6 ml/kg + 2% tween 20 2% i. p 1xday/19 days, i. p.), doxorubicin (4 mg/kg on days 0, 7, and 14, i. p.) alone or 1 h before alpha-bisabolol (50 mg/kg, once daily/19 days, p. o.) or alpha-bisabolol alone for 19 days. Body mass change was assessed daily. On day 20, electrocardiographic (ECG) parameters were evaluated and a blood sample was obtained for biochemical analysis. After euthanasia, heart samples were extracted for histopathology and measuring inflammatory markers. One- or Two-way ANOVA followed by the Bonferroni's test or Kruskal-Wallis followed by the Dunn's test were used for the statistical analysis. The differences between the groups were accepted when $P<0.05$. Ethics committee approval: CEUA 9897291019. **Results:** Doxorubicin induced a significant loss of body and cardiac masses versus the vehicle group ($P<0.05$). Additionally, the

chemotherapeutic drug induced ECG alterations (ST, QRS, and QTc interval prolongation, reduced the height of T waive and heart rate). It also caused histopathological damage characterized by the reduction of the cardiomyocyte area. Besides, doxorubicin increased serum levels of CK-BM and neutrophilic infiltrate. Inflammatory response was marked by increased expression of TLR9 and PI3K-gamma receptors, culminating in the production of IL-1beta, and IL-6. All these parameters were significantly attenuated by alpha-bisabolol treatment ($p<0.05$ vs. doxorubicin group). **Conclusion:** Alpha-bisabolol demonstrated an anti-inflammatory activity, preventing the development of doxorubicin-associated cardiotoxicity. **Financial Support:** CNPq, Capes, and Funcap.

06.013 **Antioxidant Treatment with Resveratrol during Gestational and Lactation Phase Reduces MMP-2 Activity and Arterial Hypertension in Adult Offspring**. Gomes BQ, Rocha EV, Blascke de Mello MM, Assis VO, Pernomian L, Castro MM. FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil

Introduction: Spontaneous hypertensive rats (SHR) show increased aortic MMP-2 levels and increased production of reactive oxygen species (eROs). Increased eROs can activate MMP-2 in the arteries and contribute to vascular remodeling of hypertension. The antioxidant resveratrol is able to reduce eROs and decreases MMPs activity in some cardiovascular diseases. Furthermore, treating pregnant hypertensive rats with resveratrol reduced the levels of hypertension in their offspring in their adult life. We hypothesized that treatment of SHR rats with a diet rich in resveratrol during pregnancy and lactation decreases MMP-2 activity, maladaptive vascular remodeling, and hypertension in their adult offspring. **Methods:** Female and male SHR and WKY rats were treated with resveratrol on diet at a dose of 4g/kg until the birth of the pups. Males were then removed from the cages and the female rats continued to receive resveratrol during the period of lactation. After lactation, the offspring were separated by gender and studied for more 12 weeks. In this period, systolic blood pressure (SBP) was weekly analyzed (from 8 to 12th weeks) by tail-cuff plethysmography. At the end of 12 weeks, adult offspring were euthanized and aortas were collected for gel and in situ zymography, and lucigenin analyses. Statistical analysis was done by two-way ANOVA followed by Bonferroni post-test (CEUA USP 052/2021). **Results:** The SBP of male and female SHR rats was significantly higher when compared to their respective WKY from 8 to 12 weeks. Resveratrol treatment reduced SBP in SHR female rats (n=13, 165. 35 ± 3. 23 vs. vehicle n=10, 176. 94 ± 2. 47; $P<0.05$), but not in male rats. eROs are increased in the aorta of SHR female rats (n=7, 61. 34 ± 13. 59 vs vehicle WKY females n=6, 31. 00 ± 5. 00) and treatment with resveratrol seems to decrease it. MMP-2 activity was also increased in the aortas of the adult SHR offspring. Antioxidant treatment decreased gelatinolytic activity of MMP-2 in aortas of SHR female (n=13, 22. 50 ± 1. 08 vs vehicle n=7, 36. 77 ± 2. 23; $P<0.05$) and male rats (n=10, 21. 12 ± 1. 41 vs vehicle n=8, 29. 63 ± 2. 25; $P<0.05$). **Conclusions:** Treatment with resveratrol decreased MMP-2 aortic gelatinolytic activity in the offspring (female and male) and contributed to attenuate the SBP especially in the female rats. **Financial Support:** CAPES, FAPESP, CNPq and FAEPA.

06.014 **Characterization of Abnormalities in *Corpora cavernosa* from Hypertensive Rats**. Silva LB[1], Jesus RLC[1], Araújo FA[1,2], Silva DF[1,2] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Salvador, BA, Brazil, [2]IGM-Fiocruz, Salvador, BA, Brazil

Introduction: Erectile dysfunction (ED) is often encountered in men with hypertension. The development of vasculogenic ED is associated with structural and functional abnormalities in the penile arteries resulting from arterial hypertension. In addition, there is a functional correlation between the expression of thermoreceptor TRPV1 channels (vanilloid 1) and alterations in blood pressure. Therefore, this study aimed to investigate and characterize abnormalities in the corpora cavernosa from hypertensive animals, compared to normotensive Wistar controls, with focus on the TRPV1 channels. **Methods:** To investigate TRPV1 channel activation, corpora cavernosa (CC) strips were isolated from Wistar or SHR rats and subjected to chemical or thermal stimulation. In another set of experiments, protein expression was performed to determine whether TRPV1 channel proteins are expressed in the CC of those animals. All experimental protocols were approved by Committee on Ethics in Animal Use from the Federal University of Bahia (CEUA/UFBA nº 130/2017). **Results:** Heat temperature (37°–43°C) activating temperature sensitive TRPV1 channels in corpora cavernosa (CC) induced relaxation, in both situations, strips under basal or pre-contracted tone induced by Phe (10−5 M). This relaxing effect induced by heat temperature was significantly decreased by capsazepine (TRPV1 channel blocker, 10−5 M) in the SHR rats (E42°C= 79. 78 ± 7. 78 %, n=4) when compared to their normotensive wistar controls (E42°C=100. 59 ± 9. 25 %,

n=6). In addition, capsaicin (TRPV1 activator) significantly relaxed the sustained contraction induced by Phe (10−5 M) in the CC strips. The relaxation induced by capsaicin (10-9 to 3x10-4 M) was reduced in the presence of capsazepine in hypertensive animals (88. 87 ± 4. 86 %, n=5) compared to normotensive controls (115. 21 ± 8. 59 %, n=5). Furthermore, experiments using the western blotting technique demonstrated that the immunoreactive bands indicated higher expression of the TRPV1 channels in CC isolated from SHR compared to CC strips from Wistar rats. **Conclusions:** In summary, our observations demonstrated that TRPV1 is higher expressed in the CC from hypertensive rats and their activation is able to relax this tissue. Thus, appears to activation of TRPV1 can be considered a potential therapeutic target in the treatment of hypertension-associated erectile dysfunction. **Financial Support:** CNPq, CAPES, FAPESB and UFBA

06.015 **Impact on Stomach pH of Sodium Nitrite on Gestational Hypertension Caused by the Reduced of Uteroplacental Perfusion Pressure Model in Rats**. Silva MLS, Martins LZ, Rodrigues SD, Dias-Junior CA IBB-Unesp-Botucatu, Dpt of Pharmacology, Botucatu, Brazil

Introduction: Preeclampsia (PE) is a disorder that arises in pregnancy and is characterized by elevated maternal blood pressure (140x90mmHg) accompanied by 24-hour proteinuria after the 20th gestational week. Its pathogenesis is still unclear. In general, most women use medications to relieve symptoms of symptomatic gastric reflux that is common during healthy pregnancy. Among these drugs are proton pump inhibitors (PPIs). Recent research reveals that PPIs may compromise bioavailability in a pH-dependent manner and the synthesis of nitric oxide (NO) through the inhibition of the activity of the enzyme dimethyl larginine dimethyl amino hydrolase (DDAH), necessary for the cardiovascular system homeostasis. Dietary nitrate is absorbed and activated in the oral cavity, where it is reduced to nitrite by nitrate reductases present in oral commensal bacteria. The ingested nitrite reaches the stomach and under acidic conditions of the gastric medium it is converted into NO and other species of bioactive nitrogen, suggesting its antihypertensive effects. The experimental model of gestational hypertension and PE induced by RUPP (reduced of uteroplacental perfusion pressure) has been shown to be very promising for manifesting the main features found in human PE. This study search for evaluating the impact of the use of Nitrite on the bioavailability of NO in the gestational hypertension induced experimentally. **Methods:** On the 14th day of gestation, the rat was anesthetized with isoflurane (1. 5-2%) and, subsequently, a median incision was made for implantation of a 0. 203mm silver clip in the lower abdominal aorta and another two 0.100mm (each) silver clips were implanted in the right and left branches of each ovarian artery. Norm-Preg Group: Pregnant rats that received 0. 9% saline solution by gavage. Norm+Nitrite: Pregnant rats that received 15mg/Kg/day in the 14º gestational day. RUPP group: pregnant rats submitted to the RUPP model on the 14th day of pregnancy. RUPP+Nitrite: Pregnant rats submitted to the RUPP model and that received 15mg/Kg/day in the 14º gestational day. On the 21st gestational day, pressure was measured using an invasive method, where the rats were anesthetized with isoflurane for implantation of the cannula in the carotid artery and the catheter was coupled to the data acquisition system. Soon after these measurements, the rats were euthanized and the tissues collected. Stomach pH was assessed and fetal parameters were obtained. **Results:** In invasive systolic blood pressure we observed a compromise in the RUPP group in relation to Norm-Preg (106. 0mmHg±7. 82 vs 72. 50mmHg±1. 5) and an improvement in RUPP+Nitrite (84. 35mmHg±4. 18). In the stomach pH we found interesting differences between the groups, being RUPP+Nitrite with values above RUPP (4. 60pH±0. 24 vs 3. 56pH±0. 23) and Norm+Nitrite higher than Norm (4. 75pH±0 . 16 vs 2. 76pH±0. 34). Regarding fetal weight, we observed an impairment in RUPP compared to Norm (3. 49g±0.058 vs 4. 02g±0. 091) and a reversal in RUPP+Nitrite (4. 0g±0. 09). We found impairment in RUPP compared to Norm (0. 27g±0. 003 vs 0. 33g±0. 005) and an improvement in RUPP+Nitrite (0. 31g±0. 008). **Conclusion:** Thus, RUPP-induced hypertension in pregnant rats has many of the characteristics of preeclampsia in women, and the treatment with Nitrite was able to improve this situation, being the way to advance studies of new treatments and solutions for investigating the pathophysiology of this condition that affects thousands of women. **Financial Support:** FAPESP 2020/03135-8. Approval by Ethics Committee: IBB/UNESP:6707090320

06.016 **Effects of Ouabain Administration and High-Salt Diet in Wistar Rats**. Feijó PRO[1], Panice MS[1], Morcillo LSL[2], Quintas LEM[1] ICB-UFRJ, Lab of Molecular and Biochemical Pharmacology, Lab of Renal Pharmacology

Introduction: The real involvement of cardiotonic steroid ouabain (OUA) in development or maintenance of arterial hypertension is not totally understood. Thus, our goal was to evaluate the effects in rats during the OUA

administration in high-salt diet (HSD). **Methods:** Male Wistar rats received OUA (30 µg/kg/day) or vehicle (control group: C) and normosodic (NS: Na+ 0. 5%) or hypersodic (HS: Na+ diet 3. 12%) for 14 and 35 days. Ultrasonography of animals was performed, urine was collected and on the last day of administration, systolic blood pressure (SBP) was measured. After euthanasia, kidneys were dissected. The results were expressed as mean ± SEM and analyzed using the One-way ANOVA test (significance: $p<0.05$). Protocol 046/19 of the CEUA Animal Use Ethics Committee at UFRJ. **Results:** Our model was not able to increase systolic arterial pressure of animals, which was compatible with the plasma sodium, potassium and magnesium levels, which also did not change. Ultrasound did not show significant kidney changes, but macroscopic analysis revealed the presence of cysts in groups that received OUA and the qualitative histological analysis revealed evidence of glomerular and tubular injury in all groups compared to control (C+NS). After 14 days we observed an increase in water intake in OUA+HS group (77. 3 ± 6. 6 mL, n=5) vs. OUA+NS (20. 0 ± 4. 0 mL, n=6; p= 0. 0001), C+NS (30. 9 ± 6. 0 mL, n=8; p= 0. 0005) and C+HS group (61. 0 ± 14. 0 mL, n=5; p= 0. 0064) vs. OUA+NS. Proportionally there was an increase in urinary volume in OUA+HS group (50. 8 ± 7. 0 mL, n=5) vs. OUA+NS groups (7. 8 ± 1. 0 mL, n=6; p =0. 001) and C+NS (12. 8 ± 3. 0 mL, n=3; p= 0. 006) and in C+HS group (49. 5 ± 10. 0 mL, n=3; p= 0. 016) vs. OUA+NS. After 35 days we observed the same profile, an increase in water intake in OUA+HS group (93. 4 ± 6. 0 mL, n=6) vs. OUA+NS (39. 5 ± 6. 6 mL, n=10; p=0. 0006), C+NS (42. 9 ± 7. 2 mL, n=18; p=0. 0004) and C+HS group (77. 2 ± 5. 6 mL, n=9; p=0. 0091) vs. OUA+NS and C+NS (p=0. 0073). Consistently there was an increase in urinary volume in OUA+HS group (67. 8 ± 4. 8 mL, n=6) vs. OUA+NS groups (4. 4 ± 1. 9 mL, n=10; p<0. 0001) and C+NS (11. 5 ± 1. 3 mL, n=18; p<0. 0001) and in C+HS group (61. 3 ± 9. 9 mL, n=9; p<0. 0001) vs. OUA+NS and C+NS (p<0. 0001). Proteinuria levels was performed using colorimetric kits that revealed an increasing tendency in the O+HS group (102. 1 ± 25. 2, mg/dL, n=4 compared to control (C+NS; 29. 2 ± 3. 0 mg/dL, n=3; p=0. 0850). After 35 days a higher proteinuric content in OUA+HS group (135. 4 ± 15. 6 mg/dL, n=5) vs. C+NS group (25. 8 ± 1. 5 mg/dL, n=5; p=0. 0026) and O+NS (67. 9 ± 18. 9 mg/dL, n=4; p=0. 0316). Moreover, C+HS (95. 1 ± 6. 3 mg/dL, n=3) was higher than C+NS (n=3; p=0. 0387). After 14 days renal cortex NKA activity of OUA+HS group (11. 3 ± 2. 1, n=5) was lower that of C+NS group (17. 6 ± 1. 6, n=5; p=0. 046). **Conclusion:** In conclusion OUA alone or the association of OUA with HSD do not generate increase in SBP up to 35 days. Proteinuria suggests that OUA + HSD may affect nephron integrity. The decreased NKA activity may be compensatory and justify the maintenance of SBP treated groups. Our preliminary results indicate kidney injury independent of the increase in systolic blood pressure in rats. **Financial Support:** CAPES, CNPQ, FAPERJ.

06.017 **6-Nitrodopamine is a Major Modulator of Heart Chronotropism**. Britto-Júnior J[1], Oliveira MG[1], Campos R[2], Mónica FZ[1], Antunes E[1], De Nucci G[1] [1]FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil, [2]ISCB-UECE, Fortaleza, Brazi

6-nitrodopamine (6-ND) is released by human umbilical cord vessels (Britto-Júnior et al., 2021a), human vas deferens vas deferens (Britto-Jr et al., 2022a) and by the rat isolated vas deferens (Britto-Jr et al., 2021b). In the HUCV, 6-ND is released by the endothelium and acts as a selective antagonist of the dopamine D2-like receptor (Britto-Jr et al., 2021a) whereas in the vas deferens 6-ND is released from nerve terminals and has a contractile activity which is selectively blocked by tricyclic compounds, such as tricyclic antidepressants and carbamazepine (Britto-Jr et al., 2021b), by α1-adrenergic receptor antagonists such as doxazosin, tamsulosin, and silodosin (Britto-Jr et al., 2022) and by the β1-adrenergic antagonists atenolol, betaxolol, and metoprolol (Lima et al 2022). This work aims to evaluate the endogenous release of 6-ND and the characterization pharmacological action in the rat isolated atrium. The experimental protocols were approved by the CEUA of UNICAMP (Protocols nº 5746-1/2021; 5831-1/2021). The atria were suspended vertically between metal hooks in 10-mL organ baths containing KHS, continuously gassed with a mixture of 95%O2: 5%CO2 at 37°C. Tissues were allowed to equilibrate under a resting tension of 10 mN, and the isometric tension was registered using a PowerLab system. The basal release of 6-ND, as detected in right atria. The release was significantly reduced when the atria were pre-treated with L-NAME (100 µM) similar effect in animals chronically treated with L-NAME. 6-ND (1 pM) significantly increased the atrial frequency, 100 times more potent than noradrenaline and adrenaline. Selective β1-blockers reduced the atrial frequency only at concentrations that prevented the increases in atrial frequency induced by 6-ND 1 pM. Conversely, β1-blockade but did not affect dopamine (10nM), noradrenaline (100 pM) or adrenaline (100pM) effect. The reductions in atrial frequency induced by the β1-antagonists atenolol,

betaxolol, and metropolol (0.1-1 μM) were absent in L-NAME pre-treated atria and in atria obtained from L-NAME chronically treated animals. Tetrodotoxin did not prevent the reduction in atrial frequency induced by L-NAME or by β1-blockers treated preparations. In anaesthetized rats, at 1 pmol/kg, only 6-ND caused a significant increase in heart rate. In conclusion, 6-ND is released from the rat atrium and its synthesis is inhibited by L-NAME. 6-ND induces a positive chronotropic effect 100 times more potent than noradrenaline and adrenaline and 10000 times more potent than dopamine. The results demonstrate that in rats the negative chronotropic effect of β1-blockers occurs due to the selective blockade of the specific receptor for 6-ND, indicating that cardiac chronotropic is modulated by the basal release of this endogenous non-neurogenic mediator. Activation of the sympathetic nervous system is responsible for the body's "Fight or Flight" reaction. Possibly due to 6-ND, one may not need to be constantly fighting or flying… Britto-Jr et al., 2021a DOI: 10.1016/j. lfs. 2021. 119425 Britto-Jr et al., 2021b DOI: 10.1016/j. ejphar. 2021. 174544 Britto-Jr et al., 2022 DOI: 10.1016/j. ejphar. 2021. 174716 Lima et al 2022 DOI: 10. 21203/rs. 3. rs-1530109/v1

06.018 **The Role of Renin Angiotensin System and Reactive Oxygen Species in Aortic Endothelial Dysfunction caused by Childhood Obesity in Female Rats**. Moura KF, Jezuino JS, Boese CM, Gonçalves CO, Uchoa ET, Ceravolo GS UEL

Childhood obesity has increased in both developed and developing countries. However, the vascular consequence of childhood obesity in female rats has not been investigated. The study aimed to evaluate the effects of childhood obesity induced by postnatal overfeeding on aortic reactivity and blood pressure in prepubertal and adult female rats. Thus, in the first day of life, litters of Wistar rats were distributed into normal litter (5 female and 5 male pups – NL (n=9)) or small litter (2 male and 1 female pups – SL (n=13)). At postnatal day (PDN) 30 and 120, female offspring were evaluated for body weight (g) and retroperitoneal, perigonadal and brown adipose deposition (values normalized by 100g of the body). The blood pressure and heart hate were evaluated by indirect method and *in vitro* thoracic aorta reactivity was evaluated for phenylephrine (Pheny), acetylcholine (ACh) and sodium nitroprusside (SNP). To understand the role of the renin-angiotensin system and reactive oxygen species in the vascular function, curves to ACh were made in the presence of: apocynin (APO) and losartan (LOS). (CEUA 112/2020). As results, at PND 30, SL had higher body weight [NL 76. 56 ±2. 12 vs SL 91. 52±1. 78], retroperitoneal [NL 0. 09±0. 01 vs SL 0.17±0. 01] and perigonadal [NL 0. 04±0. 005 vs SL 0. 09±0. 009] adipose tissue deposition than NL. At PND 120, NL and SL had similar biometric parameters, but SL had higher heart rate and blood pressure than NL. At PND 30, maxR to Phenyl and ACh and at PND 120, maxR to phenyl and SNP were similar between groups. At PND 120, the maxR to ACh in SL were decreased when compared with NL [NL 94. 05±1. 5 vs SL 84. 65±2. 5]. Also, in SL rats, LOS [SL 77. 57±1. 65 vs LOS 90. 67±1. 05] and APO [SL 77. 57±1. 65 vs APO 87. 81±1. 02] restores maxR to ACh. In conclusion, postnatal overnutrition in female rats causes childhood obesity, hypertension, and endothelial dysfunction in adulthood, probably mediated by angiotensin II AT1 receptor and reactive oxygen species.

06.019 **Antithrombotic Effect of the Polysaccharide Extract from the Stem Barks of Libidibia ferrea Associated with the Anticoagulant Rivaroxaban After Oral Treatment in Rat**. Gadelha CJMU[1], Morais EB[1], Lessa RA[2], Silva ALM, Nobre ES[2], Assreuy AMS[1], Pereira MG[2] [1]ISCB-UECE, Fortaleza, Brazil, [2]FECLESC-UECE, College of education, Science and Letters of Central Sertão, Quixadá, Brazil

Introduction: Cardiovascular diseases (CVD) are considered the leading causes of death in the world, and thrombotic events account for most of the total deaths from CVD. Conventional antithrombotic therapy has several adverse effects, including bleeding, thrombocytopenia, and the search for new therapeutic approaches is important. Several clinical conditions require the association of more than one antithrombotic agent, such as dual pathway inhibition that uses the association of an antiplatelet agent and an anticoagulant that acts by direct inhibition. Experimental results with the polysaccharides extracted from Libidibia ferrea, demonstrated the antiplatelet and anticoagulant effects, in vitro, and the antiplatelet and antithrombotic activities after oral treatment. This study aimed to investigate the antithrombotic and hemorrhagic effects of L. ferrea polysaccharide extract (PE-Lf) associated with rivaroxaban (RIVA), a direct inhibitor of factor Xa of the coagulation cascade, after oral treatment in rats. **Methods:** The dry powder (5 g) of L. ferrea stem barks was delipidated/depigmented with methyl alcohol, the polysaccharides extracted with 0.1 M NaOH, precipitated in 96% alcohol and deproteinized (trichloroacetic acid), resulting in the PE-Lf. Females Wistar rats (200-250 g) were

used in according with the Ethics Committee/UECE. The effects of PE-Lf (5 mg/g) + RIVA (0.1 mg/kg) were carried out in the venous thrombosis induced by stasis and hypercoagulability, venous thrombosis induced by iron chloride (FeCl3) and hemorrhagic tendency models and for reduced plasma glutathione levels (GSH), an endogenous antioxidante, after oral treatment. **Results:** The treatment with the association showed a superior antithrombotic effect compared to the treatments with the isolated compounds after 90 minutes (51% vs PE-Lf (33%); RIVA (32%); single dose) and 7 days (59% vs PE-Lf (33%); RIVA (31%) in the stasis and hypercoagulability-induced thrombosis model. In FeCl3-induced thrombosis, PE-Lf (5 mg/kg) alone or in association with RIVA (0.1 mg/g) showed antithrombotic effect of 25% and 33%, respectively, while the RIVA group (0.1 mg/kg) showed only a tendency to reduce thrombus weight. In the bleeding time, the treatment with the combination did not differ (1. 4x) of those with the isolated compounds (PE-Lf: 1. 7x and RIVA: 1. 4x). Plasma GSH levels showed a significant increase in the group treated with PE-Lf (5 mg/kg: 90%) or in combination with RIVA (0.1 mg/kg: 93%). **Conclusion:** The association PE-Lf+RIVA potentiates the antithrombotic effect in relation to the compounds isolated in the stasis and hypercoagulability model, without increasing the bleeding time. PE-Lf alone or in association with RIVA attenuated thrombus burden caused by FeCl3 and increased plasma GSH levels. **References:** Araujo, D. F. Int Jour Biol Macromol. v. 175, p. 147, 2021. Barquera, S. Arch med research. v. 46, p. 328, 2015 Rath, D. Herz. v. 45, n. 6, p. 528, 2020 Li, P. Jour of Thromb Thrombolysis, v. 52 p. 1, 2020. Animal Care and Use Committee of the Universidade Estadual do Ceara (n. 08241429/2020) **Financial Support:** Coordination of Improvement of Higher Education Personnel (CAPES)

06.020 **Effects of** *Euterpe oleracea* **Mart**. (**açaí**) **Seed Extract** (**ASE**) **in Mitochondrial Biogenesis and Oxidative Stress in Brown Adipose Tissue of High-Fat-Fed C57Bl/6 Mice**. Silva DLB, Santos IB, Romão MH, Menezes MP, Oliveira BC, Ognibene DT, Bem GF, Costa CA, Resende AC UERJ, Dpt of Pharmacology, Rio de Janeiro, Brazil
The rising rates of obesity and overweight represent an urgent public health concern and are a major risk factor for metabolic syndrome. Excess lipids favor energy imbalance, leading to remodeling of adipose tissue and suggesting a directly association with the induction of obesity. Brown adipose tissue (BAT) is related to the dissipation of energy in the form of heat during adaptative thermogenesis, contributing to energy expenditure. The activity of the mitochondrial biogenesis pathway is reduced by several factors, including high fat environment. In this way, the impairment of mitochondrial biogenesis and function has been related to metabolic diseases, such as obesity. Evidence suggests that low-grade inflammation in BAT contributes to excessive ROS production and is associated with oxidative stress. The açai seed extract (ASE) promotes an anti-obesity effect, whose mechanisms are still poorly understood. Therefore, this work aims to evaluate the effects of treatment with ASE on BAT remodeling and its role in mitochondrial biogenesis in BAT. All experimental procedures were approved by the Ethics Committee for Experimental Animals Use and Care of IBRAG/UERJ (CEUA nº 004/2021). Male C57BL/6 mice were divided into three groups: control (10% lipid diet); HF (60% lipid diet) and HF+ASE (60% lipid diet + 300 mg/kg/day by intragastric gavage). The diet was administered concurrently with the treatment for 12 weeks. Body mass was measured weekly, the blood glucose at the beginning and at the end of the treatment. The lipid profile, the expression of markers related to mitochondrial biogenesis, as well as the activity of antioxidant enzymes, and oxidative damage were evaluated in BAT homogenate. The morphological alterations of BAT and white adipose tissue (WAT) were analyzed histologically. ASE prevented the body mass gain, blood glucose and morphological changes in WAT and BAT in the HF+ASE compared to the HF group. In BAT, ASE treatment prevented the reduced expression of mitochondrial biogenesis markers pAMPK, pLKB1, SIRT-1, PGC-1α, NRF1 and CPT-1 observed in the HF group. ASE treatment also reduced the levels and 8-isoprostane immunostaining, indicating improvement of oxidative damage, and increased the antioxidant activity of SOD, without changing the enzymatic activity of GPx and catalase in the HF+ASE compared to the HF group. The extract also prevented the increase of inflammatory markers MCP-1 and TNF-α in BAT. In conclusion, the treatment with ASE prevented structural changes in the BAT of high-fat-fed mice and increased the expression of proteins related to mitochondrial biogenesis. The improvement of oxidative stress and inflammation in BAT may contribute to the beneficial effects of ASE. These findings support ASE as an approach to preventing obesity.

06.021 **Pharmacological Inhibition of FAK-Pyk2 Pathway Protects Against the Hyper-Inflammatory State in Sepsis and Prolongs Mice Survival**. Alves GF[1,2], Aimaretti E[3], Einaudi G[4], Mastrocola R[3], Oliveira JG[2], Collotta D[1],

Porchietto E[4] , Aragno M[3], Cifani C[4], Sordi R[2], Thiemermann C[5], Fernandes D[2], Collino M[6] [1]University of Turin, Dept of Drug Science and Technology, Turin, Italy, [2]UFSC, Dept of Pharmacology, Florianópolis, Brazil, [3]University of Turin, Dept of Clinical and Biological Sciences, Turin, Italy, [4]University of Camerino, Pharmacology Unit, School of Pharmacy, Camerino, Italy, [5]Queen Mary University of London, Centre for Translational Medicine and Therapeutics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom, [6]University of Turin, Dept of Neurosciences (Rita Levi Montalcini), Turin, Italy

Introduction: Sepsis is associated with high mortality and is considered one of the major public health concerns. The onset of sepsis is known as a hyper-inflammatory state that contributes to organ failure and mortality. Recent findings suggest a potential role of two non-receptor protein tyrosine kinases, namely Focal adhesion kinase (FAK) and Proline-rich tyrosine kinase 2 (Pyk2), in the inflammation associated with cancer, atherosclerosis and asthma. Therefore, we aimed to investigate the role of FAK-Pyk2 in the pathogenesis of sepsis and the potential beneficial effects of the pharmacological modulation of this pathway by administering the potent reversible dual inhibitor of FAK and Pyk2, PF562271 (PF271) in a murine model of cecal ligation and puncture (CLP)-induced sepsis. **Methods:** Five-month-old male C57BL/6 mice underwent CLP or Sham surgery and one h after the surgical procedure, mice were randomly assigned to receive PF271 (25 mg/kg, s. c.) or vehicle. Organs and plasma were collected 24h after surgery for analyses. In another group of mice, survival rate was assessed every 12h over the subsequent 5 days. **Results:** Experimental sepsis led to a systemic cytokine storm resulting in the formation of excessive amounts of both pro-inflammatory cytokines (TNF-α, IL-1β, IL-17 and IL-6) and the anti-inflammatory cytokine IL-10. The inflammatory response was accompanied by high plasma levels of ALT, AST (liver injury), creatinine (renal dysfunction) and lactate, as well as a high clinical severity score. All parameters were attenuated following PF271 administration. Septic mice had an overactivation of FAK and Pyk2 in liver and kidney, which was associated to p38 MAPK activation, leading to increased expression of several pro-inflammatory markers, including the NLRP3 inflammasome complex, the adhesion molecules (ICAM-1, VCAM-1, E-selectin) and the enzyme iNOS and myeloperoxidase. Treatment with PF271 inhibited FAK-Pyk2 activation, thus blunting the inflammatory abnormalities orchestrated by sepsis. Finally, PF271 significantly prolonged the survival of mice subjected to CLP-sepsis. **Conclusions:** Taken together, our data show for the first time that FAK-Pyk2 pathway contributes to sepsis-induced inflammation and organ dysfunction and that the pharmacological modulation of this pathway may represents a new strategy for the treatment of sepsis. **Financial Support:** Foundation for Research and Innovation of the State of Santa Catarina (2021TR000318); Università degli Studi di Torino (Ricerca Locale 2020 and 2021). Ethical committees: (7936220321, Brazil; 420/2016-PR, Italy). **References:** Murphy, J. M. Scientific reports, 9(1), 1. 2019. Guido, M. C. Shock, 37(1), 77. 2012.

06.022 **Sarcoplasmic Reticulum Calcium ATPase (SERCA) Proteolysis by Matrix Metalloproteinase-2 Results in Hypertension-induced Morphofunctional Vascular Alterations**. Mello MMB, Neves VGO, Pernomian L, Parente JM, Rocha EV, Silva PHL, Castro MM FMRP-USP, Dpt of Pharmacology, Ribeirão Preto, Brazil

Introduction: Increased activity of matrix metalloproteinase (MMP)-2 contributes to vascular smooth muscle cells (VSMCs) migration and proliferation as well as extracellular matrix proteolysis, thus resulting in hypertension-induced vascular remodeling and dysfunction. Many intracellular proteins, such as calponin-1, are also proteolyzed by MMP-2, thus contributing to switch the phenotype of VSMCs from contractile to synthetic to contribute to remodeling. Therefore, MMP inhibitors, such as doxycycline in subantimicrobial doses, ameliorate hypertension-induced vascular remodeling and dysfunction. In myocardial ischemia and reperfusion injury, MMP-2 proteolyzes the sarcoplasmic reticulum calcium ATPase (SERCA), thus impairing contractile function. SERCA activity can be also reduced in the arteries of hypertensive animals. The hypothesis is increased activity of MMP-2 contributes to proteolyze SERCA in aortas during hypertension, thus causing defect in its activity, calcium accumulation and aortic remodeling and dysfunction. Method: Male Sprague-Dawley rats were submitted to the two kidney-one clip (2K-1C) model of hypertension and treated with doxycycline (Doxy, 30mg/kg/day) by gavage from the third to seventh day post-surgery. Control rats were submitted to sham surgery. Systolic blood pressure (SBP) was daily measured by tail-cuff plethysmography and after seven days, aortas were processed for gelatin and in situ zymography, SERCA protein levels by Western blot, calcium immunofluorescence using Rhod-2AM, morphological analysis by hematoxylin and eosin mark, Ki-67

immunofluorescence, vascular reactivity to phenylephrine and acetylcholine and ATPase (SERCA) activity assay. Statistical analysis was done by two-way ANOVA followed by Tukey post-test. The Ethics Committee for Animal Research of the Ribeirao Preto Medical School approved all protocols (122/2019). **Results:** Interestingly, 2K-1C rats had increased SBP vs. Sham groups (160,363 ± 2,980 vs. 119,480 ± 1,719), as our group described in previously studies, and Doxy did not reduce it (n=9; p<0.05). Meanwhile, MMP-2 activity was increased in the aortas of 2K-1C rats (vs. controls; p<0.05, n=5-8) and it was reduced by Doxy (n=5-8; p<0.05). SERCA proteolysis was increased in the 2K-1C aorta (n=4-8; p<0.05 vs. controls) and Doxy prevented it (0. 49±0. 07 2K-1C+Doxy vs 1. 42±0. 42 2K-1C). In addition, the activity of SERCA was reduced in the 2K-1C vs. controls (n=5-8; p=0.0523) and Doxy seems to ameliorate it. Cytosolic calcium trended to increase in 2K-1C aorta (n=3; p=0. 08) and Doxy decreased it (n=3; p<0.05). Calcium accumulation results in VSMC proliferation and vascular remodeling. Cross sectional area and the immunofluorescence of Ki-67 were increased in aortas of hypertensive rats vs. controls (n=3-4; p<0.05) and Doxy decreased cell proliferation (n=5; p<0.05). The 2K-1C rats also showed increased arterial contraction in response to phenylephrine (n=5-6; p<0.05 PD2) and impaired relaxation in response to acetylcholine (n=4-6; p<0.05 PD2; p=0. 06 Emax.). Treatment with Doxy seems to prevent this effect (n=4-6; p=0. 06 Emax). **Conclusions:** Increased MMP-2 activity seems to reduce the levels and activity of SERCA in aortas of hypertensive rats and contributes to cause structural and functional vascular alterations. These effects were ameliorated in the presence of Doxy, an MMP inhibitor. **Financial Support:** CAPES, CNPq and FAPESP.

06.023 **7-Hydroxycoumarin Induces Hypotension and Vasorelaxation in SHR Rats: A Promising Molecule for the Treatment of Hypertension**. Silva ILP[1,2], Jesus RLC[1,2], Brito DS[1], Lima GBC[1], Silva LB[1], Araújo FA, Moraes RA, Alves QL, Silva DF [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Health Sciences Institute, Salvador, Brazil; [2]FF-UFBA PPG in Pharmaceutical Sciences, Salvador, Brazil

Introduction: Hypertension remains the most prevalent risk factor for cardiovascular diseases (CVD). However, an important portion of the population has uncontrolled blood pressure levels despite the use of different classes of antihypertensive drugs. Thus, it is necessary to search for new therapeutic strategies to reduce the morbidity and mortality induced by hypertension. Coumarins exhibit a wide variety of biological effects. In previous studies carried out by our research group, the 7-hydroxycoumarin (7-HC) had promising cardiovascular effects in normotensive rats. This study aimed to investigate the vascular and cardiac effects of 7-HC in vivo and *in vitro* approaches in an animal model with hypertension. **Methods:** Male SHR rats (300-350g) were euthanized, and the superior mesenteric artery was isolated for subsequent vascular reactivity studies. In another set of experiments, SHR rats were fitted with polyethylene catheters inserted into the lower abdominal aorta and inferior vena cava through the left femoral artery and vein, respectively, to record blood pressure and heart rate. 7-HC was intravenously administered at 2. 5; 5; 10, and 20mg/kg. All surgical and experimental procedures were approved by the local Animal use and care ethics committee – CEUA/ICS/ UFBA (130/2017). **Results:** In studies performed with superior mesenteric artery rings precontracted with phenylephrine (Phe,1µM), 7-HC (10-9 - 3x10-4M) induced an endothelium-independent vasorelaxation effect. Furthermore, 7-HC induced vasorelaxation, which was significantly attenuated in artery rings precontracted with depolarizing tyrode solution with KCl 80mM. These results suggest a moderated participation of potassium channels in effect induced by 7-HC. Additionally, in the presence of 4-aminopyridine (1mM, delayed rectifier K+ channels blocker), TEA (1mM, large-conductance calcium-activated potassium channels – BKca blocker), or glibenclamide (10µM, ATP-sensitive potassium channels blocker), the 7-HC-induced effects were significantly attenuated. However, no change was observed in the relaxation induced by 7-HC in the presence of BaCl2 (30µM, inward rectifier K+ channels -Kir blocker). Furthermore, 7-HC inhibited the vasoconstriction induced by CaCl2 in depolarizing nominally Ca2+-free medium, indicating that the vasorelaxation seems to involve inhibition of Ca2+ influx through L-type voltage-dependent calcium channels (Cav type-L). In addition, 7-HC (3x10-5 or 3x10-4M) significantly reduces phenylephrine and caffeine-induced calcium mobilization by the reticulum. This result suggests the participation of calcium channels in 7-HC relaxation. Furthermore, preincubation of artery rings with 7-HC (10-4) reduces responsiveness to α1-adrenergic agonists (Phe, 10-10 to 3x10-5M) and increases responsiveness to muscarinic agonists (Ach, 10-11 to 3x10-6M) and nitric oxide donor (SNP, 10-11 to 3x10-6M). In another set of experiments, 7-HC reduced blood pressure in non-anesthetized SHR rats. **Conclusion:** Our results suggest that 7-HC induces vasorelaxation artery endothelium-independent way, probably involving

potassium channels activation (KIR, KATP, and BKCa) and reducing the calcium influx. In addition, 7-HC reduced blood pressure, becoming a promising molecule for the treatment of hypertension. **Financial Support:** CAPES, CNPq, FAPESB and UFBA.

06.024 **NONO2P**, **NO Donor**, **Induces Vascular Tolerance Involving Endothelium-Derived Prostanoids**. Moraes RA[1], Araujo FA[1,2], Brito DS[1,3], Lima GBC[1,3], Sá DS[4], Silva CDS[4], Rocha ZN[3], Silva DF[1,2,3] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Bioregulation Department, Salvador, Brazil, [2] FIOCRUZ, Gonçalo Moniz Institute, Salvador, Brazil, [3]UFBA, Salvador, Brazil, [4]IFBA, Salvador, Brazil

Introduction: Cardiovascular diseases are the principal cause of death worldwide. Additionally, the decreased synthesis and/or bioavailability of the nitric oxide (NO) are linked with several cardiovascular diseases, such as arterial hypertension and coronary diseases. Due to the endothelial dysfunction that occurs in these pathologies, NO donors have been developed to replace the deficiency in endogenous NO, although can exhibit toxicity or vascular tolerance. In this way, the aim of this study was to investigate whether NONO2P, a new NO donor, can induce vascular tolerance. **Methods:** Male Wistar rats were euthanized, and the superior mesenteric artery was isolated for recordings of isometric tension. Tolerance to NONO2P was evaluated by incubating the endothelium-intact superior mesenteric artery rings previously with NONO2P at 1µM (EC100) for 15, 30, or 60 min. After 80 min of washing, the rings were contracted with Phe 1µM. After 40 min, a cumulative concentration-response curve to NONO2P (from 10-13 to 3x10-6M) was performed. It was approved by the Ethics Committee on Animal Use from the Federal University of Bahia (CEUA/UFBA nº 4169290420). **Results:** Cumulative administration of the NONO2P (10-13 to 3x10-6M) induced endothelium-independent vasorelaxation (Emax:111. 51 ± 2. 31%; pD2: 8. 51 ± 0. 08, n=9) in pre-contracted rings with phenylephrine (Phe,1µM). Preincubation with NONO2P for 15 or 60 min was not enough for NONO2P to induce tolerance in the arteries rings. However, exposure to NONO2P for 30 min induced tolerance in the tissue and a concentration-response curve of NONO2P was significantly rightward shifted. Interestingly, the combined preincubation with NONO2P and indomethacin (10µM) for 30 min significantly restored the NONO2P-induced vasorelaxation, indicating that the inhibition of the vasoconstrictors molecules production derived from cyclooxygenase (COX), such as prostaglandin H2 (PGH2) and thromboxane A2 (TXA2), can recover the relaxation promoted by NONO2P. **Conclusion:** These data indicate that NONO2P tolerance develops on exposure of vascular rings preincubated for 30 min and is probably related to endothelium-derived prostanoids. However, NONO2P does not induce vascular tolerance when preincubated by 15 or 60 min. NONO2P is a promising molecule as a new possible therapeutic alternative for the treatment of cardiovascular diseases. **Financial Support:** CAPES, FIOCRUZ-BA, PGBSMI and FAPESB.

07. Endocrine, Reproductive and Urinary Pharmacology

07.001 **Changes in Estrous Cyclicity and Libido on Females Rats Exposed to Aripiprazole**. Angelo ABS[1], Silva AGG[1,2], Moura MJN[1,2], Pereira AKH[1], Felix RGS[1], Santos CCA[1], Pereira MLS[1], Silva ALS[1], Freire LHF[1], Rozza AL[3], Borges CS[1,2] [1]CCBS-UFERSA, Lab of Tissue Biology and Developmental Toxicology, Mossoró, Brazil, [2]UERN, Multicenter Graduate Program in Biochemistry and Molecular Biology, Mossoró, Brazil, [3]IBB-Unesp, Dept Structural and Functional Biology, Botucatu, Brazil

Introduction: Aripiprazole is an antipsychotic/antidepressant that acts on dopaminergic, serotonergic and noradrenergic receptors. Due to its broad spectrum of action, this drug is indicated for the most diverse treatments, including as an adjuvant for mental disorders. These groups of drugs are also known to have an impact on reproduction. However, little is known about the action of dopamine antagonist drugs on the female reproductive system. In this way, the present study aimed to evaluate the possible impacts of exposure to different doses of aripiprazole on the female reproductive system, with emphasis on estrous cyclicity and libido. **Methods:** Adult female Wistar rats (n=11/group) from control group (CTRL), group treated with 0. 3mg/kg (EXP1), 3. 0mg/kg (EXP2) 6. 0mg/kg (EXP3) of aripiprazole were treated during 15 days and the estrous cycle of the rats was monitored. After the end of the treatment, in the first estrus, six female rats/group were weighted and euthanized by decaptation. Blood samples were collected to hormonal levels. Vital organs (kidney, adrenal, heart, liver, brain, pituitary and thyroid) were collected and weighed. The ovaries and uterus were collected, weighed and fixed for further histopathological processing. The remaining females (n=5/group) were used to

evaluate sexual behavior performance. Ethics Committee (UFERSA-23091. 014949/2019-90). Statistical analysis: ANOVA (P<0.05). **Results:** No alterations were observed in the final body weight of the rats exposed to different doses of aripiprazole, as well as no alterations in the absolute and relative weights of reproductive and vital organs, when compared to the CTRL group. However, when compared between the experimental groups, the relative weight of the pituitary was significantly increased (p<0.05) in the EXP1 group (0. 07+0. 01mg/g) in relation to the EXP2 group (0. 04+0. 01mg/g). The evaluation of the estrous cycle showed a significant decrease in the number of estrus in the EXP3 group (2. 4+0. 5) when compared to the CTRL group (5. 2+0. 7). On the other hand, when performing sexual behavior, the only group that showed a significant reduction in relation to the CTRL group was the EXP1 group (62% x 34%; p<0.05). **Conclusion:** The exposure to aripiprazole promoted impairment on female cyclicity and libido in this experimental model. More studies are being carried out to assess the extent of these alterations. **Financial Support:** PIVIC UFERSA and UFERSA/PROPPG (grant number 23091. 014593/2019-02).

07.002 **Estrous Cycle and Gonadal Histology of Female Rats Chronically Submitted to Different Diets and Exercise Protocols**. Pereira AKH[1], Gomes FTS[2], Santos CCA[1], Felix RGS[1], Angelo ABS[1], Moura MJN[1,3], Silva AGG[1,3] , Fonseca IAT[2], Borges CS[1,3] [1]CCBS-UFERSA, Lab of Tissue Biology and Developmental Toxicology, Mossoró, Brazil, [2]CCBS-UFERSA, Multicenter Graduate Program in Physiological Sciences (PPGMCF), Mossoró, Brazil, [3]UERN, Multicenter Graduate Program in Biochemistry and Molecular Biology, Mossoró, Brazil

Introduction: The search for a healthy life makes new studies to be designed combining different types of diets and physical activity. In this context, is important to be aware of the fact that the female reproductive system is directly dependent on the amount of cholesterol produced and ingested throughout life. Despite that, there are few studies that assess the extent of the long-term impacts from that perspective. Thus, we aimed to investigate the possible impacts of different lipidic diets with or without physical activity during a period of 180 days on reproductive morphological parameters of adult wistar rats. **Methods:** Adult female Wistar rats were divided (n=8/group) into standard chow group (control, 10% lipid and 20% protein content) without physical exercise (sedentary) - SDCNT; standard chow with physical exercise group - EXCNT; cashew nut group (diet enriched with vegetable fat from cashew nut, 40% lipid and 20% protein content) sedentary - SDCSC; cashew nut group with exercise - EXCSC; lard group (diet enriched with fat of animal origin based on lard, 40% lipid and 20% protein content) sedentary - SDBHP and lard group with physical exercise - EXBHP. The physical exercise groups were submitted to 30 minutes of daily physical exercise, following the running protocol on the treadmill (8m/min for 5 minutes, 12m/min for 20 minutes and 8m/min for the last 5 minutes, during the experimental protocol). The treatment occured during 180days and in the last 15 days, the estrous cycle of the rats was monitored. After that, in the first estrus, the rats were euthanized for collection, weighing and fixation of the ovaries and uterus, followed by further histopathological analysis. Ovaries and uterus were fixed in formaldehyde, processed and stained with eosin-hematoxylin for histopathological (qualitative) analysis. The study was approved by Ethics Committee (007/19 and 10006-2021). **Results:** There were no statistical differences observed in the body weight of the animals and also in the uterine and ovarian absolute and relative weights (p>0.05). In addition, no alterations were observed in the number of estrous cycles and in the duration of these cycles between the groups (p>0.05). However, when each phase was analyzed individually, a higher frequency of the diestrus phase was seen in the EXCSC group (54. 81+6. 41) when compared to the SDBHP group (25. 96 + 8. 09). In the histopathological evaluation of the ovaries and uterus, no significant changes were identified. All groups had well-defined and characteristic gonads and uterus. **Conclusion:** There was no deleterious effects caused by the different types of high-fat diets and physical activity in the on the female reproductive system. On the one hand, this result opens new perspectives for studies on the impacts of the intake of different types of fat on health and fertility. **Financial Support:** PIBIC (CNPq) and PIVIC UFERSA Scholarship.

07.003 **Three Months Exposure to Different Lipidic Diets and Physical Exercises: A Look at the Female Reproductive System**. Santos CCA[1], Gomes FTS[2], Pereira AKH[1], Felix RGS[1], Angelo ABS[1], Moura MJN[2], Silva AGG[2], Fonseca IAT[2], Borges CS[1] [1]UFERSA, [2]UERN

Introduction: The consumption of foods rich in fat and sugar has been increasing in recent years. In addition, the sedentary lifestyle has progressively impacted the increase in obesity and chronic diseases. Obesity is considered

a global public health problem and different approaches have been the focus of studies to reduce the impact of weight gain, especially with regard to reduced fertility. It is also known that obesity directly impairs reproduction, altering hormone levels and gamete production. Thus, we aimed to evaluate and compare the possible beneficial or deleterious effects of physical training associated with diets rich in cashew nut fat or lard in reproductive systhem of adult rats. **Methods:** Adult female Wistar rats were divided (n=8/group) into standard chow group without physical exercise (sedentary) - SDCNT; standard chow with physical exercise group - EXCNT; cashew nut group (diet enriched with vegetable fat from cashew nut, 40% lipid and 20% protein content) sedentary - SDCSC and exercise - EXCSC; lard group (diet enriched with fat of animal origin based on lard, 40% lipid and 20% protein content) sedentary - SDBHP and exercise - EXBHP. During 90 days, the food was offered ad libitum, and consumption was monitored. The physical exercise groups were submitted to 30 minutes of daily physical exercise. In the last 15 days, the estrous cycle of the rats was monitored and after that, in the first estrus, the rats were euthanized for collection, weighing and fixation of the ovaries and uterus, followed by further histopathological analysis. The study was approved by the Ethics Committee of UERN 007/19 and UFERSA (PIA10006-2021). **Results:** Feed consumption showed a significant difference ($p<0.05$) between groups SDCSC (14. 23+0. 83), EXCSC (16. 54+0. 60), SDBHP (13. 69+0. 47), EXBHP (16. 56+0. 58) when compared to both EXCNT (22. 15+0. 41) and SDCNT (19. 19+0. 68). The final body weight of the rats revealed a significant increase ($P<0.5$) in the weight of the exercise groups when compared to the sedentary groups, except the SDCSC group compared to the EXCNT group. The uterine weight of the SDCSC group was also significantly lower compared to the EXBHP group. There was no alterations on ovary weight and histology ($p>0.05$). Uterine histology revealed the presence of leukocyte infiltrates, however, this finding could also be observed in the SDCNT and EXCNT groups. As for cyclicity, it was observed that there was a lower percentage ($p<0.05$) of proestrus in the EXCSC group (7. 80+2. 07) in relation to the SDCNT group (19. 94+4. 03), but not directly impacted the size and number of estrous cycles when compared between groups ($p>0.05$). **Conclusion:** Therefore, it can be concluded, based on this experimental model, that both diets do not have a direct impact on female reproduction. **Financial Support:** PIBIC (CNPq) and PIVIC UFERSA Scholarship.

07.004 *Spirulina platensis* **Supplementation Prevents Histomorphometric Changes in the Adrenal Gland of Wistar Rats submitted to Progressive Strength Training**. Francelino DMC, Ferreira PB, Barros BC, Diniz AFA, Lacerda Júnior FF, Alves AF, Silva BA UFPB

Introduction: Physical exercise improves self-esteem and the risk of developing chronic diseases in women (REZENDE et al., Braz. J. Hea. Rev, v. 3, 2020). However, if misdirected, it can lead to an increase in oxidative stress in the adrenal cortex, resulting in a stimulation of cortisol production and inhibition of sex hormones (PRASAD, R. et al., J. Endocrinol, v. 221, 2014). In this context, the objective of this study was to evaluate the histomorphometric alterations induced by progressive strength exercise (PTT) and/or supplementation with *Spirulina platensis* (SP), algae with antioxidant activity, in the adrenal gland of female Wistar rats. **Methods:** Wistar rats (150-200g) were divided into 7 groups: group supplemented with saline solution (0. 9%) (GS) and supplemented with SP at doses of 50 (GSP50) and 100 mg/kg (GSP100), adapted only group (GC, control), group trained for 8 weeks (GT) and trained and supplemented with SP at a dose of 50 (GT50) and 100 mg/kg (GT100). The adrenal gland samples were isolated and fixed in 10% buffered formaldehyde solution, embedded in paraffin, cut (3 μm), mounted on histological slides and observed in the cortex the glomerulosa, fasciculate and reticulate layers, in addition to its medullary layer. Results were expressed as mean and standard error of mean (e. p. m.), statistically analyzed using one-way ANOVA followed by Tukey's post-test. **Results:** Regarding the glomerulosa layer, no alteration was observed through supplementation or strength training, as well as in the association of both, GSP50 (0. 4 ± 0. 01), GSP100 (0.18 ± 0. 02), GT (0.18 ± 0. 01), GT50 (0.18 ± 0. 01). 0. 02) and GT100 (0.12 ± 0. 006), when compared to GS (0.17 ± 0. 008). In the fasciculate layer, in the groups GSP50 (2. 0 ± 0. 04) and GSP100 (2. 4 ± 0.17) there was no change, but in relation to the GT (2. 6 ± 0. 08) there was an increase and in the GT50 (1. 8 ± 0. 02) and GT100 (1. 8 ± 0.1) decrease of this parameter in relation to GS (2. 1 ± 0. 04). In the evaluation of the lipid degeneration area of the fasciculata layer, suggestive of the presence of cortisol, an increase in the number of these vacuoles can be noted in GSP100 (35. 5 ± 0. 5) and GT (49. 8 ± 2. 0) compared to GS (17. 8 ± 1. 0) and supplementation in the GT50 (15. 2±0. 8) and GT100 (27. 2 ± 0. 5) groups decreased these values. In the reticulous layer, there was a decrease in the GSP100 (0. 26 ± 0. 03), GT (0. 7 ± 0.

01), GT50 (0. 7 ± 0. 006) and GT100 (0. 71 ± 0. 02) group compared to the GC (0. 86 ± 0.05). Regarding the analysis of the medullary area, only the GSP100 (2. 0 ± 0. 08) decreased this parameter compared to the GS (2. 3 ± 0. 2). In the GT (2. 0 ± 0.05), GT50 (2. 5± 0. 2) and GT100 (2. 4 ± 0. 09) groups, no alteration was observed in the area of the medullary layer compared to the CG (2. 3 ± 0. 2). **Conclusion:** It is concluded that changes in the adrenal gland of trained rats are suggestive of decreased production of sex hormones, which may be related to disorders in the female reproductive system such as late menarche and amenorrhea, which is associated with the increased presence of cortisol storage deposits, which contributes to the exacerbation of oxidative stress. In addition, the synergism of both training and supplementation indicates a likely reduction in cortisol production, preventing the deleterious effects resulting from increased oxidative stress. However, to prove the hypotheses, studies on the dosage of these hormones are needed. **Financial Support:** CAPES, CNPq, PPgPNSB/UFPB. CEUA/UFPB- 0211/2014.

07.005 **Targeting NOX2 Ameliorates Cyclophosphamide-Induced Bladder Injury Via Attenuation of Urothelial Barrier Dysfunction**. Garcia MO[1,2], Piccoli BS[1,2], Passos GR[2], Monica FZ[2], Antunes E[2], Oliveira MG[2] [1]PUCamp, Campinas, Brazil, [2]FCM-Unicamp, Dept of Translation Medicine (Pharmacology area), Campinas, Brazil
Background: Bladder inflammation induced by cyclophosphamide (CYP) in rodents is a well-established experimental model that shares many features common to the cystitis occurring in patients. After systemic administration, CYP is partly metabolized to acrolein, which accumulates in the bladder resulting in inflammation and loss of barrier integrity. Morphological changes in the urothelium barrier are often accompanied by urinary symptoms, including bladder overactivity, and is also associated with the accumulation of reactive oxygen species (ROS). NADPH oxidases (NOX) generate ROS that are critical in regulating a variety of cell functions. NOX2-derived oxidants are crucial for host defense, but also have an important role in inflammation and injury. The selective NOX2 inhibitor, GSK2795039, exhibit a strong anti-oxidative activity1. This study aimed to investigate the contribution of NOX2 to urothelial barrier dysfunction induced by CYP in mice. **Methods:** All experimental protocols were approved (CEUA-UNICAMP, No 58291-1). Female C57BL/6 mice (10 weeks) were divided into 3 different groups, named: 1) Control: saline injection (1 mL/kg, ip) followed by an injection of vehicle (Cremophor® 15% in saline, ip) after 1, 8 and 16 h; 2) CYP: injection of CYP (300 mg/kg, ip) followed by an injection of vehicle after 1, 8 and 16 h; 3) CYP+GSK: injection of CYP (300 mg/kg, ip) followed by an injection of the selective NOX2 inhibitor GSK2795039 (5 mg/kg, ip) after 1, 8 and 16 h. After 24h of CYP injection, bladders were excised and destined to different experiments, as listed: i) bladder morphometric, ii) TUNEL apoptosis assay and iii) RT-PCR for genes involved in tight-junction (TJ) structure, including junction adhesion molecules (JAM-A), claudins (CLDN2, CLDN4), occludin (OCLN) and zonula occludens-1 (TJP1). Data is expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA, followed by Bonferroni. $P<0.05$ was considered significant. **Results:** Bladder weight was higher in CYP group (55±2. 3 mg) in relation to Control (20±0. 7 mg, $p<0.05$) and CYP+GSK groups (35±1. 2 mg, $p<0.05$). Histomorphometry revealed that CYP exposure caused severe edema in both detrusor smooth muscle and submucosal layers, with increased thickness ($p<0.05$ vs Control). In CYP+GSK group, a mild edema was observed ($p<0.05$ vs CYP). The thinning of the bladder urothelium was marked in CYP group ($p<0.05$ vs Control). Interestingly, the urothelium of CYP+GSK groups remained almost intact. Apoptosis (% TUNEL positive) of urothelial cells was higher in CYP (6. 89±1. 6%) than in Control (0.15±0.15%, $p<0.05$) and CYP+GSK groups (2. 65±1. 2%, $p<0.05$). Expression of OCLN was reduced by about of 92% ($p<0.05$ vs Control). Conversely, ZO-1 increased by about of 80% in CYP group ($p<0.05$ vs Control). In CYP+GSK group, both ZO-1 and OCLN levels remained close to Control ($p<0.05$ vs CYP). No changes were observed for JAM-A, CLDN2 and CLDN4 expression. **Conclusion:** GSK2795039 treatment preserved the urothelial layer integrity in CYP-induced cystitis and reduced the apoptosis of urothelial cells. Additionally, changes in ZO-1 and OCLN, mRNA were both normalized. Many studies demonstrated that increase in epithelial paracellular permeability by ROS is associated with a disruption of TJ2. NOX2 activity may be an important modulatory mechanism for the urothelium TJ disruption after injury, which will be further explored. **References:** 1. Hirano et al, Antioxid Redox Signal. 2015;23(5):358-74; 4. Rao, Front Biosci. 2008;13:7210:7226.

07.006 **Impairment of Male Reproductive System after Subchronic Exposure to Aripiprazole**. Felix RGS[1], Santos CCA[1], Pereira AKH[1], Angelo ABS[1], Pereira MLS[1], Moura MJN[1,2], Silva AGG[1,2], Rozza AL[3], Borges CS[1,2] [1]CCBS-

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Introduction: Aripiprazole has high affinity dopamine and also serotonin and noradrenaline receptors, that could directly influence the reproductive function. However, there are few reports of the aripiprazole effects on male reproductive system and fertility. Thus, we aimed to evaluate the impact of subchronic aripiprazole exposure on male reproductive system, with emphasis on sperm parameters and fertility. **Methods:** Adult male Wistar rats were divided (n=12/group) into control group (CTRL, treated with vehicle solution) and group treated with 3. 0mg/kg (EXP1) and 6. 0mg/kg of aripiprazole diluted in vehicle (EXP2). The animals were treated during 28 days. After the end of the treatment, Seven animals/group were weighted and euthanized by overdose of anesthetic xylazine/ketamine. Vital organs (kidney, adrenal, heart, liver, brain, pituitary and thyroid) were collected and weighed. The reproductive organs (testis, epididymis, ventral prostate, full and empty seminal vesicle) were also collected and weighed. The right testis and epididymis were fixed in modified Davidson's solution (MDF) to morphometry assay. The left epididymis was removed and the sperm sample was used to determine the sperm motility and count. The remained animals (n=5/group) were used to perform sexual behavior and fertility test. The study was approved by the UFERSA Ethics Committee (23091. 014948/2019-20). Statistical analysis: ANOVA or Kruskal Wallis ($P<0.05$). **Results:** There is no alterations observed in the final body weight of the rats exposed to different doses of aripiprazole. Considering the absolute and relative weights of vital organs, there is also no alterations when compared to the CTRL group. However, when compared the reproductive organ weights there was a significant increase in the full seminal vesicle from EXP2 group when compared to CTRL group ($p<0.05$). The morphometry of testis sections showed no significant difference in both parameters, height of the epithelium and diameter of the seminiferous tubule when compared to the CTRL group. The evaluation of the sperm motility showed a significant reduction on mobile sperm with progressive moviment from EXP1 compared to CTRL group (57. 7% x 37. 7%; $p<0.05$). After performed the sexual behavior, it was observed that the number of mounts before the ejaculation was significantly decreased in EXP1 group when compared to the CTRL group (16. 0 + 3. 2 x 6. 0 + 1. 5; $p<0.05$). On the other hand, evaluating the fertility test, the EXP2 showed a significant reduction on fertility potential compared to CTRL group (83. 0+6. 9 x 93. 0+2. 4; $p<0.05$). **Conclusion:** Therefore, subchronic exposure to aripiprazole in this experimental model impairs the male reproductive system, mainly in male sperm quality and fertility, without causing systemic intoxication effects. **Financial Support:** PIBIC-CNPq and PROPPG (grant number 23091. 014593/2019-02).

07.007 **Analysis of Phenotypic and Metabolic Changes in Neurolysin (Nln-/-) Knockout Animals in a Diet-Induced Obesity Model**. Caprioli B, Gewehr MCF, Eichler RA, Ferro ES USP

Introduction: First identified as “Neurotensin-degrading enzyme” (Checler, 2018 et. al), Neurolysin (Nln), is an oligopeptidase with pharmacological action and, possibly, actions on angiogenesis, tumor growth, and sepsis. In a previous study of our group (Cavalcante, 2014 et al.) the Nln role on energetic metabolism was observed by a slight decrease in body mass gain, and by an increased glucose uptake and insulin sensitivity. **Objectives:** Our intention is to identify the role of Neurolysin in the energy metabolism by inducing obesity in Nln-/- and wild type (WT) C57BL/6 mice. **Methods:** Groups of animals four weeks old started to be fed, by eight weeks, either standard diet (SD) or high-fat diet (HFD) supplemented with condensed milk. Body weight was determined weekly, while fasting glucose and insulin levels were determined together with insulin- tolerance test (ITT) and glucose tolerance test (GTT) after six weeks of diet. Weighing and storage of liver tissue and gonadal, retroperitoneal and inguinal adipose tissues. Real- time PCR (qPCR) was used to determine the relative expression level of specific genes related to lipid and adipogenesis regulation on adipose tissues, and the enzymes IDE (insulin degrading enzyme), ECA1(Angiotensin converting enzyme), NEP (Neutral endopeptidase), POP (Prolil oligopeptidase) and DPP4 (Dipeptidil peptidase 4). Analyzes for statistical purposes of mass gain were performed by "two-way ANOVA" and Sidak test. For the analysis of glucose, insulin, tissue mass and gene expression tests, two-way ANOVA and Tukey's test were performed. **Results:** The HFD caused, as expected, both in wild type males and females (n=5-8) and in Nln-/-(n=5-8) marked body mass gain. Noteworthy, this body mass gain were more pronounced in Nln-/- animals. Regarding glucose tolerance, Nln-/- animals fed with SD showed an improved glucose uptake. However, this effect was lost in Nln -/- males fed with HFD as they showed an

intolerance profile, as seen in HFD wild type animals. On the other hand, in females animals, the HFD worsened the glucose uptake in wild type animals. Although, the Nln-/- protected the females animals from the HFD effects on glucose uptake. Greater insulin sensitivity was observed in SD Nln-/- males fed animals, while HFD Nln-/- males fed animals acquired some insulin resistance. In the SD male Nln-/- genotype the IDE enzyme is increased and in this same HFD fed genotype the F4-80, CD11-c and Pparα genes were expressed more often. Meanwhile, in the SD female Nln-/- genotype the PGC1α gene is increased and in this same genotype, but in HFD fed animals the FAS, FABP4, F4-80, LPL, CD36, CD206, CD11-c, Pparα and enzymes DPP4 and ECA1 are expressed more often. **Conclusion:** It was possible to observe that the Neurolysin plays a role in glucose and insulin metabolism, since we confirmed that male knockout animals in SD glucose uptake more effectively and are more sensitive to insulin. We continue to investigate the role of Neurolysin oligopeptidase in energy metabolism by inducing obesity in control and Nln-/- animals and to study the expression of genes related to this disease and inflammatory genes. Knowing more deeply the role of oligopeptidase in energy metabolism through the presence of intracellular peptides that would be broken by the enzyme, we will also advance the knowledge of the functions of these peptides in the body. The animals were used and maintained with a certificate approved by the CEUA ICB and standards established by the CONCEA with the protocol nº 4112010621.

07.008 **The Non-Selective Inhibitors for the Multidrug Resistance Proteins, MK571 and Probenecid Potentiated the Relaxation Induced by cAMP- and cGMP-Increasing Substances in Isolated Bladder from Healthy Pig**. Gomes ET, Passos GR, Britto-Junior J, Antunes E, Mónica FZ Unicamp, Dpt of Pharmacology, Campinas, Brazil

Introduction: Cyclic adenosine monophosphate (cAMP) in the main mediator that promotes bladder relaxation during the storage phase. The role of cyclic guanosine monophosphate (cGMP) in inducing relaxation seems to be less relevant, although, drugs that increase cGMP can improve the lower urinary tract symptoms. The intracellular concentration of cAMP and cGMP is controlled by their rate of formation and degradation through the actions of phosphodiesterases (PDEs) and/or the multidrug resistance proteins (MRPs), which pump cyclic nucleotide out of the cells or into the cells sub-compartments, thus reducing the cytosolic levels of cyclic nucleotides. As the functional role of MRPs, mainly MRP4 and MRP5, is less studied than PDEs in the bladder, this study is aimed to evaluate the *in vitro* effect of MK571 and probenecid, which are tools commonly used as MRPs inhibitors of cyclic nucleotides, in isolated bladder from pigs. **Methods:** The detrusor was isolated from a 12-week-old Large White pig (female and male). Concentration-response curves (CRCs) to fenoterol (1 nM – 100 µM); mirabegron (1 nM – 100 µM); forskolin (1 nM – 100 µM); BAY 41-2272 (1 nM - 100 µM); sildenafil (1 nM – 100 µM) and tadalafil (1 nM – 100 µM) were carried out in the absence (control) and in presence of MK571 (20 µM) or probenecid (3 mM) in tissues pre-contracted with carbachol (3 µM). In some experiments, CRCs to MK571 (1 nM – 100 µM) and probenecid (1 µM – 10 mM) were also carried out. The potency (pEC50) and maximal response values (Emax) were determined. Data are represented as mean ± SD, N=number of animals. Unpaired t-test was used and $P<0.05$ was considered significant. All protocols were approved by the ethics committee (CEUA/UNICAMP: 5585-1/2020). **Results:** In tissues pre-contracted with carbachol, MK571 and probenecid produced relaxations of, approximately, 30% and 26%, respectively. Fenoterol (N=6), mirabegron (N=8), sildenafil (N=10) and tadalafil (N=8) produced concentration-dependent relaxations. The pre-incubation with MK571 produced significant ($P<0.05$) leftward shifts of, approximately, 2-, 3-, 1. 7- and 4. 4-fold, respectively. The relaxations induced by forskolin (N=8) and BAY 41-2272 (N=5) were unaffected by MK571. In tissues pre-incubated with probenecid a significant ($P<0.05$) potentiation of, approximately, 5-, 2. 4-, 7-fold in the relaxations induced by mirabegron (N=6), sildenafil (N=3) and tadalafil (N=5) were observed. The maximal response values did not differ in the presence of both MK571 or probenecid. **Conclusion:** The cyclic nucleotide inhibitors, MK571 and probenecid potentiated the relaxing responses induced by cAMP- or cGMP-increasing substances, thus showing that cGMP and/or cAMP accumulated in the cytosolic compartment of the smooth muscle cells. More studies are needed in order to assess the cellular localization of MRP4 and MRP5.

07.009 **b1- and b1/b2-Adrenergic Receptor Antagonists Block 6-Nitrodopamine-Induced Contractions on the Rat Isolated Epididymal Vas Deferens**. Amorim AC, Lima Silva AT, Britto-Júnior J, Campitelli RR, Fregonesi A, Mónica FZ, Antunes E, De Nucci, G FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil

6-nitrodopamine (6-ND) is a novel catecholamine released from vascular tissues such as human umbilical cord vessels, C. carbonaria aorta and rat vas deferens. It has been caracterized as a major endogenous modulator of the contractility in the rat isolated epididymal vas deferens (RIEVD) and considered to be the main peripheral mediator of the emission process. The use of selective and unselective b-adrenergic receptor antagonists have been associated with ejaculatory failure. Here, the effects of selective b1- and b1/ b2- adrenergic receptor antagonists on RIEVD contractions induced by 6-ND, dopamine, noradrenaline, adrenaline and EFS were investigated. **Methods:** After euthanasia was performed by isoflurane overdose, epididymal portions of vas deferens were removed, surgically dissected (length, 1. 5 cm each) and immediately placed in Krebs-Henseleit's solution (KSH) for the functional studies. The strips were suspended vertically between metal hooks in 10-mL organ baths containing KHS, continuously gassed with a mixture of 95%O2: 5%CO2 at 37°C. Tissues were allowed to equilibrate under a resting tension of 10 mN, and the isometric tension was registered using a PowerLab system. **Results:** The selective b1 adrenergic receptor antagonists atenolol (0.1 and 1mM), betaxolol (1mM) and metoprolol (1mM) and the unselective b1/b2- adrenergic receptor antagonists propranolol (1 and 10mM) and pindolol (10mM) caused significant rightward shifts of the concentration-response curve to 6-ND (pA2 6. 41, 6. 91, 6. 75, 6. 47 and 5. 74; for atenolol, betaxolol, metoprolol, propranolol and pindolol), but had no effect on dopamine-, noradrenaline- and adrenaline-induced contractions. The effects of selective b1- and b1/ b2- adrenergic receptor antagonists at a higher concentration (atenolol 1mM, betaxolol 1mM, metoprolol 1mM, propranolol 10mM and pindolol 10mM) also reduced the EFS-induced RIEVD contractions in control but not in RIEVD obtained from L-NAME-treated animals. The selective b1- adrenoceptor agonist RO-363, the selective b2- adrenoceptor agonist salbutamol and the selective b3-adrenoceptor agonist mirabegron, up to 300 mM, had no effect on the RIEVD tone. **Conclusion:** The results demonstrate that b1- and b1-/ b2- adrenoceptor receptor antagonists act as 6-ND receptor antagonists in RIEVD, further confirming the main role of 6-ND in the RIEVD contractility. Keywords: Ejaculation disorder, nitrocatecholamines, EFS, L-NAME Competing interests: The authors declare no competing or financial interestsEthical Approval: All experimental protocols were authorized by the Ethics Committee in Animal Use of UNICAMP (CEUA/UNICAMP, protocol numbers 5952-1/2022 and 5831-1/2021). Acknowledgment: The authors thanks CAPES and FAPESP.

07.010 **Role of Advanced Glycation End-Products (AGE) in Bladder Dysfunction in ob/ob Mouse Model of Type 2 Diabetes**. Oliveira AL, Medeiros ML, Ghezzi AC , Mello GC, Monica FZ, Antunes E FCM-Unicamp, Dpt of Pharmacology, Campinas, Brazil

Introduction: Leptin-deficient ob/ob mice are hyperphagic, obese, hyperinsulinemic, and hyperglycemic, and have been widely used as a model for diabetes and obesity1. Excess of advanced glycation end-products (AGE) generation is associated with diabetic diseases2. We recently showed that prolonged methylglyoxal (MGO) intake (a major AGE precursor) induces bladder overactivity in male and female mice3,4. However, little is known about the importance of AGE formation in diabetic bladder dysfunction. Alagebrium chloride (ALT-711) is a thiazolium compound able to prevent the AGE generation since it breaks the covalent bonds formed in the cross-linked proteins, maintaining the protein function5. Here, we explored the role of AGE formation in bladder dysfunction of ob/ob mice by treating the animals with ALT-711. **Methods:** This study was approved by the Animal Use Ethics Committee of UNICAMP (protocol number 5949-1/2022). Female C57BL/6 wild-type (WT) and ob/ob mice (5-week-old) were treated with ALT-711 (1 mg/kg) in the drinking water for 8 weeks, whereas control groups received only filtered water. Urinary behavior assessment test, void spot assay, and urine collection were performed. Urinary and serum AGE levels were measured by fluorescence. Serum and urinary MGO levels were measured by enzyme test. **Results:** Compared with WT animals, ob/ob mice showed significant increases ($p<0.05$) of blood glucose (147 ± 7. 78 and 200 ± 14. 8 mg/dl), serum MGO (1. 1 ± 0.18 and 1. 7 ± 0.15 nmol) and serum AGE levels (2. 0 ± 0. 3 and 3. 9 ± 0. 35 a. u) along with decreased urinary MGO levels (9. 7 ± 0. 60 and 7. 6 ± 1. 02 nmol). Void spot assays in conscious mice revealed significant increases in total void volume and volume per void n ob/ob mice in ob/ob compared with WT mice (130% and 88%, respectively; $p<0.05$). Treatment with ALT-711 in ob/ob mice significantly reduced the serum levels of F-AGE and MGO and decreased the urinary MGO levels. Alagebrium treatment also normalized the volume per void and total void volume. In WT mice, ALT-711 had no effect on any parameter evaluated. **Conclusion:** Alagebrium normalizes the MGO and F-AGE levels and attenuates the micturition dysfunction in ob/ob mice, further confirming an important role of AGE in diabetes-

associated bladder dysfunction. **References:** 1. Fischer, AW, et al., Endocrine Reviews, 41(2), 232–260. 2020. 2. Bellier, J et al., Diabetes Res. Clin. Pract. 148, 200. 2019. 3. Oliveira A. O. et al., EJP. Eur J Pharmacol. 910:174502. 20214. Oliveira A. O. et al., Front Physiol. 28;13:860342. 20225. Desai K, et al., Recent Pat Cardiovasc Drug Discov. 2(2):89-99. **Financial Support:** CAPES (88882. 435315/2019-01)

07.011 **Alpha1-Adrenergic Antagonists Block 6-Nitrodopamine Contractions on the Rat Epididymal Vas Deferens**. Silva Lima AT, Britto-Júnior J, Fregonesi A,, Mónica FZ, Antunes E, De Nucci G Unicamp

Ejaculation is used as a synonym for the external ejection of semen and comprises two phases, namely, emission, which is the ejection into the prostatic urethra of spermatozoa mixed with fluids secreted by the accessory sexual glands through epididymis, ductus deferens, seminal vesicles, and prostate smooth muscles; and expulsion, that is defined as the release of the semen from the urethra by involuntary contractions of the striated perineal muscles (Puppo and Puppo, 2016). 6-nitrodopamine (6-ND) is released from rat isolated vas deferens and modulates electrical-field stimulation (EFS) contractions of the rat isolated epididymal vas deferens (RIEVD, Britto et al., 2021). via a specific receptor which is blocked by tricyclic antidepressants. Here, the effects of selective α1-adrenergic receptor antagonists on RIEVD contractions induced by 6-ND, dopamine, noradrenaline, adrenaline and EFS were investigated. All experimental protocols were authorized by the Ethics Committee in Animal Use of UNICAMP (5746-1/2020 and 5831-1/2021) After euthanasia was performed by isoflurane overdose, epididymal portions of vas deferens were removed, surgically dissected (length, 1. 5 cm each) and immediately placed in Krebs-Henseleit's solution (KSH) for the functional studies. The strips were suspended vertically between metal hooks in 10-mL organ baths containing KHS, continuously gassed with a mixture of 95%O2: 5%CO2 at 37°C. Tissues were allowed to equilibrate under a resting tension of 10 mN, and the isometric tension was registered using a PowerLab system. Doxazosin and tamsulosin (3–10 nM) caused significant rightward shifts of the concentration-response curve to 6-ND, but had no effect on dopamine-, noradrenaline- and adrenaline-induced contractions. Alfuzosin (10 nM) produced rightward shifts on concentration-response curves to all catecholamines. Silodosin (10 nM) and terazosin (100 nM) displaced to the right the noradrenaline, dopamine and adrenaline curves, but higher concentrations of both antagonists (10 0 and 300 nM, respectively) were required to displace the 6-ND curves. The EFS-induced contractions were significantly inhibited only at the concentrations that the α1-adrenergic receptor antagonists caused rightward shifts on the 6-ND concentration-response curves. The inhibition of EFS-induced contractions by doxazosin (10 nM), tamsulosin (10 nM), alfuzosin (10 nM), silodosin (100 nM) and terazosin (300 nM), were not observed in RIEVD obtained from animals chronically treated with L-NAME. This work demonstrates that α1-adrenoceptor antagonists act as 6-ND receptor antagonists in RIEVD, opening the possibility that many actions previously attributed to noradrenaline could be due to 6-ND antagonism. In addition, blockade of the 6-ND receptors by both tricyclic antidepressants and α1-adrenergic receptor antagonists may represent the common mechanism of action responsible for their therapeutic use in the treatment of premature ejaculation. The authors thanks FAPESP (2021/13593-6) and Capes. Reference Puppo, V., Puppo, G., 2016. Doi: 10.1002/ca. 22655. Britto-Jr et al., 2021. Doi: 10.1016/j. ejphar. 2021. 174716

07.012 *Spirulina platensis* **Prevents Uterine Morphological Changes Promoted by Strength Training and Inhibits NADPH Oxidase**. Barros BC, Lacerda Júnior FF, Diniz AFA, Souza PPS, Alves AF, Ferreira PB, Silva BA UFPB

Introduction: Progressive strength training (PTT) is performed with gradual overload for a short period. If prescribed inappropriately, it can cause oxidative stress and changes in the female reproductive system, leading to menstrual dysfunction (SEMERARO, Eur J Nutr, 61, 2022). Thus, it was observed that PTT increased the efficacy and decreased the contractile potency of KCl and supplementation with *Spirulina platensis* (SP), an algae with antioxidant properties, at a dose of 100 mg/kg prevented such effects in the uterus of Wistar rats (FERREIRA, Nutr, 13, 2021). Based on this, it was decided to investigate whether the alterations in uterine contractility in rats submitted to PTT and supplemented with SP are due to changes in the histomorphometric parameters, as well as whether the mechanism of contractile electromechanical action involves the reactive oxygen species. **Methods:** Female rats were divided into 3 groups: control (GC); trained (TG); trained and supplemented with SP 100 mg/kg (TGSP100), orally. Animals were submitted to PTT and supplemented orally for 8 weeks, 24 hours before euthanasia, diethylstilbestrol (1 mg/kg, s. c.) was administered for estrus induction. For the histological analysis, the samples were isolated and fixed using standard histological technique. Results

were expressed as mean and standard deviation of the mean and analyzed by one-way ANOVA followed by Tukey's post test. **Results:** Histomorphometric parameters showed endometrium preserved, with no morphological lesion in GC. However, in TG, it was found that the endometrial glands are individualized and have a unique and diffuse morphological distribution, interestingly, treatment with SP (TGSP100) prevented these changes. In the myometrium, the GT showed an increase in the muscle layer (333. 0±5. 5µm2) when compared to the GC (227. 8±4. 6µm2), in the TGSP100 it did not prevent the increase in the uterine muscle layer (351. 2±9, 6µm2). In the uterine contractile reactivity, in the presence of apocynin, in the TG group, an increase in potency was observed with no change in the contractile efficacy of KCl (pEC50=2. 2±0. 06), when compared to TG in the absence of this inhibitor (pEC50=1. 0±0. 03). When comparing TG with GC, in the presence of apocynin, it prevented the decrease in potency, but not in contractile efficacy (pEC50=2. 2±0. 06; pEC50=2. 0±0. 07, respectively). In TGSP100, the presence of apocynin increased the effectiveness of KCl with no change in contractile potency (Emax=170. 0±16. 3%) compared to the absence of the inhibitor (Emax=119. 7±9. 1%). When evaluating the superoxide dismutase (SOD) enzyme, in the presence of tempol, there was a decrease in efficacy and an increase in contractile potency in TG (Emax=127. 2±7. 3%;pEC50=2. 3±0. 06), when compared in the absence of this mimetic (Emax=172. 7±8. 1%;pEC50=1. 0±0. 03), the TG curve in the presence of tempol prevented the increase in contractile efficacy, but increased the potency when compared to GC (Emax=100%;pEC50=2. 0±0. 07). In TGSP100, in the presence of tempol, contractile efficacy and potency increased (Emax=187. 3±10. 6%;pEC50=2. 4±0. 06). **Conclusions:** It is concluded that PTT leads to myometrial hypertrophy, increased production of superoxide anion and decreased SOD activity, which could be associated with increased electromechanical contractile efficacy. SP supplementation prevents uterine morphological changes and inhibits NADPH oxidase. Thus, the promising role of SP against disorders related to uterine hypercontractility. Support: CAPES, PPgPNSB/UFPB. Research approval:CEUA/UFPB(5191200320).

07.013 **Braylin Favors Penile Erection in a Model of the Hypertension-Associated Erectile Dysfunction**. Araújo FA[1,2], Jesus RLC[1,3], Moraes RA[1,2], Silva LB[1,3], Lima GBC[1], Brito DS[1], Campos L[4], Santos V[4], Azeredo FJ[4], Costa RS[5], Souza OP[5], Velozo ES[5], Silva DF[1,2,3] [1]UFBA, Lab of Cardiovascular Physiology and Pharmacology, Health Sciences Institute, Salvador, Brazil,[2]IGM-Fiocruz PPG in Biotechnology in Health and Investigative Medicine, Salvador, Brazil, [3]FF-UFBA PPG in Pharmaceutical Sciences, Salvador, Brazil, [4]UFBA, Lab of Pharmacokinetics and Pharmacometry, Salvador, Brazil, [5]UFBA, Lab of Research in Medical Matter, Salvador, Brazil

Introduction: Erectile dysfunction (ED) is defined as the recurrent and persistent inability to achieve or maintain satisfactory penile erection. It is important to note that clinical studies have provided robust data indicating that ED is a sentinel symptom in patients with occult cardiovascular diseases (CVD) and ED is frequently encountered in patients with arterial hypertension. Due a low pharmacological response to phosphodiesterase type 5 inhibitors in patients with vascular endothelial damage, the search for new drugs and therapeutic targets is of paramount importance for ED treatment. In that regard, natural products have served as an important source of drug for centuries. In previous studies conducted by our research group, we have demonstrated that the coumarin braylin induced vasorelaxation in iliac artery, important irrigation vessel for the lower body. Additionally, we also demonstrated the braylin induced relaxation in corpus cavernosum evolving NO-sGC pathway. Thus, we evaluated the therapeutic potential of coumarin braylin for the treatment of the hypertension-associated ED. **Methods:** All experimental protocols were approved by animal research ethical committee-Health Sciences Institute/Federal University of Bahia (130/2017). Young (wistar, 11-15 weeks) and older (spontaneously hypertensive rats, SHR 24-26 weeks) rats were used. The rats were recorded for 40 min after drug administration to assess its erectile function. Animals were separated into four groups receiving: vehicle (i. p.;cremophor + NaCl 0. 9% solution), braylin (i. p.; 4mg/kg), apomorphine (s. c.; 80µg/kg) and apomorphine + braylin (s. c; 80µg/kg and i. p. 4mg/kg, respectively). The apomorphine is a well-known inducer of erection. For the pharmacokinetics experiments, blood samples were collected at different time points after braylin administration (i. p.; 4 mg/kg) from the caudal lateral vein. All results are expressed as mean±S. D. analyzed using unpaired Student's t-test. **Results:** Braylin induced erection in young wistar rats (vehicle: 0. 2±0. 44, braylin: 2. 2±1. 7, $p<0.05$, n=5 for all groups) and also improved apomorphine induced-erections (apomorphine: 3. 4±1. 3, apomorphine+braylin: 5. 6±1. 1, $p<0.05$, n=5 for all groups). In older SHR, a model of erectile dysfunction, all animals receiving apomorphine+braylin had erections, however this was not observed

when animals received only apomorphine. The pharmacokinetic assay demonstrated both the braylin concentration on the blood samples Cmax (0. 54±0.17 µg/mL, n=5), and in penile tissue isolated from rats (0. 36±0. 083 µg/mL, n=5). **Conclusion:** Braylin can be absorbed after intraperitoneal administration and reach penis tissue, this can corroborate with its proerectile effect. Taking these data into account, braylin could be a potential molecule for the treatment of ED. **Financial Support:** CAPES, CNPq, FAPESB, UFBA.

07.014 **The Impact of Gender Differences on the Anti-Inflammatory and Analgesic Effects of Hydrogen Sulfide in a Model of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)**. Santos LG[1], Teixeira SA[1], Oliveira MG[2], Dallazen JL[1], Oliveira JP[1], Whiteman M[3], Muscará MN[1], Mónica FZ[2], Antunes E[2], Costa SKP[1] [1]USP, Dpt of Pharmacology, São Paulo Brazil, [2]Unicamp, Dept of Pharmacology, Brazil [3]University of Exeter, England

Introduction: Evidences suggest that the inflammatory response, as well as pain perception, may vary between male and female, which may justify the difference in the efficacy of some drugs used in the clinic to treat inflammatory diseases between genders1,2. We have previously shown that the H2S-releasing nonsteroidal anti-inflammatory ketoprofen compound ATB-352 alleviates bladder pain/referred allodynia and improved bladder contractile function elicited in a murine male model of interstitial cystitis/bladder pain syndrome (IC/BPS; Santos et al., SBFTe 2021). However, whether H2S has a similar protective effect in the IC/BPS in the female remains unclear. This study examined the effects of sex on the potential protective effects of a hydrogen sulfide donor, GYY-4137, in a murine model of IC/BPS in vivo and functionally *in vitro* (isolated bladder). Method: Cystitis was induced in male and female C57Bl/6 mice (8-10 weeks old; n=6) by an intraperitoneal injection of cyclophosphamide (CYP; 300 mg kg-1) or vehicle (saline; 10 ml kg-1) for control group. One hour after cystitis induction, male and female mice were treated with GYY-4137 (37. 5, 50 or 75 mg kg-1-; s. c.; n=6) or vehicle (saline; 10 ml kg-1) and mechanical allodynia was measured at 1, 2, 4, 6, 8 and 24 h, via the von Frey test. After 24h, mice were euthanized and bladders were removed and set in an organ bath apparatus to measure the contractility to KCl (80 mM; n=6) or carbachol (0. 001–30 µM; n=6). The bladder edema formation was assessed by calculating the ratio between the bladder wet weight and body weight. Data were analyzed by one-way or two-way ANOVA plus Tukey's test and were considered statistically significant when $p<0.05$. **Results:** Treatment with GYY-4137 (37. 5, 50 or 75 mg kg-1) promoted, respectively, an anti-allodynic effect, reducing CYP-induced mechanical allodynia by 42, 44 and 46 % in male and 52, 48 and 47 %, in female mice, compared to IC/BPS untreated group (100%). At all tested doses (37. 5, 50 or 75 mg kg-1), treatment with GYY-4137, prevented carbachol or KCl-mediated reduced bladder contractility in males; however, none of the GYY-4137 doses reestablished the contractile dysfunction promoted by CYP, either for KCl or carbachol stimuli. Inflammatory edema was significantly higher in the CYP group compared with control mice, and at the lowest dose (37. 5 mg kg-1), treatment with GYY-4137 reduced the edema formation in males, but not in females. **Conclusion:** The H2S donor GYY-4137 treatment ameliorated visceral (bladder) pain in both male and female mice, but the similar treatment improved the associated inflammatory response and contractile dysfunction in male, but not in female bladder. Our study highlights the importance of screening for H2S donors efficacy within-gender differences. References [1] Duma et al. (2010) Sci Signal 3(143):ra74. [2] Meibohm et al. (2012) Clin Pharmacokinet 41(5):329-42. ETHICS COMMITTEE ON ANIMAL USE (CEUA-ICB/USP, Protocol no. 2055050819). Acknowledgments: FAPESP (2021/ 09216-2), CAPES (Finance Code 001; 88887. 621476/2021-00) and CNPq (312514/2019-0).

07.015 **MK571, A Multidrug Resistance Proteins Inhibitor, Restored the Erectile Function of Obese Mice Through cGMP Accumulation**. Oliveira MG[1]., Passos GR., Gomes ET, Leonardi GR, Zapparoli A, Antunes E., Monica FZ FCM-Unicamp, Dpt of Translation Medicine (Pharmacology area), Campinas, Brazil

Background: Erectile dysfunction (ED), defined as the inability to achieve and/or maintain an erection adequate for intercourse, is a condition with large prevalence in the general population and have been proven to cause various degrees of impairment in quality of life. Penile erection is primarily initiated by nitric oxide (NO) that binds to soluble guanylyl cyclase (sGC) to increase cyclic guanosine monophosphate (cGMP) and hence corpus cavernosum (CC) relaxation. The action of cGMP is terminated by the actions of phosphodiesterase type 5 (PDE5) and multidrug resistance proteins type 4 (MRP4) and 5 (MRP5)1. A study showed the role of MK571 in CC from healthy mice, which potentiated the relaxation induced by the NO-donor and PDE inhibitor2. Because obesity is an important risk factor that impairs erectile function, this study is aimed to evaluate *in vitro* and in vivo the

effect of a 2-week treatment with MK571 in the erectile function of obese mice. Materials and **Methods:** All protocols were approved by the Institutional Committee for Ethics in Animal Research of the University of Campinas (CEUA/UNICAMP number: 4201-1). Mice were divided in three groups: i) lean, ii) obese and iii) obese + MK571. The corpus cavernosum (CC) were isolated and concentration-response curves to acetylcholine (ACh), sodium nitroprusside (SNP) and tadalafil in addition to electrical field stimulation (EFS) was carried out in phenylephrine pre-contracted tissues. Expression of ABCC4 and ABCC5, intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), the protein levels for pVASPSer157 and pVASPSer239 and the intracavernous pressure were also determined. The intracellular and extracellular (supernatant) ratio in CC from obese and lean stimulated with a cGMP-increasing substance (BAY 58-2667) in the absence and presence of MK571 (20 μM, 30 minutes) were also assessed. **Results:** The treatment with MK571 completely reversed the lower relaxing responses induced by EFS, ACh, SNP and tadalafil observed in obese mice CC in comparison with untreated obese mice. Cyclic GMP and p-VASPSer239 expression were significantly reduced in CC from obese groups. MK571 promoted a 6-fold increase in cGMP without interfering in the protein expression of p-VASPSer239. Neither the cAMP levels nor p-VASPSer157 were altered in MK571-treated animals. The intracavernous pressure was ~50% lower in obese than in the lean mice, however, the treatment with MK571 fully reversed this response. Expression of ABCC4 and ABCC5 were not different between groups. The intra/extracellular ratio of cGMP was similar in CC from obese and lean mice stimulated with BAY 58-2667. **Conclusions:** The erectile dysfunction seen in obese mice was reverted after a 2-week treatment with MK571, accompanied by greater intracellular accumulation of cGMP, but not cAMP. These results suggest that MRPs inhibition by MK571 favored the accumulation of cGMP in the smooth muscle cells, thus improving the smooth muscle relaxation and the erectile function in obese mice. **References:** 1. Adv Pharmacol. 2016; 77:1-27; 2. J Sex Med. 2017;14(4):502-9.

07.016 *Spirulina platensis* **Supplementation Prevents Histomorphometric Changes in the Uterus of Wistar Rats Submitted to Progressive Strength Training**. Ferreira PB, Lacerda Júnior FF, Souza PPS, Barros BC, Diniz AFA, Alves AF, Silva AS, Silva BA UFPB

Introduction: Several studies have reported that the female reproductive system is highly sensitive to physiological stress, and training with excessive loads is related to reproductive disorders, in addition to increasing *in vitro* uterine contraction and oxidative stress and that supplementation with *Spirulina platensis* (SP), an antioxidant and anti-inflammatory algae, prevents this effect. (FERREIRA et al., Nutrients, v. 13, 2021). Thus, the objective of this study was to evaluate the histomorphometric alterations in rat uterus induced by progressive strength exercise (PTT) and/or supplementation with SP, in the uterus of female Wistar rats. **Methods:** Wistar rats (150-200g) were divided into 7 groups: group supplemented with saline solution (0. 9%) (GS) and supplemented with SP at doses of 50 (GSP50) and 100 mg/kg (GSP100), adapted only group (CG, control), group trained for 8 weeks (TG) and trained and supplemented with SP at a dose of 50 (TG50) and 100 mg/kg (TG100). The uterine horns samples were isolated and fixed in 10% buffered formaldehyde solution, embedded in paraffin, cut (3 μm), mounted on histological slides and observed in the number of eosinophils and blood vessels and on the vascular and muscular area. Results were expressed as mean and standard error of mean (e. p. m.), statistically analyzed using one-way ANOVA followed by Tukey's post-test. **Results:** Regarding the number of eosinophils, in GSP50 (40. 0 ± 2. 9) and GSP100 (42. 0 ± 1. 8) there was no change in relation to the GS (39. 8 ± 1. 9) and in the rats submitted to strength training (25. 5 ± 0. 9) a decrease in the number of eosinophils compared to the CG (39. 8 ± 1. 9); Only in the animals trained and supplemented at a dose of 100 mg/kg (32. 8 ± 1. 5) a increase in the number of eosinophils in relation to TG. In the evaluation of number of vessels there was a dose-dependent increase in relation to the CG (5. 8 ± 0. 2) compared to the GSP50 (14. 5 ± 1. 0), GSP100 (19. 5 ± 1. 0) and TG (17. 8 ± 1. 1) increased in the uterus compared to the CG (5. 8 ± 0. 2). Food supplementation at a dose of 50 mg/kg (14. 2 ± 0. 2) and 100 mg/kg (17. 8 ± 1. 2) did not change in relation to the TG. When the vascular area was quantified, it was observed that SP increased the vascular area in GSP50 (0. 8 ± 0. 03) and GSP100 (0. 89 ± 0. 07) in compared to GS (0.13 ± 0.05) and strength training increased the vascular area in relation to the control (0.13 ± 0.05), but food supplementation with seaweed decreased in GT50 (0 . 44 ± 0. 03) and GT100 (0. 34 ± 0.05) when compared to TG (0. 81 ± 0. 03). In sedentary rats, an increase in the area of the myometrium was observed in GSP50 (1. 2 ± 0. 5) and in GSP100 (1. 1 ± 0.1) compared to the GS (0. 5 ± 0.

07), and in the rats of TG (0. 95 ± 0. 06) an increase in muscle area was observed in relation to CG (0. 5 ± 0. 07). In TG50 (0. 8 ± 0. 03) did not change this parameter, different from that observed in TG100 (0. 71 ± 0.05) where there was a decrease in the area of the myometrium compared to the CG (0. 5 ± 0. 07). **Conclusion:** In conclusion, it was observed the increases vascularization and vascular area and prevents the increase in myometrial thickness induced by progressive strength training, corroborating the attenuation of contraction observed, suggesting the promising potential of dietary supplementation with *Spirulina platensis* in pathophysiological processes that involve dysregulations in uterine contractile homeostasis such as dysmenorrhea, premature birth, spontaneous abortion. **Financial Support:** CAPES, CNPq, PPgPNSB/UFPB. CEUA/UFPB- 0211/14.

07.017 **Lipopolysaccharide and Lipoteichoic Acid Differentially Regulate Toll-like Receptor Signaling Pathway-Associated Genes in the Mouse Epididymis**. Silva EJR[1], Kushima H[1], Avellar MCW[2], Pleuger C[3], Andrade AD[1] [1]IBB-Unesp-Botucatu, Dpt of Biophysics and Pharmacology, Botucatu, Brazil, [2]Unifesp-EPM, Dpt of Pharmacology, São Paulo, Brazil, [3]Justus-Liebig-University Giessen, Institute of Anatomy and Cell Biology and Hessian Centre of Reproductive Medicine, Giessen, Germany

Introduction: Epididymitis, inflammation of the epididymis, is a relevant factor in male infertility. Studies showed that the regions of the epididymis (initial segment, caput, corpus, and cauda) display unique inflammatory gene expression and immune cell distribution, which may contribute to the distinct regional responses during epididymitis. For instance, genes encoding Toll-like receptors such as TLR2, TLR4, TLR6, and their associated signaling molecules, which are crucial for detecting and orchestrating inflammatory responses to bacteria, are differentially expressed in the rodent epididymis. Accordingly, we previously demonstrated that the bacteria-derived products lipopolysaccharide (LPS, TLR4 agonist) and lipoteichoic acid (LTA, TLR2/TLR6 agonist) induced distinct cytokine responses in the initial segment (IS) and cauda epididymidis (CD) in mice. Here, investigated whether LPS- and LTA-induced epididymitis affect the transcript profile of TLR signaling pathway-associated genes in the IS and CD in mice. **Methods:** Male C57BL/6 mice (90 days, n=4-6/group) were euthanized, their epididymides were dissected, the IS and CD were isolated, and incubated in DMEM medium for 30 min (34ºC and 5%/95% CO2/air). Tissues were incubated in the absence (control) or presence of ultrapure LPS (0. 01, 0.05, and 0.1 ug/ml), or LTA (0.1, 1. 0, and 10 ug/ml) for 3 h under the same conditions. Tissues were processed for RT-qPCR studies to evaluate the mRNA levels of pro-inflammatory cytokines (Il6 and Tnf), Toll-like receptors (Tlr1, Tlr2, Tlr4, and Tlr6), TLR-adaptors and -accessory elements (MyD88, Trif, Cd14, Cd36, Traf3, and Traf6), and hypoxanthine-guanine phosphoribosyl transferase (Hprt, endogenous control). Data were analyzed by ANOVA followed by the Dunnett test ($p<0.05$ was considered significant). **Results:** LPS and LTA induced an increase in the transcript levels of inflammatory markers Il6 and Tnf in the IS and CD, reaching a plateau at 0.05 ug/ml LPS (IS: 4. 5 and 2. 2 fold, respectively; CD: 6. 3 and 3. 5 fold, respectively) and 1 ug/ml LTA (IS: 3. 1 and 1. 8 fold, respectively; CD: 3. 0 and 2. 6 fold, respectively). LPS (0.05 ug/ml) upregulated the transcripts levels of Tlr2 (2. 8 fold), Myd88 (1. 3 fold), Trif (1. 4 fold), Cd14 (2. 6 fold), and Traf3 (1. 3 fold) in the IS, and Tlr2 (2. 9 fold), Myd88 (2. 0 fold), Trif (1. 6 fold), Cd14 (2. 8 fold), Traf3 (1. 5), and Traf6 (1. 4 fold) in the CD compared to saline-control. Conversely, LTA (1. 0 ug/ml) upregulated the transcript levels of Traf3 (1. 3 fold) in the IS only. **Conclusion:** We show that LPS and LTA differentially regulate the expression of key genes associated with the TLR signaling pathway in the proximal and distal epididymidis. These responses were triggered by direct stimulation of epididymal cells by LPS and LTA and were independent of systemic factors. Our results indicate the existence of region-specific mechanisms triggered by activation of TLR4 and TLR2/TLR6 by bacteria-derived products during epididymitis. **Financial Support:** FAPESP (2021/04746-3) and CAPES (88887. 657630/2021-00). Ethics approval: 6272050320-IBB/CEUA.

08. Respiratory and Gastrointestinal Pharmacology

08.001 **Can Gastric Healing be Altered in Obese Animals? Evaluation of the Antiulcerogenic Effect of Citral in Mice Fed with High-Fat Diet**. Dario FL, Ohara R, Rocha LRM, Hiruma Lima CA IBB-Unesp-Botucatu, Dpt of Structural and Functional Biology (Physiology), Botucatu, Brazil

Introduction: In Brazil, 60. 3% of the adult population is overweight and 25. 9% is obese. This condition promotes higher susceptibility to the development of gastric ulcers and compromises the healing process. The available treatments for gastric ulcers include the use of antacids and proton pump inhibitors, which do not promote

effective tissue recovery. Experiments conducted by our group demonstrated that Citral is capable of promoting healing acceleration through modulation of inflammatory mediators in gastric ulcers induced by acetic acid in rats, however, its healing action associated with obesity is unknown. Objective Evaluate the healing effect of Citral in gastric ulcers induced by acetic acid in obese mice and characterize possible action mechanisms involved in this effect. **Methods:** C57BL/6J male mice were divided into two groups and fed with a standard diet (SD) or high-fat diet (HFD) ad libitum. After 12 weeks, animals were submitted for surgery for gastric ulcer implantation by acetic acid. To evaluate Citral's healing effect, the animals were redivided into groups (n = 6-8), which were orally treated for 3 or 10 consecutive days, one day after the surgery: Citral (25, 100, and 300 mg/kg), positive control – Lansoprazole (30 mg/kg) and negative control – Vehicle (1% Tween 80 at 10 mL/kg). One group (Sham) was only subjected to laparotomy and suture of the abdomen (CEUA-IBB, nº 1208). All stomachs were collected for morphologic and zymographic analysis (matrix metalloproteinase [MMP]-2 and 9). For statistical analysis, ANOVA was used followed by Tukey's, Dunnett's, or Bonferroni's post-test. The minimum significance level adopted was $p < 0.05$. Results After 12 weeks of diet ingestion, animals fed with HFD presented corporal weight 42% higher than animals fed with SD ($p < 0.0001$). Carrying out the analysis comparing the two healing periods inside each treatment and diet group, all groups fed with SD exhibited a reduction in the ulcer area (mm2), with a mean of 73. 2% of reduction. The animals fed with HFD exhibited 84. 5% and 70.1% of reduction in the ulcer area only for the groups treated with Citral at doses of 100 and 300 mg/kg, respectively. In the zymographic analysis the relative activation of MMP-2 was evaluated and, except for Sham groups and animals SD treated with Citral at 100 and 300 mg/kg, all groups showed an elevation of MMP-2 activity through time. Lower MMP-2 activity in the later stages of healing is a predictor factor of healing quality. After 3 days of treatment, animals from the HFD group treated with Citral (25 mg/kg) exhibited a reduction of 51% of the MMP-2 activity when compared to the Vehicle HFD group. Animals fed with SD and HFD and orally treated with Citral for 10 days exhibited a significant reduction of total MMP-9 activity ($p < 0.05$). The reduction of the MMP-9 activity is also a predictive factor of the healing quality of gastric mucosa. **Conclusion:** Treatments with Citral at 100 and 300 mg/kg for 10 days accelerated the healing rate of gastric ulcers in obese mice and provided changes in the MMP-2 and 9 activity profiles that are favorable to the development of a better-quality healing. In animals fed with SD, Citral has changed MMPs' activity profiles at doses of 25 and 300 mg/kg, also favoring a better-quality healing. These data qualify Citral as a possible drug to be used in the treatment of gastric ulcers in both eutrophic and obese people. **Financial Support:** FAPESP (2020/07384-2) and CNPq.

08.002 **Evaluation of the Involvement of Prostaglandins in the Gastroprotective Effect of the Hydroethanolic Extract of the Stem Barks of *Ximenia americana* L. – EIPGEHESBXA**. Silva AB[1], Pessoa RT[1], Santos LYS[1], Alcântara IS[1], Costa RHS[1], Silva TM[1], Muniz DF[2], Oliveira MRC[3], Martins AOBPB[1], Menezes IRA[1], [1]URCA, [2]UFPE, [3]UECE

Introduction: *Ximenia americana* L. is a popular specie used in ethnomedicine to treat gastric ulcers, cancer, and inflammatory processes. This study aimed to evaluate the gastric protective effect of hydroethanolic extract of *Ximenia americana* L. stem bark (EHXA) and your involvement of the prostaglandins pathway against damage caused by ethanol 96%. **Methods:** *Swiss* mice were divided into four groups of six animals, treated orally with water (H2O) (0,1 mL/10 g), misoprostol (0,016 mg/kg), and indomethacin (10 mg/kg; or), and EHXA (50 mg/kg). The groups received prior administration, and after 1 hour of the oral treatments, the animals received ethanol 96% (0. 2 ml/animal, or). After 30 minutes of ethanol administration, the animals were euthanized, the stomachs were removed and opened by the greater curvature, scanned, and analyzed in software (ImageJ, Bethesda, MD, USA). After euthanasia, the mucosa was removed, weighed, and incubated for mucus determination using 10 ml of 0.1% Alcian blue solution. The excess Alcian blue was removed with 0. 25 mol/L sucrose solution, dry, and the complexed mucus-corant was extracted with 5 ml of magnesium chloride (0. 5 mol/L). The supernatant solution (3 ml) was mixed with 3 ml of ethyl ether and stirred until an emulsion formed and centrifuged at 3600 rpm for 10 min. The concentration of Alcian blue in the samples was determined by spectrophotometric reading at 598 nm and quantified by interpolating the standard curve. The study was submitted and approved by the animal experimentation committee from the Regional University of Cariri and registered under number 00157/2021. 2. Results were expressed as mean ± standard error of the mean (S. E. P. M). Differences between means were analyzed by one-way analysis of variance (ANOVA) followed by *Tukey's* multiple comparisons test. Statistical analysis was performed using GraphPad Prism 6. 1. The significance level

for rejection of the null hypothesis was set at 5% ($p < 0.05$). **Results:** The treatments with EHXA and misoprostol significantly reduced the ulcerative lesions of the animals' stomachs by 65, 28; 73, 42%, respectively, when compared to the negative control. After pre-treatment with indomethacin, the EXHA and misoprostol group reversed the gastroprotective effect, thus evidencing its action on the prostaglandin E2 pathway. Regarding mucus, the treatments with EHXA and misoprostol significantly increased the production of mucus adhered to the gastric mucosa by 40,40 and 79, 92%, respectively, compared to the negative control. Thus, these results suggest the influence of the eicosanoid pathway on the gastroprotective effect. **Conclusion:** From these results, it can be concluded that EHXA presents effective gastroprotective activity in the involvement of the eicosanoid pathway, besides promoting the increase of mucus, thus contributing to the research of natural products for the treatment of gastrointestinal problems. **Financial Support:** CNPq, Capes, FUNCAP **Acknowledgments**: Regional University of Cariri, CNPq, Capes, FUNCAP.

08.003 **Food Supplementation with *Spirulina platensis* Prevents Damage to Ileal Contractile Reactivity by Modulating NO and COX Pathways in Rats Fed a Hypercaloric Diet**. Claudino BFO, Diniz AFA, Francelino DMC, Barros BC, Lacerda Júnior FF, Souza PPS, Ferreira PB, Silva BA UFPB

Introduction: Obesity is defined as an abnormal accumulation of fat that can harm health, caused by an energy imbalance between calories consumed and expended, favoring the development of various gastrointestinal disorders (HEYMSFIELD et al., New England Journal of Medicine, v376, p254, 2017; WHO, HealthTopics, 2021). So, research for new alternatives is growing more and more, especially with natural products, which have fewer side effects. Thus, *Spirulina platensis* (SP) appears, a blue-green algae with potential antioxidant (ABDEL-MONEIM et al., SaudiJournalofBiolSci, v29, p1197, 2022) and anti-inflammatory effects (ABOUZED et al., Toxicology Research, v11, p169, 2022). Furthermore, previous studies demonstrated that SP prevented the reduction in ileal contractile reactivity caused by the hypercaloric diet (DINIZ et al., Oxidative Medicina and Cellular Logevity, v2021, 2021). Thus, the present study elucidates the possible mechanisms of preventive action of SP involved with the nitric oxide (NO) and cyclooxygenase (COX) pathways. **Methods:** Wistar rats (8 weeks old) were divided into rats that received standard diet (SD), hypercaloric diet (HCD) or hypercaloric diet + oral supplementation with S. platensis powder at 25 mg/kg (HCD+SP25). The isolated ileum of the rats was mounted in bath vats for isolated organs to monitor reactivity. Results were expressed as mean and standard deviation of the mean and analyzed by one-way ANOVA followed by Tukey's post-test ($p < 0.05$, n=5). **Results:** In the group fed with a hypercaloric diet, there was a reduction in the maximum effect (HCD 32. 0 ± 2. 9%) when compared to the contraction curve of the group of animals that were fed with SD (100%) without altering the pEC50 (6. 6 ± 0. 01 and 6. 3 ± 0. 04 respectively). Interestingly, supplementation with 25 mg/kg (EMAX = 59. 9 ± 1. 2%) of seaweed prevented the decrease in contractile efficacy of CCh in relation to the HCD group. Regarding the mechanisms of action involved in changes in intestinal contractile reactivity, there was a decrease in intestinal contractility to CCh in the SD group in the presence of L-NAME, an inhibitor of NO synthase (EMAX = 93. 3 ± 0,1%) and that similarly in the presence of indomethacin, a COX inhibitor, the contractile efficacy was also reduced (EMAX = 71. 4 ± 3. 4 %), when compared to the absence of this inhibitor (EMAX = 100%). The contractile efficacy of CCh was also reduced in the HCD group in the presence of L-NAME (EMAX = 19. 4 ± 1. 1%) when compared to the absence of this substance (EMAX = 32. 7 ± 7. 5%). Furthermore, in the presence of indomethacin in the HCD group, the contractile efficacy of CCh was also reduced (EMAX = 21. 6 ± 2. 2%). Food supplementation with 25 mg/kg of SP in the HCD group provided a decrease in contractile efficacy in the presence of L-NAME (EMAX = 26. 6 ± 2. 3%), as well as in the presence of indomethacin (EMAX = 25. 0 ± 2. 0%) when compared in the absence of these inhibitors (EMAX = 63. 9 ± 0. 9). **Conclusions:** In view of the results evidenced in this research, it can be concluded that SP prevents the damage caused by the hypercaloric diet in the contractile reactivity of the ileum by involving the participation of the NO pathways, increasing its synthesis, and COXs decreasing the production of contractile prostanoids, mechanisms linked to their antioxidant and anti-inflammatory properties, thus emerging as an important therapeutic alternative in the prevention of intestinal diseases caused and/or aggravated by obesity. Research approval: CEUA/UFPB (2352101019). **Financial Support:** CNPq, CAPES, PROEX.

08.004 **Gastroprotective Effect of the Hydroethanolic Extract of the Stem Barks of *Ximenia americana* L. on the Involvement of α2-adrenergic Receptors – GEHESBXAIAR**. Silva ES[1], Pessoa RT[1], Santos LYS[1], Alcântara IS[1], Silva TM[1], Costa RHS[1], Oliveira MRC[2], Muniz DF[3], Martins AOBPB[1], Menezes IRA[1] [1]URCA, [2]UECE, [3]UFPE

Introduction: Ximenia americana L. is popularly known as wild plum, and its barks are used to treat inflammatory disorders such as gastritis and ulcers in the skin or stomach. This study aimed to evaluate the gastroprotective action of the hydroethanolic extract of the stem barks of Ximenia americana L. (EHXA) and the involvement of α2 - adrenergic receptors. **Methods:** Eight-week-old *Swiss* mice of both sexes were divided into 5 groups of 6 animals and treated orally (o. r), the first 3 groups were: negative control (H2O, 0.1 mL/10 g/o. r), positive control: clonidine (0.05 mg/kg/o. r) and EHXA (50 mg/kg/o. r). Prior intraperitoneal (i. p.) administration of yohimbine (2 mg/kg) was performed 20 min prior to EHXA or clonidine administration. After 1 hour of the treatments (o. r) or 30 min (i. p), the animals received ethanol 96% (0. 2 ml/animal, o. r). After 30 min, the animals were euthanized, the stomachs removed and opened by the major curvature, scanned, and analyzed in software of ImageJ (Bethesda, Maryland, United States). Differences between the mean were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey multiple comparison test. Statistical analysis was performed using GraphPad Prism 6. 1. The significance level for rejection of the null hypothesis was set at 5% ($p < 0.05$). The procedure is approved by the Committee on Experimentation and Use of Animals of the Regional University of Cariri (CEUA/URCA) under register number 157/2021. 2. **Results:** The treatments with EHXA (50 mg/kg) and clonidine (0.05 mg/kg) significantly reduced the ulcerative lesions in gastric tissue by 96% ethanol with a percentage of 79. 76 and 73. 68%, respectively, when compared to the negative control group. However, when the animals in the EHXA group received pretreatment with yohimbine (specific inhibitor of the alpha-adrenergic pathway), there was a reversal of the gastroprotective effect of EHXA and clonidine then these results evidence its possible participation in the α2-adrenergic receptors pathway in the gastroprotection. **Conclusion:** Given the results obtained, the EHXA showed effective gastroprotective activity in the model evaluated, demonstrating that the α2 - adrenergic receptors pathway contributes to the reduction of gastric lesions showing that this natural product can be an important alternative for the treatment of gastric ulcers. **Financial Support:** National Council for Scientific and Technological Development - CNPq, Coordination for the Improvement of Higher Education Personnel - CAPES, Cearense Foundation for Support to Scientific and Technological Development - FUNCAP Acknowledgments: Regional University of Cariri, CNPq, CAPES, FUNCAP.

08.005 **Antidiarrheal Activity and Effects on Gastrointestinal Motility of Carveol in animal models**. França JS[1], Pessôa MLS, Alves VP[1], Pessôa MLS[2], Alves Júnior EB[2], Araruna MEC[2], Pessoa MMB[2], Batista LM[2] [1]UFPB, Graduate Student in Pharmaceutical Sciences, João Pessoa, Brazil, [2]UFPB, PPG in Natural and Synthetic Bioactive Products, Health Sciences Center, João Pessoa, Brazil

Introduction: Diarrhea is one of the most prevalent disorders affecting the gastrointestinal tract worldwide and also one of the main causes of childhood morbidity and mortality. The current pharmacological treatment consists of reducing the symptoms of the disease, but it still has several limitations, such as the high incidence of side effects and lack of specificity of therapeutic agents. In this context, natural products, especially medicinal plants, are an interesting therapeutic alternative for discovery of bioactive molecules. The present investigation evaluates antidiarrheal activity, the effects on gastrointestinal motility and the antisecretory mechanism of the monoterpene carveol in experimental models. **Methods:** *Swiss*, albino male mice (Mus musculus) weighing between 25-35g were used for the research. The animals were divided and treated orally with 5% tween 80 vehicle (10 ml/kg), loperamide (5 mg/kg) or test substance at different doses. Carveol (p-Mentha-6,8-dien-2-ol) is of natural origin, however it was obtained by synthesis and purchased from SIGMA-ALDRICH Brasil Ltda. To evaluate the antidiarrheal activity of carveol, was used the model conducted by Awouters et al. (1978) with modifications. To evaluate the effect of carveol on gastric emptying, the model recommended by Scarpignato et al. (1980) was used. Intestinal transit was assessed by the castor oil-induced transit protocol (Stickney; Northup, 1959) and to assess intraluminal fluid accumulation, was used the protocol by Ezeja et al. (2010) of castor oil-induced enteropooling. The experimental procedures were approved by the Ethics Committee on Animal Use (CEUA/UFPB) under protocol numbers 2819220420 and 3679210521. Results were expressed as mean ± standard deviation for parametric data and median (minimum-maximum values) for non-parametric data. The Kruskal-Wallis test was used for statistical analysis of the non-parametric data, followed by Dunnet or

Tukey post-tests. **Results:** In the castor oil-induced diarrhea model, it was found that doses of 100 and 200 mg/kg of carveol reduced the evacuation index to 13 for both doses, when compared to the negative control group, which presented an evacuation index of 32, thus showing a percentage of inhibition of diarrhea of 59% (p<0,001) for both doses. In the intestinal transit model, doses of 100 and 200 mg/kg of carveol significantly reduced intestinal motility compared to the negative control group, with inhibition percentages of 51% (p<0. 001) and 50% (p<0. 001), respectively. In the gastric emptying model, carveol (100 and 200 mg/kg) significantly reduced gastric emptying to 78. 5% (p<0. 001) and 81% (p<0. 001), respectively, when compared to the negative control group. In the evaluation of the antisecretory mechanism, the model of enteropooling induced by castor oil was used, carveol at a dose of 100 mg/kg showed a significant reduction in the weight of intestinal fluid (0. 62 ± 0. 03), when compared to the negative control group (0. 82 ± 0.05). Conclusion: From the results, it can be inferred that the monoterpene carveol has antidiarrheal activity, and this activity is related to the antimotility effect and antisecretory and/or pro-absorptive mechanisms. KEY WORDS: antisecretory. carveol. diarrhea. monoterpene. motility.

08.006 **Study of the Gastroprotective Activity of the Juice and Hydroethanolic Extract of the Fruit Peels of *Plinia peruviana* (Poir.) Govaerts (Myrtaceae) on the Involvement of Nitric Oxide Action – EAGSEHCFPPPGMEAON**.

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Introduction: The species Plinia peruviana belongs to the Myrtaceae family, is popularly known as jabuticaba, and is widely used in traditional medicine in the form of tea, obtained from the fruit peel, for the treatment of diarrhea, dysentery and cough. The study aimed to evaluate the gastroprotective activity of the juice and hydroethanolic extract of Plinia Peruviana (Poir.) fruit peels (SPP and EHPP, respectively) in the involvement of nitric oxide action, dosage nitrite and nitrate . **Methods:** Swiss (Mus musculus) mice (number=6) were divided into 5 groups, and received treatment: control (NaCl 0. 9%/oral route (o. r.)), L-arginine (600 mg/kg/intraperitoneal (i. p.) nitric oxide precursor), SPP and EHPP (100 mg/kg/o. r.), the other 4 groups associated with prior administration with L-NAME (20 mg/kg/i. p. nitric oxide synthase enzyme). 30 minutes before treatment with L-arginine, SPP or EHPP after 1 hour (o. r.) or 30 minutes (i. p.) the animals received ethanol 96% (0. 2 ml/animal/v. o.). Thirty minutes after ethanol administration, the animals were euthanized, the stomach was removed and washed, and the area of the removed lesion was scanned and analyzed by computerized planimetry using ImageJ software (Bethesda, Maryland, United States). For the dosage of nitrite and nitrate, equal parts of 5% phosphoric acid, 0.1% N-1-naphthylenediamine (NEED), 1% sulfanilamide in 5% phosphoric acid, and distilled water were used. To perform the assay, 100 µL of 10% stomata homogenate supernatant made in potassium phosphate buffer was added to 100 µL of Griess reagent. For the blank, 100 µL of reagent was added in 100 µL of buffer, to obtain the standard curve, serial dilutions of nitrite were made (100, 50, 25, 12. 5, 6. 25, 3. 12, 1. 56 µM). readings were performed in the absorbance range of 540 nm. (Committee on Experimentation and Use of Animals of the Regional University of Cariri- number 03/2021.1.). **Results:** The data obtained when compared with the negative control group, showed that treatment with SPP, EHPP (100 mg/kg) and L- arginine (600 mg/kg) showed percentage of inhibition after administration of absolute ethanol at 58. 19; 55. 46 and 73. 89%. When investigating the role of nitric oxide in the gastric protection of SPP and EHPP, the levels of nitrite (NO_2^-) and nitrate (NO_3^-) were dosed, in which, they showed that the group pretreated with SPP, EHPP and L-arginine (600 mg/kg) showed relevant nitrite levels in 125. 42%; 139. 96 and 180. 86%, with respect to the control group. Confirming with the previous results, suggesting that nitric oxide is involved in the protection induced by SPP and EHPP. **Conclusion:** From the results obtained in this study, we can conclude that the oral administration of SPP and EHPP presents an activity with participation or involvement of nitric oxide, starting from the inhibition of lesions and dosage of nitrite and nitrate dosage, making them a promising alternative in the treatment of gastric diseases by the society. **FINANCIAL SUPPORT:** National Council for Scientific and Technological Development - CNPq, Coordination for the Improvement of Higher Education Personnel - CAPES, Cearense Foundation for Support to Scientific and Technological Development - FUNCAP, Foundation for Support of Science and Technology of Pernambuco – FACEPE ACKNOWLEDGMENTS: Regional University of Cariri, Federal University of Pernambuco, CNPq, CAPES, FUNCAP.

08.007 **Evaluation of Antidiarrheal Activity, Effects on Motility and Mechanism of Action of Estragole in Animal Models**. Alves VP, Silva LMO, Pessoa MMB, Pessôa MLS, Alves Júnior EB, Araruna MEC, Batista LM, França JS UFPB

Introduction: Diarrhea is a gastrointestinal disorder characterized by an abnormal increase in frequency, fluidity, and volume of stools over 24 hours. Estragole is a natural compound of the phenylpropanoid class that can be found in species such as *Ravensara anisata* and Ocimum basilicum. The aim of this study was to evaluate the antidiarrheal activity, the effects on gastrointestinal motility and the mechanisms of action related to this phenylpropanoid. **Methods:** The animals used for the experiments were male Swiss mice (Mus musculus) (n=7) weighing 28-35 g. For antidiarrheal activity, the castor oil-induced diarrhea protocol was used (Awouters C. J. et al. J. Pharm. Pharmacol. 30, 41-45, 1978). For gastric emptying, the protocol for evaluating effects on gastric emptying was used (Scarpignato, C. A. et al. Arch. Int. Pharmacodyn. Ther. 246, 286-294, 1980). Transit was assessed by the castor oil-induced transit protocol (Stickney, J. C. and Northup D. W. Proc. Soc. Exp. Biol. Med. 101, 582-583, 1959). To assess intraluminal fluid accumulation, the castor oil-induced enteropooling protocol was used (Ezeja, M. I. and Anaga A. O. Int. J. Toxicol. Pharmacol. Res. 40-44, 2010). In order to evaluate the activity of the estragole on the receptors, the protocol of evaluation of the participation of muscarinic and adrenergic receptors in the antimotility mechanisms in the intestinal transit model was used (Santos F. A. and Rao, V. S. N. Eur. J. Pharmacol. 364. 193-197, 1999). Results were analyzed by ANOVA followed by Dunnett's test (mean ± standard deviation) followed by Tukey's post-hoc and Kruskal-Wallis test. **Results:** Estragole showed antidiarrheal activity at doses of 125 and 250 mg/kg (orally) with percentages of inhibition of 61 and 75% respectively, reducing the percentage of leakage to 62 and 70% respectively when compared to the control group (5% tween 80). In the intestinal transit (doses 31. 25; 62. 5; 125 and 250 mg/kg) reduced motility to 37, 35, 32 and 24%, respectively, when compared to the control group. In the assessment of the anti-secretory and/or pro-absorptive mechanism, the intestinal content was reduced by 0. 037g ± 0. 03 when compared to the control group (5% tween 80). With regard to antimotility mechanisms, the traffic percentage was reduced by 53% of the amount of estragole compared to the control group (72%), 79% respectively - In the experimental models the positive control used was loperamide (5mg/kg). **Conclusions:** Based on the results, it can be concluded that estragole has antidiarrheal activity, antimotility effect by reducing gastric transit and emptying and acts both by antisecretory and/or pro-absorptive mechanisms, as well as by mechanisms involving muscarinic and adrenergic receptors. Acknowledgements: CNPq / UFPB / PgPNSB / IpeFarM. Ethics Committee (CEUA/UFPB): 4653290419 and 2819220420.

08.008 **The Gastroprotective Effect of the Cashew Bark Aqueous Extract** (*Anacardium occidentale* L). Pereira YLG[1], Mello VJ[2], Diniz LA[1], Hamoy M[2], Paz APS[2], Souza KR[2] [1]UFPA, Faculty of Medicine, Belém, Brazil, [2]UFPA, Institute of Biological Sciences, Belém, Brazil

Introduction: Cashew (*Anacardium occidentale* L.) is a Brazilian plant widely available in the coastal region, extending from the Amazon to the Northeast (1). The bark of this tree can be used in the preparation of infusions and decoctions to maintain health and is widely consumed by the population for the treatment of various diseases in popular medicine, such as cancer and diabetes (2). Ethnopharmacological reports from the northern region describe the use of bark decoction in the treatment of gastric ulcers, but they were not confirmed experimentally. **Methods:** The plant stem barks were collected in Belém-PA. The biological material was dried, ground, subjected to decoction in distilled water at 100°C (200g\1000mL) and lyophilized (ACE). For the phytochemical analysis, the following were determined: the content of total phenolics and flavonols (3,4,5); the anthocyanin content (6); and antioxidant capacity (7,8). To evaluate the cytoprotection after the induction of gastric lesions with absolute ethanol (9,10) and indomethacin (9), 64 Wistar rats (both sexes) of 150-200g were used, kept in a light/dark cycle, with water and food. ad libitum, at the Lab of Pharmacology and Toxicology of Natural Products of the ICB-UFPA. Treatments with oral dose-dependent ACE (75 mg/kg, 150 mg/kg and 300 mg/kg), as well as vehicle gavage for the negative control group, were performed 30 minutes before the induction of lesions. At the end, the animals were euthanized (with xylazine 30 mg/kg and ketamine 300 mg/kg) to quantify the lesions in the stomach mucosa. **Results:** ACE has a high ability to scavenge free radicals. In addition, the tea-decoction, a traditional preparation method, promoted the extraction of a significant amount of bioactives with relevant antioxidant capacity. However, anthocyanins were not detected. For the 20 animals

of the indomethacin induction model, the following means ± standard error (SE) of the ulceration indices were revealed: 8. 25 ± 1. 60; 7. 25 ± 1. 11; and 4. 50 ± 0. 50 at doses of 75, 150 and 300 mg/kg of ACE and 21. 50 ± 2. 75 for the control group; with inhibition percentages of 61. 62%; 66. 28% and 79. 07% for ACE doses, respectively. For the 44 animals in the absolute ethanol induction protocol, the results showed that the negative control group showed intense damage to the gastric mucosa after ethanol gavage (SE: 28. 76 ± 3. 73), while the groups treated with ACE at doses of 75, 150 and 300mg/kg had SE of 23. 60 ± 3. 07; 7. 75 ± 2. 45 and 6. 74 ± 2. 75, respectively. Doses of 150 and 300 mg/kg were efficient in reducing the injured area by 73. 05% and 76. 56% when compared to the induced-only group. **Conclusion:** ACE from *A. occidentale L. * has potential gastric cytoprotective activity, associated with its antioxidant activity and protective effects on the gastric mucosa. However, further studies need to be done to better understand the mechanisms involved. **Financial Support:** UFPA/FAPESPA. **References:** 1. Salehi B. Biomolecules, v. 9, p. 465, 2019; 2. Coast AR. S Afr J Bot, v. 135, p. 355, 2020; 3. George SP. J Agric Food Chem, v. 53, p. 1370, 2005; 4. Quettier-Deleu CB. J Ethnopharmacol, v. 72, p. 35, 2000; 5. Delcour JA. J Inst Brew, v. 91, p. 37, 1985; 6. Falcon AP. Cienc Tecnol Aliment, v. 27, p. 637, 2007; 7. Silva EM. Sep Purif, v. 55, p. 381, 2007; 8. Brad-Williams W. LWT-Food Sci Technol, v. 28, p. 25, 1995; 9. Mello VJ. Phytomedicine, v. 15, p. 237, 2008; 10. Moraes TC. Chem-Biol Interact, v. 183, p. 264, 2010. **Ethics committee license number**: CEUA-UFPA 3807311019.

08.009 **Impact of Cyclic AMP Efflux Induced by Phosphodiesterase Inhibitors and β2 Adrenoceptor Agonists on Airway Smooth Muscle Relaxation**. Satori NA, Pacini ESA, Godinho RO Unifesp-EPM, Div of Cellular Pharmacology, Dept of Pharmacology, São Paulo, Brazil

Introduction: Previous studies from our group have shown that β2 adrenoceptor agonists induce cAMP efflux through ABCC transporters in rat trachea (Pacini et al., J. Pharmacol. Exp. Ther., 366, 75, 2018). Then, the extracellular cAMP is converted into the bronchoconstrictor nucleoside adenosine by the ectoenzymes ecto-phosphodiesterases (ecto-PDE) and ecto-5'-nucleodidases (ecto-5'-NT) (Pacini et al., Biochem. Pharmacol., 192, 2021). However, it is not known whether PDE inhibitors are also able to promote the efflux of cAMP or the impact of PDE-induced cAMP efflux on the airway relaxation. Then, in the present study, we evaluated the effects of PDE inhibitors IBMX and aminophylline (non-selective) and roflumilast (PDE4-selective) on both the cAMP efflux and the relaxation of rat tracheal smooth muscle, comparing them with those of β2 adrenoceptor agonist formoterol. **Methods:** Isolated tracheal segments from adult male rats (Wistar, 3–4-month-old) were incubated for 60 min with IBMX (100 µM), aminophylline (1 mM), roflumilast (50 µM) or formoterol (10 µM), in the presence of ABCC transporter inhibitor MK-571 (40 µM), and the concentrations of extracellular cAMP were measured by immunoassay (n =4-8). In another set of experiments, we evaluated the relaxing effects of these PDE inhibitors on tracheal segments pre-contracted with carbachol (EC50 = 30. 5 ± 3. 9 µM), in the presence or absence of MK-571 (n =6). **Results:** All bronchodilators tested significantly increased the basal extracellular concentrations of cAMP (1,76 ± 0,12 µM) by 2014% (formoterol), 248% (IBMX), 114% (aminophylline) and 190% (roflumilast) ($p < 0.05$, Student's T test). The increment of extracellular cAMP induced by these drugs was prevented by pretreatment of tracheas with MK-571. All bronchodilators tested induced concentration-dependent relaxation of CCh-precontracted tracheas. However, while MK-571 potentiated the formoterol induced-relaxation (formoterol pEC50 = 5. 7 ± 0.1 versus +MK-571 pEC50 = 7. 2 ± 0.1, $p < 0.05$, Student T test), it did not change the relaxation of PDE inhibitors. **Conclusion:** In summary, our data show that all bronchodilators tested were able to induce cAMP efflux, with different impacts on tracheal smooth muscle relaxation depending on the type of drug used. Animal Ethics Committee: CEUA #1021240519 **Financial Support:** CAPES, CNPq 310498/2019-8 and Fapesp 18/21381-6.

08.012 **Farnesol Presents Low Toxicity and Gastroprotective Activity in Mouse Animal Models**. Pessôa MLS, Pessoa MMB, Araruna MEC, Alves Júnior EB, Alves VP, Batista LM UFPB Depto de Ciências Farmacêuticas, João Pessoa, Brasil

Introduction: Terpenes consist of a class of secondary metabolites present in the main medicinal activities of medicinal plants and are mainly diverse. It is in this context that the present study aimed to evaluate the gastroprotective activity of farnesol, which is a product of natural origin, belonging to the class of sesquiterpenes, being widely found in propolis and essential oils of aromatic plants. **Methods:** To evaluate the acute toxicity, male Swiss mice (mus musculus) were used, negative doses of 4h, divided into two groups (n=3):

control group (tween 80 5%) and test group (farnesol), of 300 mg/kg and 2000 mg/kg, treated orally. After treatment, general effects were observed within the first four hours. The intake of food and water was evaluated in the range of 1-14 days after the administration of the tested substance. At the end of this period, the organs were removed, and their organs (euthanized formation, hygiene, spleen and rinsing) were separated for analysis of the macroscopic index of organs (ALMEIDA et al., Brazilian Journal of Pharmacological Sciences, 80: 72, 1999). The gastroprotective activity was evaluated by the experimental protocol of gastric ulcer induced by immobilization and cold stress and non-steroidal anti-inflammatory drug (AINE) induced gastric ulcer. For this, mice were used, buds were fasted for 24 hours and treated with tween 80 5% (negative control), ranitidine 50 mg/kg (positive control) and farnesol at different doses. After 3 minutes, the animals were immobilized for 3 minutes in restraint and conditioned at a temperature of 4°C for a period of 3 hours to induce visits. Then, the stomachs were removed, and ulcers were found by quantifying the ulcerative lesion index (ILU) (LEVINE, et al., Munksgaard, Copenhagen, 30:92, 1971). For the A-induced gastric consultation protocol, the animals were treated according to the previous protocol, after 30 minutes, the consultation was induced by subcutaneous administration of piroxicam 30 mg/kg and 4 hours after this administration, the mice were euthanized, open and open stomachs for ILU determination (PUCAS et al., Drug Research, 47:568, 1997). Data were observed when $p<0.05$. **Results:** After the observation of the acute toxicity protocol, the animals treated with farnesol at the experimental doses showed no changes in the CNS and ANS toxicity protocol level, and there were no changes. Thus, it was possible to estimate that the LD50 of farnesol is equal to or greater than 5000 mg/kg. There was no significant reduction in the stress consultation of groups that were pre-treated with farnesol at the reduced doses of 25, 50, 100 and 200 mg/kg had significant ILU when compared to the negative control group, with a proportion reduction of 29%, 38%, 54% and 54% respectively. The same AINE consultation model was not observed for any dose calculated compared to the ILU when compared to the group when compared with the 3% control ratio of 3%, 4%, and 5% respectively. **Conclusion:** Thus, it is possible to suggest that farnesol has low toxicity and gastroprotective activity in the models and doses tested. Acknowledgments: Capes/UFPB/PgPNSB/IPeFarm. Ethics Committee on Animal Use (UFPB): 2022/1317290422

08.013 **Estragole Prevents Duodenal Ulcer and Improves Gastric Healing with Involvement of Antioxidant and Immunomodulatory Pathways in Animal Models**. Alves Júnior EB[1], Serafim CAL[1], Araruna MEC[1], Pessôa MLS[1], Pessoa MMB[1], França JS[1], Antunes AA[2], Batista LM[1] [1]UFPB, [1]UFRN

Introduction: Estragole is a phenylpropanoid derived from cinnamic aldehydes present in essential oils of plant species such as *Ravensara anisata* (Madeira) and *Ocimum basilicum* (Manjericão). Pharmacological studies report its gastroprotective activity, including gastroprotection. Therefore, the present study aimed to evaluate the duodenal antiulcerogenic activity in the cysteamine-induced ulcer model and the antioxidant and immunoregulatory mechanisms involved in gastric healing in the acetic acid-induced ulcer model in rats. **Methods:** It was used male Wistar rats (Rattus norvegicus) 180-250g. From the cysteamine-induced ulcer model, animals (n=10) were submitted to induction of duodenal ulcer by cysteamine (SZABO, S. et al. Pharmacology Experimental Ther, v. 240, n. 3, p. 871, 1987) and treated (v. o) with 5% tween 80 (control), lansoprazole 30 mg/kg (positive control) or estragole (31; 62; 125 or 250 mg/kg), ulcers were determined by the ulcerative lesion area (ULA) and macroscopic evaluation of the lesion were evaluated. In gastric healing in the acetic acid-induced ulcer model (TAKAGI, K. Japanese Journal of Pharmacology, v. 3, p. 418, 1969), animals (n=12) were divided into the following groups: 5% tween 80, lansoprazole 30 mg/kg or estragole (250 mg/kg). After 14 days of treatment with daily doses, ULA, repeated dose toxicity, and tissue fragments of stomachs approximately 2 cm2 to measure levels of antioxidants and cytokines. The antioxidants evaluated were reduced glutathione (GSH) (FAURE, P. Birkhäuser Basel, v. 1 p. 237, 1995.), malondialdehyde (MDA), myeloperoxidase (MPO) (KRAWISZ, J. E. Gastroenterology, v. 87, p. 1344, 1984). The cytokines evaluated were interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10), by the ELISA method. Results were expressed as mean ± standard deviation (s. d.) and ANOVA was used followed by Dunnett and/or Tukey post-tests, analyzed with the software, GraphPad Prism 6. 0. The assay was considered significant when $p<0.05$. **Results:** In the cysteamine-induced duodenal ulcer model in rats, it was shown that estragole 31, 62, 125, and 250 mg/kg and lansoprazole (30 mg/kg) reduced ALU significantly ($p<0.001$) when compared to the negative control group (5% tween 80) with percentages of injury inhibition of 52, 53, 72, 87 and 77%, respectively. In the acetic acid-induced gastric

ulcer induction model in rats, the most effective dose of estragole (250 mg/kg) and lansoprazole (30 mg/kg) significantly reduced ULA (p<0. 001) when compared to the control group (5% tween 80), presenting percentages of gastric healing of 60 and 73%, respectively. Estragole the most effective dose (250 mg/kg) increased (p<0,001) levels of reduced glutathione (GSH) to 19. 82 ± 2,4 nmol of GSH/mg and reduced (p<0,001) levels of malondialdehyde (MDA) and myeloperoxidase (MPO) to 70,98 ± 7,36 nmol of MDA/g and 7,11 ± 1,24 unit of MPO/g, respectively. It reduced (p<0,001) the levels of IL-1β and TNF-α to 66,51 pg of IL-1β/mL and 1,527 ± 226. 9 pg of TNFα/mL, respectively, and increased (p<0,001) levels of IL- 10 to 271,6 ± 14,7 pg of IL-10/mL. **Conclusions:** Thus, it was possible to conclude that the estragole presents high safety and low toxicity when administered in repeated doses for 14 days, with duodenal anti-ulcer activity and potential pro-healing effect on gastric lesions with the involvement of immunoregulatory and antioxidant pathways. Acknowledgment: CNPq/UFPB/PgPNSB/IPeFarM. Ethics Committee on Animal Use (UFPB): Protocol number 4120010819/20.

08.014 **The Local Anaesthetic Derivative JME-209 Improves Steroid Resistance in Distinct Murine Models of Lung Airway Diseases: Impact on Oxidative Stress**. Gomes: HS[1], Coutinho DS[1], - Cotias AC[1], Costa JCS[2], Carvalho VF[1], Martins PMRS, Martins MA[1] [1]IOC-Fiocruz – Lab Immunopharmacology, Rio de Janeiro, Brazil, [2] IOC-Fiocruz – Production and Innovation in Health

Lung inflammatory diseases constitute a significant health problem worldwide, with high mortality and morbidity rates. In these diseases, inflammation plays a central role, closely related to airway obstruction and tissue remodelling. Glucocorticoids are by far the most effective treatment for this group of diseases. However, for an estimated 5% of asthmatic patients and almost all COPD patients, novel forms of therapy are badly needed since their symptoms remain uncontrolled even after a high dose of steroidal anti-inflammatory drugs. Prior investigations have demonstrated that local anaesthetics like lidocaine and mexiletine could inhibit bronchoconstriction and inflammation in severe asthmatic patients. However, the anaesthesia of airways results in the blockade of protective bronchodilator reflexes, limiting their putative use in treating lung inflammatory diseases. The current study was undertaken to test the hypothesis that the mexiletine analogue JME-209, which has been screened for the attenuated inhibitory effect on sodium channels, possesses anti-inflammatory and bronchodilator activity under conditions of steroid resistance. In this context, we sought to evaluate JME-209 activity in distinct murine models of lung airway diseases marked by glucocorticoid-resistant inflammation. **Methods:** For the LPS and Poly I:C protocols, male A/J mice were exposed to LPS or Poly I:C for three consecutive days. Treatments with dexamethasone or JME-209 were performed 1 h before each LPS or Poly I:C instillation. For the cigarette smoke exposure protocol, female C57BL/6 mice were exposed to cigarette smoke for four consecutive days. The animals were treated with mexiletine, roflumilast or JME-209 1 h before each smoke exposure. The analysis was performed 24 h after the last LPS, Poly I:C or cigarette smoke exposure. The statistical analysis was performed using the GraphPad Prism Software (Version 5. 0) and the results are expressed as the means ± SEM. All data were evaluated to ensure normal distribution and were statistically analyzed by the one-way ANOVA test followed by the Newman–Keuls–Student test or by two-way ANOVA test followed by Bonferroni test. Differences in values were considered statistically significant if p< 0.05. **Results:** While the corticosteroid drug dexamethasone was ineffective, JME-209 inhibited the airway hyper-reactivity and the corticosteroid-resistant inflammation in a mechanism related to the reduction of the pro-inflammatory cytokines KC, MIP-1α and IL-1β in mice lungs caused by LPS or Poly I:C. We also observed that JME-209 and roflumilast, but not mexiletine, were effective in inhibiting the inflammatory infiltrate and the augmented pro-inflammatory mediator levels in cigarette smoke-exposed mice. In addition, only JME-209 treatment could inhibit oxidative damage in mice lungs. **Conclusion:** The biphenoxy-alkyl-amine JME-209 combines anti-inflammatory and anti-spasmodic properties and may be a promising drug for treating corticosteroid-insensitive neutrophilic airway inflammation associated with lung diseases such as COPD and severe asthma. **Financial Support:** CAPES, CNPq and Faperj. The licence number of the ethics committee: (CEUA license number – L002/20).

08.015 **(-)-Fenchone Prevents Cysteamine-Induced Duodenal Ulcers and Accelerates Healing of Gastric Ulcers in Rats Via Antioxidant and Immunomodulatory Mechanisms**. Araruna MEC[1], Alves Júnior EB[1], Serafim CAL[1], Pessôa MLS, Pessoa MMB[1], Alves VP[1], Araújo AA[2], L Batista LM [1]UFPB, [2]UFRN

Introduction: (-)-Fenchone is a naturally occurring monoterpene in the essential oil of plants such as Foeniculum vulgare, Thuja occidentalis, *Peumus boldus* and *Mesosphaerum sidifolium*. Pharmacological studies report its antinociceptive, antimicrobial, anti-inflammatory, antidiarrheal and antioxidant activity. Therefore, the present study aimed to evaluate the duodenal antiulcer activity, gastric healing and toxicity of (-)-Fenchone in rats. **Methods:** It was used male Wistar rats (Rattus norvegicus) 180-250g. From the cysteamine-induced ulcer model, animals (n=10) were submitted to induction of duodenal ulcer by cysteamine and treated (v. o) with 5% tween 80 (control), lansoprazole 30 mg/kg (positive control) or (-)-fenchone (37. 5, 75, 150 or 300mg/kg), ulcers were determined by the ulcerative lesion area (ULA) and macroscopic evaluation of the lesion were evaluated. In gastric healing in the acetic acid-induced ulcer model, animals (n=12) were divided into the following groups: 5% tween 80, lansoprazole 30 mg/kg or (-)-fenchone (150 mg/kg). tissue fragments of stomachs approximately 2 cm^2 to measure levels of antioxidants and cytokines. The antioxidants evaluated were reduced glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO). The cytokines evaluated were interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10), by the ELISA method. Results were expressed as mean ± standard deviation (s. d.) and ANOVA was used followed by Dunnett and/or Tukey post-tests, analyzed with the software, GraphPad Prism 6. 0. The assay was considered significant when $p<0.05$. **Results:** In the cysteamine-induced duodenal ulcer, fenchone (37. 5 –300 mg/kg) decreased significantly the ulcer area ($p<0. 001$) with injury inhibition percentages of 31, 68, 74 and 76%, respectively. In the acetic acid-induced ulcer model, fenchone (150 mg/kg) reduced ($p<0. 001$) the ulcerative injury. These effects were related to an increase in the levels of reduced glutathione (GSH) (79. 9 ± 9. 4 nmol GSH/mg protein), superoxide dismutase (SOD) (5. 9 ± 0. 48 U of SOD/mg of protein) and interleukin (IL)-10 (207. 4 ± 17. 30), and reduced ($p<0. 001$) malondialdehyde (MDA) (57. 9 ± 6. 4 nmol MDA/g of tissue), myeloperoxidase (MPO) (5. 7 ± 1. 7 unit of MPO/g of tissue), interleukin-1 beta (IL-1β) (258. ± 24. 58) and tumor necrosis factor-alpha (TNF-α) (1398 ±86. 20) levels. Oral toxicity investigation for 14 days revealed no alterations in heart, liver, spleen, and kidneys weight nor the biochemical and hematological assessed parameters. (-)-Fenchone protected animals from body weight loss maintaining feed and water intake. **Conclusion:** (-)-Fenchone presents low toxicity, prevent duodenal ulcers and gastric healing activities. Antioxidant and immunomodulatory properties seem to be involved in the curative effect. Acknowledgments: CNPq / CAPES / UFPB. Ethics Commission on Animal Use (CEUA/UFPB): 7216040119/19.

08.016 *Cissampelos sympodialis* **extract attenuates cigarette smoke-induced acute lung injury in mice**. Queiroz Neto RF[1], , Oliveira-Melo P[2], Barbosa-Filho JM[3], Silva FAC[1], Manzuti GM[2], Santos CCA[1], Silva AGG, Moura MJN[1], Silva GM[1], Borges CS[1], Kennedy-Feitosa E[1], Oliveira MF [1]UFERSA [2]InCor-HC-USP, [3]UFPB

Introduction: Cigarette smoke (CS) is able to induce acute lung injury (ALI) with increase of inflammatory cells and mediators release following tissue damage. The hydroalcoholic extract of *Cissampelos sympodialis* (ECsy) is rich in alkaloids and has been used in the treatment of respiratory diseases due to its anti-inflammatory and antioxidant activity. Aim: To evaluate the pharmacological action of the ECsy on CS-induced acute lung injury in mice. **Methods:** CEUA (16/2020). Male C57BL/6 mice (±23g) were divided into five groups: Control, Cigarette smoke (CS), CS + 10, CS + 100 and CS + Dexa. The CS groups were exposed to 12 cigarettes/day for 5 days and treated with salina (CS), ECsy (10 or 100mg/mL by nebulization; 15min/day; CS + 10 and CS + 100) or dexamethasone (0,4 mg/mL i. p; CS + Dexa) for 5 days. The control group was exposed to ambient air and treated with salina. After 5 days, lungs were collected to evaluate the inflammatory and oxidative stress profile. Significant difference was considerate when $p<0.05$. **Results:** Number of cells (106/mL) increased in CS group when compared to control group (0. 96 ± 0. 04 vs. 0. 41 ± 0. 04; $p<0. 0001$). CS + 10, CS + 100 and CS + Dexa showed a decrease of this number of cells (0. 09 ± 0. 02; 0.19 ± 0. 01 and 0.142 ± 0. 02; $p<0. 0001$). MDA levels were significantly increased in the CS group when compared to the control group (321. 4 ± 37. 2 vs. 158. 9 ± 14. 6; $p<0. 001$), as well as a significant reduction in the CS + 10 (227. 8 ± 16. 0), CS + 100 (218. 5 ± 15. 7; $p<0.05$) and CS + Dexa groups (194. 8 ± 18. 7; $p<0. 01$). Myeloperoxidase (MPO) activity increased in the CS group when compared to the control group (16. 08 ± 2. 56 vs. 6. 08 ± 0. 59; $p<0.05$) and it was reduced in the CS + 100 (0. 84 ± 0.13; $p<0. 0001$) when compared to all of the groups. The increase of reactive oxygen species (ROS) was

evident in the CS group (0.12 ± 0. 01) when compared with the control group (0. 06 ± 0. 00; p<0.05). ROS levels decreased in the CS + 100 (0. 06 ± 0. 00; p<0.05) and CS + DEXA (0.05 ± 0. 00; p<0. 001) groups. **Conclusion:** These results demonstrate the anti-inflammatory and antioxidant potential of ECsy cigarette smoke-induced acute lung injury.

08.017 **Supplementation with *Spirulina platensis* Prevents Changes in Intestinal Contractile Reactivity by Inhibiting ROCK and Increasing SOD In Rats Fed a Hypercaloric Diet**. Ravilly RAA, Diniz AFA[1], Claudino BFO[1], Francelino DMC[1], Barros BC, Lacerda Júnior FF[2], Ferreira PB, Silva BA [1]UFPB, [2]UFPE

Introduction: Characterized by the growing and excessive accumulation of body fat, obesity is due to the imbalance between an individual's caloric consumption and energy expenditure (LOPES et al., BrazJHealthRev, v5, p578, 2022). Predominantly multifactorial, complex and with a chronic inflammatory basis, it is associated with numerous complications, including insulin resistance, cardiovascular diseases and gastrointestinal disorders (KAJANI et al., Molecular Metabolism, v. 56, 2022). Thus, it is necessary to search for new therapeutic alternatives that help in the treatment of these comorbidities. *Spirulina platensis* (SP) a blue-green algae has anti-obesity (ZHAO et al., PloSOne, v14, 2019) and antioxidant (ABDEL-MONEIM et al., SaudiJournalofBiolSci, v29, p1197, 2022) properties, as well as our group of research has shown effects on the intestinal tract of obese rats (DINIZ et al., OxidMedCellLongev, 2021). Therefore, the objective of this work was to investigate the mechanisms of action of S. platensis involved in the prevention of damage caused by the hypercaloric diet on contractile reactivity and oxidative stress. **Methods:** Wistar rats (8 weeks old) were divided into 3 experimental groups, which received standard diet (SD), hypercaloric diet (HCD) and/or hypercaloric diet and supplemented simultaneously with S. platensis powder at the of 25 mg/kg (HCD + SP25). The isolated ileum of the rats was mounted in bath vats for isolated organs and the organ reactivity was monitored. The animals received the different diets and supplementation for a period of 8 weeks. Results were expressed as mean and standard deviation of the mean and analyzed by one-way ANOVA followed by Tukey's post-test ($p < 0.05$, n=5 per test group). **Results:** In the group fed only the hypercaloric diet, there was a reduction in contractile efficacy (Emax = 23. 5 ± 1. 7%), when compared to the concentration curve in the absence of tempol, a mimetic of superoxide dismutase (SOD) (Emax = 32. 7 ± 7. 5%), without changes in carbachol potency (CCh). In this group, in the presence of Y27632, a ROCK (Rho kinase) inhibitor, a reduction in the maximum effect of CCh (Emax = 21. 9 ± 1. 1%) is observed when compared to the absence of this inhibitor. Food supplementation with S. platensis at a dose of 25 mg/kg promoted a decrease in the maximum effect of CCh in the presence of tempol (Emax = 31. 3 ± 2. 5%), when compared to its absence (Emax = 63. 9 ± 0. 9 %). Similarly, in the presence of the ROCK inhibitor, seaweed supplementation promoted a 2. 3-fold reduction in the contractile efficacy of CCh (Emax = 27. 4 ± 3. 3%) when compared to its absence (Emax = 63. 9 ± 0. 9 %). **Conclusions:** In view of the results, it can be concluded that *Spirulina platensis* prevented the damage caused by the consumption of the hypercaloric diet in the contractile reactivity of the ileum of rats, and that such effects may be associated with the ROCK pathways, decreasing the expression and/or activity of this enzyme and also to the antioxidant effect, increasing the availability of SOD. Support: CnPq, PPgPNSB/UFPB. Research approval: CEUA/UFPB 2352101019.

08.018 **Mechanism of Action of *Hibiscus sabdariffa* Reversing Functional Alterations in the Trachea of Wistar Rats with Obesity-Exacerbated Asthma** Ferreira SRD[1], Pessoa RF[1], Figueiredo IAD[1], Martins AMO[2], Vasconcelos LHC[3], Cavalcante FA[3] [1]UFPB-PPgPNSB João Pessoa, Brazil, [2]UFPB-PIBIC João Pessoa, Brazil, [3]UFPB, Dpt of Physiology and Pathology, João Pessoa, Brazil

Introduction: Obesity-exacerbated asthma is one of the phenotypes of asthma, characterized by a greater number of symptoms, and development of resistance to corticosteroids (PETERS, J Allergy Clin Immunol, 141, 1169, 2018), making treatment difficult. In this context, a promising drug is *Hibiscus sabdariffa* (HS), popularly known as “hibiscus”, which has already shown anti-obesity activity (MORALES-LUNA, J Sci Food Agric, 99, 596, 2018) and spasmolytic action in guinea pig trachea (ALI, J Ethnopharmacol, 31, 249, 1991). Thus, the aim of this study was to evaluated effect of HS involved in reversing the functional changes induced by obesity-exacerbated asthma in rats. **Methods:** Wistar male rats (n=3-5) were divided into groups: control (CG), obese asthmatic (OAG) and obese asthmatic treated with HS 250 (OAH250G), 500 (OAH500G) and 1000 mg/kg (OAH1000G). For inducing obesity, the animals were fed with a high glycemic level index diet for 16 weeks, and for inducing

asthma they were sensitized and challenged with ovalbumin in the last 22 days of the 16 weeks (FERREIRA, Sci Rep., 1, 2022). The oral treatment with HS was performed in the last 30 days of the 16 weeks. After euthanasia, trachea was isolated and suspended in organ bath and isometric contractions were evaluated. Results were expressed as mean ± standard error of the mean and analyzed by ANOVA one-way followed by Tukey's posttest using GraphPad Prism software. **Results:** It was seen that HS reversed the increase in contractile efficacy of carbachol (CCh) observed in OAG (Emax=152. 6±5. 5%) only in OAH500G (Emax=114. 9±5. 6%), compared to CG (Emax=100%). To investigate nitric oxide pathway, the trachea was pre-incubated with L-NAME, a non-selective NO synthase inhibitor, prior to CCh-induced cumulative contractions and no change in CCh contractile potency or efficacy between groups was observed. Oxidative stress pathway also was evaluated employing apocynin, an NADPH oxidase inhibitor, observing in OAH500G a reduction in both contractile efficacy and potency of CCh in the presence of the inhibitor (EC50=5. 1±0.1x10-7 M; Emax=79. 0±5. 5%), compared to CG (EC50=1. 7±0. 5x10-6M;Emax=93. 3±5. 9%) and OAG (EC50= 2. 2±0. 3x10-6M; Emax=99. 3±3. 8%). In the presence of tempol, a mimetic of superoxide dismutase, contractile potency of CCh was not altered between groups, however the increase in contractile efficacy observed in GOA was reversed in OAH500G (Emax=86. 8±2. 6;97. 7±4. 0 and 85. 0±1. 2% for CG, OAG and OAH500G, respectively). In the evaluation of involvement of prostanoids and leukotrienes, there was reduction only in contractile potency of CCh in the presence of both indomethacin, a COX inhibitor (EC50 = 6. 2 ± 1. 8 x 10-6 M), and zileuton, a LOX inhibitor (EC50 = 5. 9 ± 0. 8 x 10-7M), in OAH500G compared to OAG (EC50=2. 5±0. 5x10-6M; EC50=1. 5±0.1 x 10-7 M, respectively) and CG (EC50 = 1. 3 ± 0.1 x 10-6 M; EC50 = 1. 0 ± 0. 3 x 10-6 M, respectively). In Rho-associated protein kinase (ROCK) pathway investigation, the decrease in inhibitory effect of Y-27632, a ROCK blocker, in OAG (Emax=30. 9±4. 7%), compared to CG (Emax=17. 9±3. 6%), was reverted in OAH500G (Emax=20. 6±3. 9%). **Conclusions:** Treatment with HS appears to be promising for treatment of obesity-exacerbated asthma by reducing the production of reactive oxygen species, COX and LOX products and reversing the upregulation of ROCK. Ethical Committee on Animal Use of UFPB (protocol 1162100918). **Financial Support:** CNPq, PPgPNSB/CCS/UFPB.

08.019 **Extracellular Cyclic AMP Induces Airway Smooth Contraction Through Mast Cell Degranulation in Ovalbumin-Sensitized Rat**. Pacini ESA, Tavares-de-Lima W[2], Godinho RO[1] [1]Unifesp-EPM, Dept of Pharmacology, São Paulo, Brazil, [2]ICB-USP Dept of Pharmacology, São Paulo, Brazil

Introduction: 3',5'-cyclic AMP (cAMP) is a universal intracellular second messenger involved in many biological processes, such as muscle contraction, cell proliferation and gene expression. In the respiratory tract, intracellular cAMP has a crucial role in the smooth muscle relaxation induced by β2-adrenoceptors (β2-AR)/Gs protein/adenylyl cyclase axis. In addition to its classical intracellular function, in airways cAMP works as an extracellular third messenger, which depends on its efflux and extracellular conversion into 5'-AMP and adenosine by ecto-phosphodiesterase and ecto-5'nucleotidase, respectively (Pacini et al., Front. Pharmacol. 13:866097, 2022). Nevertheless, the biological role of extracellular cAMP in the airway smooth muscle into the pathobiology of asthma and hyperresponsiveness is unknown. **Methods:** Male Wistar rats (8-9 weeks) were sensitized with 10 µg of ovalbumin (OVA) suspended in ImjectTM Alum (Thermo Fisher Scientific Inc.) on days 0 (ip) and 7 (sc). On day 14, animals were euthanized and tracheal segments were mounted in an organ-bath system containing Krebs-bicarbonate buffer at 37°C. After tissue stabilization, tracheas were preincubated with increasing concentrations of ovalbumin (0. 01-10 µg. ml-1) for 60 min, and then were stimulated with cAMP (300 µM) and adenosine (100 µM). In another set of experiments, tracheas were treated with Compound 48/80 (100 µM) and after 30 min of exposure were preincubated with ovalbumin (0. 01 µg. ml-1) for 60 min. Next, tracheas were incubated with cAMP (300 µM) or adenosine (100 µM) and isometric tension was continuously measured with a force transducer. All values were expressed as mean ± S. E. M. and normalized as percentage of maximal response to carbachol (CCh 1 µM). **Results:** Incubation of tracheal segments from sensitized rats with increasing non-cumulative concentrations of ovalbumin (0. 01-10 µg. ml-1) resulted in phasic contractions that reached amplitude of 19. 3% ± 5. 7 to 41. 7% ± 3. 9 (n=10-12) and returned to basal tone after 15 min. After 60 min exposure to ovalbumin (0. 01-10 µg. ml-1), exogenous cAMP and adenosine also induced phasic contractions. however, the maximal amplitude of cAMP-induced contraction was inversely proportional to the concentration of ovalbumin used, reaching 15. 6% ± 3. 8 and 2. 9% ± 1. 2 of CCh contraction ($P<0.05$; t-test) in the presence of 0. 01 µg. ml-1 and 10 µg. ml-1 ovalbumin, respectively (n=6). After exposure to ovalbumin,

adenosine-induced contraction obeyed the same profile observed for cAMP, reaching 25. 5% ± 4. 6 and 10.1% ± 2. 7 of CCh contraction (P<0.05; Mann-Whitney test) in the presence of 0. 01 µg. ml-1 and 10 µg. ml-1 ovalbumin, respectively (n=6). In addition, pretreatment of tracheal segments from sensitized rats with the mast cell degranulator compound 48/80 reduced by 3-fold and 8-fold (P<0.05; t-test) the cAMP and adenosine amplitude of contraction, respectively (n=7), whereas incubation of sensitized tracheas with compound 48/80 alone caused a phasic contraction (25. 7% ± 3. 6 of CCh contraction) (n=14). **Conclusion:** Our results show that extracellular cAMP and adenosine induce tracheal smooth muscle contraction via mast cell degranulation and release of inflammatory mediators, indicating a role of the extracellular cAMP-adenosine pathway in the pathophysiology of airway obstruction and hyperresponsiveness. CEUA: #9987150714 **Financial Support:** CAPES, CNPq 310498/2019-8 and Fapesp 18/21381-6.

08.020 **Nanoemulsion Containing Pequi Oil Improves Lipopolysaccharide-Induced Lung Inflammation in Mice**. Coutinho DS[1], Pires J[2], Gomes HS[1], Pohlmann AR[3], Guterres SS[4], Martins PMRS, Martins MA[1], Ferrarini SR[2], Bernardi A[1] [1]IOC-Fiocruz, Lab Immunopharmacology, Rio de Janeiro, Brazil, [2]ICS-UFMT, Sinop, Brazil, [3]UFRGS, Dpt of Organic Chemistry, Porto Alegre, Brazil, [4]UFRGS, PPG Pharmaceutical Sciences, Porto Alegre, Brazil
Introduction: Inflammatory lung disorders are important health problem due to their high mortality and morbidity. Current therapy consists of the use of steroidal anti-inflammatory drugs and bronchodilators, however, adverse effects and refractoriness to treatment are described. Pequi (*Caryocar brasiliense* Cambess) is a Brazilian Cerrado fruit, widely used in folk medicine to control lung diseases such as asthma and bronchitis. However, the hydrophobic and easily oxidized profile of pequi oil is an obstacle to its administration in biological models. In this scenario, the use of nanotechnology becomes a promising way to overcome such barriers. So, the aim of this study was the development of nanoemulsions containing pequi oil and the evaluation of their potential pharmacological effect in a murine model of lung inflammation induced by lipopolysaccharide (LPS). **Methods:** The nanoemulsion formulations were prepared by spontaneous emulsification method. Regarding the pharmacological evaluation, male A / J mice were treated 16 and 4 h before LPS instillation, with unloaded nanoemulsion, with the free pequi oil or with nanoemulsion containing Pequi (Pequi-NE) at dose of 20 mg/kg, orally. After 18 h of LPS exposure the analysis were performed. Statistical analysis was performed using the GraphPad Software 5. 0. All data were evaluated to ensure normal distribution and statistically analyzed by one-way ANOVA followed by the Newman–Keuls–Student test or two-way ANOVA followed by Bonferroni test. $P \leq 0.05$ was considered significant. **Results:** The analysis indicated that nanoparticles presented an average diameter of 174–223 nm, zeta potential of -7. 13 ± 0. 08 mV and pH of 5. 83 ± 0.12 (Mean ± standard deviation of 3 batches). The in vivo analysis showed that oral pre-treatment with Pequi-NE improves the free pequi oil anti-inflammatory effect, abolishing the leukocyte accumulation into bronchoalveolar fluid (BALF). Pequi-NE, but not free pequi oil or unloaded nanoemulsion, reduced also the pulmonary myeloperoxidase (MPO) levels and the production of the pro-inflammatory mediators: TNF-α, IL-1, IL-6, MCP-1 and KC. Moreover, the treatment with pequi-NE abolished LPS-induced airway hyperreactivity (AHR), as attested by lung elastance response. To determine whether the effects of pequi-NE were related to its major component, we compared the effect of nanoemulsions containing pequi to nanoemulsion containing oleic acid in the LPS-induces murine lung inflammation model. Similar anti-inflammatory effects were observed when LPS-exposed animals were pre-treated with the nanoemulsion containing Pequi or oleic acid. **Conclusion:** In conclusion, these results suggest that formulation of nanoemulsion containing pequi can improve its anti-inflammatory properties and that the pequi therapeutic effect is probably due its high levels of oleic acid. Financial Support FAPERJ, CAPES and CNPq. Animal Research Ethical Committees: CEUA license number - LO30/15

08.021 **Respiratory Parameters and Respiratory Mechanics in Senescence Mice Model**. Oliveira MA[1], Lino Alvarado AE[3], Maia OAC[2], Moreira TS[2], Tavares-de-Lima W[1], Moriya HT[3] [1]ICB-USP, Dept of Pharmacology, São Paulo, Brazil, [2]ICB-USP, Department of Physiology, São Paulo, Brazil, [3]USP, Lab of Biomedical Engineering, Escola Politécnica, São Paulo, Brazil
Respiratory parameters and respiratory mechanics in senescence mice model. **Introduction:** Neurodegenerative disorders such as Alzheimer's Disease (AD) account for aging and may induce respiratory failure (RF). Despite the clinical and experimental studies, the mechanisms of RF are not fully clarified. Senescence Accelerated Mouse Prone 8 (SAMP8) is a senescence model with AD traits and has been widely used to evaluate this disorder

[Grinán-Ferré et al. J. Alzheimer's Dis. 2018; 62: 943-963]. OBJECTIVE: To evaluate possible changes in respiratory parameters and respiratory mechanics in SAMP8. **Methods:** Male SAMP8 and its respective control, SAMR1 (10 months old), were used to quantify tidal volume (VT), respiratory rate (fR), and ventilation (VE) using whole-body plethysmography (EMKA Technologies). Airway resistance (Raw), parenchymal resistance (G), and the elastance of the pulmonary parenchyma (H) were evaluated (FlexiVent, SCIREQ®, Canada) after the Methacholine (MCh) challenge (CEUA – ICB/USP: 6155190718). All data were analysed using Two-way analysis of variance (ANOVA) followed by Sidak's multiple comparisons test (using Graph-Pad Prism, version 6. 01). Data are reported as mean values ± standard error of the mean (SEM), with "n" indicating the number of experiments. For all comparisons, differences were considered statistically significant at $p<0.05$. **Results:** Under baseline conditions SAMP8 showed an increase in VT (SAMR1: 12. 47 ± 1. 27, n=9 vs SAMP8: 19. 75 ± 1. 22 µL/g*, n=14). Hypoxia (5 min) and hypercapnia (5 min) increased VT in SAMP8 (Hypoxia - SAMR1: 11. 94 ± 1. 07 vs SAMP8: 20.14 ± 1. 11 µL/g*), (Hypercapnia - SAMR1: 17. 83 ± 1. 47 vs SAMP8: 28. 70 ± 1. 38 µL/g*). In the same condition, hypoxia and hypercapnia decreased fR (Hypoxia - SAMR1: 278. 40 ± 12. 07 vs SAMP8: 182. 40 ± 12. 92 breaths/min*), (Hypercapnia: SAMR1: 242. 70 ± 5. 07 vs SAMP8: 200. 90 ± 10. 78 breaths/min*). MCh challenge promoted lower response in Raw and G in SAMP8 in comparison with SAMR1 (Raw - SAMR1: 658. 80 ± 87. 84, n=14 vs SAMP8: 283. 80 ± 34. 01%*, n=16 and G – SAMR1: 124. 3 ± 14. 69, n=14 vs SAMP8: 44. 82 ± 6. 26%*, n=16). *$p<0.05$ in comparison with SAMR1. **Conclusion:** Our data suggest that middle-aged SAMP8 strain developed changes in respiratory parameters and respiratory mechanics likely associated with the senescence process. **Financial Support:** Fapesp, Capes and CNPq.

08.022 **Use of Phytotherapy with Anti-Inflammatory and Antioxidant Potential in Celiac Patients**. Marques CRS[1], Saboia KA[1], Costa LA[2], Milhome Y[1], Borges AG[1] [1]Centro Universitário Estacio do Ceará, [2]ICC-Hospital Haroldo Juaçaba, Fortaleza, Brazil

Celiac Disease is a permanent autoimmune enteropathy triggered by previous exposure to gluten that influences an inflammatory and oxidative process, mainly in the small intestine mucosa, inducing atrophy or loss of villi, resulting in malabsorption of nutrients. Herbal medicines are drugs prepared exclusively with medicinal plants or parts of plants that have recognized properties for symptomatic treatment of diseases and have obtained promising results in pharmacological models of inflammation Considering that the only treatment available to date for Celiac Disease is the permanent and definitive gluten-free diet. The Objective of the present study was to evaluate the use of herbal medicines with anti-inflammatory and antioxidant potential in celiac patients, since herbal medicines are medicines prepared exclusively with medicinal plants or plant parts that have recognized properties for the symptomatic treatment of diseases and have obtained promising results in pharmacological models of inflammation. Methodology: Exploratory and quantitative transversal analysis, approved by the Ethics Committee under opinion number 3. 550. 796. The research was carried out through the applicability of an electronic questionnaire using the Google Forms platform, available on the ACELBRA-CE website and social networks between the months of August and November of the year 2021. The collection was carried out for convenience, resulting in 21 patients celiacs who were members of the association. **Results:** The highest incidence of Celiac Disease was in females, 90. 5%; 57. 1% of patients have comorbidities, among which: allergies 28. 6%, gastritis/ulcer 28. 6%, diabetes 19%, respiratory 19% and arthritis/arthritis 9. 6%; 47. 6% of patients reported using some type of medication daily, including: vitamin supplements 33. 3%, analgesics 14. 3%, antiepileptics 9. 6%, probiotics 9. 6%, non-steroidal anti-inflammatory drugs 9,6 %, steroidal anti-inflammatory drugs 4. 8%, and antidepressants 4. 8%; regarding complementary integrative practices: 66. 7% of the patients had or are undergoing some treatment considered alternative medicine, among which: acupuncture 57. 1%, herbal medicine 14. 3%, homeopathy 14. 3% and thermalism 14. 3%, 61. 9% stated that the treatment was efficient, 85. 7% claimed to know herbal medicines, 38. 1% stated that they use or have used herbal medicines, 81% stated that they would use herbal medicines for the treatment of Celiac Disease and 61. 9 % usually drink herbal teas, including: Chamomile 28. 6%, mint 19%, fennel 19%, cider 14. 3%, aloe vera 14. 3%, ginger 9. 6% and boldo 9. 6 % and; 71. 4% of the patients underwent specific blood tests for Celiac Disease and in 84. 6% of the tests some biochemical marker for inflammation or oxidation was detected, including: HSV, anti-tTG, antigliadin. **Conclusion:** The results of the present study show the use of herbal medicines by celiac patients, and it was also observed that the use of complementary integrative practices showed an effective response in the

reactivation of the symptoms of Celiac Disease. keywords celiac disease, herbal medicines, Intestinal. References SOMANI, S. J.; MODI, K. P.; MAJUMDAR, A. S.; SADARAN, B. N. Review of phytochemicals and their potential usefulness in inflammatory bowel disease. Research in Phytotherapy, 2015. SZONDY, Z.; et al. Transglutaminase 2 in human diseases. Biomedicine, Taipei, 2017.

09. Natural Products and Toxinology

09.001 **Inhibition of *Aedes aegypti* Larvae Angiotensin Converting Enzymes (ACE 1/ACE 2) Homologues by *Cecropia glazioui* Sneth Extracts. A Potential Non-Toxic Insecticide**. Pederiva VP, Tanae MM, Myamoto DT, Lapa AJ EPM-Unifesp, Dpt of Pharmacology, São Paulo, Brazil

Introduction: Mosquitoes that transmit arboviruses (dengue, zika, chikungunya, yellow fever), or malaria and filariasis, are becoming more resistant to insecticides of low human toxicity. The lack of vaccines and specific drugs against those vectorial diseases is aggravated by the low output in the search for new insecticides to prevent outbreaks of these diseases [1,2]. Therefore, natural insecticides could be promising to the emergent control of vectors, mainly if the mechanisms of action differ from those which developed pharmacological resistance. This work correlates the ACE inhibition in Aedes aegypti larvae to the growth inhibition and death produced by C. glazioui and its chemical compounds. **Methods:** ACE was determined by the quenched fluorescence method (FRET) [3,4] using the substrates: Abz-FRK (Dnp)P-OH for ACE1 and Mca-APK(Dnp) for ACE2. In either case, ACE dissociates the quencher acceptor from the fluorescent group. Since the semi-purified butanolic fraction (Fbut (0,03-1 mg/mL) and the flavonoids (orientin, isoorientin and isovitexin (10-100 µM) inhibited the *in vitro* ACE activity, they were chosen to be tested in vivo. The larvicidal test [5] was performed in 24-well clear plates by exposing L1 instar stage of Aedes aegypti larvae to Fbut (0. 3-30. 0 mg/mL) or flavonoids (0. 03-0. 3 mg/mL). Lethality was recorded after 24, 48 and 72h comparatively to the control group (distilled water). The larvae development into pupae was followed up for 2 weeks. Results: ACE activity in the larvae homogenate was a mix of ACE1 and ACE2. Fbut inhibited ACE1 activity with EC50 ~ 0,27 mg/mL and inhibited ACE2 activity in the homogenate with EC50 ~ 0,10 mg/mL. The flavonoids (up to 100 µM) inhibited the larvae homogenate ACE2 activity by no more than 33%. The in vivo results using alive larvae showed that Fbut (0,3 -30 mg/mL) was lethal to L1 instar within 24h with a DL50 ~ 3 mg/mL. In the absence of inhibitors, all larvae survived and turned into pupae after 13 days. The flavonoids killed less than 12% of L1, but larval growth was inhibited and the development of pupae was delayed. At the end of the 13th day for L1 stage, 100% of the control group had turned into pupae, while in the orientin (300 µg/mL) group 30% turned into pupae. In the isoorientin and isovitexin (300 µg/mL) group, 45% and 50% turned into pupae, respectively. **Conclusions:** In vitro, Fbut inhibited non-selectively ACE activity of the larvae homogenate. ACE2 activity predominates in the larvae homogenate. Flavonoids were less active than the Fbut. The in vivo results obtained by incubation of the compounds to alive larvae have shown that Fbut and its flavonoids interfere with early insect larval development by stunting larval growth and increasing mortality. This may be related to the ACE homologues inhibition, but additional mechanisms could not be definitely excluded. This project is approved by the ethical committee (CEUA) under nº 6223021021**References:** Brogdon, W. Emerg Infect Dis. vol. 4(4): 605-13 (1998)Scott, M. L. Am J Trop Med Hyg. vol. 104(3): 1111-1122 (2021)Carmona, A. K. Nat Protoc. vol. 1(4): 1971-6 (2006)Sriramula, S. **Methods:** Mol Biol vol. 1527: 117-126 (2017)Abu-Hasan, Z. I. Sci Rep, vol. 7: 45409 (2017)

09.002 **Inhibitory Effect of Methyl Cinnamate on TGF-β-Induced Epithelial to Mesenchymal Transition in Alveolar Epithelial Cells**. Ferreira E, Barros ABB, Silva JP, Carmo JOS, Barreto EO UFAL, Lab de Biologia Celular

Introduction: Recent studies have been suggested that epithelial-mesenchymal transition (EMT) of alveolar epithelial cells and reactive oxygen species influences development of pulmonary fibrosis. Methyl cinnamate (MC) is a methyl ester of cinnamic acid, which exhibits a wide range of biological activities, including antioxidant properties. However, the role of MC in the regulation of EMT remain unknown. In this study, we explored the effect of MC on EMT induced by transforming growth factor β (TGF-β) in A549 alveolar epithelial cells. **Methods:** A549 cells were exposed to MC (purchased from Sigma Aldrich) during 24 hours, and cell viability determined by MTT assay. EMT induction was performed by culturing cells in DMEM media supplemented 2% of fetal bovine serum containing TGF-β (10 ng/mL), MC (10 µM), or both TGF-β/MC for 24 h. Morphological changes of cells was observed with optical microscope, and mesenchymal marker vimentin was evaluated by

immunofluorescence staining. In another set of experiments, the change in migration capacity of A549 cells by scratch assay was evaluated. For this, epithelial cells were cultured until reach confluence. Then a linear scratch was created and cells were treated with MC. Two representative areas of the scratch in each culture were photographed and the scratch area was quantitated using image analysis software (ImageJ). Statistical significance between groups was determined by ANOVA followed by Tukey's test ($p<0.05$). **Results:** Our results showed that all concentrations tested of MC (0,1, 1, and 10 µM) had no cytotoxic effects. A549 cells cultured in the absence of TGF-β maintained a classic epithelial cobblestone morphology. After TGF-β treatment for 24h, cells acquired a spindle-shaped with fibroblast-like morphology and reduced their cell-cell contact. Concomitantly with the change in morphology, the mesenchymal phenotype marker vimentin was remarkably upregulated. The incubation with MC inhibited the effects of TGF-β-induced EMT, retaining A549 cells to their epithelial-like morphology, as well as decreased the levels of mesenchymal marker vimentin. Functional assay demonstrated that TGF-β stimulation induced a significant increase in migratory activity in A549 cells, phenomenon which was suppressed by MC treatment. **Conclusion:** Taken together, our results demonstrated that methyl cinnamate inhibited the TGF-β induced EMT process, preventing the changed the cell morphology, the mesenchymal marker expression, and migratory ability induced by TGF-β in A549 cells. **Financial Support:** CNPq.

09.003 *Crotalus durissus terrificus* and *Crotalus durissus collilineatus* Snake Venoms Coagulotoxic Profile. Padueli LD[1,2], Galizio NC[1], Vidueiros JP[1], Azevedo AMT[1], Zani KM[1] [1]Instituto Butantan, Lab de Herpetologia, São Paulo, Brasil, [2]FCF-USP, São Paulo, Brasil

Snakebites represent a serious public health problem for tropical and subtropical countries due to the range of snake species and the frequency of accidents. The only treatment for snakebite envenomation is the snake antivenom. Crotalus snake venom is a mixture of biologically active peptides and proteins with enzymatic activity, mainly crotoxin, contabilizing 70 to 90% of the venom of this genus, and crotamine is also an important myonecrotic toxin. *C. durissus* spp venom has high individual and geographic variability, which may represent a challenge to the production of new antivenoms. This specie's venom also has fibrinogenolytic activity which is extremely important for the venom's action. This study aims to analyze and characterize the coagulotoxic profile of *C. d. terrificus* (Cdt) and C. d. collilineatus (Cdc) snake venoms. The analysis included SDS-PAGE, HPLC, enzymatic activity, fibrinogen cleavage profile and thrombin-like activity. In the SDS-PAGE analysis, it was noted that all of the Cdc and Cdt snake venoms presented main bands at approximately 30kDa associated with the presence of SVSP and 14kDa associated with the presence of phospholipase A2 (PLA2). Most notably, all three individual venoms that showed high PLA2 activity (p-value <0,05) had bands slightly above the main 14kDa bands, which is observable in the HPLC chromatograms of these individuals. It was also noted that most males and most Cdc venoms presented bands at approximately 10kDa, associated with the presence of crotamine, which was also observed in the HPLC chromatograms of these venoms. Regarding coagulation tests, fibrinogen cleavage profile showed that none of the venoms were able to completely cleave any of the three fibrinogen chains, in the time intervals evaluated (15 to 60 min). However, it was noted a decrease in intensity of the alpha chain in most of the venoms and the beta chain in a lesser scale, observing that the alpha chain is degraded primarily by the venom; none of the venoms degraded the gamma chain. In the thrombin-like activity, it was observed that most of the venoms that showed high activity were from the Southeast region of Brazil (p-value <0,0001). In all the antivenom studies, the antivenom showed to be able to completely or partially inhibit the venom's activity, noticing that incubation with the antivenom lowered the thrombin activity in about 80% for Cdc venoms and 83% for Cdt venoms. To conclude, the study and characterization of snake venom profiles are of utmost importance to the improvement of existing antivenoms and the discovery of new biologically active compounds, especially when the high variability that snake venoms showed in this study is considered. Supported by: FAPESP (2020/07268-2 and 2020/08246-2) SISGEN n° AC75E7B

09.005 *Hibiscus sabdariffa* Improves Murinometric Parameters in a Model Obesity-Exacerbated Asthma in Wistar Rats. Martins AMO[2], Ferreira SRD[1], Pessoa RF, Figueiredo IAD[1], Vasconcelos LHC, Cavalcante FA, UFPB

Introduction: Obesity is known to be a major risk factor and disease modifier of asthma in adults. Research reported that individuals with body mass index (BMI) ≥ 30 kg/m2 (obese) had an increased risk of new-onset

asthma by 2. 7 folds (ASTRUP et al., The Lancet, v. 374, p. 1606, 2009). Since treatments for the management these disorders are still scarce, a search for a therapeutic alternative is necessary. One option is natural products, such as *Hibiscus sabdariffa* (popularly known as "hibiscus"), that has already been described with anti-obesity activity in rats (MORAES-LUNA, J. Sci Food Agric, v. 99, p. 596, 2018), antiobesogenic in humans (CHANG et al., Food Funct., v. 57, p. 734, 2014) and spasmolytic in guinea pig trachea (ALI et al., J. Ethnopharmacol., v. 31, p. 249, 1991). Since an increase in several murinometric parameters has already been observed in a model of obesity-exacerbated asthma (FERREIRA et al., Sci Rep. p. 1 2022) the aim of this study was to evaluate the effect of "hibiscus" on the improvement of the murinometric parameters in obese asthmatic animals. **Methods:** Wistar rats were randomly divided into control (CG), obese asthmatic (OAG) and obese asthmatic treated with "hibiscus" at doses of 250 (OAH250G), 500 (OAH500G) and 1000 mg/kg (OAH1000G) groups. CG was fed for 16 weeks with standard diet, whereas the other groups received high glycemic level index (HGLI) diet for inducing obesity (Adapted of LUZ, A. B. S. Biosci rep, v. 38, p. 1, 2018). For asthma induction, the animals underwent sensitization with ovalbumin in the last 22 days of the 16 weeks. Non-asthmatic animals received saline 0,9% instead of ovalbumin (Adapted of GALVÃO et al., Inflamm. Res., v. 66, p. 1117, 2017). The treatment with "hibiscus" was performed in the last 30 days of the 16 weeks orally by gavage. At the end of 16 weeks animals were euthanized. All experimental protocols were approved by Ethical Committee on Animal Use of UFPB (protocol 1162100918). All results were expressed as mean ± standard error of the mean (S. E. M.) and statistically analyzed by ANOVA one-way followed by Tukey's posttest using GraphPad Prism® software version 5. 01. **Results:** The increase on body weight observed on OAG (466. 3 ± 9. 9 g), compared to CG (369. 0 ± 4. 4 g), was reversed only on OAH500G (416. 0 ± 17. 4 g). Any change was observed on food intake, Lee index, nasoanal length and thoracic circumference between groups. Otherwise, body mass index was increase on OAG (0,60 ± 0,01g/cm2), compared to CG (0. 54 ± 0. 02 g/cm2) and reversed on OAH500G (0. 59 ± 0. 02 g/cm2) and OAH1000G (0. 60 ± 0. 01 g/cm2). Similarly, was observed for abdominal circumference (18. 8 ± 0. 3; 21. 4 ± 0.1; 18. 8 ± 0. 5 and 19. 7 ± 0. 3 cm to CG, OAG, OAH500G and OAH1000G, respectively). For the adiposity index, we used the sum of fat deposits, both visceral (consisting of retroperitoneal and epididymal fat) and subcutaneous (inguinal) as a function of the weight of the animals. And a raise on adiposity index was observed on OAG (7. 7 ± 0. 5%), compared to CG (3. 7 ± 0. 3%), and reversion on both OAH500G (5. 7 ± 0. 5%) and OAH1000G (4. 7 ± 0. 5%). **Conclusions:** treatment with "hibiscus" improves murinometric parameters at doses of 500 and 1000 mg/kg. Thus, "hibiscus" may be a candidate for the management of obesity-exacerbated asthma. **Financial Support:** PIBIC/CNPq, PPgPNSB/CCS/UFPB.

09.006 **Histological and Immunohistochemical Analysis of Skin Wound Healing Influenced by the Topical Application of Brazilian Red Propolis Hydroalcoholic Extract**. Conceição M[1], Gushiken LFS[3], Aldana-Mejía JA[2], Tanimoto MH[2], Ferreira MVS[1], Miyashita MN[1], Bastos JK[2], Beserra FP[1,2], Pellizzon CH[1] [1]IBB-Unesp, Botucatu, São Paulo, Brazil, [2]FCFRP-USP, Ribeirão Preto, Brazil, [3]Unicamp, Campinas, Brazil

Introduction: Skin wound healing is a highly complex process that when unbalanced leads to pathological situations such as chronic wounds, keloids and others. Brazilian Red Propolis (BRP), a resinous material collected by bees from plant resins and exudates, has been studied for its antioxidant, anti-inflammatory, antitumoral, among other biological activities. Our research focus on acquiring the chemical composition of BRP and investigating its wound healing actions. **Methods:** The chemical profile of the BRP was obtained by high performance liquid chromatography coupled to a diode array detector, the compounds being identified and confirmed by mass spectrometry and nuclear magnetic resonance following the methodology of Aldana-Mejía 2021a and 2021b (SisGen number: AF234D8) [1, 2]. Male Wistar rats (6 animals by group) were divided as followed: FST/Control: wounded animals without treatment; HLC: wounded animals treated with hydroalcoholic solution; HLC+P: wounded animals treated with BRP extract at 1%; PAS: wounded animals treated with cream; PAS+P: wounded animals treated with cream containing BRP at 1%; Physiological control: animals without lesion nor treatment. Wound excision was performed, animals were treated for 3, 7 or 14 days and then euthanized (Ethics Committee approval under protocol IBB-9793211119) [3, 4]. Wound retraction percentage was calculated, and clinical parameters evaluated by using a four-point scale classification in which 0 - absence (0%) and 3 – Very much (>70%) [5]. Histological analysis and immunohistochemical technique were used to analyze total content of cells; total content of collagen; α-SMA, collagen I, collagen III, bFGF, Ki67, MMP-9, S100A4, TGF-

β3 and VEGF. Statistical analyses were performed using GraphPad Prism 5. 01 with 5% of significance. Results BRP characterization showed that vestitol, followed by medicarpin and neovestitol, were major compounds. Regarding wound contraction, at 14 days of treatment, HLC+P group showed higher percentage of contraction compared to FST. Both propolis formulations showed less crust formation. HLC+P group also showed a better epithelialization process. There was no statistical difference regarding total cell and collagen count. The following results regard immunohistochemical analysis by comparing all experimental groups with the control group FST. PAS+P treatment led to the decrease of α-SMA (3, 7 and 14 days), collagen I (14 days), collagen III (7 days), bFGF (3 and 14 days), Ki67 (3 and 7 days), MMP-9 (3, 7 and 14 days), TGF-β3 (7 and 14 days); and increase of collagen I (3 days) and VEGF (3 and 7 days). HLC+P treatment led to the decrease of α-SMA (14 days), collagen III (3 and 7 days), bFGF (3 days), Ki67 (3 and 7 days), MMP-9 (3, 7 and 14 days), S100A4 (7 days), TGF-β3 (7 and 14 days); and increase of collagen I (3 days), S100A4 (14 days) and VEGF (3 and 7 days). **Conclusion:** Thus, BRP into a hydroalcoholic extract at 1% has beneficial effects on wound healing by modulating the expression of molecules related to the proliferative and tissue remodeling phases and promoting wound closure, evidenced by macroscopic and microscopic analysis. **Financial Support**: São Paulo Research Foundation (FAPESP) for the Financial Support at process 2021/01258-8. ReferencesAldana-Mejía JA. Chem Res Toxicol. 34(4):1024. 2021a. Aldana-Mejía JA. Pharm Biomed Anal. 198:114029. 2021bProfyris C. J Am Acad Dermatol. 66(1):1. 2012 Gushiken LFS. Evid Based Complement Alternat Med. 2017:6589270. 2017 de Oliveira ML. J Ethnopharmacol. 153(1):283. 2014.

09.007 **Characterization of the Tocolytic Mechanism of Action of the Ethanolic Extract of** *Varronia dardani* (**Taroda**) **J.S. Leaves in Rats**. Fernandes JM, Figueiredo IAD, Ferreira SRD, Pessoa RF, Veloso CAG, Costa VCO, Silva MS, Cavalcante FA UFPB

Introduction: The myometrial function of contraction and relaxation of uterine smooth muscle is important in many in physiological processes such as the menstrual cycle. Changes in these processes can cause gynecological disorders, such as dysmenorrhea, causing painful contractions in the pelvic region (BAFOR, J Med Food, 24, 541, 2020). The use of plants to treat and prevent disease is one of humanity's oldest forms of medicinal practice. Thus, considering that the ethanolic extract obtained from *Varronia dardani* (Taroda) J. S. leaves (VD-EtOHL) had a non-selective spasmolytic effect in tonic and phasic smooth muscle models, being more potent in rat uterus (VELOSO et al., Nat. Prod. Res., 35, 4197, 2020), it was decided to characterize the tocolytic mechanism of action *in vitro* in rats. **Methods:** The Wistar female rats were treated 24 hours before euthanasia with diethylstilbestrol (1 mg/kg, s. c.) for hormonal synchronization of estrus. After this time, the two uterine horns were isolated and suspended in organ baths under appropriate conditions, and isotonic and isometric contractions were monitored and recorded. All results obtained were expressed as mean ± standard error of the mean (S. E. M.) and statistically analyzed using the “t” test (unpaired) or one-way analysis of variance (ANOVA) followed by Tukey's post test. All experimental protocols were approved by the Ethical Committee on Animal Use of UFPB (3864230519). **Results:** VD-EtOHL relaxed the rat uterus pre-contracted both by KCl (EC50 = 27. 7 ± 3. 1 μg/mL) and by oxytocin (EC50 = 33. 1 ± 0. 7 μg/mL), suggesting that the extract can exert its tocolytic effect through a common step between the two pathways, such as voltage-gated calcium channels (Cav). Therefore, cumulative curves for CaCl2 were performed in the absence (EC50 = 4. 7 ± 0. 2 x 10-4 M) and in the presence of VD-EtOHL, and it was observed a shift to the right of the control curve with a reduction in spasmogenic potency only at the concentration of 729 μg/mL (EC50 = 7. 9 ± 1. 8 x 10-3 M), suggesting that the blockade of Ca2+ influx through the CaV is not the main tocolytic mechanism of the extract. It was also observed that the potassium channels, β-adrenergic receptors, cyclooxygenase and nitric oxide pathways are not involved in the tocolytic mechanism of VD-EtOHL. Furthermore, since the relaxation of the myometrium can be caused by inhibition of contractile pathways, the participation of the Rho-associated protein kinase (ROCK) pathway in the tocolytic effect of VD-EtOHL was evaluated. In the presence of Y-27632, a non-selective ROCK blocker, the extract relaxation control curve (EC50 = 33. 1 ± 0. 7 μg/mL) was shifted to the left, with an increase in relaxing potency about 2 times (EC50 = 14. 5 ± 2. 7 μg/mL), suggesting that VD-EtOHL negatively modulates the RhoA/ROCK pathway in its tocolytic mechanism. Whereas, calmodulin plays a key role in Ca2+ signaling and smooth muscle contraction, the participation of this protein in the tocolytic mechanism of action of VD-EtOHL was evaluated, and an increase in the relaxing potency of the extract about 17 times was observed in the presence of calmidazolium, a calmodulin

blocker (EC50 = 2. 0 ± 0. 3 µg/mL), suggesting that the VD-EtOHL exerts its tocolytic mechanism by negatively modulating calmodulin. **Conclusion:** These results can indicate that the VD-EtOHL negatively modulates the RhoA/ROCK pathway and calmodulin in rat uterus, thus it may be a promising drug in the treatment of primary dysmenorrhea. **Financial Support:** PIBIC/CNPq, PPgPNSB/CCS/UFPB.

09.008 **Cardiotoxic Action of** *Micrurus dumerilii carinicauda* **and** *Micrurus corallinus* (**Elapidae**) **Venoms and Neutralization by Brazilian Coral snake Antivenom and Selective Phospholipase A2 Inhibitor**. Gaspar MZ[1], Yabunaka AC[1], Silva-Carvalho R[1], Nascimento CU[4], Brinholi RB[4], Silva EO[2], Gerez JR[3], , Silva Júnior NJ[5] , Hyslop S[6], Pacagnelli FL[4], Floriano RS[1] [1]Unoeste, PPG in Health Sciences, Lab of Toxinology and Cardiovascular Research, [2]Unoeste, Lab of Pathological Anatomy, Veterinary Hospital, [3]UEL, Dpt of Histology, [4]Unoeste, PPG in Health Sciences, Lab of Cardiac Structural and Functional Assessment, [5]PUC Goiás PPG in Environmental Sciences and Health, [6]FCM-Unicamp, Section of Pharmacology, Dpt of Translational Medicine,
Introduction: Studies related to the cardiotoxicity by coralsnake (Micrurus spp.) venoms have been neglected for over forty years. In this study, we examined the action of two South American coralsnake (*M. dumerilii carinicauda* 'MDC' and M. corallinus 'MC') venoms on the rat heart function, based on echocardiographic, biochemical, fractal, and histopathological analysis, following neutralization by a Brazilian coralsnake antivenom (CAV) and varespladib (VPL). **Methods:** Anesthetized (ketamine 50 mg/kg:xylazine 0. 5 mg/kg - i. p.) male Wistar rats were injected with saline (control; G1), or exposed to venom alone (1. 5 mg/kg - i. m.; G2 and G3 for MDC and MC, respectively), or immediately treated with CAV (antivenom:venom ratio 1:1. 5 'v/w' – i. p.; G4 and G5 for MDC and MC, respectively), VPL (0. 5 mg/kg – i. p.; G6 and G7 for MDC and MC, respecively), or both of these treatments (G8 and G9 for MDC and MC, respecively). Animals were monitored for 2 h and then subjected to determine alterations in echocardiographic parameters, serum CK-MB levels, and cardiac histomorphology, the latter using a combination of fractal dimension and histopathological **Methods: Results:** MDC (G2) and MC (G3) venoms did not induce cardiac functional changes in rats 2 h post-venom injection; however, MC venom (G3) caused a significant increase in the heart rate in rats 2 h post-venom injection, with all the treatments being effective to prevent this alteration. MDC (G2) and MC (G3) venoms caused a moderate increase in the heart lesional score and serum CK-MB levels ($p < 0.05$ vs. control G1, n = 6); only the combination of CAV + VPL (G8 and G9) were able to prevent these alterations ($p < 0.05$ vs. venom G2 and G3, n = 6), while VPL alone (G7) was able to attenuate the MC venom-induced CK-MB release ($p < 0.05$ vs. venom G3, n = 6). In addition, only MC venom (G3) increased the heart fractal dimension measurement, with all the treatments failing to prevent such alteration. **Conclusion:** In conclusion, MDC and MC venoms show to be potentially cardiotoxic in rats by inducing heart morphological changes and increasing the serum biomarker (CK-MB) for myocardial injury, while MC venom also causes tachycardia. Such alterations were mostly prevented by combination of CAV and VPL. **Financial Support:** This work was funded by institutional resources University of Western São Paulo (UNOESTE) and São Paulo Research Foundation (FAPESP, grant no. 2020/04287–6). M. Z. G. was supported by a studentship from FAPESP (grant no. 2020/14191–6). Approval by Animal Research Ethical Committee: The experimental procedures were approved by Committee for Ethics in Animal Use of the University of Western São Paulo (CEUA/UNOESTE, protocol no. 6321/2020).

09.009 **The Amazonian Fruit Tucumã** (*Astrocaryum aculeatum*) **modulates the genotoxicity associated with superoxide**, **hydrogen peroxide**, **nitric oxide imbalance in human fibroblasts**. Bonotto N[1], Azzolin VF[2], Ribeiro Filho E[2], Azzolin VF[2], Duarte MMF[3], Duarte T[1], Pellenz NLK[1], Ribeiro EAM[2], Cruz IBM[1], Barbisan F[1,4] [1]UFSM, Biogenomics Lab, Dept of Morphology, Santa Maria, Brazil, [2]FUnATI, Manaus, Brasil, [3]ULBRA, Torres, Brazil, [4]UFSM, Department of Pathology, Santa Maria, Brazil
Introduction: Chronic changes in oxy-inflammatory processes are associated with diseases and tissue aging, especially of the skin. The identification for the production of DAMPs (Damage-associated molecular pattern) is of great pharmacological interest. Tucumã (*Astrocaryum aculeatum*) is an Amazonian palm widely used by traditional peoples, whose fruits are used for human consumption, consumed in natura, accompanied by manioc flour, or in the form of sandwiches. In traditional medicine, the fruit is used in the treatment of various diseases associated with low-grade chronic inflammation such as diabetes. Tucumã is rich in unsaturated fatty acids, polyphenols and carotenoids, having 23 types of retinoid acids in its chemical composition. Previous

experimental investigations have described its antioxidant and anti-inflammatory effect. It is possible that tucumã may also exert a genoprotective effect against chemopharmaceuticals that cause superoxide, hydrogen peroxide, nitric oxide (S-HP-ON) imbalance. To test this hypothesis, the present work aimed to evaluate the genoprotective effect of the tucumã hydroalcoholic extract on human fibroblasts exposed to three chemopharmaceuticals that induce oxidative stress. **Methods:** Human fibroblasts of the HFF-1 strain were obtained commercially and cultured under appropriate conditions. The cells were treated with 5 different concentrations of each of the stressors Sodium Nitroprusside, Hydrogen Peroxide, and Methyl Viologen (Paraquat), concomitantly treated with tucumã at the previously defined concentration of 100 µg/mL and, after 72 hours, the 8-hydroxy-2'-deoxyguanosine test was performed using an Elisa immunoassay according to the ABCAM® manufacturer's instructions. Treatments were statistically compared by analysis of variance followed by Tukey's post hoc test. As this was an *in vitro* study with a commercial cell line, there was no need for approval by the ethics and research committee. **Results:** Tucumã showed a genoprotective effect to Paraquat, which generates high levels of superoxide anion, and to Sodium Nitroprusside, which generates high levels of nitric oxide. These data support the suggestion that tucumã has an anti-inflammatory effect, since superoxide and nitric oxide are two molecules associated with the initiation of the inflammatory response. The effect on fibroblasts exposed to hydrogen peroxide was less intense. **Conclusion:** The study demonstrates *in vitro* results of tucumã fruit on human fibroblasts, showing an effect on oxidative stress. **Financial Support:** FAPEAM and CNPq

09.010 **Limonene Acts on Cell Differentiation Through Modulation of Adipogenic Factors in 3T3-L1 Cells**. Assunção R[1], Pinto TS[2], Emilio-Silva MT[1], Andrade AFC[2], Zambuzzi WF[2], Hiruma Lima CA[1], [1]IBB-Unesp-Botucatu, Dept of Structural and Functional Biology (Physiology), Botucatu, SP, [2]IBB-Unesp-Botucatu, Dept of Chemical and Biological Sciences, Botucatu, Brazil

Introduction: In Brazil, 25. 6% of the adult population is obese, therefore it is necessary to find more efficient treatments with fewer side effects than those currently on the market. Limonene is the major compound present in Citrus aurantium L. essential oil, a monoterpene with anti-inflammatory activity, with a promising action in reversing the inflammation caused by obesity. This study aimed to evaluate the activity of Limonene (Sigma, 183164) on pre-adipogenic cells of mice (3T3-L1) and to evaluate their potential for the treatment of obesity. **Methods:** The pre-adipocytes 3T3-L1 cells were subjected to the treatments with Limonene at the concentrations tested (0. 39-100 µg/mL) using DMSO 1% as the vehicle. The treatment was conducted together with the differentiation, by using insulin 1 mg/mL, dexamethasone 1 mM, and 3-isobutyl-1-methylxanthine in the culture medium containing SFB (serum fetal bovine) and antibiotics for three days and then four days later with a culture medium containing only insulin. To assess cytotoxicity and define the treatment concentration of Limonene, the cell viability assay (MMT assay) was performed. After seven days of differentiation, the mRNA was extracted to gene expression by RT-qPCR for detection of genes related to cell survival (Src), cell cycle (Cdk2, Cdk4, and p15), differentiation (Leptin, leptin-receptor, and PPar-γ) and inflammation (IL-1β and TNF-α). The culture medium was collected for zymographic analysis to evaluate the activity of metalloproteinase (MMP)-2 and –9, which are present in the differentiation of adipocytes. For statistical analysis, Test t was used. The minimum significance level adopted was $p < 0.05$. **Results:** The MTT assay showed that the monoterpene was non-toxic to 3T3-L1 in all concentrations tested (0. 39-100 µg/mL), demonstrating greater cell viability at 15 µg/mL for Limonene. After differentiation, RT-qPCR demonstrated the ability of the monoterpene to modulate the expression of genes related to cell differentiation. Treatment with Limonene induced a significant decrease in IL-1β (p=0. 0375) and TNF-α(p=0. 0405) gene expression, indicating that Limonene was able to control pro-inflammatory cytokines. Furthermore, the Limonene can reduce Cdk-2(p=0. 0063) and leptin (p=0. 0352), indicating a reduction in the differentiation process. Corroborating the results of Cdk-2 and leptin, zymography showed that 3T3-L1 cells treated with Limonene have lower activity of MMP-9, in the active(p=0. 0015) and intermediate (p=0. 034) forms, and of MMP-2 in the pro(p=0. 0002) and intermediate forms (p=0. 0037.), indicative of lower cell differentiation activity. **Conclusion:** Thus, our results show that Limonene acts in the reduction of pro-inflammatory cytokines and cell differentiation regulators in 3T3 cells. However, further studies are needed to better elucidate its effect on obesity development. **Financial Support:** CAPES 88887. 669273/2022-00 and 88882. 433356/2019-01FAPESP 2020/15225-1 and 2021/11110-8

09.011 **Glycosylated Chrysin Protects Against the Neurotoxicity Induced by 3-Nitropropionic Acid in Swiss Male Mice**. Pereira RM[1], Oliveira PY[1], Campos HM[1], Menegatti R[2], Ghedini PC[1] [1]ICB-UFG, Dpt of Pharmacology, [2]FF-UFG

Introduction: Huntington disease (HD) is a neurodegenerative disorder characterized by the dysfunction of locomotor and cognitive systems. The oxidative stress is one of the pathways associated with the pathophysiology of this disease. Currently, HD does not have cure, and the treatments only alleviates the symptoms or reduces their progression. Therefore, there is a need to research new treatments, those can come from natural products. Chrysin (Cr) is a flavonoid that demonstrated a neuroprotective effect in an experimental model of HD (Thangarajan et al., Biomed Pharmacother v. 84, p. 514, 2016). However, Cr presents low bioavailability due its poor absorption and rapid metabolism. Knowing these challenges, it becomes interesting to use pharmaceutical tools, as the molecules glycosylation technique, to improve their pharmacokinetics properties. Taken this information, the aim of this study was to evaluate the neuroprotective effect of Cr and glycosylated Cr (GCr) and comparing the effects of both molecules against the neurotoxicity induced by 3-nitropropionic acid (3-NP), that is an experimental model of HD. **Methods:** Male Swiss mice was divided into eight groups (N = 10): control; 3-NP (20 mg/kg); Cr 1, 3 and 10 mg/kg + 3-NP; GCr 1, 3 and 10 mg/kg + 3-NP groups. The animals were kept at a stable controlled room temperature of (22 ± 2 °C), in a cycle of 12:12hr light/darkness, with free access to food and water receiving daily oral administrations of their respective treatments for 31 days. At the end of the treatments, the animals were euthanized, and the striatum was collected for evaluation of antioxidant effect of both molecules by biochemical markers. Statistical analysis was performed using Student's t-test or ANOVA followed by Tukey's test, when appropriate. This protocol was approved by the local Ethics in Research Committee (protocol number: 053/2016) of the Federal University of Goiás. **Results:** Cell membrane lipoperoxidation levels (LPO) of 3-NP group (8. 71 ± 0. 29) was increased when compared with the control group (5. 80 ± 0. 27) ($p < 0.05$). The treatment with Cr 3 (6. 83 ± 0,49) and 10 mg/kg (6. 61 ± 0. 48) and GCr 1 (6. 70 ± 0. 29), 3 (6. 190 ± 0. 23) and 10 mg/kg (6. 13 ± 0. 41) protected against the LPO promoted by 3-NP group ($p<0.05$). The SOD activity of 3-NP group (16. 43 ± 1. 06) was decreased when compared with the control group (47. 18 ± 4. 15) ($p < 0.05$). The treatment with Cr 3 (44. 65 ± 5. 23) and 10 (58. 98 ± 6. 18) mg/kg and GCr 1 (49. 00 ± 3. 27), 3 (56. 00 ± 5. 32) and 10 mg/kg (65. 64 ± 5. 40) increased SOD activity when compared with 3-NP group ($p < 0.05$). Furthermore, CAT activity of 3-NP group (6. 41 ± 0. 29) was decreased when compared with the control group (10. 37 ± 0. 32) ($p < 0.05$). The treatments with Cr 3 (9. 86 ± 0. 48) and 10 mg/kg (10. 44 ± 0. 75), and GCr 1 (9. 22 ± 0. 50), 3 (10.10 ± 0. 48) and 10 mg/kg (12. 19 ± 0. 49) increased CAT activity when compared with 3-NP group ($p < 0.05$). In addition, GPx activity of 3-NP group (2. 46 ± 0.13) was decreased when compared with the control group (12. 72 ± 0. 47) ($p < 0.05$). The GCr 3 (14. 64 ± 0. 86) and 10 (14. 86 ± 1. 16) mg/kg increased GPx activity when compared with 3-NP group ($p < 0.05$). Differently, the treatments with all doses of Cr were not different when compared with 3-NP group ($p > 0.05$). **Conclusion:** Taken together, the results show GCr present better antioxidant effects when compared with Cr, indicating as a new potential molecule for the prevention or treatment of HD. **Financial Support:** UFG, CAPES, CNPq, FAPEG

09.012 **Glycosylated Chrysin protects Against Aluminum-Induced Neurotoxicity**. Okoh VI[1], Ferreira P[1], Pereira RM[1], Campos HM[1], Menegatti R[2], Ghedini PC[1] ICB-UFG, Dpt of Pharmacology, Goiânia, Brasil, [2]FF-UFG, Goiânia, Brasil

Introduction: Chrysin (Cr) is a flavonoid with protective effect against the neurotoxicity induced by aluminum (Al) (Campos et al., TOX., v. 465, p. 153033, 2022). However, Cr have some limitations with its pharmacokinetics, in terms of poor absorption and solubility, rapid metabolism and difficulty crossing the blood brain barrier, leading to low bioavailability. So, it becomes interesting to use the glycosylation technique as a modification process of molecules in order to improve its pharmacokinetics properties. So the objective of this work was to evaluate the neuroprotective effects of glycosylated chrysin (GCr) comparing with Cr, in a mice model of neurotoxicity induced by Al. Methodology: Ten male Swiss mice groups (n=10), allowed free access to food and water, maintained under room temperature (23 ± 2 °C), in a cycle of 12-hour light/dark were used in this study. Neurotoxicity was induced by oral administration of AlCl3 (100 mg/kg/day), and the treatments with Cr and GCr at doses of 1, 3, and 10 mg/kg, were followed for 45 days. A group without AlCl3 administration was used as a

control, another with only Al intake was the induced group, and two other groups were given only Cr and GCr without AlCl3. After the treatments, the mice were euthanized and the hippocampus was collected for evaluation of the antioxidant effect of both molecules by biochemical markers. Statistical analysis was performed using Student's t-test or ANOVA and Tukey's test, when appropriate. This protocol was approved by the local Ethics in Research Committee (protocol number: 053/2016) of the Federal University of Goiás. **Results:** Lipid peroxidation (LPO) levels of GCr at the doses of 1 (3. 56 ± 0. 24), 3 (2. 49 ± 0. 08), and 10mg/kg (2. 38 ± 0.10), showed better protection against the cell damage promoted by AlCl3 (6. 01 ± 0. 29) when compared with the similar doses of Cr (4. 55 ± 0. 33, 4. 39 ± 0. 34 and 3. 41 ± 0.15) ($p < 0.05$). Cr and GCr groups were similar to the control (2. 91 ± 0.11; $p < 0.05$) group. Superoxide dismutase (SOD) activity of GCr at doses of 1 (51. 05 ± 0. 94), 3 (79. 69 ± 1. 18) and 10mg/kg (86. 49 ± 1. 66), better protected against the decreased SOD activity induced by AlCl3 (25. 42 ± 1. 91), when compared with the similar doses of Cr (27. 13 ± 3. 43, 48. 75 ± 6. 23 and 55. 37 ± 3. 19) ($p < 0.05$), also Cr (3 and 10mg/kg) and GCr groups were similar to the control (87. 09 ± 4. 43) group. Catalase (CAT) activity of GCr at doses of 1 (5. 50 ± 0.19), 3 (4. 34 ± 0. 22), and 10mg/kg (5. 89 ± 0. 41) was best against the decreased activity induced by AlCl3 (3. 20 ± 0.19), when compared with the similar doses of Cr (3. 05 ± 0.18, 4. 34 ± 0. 22 and 5. 89 ± 0. 41) ($p < 0.05$). Cr and GCr groups were similar to the control (7. 78 ± 0. 66) group. In addition, glutathione peroxidase (GPx) activity for GCr at the doses of 1 (6. 01 ± 0. 22), 3 (6. 26 ± 0.16), and 10mg/kg (6. 94 ± 0. 21), was best against the decreased GPx activity induced by AlCl3 (2. 91 ± 0.14), when compared with the similar doses of Cr (4. 14 ± 0.15, 4. 89 ± 0. 26, and 6. 01 ± 0.18, respectively) ($p < 0.05$). Cr and GCr treatment groups were similar to the control (7. 23 ± 0. 28; $p < 0.05$) group. **Conclusion:** GCr displayed better protection against neuronal oxidative stress promoted by Al when compared with Cr, suggesting that the pharmacological effect of Cr could be improved by its glycosylation. Therefore, GCr is a potential new molecule for the prevention or treatment of diseases that involve oxidative stress, such as the neurodegenerative disorders. **Financial Support:** TETFUND, CAPES, FAPEG

09.013 *In vitro* and *In Silico* Studies of the Vasorelaxant Mechanism of Action of Synthetic Amide (E)-N-(4-Methoxyphenethyil)-3-(Thiophen-2-yl)Acrylamide in Rat Aorta. Cavalcanti-Silva ARLF, Pessoa RF, Moura TMCF, Fernandes JM, Figueiredo IAD, Ferreira SRD, Sousa NF, Scotti L, Silva LAA, Rodrigues LC, Cavalcante FA UFPB

Introduction: :(E)-N-(4-methoxyphenethyil)-3-(thiophen-2-yl)acrylamide (MFTA) is a synthetic thiophenic amide, in which the oxygen of the furan ring was replaced by a sulfur creating a novel molecule. Several activities of natural and synthetic amides have been reported on smooth muscle reactivity, including vasorelaxant activity in rat aorta (ARAÚJO-JÚNIOR et al., Emir J Food Agric, v. 23, n. 3, p. 265, 2011). Molecular docking is a type of methodology that predicts the best orientation of a molecule to a second one, when they are coupled together, forming a complex (LENGAUER, Curr. Opin. Struct. Biol., 6, 402, 1996). Considering that MFTA in a previous work had a non-selective spasmolytic effect in tonic and phasic smooth muscle models, being more potent in rat aorta (MOURA, 53º SBFTE, 2021), it was decided to characterize its vasorelaxant mechanism of action through *in vitro* and in silico assays. Methodology:The rat aorta was sectioned into rings and suspended in organ baths under appropriate conditions for each experimental protocol and isometric contractions were monitored. MFTA was submitted to molecular docking in Molegro Virtual Docker, using voltage-gated calcium channels (Cav) complexed to nifedipine, obtained from the Protein Data Bank. The results were expressed as the mean and standard error of the mean, and statistically analyzed by the Student's t-test. All experimental protocols were approved by the Ethical Committee on Animal Use (8073300419). Results:In a previous work, it was suggested that the vasorelaxant effect of the MFTA appears to be by inhibiting the Ca^{2+} influx through Cav. This hypothesis was confirmed, since the amide (10-5; 3x10-5; 10-4 and 3x10-4 M) inhibited the cumulative contractions induced by CaCl2 (n = 5) in depolarizing medium (80 mM KCl) nominally without calcium, with shift to the right of control curve and reduction of Emax from 100% (control) to 95. 6±4. 5; 68. 4±5. 2; 54. 0±3. 4; 19. 4±3. 5% and EC50 values of CaCl2 of 2. 0 ± 0. 2x10-3 M (control) for 1. 5±0. 2; 2. 8±0. 2; 7. 0±1. 2 and 11. 6±4. 9x10-3 M, respectively. In addition, MFTA relaxed in an equipotent and concentration-dependent manner the rat aorta pre-contracted with S-(-)-Bay K8644 (n = 5), a Cav1 agonist (Emax = 100%; EC50 = 9. 2±0. 9x10-5 M), compared to the effect observed with KCl 80mM (Emax = 98,7 ± 1,3%; EC50 = 1,0±0,2x10-4 M), demonstrating that the MFTA directly inhibits the influx of Ca^{2+} through Cav1. Moreover, the inhibition of contractile pathways can also cause relaxation of the rat aorta. Thus, the participation of the Rho-associated protein kinase (ROCK) pathway

in the vasorelaxant effect of MFTA was also investigated. And it was observed that there was no change in the efficacy (Emax = 100%) or in the relaxing potency (EC50 = 5. 4±1. 1x10-5 M) of the amide in the presence of Y-27632, a ROCK blocker, (Emax = 100% and EC50 = 1. 0±0. 2x10-4 M, n = 3), ruling out the participation of this pathway in the *in vitro* vasorelaxant effect of the amide. In silico studies, specifically in molecular docking, MFTA showed more negative energy values, -132. 993 and -111. 595 kcal/mol, while nifedipine presented energy of -81. 7718 and 122. 982 kcal/mol, both for Moldock and for Rerank score respectively, thus confirming the *in vitro* studies. **Conclusion:** MFTA has a vasorelaxant effect by blocking type 1 Cav, so that the more negative scores of energy values in MD corroborate the confirmation of this hypothesis. **Financial Support**:CAPES, CNPq, PPgPNSB/CCS/UFPB.

09.014 **Gastroprotective Effect of *Egletes viscosa* Chemotype a Infusion on Ethanol-Induced Gastric Lesions in Mice**. Portela BYM[1], Nunes PIG[2], Freire GP[2], Lima RP[1], Viana AFSC[1], Carvalho KR[3], Canuto KM[3], Santos FA[1,2] [1]UFC, PPG Pharmacology, Fortaleza, Brazil, [2]UFC, PPG Medical Sciences, Fortaleza, Brazil, [2]Embrapa Tropical Agroindustry

Introduction: Gastric ulcer (GU) is a disease consisting of lesions in the gastrointestinal tract that may occur in the stomach or duodenum. The etiology of the gastric lesions (GL) is multifactorial, mainly caused by *H. pylori* infection, use of non-steroidal anti-inflammatory drugs, and lifestyle habits such as alcoholism and smoking. Ethanol-induced gastric lesions involve different mechanisms, such as the generation of free radicals, increased lipid peroxidation, and increased inflammatory response. The undesirable side effects of conventional treatment have encouraged studies using natural products to discover new compounds with gastroprotective effects. *Egletes viscosa*, popularly known as macela, is a small herb largely grown in northeast Brazil, and infusions made from its flower buds are commonly used in popular medicine for the treatment of gastrointestinal diseases. Two different chemotypes (A and B) were reported for *E. viscosa* from the analysis of volatile constituents of the flower buds. This work aims to investigate the gastroprotective effect and antioxidant potential of *E. viscosa* chemotype A infusion (EVCA). **Methods:** Flower buds of *E. viscosa* were collected in Aiuaba City, Ceará, in March 2017. A voucher specimen was deposited at Prisco Bezerra Herbarium at the UFC (#38254). Male Swiss mice (25-30g, n=8) were treated orally with vehicle (saline), EVCA (25, 50, 100 or 200mg/kg) or N-acetylcysteine(NAC, 200mg/kg). Sixty minutes later, the mice received absolute ethanol(99. 5%, 0. 2ml, p. o.) to induce GU, and 30 minutes later they were euthanized. A group of mice that did not receive ethanol was included (normal group). Stomachs were excised and the GL area was quantified by planimetry (mm2) using the ImageJ software. Gastric homogenates (10%, w/v) were used to quantify levels of malondialdehyde(MDA), reduced glutathione(GSH), nitrite/nitrate, and as well as the catalase(CAT), superoxide dismutase(SOD), and myeloperoxidase(MPO) activity. Results were expressed as mean±SEM. Statistical analysis was performed using one-way ANOVA, followed by Tukey's multiple comparison test. Values of $p<0.05$ were considered statistically significant. This study was approved by CEUA-UFC(no. 1860060721) and registered at SisGen(no. A7B4712). **Results:** Mice that received ethanol (vehicle) showed an area of GL of 21. 79±2,01 mm2. EVCA 25, 50, 100, or 200mg/kg significantly reduced the area of GL by 67. 7, 76. 5, 73. 3, and 81. 6%, respectively, compared with the vehicle group. In the NAC group, the area of GL was reduced by 72. 8%. Ethanol-induced increases in MDA level and MPO activity in 3. 8 and 3. 3-fold, respectively when compared to the normal group. EVCA(100mg/kg) reduced MDA and MPO levels by 45. 9 and 82. 9%, respectively, when compared to the vehicle group. Ethanol significantly decreased the levels of GSH and nitrite/nitrate in gastric tissues by 97. 1 and 78. 9%, as well as reduced the activity of SOD and CAT by 67. 7 and 69. 3%, respectively, when compared to the normal group. EVCA(100mg/kg) inhibited the decrease of GSH level by 76. 0% and nitrate/nitrite level by 22. 9% and reduced the activity of SOD by 10. 3% and of CAT by 31. 1%. NAC(200mg/kg) reduced MDA and MPO levels, prevented the decrease of GSH and nitrite/nitrate levels, and reduced the activity of SOD. In addition, NAC stimulated the activity of CAT. **Conclusion:** These results demonstrate the gastroprotective effect of EVQA thus proving its popular use, in addition, its antioxidant activity participates in the gastroprotection mechanism. **Financial Support:** CNPq; CAPES; FUNCAP.

09.015 **Influence of Phospholipase A2 on the Neuromuscular Blockade Caused by Coral Snake (Elapidae) Venoms in Mouse Phrenic Nerve-Diaphragm Preparations *In Vitro***. Couceiro FYG[1], Demico PJ[1], Diamante CF[1], Dias SR[1] , Silva Júnior NJ[2], Grego KF[3], Sant'Anna SS[3], Zani KM[3], Hyslop S[4], Floriano RS[1] [1]Unoeste, PPG em Ciências da Saúde, Lab de Toxinologia e Estudos Cardiovasculares, Presidente Prudente, Brazil, [2]PUC Goiás, PPG em Ciências

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Envenomation by coralsnakes (Micrurus spp.) is characterized by peripheral neurotoxicity mediated by two major groups of toxins: α-neurotoxins that block post-synaptic nicotinic cholinergic receptors, and presynaptically active phospholipase A2 (PLA2) β-neurotoxins that supress acetylcholine release from motor neurons. However, the extent to which presynaptically active PLA2 can influence the neuromuscular blockade caused by coralsnake venoms remains unclear. In this work, we compared the neuromuscular blockade induced by venoms from four Micrurus spp. (M. altirostris, M. corallinus, M. spixii, and *M. dumerilii carinicauda*) and the ability of varespladib (VPL), a PLA2 inhibitor, to attenuate this blockade. Neurotoxicity was assayed in mouse phrenic nerve-diaphragm (PND) preparations mounted for conventional myographic recordings, using a single concentration of venom (10 mg/ml). For some experiments, the venoms were pre-incubated with VPL (300 mM) for 20 min at 37 °C prior to testing for residual neurotoxicity. The results were expressed as the mean ± SEM (n=4), with $p<0.05$ indicating significance. Micrurus spixii venom caused the quickest neuromuscular blockade (times for 50% and 90% blockade: 16 ± 1 min and 35 ± 1 min, respectively), which was unaffected by VPL (times for 50% and 90% blockade: 16. 5 ± 1 min and 35. 5 ± 1 min, respectively). Micrurus altirostris and M. corallinus venoms produced similar neuromuscular blockade [times for 50% and 90% blockade: 42. 5 ± 1. 5 min and 77 ± 1 min (M. altirostris) and 39. 5 ± 1. 5 min and 76. 5 ± 1. 5 min (M. corallinus), respectively]; however, VPL delayed the M. corallinus venom-induced blockade, with the time for 90% blockade increasing to 120 ± 2 min ($p<0.05$). VPL also delayed the M. altirostris venom-induced blockade, with the time for 90% blockade increasing to 102. 5 ± 1. 5 min ($p<0.05$). *M. dumerilii carinicauda* venom caused the slowest neuromuscular blockade (times for 50% and 90% blockade: 42 ± 2. 5 min and 94. 5 ± 2 min, respectively). VPL was most effective in attenuating the blockade by this venom, with the time for 50% blockade increasing to 86. 5 ± 1. 5 min; $p<0.05$) and 90% blockade requiring >120 min. These results indicate that M. spixii venom-induced neuromuscular blockade is PLA2-independent, being most likely mediated by α-neurotoxins, whereas PLA2 contribute more to the neuromuscular blockade produced by M. altirostris, M. corallinus and *M. dumerilii carinicauda* venoms in PND preparations. Financial Support: This work was funded by the Universidade do Oeste Paulista (UNOESTE) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, grant no. 2020/04287-6). Approval by Animal Research Ethical Committee: The experimental procedures were approved by an institutional Committee for Ethics in Animal Use (CEUA/UNOESTE, protocol no. 7061/2021). Brazilian National System for the Management of Genetic Patrimony and Associated Traditional Knowledge (SISGEN, registration no. A08F610).

09.016 *Rhinella schneideri* (*Rhinella diptycha*) **Skin Secretion Bioprospection: New Tools for Neurodegenerative Diseases Treatment**. Caires GA[1], Pimenta DC[2], Sciani JM[3], Búfalo MC[4], DeOcesano C[4], Kerkis I[1], Vigerelli H[1] [1]IBu Lab de Genética, São Paulo, Brasil, [2]IBu, Lab de Bioquímica, São Paulo, Brasil, [3]UFS, Lab Multidisciplinar de Pesquisa, Bragança Paulista, Brasil, [4]IBu, Centre of Excellence in New Target Discovery, São Paulo, Brasil

Introduction: Neurodegenerative disorders are characterized by a slow progressive loss of neurons and their connections, such as in Dementia, Parkinson's, and Alzheimer's Disease (AD). These diseases have no cure, and palliative treatment remains the only therapeutic approach. Mitochondrial function and lysosomal-autophagic system alterations induce the transport of enzymatically active lysosomal cathepsin B (CatB) to the cytosol, activating inflammatory pathways, leading to neurodegeneration and behavioral deficits in AD, traumatic brain injury, and related brain disorders. Since current CatB inhibitors are poorly selective or irreversible, the discovery of new CatB inhibitors is extremely relevant. Objectives: To test the Skin Secretion (S) of *Rhinella schneideri* and chemically extracted Polar (P) or Nonpolar (NP) fractions and their subfractions on (i) CatB inhibitory activity and (ii) cytotoxicity and morphological alterations in neuron-like cells. Methodology: P or NP fractions were obtained by H2O-CH2CL2 partition. Fractions of S and subfractions of P and NP were obtained by RP-HPLC. Molecules present in S were identified by LCMS-IT-Tof mass spectrometry (MS). In order to confirm the differentiation of SH-SY5Y into Neuron-like cells, β-III tubulin and nestin proteins were marked and the immunofluorescence was analyzed. Inhibition of CatB enzymatic activity after incubation with S, P, or NP and their subfractions was evaluated on fluorogenic substrate Ac-RR-AFC. Assessment of Neuron-like cell culture viability was performed with CCK8 kit. Morphological alterations in Neuron-like cells were evaluated by High Content Screening. Results: MS and MS/MS analyses led to the identification of eight different molecules, e. g. bufotenine and

marinobufagin. Immunofluorescence labeling of β-III tubulin demonstrates a clear change in cell morphology and formation of neurites. Also, immunofluorescence labeling of nestin, a marker of immature cells, showed a decrease in this protein expression. These results confirm the differentiation of SH-SY5Y into Neuron-like cells. According to cell viability assays, the concentrations of 100 and 250 ng/mL of S and P, and concentrations of 250, 500 ng/mL of NP, and all subfractions are non-toxic and were chosen to be used in future experiments. S inhibited 100% of CatB hydrolytic activity on the fluorogenic substrate and all the other stimuli evaluated partially inhibited (20-70%) the CatB activity. SfNP5 improved all morphological parameters analyzed in Neuron-like cells, such as cell total outgrowth, number of branches, maximum neurite length, and number of neurites were enhanced (72 %, 120 %, 60 %, and 35%, respectively). Results were expressed as mean + standard error of the mean. One-way ANOVA was used, followed by the Bonferroni test, for multiple comparisons ($p < 0.05$). **Conclusion:** Our data show that S and/or its fractions and subfractions are capable to reduce CatB enzymatic activity and contribute to the improvement of the neural network, being a promising source of molecules that can be employed in the discovery and development of new neurodegenerative diseases treatments. Support: FAPESP – Research Support Foundation of the State of São Paulo (2019/19929-6), National Council for Scientific and Technological Development CNPq. Keywords: Neurodegenerative Diseases, *Rhinella schneideri*, skin secretion, CatB. BALLARD, C. et al. Alzheimer's disease. The Lancet, v. 377, p. 1019, 2011.

09.017 **Cytotoxic evaluation of the hydroalcoholic extract from stem bark of *Hymenaea courbaril* L. in RAW264.7, L929 and MRC-5 cells**. Lobo LAC[1], Ethur EM[2], Silva FC[3], Pereira P[1], Goettert MI[2] [1]UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, [2]Univates, Cell Culture Laboratory, PPG in Biotechnology [3]UniSL, Lab of Phytochemical Analysis, Ji-Paraná, Rondônia

Introduction: The use of medicinal plants in the traditional medicine is known for a variety of illnesses and conditions for centuries. Natural products, including compounds derived from plants, have been used for the development of new drugs and requires prior knowledge of its active compounds, as well the determination of its potential and toxicological properties. The genus Hymenaea (family Fabaceae, subfamily Caesalpinioideae) includes sixteen species, nine of which are found in several Brazilian regions, including lower tropical ecosystems that follow a uniform distribution in the Amazon rainforest. *Hymenaea courbaril* L., popularly known in Brazil as "jatobá", is a tree whose leaves, roots, fruits and especially the stem bark are traditionally used in folk medicine through infusions and decoctions to treat different conditions. Is used in folk medicine to treat anemia, kidney problems, sore throat, and other dysfunctions of the respiratory system, such as bronchitis and asthma. Although studies have demonstrated some biological activities of H. courbaril such as anti-inflammatory and myorelaxant activity, toxicity studies are still needed. The aim of study was to evaluate the biological and toxicological profile of the hydroalcoholic extract from stem bark of *Hymenaea courbaril* L. using cell lines as an *in vitro* model. Material and **Methods:** The phytochemical profile determination of the H. courbaril extract was performed by qualitative analysis. The antioxidant activity was determined by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging ability, the DPPH assay. Cytotoxic activity was determined by the 3-[4, 5-dimethylthiazol- 2-yl]-2, 5-diphenyltetrazolium bromide (MTT) colorimetric assay in RAW 264. 7 (murine macrophage), L929 (murine fibroblast) and MRC-5 cells (human fetal lung fibroblast), assessments of cell viability. Cells were cultured in 96-well microplates and treated in with plant extract at different concentrations (6. 25, 12. 5, 25, 50 and 100 µg/ml), after 24 and 48 h incubation, absorbance was read at 540 nm. All experiments were done in triplicate and results were expressed by the cell viability percentage. Statistical analyses were performed using ANOVA followed by Dunnett's test, performed using GraphPad Prism 5. 0 (GraphPad Software, Inc). A $p<0.05$ value was considered statistically significant. **Results:** The main phytoconstituents of the H. courbaril hydroalcoholic extract were identified by qualitative screening revealing that it contained saponins, coumarins, tannins, flavonoids and phenolic compounds. The extract exhibited a potent antioxidant activity (IC50 3. 62 µg/ml), similar to the control ascorbic acid (IC50 of 2. 95 µg/ml). The extract did not altered the cell viability by 24h and 48h of treatment at different concentrations. In conclusion, the hydroalcoholic extract of H. courbaril demonstrated an antioxidant activity and did not produce cytotoxicity in murine and human cell lines. **Financial Support:** This study was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES). Approval by human or animal research ethical committees: Not applicable. Conflicts of Interest: The authors declare no conflict of interest.

09.018 **Hepatoprotective Effect of Piperine in Acetaminophen-induced Liver Injury in Mice**. Coelho AM, Queiroz IF, Souza MO, Lima WG, Costa DC UFOP

Introduction: Acetaminophen (APAP) is widely used in the world for presenting analgesic properties and antipyretic however, its use in high doses can result irreversible liver damage. Preliminary studies suggest that piperine acts by inhibiting cytochrome P450, whom is involved in the metabolism of different xenobiotics, including paracetamol. With that our hypothesis that piperine could be a possible therapeutic target to minimize APAP-induced hepatotoxicity. The aim of this study was to evaluate the hepatoprotective effect of piperine in association or not with N-acetylcysteine (NAC) in a model of paracetamol-induced hepatotoxicity in C57BL/6 mice. **Methods:** The groups (n=7) were distributed into: control, APAP, APAP+P20, APAP+P40, APAP+NAC, APAP+P20+NAC, APAP+P40+NAC. Paracetamol was administered (500mg/Kg) and after 2 hours the treatments were performed with piperine 20 mg/kg (P20) and 40 mg/Kg (P40) in association or not with NAC (300 mg/kg). All treatments were performed orally through gavage. The animals were euthanized 12 hours after APAP administration. We evaluate hepatic function, in addition to histological analysis and redox-hepatic status. All procedures were approved the Ethics Committee on Animal Use (CEUA) from the Federal University of Ouro Preto, Brazil. **Results:** The results showed that treatment with piperine 20 mg/kg associated with NAC reduced the activity of the hepatic enzyme ALT, reduced MMP-9 and increased the sulfhydryl group (-SH) compared to the APAP group. AST activity, and TBARS decreased in NAC, NAC+P20 and NAC+P40 groups when compared to APAP. The area of hepatic necrosis and carbonyl protein levels decreased in groups P40, NAC, NAC+P20 and NAC+P40 compared to APAP. . **Conclusion:** Based on these results, piperine has been shown to be a possible adjuvant to NAC for the treatment of hepatotoxicity. Keyword: Acetaminophen, hepatotoxicity, piperine **Financial Support:** UFOP, FAPEMIG e CAPES

09.019 **Toxicological and Antioxidant Evaluation of Geniposide in the** *Caenorhabditis elegans* **Model**. Uczay M[1], Santos PA[1], Poser G[2], Vendrúsculo MH[2], Pereira P[1] [1]ICBS-UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, Porto Alegre, Brazil, [2]FacFar-UFRGS, Lab of Pharmacognosy, Porto Alegre, Brazil

Introduction: Geniposide (GP) is an iridoid that has been shown various biological properties such as reduction of inflammation, oxidative stress, and neuroprotection. In this study, we used the Caenorhabditis elegans model to evaluate GP lethality and antioxidant properties in vivo. Material and **Methods:** Wild-type Bristol (N2), CF1553 (sod-3:GFP) and CL2166 (gst-4:GFP) strains of C. elegans worms were obtained from the Caenorhabditis Genetics Center (CGC) and grown on NGM agar plates seeded with a lawn of Escherichia coli (OP50) in 20° C. For both the experiments, adult hermaphrodites were synchronized using an alkaline hypochlorite solution. To the lethality assay wild type (N2) worms were used. About ten worms were transfered to each well in 24-well plates which contained serial dilutions of GP in triplicates (0.1 mM, 0. 5 mM, 1 mM and 2 mM). The negative control (only the K-medium) was also included in triplicate. Plates were incubated at 20 °C in the dark for 24 h. After exposure, the number of live and dead worms was recorded by visual inspection under a dissection microscope. Nematodes were considered dead if they did not respond to stimuli when touched with a metal wire. To the sod-3 and gst-4 expression assay, approximately 100 age synchronised L4 CF and CL worms tagged with GFP protein were transferred to 24-well plates. Following that, larvae were exposed to GP (0. 5, 1 or 2 mM) + hydrogen peroxide (0.1 mM), just hydrogen peroxide (0.1 mM) as a positive control or K-medium (negative control) for one hour. Then, the worms were anesthetized with 0. 5 mM sodium azide (0. 5 mM), transferred to histological slides, and covered with coverslips. The slides were analyzed under a fluorescence microscope at 10X magnification, ten worms per treatment were photographed and analyzed. The experiments were performed in triplicate, and GFP fluorescence signals were measured using NIH ImageJ software. The statistical analysis was performed using GraphPad Prism software. One-way ANOVA test was used, and differences were considered significant at $p \leq 0.05$. **Results:** GP exhibited a dose-dependent effect on the mortality of adult nematodes after 24 h of exposure. Concentration of 1 and 2 mM increased the mortality compared to control group ($p \leq 0.05$), but not 0.1 or 0. 5 mM. In the fluorescence analysis, we observed that in the SOD-3 expression assay, fluorescence was higher in the group treated only with hydrogen peroxide ($p < 0.0001$). The groups treated with 1 and 2mM of GP did not differ from the control group but differed from the positive control group ($p < 0.05$). In the gst-4 fluorescence analysis all the groups differ from the negative control ($p < 0.0005$ and $p < 0.0001$), but statistically similar to the positive control. **Conclusion:** GP in the 1 and 2 mM concentrations

induced mortality, but also was capable of reduced SOD-3 expression after damage induced by hydrogen peroxide in C. elegans model.

09.020 **Investigation of Proliferative Potential of Monoterpene Citral in Lineage of Intestinal Cells Caco-2**. Fagundes FL[1], Zarricueta ML[1], Caxali GH[2], Aal MCE[2], Delella FK[2], Hiruma-Lima CA[1] [1]Unesp-Botucatu, Lab of Biological Assays with Natural Products, Dept of Structural and Functional Biology, Sector of Physiology, [2]Unesp-Botucatu, Lab of Studies of Extracellular Matrix, Dept of Structural and Functional Biology, Sector of Morphology
Introduction: The healing process in the Inflammatory Bowel Disease (IBD) is a complex event that involves the mobilization of epithelial cells (EC), the release of growth factors by stroma and the interaction of immune cells. In this sense, molecules that stimulates the proliferation of EC can be novel targets in the IBD treatment. Citral (C10H16O) is a monoterpene present in some vegetal species, i. e., ginger (Zingiber officinale), used in the food and cosmetic industry. This molecule has analgesic, antimicrobial, and healing activity in the peptic ulcer already described in the literature, however, there is no evidence that point the proliferative potential of this compound in intestinal EC. **Methods:** To evaluate this effect, caco-2 cells, 53rd passage (ATCC HTB-37™) cultivated in DMEM containing 20% of fetal bovine serum, 1% of antibiotic/antimycotic and maintained in 37ºC and atmosphere of 5% CO2 were employed. After the cells reach confluence of 80% in the culture flask of 75 cm2, it was tripsinized and transferred to cell plates of 96 wells (1x104/well). A day after, the culture was treated with Citral (1-100 µM) or with agonist of estrogen receptors 17-β-estradiol-3-benzoate (1-1000 nM). A solution containing the MTT salt [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was inserted into the culture plate and followed for 3 hours, the cells were lysed with the dimethylsulfoxide (DMSO), and the absorbance was read in 540 nm using a spectrophotometer. The data were expressed as mean and standard error of mean considering experiments realized in quadruplicates. Statistical analyses were conducted using one-way analyses of variance (ANOVA) followed by Dunnett posteriori test to comparisons with control group. RESULTS Citral in the concentrations of 40 and 80 µM increased the cell viability of caco-2 cells within 48 hours of treatment, when compared to the control group, without altering the viability in the time 24 and 72 hours. 17-β-estradiol-3-benzoate increased the proliferation in 24 hours (10, 500 e 1000 nM), 48h (100 e 1000 nM) and 72h (500 nM) compared to DMSO group. **Conclusion:** The results showed a proliferative potential of monoterpene Citral and estradiol in Caco-2 cells lineage that should be investigated through additional experiments as a scratch assay. **Financial Support** CAPES (88887. 689603/2022-00), Fapesp (19/01869-7) and CNPq (311957/2020-0)

09.021 **Survival Rates and Antioxidant Activity Evaluation of the Aqueous Extract of *Achyrocline satureioides* in the *Caenorhabditis elegans* Model**. Santos PA[1], Uczay M[1], Lobo LAC[1], Brittes RM[2], Siqueira IR[1], Pereira P[1] [1]ICBS-UFRGS, Lab of Neuropharmacology and Preclinical Toxicology, Porto Alegre, Brazil, [1]ICBS-UFRGS, Lab of Microbiology and Parasitology, Porto Alegre, Brazil
Introduction: *Achyrocline satureioides* (Lam.) D. C., Asteraceae (SisGen code A928BF2), is a plant widely used in traditional folk medicine in South America, being native from this region. Among its biological activities, its antioxidant property stands out. The objective of this work was to evaluate the A. satureoides aqueus extract on the C. elegans survival, and to investigate its effect on the expression of the sod and gst enzyme. Material and **Methods:** The aqueous extract was obtained from the inflorescences of the plant being subjected to extraction by infusion in hot water at 80°C for 15 minutes with solvent and plant ratio, to obtain the concentrations C1=10,000, C2=15,000, C3=25,000, C4=50,000 and C5=100,000 µg/ml. Wild-type Bristol (N2), CL2166 (gst-4:GFP) and CF1553 (sod-3:GFP) strains of C. elegans worms were obtained from the Caenorhabditis Genetics Center (CGC) and grown on NGM agar plates seeded with a lawn of Escherichia coli (OP50) in 20° C. For both the experiments, adult hermaphrodites were synchronized using an alkaline hypochlorite solution. To the lethality assay wild type (N2) worms were used. Ten worms were transferred to each well in 24-well plates which contained serial concentrations the aqueous extracts in triplicates (C1,C2,C3,C4,C5). The negative control was also included in triplicate. Plates were incubated at 20 °C in the dark for 24 h, and the number of live and dead worms was recorded by visual inspection under a dissection microscope. Nematodes were considered dead if they did not respond to stimulus when touched with a platinum wire. To the sod-3 and gst-4 expression assay, approximately 100 age synchronized L4 CF or CL transgenic worms tagged with GFP protein were transferred to 24-well plates. Following that, larvae were exposed to aqueous extracts (C1,C2,C3,C4). + hydrogen peroxide (0.1 mM), just hydrogen peroxide (0.1 mM) as a positive control or K-medium (negative control) for

one hour. Then, the worms were anesthetized with 0. 5 mM sodium azide (0. 5 mM), transferred to histological slides, and covered with coverslips. The slides were analyzed under a fluorescence microscope at 10X magnification, ten worms per treatment were photographed and analyzed. The experiments were performed in triplicate, and GFP fluorescence signals were measured and analyzed using NIH ImageJ software. The statistical analysis was performed using GraphPad Prism software, one-way ANOVA test was used (significant at $p \leq 0.05$). **Results:** The extract demonstrated a concentration-dependent toxicity on nematodes after 24 hours of exposure. The concentrations of C1 and C2 had no significant difference compared to the control group, but C3, C4 e C5 showed significant difference in lethality ($p \leq 0.0001$). The sod-3 and gst-4 expression evaluation showed that the negative control showed a significant difference when compared to the positive control. The C1, C2 and C3 concentrations after one hour of exposure together with the stressor agent demonstrated a significant decrease in relative fluorescence when compared to the positive control ($p \leq 0,0001$), but not compared to the negative control. However, the C4 showed a significant difference when compared to the positive and negative controls ($p \leq 0,001$). **Conclusion:** Increasing the concentration of the extract significantly increased the lethality of the worm, and it was able to significantly reverse the stress caused by hydrogen peroxide in strain CF1553 and CL2166, suggesting an A. satureoids protective effect. **Financial Support** CAPES

09.022 **Gastroprotective Effect of *Lonchocarpus sericeus* on Ethanol-induced Gastric Lesion in Mice: Role of Prostaglandins and Nitric Oxide**. Freire GP[1], Almeida Filho LCP[2], Nunes PIG[1], Portela BYM[1], Lima RP[1], Carvalho AFFU[2], Santos FA[1] [1]UFC, Dept of Physiology and Pharmacology, Fortaleza, Brazil, [2]UFC, Dept of Biochemistry, Fortaleza, Brazil

Introduction: Peptic ulcer affects at least 1 in 10 patients during their lifetime. The injury occurs when there is an imbalance between the protective mechanisms and the aggressive factors of the gastric system. Current clinical treatment is associated with high recurrence rates and a low cure rate and therefore remains a major challenge. In this context, the gastroprotective effect of the hexane extract of *Lonchocarpus sericeus* (LsHE) in ethanol-induced gastric lesions in mice has been previously reported, and this work aims to investigate the mechanism by which LsHE acts to protect the gastric mucosa. **Methods:** Male Swiss mice (25-30g, n=8/group) were pretreated with indomethacin (30 mg/kg, s. c.), a nonselective COX inhibitor, glibenclamide (3 mg/kg, i. p.), a KATP channels blocker or L-NAME (20 mg/kg, i. p.), a NO synthases inhibitor, 30 min before the administration of LsHE (1. 6 mg/kg, p. o.) or the respective controls, misoprostol (50 µg/kg, p. o.), diazoxide (3 mg/kg, i. p.) or L-arginine (600 mg/kg, i. p.). Sixty min after the treatments, mice were orally treated with absolute ethanol (99. 5%, 0. 2 mL). Thirty minutes after ethanol administration, animals were euthanized and gastric lesions were measured by planimetry (mm2) using ImageJ software. A group of mice pretreated with vehicle (saline) or LsHE (1. 6 mg/kg, p. o.) before ethanol administration was included in the study. Results were expressed as mean ± EPM. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test. P values < 0.05 were considered statistically significant. This study was approved by CEUA (n° 1933011019) and registered with SisGen (n°AD3CC8F). **Results:** LsHE (1. 6 mg/kg) significantly reduced the gastric lesion area (8. 24 ± 0. 89 mm2) when compared to vehicle-treated animals (21. 63 ± 0. 98 mm2). Misoprostol (6. 42 ± 0. 87 mm2), L-arginine alone (6. 07 ± 0. 91 mm2), and Diazoxide (4. 35 ± 0. 98 mm2) also effectively reduced the gastric lesion area when compared to the vehicle control group. The pretreatment with indomethacin (30 mg/kg) completely blocked the gastroprotective effect of LsHE (20. 6 ± 0. 97 mm2) and of misoprostol (21. 11 ± 0. 86 mm2). Similarly, pretreatment with L- NAME (20 mg/kg) also significantly blocked the gastroprotective effect of LsHE (21. 09 ± 1. 54 mm2) and of L-arginine (21. 19 ± 1. 12 mm2). However, the pretreatment with glibenclamide (3 mg/kg) had no effect on LsHE-induced gastroprotection (9. 96 ± 0. 59 mm2), but it blocked the gastroprotective effect of diazoxide (21. 05 ± 0. 85 mm2). **Conclusion:** The gastroprotective effect of LsHE against ethanol-induced gastric lesions should involve pathways related to the production of prostaglandins and/or nitric oxide, but not involve the participation of KATP channels. **Financial Support:** CNPq; CAPES; FUNCAP.

09.023 **Ethanolic Extract of *Varronia dardani* (Taroda) J.S. Leaves Inhibits Writhing in a Primary Dysmenorrhea Mice Model**. Figueiredo IAD, Ferreira SRD Pessoa RF- Veloso CAG, Costa VCO, Silva MS, Cavalcante FA UFPB

Introdution: Dysmenorrhea, also known as menstrual cramps, causes painful contractions in the pelvic region, occurring before or during menstruation (BANDARA, E. M. I. A. et al., Sci. Rep., 12, 1, 1-13, 2022). Excessive release of prostaglandins by the uterine endometrium has been associated with dysrhythmic uterine

contractions (YOUSEFI et al., Gynecol. Endocrinol., 1-5, 2019). Natural products are an essential source of therapeutic agents originating from the world's biodiverse flora and fauna. Thus, considering that the ethanolic extract obtained from *Varronia dardani* leaves (VD-EtOHL) had a non-selective spasmolytic effect in tonic and phasic smooth muscle models, being more potent in rat uterus (VELOSO et al., Nat. Prod. Res., 35, 4197, 2021), we investigated the in vivo tocolytic effect of VD-EtOHL in the model of oxytocin-induced abdominal writhing in female mice and *in vitro* on tonic contractions induced by PGF2α in isolated rat uterus. **Methods:** Initially, behavioral screening and evaluation the acute toxicity in female mice (n = 6) were performed according to OECD guideline no. 423 (OECD, guideline for testing of chemicals n. 423, 2001). For in vivo assays, mice (n = 6) were treated during 3 days with diethylstilbestrol (1 mg/kg, i. p.), except negative control. On fourth day, they were divided into groups: negative control (saline 10 mL/kg plus Cremophor 0. 01%), model group (saline 10 mL/kg plus Cremophor 0. 01%), positive control (ibuprofen 50 mg/kg) and VD-EtOHL (various doses) (p. o.). After 30 minutes of administration, all groups (except negative control) received oxytocin 50 IU/mL i. p. and the number of abdominal writhing were counted for 30 minutes (LI et al., J. Ethnopharmacol., 245, 112181, 2019). For *in vitro* assays, the Wistar female rats after hormonal synchronization of estrus with diethylstilbestrol (1 mg/kg, s. c.) were euthanized, uterine horns were isolated and suspended in organ baths under appropriate conditions and isometric contractions were monitored and recorded (n = 5). All results obtained were expressed as mean ± standard error of the mean and statistically analyzed using the “t” test or ANOVA followed by Tukey's posttest. All experimental protocols were approved by the Ethical Committee on Animal Use of UFPB (3834230519). **Results:** In acute toxicity assay, VD-EtOHL (2000 mg/kg) did not induce toxicity signs on female mice under the experimental conditions evaluated during the 4 hours of observation, as well as during the observation period of 14 days there was no death of animals, change in weight evolution, water intake, feed intake and relative weight of organs. In the dysmenorrhea primary model in mice, the model group showed an increase in abdominal writing (100%) induced by oxytocin compared to negative control group. The positive control group showed inhibition of writing (Emax = 96. 0 ± 2. 0%) compared to the model group. VD-EtOHL dose-dependently (ED50 = 105. 5 ± 14. 8 mg/kg) inhibited abdominal writhing at doses of 125 (Emax = 9. 1 ± 8. 1), 250 (Emax = 40. 3 ± 6. 9%), 500 (Emax = 76. 9 ± 4. 9%) and 1000 mg/kg (Emax = 80. 2 ± 10.1%). In the *in vitro* assays, VD-EtOHL (0. 01-243 µg/mL) concentration-dependently relaxed the rat uterus pre-contracted with PGF2α 10-6 M (Emax = 100. 4 ± 7. 2% and EC50 = 15. 4 ± 3. 5 µg/mL). **Conclusion:** The present study shows that VD-EtOHL has tocolytic activity in vivo and may be a promising drug in the treatment of primary dysmenorrhea. **Financial Support:** CAPES, CNPq, PPgPNSB/CCS/UFPB.

09.024 **Protective Effect of Chalcone 2-Hydroxy-3,4,6-Trimetoxyacetophenone (HTMCX) on Ketamine-Induced Cytotoxicity in Renal Tubular Cells**. Alencar MMC[1,3], Magalhães EP[2,3], Almeida IM[3], Ali A[1,3], Bezerra de Menezes RRPP[2,3], Sampaio TL[1,3], Martins AMC[1,3] [1]UFC, PPG in Pharmacology, Fortaleza, Brazil, [2]UFC, PPG n Pharmaceutical Sciences, Fortaleza, Brazil, [3]UFC, Dept of Clinical and Toxicological Analysis, Fortaleza, Brazil

Introduction: Acute kidney injury (AKI) is a condition associated with high morbidity and mortality characterized by a reduction in glomerular filtration rate, associated with reduced renal blood flow and tubular dysfunction. Drug toxicity accounts for 15–25% of AKI cases. Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone), a fast-acting intravenous anesthetic, is used in clinical practice as the drug of choice in veterinary procedures, field medicine, and pediatric anestesia. The renal toxicity of ketamine can be decisive for the recovery of patients, and its use should be evaluated to avoid the development of AKI. The mechanism of toxicity of this drug is still unclear and includes the expression of genes linked to the apoptotic process, oxidative stress and activation of the inflammatory system. Antioxidant and anti-inflammatory substances, especially those of natural origin, have been studied as an adjuvant strategy to the cytotoxicity induced by this drug. Chalcone 2-hydroxy-3,4,6-trimethoxyacetophenone (HTMCX) found in the stem bark of plants of the genus Croton sp. It has antioxidant and anti-inflammatory potential. Thus, the present work investigated the possible cytoprotection of chalcone HTMCX in an *in vitro* model of ketamine-induced AKI. **Methods:** An immortalized human proximal tubular cell line, HK2 cells, was used. The dimethylthiazolyldiphenyltetrazolium (MTT) reduction assay was performed to determine working concentrations of HTMCX and Ketamine. To evaluate cytoprotection, cells were exposed for 24 hours to Ketamine at a concentration capable of reducing cell viability by 50% (IC50 = 2. 55 µM), then the cells were treated with non-toxic concentrations of HTMCX (62 . 5-15. 62 µM). The cell death

mechanism involved in the process was evaluated by flow cytometry, by labeling the cells treated with Propidium iodide and Annexin V. The levels of interferon-gamma (INF-γ) and interleukin-6 (IL-6) in the cell supernatant were also evaluated to observe the anti-inflammatory effect of the substance. As negative control (NC) untreated cells were considered. Statistical analysis was performed with one-way ANOVA, and Bonferroni post-test ($p<0.05$). **Results:** Ketamine reduced cell viability compared to NC (54. 4 ± 1. 8 vs. 100 ± 1. 6 %). HTMCX partially reversed the reduction in cell viability observed in the ketamine group, highlighting concentrations of 31. 25 µM (80. 7 ± 2. 7 %) and 15. 62 µM (80. 5 ± 3. 5 %). Exposure to ketamine generated an apoptotic stimulus, with HK-2 cells predominantly marked by Annexin V (25. 78 ± 0.17 % of cells). HTMCX was able to reduce the apoptotic process (percentage of labeled cells equal to 20. 46 ± 0. 36 %) installed by the drug, at a concentration of 31. 25 µM. The dosages of pro-inflammatory mediators showed that treatment with Ketamine (IC50) was able to increase IFN-gamma levels by 17. 33% and IL-6 by 35. 96%, when compared to the negative control and treatment with HTMCX (31. 2 and 15. 6 µM) was able to significantly reduce the levels of these mediators to values similar to the negative control. **Conclusion:** It is concluded, then, that HTMCX partially reversed ketamine-induced cytotoxicity in HK2 cells, as well as was able to reduce the levels of inflammatory biomarkers. **Keywords:** Kidney cells. Cytotoxicity. Natural products. Apoptosis. Interferon-gamma.

09.025 **Inhibition of the AGE/RAGE Pathway in an Experimental Model of Non-Alcoholic Fatty Liver Disease: A Focus on Anti-Inflammatory and Antioxidant Mechanisms**. Silvares RR, Araujo BP, Lima LN, Rodrigues KL, Pereira ENGS, Silva VVD, Daliry A IOC-Fiocruz, Lab of Cardiovascular Investigation, Rio de Janeiro, Brazil

Background: Obesity is one of the biggest public health problems worldwide and its prevalence has grown substantially. In the liver, obesity influences the excessive production of triacylglycerol, which contributes to the development of non-alcoholic fatty liver disease (NAFLD). NAFLD affects one third of the adult population and is currently guided by the multiple hits hypothesis, in which the interaction between multiple factors affects the fat content of hepatocytes and the hepatic inflammatory environment, leading to a state of chronic hepatic inflammation. However, the molecular and immunological mechanisms responsible for disease progression remain unclear. In the present study, we aimed to evaluate in greater detail the type of inflammatory response and the oxidative stress pathways activated in NAFLD animals, in the presence or absence of Pyridoxamine. The effect of RAGE receptor inhibition will also be evaluated, in the same parameters, by treating NAFLD animals with a RAGE receptor antagonist, FPS-ZM1. **Methods:** The NAFLD model was induced in C57BL/6 mice by 12 weeks of HFHC+COL2% feeding. They were treated daily with pyridoxamine (200mg/kg/day, v. o. by gavage) gavage or FPS-ZM1 (1mg/kg/day, i. p. by intraperitoneally injected) between weeks 6 - 12 and biochemical markers were analyzed at the end of the protocol. In the liver microcirculation, the recruitment of leukocytes was examined by in vivo microscopic observations. Tissue perfusion was accessed by laser speckle contrast imaging (LSCI). Oxidative stress parameters were analyzed by thiobarbituric acid reactive species (TBARS), hepatic ROS levels and catalase enzyme activity and inflammatory markers by flow cytometry (IL-2/4/6/10/17-A, TNF -α and INF-γ). All procedures were approved by the Oswaldo Cruz Foundation Animal Welfare Committee (L-012/2018 A2). **Results:** C57BL/6 mice fed with an HFHC+COL2% diet showed increased body weight, visceral and subcutaneous fat content, fasting glucose, serum cholesterol and ALT, and hepatic cholesterol and triglycerides. And the treatments were able to reverse all the parameters analyzed. Regarding the hepatic microcirculatory parameters, the HFHC+COL2% group showed an increase in leukocyte rolling and adhesion and a decrease in tissue perfusion. Pir and FSP-ZM1 showed a vasoprotective effect on hepatic microcirculation of NAFLD induced by HFHC+COL2%. The liver tissue of the HFHC+COL2% group showed an increase in oxidative and inflammatory stress while the treated groups showed a reduction in these parameters. **Conclusion:** In the present study, we suggest that inhibition of AGE formation or RAGE receptor blockade are both able to modulate metabolic effects, fat accumulation, microcirculatory damage, and oxidative and inflammatory states, which are important steps to limit the progression of NASH. This work was funded by CNPQ, FAPERJ e PAPES/FIOCRUZ.

09.026 **Analysis of the Healing Potential of** ***Montrichardia linifera in vitro***. Bastos AC[1], Gomes MF[1], Amarante CB[2], Pinheiro WBS[1], Botelho AS[1], Khayat AS[1], Yamada ES[1], Bastos GNT[1] [1]UFPA, [2]Museu Paraense Emílio Goeldi

Introduction: Chronic skin injuries occur when the healing process is inefficient. Therefore, research for new drugs to restore skin homeostasis is necessary. *Montrichardia linifera* is commonly used by some Amazonian communities for the treatment of skin wounds. Thus, this study aimed to investigate the healing activity of

extracts of this species in vitro. **Methods:** The *in vitro* experiment was conducted using Fibroblasts, L929 cells. The ethanolic extracts of the leaves, petiole and stem were used (SISGEN registration A91B68B). MTT assay was performed to evaluate cell viability in the presence or absence of different concentrations of each extract (100 to 0.19µg/ml), in time-dependent effects (24;48; or 72h). The scratch assay was used to evaluate the lesion area in vitro. Fibroblast proliferation was quantified by counting cells positive for BrdU. **Results:** The extracts failed to promote cytotoxicity at the time/concentrations of the extracts. However, cells treated with the stem extract showed the viability of 109. 60±8. 223, 111. 60±9. 517, 111. 80±10. 64, 114. 50±12. 11, 120. 50±12. 79% in 24h at concentrations of 3. 125, 1. 56, 0. 78, 0. 39, 0.19 µg/ml, respectively; In 48h and 72h the viability was 107. 40±7. 862 and 113. 6±6. 053%, respectively, in the concentration of 0.19 µg/ml, groups that showed a significant increase in relation to the control. Cells treated with 0.19 µg/ml of petiole extract showed cell viability of 111. 70±8. 011% in 48h, significantly increasing viability over the control. Cells treated with leaf extract for 24h showed viability of 106. 80±6. 485, 108. 80±6. 485, 109. 20±5. 921% at concentrations of 0. 78, 0. 39, 0.19 µg/ml, respectively; while at concentrations of 12. 5, 6. 25, 3. 125, 1. 56, 0. 78, 0. 39, 0.19 µg/ml, the viabilities after 48h were 113. 7±9. 908, 119. 3±12. 32, 127. 8±15. 13, 126. 6±15. 55, 130. 7±14. 71, 15. 55, 130. 7±14. 71 111. 70±8. 011% respectively; and after 72h were 125. 5±20. 35, 127. 7±25. 69, 131. 1±25. 07, 132. 6±22. 74, 134. 8±24. 84, 137. 8±20. 83, 149. 8±20. 91%, respectively, these groups showed significant increase over control; the other groups showed no significant difference in cell viability over control group. For the lesion area tests, concentrations of 0. 78, 0. 39; 0.19 µg/ml for each extract were used. In the analysis of the group treated with stem extract showed lesion area in 12h of 32. 29±16. 62% in the concentration of 0.19 µg/ml, in 24h of 10. 67±7. 94, 10.15±7. 35% in concentrations of 0. 39 and 0.19 µg/ml, respectively, showing significant difference in relation to the control. The group treated with the petiole extract in 24 hours showed a lesion area of 12. 40±7. 72% at the concentration of 0.19 µg/ml, demonstrating significant difference compared to the control. The other groups showed no significant difference in lesion area compared to the control group in the cell proliferation analysis, the number of cells treated for 24h with 0. 39 and 0.19 µg/ml of stem extract were 37. 889±7. 407, 29. 778±4. 521 BrdU positive cells, respectively; the number of cells treated for 24h with 0.19 µg/ml stem extract was 24. 889±3. 551 BrdU positive cells, the other groups showed no significant increase in the quantification of BrdU positive cells. **Conclusion:** *Montrichardia linifera* extracts presented a potential healing effect, without cytotoxicity and also promoted an increase in migratory and proliferative activity.

09.027 *Spirulina platensis* **Prevents the Increase in IL-1β levels and Improves the Antioxidant Capacity of the Ileum of Obese Rats Fed a Hypercaloric Diet**. Diniz AFA, Claudino BFO, Francelino DMC, Barros BC, Lacerda Júnior FF, Ferreira PB, Alves AF, Silva BA UFPB

Introduction: The intestinal tract plays a crucial role in the homeostasis of the organism, protecting against harmful and pathogenic substances. In addition, the consumption of hypercaloric diets favors the increase in the production of pro-inflammatory cytokines as well as reactive species through adipose tissue (ASMAZ; SEYIDOGL, Food S. and Human W., v. 1, 2022). An important seaweed stands out for having important nutritional properties, potential therapeutic, antioxidant and anti-inflammatory effects on intestinal health (SEYIDOGLU; AYDIN, The Health Benefits of Foods, v. 61, 2020). In this context, the objective of this study was to evaluate the preventive effect of food supplementation with S. platensis (SP) on the production of interleukin 1 beta (IL-1β) and on tissue antioxidant capacity (CAT). **Methods:** Wistar rats (8 weeks of age) were divided into rats that received standard diet (SD), hypercaloric diet (HCD) or hypercaloric diet + orally supplementation with S. platensis powder at 25 mg/kg (HCD + SP25). Animals received different diets for 8 weeks. Histological sections of ileum in immunohistochemistry reaction against interleukin 1-β against stained with Harris hematoxylin. The reaction was revealed using 0. 024% Diaminobenzidine (DAB) solution. In addition, the antioxidant capacity of the ileum was also analyzed through the calorimetric method of reducing DPPH (1,1-diphenyl-2-picryl-hydrazyl). Results were expressed as mean and standard deviation of the mean and analyzed by one-way ANOVA followed by the Tukey post-test (n=5). **Results:** In the evaluation of the immunohistochemical parameters of the SD group, the presence of enterocytes marked by interleukin (brown color) is observed. In rats fed a hypercaloric diet, it is possible to identify the increase in the labeling expression of multiple intracytoplasmic IL-1β-labeled cells. Additionally, in the HCD + SP25 group, the presence of cytokine staining is observed both in the enterocytes and in the polymorphonuclear cells of the ileal endothelium mucosa, but with lower expression when compared to

the HCD group. When analyzing the tissue antioxidant capacity of the HCD group (73. 0 ± 2. 7%) it is possible to observe a reduction in the antioxidant activity present in the ileum when compared to the SD control group (89. 4 ± 2. 2%), interestingly the supplemented group with the seaweed at a dose of 25 mg/kg (85. 4 ± 2. 8%) it is observed that the organ CAT does not differ from the SD group, but when compared to the HCD group (73. 0 ± 2. 7%) the Ileal CAT is significantly lower and compromised. **Conclusions:** These results show that food supplementation with the alga S. platensis was able to prevent the increase in the production of interleukin IL-1β with a consequent reduction in the inflammatory profile caused by the hypercaloric diet, as well as preventing the reduction of the tissue antioxidant capacity of the ileum of obese mice. Thus, this study highlights the promising preventive role of *Spirulina platensis* supplementation with anti-inflammatory and antioxidant action, against intestinal disorders promoted by obesity. Support: CnPq, PPgPNSB/UFPB. Research approval: CEUA/UFPB 2352101019.

09.028 **Liver Histopathology of Silver Catfish Infected by** *Aeromonas hydrophila* **and Treated with Extract of** *Hesperozygis ringens* (**Benth**.) **Epling**. Rosa IA[1], Bandeira Junior G[1], Bianchini AE[1], Pereira da Silva HN[1], Ferrari FT[2], Costa ST[3], Baldisserotto B[1], Heinzmann BM[1,2] [1]UFSM, Department of Physiology and Pharmacology, Santa Maria, Brazil, [2]UFSM, Department of Industrial Pharmacy, Santa Maria, Brazil, [3]UFSM, Dept of Morphology, Santa Maria, Brazil

Introduction: Outbreaks of bacterial infections in aquaculture have been one of the biggest challenges in this sector (Bandeira Junior and Baldisserotto, 2020). The bacterium Aeromonas hydrophila is characterized as one of the main pathogens, affecting several species of fish (Barcellos et al., 2008; Algammal et al., 2020). Recent studies have shown that the hexane extract of Hesperozygis ringens (Benth.) Epling (HEHR) leaves increased the survival rate of silver catfish experimentally infected by A. hydrophila (Rosa et al., 2019). However, so far, the effects of this extract on the histology of fish have not been demonstrated. For this reason, the liver histopathology of silver catfish experimentally infected by A. hydrophila and treated with the HEHR was evaluated. **Methods:** For this, after acclimatization, healthy silver catfish (n = 72) or experimentally infected by A. hydrophila MF 372510 (n = 72) were submitted to the control, ethanol, florfenicol (FLOR, 4 and 30 mg/L) and HEHR (15 and 30 mg/L) treatments via immersion bath for seven days (protocol approved by the Ethics Committee on the Use of Animals – UFSM 5290190919). Liver tissues from fish (n = 2, per treatment) were collected after euthanasia by medullary section and stored in 10% buffered formalin solution for histopathological analysis. Fragments of liver tissues were embedded in paraffin for sagittal sections of 5 µm, and stained with hematoxylin and eosin (HE) to identify standard structures. The slides were analyzed by two histopathologists in a double-blind manner using light microscopy. **Results:** Healthy fish from the control, ethanol, FLOR4, FLOR30, HEHR15 and HEH30 groups showed no histological changes in the liver and the tissue architecture was preserved. The infected and untreated fish showed centers of melanomacrophages, endothelium loss, leukocyte infiltration and necrosis. Vessel obstruction, endothelium loss and leukocyte infiltrate were observed in the liver of fish infected and treated with ethanol. Fish infected and treated with FLOR4 presented vessel obstruction and leukocyte infiltration, while those treated with FLOR30 presented, in addition to vessel obstruction, the presence of clots. For fish infected and treated with HEHR15, vessel obstruction, leukocyte infiltrate and hemorrhage were observed, while in those treated with HEHR30, vessel obstruction and the presence of clots were observed. **Conclusions:** In summary, although the changes seen in the liver tissue of fish infected and treated with FLOR30 and HEHR30 were similar, none of the treatments was effective in totally preventing the histopathological damage to the liver caused by the bacterium A. hydrophila. Based on the above, more studies are needed in order to find new natural antimicrobials, including compounds from the H. ringens species, that are capable of protecting against liver damage found in cases of aeromonosis. **Financial Support:** PIBIT-CNPQ and CAPES. Acknowledgments: To CAPES and CNPQ for their financial support. **References:** Algammal, A. M. Pathogens. 9, 238, 2020. Bandeira Junior, G. J. Appl. Microbiol. 131, 1083, 2020. Barcellos, L. J. G. B. Inst. Pesca. 34, 355, 2008. Rosa, I. A. J. Appl. Microbiol. 126, 1353, 2019.

09.029 **Comparative Compositional and Functional Activities of** *Lachesis muta* **Venom from Adult and Juvenile Individuals**. Galizio N[1], Torres-Bonilla KA[2], Varón JCG[2], Moraes-Santos LS[3]., Yabunaka AC[3], Silva Júnior NJ[4], Hyslop S[2], Tanaka-Azevedo AM[1], Floriano RS[1], Floriano RS[3] [1]Ibu, Lab of Herpetology, Instituto Butantan, Sao Paulo, SP, Brazil, [2]FCM-Unicamp, Section of Pharmacology, Dpt of Translational Medicine, Campinas, Brazil, [3]PPG in

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Lachesis envenoming are characterized by clinical manifestations such as local necrosis, systemic myotoxicity, renal failure, haemorrhage, coagulopathy, and hypotension. The treatment is conditioned to the use of polyvalent antivenom serum and there are no studies comparing the biochemical and toxicological differences of venoms from adult and young Lachesis specimens, nor the effectiveness of antivenoms. In addition, the investigation of snake venom composition may be important for the bioprospecting of new drugs and bioproducts. Thus, the present work aims the characterization of compositional and enzymatic profile, including the coagulotoxicity, of an adult and its offspring (seven siblings) from Lachesis muta species. Compositional profile was achieved using RP-HPLC and SDS-PAGE, while phospholipase A2 (PLA2), L-amino acid oxidase (LAAO), phosphodiesterase (PDE), snake venom metalloproteinase (SVMP) and serine proteinase (SVSP) activities were evaluated to access enzymatic profile of these venoms. Minimum coagulant dose (MCD), thrombin-like activity and Factor X activation were performed for investigate the venoms coagulotoxicity. Chromatographic profile of the venom obtained from the adult specimen exhibited 17 major peaks, while the venoms from six offspring (F) exhibited between 7 and 11 major peaks; the F7 offspring exhibited the same 17 major peaks seen in the adult specimen. SDS-PAGE was performed with 15% acrylamide concentration and demonstrated few differences among the individuals. The venom from the adult specimen shows two protein bands between 20 and 25 kDa with higher intensity than the venoms from juvenile snakes. Venoms did not differ in the level of enzymatic activity for PLA2, LAAO and PDE. Enzymatic activity for SVSP was ~34% higher in juveniles in relation to the adult specimen, while the enzymatic activity for SVMP was ~76% lower in the juveniles compared to adult. There was a high variation in metalloprotease activity among the siblings, ranging from 20 to 210 U/mg. Few differences were observed in thrombin-like and Factor X activation, however MCD demonstrated that juveniles are more coagulant than adult, in general. Even knowing the effectiveness of the antibotropic-lachetic antivenom, it was not able to neutralize the coagulant activities in vitro. This pattern is observed in other Viperidae snake species, including species from genus Bothrops. The variations observed in the chromatographic and enzymatic aspects of these venoms allow us to suggest that juvenile Lachesis muta venoms present less complexity in terms of toxins composition compared to the adult specimen and less SVMP, although they are equally active for other enzymatic groups. Nevertheless, juvenile venoms show more SVSP than adult venom which can contribute to higher coagulotoxicity in these venoms. Ontogenetic changes in composition of snake venoms are already described in species from genus Bothrops and presented similar pattern – while the venom of juveniles is more coagulotoxic, the venom of adults can be more haemorrhagic.

09.030 **Antinociceptive Activity of Aqueous Extract of** *Bauhinia pulchella* **Benth in Mice**. Nunes PIG[1], Estevão VA[1], Maurício MTA[1], Lima RP[1], Portela BYM[1], Freire GP, Carvalho AA[2], Chaves MH[3], Santos FA[1] [1]FM-UFC, [2]IFPI, Piripiri, Brazil, UFPI, Chemistry Department, Teresina, Brazil

Introduction: Many species of the genus Bauhinia are widely used in folk medicine for their analgesic and anti-inflammatory effects. However, there are few studies addressing the pharmacological potential of Bauhinia pulchella. Therefore, the aim of this study was to evaluate the antinociceptive activity of the aqueous extract of *B. pulchella* (AEBP) as well as its mechanism of action. **Methods:** The leaves of *B. pulchella* Benth were collected in Jatobá do Piauí - PI and registered under the exsiccata nº TEPB 17161 in the Herbarium Graziela Barroso at UFPI. The antinociceptive effect of AEBP (12. 5, 25, and 50 mg/kg, p. o.) was evaluated in acute chemical-type models (acetic acid-induced abdominal writhing, formalin-induced hind paw licking, and capsaicin-induced hind paw licking) and thermal models (hot plate and tail-flick tests) and in LPS-induced inflammatory hyperalgesia in mice. 0. 9% saline solution (10ml/kg, p. o.) was used as vehicle control, and morphine (5 mg/Kg, i. p.) was used as the positive control. Male Swiss mice (n=8, 25-30 g) were used. Results were expressed as mean ± SEM. For multiple comparisons of parametric data, one-way ANOVA was used, followed by the Student Newman-Keul's test. P-values < 0.05 were considered statistically significant. This work was registered in SisGen (nº A27C3A4) and experiments were throughout as approval by the Ethics Committee on the Use of Animals of the Federal University of Ceará (CEUA-UFC) under nº 8689230921. **Results:** AEBP 12. 5, 25, and 50 mg/kg significantly reduced in 31, 83, and 86%, respectively, the number of writhes induced by acetic acid (97%, 10 ml/kg, i. p., 51.

13 ± 3. 23 number of writhes) compared to the vehicle control group (3. 5 ± 0. 93 number of writhes). AEBP at all doses tested significantly reduced both phases of the formalin test when compared to the vehicle control group. In the capsaicin test, AEBP 12. 5, 25, and 50 mg/kg significantly reduced paw licking time in 37%, 58%, and 65%, respectively, compared to the vehicle control group (95. 05 ± 2. 18 seconds). Morphine (5 mg/kg) produced an antinociceptive effect in all the chemical tests used. Naloxone (5 mg/Kg) was able to inhibit the antinociceptive effect of AEBP (25 mg/kg) and morphine in all the chemical tests used. AEBP 12. 5, 25, and 50 mg/kg produced an antinociceptive effect against thermal nociception induced by hot plate (51 ± 0. 5 ºC) as well as in the tail-flick test (55 ± 0. 5 ºC) in all evaluation periods. AEBP at all doses used was able to reduce reaction time in the hot plate test in LPS-induced inflammatory hyperalgesia. In the thermal nociception and inflammatory hyperalgesia tests, morphine (5 mg/Kg) was able to reduce the nociceptive response of the animals. In addition, acute oral administration of AEBP (2000 mg/kg) produced no mortality or signs of toxicity. **Conclusion:** These results suggest that aqueous extract of *B. pulchella* has peripheral and central antinociceptive effects whose mechanism of action involves the participation of opioid receptors. Support or financing information: CAPES. CNPq. FUNCAP.

09.031 **Taraxasterol Acetate, Isolated from *Eupatorium balotteifolium*, Improves Glucose Uptake by Increasing Membrane GLUT4 Expression in TNFα-Induced 3T3-L1 Cells**. Lima RP[1], Oliveira FTB[2], Freire GP[2], Portela BYM[1], Nunes PIG[2], Albuquerque MRJR[3], Pessoa ODL[3], Santos FA[1] [1]UFC, PPG Pharmacology, Fortaleza, Brazil, [2]UFC, PPG Medical Science, Fortaleza, Brazil; [3]UFC, PPG Chemistry, Fortaleza, Brasil

Introduction: Insulin resistance (IR) is defined as the inability of cells or tissues to respond to physiological levels of insulin and is related to metabolic disorders, such as type 2 diabetes (T2D) and obesity. Obesity is associated with modifications in the physiological function of adipose tissue, leading to altered secretion of adipocytokines, like TNF-α and IL-6, and a state of chronic inflammation and insulin resistance. Adipose tissue-derived TNF-α suppresses the expression of many proteins that are required for insulin-stimulated glucose uptake in adipocytes, such as the insulin receptor, IRS-1, and GLUT4. Herbal compounds such as triterpene have been shown to be promising in preventing or supporting therapy for some metabolic conditions, including T2D and obesity. We investigated the effects of taraxasterol acetate (TXA), a pentacyclic triterpene isolated from *Eupatorium balotteifolium*, in TNFα-induced IR in 3T3-L1 adipose cells. **Methods:** Samples of the aerial part of *E. ballotaefolium* were collected in the Meruoca region, Sobral-CE, in April 2003, and the exsiccate was registered in the Prisco Bezerra Herbarium at UFC (nº27. 646). 3T3-L1 pre-adipocytes were differentiated into mature adipocytes for 10 days. TXA was dissolved in DMSO (0.1% v/v) and added to the medium for final concentrations of 0. 5–200 µM on day 10 of differentiation and cell viability was evaluated by the MTT assay. Vehicle control cells were treated with the same volume of 0.1% DMSO. To assess the effect of TXA on TNFα-induced IR, mature adipocytes were divided into 6 groups: vehicle control, insulin-stimulated control (insulin control), TNFα-induced IR (TNFα-IR), and TNFα-IR treated with TXA (25 and 50 µM) or rosiglitazone (ROS, 20 µM) for 24 h, followed by assessment of glucose uptake with 2-NBDG. Proteins from 3T3-L1 cells were extracted to evaluate GLUT4 translocation in the membrane and protein expression of IRS, PI3K, and AKT. The protein concentration of each sample was determined by the Lowry method. Results were expressed as mean ± SEM of three independent experiments. One-way ANOVA was used for multiple comparisons of parametric data, followed by the Student Newman-Keul's test. P-values <0.05 were considered statistically significant. This study was registered in SisGen (nº ACB11B8). **Results:** TXA (0. 5–200 µM) didn´t reduce 3T3-L1 cell viability in comparison with the vehicle group. In mature adipocytes, insulin increased glucose uptake by 31. 4% compared to the vehicle group, while TNFα reduced glucose uptake by 31. 6% after insulin stimulation compared to the insulin control group. In the TNFα-IR cells, TXA 25 and 50 µM and ROS 20 µM increased glucose uptake by 52. 2%, 55. 8%,and 55. 7%, respectively, in comparison with the TNFα-IR group. TNFα reduced membrane GLUT4, PI3K, and AKT protein expression when stimulated with insulin compared to the insulin control group. In the TNFα-IR cells, TXA 50 µM and ROS 20 µM increased PI3K and AKT protein expression as well as membrane GLUT4 protein expression, compared to the TNFα-IR group. In addition, TNFα increased IRS1 phosphorylation (Ser307) when stimulated with insulin compared to the insulin-stimulated control group. In TNFα-IR cells, 50 µM of TXA and 20 µM of ROS reduced IRS1(Ser307) phosphorylation compared to the TNFα-IR group. **Conclusion:** These results suggest that TXA improves glucose uptake in TNFα-induced insulin resistance in 3T3-L1 cells by increasing the translocation

of GLUT4 to the plasma membrane by IRS-PI3K-AKT pathway. Support or financing information: CAPES; CNPq; FUNCAP.

09.032 **Coumestrol: A Promising Molecule for Wound Healing**. Bianchi SE, Bassani VL UFRGS, PPG em Ciências Farmacêuticas, Porto Alegre, Brazil

Introdution: Coumestrol is a coumestan that has received special attention due its beneficial effects on the skin, such as protection against photoaging and improvement of skin thickness and elasticity in postmenopausal women. Thus, the present report provides a scientific evaluation in two-step experiment for the wound healing effect of coumestrol. **Methods:** A scratch assay using an *in vitro* artificial wound model was performed in fibroblasts culture, to compare the effects of coumestrol free (Sigma-Aldrich®), dissolved in dimethyl sulfoxide (DMSO) or Dulbecco's modified Eagle's medium (DMEM), or in association with hydroxypropyl-β-cyclodextrin (HPβCD). Thereafter, coumestrol/HPβCD was incorporated into hydrogel and revealed similar efficacy in wound healing experimental model *in vivo* (Wistar rats) in comparison to the positive control (Dersani®). The experimental protocol was approved by the Animal Use Ethics Committee (CEUA, FURG, authorization number 23116. 00350/2015-11). **Results:** The 50 µM (66. 1%) and 10 µM (56. 3%) coumestrol associated to HPβCD induced cell proliferation and migration in inflicted wounds. The *in vivo* study also demonstrated that wound healing was achieved in a shorter time for coumestrol associated to HPβCD incorporated into hypromellose (HPMC) compared to the positive control (Dersani®). **Conclusion:** These results successfully showed the wound healing effect of coumestrol/HPβCD incorporated into hydrogel. Moreover, they also underline the feasibility of the biological tests with the use of HPβCD instead DMSO.

09.033 **Caspase-1 and Cathepsin B Inhibitors from Marine Animals, as Modulators of Neuroinflammation in Alzheimer's Disease**. Moreno RI[1,2], Zambelli VO[3], Picolo G[3], Cury Y[3], Morandini AC[4,5], Marques AC[4], Sciani JM[1] [1]USF, Lab Multidisciplinar de Pesquisa, Bragança Paulista, Brazil, [2]UNIFAG, Bragança Paulista, Brazil, [3]IBu, Lab Dor e Sinalização, São Paulo, Brazil, [3]IB-USP, Dept de Zoologia, Centro de Biologia Marinha, São Sebastião, Brazil, [4]IB-USP, Dept de Zoologia, São Paulo, Brazil

Introduction: The chronic neuroinflammation is observed in Alzheimer's Disease (AD) after cytokines release, caused by amyloid plaques' stimulation in cells (1). Mechanisms that described AD neuroinflammation include caspase-1 and cathepsin B activities. Amyloid peptides (Aβ) and oligomers cause inflammasome assembly by the NLRP3 pathway, in microglia and astrocytes, and activate caspase-1 to release IL-1β (2). Aβ also cause lysosome disruption and extravasated cathepsins B from lysosome to cytosol, which activate caspase-1 and can initiate apoptosis pathway mediated by caspase, besides increasing reactive oxygen species release, contributing to the inflammation (3,4). Thus, the inhibition of such enzymes would be an alternative to control the neuroinflammation caused by amyloid plaques in the AD. Inhibitors have been studied, but all of them have failed in clinical trials due to high toxicity and/or adverse effects, principally by its irreversible nature. The marine animals' secretions represent a rich source of new compounds, few explored so far, and can provide new chemical entities with relevant biological activities, with high potency and selectivity. **Methods:** Methanolic/acetic acid extracts were obtained from 10 species of marine invertebrates, collected in São Sebastião, SP, Brazil (IBAMA license #16802-2). Extracts were tested in commercially available enzymes cathepsin B and caspase-1 to verify its inhibition. An appropriated buffer was added to the enzyme previously treated with dithiothreitol and then samples (10 µg) were incubated for 10 minutes in room temperature. The specific subtract was added to the reaction and fluorescence values were obtained in each 10 minutes, until 60 minutes. Values were compared to the enzyme without sample and to a known inhibitor. Active extracts were fractionated by high performance liquid chromatography (HPLC) to obtain pure active molecules, characterized by mass spectrometry. **Results:** Chiropsalmus quadrumanus extract was able to inhibit 70% of the caspase-1 activity. After two steps of fractionation, one molecule could be identified as inhibitor, and has m/z 155. 0627. This compound is being characterized, as it was not found in databases. C. quadrumanus extract partially inhibited cathepsin B, but others could inhibit 100% of the enzyme activity, such as Aiptasia pallida. This extract was also fractionated, and the molecule attributed to the effect was betaine, naturally occurring in plants and animals. This molecule has inhibitory effect on nitric oxide release in microglia and it is considered effective to control neurological disorders (5). It is important to mention that both samples were not able to cause toxicity in SH-SY5Y neuron-like, according to MTT assay. **Conclusion:** it was possible to obtain at least 2 isolated

molecules with inhibitory activity of caspase-1 and/or cathepsin B, which represents potential alternatives for the control of neuroinflammation in AD. **Financial Support:** FAPESP (2019/19929-6). **References:** (1) Heneka. J. Neuroimmunol., 184, 69, 2007; (2) Zhang. Sig. Transduct. Target Ther., 5, 37, 2020; (3) Ni. Brain pathol., e13071, 2022; (4) Campden. Arch. Biochem. Biophys., 670, 32, 2019. (5) Amiraslani. Iran Biomed. J., 16, 84, 2012.

09.034 **Evaluation of the Effects of *Marrubium vulgare* L. Infusion on Zootechnical Performance Parameters and Blood Metabolomics in Weaned Piglets**. Schlemper V[1], Tizziani T[2], Sandjo LP[2] [1]UFFS, Veterinary Medicine Course, Realeza, Brazil, [2]UFSC, Departament of Chemistry, Florianópolis, Brazil

Introduction: Until recently, pig feed contained antibiotics to prevent diseases and promote growth in industrial pig farming. Attention has increased on alternative feed additives to replace antibiotics, including phytogenic product, as a safer biological alternative. This action has been growing considerably around the planet with the potential for the agricultural antibiotics to contribute for the development of antibiotic-resistant bacteria. *M. vulgare* L. (Labiateae), due to its pharmacological properties mainly as antioxidant, antimicrobial, and digestion improvement demonstrated in preclinical experiments, prompted us to investigate an alternative additive to promote pig growth. **Methods:** The study was carried out in a unit producing termination piglets. 3 to 4 months old pigs received a single dose of *M. vulgare* infusion (IMV) and after 5, 10, and 15 minutes blood from jugular vein was collected for a metabolomic analysis of the plant before and after the absorption. For the analysis of zootechnical parameters, IMV was administered orally to 5 groups of 6 piglets each for 28 days. The groups (Gx) were distributed in G1 (negative control) which received physiological solution; G2 (positive control) received clembuterol 0. 08 mg/kg; G3 received IMV at a concentration of 1% (IMV1); G4 received IMV 10% (IMV10); finally G5 was administered IMV 20% (IMV20). On days 0, 7, 14, 21 and 28 the animals were weighed and blood was collected from the jugular vein for hematological and biochemistry analysis. **Results:** After 10 minutes of administration, the UPLC-ESI-QTOF-MS data revealed that in the plasma chemical profile collected showed the presence of dihydroxytrimethoxyflavanone sulphate (m/z 471. 0612 \[C19H20O12S-H]-), and after 5 min the presence of hydroxytrimethoxyflavanone sulphate (m/z 449. 0545 \[C18H18O10S+Na]+). Different cholesterol derivatives such as deoxycholic acid (m/z 437. 2916\[C24H40O4+HCO2]-) were also identified in the plasma after 5, 10, and 15 minutes of blood collection. UPLC-MS chemical profile of IMV showed the presence of flavonoids such as luteolin 5-glucuronide or kaempferol glucuronide, apigenin, and chrysoeriol 7-glucuronide. 1-O-β-D-galactopyranosyl-3-O-linolenoylglycerol and its isomeric derivative corroborating the presence of mono-linoleoyl glycerol in pig plasma. Interestingly, the series of labdane diterpenoids derivatives (ex: marrubiin) identified in IMV crude extract were not found in pig plasma, suggesting a low intestinal absorption. Treatment for 28 days resulted in increases in feed conversion in IMV1 with -12. 14 and IMV10 with -12. 21 compared to G2 and final weight of 7. 35% and 4. 03%, respectively, in relation to G2. The weight gain was 9. 0% and 9. 49%, respectively, in relation to G2. Treatment with IMV in maximal doses did not cause hematological or biochemical changes. **Conclusions**: Our results suggest that the IMV significantly improved zootechnical parameters, contributing with a possible phytobiotic activity of *M. vulgare*, removing the possibility of toxigenic effects. A strong absorption of polyphenols led the production of the sulphate metabolic products and also showed that herbal medicines are molecular cocktails of phytochemical compounds that promote multiple biological benefits and their exploration as growth promoters to replace antibiotics represents a rewarding task to combat multidrug resistance in humans and animals. **Financial Support:** FAPESC (Project 2021TR000341). Approval by UFFS Animal Research Ethical Committee under number 23205. 001521/2018-11.

09.035 **Nociceptive Evaluation of the Lyophilized Extract of *Lupinus mutabilis* Sweet (TARWI) in Experimental Animals**. Gamarra F[1], Salazar-Granara A[1], Martínez Herrera J[2], Jurado RB[3] [1]Universidad de San Martín de Porres, Facultad de Medicina Humana, [2]Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias, [3]Universidad de la Laguna, San Cristóbal de La Laguna, Tenerife, España

Objective: To determine by means of the plantar test (Hargreaves method) in albino rats the nociceptive effect of the lyophilized extract of *Lupinus mutabilis* sweet (ELLMS). Materials and **Methods:** Experimental research using a method of measuring thermal nociception in cutaneous hyperalgesia in animal models, considering the IASP Guide and ethical management regarding experimental pain in animals. 60 albino male rats were used, with

an average weight of 200 gr, that were randomly distributed in 6 groups: 4 of them were given different ELLMS doses, and the rest, distilled water and morphin. The nociceptive effects of the lyophilized extract of *Lupinus mutabilis* Sweet (tarwi) compared to Placebo and Morphine were evaluated, observing the paw withdrawal time using a plantar test kit in albino rats. The statistical evaluation was made using the Shapiro Wilk, one-tailed ANOVA and Tukey tests. Results: The response of the thermal heat produced in planting tests in the albino rats treated with the lyophilized extract of *Lupinus mutabilis* Sweet (Tarwi) administered at the rate of 1000 doses. 1250, 1500 and 1800 mg / Kg, regarding the nociceptive effect in the times of reaction (TR) in the evaluated time 15, 30 and 60 min was evaluated as having the Tukey pairing test. **Conclusion:** Statistical significance and effect were found in the Plantar Test test in albino rats to assess the antinociceptive effect. Key words: Plantar test, Lupinus mutabilis, nociception, Hargreaves method.

09.036 **Antinociceptive Effect of Ethanol Extract of** *Nephelium lappaceum* **L. Fruit Peel Involves Opioid Receptors, Nitric Oxide and ATP-Sensitive Potassium Channels**. Oliveira AS[1], Biano LS[1], Palmeira DN[1], Kohlhoff M[2], Sousa JAC[3], Brandão GC[3], Oliveira e Silva AM[1], Grespan R[1], Camargo E[1] [1]UFS, [2]Fiocruz, [3]UFOP

Introduction: Bioactive compounds from plants with antinociceptive activity have been the target of many researchers seeking new treatment alternatives. Nephelium lappaceum L., popularly known as rambutan or hairy litchi, belongs to the Sapindaceae family and is native to Malaysia, but can now be found in other parts of the world, such as Brazil. Objective: This study investigated the antinociceptive effects and mechanisms of the ethanol extract of the fruit peel of N. lappaceum (EENL). **Methods:** We performed chromatography coupled to mass spectrometry and evaluation of nociception and locomotor activity of mice. The experiments were approved by the Ethics Committee on Animal Use of Federal University of Sergipe (# 1122270819). **Results:** Procyanidin B, (epi)-catechin, ellagic acid and its derivatives were identified in EENL. Oral pretreatment of mice with EENL (200 mg/kg) did not change the locomotor activity. At 50, 100 or 200 mg/kg, EENL significantly reduced the acetic acid-induced abdominal constrictions (30±6%, 54±6, 63±6% of inhibition respectively) as did aminosalicylic acid (300 mg/kg, 63±5%). Pretreatment with EENL (100 and 200 mg/kg, p. o.) reduced (p<0. 001) the licking/biting time in both first (61±4% and 58±7%, respectively) and second phase (77±10% and 80±7%, respectively) of formalin testing, as did morphine (71±5% and 94±3% respectively for 1st and 2nd phases). EENL (100 and 200 mg/kg, p. o.) also decreased (p<0. 001) capsaicin induced licking/biting time (58±7% and 55±6%, respectively), as well as morphine (75±4% of inhibition). After 4 h of treatment with EENL, we observed increased (p<0. 001) carrageenan-induced mechanical paw withdrawal threshold (2. 8±0. 4; 6. 4±0. 4; 6. 8±0. 3; 6. 5±0. 4 g; respectively for vehicle, 100 or 200 mg/kg of EENL and indomethacin groups), indicating the antihyperalgesic effect of EENL. In the hot plate test, oral pretreatment with EENL (50, 100 and 200, p. o.) significantly increased (p<0. 001) latency time (9. 1±0. 8; 18. 6±0. 6; 22. 0±0. 8; 26. 8±1. 6; 32. 1±0. 9 arbitrary units [AU] for the area under the 0-2 h curve; respectively for vehicle, 50, 100 or 200 mg/kg of EENL and morphine groups. This antinociceptive effect was reversed by naloxone (opioid antagonist, 10. 8±1. 1 arbitrary units), L-arginine (a nitric oxide precursor; 11. 7±1. 4 AU) and glibenclamide (a KATP channel blocker, 8. 1±1. 0 AU) when compared to EENL (100 mg/kg; 22. 9±1. 3 AU, p<0. 001 for all treatments). **Conclusions:** EENL causes antinociception with the participation of opioid receptors, nitric oxide and KATP channels, without affecting the locomotor activity of mice. **Financial Support:** CNPq and CAPES.

10. Cancer Pharmacology

10.001 **Peri/Epicellular Protein Disulfide Isomerase (pecPDI) inhibition decreases Migration and Colony Formation and Sensitizes Melanoma cells to B-RAF Inhibitors**. Mota AN, Lopes LR, Machado Neto JA ICB-USP, Pharmacology Dept, São Paulo, Brazil

Introduction: Melanoma is the most aggressive form of skin cancer and has the worst prognosis due to its great metastatic and invasive potential and resistance to the current chemotherapy. Most of the patients present the BRAF V600E mutation and are treated with BRAF inhibitor vemurafenib but they acquire resistance to this inhibitor which causes relapse of the tumor. Peri epicellular Protein disulfide isomerase (pecPDI) is a redox chaperone highly expressed in the surface of melanoma cells. Our group has demonstrated that pecPDI regulates NADPH oxidase expression and activity in different cell types. Nox4 is also highly expressed in melanoma and responsible for constitutive reactive oxygen species (ROS) production, which is important for

tumor cell survival. Focal adhesion tyrosine kinase (FAK) activate MAPK signaling pathways altering the dynamics of focal adhesions and promoting cytoskeletal rearrangements essential for the survival of melanoma cells. Recent studies by our group demonstrate that pecPDI plays an important role in the regulation of the vascular cytoskeleton and its inhibition decreases FAK phosphorylation and focal adhesion formation. Thus, targeting pecPDI dependent signaling pathways in melanoma may represent a new approach in the treatment of this disease. Goal: To evaluate the role of pecPDI in the regulation of single cell migration and colony formation in melanoma BRAF inhibitor sensitive and resistant cells. **Methods:** Human primary melanoma cells SKMEL-28 and the vemurafenib resistant lineage A375R were treated for 24 or 48 hours with the flavonoid quercetin-3-rutinoside (Rutin) or the Nox inhibitors diphenyleneiodonium chloride or Setanaxib (DPI, 2 and Setanaxib, 20 µM) in combination or not with the BRAF-inhibitor vemurafenib (3 and 6µM). Rutin is a pecPDI inhibitor. Colony formation was analyzed after 10 days. Single cell migration was evaluated in melanoma cells from both strains cultured in fibronectin covered plates. Migration was analyzed in a Cell Analyzer 2200 GE (CEFAP-USP) during 20 hours (6 images/hour). **Results:** Colony formation was observed in the non-treated cells from both lineages. Colonies were more numerous in the resistant strain, as expected. However, in cells treated with PDI or Nox inhibitors there was no formation of colonies as well as in cells treated with the combination of the PDI or Nox inhibitor with vemurafenib. Single cell migration analysis revealed similar results in non-treated cells. PDI and Nox inhibition altered the polarity and direction of the resistant but not the sensitive BRAF inhibitor cell line. **Conclusions:** The inhibition of cell surface PDI and NADPH oxidase decreased colony formation and migration of melanoma B-RAF inhibitor resistant cell lines. In fact, the treatment with the combination of the inhibitors and vemurafenib sensitized resistant melanoma cells to the effects of the BRAF inhibitor. Therefore, we propose that cell surface protein disulfide isomerase could represent a novel therapeutic target to treat resistance to BRAF inhibitors in melanoma. **References:** Soares Moretti A. I. Archives of Biochemistry and Biophysics . 2016. Dar, M. A. International Current Pharmaceutical Journal; 1; 431-435 . 2012. Paes A. M. J Leukoc Biol; 90; 799-810. 2011. Pescatore L. A. J Biol Chem; 287; 29290-300. 2012. Ribeiro-Pereira C. PLoS ONE; 9. 2014. Ethics approval: Institute of Biomedical Sciences Ethics Committee of the University of São Paulo, Brazil #1232/2022. Funding: Redoxoma FAPESP #2013/07937-8 and CNPq # 313492/2020-4.

10.002 **The Aqueous Extract Obtained from** *Abelmoschus esculentus* (**L.**) **Moench. has an Antitumor Effect in the Ascitic Ehrlich Tumor Model** (**EAC**). Silva ELES, Souza TPM[1], Carmo JOS[1,], Almeida JH[1], Silva JYR[2], Alves Júnior S[2], Ferro JNS[1] [1]UFAL, [2]UFPE

Introduction: The *Abelmoschus esculentus* (EA) - Okra - is a medicinal plant exhibiting many pharmacological activities, such as anti-inflammatory and antioxidant (XIONG, Int J Biol Macromol. v. 181, p. 824, 2021). Recently, it has been reported that Lectin isolated from EA has cytotoxic and apoptotic effects on cancer cells *in vitro* (MUSTHAFA, Toxicon. v. 202, p. 98, 2021), illustrating its promise as a potential candidate for the development of anti-cancer drugs. Aim: Hence, we aimed to investigate the antitumoral activity of extract of *Abelmoschus esculentus* (EAE) against Ehrlich ascites carcinoma tumor model (EAC). **Methods:** Female Swiss mice 10–14-week-old were injected by intraperitoneal route with EAC cells ($5x10^6$) and distributed into groups: tumoral group (TM), 5-Fluorouracil (25 mg/Kg, 5-FU) and EAE (25 or 100 mg/Kg). Animals were treated with 5-FU or EAE once daily on days 6 to 10 after tumor induction. On days 1, 6, and 11 after tumor induction, photographic images were captured, x-ray and recorded as measures of weight gain and abdominal circumference. On the 11th, the animals were euthanized, and the ascitic volume and cellularity of the tumor fluid quantified. An organ collection was performed and the area of vessels present in the abdominal region was quantified. In the tumor cells of the peritoneal fluid, morphological parameters indicative of cell damage were analyzed por optical microscopy. In addition, oxidative stress mediators in the supernatant (NO levels) and in tumor cells (reacting species, ROS) were evaluated. The results were significant when $p<0.05$. **Results:** The treatment with EAE was able to reduce all parameters of tumoral development evaluated, which are reflected in the macroscopic imaging follow-up. Similarly, 5-FU treatment also reduces all parameters evaluated. As from the ascitic fluid from the peritoneal cavity the EAE-treated animals observed a significant reduction in total cell content (39% to EAE25 and 42. 3% to EAE100). This reduction reflected a lower number of tumor cells after treatment with EAE at 25 or 100 mg/Kg to 61. 3% and 53,5%, respectively, without changing the number of leukocytes present in the ascitic cavity. When evaluating the formation of vessels, no significant changes were observed. The production

of ROS and other mediators of oxidative stress is related to the promotion of proliferation and DNA mutagenesis pathways, but at high levels, these mediators can activate pathways that lead to cell death. The tumor cells recovered from peritoneal lavage fluid were discriminated based on size and granularity and had their intracellular ROS levels measured indicate that compared the control group, cells from EAE25 and EAE100 treated animals showed an increase in ROS levels and NO. It should be noted that treatment with EAE increased the survival of the animals to 33 days, compared to 23 days in the TM group. In addition, EAE increases the number of bone marrow cells, without changing the weight of the organs, which is indicative of the absence of toxicity. **Conclusion:** These findings indicate that EAE is a potential natural product that has promising antineoplastic efficacy. However, more studies are needed to assess other tumor growth parameters and the mechanisms by which EAE decreases tumor progression in this in vivo experimental model. License number of ethics committee: CEUA/UFAL: protocol number 20/2019. Keywords: Cancer. Natural Product. Oxidative Stress.

10.003 **Establishment of Patient Tumor Cell Lines and Prediction of Growth Profiles and Responsiveness to New Treatments Derived from *Phoneutria nigriventer* Venom (PnV)**. Silva MVR[1], Santos NB[2], Rocha-e-Silva TAA[3], Sutti R[4], Vitorino-Araújo JL[4], Sciani JM[5], Verinaud L[2], Carneiro CRD[2] [1]FCF-Unicamp, Campinas, São Paulo, Brasil, [2]IB-UNICAMP, Campinas, São Paulo, Brasil, [3]Albert Einstein Israeli Faculty of Health Sciences, São Paulo, SP, Brasil, [4]FCMSCSP, São Paulo, SP, Brasil, [5]LMP-USF, Bragança Paulista, SP, Brasil

Gliomas are the most prevalent primary CNS neoplasms, corresponding to one-half of all malignant brain tumors in adults. Such neoplasms are heterogeneous, ranging from minor tumors to glioblastoma (GBM). GBMs present greater aggressiveness and a worse prognosis, with less than 2 years of survival. The available therapeutic alternatives are limited and the search for new drugs is necessary. Our group demonstrated that subfractions (SFs) isolated from Phoneutria nigriventer spider venom (PnV), named SF3 and SF5, showed cytotoxic action in human GBM lineage NG97 established 25 years ago. The viability of NG97 was reduced in 40% when compared with the no treated group. It remained to be seen whether primary tumors from different patients would also be responsive to SFs. The present study aimed to establish patient glioma lineages, analyzing their proliferation curves and the cytotoxic effect of the SFs. In addition, we molecularly characterized SF3 by mass spectrometry (MS). Cells were treated with SFs (concentration of 0.1 µg/mL as previously determined with NG97 screening published assays) after three different times: 1, 5, and 24 hours. We performed clonogenic and colorimetric assays with sulforhodamine B to establish the proliferation curves of the strains and to evaluate the cytotoxic effects of the subfractions. The treatment reduced cell viability, especially after 5 hours and SF3 exhibited better results than SF5. The low-grade lineage showed delayed response, while the higher-grade tumor cells showed a sustained response. SF3 is a polyamine of 615. 03 Da according to MS analysis. Also, the growth profiles of the strains were consistent with the histopathological classification. The results indicate that high-grade gliomas as more promising candidates for a potential drug developed from SF3. Funding: FAPESP (#2015/04194-0); CNPq (#148156/2019-3); FAEPEX/UNICAMP (#2057/20 – Undergraduate scholarship).

10.004 **Bioguided Study of Cytotoxicity and Phytochemical Screening of Extract and Fractions from the Bark of *Gamela laurel* (*Sextonia rubra* (Mez) van der Werff) from Logging Residue**. Pereira JVM[1], Mota JA[1], Manso MP[1]., Sales SLA[1], Costa PMS[1], Flores SLG[1], Araújo IM[2], Alves TS[2], Veiga Junior V[3], Guimarães AC[2], Guimarães CJ[1], Pessoa C [1] [1]LOE-NPDM-UFC, [2]Q-BIOMA-UFAM, [3]Military Engineering Institute

Cancer is a disease with multifactorial etiology, with extensive proliferative capacity and mechanisms of resistance to cell death. This has been promoting the search for new compounds with better efficacy during chemotherapy to circumvent the barriers of this pathology, this is a proposal for the prospection of new compounds with low toxicity during bioprospecting of new substances for use in cancer therapies. The plant *Sextonia rubra* (Mez) van der Werff is a species of the Lauraceae family, with confirmed occurrence in the northern region of Brazil. The species has been used for timbering purposes and its extracts have shown antifungal activity. The objective of this work was to perform phytochemical analysis and to evaluate the cytotoxic potential of the extracts and fractions of the plant, coded as LLG (hydroalcoholic extract), LLG01 (hexanic fraction), LLG02 (chloroformic fraction), LLG03 (ethyl acetate fraction), LLG04 (butanolic fraction) LLG05 (hydroalcoholic residue). The peels were extracted with 70% ethanol under reflux for 72 hours. The crude extract (LLG-94. 57g) was partitioned with hexane (LLG01-0. 91g), chloroform (LLG02 -3. 66 g), ethyl acetate (LLG 03-11. 64g) and butanol (LLG04-35. 74 g), (LLG 05- hydroalcoholic residue-42. 60g), generating five

fractions. Phytochemical analysis in test tubes revealed the presence of condensed tannins, chalcones and aurones, triterpenes, saponins and alkaloids in the crude extract (LLG). Unchain steroids were detected in LLG01 and LLG02. Condensed tannins, flavanonois, triterpenes, and saponins were detected in LLG03. In LLG04 and LLG05, alkaloids, saponins, flavanonois, and condensed tannins were indicated. The cytotoxic evaluation was performed on the tumor cell lines: SNB-19 (glioblastoma), HCT-116 (colon carcinoma), PC3 (prostate carcinoma and HL-60 (Promyelocytic). The method applied was MTT(3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2-H-bromide tetrazolium) assay. The samples were submitted to Single Concentration Evaluation (SCA), and those showing inhibitory capacity above 60% went on to determine the Average Inhibitory Concentration (IC50). For IC50, the samples were submitted to serial dilutions with concentrations ranging from 0. 08 to 250 µg/mL. Among the samples evaluated, only LLG01 and LLG02 obtained growth inhibition greater than 60%. The CI50 in the SNB-19, PC3, HCT-116, and HL-60 strains were 8. 11; 20. 45; 20. 47, and 9. 21ug/mL for LLG01 and 27. 90; 5. 58; 7. 48, and 8. 77 ug/mL for LLG02. The best cytotoxic results demonstrated were from LLG01 and LLG02 fractions. This evaluation demonstrated the cytotoxic potential of apolar extracts of *Sextonia rubra*. The activity presented by LLG02 on the PC3 strain was promising and motivates for the future isolation and identification of the active compounds present.

10.005 **Cannabidiol Protects Myoblasts and their Differentiation into Myotubes from the Cytotoxic Effects of Cisplatin while Decreasing the Viability of MCF7 Tumor Cells**. Santos MRM, Zamarioli LS, Pereira THR, Guariglia L, Smaili SS, Pereira GJS, Trindade CB Unifesp-EPM, Dept de Farmacologia, São Paulo, Brasil

Introduction: Skeletal muscle atrophy is a serious condition that involves loss of muscle mass and quality of life. This condition can be induced by several pathophysiological factors, as well as by treatment with antitumor drugs such as cisplatin (CDDP). Therefore, research into specific pharmacological targets that control muscle atrophy should be encouraged (CONTE et al., 2020). Cannabinoid compounds stand out in this context, as they have demonstrated cytoprotective effects in different cell models. Objective: Thus, in this study we are evaluating the possible cytoprotective role of Cannabidiol (CBD), Cannabidivarin (CBDV), Cannabigerol (CBG) and Δ8-Tetrahydrocannabivarin (Δ8-THCV) against CDDP-induced muscle atrophy and the underlying mechanisms involved. The effects of the CBD compound on human breast cancer MCF7 cells are also being evaluated as studies have demonstrated anticancer effects for this compound. **Methods:** The viability of C2C12 myoblasts and MCF7 cells was evaluated by the MTT reduction test after exposure to CBD, CBDV, CBG and Δ8-THCV (6. 2µM - 50 µM) and CBD (10 µM-50 µM), respectively after 24 h of treatment. Myosin heavy chain (MHC) expression is being evaluated in myotubes differentiated from C2C12 cells by immunofluorescence assay using the MHC antibody. The nuclei of these cells were stained with DAPI. The percentage of MHC/DAPI area was analyzed by the FIJI software. **Results:** By the MTT assay, it is observed that CBD, CBDV, CBG and Δ8-THCV are not cytotoxic to C2C12 cells at concentrations up to 50 µM after 24 h of exposure. When myoblasts are exposed to the cytotoxic concentration of CDDP (25 µM), in the presence of CBD (15 µM), these cells are protected from the toxic effects of CDDP, as their viability is close to control. In a preliminary study, CBD also showed a tendency to increase the MHC/DAPI area percentage compared to the CDDP-treated group, suggesting protective effects on myotube formation after exposure to CDDP. However, CBD treatment for 24 h (10 µM - 100 µM) significantly reduced the viability of MCF7 breast tumor cells when compared to the untreated control. **Conclusions:** Based on these results, CBD, CBDV, CBG and Δ8-THCV are not cytotoxic to myoblasts up to 50 µM after 24 h of treatment and CBD at 15 µM protected myoblasts from the cytotoxic effects of CDDP (25 µM) and also showed a tendency to protect myotubes from the cytotoxic effects of CDDP (50 µM - 100 µM). At the same time, CBD significantly decreased the viability of MCF7 tumor cells, suggesting distinct effects for this compound, dependent on cell models. Additional experiments are underway to conclude on the possible protective effects of the aforementioned cannabinoids during myogenesis and the underlying mechanisms involved. The anticancer effects of CBD are also being conducted in MCF7 cells to understand the molecular effects of CBD on this cell line. **Financial Support:** CNPq, CAPES and FAPESP CONTE, E. et al. Int. J. Mol. Sci, v. 21, p. 1, 2020.

10.006 **Evaluation of the Antineoplastic Effects of Polysaccharides Extracted from Tucum-do-Cerrado Fruits** (*Bactris setosa* **Mart**) **in Mice**. Oliveira KM, Radulski DR, Faria BC, Galindo CM, Pereira GS, Stipp MC, Cordeiro LMC, Acco A UFPR, Department of Pharmacology, Curitiba, Brazil

Introduction: Cancer is one of the world's major public health problems. The classic treatment for cancer is chemotherapy, despite their cytotoxic and side effects (SBC, 2016). Among some molecules that have been studied in this area are polysaccharides. Currently these molecules have been shown to have extensive pharmacological actions and antitumor, anti-inflammatory and antimutation activities (YU et al., 2018). Therefore, we aim to characterize and test, for the first time, the in vivo antineoplastic activity of polysaccharides extracted from the edible fruit of tucum-do-cerrado (*Bactris setosa* Mart, TUC) in Ehrlich carcinoma model in mice, which is originated in mammary tissue. **Methods:** TUC polysaccharides were characterized by nuclear magnetic resonance; and high-performance size exclusion chromatography (HPSEC) was applied to access the homogeneity and relative molecular weight (Mw) of soluble TUC polysaccharides. Female Swiss mice received 50 or 100 mg. kg-1 TUC, or vehicle, v. o., once a day, or 1. 5 mg. kg-1 of methotrexate i. p., every 3 days (positive control), for 21 days after subcutaneous inoculation of 2x106 Ehrlich tumor cells. The tumor development was daily monitored and in the end of the treatment the animals were anesthetized and euthanized for biological material collection. Hematological parameters were performed, besides measurements of inflammatory markers (NAG, NO and MPO) and oxidative stress in tumor and liver tissue (GSH, LPO and SOD), and fragments of the tumors were prepared and stained with HE to histological evaluation. In addition, in liver tissue, total CYP levels were measured. All the experimental protocols were approved by the Ethical Committee for Animal Use (CEUA) of Biological Sciences Section of UFPR (№ 1374). **Results:** TUC presented a complex monosaccharide composition, with 27. 5% of uronic acids and mannose (26. 5%), xylose (12. 0%), glucose (11. 3%), arabinose (10. 6%), galactose (9. 8%), rhamnose (1. 9%) and fucose (0. 5%) as neutral sugars. Both doses of TUC significantly reduced tumor weight and tumor volume compared to the vehicle group. This reduction was associated with the fact that TUC probably modulates both the oxidative stress pathway and the inflammatory via. The decrease of GSH level and increase of LPO levels and SOD activity in tumor tissues of treated groups, compared to the vehicle group, support this hypothesis. The increase in inflammatory biomarkers, such as NAG and NO, also points to the inflammatory pathway as a possible mechanism of TUC. Furthermore, the histological analysis of the tumors evidenced areas of necrosis and leukocyte infiltration in the treated groups. With the data of total CYP and oxidative stress parameters in the liver, and the levels of plasmatic ALT, we were able to state that TUC is non-hepatotoxic. **Conclusion:** The polysaccharides extracted from the tucum-do-cerrado have antineoplastic effects against Ehrlich carcinoma in mice, modulating the oxidative stress and the inflammation in the tumor microenvironment, without induce hepatotoxicity. Thus, these polysaccharides have therapeutic potential against solid tumors, mainly the mammary tumors, considering that Ehrlich tumor is a model of breast cancer. **Financial Support:** CAPES, CNPq. **References:** SBC – Sociedade Brasileira de Cancerologia. Disponível em: http://www. sbcancer. org. br/conheca-os-principais-tipos-de-tratamentos-de-cancer/. Acesso em 01/06/2022Yu Y et al. (2018) Biological activities and pharmaceutical applications of polysaccharide from natural resources: A review. Carbohydr. Polym. 183, 91–101

10.007 **Palladium (II) Complexes Containing Orthometallated Oximes are Cytotoxic to Resistant Human Osteosarcoma Cells by Inducing Apoptosis and Lysosomal Membrane Permeabilization**. Pereira THR[1], Santos MRM[1], Zamarioli LS[1], , Justo GZ[1], Moura TR[2], Pereira GJS[1], Godoy Netto AV, Trindade CB[1] [1]Unifesp, [2]Unesp

Introduction: Osteosarcoma (OS) is a malignant bone tumor that occurs mainly in adolescents and the elderly (Rickel et al., 2016). Current treatment includes a combination of anticancer chemotherapy and amputation of affected limbs (Misaghi et al., 2018). With this strategy, long-term disease-free survival is about 60-76%. OS is highly resistant to classic chemotherapeutic drugs, such as methotrexate, adriamycin and cisplatin, due to genetic mutations that end up interfering with the ability of these drugs to induce cell death (Rickel et al., 2016). Therefore, there is an urgent need to explore new compounds that may have more effective actions and control resistance mechanisms in OS. In this sense, palladium (II) complexes containing orthometallated oximes (CPcO) have been investigated by our group as cytotoxic agents in cancers including OS. The CPcO of the type [Pd(C2,N-afox)(Cl)(L)] (afox = acetophenoneoxime; L = pyridines) is susceptible to the aquation reaction at pH 3-10, forming species [Pd(C2, N-afox)(OH)(L)] and [Pd(C2,N-afox)(OH2)(L)]+ in solution. This reaction can produce reactive species inside cancer cells, leading to cell death. Therefore, CPcO Pd-BtoxP (1), Pd-BtoxM (2), Pd-BPO (3) and Pd-BMO(4) are being studied as antitumor agents in human SaoS-2 and U20S cells. Material and **Methods:** MTT and clonogenic assays were used to evaluate the viability of OS and the clonogenic properties of

these cells, respectively, after treatment with CPcO complexes. Cell death was assessed following exposure to CPcO after Annexin/FITC-7AAD staining followed by flow cytometry. The acridine orange (AO) staining was used to assess lysosomal membrane integrity. Cisplatin was used as a control of cytotoxic activity. **Results:** All complexes were cytotoxic to U02S cells (cell viability was 15% when exposed to 100 µM of all complexes). However, in SaoS-2 cells only complexes 3 and 4 were cytotoxic. Cisplatin at 100 µM reduced the OS cell viability by only 20% when compared to the untreated cells, suggesting a greater cytotoxic activity for the compounds under study. In the clonogenic assay, 35 µM of complexes 3 and 4 decreased the clonogenic capacity of SaoS2 cells in relation to both control and cisplatin-treated groups (35 µM). Flow cytometry indicated that most cells, when in contact with complexes 3 and 4 (35 µM) SaoS-2 cells enter late apoptosis. From the AO assay, it was observed that complexes 3 and 4 induced lysosomal membrane permeabilization, expressed by a colocalization between green and red fluorescence, indicating extravasation of lysosomal contents to the cytoplasm. These events may be associated with the late apoptosis response observed in these cells when treated with CPcO. **Conclusions:** CPcO are more cytotoxic than cisplatin for OS cells and induce late apoptosis, which can be explained by lysosomal membrane permeabilization. These results drive the continuity of these studies aimed at the development of new drugs for tumors that are difficult to manage pharmacologically. Studies are underway to address these preliminary findings. **Financial Support:** CAPES, CNPq and FAPESP. **References:** Misaghi, A. . SICOT-J Vol. 4, Pág. 12 (2018) Rickel, K., Bone, Vol. 102, Pág. 69 (2017)

10.008 **Evaluation of the Antitumor Activity of the Constituents of *Sinningia reitzii* on Solid Ehrlich Tumor Model in Mice**. Radulski DR, Pereira GS, Acco A UFPR

Introduction: Cancer is a public health problem, with high mortality rates. Several regulatory mechanisms are involved in tumor progression, including the oxidative stress, inflammation and angiogenesis. The most used antineoplastic drugs have a low therapeutic index and cytotoxicity to normal cells, causing several side effects. In this context, new anticancer agents with fewer side effects are being sought. Among the compounds studied, extracts and substances isolated from plants stand out for their antitumor, immunostimulating and anti-inflammatory properties. Recently, the phytochemical study of the components of *Sinningia reitzii* (Gesneriaceae) led to the isolation of a naphthoquinone 6,7-dimethoxydunnione (SR4) that showed antitumor activity *in vitro* using PC-3, SKMEL 103 and HeLa cells. Therefore, the aim this study was to investigate the antitumor activity of the constituents of *Sinningia reitzii* on solid Ehrlich tumor, a breast cancer origin cell of mice. **Methods:** female Swiss mice received extract of *Sinningia reitzii* (10, 30 or 100 mg. kg-1), SR4 (3 mg. kg-1) or vehicle, orally, once a day, for 21 days after subcutaneous inoculation of 2x106 Ehrlich tumor cells. The tumor development was daily monitored and in the end of the treatment the animals were anesthetized for biological material collection. Blood count and plasma biochemistry were performed, besides measurements of tumor inflammatory parameters and histology [Hematoxylin & Eosin staining]. Sequentially, the mice were submitted to euthanasia, under anesthesia. All the experimental protocols were approved by the Ethical Committee for Animal Use (CEUA) of Biological Sciences Sector of UFPR (№ 1370). **Results:** Both doses of extract and SR4 reduced significantly the tumor weight and volume (approximately 50% and 34%, respectively) compared with the control (vehicle). The treatment with 10 and 30 mg. kg-1 of extract and SR4 modulated the blood immune and inflammatory response, by increasing the lymphocytes number. No alterations were observed in plasma biochemistry among the treatments and also no animals died. Also, the treatment with both doses of extract reduced the tumor activity of myeloperoxidase (MPO). The tumor histology showed high degree of necrosis in animals treated with extract and SR4. **Conclusion:** The constituents of *Sinningia reitzii* showed antineoplastic activity against the solid Ehrlich tumor in rats. This effect seems to be related to the inflammation pathway and necrosis mechanisms. To confirm this hypothesis both mechanisms will be further studied through gene and protein expression and cytokines measurements. **Financial Support:** CAPES, CNPq. *References*: SILVA, Adson S. et al. A new cytotoxic naphthoquinone and other chemical constituents of Sinningia reitzii. Journal of the Brazilian Chemical Society, v. 30, p. 2060, 2019. SOARES, Adson S. et al. Naphthoquinones of *Sinningia reitzii* and anti-inflammatory/antinociceptive activities of 8-hydroxydehydrodunnione. Journal of natural products, v. 80, n. 6, p. 1837, 2017.

10.009 **Cellular and Molecular Effects of Eribulin in Pre-clinical Models of Hematological Malignancies**. Vicari HP, Lima K, Costa-Lotufo LV, Machado-Neto JA ICB-USP, Dpt of Pharmacology, São Paulo, Brazil

Introduction: Acute leukemias comprises a poor prognosis hematological neoplasms group originating from mutated bone marrow progenitor cells. High mortality and relapse rates related to these diseases make the research for new therapeutic options imperative. Eribulin is a novel microtubule inhibitor currently used in breast cancer therapy, but its effects on acute leukemias have been poorly explored. In addition, understanding eribulin-related resistance mechanisms may help improve treatment response. Therefore, the aim of the study was to investigate the cellular and molecular effects of eribulin on leukemia phenotype and to evaluate possible biomarkers of response to eribulin, using a molecularly heterogeneous panel of blood cancer cells. **Methods:** A panel containing 13 myeloid neoplasms and 12 lymphoid neoplasms cell lines were used for initial cell viability assays. NB4, NB4-R2, OCI-AML3, MOLM13, Jurkat, and Namalwa cell lines were selected for additional detailed analyzes. Cells were treated with increasing concentrations of eribulin (0-100 nM). Cell viability was assessed by MTT, clonogenicity by colony formation assay, apoptosis by annexin-V/7AAD staining and flow cytometry, cell cycle by propidium iodide staining and flow cytometry, and cell morphology by H&E staining and optical microscopy. Molecular markers of proliferation (STMN1), apoptosis (PARP1), and DNA damage (p-H2AX) were investigated by Western Blot. A correlation was performed between the IC50 for eribulin and gene and protein expression of pathways previously associated with eribulin resistance. Statistical analyzes were performed by ANOVA and Bonferroni post-test and Spearmen test. A p-value <0.05 was considered significant. **Results:** Eribulin presented high cytotoxicity in blood cancer cells, only 5 of out 21 cells were considered resistant to the drug (IC50 >100 nM). Eribulin-sensitive cells displayed dose and time-dependent cytotoxicity (IC50 ranged from 0.13 to 12. 12 nM for 72 h). In acute leukemia cells, eribulin significantly decreased clonogenicity to long-term exposure, increased apoptosis, induced subG1 cell accumulation, and cell cycle arrest at the G2/M phase upon 48 h of drug exposure (all $p<0.05$). Morphological analysis indicated aberrant mitosis, which corroborates cell cycle findings. In the molecular scenario, eribulin reduced STMN1 expression and activity, and induced PARP1 and H2AX phosphorylation, indicating a reduction of cell proliferation, apoptosis, and DNA damage (all $p < 0.05$). Notably, higher IC50 for eribulin was significantly correlated with high expression of NFkB p65 (total and phosphorylated), MDR1 (ABCB1 and ABCC1), and AKT phosphorylation in blood cancer cells (all $p<0.05$). **Conclusion:** Eribulin reduced the cell viability of acute leukemia cells by disturbing microtubule dynamics and leading to mitotic collapse and cell death, proving to be a potential therapeutic option for blood cancers. Our data indicate that NFkB, MDR1, and PI3K/AKT expression and activation may be useful biomarkers of responsiveness to eribulin in hematological malignancies. **Financial Support:** FAPESP, CNPq and CAPES

10.010 *In vitro* **Evaluation of Cytotoxic Activity of** *Tithonia diversifolia* (**td**) **in HCT-116 a Colorectal Carcinoma Lineage**. Madrid MFM, Hernández ENM, Mota JA, Rocha DD, Moraes Filho MO, Pessoa CO UFC, PPG of Physiology and Pharmacology, Fortaleza, Brazil

Introduction: Nowadays, cancer is one of the greatest public health concerns, as it is a leading cause of death worldwide. In this context, studies of new anticancer molecules obtained from natural resources, are a very promising field. Within this perspective, Tithonia diversifolia (TD) is a species that has aroused interest because its high pharmacological potential, its main constituents have several pharmacological properties, such as spasmolytic, antimalarial, anti-inflammatory, and antimicrobial (GOFFIN et al., 2002). Since 2002, studies have reported its *in vitro* antiproliferative effect in different tumor cell lines. Thus, it aroused the interest in evaluating the *in vitro* antiproliferative potential of the TD ethanolic extract. **Methods:** A screening of cytotoxicity of the molecule was performed, to evaluate the potential of TD, using different human tumoral cells and one non-tumoral cell line using MTT assay (Mosmann, 1983). Additionally, it was performed in the presence or absence of 4 µM Nacetyl-L-cysteine (NAC). Additionally, flow cytometry was used to analyze simultaneous multiple physical characteristics of cells (DICKINSON, 2000). Therefore, fluorescence microscopy was done for determination of acidic vesicular organelles (AVOs) such as autolysosome and lysosomes (THOMÉ et al., 2016) and evacuation of DNA damage induction by the comet assay (COLLINS, 2004). Results:The TD ethanolic extract showed cytotoxic activity in the tested tumor lines, showing half maximum inhibitory concentration (IC50) values ranging from 6. 00-35. 39 µg/mL, after 72 hours of treatment. HCT-116 cells presented a IC50 of 8. 74 and 7. 15 µg/ml, at 24 h and 72 h, respectively. While for the non-tumor lineage (L929) this value was higher (31. 45 µg/ml) after 24 hours and lower for 72 hours (25. 58 µg/ml), demonstrating its selectivity for cancer cells. Studying the mechanism of death induced, it was observed that TD ethanolic extract in HCT-116 cells produced apoptosis,

after 24 hours of treatment, probably induced by the intrinsic pathway, in addition, the extract induced cellular stress and the presence of AVOs after the same incubation period. It was noticed DNA damage by the comet assay and the presence of lipid peroxidation and nitric oxide by-products. These effects on HCT-116 could be related to the observed protein depletion of glutathione, showing pro-oxidative effects, NAC treatment proved the results of inhibition of the pro-oxidative effects, this fact reinforced the role of the generation of reactive oxygen species in antitumor activity. **Conclusion:** The TD showed promising results against tested cell lines, with relevance in colorectal carcinoma lineage, indicating the extract may be a future source of prototypes of antitumor drugs. **Financial Support:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). **References:** COLLINS, A. R. The comet assay for DNA damage and repair: Principles, applications, and limitations. Appl. Biochem. Biotechnol., v. 26(3), p 249, 2004DICKINSON, B. Introduction to flow cytometry. A Learning Guide, 2000GOFFIN, E. et al. *In vitro* Antiplasmodial Activity of Tithonia diversifolia and Identification of its Main Active Constituent: Tagitinin C. Planta Med., v. 68(6), p. 543, 2002MOSMANN, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J. Immunol. Methods, v. 65, p 55, 1983. THOMÉ, M. P. et al. Ratiometric analysis of Acridine Orange staining in the study of acidic organelles and autophagy. J. Cell Sci., v. 129(24) p. 4622, 2016.

10.011 **Antileukemic Potential of EMT to Eliminate Leukemic Stem Cells from Acute Myeloid Leukemia in an *in vitro* and *in vivo* Model**. Silva SLR[1], Costa RGA[1], Dias IRSB[2], Rodrigues ACCB[2], Oliveira MS[2], Bezerra DP[2] [1]FF-UFBA, Salvador, Brazil, [2]IGM-Fiocruz-BA, Salvador, Brazil

Introduction: Acute myeloid leukemia (AML) stands out as the most lethal among leukemias (American Cancer Society, 2020). Current treatment generally leads to high remission rates, but most patients end up relapse due to the failure of therapies to eliminate leukemic stem cells (LSC) (Rodrigues et al., 2020). LSC are a population of cells with self-renewal capacity, unlimited repopulation potential and permanence in a quiescent state (Pollyea et al., 2014), functioning as a reservoir of resistant cells with the potential to generate relapses (Yang et al., 2020). The NF-kB signaling pathway is activated in human AML LSC, but not in normal hematopoietic stem cells, making it a target to eliminate LSC more selectively. EMT is a drug that is used, mainly as an antiparasitic and has been shown to inhibit NF-kB signaling. This drug is under patent analysis so it appears in this work as EMT code. Objective: Evaluate the antileukemic potential of EMT to eliminate LSC from AML in a translational model *in vitro* and in vivo using KG-1a cells. Methodology: EMT was tested against a panel of cancerous and non-cancerous cells to assess its cytotoxicity using the alamar blue assay. The identification of LSC was performed with labeling for anti-CD34 PE, anti-CD38 BV421, anti-CD13 PE-CF594, anti-CD33 BV510 and anti-CD123 BV605 antibodies. Studies of mechanism of action were performed in KG-1a cells through flow cytometry as analysis of cell viability, caspase 3 and parp-1 activity, mitochondrial transmembrane potential, generation of reactive oxygen species, cell cycle assessment. Real-time polymerase chain reaction (qPCR) assay was performed to evaluate a panel of 92 genes of interest, after EMT treatment. In addition, the xenotransplantation of KG-1a cells in NSG animals and subsequent treatment with EMT at 10mg/kg was performed (Ethics Committee Approval: CEUA 016/2018). **Results:** EMT showed a potent cytotoxic effect for all tumor cell lines tested with inhibitory concentration of 1. 7 µM for KG-1a. This compound also reduced cell viability. The LSC marker CD123 was reduced after treatment with the compound for 48h. We observed that EMT promoted an increase in caspase-3 activation and an increase in PARP-1 cleavage. The pretreatment of cells, the caspase-3 inhibitor, Z-VAD-(OMe)-FMK, prevented the increase in the number of apoptotic cells. Treatment with EMT also caused depolarization of the mitochondrial membrane and increased generation of reactive oxygen species. Pretreatment with an inhibitor of reactive oxygen species, N-acetyl-L-cysteine (NAC) decreased the percentage of cells in apoptosis. EMT also caused DNA fragmentation. We also observed the inhibition of p65 NF-kB expression (pS529) by flow cytometry. The qPCR analysis showed that 54 genes were up-regulated and 5 were down-regulated, namely Twist 1, Wnt-10b, PARP-1, PPARGC1β and BCL-2, both with an anti-apoptotic role. In vivo, was seen that EMT treatment was able to significantly reduce the number of human leukemia cells in the animals' blood and bone marrow without cause significant weight loss. **Conclusion:** These results shows that EMT is promising cytotoxic compound, capable of eliminating AML leukemic stem cells *in vitro* and in vivo. The authors thank the Federal University of Bahia, flow cytometry nucleus of FIOCRUZ-Bahia. Also to CNPq and Fundação Oswaldo Cruz for the **Financial Support**. **References:** AMERICA CANCER SOCIETY, 2020. POLLYEA, DA.;

Hemat., 99(8):1277, 2014. RODRIGUES, ACBDC.; Crit Rev Oncol Hematol, 160:103277, 2021. YANG, L. Sig. Transduct. Targ. Ther., 5; 8, 2020.

10.012 **NRF2 Pathway Activation and Tumor Recurrence Correlate with Thioredoxin Reductase-1 up-Regulation in Non-Small Cell Lung Cancer**. Delgobo M[1], Gonçalves RM[1], Delazeri MA[2], Falchetti M[1], Zandoná S[2], Neves RN[1], Almeida K[1], Fagundes AC[1], Gelain DP[3], Fracasso JI[2], Macêdo GB[2], Priori L[2], Forcelini CM[2], Moreira JCF[3], Zanotto-Filho A[1] [1]UFSC, Dpt of Pharmacology, Florianópolis, Brazil. [2]UPF, Dpt of Medicine, Passo Fundo, Brazil. [3]UFRGS, Dpt of Biochemistry, Porto Alegre, Brazil

Introduction: Worldwide, lung cancer is one of the most common malignancies and the leading cause of cancer-related death, near to 85% of all lung cancers are categorized as non-small cell lung cancer (NSCLC). The cells have developed multifaceted antioxidant systems such as those involving NRF2 pathway, glutathione (GSH) and the thioredoxin/thioredoxin-reductase-1 (TXNRD1/TXN) pair amid others. Activating mutations in the KEAP1/NRF2 pathway have been characterized and associated with chemoresistance and poor prognosis in a subset of NSCLC patients. Due to their role in various cancer-related processes, the TXNRD1/TXN pair has emerged as a potential target for cancer therapy, especially in tumor types that are susceptible to oxidative stress. Drugs such as auranofin (AUR) have gained interest as an anticancer agent through TXNRD1 activity inhibition. We suppose that TXNRD1/TXN upregulation and the NRF2 pathway provide a survival advantage to lung tumors. **Methods:** We evaluated the expression of 64 oxidative stress-related genes with patient survival in 35 published lung cancer datasets and based on this initial screening, the survival impact of the selected gene (TXNRD1) was then evaluated by immunohistochemistry (IHC) in a retrospective cohort, which included 65 patients diagnosed with NSCLC at the Hospital São Vicente de Paulo (HSVP), Passo Fundo, RS, Brazil. Cell viability experiments were carried out in the A549 lung cancer cell line. **Results:** Kaplan Meier survival screen revealed TXNRD1 as the strongest predictor of poor survival among the 64 oxidative stress-related genes evaluated. Our cohort demonstrated a high IHC score of TXNRD1 in tumors was associated with shorter disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS). Bioinformatics analysis revealed that TXNRD1 expression correlates with NRF2 target gene signature score, and TXNRD1 overexpression overlaps with tumors harboring KEAP1, NFE2L2, and CUL3 mutations, and NFE2L2 amplification, but no other genetic changes typical of NSCLC. Functional cell assays revealed that high TXNRD1 in KEAP1 mutant lung cancer cells is not a major determinant of malignancy; NRF2 seems to be more relevant. KEAP1 mutant cells are resistant to TXNRD1 inhibitor AUR, which also affected neither cell migration and nor sensitivity to cisplatin. KEAP1 mutant cells compensate for TXNRD1 inhibition by upregulating NRF2 and dependence upon GSH; NRF2 knockdown and glutathione depletion sensitized cells to AUR and cisplatin. **Conclusion:** The results indicate that high TXNRD1 at diagnosis predicts shorter time to local and distal recurrences after tumor resection and platinum-based adjuvant chemotherapy, an effect possibly associated with upregulated NRF2 pathway, and not directly to a TXNRD1-dependent malignant phenotype. **Financial Support:** Programa de Pesquisa para o SUS [PPSUS; 17/2551-0001-408-1] to JCFM and AZF, and in part by the CAPES – Finance code 001. Acknowledgements: PPSUS, CNPq, CAPES, and FAPESC research funding agencies; our core facility LAMEB/UFSC for providing equipment and technical support. All aspects related to ethics in human research were approved by Institutional Ethics Committee (CEP-UFRGS and CEPSH-UFSC), reference number CAAE 83271317. 1. 0000. 5347.

10.013 **Protective Effect of Ethanolic Extract of *Chuquiraga spinosa* Less (huamanpinta) and *Senecio rhizomatus* Rusby (Llancahuasi) on Prostatic Neoplasia Induced with Testosterone, NMU and Cyproterone in Rats**. Arroyo Acevedo JLA[1,2], Rojas-Armas JP[1,2], Justil-Guerrero HJ[2], Calva-Torres JW[3], Cieza-Macedo EC[2], Condorhuamán-Figueroa YM[4], García-Bustamante CO[2], Villena-Tejada M[5], Chavez-Asmat RJ[6], Herrera-Calderón O[7], Chamba-Granda DF[7] [1]Universidad Nacional Mayor de San Marcos – Clinical Research Institute School of Medicine "San Fernando", Lima, Perú, [2]Universidad Nacional Mayor de San Marcos, Lab of Pharmacology, Lima, Perú, [3]Chemistry Dept, Universidad Técnica Particular de Loja, Loja, Ecuador, [4]Universidad Nacional Mayor de San Marcos, Research Institute of Pharmaceutical Sciences and Natural Resources, Lima, Perú, [5]Universidad Nacional de San Antonio Abad del Cusco., Academic Dpt of Pharmacy, Faculty of Health Sciences, Cusco, Perú, [6]Universidad Nacional Mayor de San Marcos, Association for the Development of Student Research in Health Sciences, Faculty of Medicine, Lima, Perú, [7]Universidad Nacional Mayor de San Marcos, Faculty of Pharmacy and Biochemistry

Introduction: Cancer is a public health problem in Peru and the world (1); the risk of becoming ill from prostate cancer ranks first and dying second (2). Objective: To determine the protective effect of ethanolic extract of ChL or Chuquiraga spinosa Less (huamanpinta) and SrR or Senecio rhizomatus Rusby (Llancahuasi) on prostatic neoplasia induced by Testosterone, NMU and Cyproterone in rats. Methods: The phytochemical study was by gas chromatographic analysis, using a gas chromatograph coupled to a mass spectrometer. The protection of prostatic neoplasia in rats was done with the following distribution of experimental groups 1) normal or negative control with physiological serum 2 mL/kg; 2) positive control Testosterone 100 mg/kg + Cyproterone 50 mg/kg + NMU 50 mg/kg (TCN); 3) TCN and Ch L 250 mg/kg; 4) TNC and Sr R 100 mg/kg); 5) TNC and Ch L 50 mg/kg and Sr R 100 mg/kg; 6) TNC and Ch L 250 mg/kg and Sr R 100 mg/kg; 7) TNC and Ch L 500 mg/kg and Sr R 100 mg/kg. The present investigation was evaluated by the Ethics Committee of the Faculty of Pharmacy and Biochemistry of the Universidad Nacional Mayor de San Marcos, by means of certificate with registration No. 003-CE-UDI-FFB-2020. Results: The positive control presented an increase in serum catalase, GSH, MDA, and prostate size; on the other hand, prostate width x height was lower in the groups TCN + ChS 250, TCN + ChS 250 + SrR 100 and TCN + ChS 500 + SrR 200 compared to TCN ($p<0.05$). Conclusion: The association of Ch L and Sr R exerts a synergistic dose-independent protective effect on prostatic neoplasia by Testosterone, NMU and Cyproterone in rats. Key words: Prostate neoplasia, Senecio rhizomatus Rusby, chemopreventive, Chuquiraga spinosa (source: DeCS BIREME). References 1 Zafra-Tanaka JH, Tenorio-Mucha J, Villarreal-Zegarra D, Carrillo-Larco R, Bernabe-Ortiz A. Cancer-related mortality in Peru: Trends from 2003 to 2016. PLoS ONE 2020;15(2): e0228867. https://doi. org/10.1371/journal. pone. 0228867 2 Siegel R, Miller K, Fuchs H, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33. DOI 10. 3322/caac. 21708 3 Barros ACSD, Muranaka ENK, Mori LJ, Pelizon CHT, Iriya K, Giocondo G, Pinott, JA. Induction of experimental mammary carcinogenesis in rats with 7,12-dimethylbenz(a)anthracene. Revista Do Hospital Das Clínicas, 2004;59(5), 257–261. doi. org/10.1590/S0041-87812004000500006 4 Arroyo-Acevedo JL, Herrera-Calderon O, Rojas-Armas JP, Chávez-Asmat R, Calva J, Behl T. Histopathological evaluation of Senecio rhizomatus Rusby in 7,12-dimethylbenz(α) anthracene-induced breast cancer in female rats. Veterinary World, 2021;14(3), 569–577. doi. org/10.14202/VETWORLD. 2021. 569-577

11. Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Toxicology

11.001 **Physiologically Based Pharmacokinetic Modeling (PBPK) to Predict the Pharmacokinetics of Hydroxychloroquine Enantiomers According to Gene Polymorphisms of CYP2D6 and CYP2C8**. Ribeiro GSG[1], Moraes NV[2] [1]Unesp-Araraquara, Ararquara, Brazil São Paulo State University, Araraquara, Brazil, [2]University of Florida, Center for Pharmacometrics & Systems Pharmacology, USA

Introduction: Hydroxychloroquine (HCQ) is an antimalarial drug used to treat parasitic infections caused by *Plasmodium* sp, inflammatory and autoimmune diseases. HCQ is a chiral drug available as a racemic mixture of (-)-R-HCQ and (+)-S-HCQ. Its enantioselectivity is described in both pharmacokinetics (PK) and pharmacodynamics. HCQ is primarily metabolized in the liver by the enzymes CYP2D6, 3A4, and 2C8. We aimed to develop PBPK models to assess the effect of CYP2D6 and CYP2C8 gene polymorphisms on the pharmacokinetics of HCQ enantiomers. Methods: PBPK modeling was developed using the Simcyp V21 simulator. The full-PBPK model was based on *in vitro* PK parameters and clinical data observed in volunteers after oral and intravenous administration of HCQ. The volume of distribution was predicted by the method of Rodgers and Rowland. Leveraging previous efforts [1], the model incorporated enzyme kinetics data for CYP2D6, CYP2C8, and CYP3A4 enzymes. The intrinsic clearance values were defined by retrograde extrapolation to capture the contribution of each isoform in the total elimination of HCQ. The first-order absorption model with a lag time of 0. 2 h was used. Predictions using the final PBPK models were verified with observed PK data in 4 independent clinical studies (intravenous and oral administration) by visually inspecting plots of blood concentration versus time and by comparing observed and predicted PK parameters [2-4]. Results: The mean error (predicted PK parameter/observed PK parameter) for the area under the blood concentration versus time (AUC) curve of (-)-R-HCQ and (+)-S-HCQ after IV administration was 0. 98 and 1. 55. The error for (-)-R-HCQ after oral administration ranged from 0. 75-1. 25, 0. 57-1. 3, and 0. 52-0. 98 for the parameters AUC, maximum blood concentration (Cmax), and time to reach Cmax (tmax). For the (+)-S-HCQ enantiomer, the errors were between

0. 92-1. 79, 0. 72-1. 61, and 0. 64-2. 24 for AUC, Cmax, and tmax, respectively. The predicted/observed (-)-R-HCQ/(+)-S-HCQ ratios for AUC (0. 63-0. 82) and Cmax (0. 68-0. 93) showed a tendency of underestimation of the enantioselectivity compared to observed data. PBPK models for HCQ enantiomers were used to simulate blood concentration profiles and PK parameters in normal metabolizers (NM), poor metabolizers (PM) and ultrarapid metabolizers (UM) of CYP2D6 and CYP2C8. The simulations showed a 1. 1-fold increase in the AUC of HCQ enantiomers in CYP2D6 PM subjects and a 0. 9-fold decrease in CYP2D6 UM subjects relative to CYP2D6 NM subjects. Simulations also showed a 1. 2-fold increase in the AUC of HCQ enantiomers in CYP2C8 PM subjects compared to the CYP2C8 NM phenotype. **Conclusion:** In conclusion, the PBPK models were suitable for predicting the enantioselective kinetics of HCQ. The model may be applied to investigate other clinical scenarios, such as complex drug-drug-gene interaction networks. **References:** [1] Zhang et al. Frente. Pharmacol, v. 11, p. 1663, 2021. [2] Ducharme et al. Br. J. Clin. Pharmacol, v. 40, p. 127, 1995[3] McLachlan et al. Chitality, v. 6, p. 360, 1994. [4] Midha et al. Euro. J. Pharm. Sci, v. 4, p. 283, 1996.

11.003 **Population Pharmacokinetics of Intravenous Busulfan in Brazilian Pediatric Patients**. Olivo LB[1], Zuckermann J[3], Pinhati AV[2,3], Correa GG[2], Daudt LE[4], Dalla Costa TCT[1], Araújo BV[1,2] [1]UFRGS, PPG Pharmaceutical Sciences; Porto Alegre; Brazil, [2]UFRGS, PPG Medical Sciences, Porto Alegre, Brazil, [3]HCPA-UFRGS, Pharmacy Service, Porto Alegre, Brazil, [4]HCPA-UFRGS, Hematology Service, Porto Alegre, Brazil

Introduction: Busulfan (BU) is used for conditioning before hematopoietic stem cell transplantation (HSCT)[1]. Due to its high interindividual variability (IIV) in children, BU is amenable to therapeutic drug monitoring[2]. The aim of this work was to develop a population pharmacokinetics (popPK) model of BU for Brazilian pediatric patients at Hospital de Clínicas de Porto Alegre. **Methods:** Children were given 1 dose of BU per day, by a three-hour infusion, for 4 days. Plasma concentrations were measured by a previously in-house validated analytical method. The model was built using MONOLIX (SimulationsPlus Inc.). The interoccasion variability (IVO) was analyzed between the doses as well as IIV. To explain IIV we evaluate demographic and biochemical covariates. This work was approved by Ethics Committee # 2. 713. 246. **Results:** A one-compartment model was built from samples of 14 patients (0. 5 – 16 y. o.) treated with BU. IIV and IVO were explained by adding body weight as a covariate in volume of distribution (Vd) and patients' age as a covariate in clearance (CL). Both covariates were normalized according to their respective weighted averages. The typical value of CL and Vd were estimated to be 3. 06 L/hr and 10. 51 L, respectively. The IIV of CL and Vd were 33 and 22%, respectively. The IVO of CL and Vd was 12% in both. Model internal validation was performed through a visual predictive check. **Conclusion:** A popPK model of BU was successfully built for Brazilian pediatric patients. The results showed that body weight and patients' age are determining factors for this pharmacokinetic population parameters. The model will be used for individualized BU therapy and ensure the successful conditioning of children who will undergo HSCT. Acknowledgments: This work was financed by the PPSUS/MS-FAPERGS, Rio Grande do Sul, Brazil [#17/2551-0001438-3]. References[1] Diestelhors, C; et al; Eur J Clin Pharmacol; v70; p839; 2014[2] Hadjibabaie, M; et al; DARU; v19; p216; 2011

11.004 **Pharmacogenetic Testing-Guided Treatment for Oncology: An Overview of Reviews**. Lara DV[1], Melo DO[2], Kawakami DY, Gonçalves TS[1], Santos PCJL[1] [1]Unifesp-EPM, Dpt of Pharmacology, São Paulo, Brazil, [2]ICAQF-Unifesp-Diadema, Dpt of Pharmaceutical Sciences, Diadema, Brazil l

Introduction: Pharmacogenetics (PGx) is the relationship between an individual's genetic variations and their response to pharmacological treatment. However, there are still some barriers to the wide implementation of PGx in the clinical practice for oncology, mainly due to a lack of evidence. We chose to conduct an overview of reviews on the use of post-treatment pharmacogenetic testing for oncology, based on clinically relevant gene-drug pairs. In addition, we discussed the quality of the evidence. **Methods:** We conducted a literature search on Pubmed, Embase and Cochrane Library, from their inception to June 18, 2020, without language limitations. The selection process was conducted by two authors independently. The overview of reviews was conducted as recommended by the Cochrane Collaboration, and quality assessments were performed by two authors, using A Measurement Tool to Assess Systematic Reviews (AMSTAR-2). **Results:** The search strategy identified 592 records and we removed 34 duplicates. We excluded 540 records during the first step of selection, resulting in 18 studies for full-text review. In the second step, we selected 6 eligible systematic reviews (SRs). The most studied gene-drug pairs were tamoxifen - CYP2D6 and fluorouracil - DPYD, accounting for 83% (n = 5) and 17%

(n = 1) of the SRs, respectively. Most reviews did not assess the risk of bias (RoB) in primary studies with an appropriate tool, classified as critically low quality (n = 4; 67%) or low quality (n = 2; 33%). **Conclusion:** Therefore, it is evident that there is a need for higher quality primary studies, as well as SRs that assess RoB, with more consistent definitions of clinical outcomes, to assess the benefits of pharmacogenetic tests in the field of oncology. **Financial Support:** 141302/2020-8 - Conselho Nacional de Desenvolvimento Científico e Tecnológico; 001 - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; 2019/08338-7 - Fundação de Amparo à Pesquisa do Estado de São Paulo. Acknowledgments: The authors would like to thank DM Toita from the Dept of Pharmaceutical Sciences for her assistance in the selection of the studies.

11.005 **Are Ciprofloxacin Plasma Concentrations Influenced by Different Gram-Negative Bacteria Infection**? Lock GA[1], Dias BB[1], Helfer VE[1], Barreto F[2], Araújo BV[1,], Dalla Costa T[1] [1]UFRGS, PPG Pharmaceutical Sciences, Pharmacokinetics and PK/PD Modeling Lab, [2]LFDA-RS

Introduction: Plasma concentrations are analyzed in therapeutic drug monitoring as a surrogate for concentrations at the site of action. Previously we have shown that plasma and pulmonary ciprofloxacin (CIP) concentrations can be altered by Pseudomonas aeruginosa lung infection[1,2]. Objectives: Knowing that CIP is substrate to membrane transporters[3] and that bacteria endotoxins can alter hepatic transporters expression[4], this study aims to evaluate the influence of Klebsiella pneumoniae lung infection on CIP plasma concentrations in comparison to P. aeruginosa infection, considering acute and chronic infection stages. **Methods:** Project approved by UFRGS' Ethics Committee in Animal Use (#36515). Acute (2 d)[1] and chronic (14 d)[2] pneumonia were developed in male Wistar rats with intratracheal administration of K. pneumoniae ATCC 13833 inoculum (108 UFC/mL). Two groups were investigated: acute infection (n = 6), chronic infection (n = 7). On the day of the experiment, animals were anesthetized (urethane 1. 25 g/kg i. p.) before carotid artery cannulation for blood sampling and i. v. bolus CIP 20 mg/kg administration via the femoral vein. Blood samples were collected into heparinized tubes up to 12 h post-dosing. Plasma samples were processed for CIP quantification in an LC-MS/MS method previously validated[5]. A non-compartmental analysis was carried using PKAnalix®, and statistical analysis was performed using SPSS® (ANOVA, α = 0,05). Data from equivalent groups infected with P. aeruginosa and healthy animals, from previous studies, were used for comparison [1,2]. **Results:** No statistical differences were found in the pharmacokinetic parameters investigated between both chronically infected groups. [TDC1] [GL2] Statistically similar [GL3] plasma exposure (AUC0-∞) was shown by acute (35. 9 ± 14. 5 mg·h/L) and chronically (25. 8 ± 6. 9 mg·h/L) K. pneumoniae infected animals. Only the acutely K. pneumoniae infected group showed a significant increase in plasma exposure in comparison to healthy (13. 2 ± 3. 5 mg·h/L) and acute P. aeruginosa (16. 5 ± 4. 7 mg·h/L) groups. Although no statistical difference was found in clearance between K. pneumoniae infection stages, both clearances from acute (0. 64 ± 0. 26 L/h/kg) and chronic (0. 82 ± 0. 20 L/h/kg) infections showed a trend of reduction in comparison to healthy (1. 61 ± 0. 42 L/h/kg) and acute P. aeruginosa (1. 30 ± 0. 38 L/h/kg) groups. The volume of distribution of the acute K. pneumoniae (3. 8 ± 1. 0 L/kg) group was statistically different from those observed for acute P. aeruginosa (7. 2 ± 2. 9 L/kg) and healthy (6. 9 ± 1. 0 L/kg) groups. The elimination rate constant and half-life were statistically similar in all groups evaluated. **Conclusions:** Our results suggest that acute infection by K. pneumoniae alters plasma CIP pharmacokinetic parameters differently than chronic infection by the same bacteria or infection by P. aeruginosa in both stages. The impact of these alterations on CIP distribution to the infection site and antibacterial effect is under investigation. Acknowledgements: **Financial Support** from CNPq/Brazil and doctoral scholarship from CAPES/Brazil. **References:** 1. LOCK, G. A. Dissertação de Mestrado em Ciências Farmacêuticas/UFRGS, 2018. Disponível em: https://lume. ufrgs. br/handle/10183/1802152. TORRES, B. G. S. et al. Antimicrob. Agents and Chemother. 61, 1, 2017. 3. ONG, H. X. et al. Antimicrob. Agents and Chemother. 57, 2535, 2013. 4. UEYAMA, J. et al. Eur. J. Pharmacol., 510, 127, 2005. 5. BARRETO, F. et al. J. Chromatogr. A, 1521, 131, 2017.

11.006 **Hepatic CYP3A4 Activity in Obese and Post-Bariatric Patients: An Exploratory Analysis Using Midazolam Single Time Point Concentration**. Medeiros JIM[1], Yamamoto PA[2], Santos BM[1], Salgado Junior W[3], Santos JS[3], Kemp R[3], Sankarankutty AK[3], Vozmediano V[4], Cristofoletti R[4], Moraes NV[4] [1]Unesp-Araraquara, Dept of Drugs and Medicines, Araraquara, Brazil, [2]FMRP-USP, Ribeirao Preto, Brazil, [3]FMRP-USP, Ribeirao Preto, Brazil, [4]University of Florida, Center for Pharmacometrics & Systems Pharmacology, Orlando, USA

Hepatic CYP3A4 activity in obese and post-bariatric patients: an exploratory analysis using midazolam single time point concentration. **Introduction:** Obesity is a global problem associated with complex physiological alterations that are likely to affect pharmacokinetics. Low-grade chronic inflammation in the adipose tissue increases IL-6 and TNF-alpha levels, potentially altering the expression of drug-metabolizing enzymes in obese patients. The Roux-en-Y gastric bypass (RYGB) is one of the most common surgical treatments due to the effective remission of obesity-associated conditions. It is largely unknown whether enzyme expression after RYGB completely change to levels observed in non-obese subjects. We aimed to assess the effect of RYGB on the hepatic CYP3A4 activity using midazolam total clearance as a sensitive index. **Methods:** Thirty-seven subjects, including obese (n=21, body mass ≥ 30 kg/m2) and post-Roux-en-Y gastric bypass (n=16, time post-RYGB: 356-2752 days) were investigated. All patients received a single dose of 2-3. 5 mg midazolam intravenously (iv). After 4-h, a 4 mL blood sample was collected, and plasma was stored for analysis. Plasma midazolam concentrations were determined by liquid chromatography-mass spectrometry (LC-MS). Midazolam single plasma concentrations were used to estimate midazolam exposure and total clearance using traditional approaches (1,2) and population pharmacokinetics analysis (3). **Results:** The conventional approach leveraged AUC and plasma concentration correlations previously described by two independent groups (1,2). A strong correlation was observed for the estimated total clearance values using two independent equations (Pearson correlation = 0. 91, p<0. 001). Previous populational pharmacokinetic modeling (3), based on 10 clinical studies (n=152), was used to estimate midazolam clearance. Prior distribution of the population parameters (3) and a penalized maximum likelihood estimation was applied to estimate individual total clearance values. Midazolam total clearance estimated using the PopPk approach showed moderate correlations with the traditional approaches (Pearson correlation=0. 698 and 0. 861, p<0. 001). The populational approach incorporates variations on blood sampling time in the predictions. It also includes the effect of age and sex as covariates on midazolam pharmacokinetics. Considering the PopPk approach, obese and post-RYGB patients showed similar plasma midazolam exposure with median total clearance of 25. 2 and 25. 0 µg. h/L (Mann-Whitney, p>0.05), respectively. **Conclusion:** This exploratory analysis suggests that hepatic CYP3A4 activity is not altered after weight loss in post-RYGB patients. **Financial Support:** FAPESP, Grant #2018/06569-9; CAPES – Finance Code 001. Approval by human ethical committee: HCFMRP-USP CAAE 94756418. 0. 3001. 5440 References Lin YS et al. Pharmacogenetics. 11: 781, 2001. Miura M et al. Biol Pharm Bull. 42: 1590, 2019. Yang et al. J Clin Pharmacol. 58: 1205, 2018

11.007 **Interferon-Beta Injection in Multiple Sclerosis Patients Related to the Induction of Headache and Flu-Like Pain Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**. Pereira LG, Rodrigues P, Frare JM, Ramanzini LG, Viero FT, Santos GT UFSM, Depto de Fisiologia e Farmacologia, Santa Maria, Brasil
Multiple sclerosis (MS) is a chronic, inflammatory and autoimmune neurodegenerative disease characterized by demyelination of neurons in the nervous system. One of the main approaches for treating MS is the use of disease-modifying therapies (DMTs). Among the DMTs there are interferons (IFNs), which are cytokines responsible for controlling the activity of the immune system while exerting immunomodulatory, antiviral, and antiproliferative activities. Furthermore, among the three types of MS, it is estimated that 86% of the cases are RRMS, with IFN beta (IFN-β) being the treatment of choice. It acts by exerting immunomodulatory activity. In addition, MS patients suffer from painful symptoms such as headache and muscle and neuropathic pain. Therefore, treatment with IFN-β is a fundamental approach, improving the patient's quality of life. However, IFN-β treatment in MS patients causes painful adverse effects, such as painful flu-like symptoms (reported painful symptoms of the flu-like syndrome, such as headache, myalgia, and arthralgia) and headache in such a way as to impair treatment adherence. Therefore, this study aimed to investigate the headache and flu-like pain symptoms observed after IFN-β injection in MS patients using a systematic review and meta-analysis of randomised controlled trials. A total of 2370 articles were identified through research databases. Nine articles were included (three involving IFNβ-1b and six involving IFNβ-1a). All studies included in the meta-analysis had a low risk of bias. The odds ratio of headache and flu-like pain symptoms increased in MS patients treated with IFN-β. The results are valid in 95% of cases (p<0.05). Both meta-analyses showed high confidence in the results. Thus, the adverse effects of headache and flu-like pain symptoms appear to be linked to IFN-β treatment in MS. Studies are needed to provide palliative treatment for this adverse effect for better adherence to IFN-β

treatment in patients with MS. The protocol of the study was registered in the Prospective International Registry of Systematic Reviews (registration number CRD42021227593).

11.008 **Praziquantel and *Moringa oleifera* Extracts Combination: Bioavailability in Rats and Cysticidal Activity in a Murine Model**. Castro N[1,2], González Esquivel DF[1], Palomares Alonso F[1], Rojas Tomé IS[1], Vidal-Cantú GC[3], González Hernández I[1], Jung H[1,2] [1]MVS, Inst Nacional de Neurología y Neurocirugía, Cidade do México, México, [2]UNAM, Facultad de Química, [3] CDMX, Dpt de Farmacobiología, Centro de Investigación y de Estudios Avanzados, Cidade do México, México

Introduction: Praziquantel (PZQ) is an anthelmintic drug included in the WHO list of essential medicines for neglected tropical diseases, shows low oral bioavailability and high variability in plasma levels due to the first-pass metabolism. Various approaches have been used to increase the plasma levels of PZQ, including the co-administration with Cytochrome P450 inhibitors. *Moringa oleifera* Lam., Moringaceae, is an appreciated plant for its nutritional value and is widely used in traditional medicine. It contains a number of potential active compounds including flavonoids and phenolic components that can alter Cytochrome P450 activity. This aimed to evaluate the effect of M. oleifera leaf and seed extracts on the praziquantel bioavailability and assess its in vivo effect on a Taenia crassiceps murine model. **Methods:** Experimental protocols (numbers 83/13, 49/16) were approved by the Institutional Research Committee of the National Institute of Neurology and Neurosurgery. Rats were divided into three groups of treatments. All groups received the same PZQ oral dose of 50 mg/kg. Group A received PZQ alone; group B received PZQ and the leaf extract of M. oleifera in a dose of 75 mg/kg body weight, and group C received PZQ and the seed extract of M. oleifera in a dose of 75 mg/kg body weight. A validated method by high-performance liquid chromatography with DAD detection for determination of PZQ plasma levels was used. To evaluate the efficacy, a lower dose of PZQ in combination with the extract of M. oleifera that showed a major increment in plasma levels was used to observe differences between treatments. The cysticidal activity of extracts and their combination with PZQ was evaluated on Taenia crassiceps (ORF strain) cysts. The experimental infection of the animals and the conditions used for the experiment were previously described (Palomares-Alonso, Exp Parasitol 149:1,2015). This study received **Financial Support** from CONACYT (grant number 229785) Results. After the oral administration of PZQ with M. oleifera, the maximum plasma concentration of PZQ increased by 2. 4- and 5. 6-fold with leaf and seed extracts respectively. The area under the curve ratio values, from the time 0 to 120-min, between the combinations and PZQ alone were 1. 8 and 3. 6 for leaf and seed extracts, respectively ($p < 0.05$). Cysticidal activity of the combination of PZQ and seed extract, a dose of 200 mg/kg, was significantly greater than the administration of PZQ alone, the more evident effect observed was the decrease in the number of parasites as well as reduction in its motility. the mean percentage of parasite reduction was 22% for PZQ alone and 39 % for the combination PZQ and seed extract ($p < 0.05$). **Conclusion:** s. Considering the pharmacological properties of M. oleifera, the simultaneous administration could be an inexpensive alternative for therapeutic use, improving the efficacy of PZQ. Clinical studies are necessary to evaluate the impact of this interaction principally with the human use of M. oleifera.

12. Drug Discovery and Development

12.001 **New Perspectives for Melanoma and Fungal Infections Treatment: Development of Polymeric Nanoparticles for Seriniquinone Delivery**. Miguel RA[1], Hirata AS[1], Barroso VM[1], Furtado LC[1], Ishida K[2], Costa-Lotufo LV[1], Lopes LB[1] [1]ICB-USP, Dpt of Pharmacology, São Paulo, Brazil, [2]ICB-USP, Dpt of Microbiology, São Paulo, Brazil

Seriniquinone (SQ), initially described as a cytotoxic secondary metabolite synthesized by the rare marine bacterium *Serinicoccus* sp., is increasingly promising. The first reports with this substance demonstrated a special selectivity to melanoma cells and outlined the first notions of SQ mechanism of action: targeting dermcidin, a cytosolic protein involved in cell survival, and inducing autophagocytosis and apoptosis. [1][2] More recently, our group also observed antifungal activity of SQ against strains of Candida spp. and Cryptococcus spp. comparable to fluconazole. Thus, SQ could be a novel drug candidate in antimelanoma and antifungal therapies, since both of thempresent few approved pharmacological entities and multidrug resistance. [3][4] Nevertheless, poor solubility in water of SQ (0. 06 μM) and the low availability of safe non-polar vehicles hinder the progression of preclinical and clinical studies. [5] In this study, poly(lactide-co-glycolic acid) (PLGA) nanoparticles (NPs) were

developed to encapsulate SQ and enable drug administration, since they can be dispersed in aqueous-based vehicles. PLGA-NPs were developed using the single emulsion/solvent evaporation method. [7] SQ and PLGA were dissolved in the organic phase, emulsified in water with vitamin E-TPGS through probe sonication, and the organic phase wasevaporated by stirring at room temperature. NP size was evaluated by dynamic light scattering (DLS). Percent yield was calculated after freeze drying and weighing of NPs. Drug encapsulation was determined after centrifugation by high performance liquid chromatography (HPLC) at 210 nm (UV-vis). To assess the influence of SQ encapsulation on its cytotoxicity, SK-Mel-28 (BRAFV600E) cells were treated for 48 h with unloaded or SQ-loaded nanoparticles (0.14-237 ng/mL) and viability was assessed by the sulforhodamine B (SRB) assay. SQ solution in DMSO was employed as a control (0. 00032-5 uM). To assess the antifungal effect, broth microdilution tests were carried out to determine the minimal inhibitory concentration (MIC) for yeast growth against strains of Candida spp. and Cryptococcus spp. PLGA-NPs developed in this work present 288. 5+/-18. 6 nm, with a percent yield of 81. 9+/-1. 5% and were able to incorporate 83. 1+/-4. 6% of SQ. The antiproliferative and cytotoxic activity of PLGA-SQ-NPs and SQ in solution were comparable, while unloaded PLGA-NPs did not reduce cell growth to less than 50% in the highest concentration tested. A bigger increase in MIC against Candida spp. was observed with encapsulation, which is expected since these yeasts present a quick growth. On the other hand, treatment of Cryptococcus spp. demonstrated similar activity of SQ in solution and in PLGA-SQ-NPs, which might be justified by the slower fungal growth and drug release within the timeframe of the experiment. These results demonstrated that the NPs i) enable SQ encapsulation and dispersion in aqueous vehicles; ii) were able to encapsulate SQ with a high efficiency and iii) did not preclude SQ activity in *in vitro* assays. These data support study progression towards in vivo models.

12.002 **Wound Healing Potential of Mitochondria-Targeted Hydrogen Sulfide (H_2S) Donors: ROLE of hyperglycemia**. Gois GA, Amorim LA, Cerqueira ARA, Oliveira JP, Teixeira SA, Muscará MN, Costa SKP ICB-USP

Tissue injury such as mechanical, thermal and chemical, as well as chronic wounds, disrupts the skin integrity. Chronic wounds are associated with high costs, poor quality of life, and significant morbidity and mortality (Oliveira et al., 2019). The wound healing begins after an injury and comprises a complex process dependent on the presence of various types of cells, growth factors, cytokines and elements of extracellular matrix. Obesity and diabetes are likely to interfere with the healing process (Anderson & Hamm, 2012). The World Health Organization (WHO, 2021) report shows that the number of individuals living with obesity tripled between 1975 and 2016. Thus, additional knowledge concerning the mechanisms of wound healing is essential in addition to new therapeutic approaches. Recent evidences show that topical or systemic treatment with new gasotransmitter (hydrogen sulfide, H2S) donors exerted protective effect in inflammatory skin conditions (Coavoy-Sánchez, Costa & Muscará, 2020) but little attention has been paid to its potential pro-healing effect on skin wound. The goal of this study was to evaluate the efficiency, cytotoxicity and tolerance of a mitochondrial H2S donors (AP39 and AP123) on a *in vitro* wound model *in vitro* (scratch assay), and to investigate the influence of hyperglycemia in the healing process. **Methods:** Fibroblasts (3T3 cell line), keratinocytes (HaCat cell line) and macrophages (RAW cell line) were cultured in DMEM medium with low (1 g/L) or high glucose (4. 5 g/L). The cell viability of each cell line (1x10^6/mL, 24 hours) was tested upon increasing concentrations of AP39 and AP123, from 0. 0078 to 2 mM, via the MTT test. For the healing (scratch) test in fibroblasts (1x10^6/mL, 24 h), kept in physiological or high glucose, a lesion was performed in the cell monolayer with a 10 µL pipette tip. Images of 5 random fields of each well were obtained with an inverted microscope (Leica, AF6000, Germany) immediately after the lesion, and thereafter treatments with AP39 (0. 2, 2 and 20 µM concentrations) or vehicle at intervals of 6, 12 and 24 hours. The measurements of the monolayer healing were performed in the images with the aid of the Leica Application System software and the Image J 1. 8. 0 software. **Results:** The MTT revealed a AP123 IC50 of 90 µM (± 18. 9) and 86. 3 µM (± 9) for fibroblasts and macrophages, respectively. The parameter could not be defined yet for AP39 and also AP123 in keratinocytes, as we have not been able to establish this culture. In the scratch test in 3T3 fibroblasts, kept in a physiological glucose medium, the concentration of AP39 (0. 2 µM) was effective in promoting significant cell migration within 24 h (13. 5% empty area) as compared to the control (23. 3% empty area). Likewise, the same concentration of AP39 evoked a significant cell migration of 3T3 fibroblasts kept in the hyperglycemic ambient (27. 8% empty area control, 13. 5% treatment). **Conclusions:** The IC50 of AP123, established as 90 µM (± 18. 9) and 86. 3 µM (± 9) for fibroblasts and macrophages, respectively,

is an important parameter for cell viability in further studies. AP39 effectively promoted *in vitro* wound healing by enhancing the migration of fibroblasts using the scratch model. Increasing glycemia did not show to affect the effect evoked by H2S donor. Acknowledgments: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

12.003 **Drug-Target Kinetics in Drug Discovery: Using of K+-pNPPase Activity to Characterize the Kinetics of Cardiotonic Steroids on Na+/K+-ATPase in a Cheap Way**. Azalim P[1], Liu X[2], Silva SC[3], Barbosa LA[3], O'Doherty GA[2], Quintas LEM[1], Noël FG[1] [1]ICB-UFRJ, Lab de Farmacologia Bioquímica e Molecular, Rio de Janeiro, Brazil, [2]Northeastern University, Dpt of Chemistry and Chemical Biology, Boston, USA, [3]UFSJ, Lab de Bioquímica Celular, Divinópolis, Brasil

Introduction: In the target-based drug discovery approach, structure-activity relationships are usually performed using affinity or potency parameters. However, Copeland et al. (Nat. Rev. Drug Discov. 2006, 9:730-739) proposed that the time that a ligand spends in its binding site (residence time, 1/koff) could have a major influence on its clinical efficacy. The Na+/K+-ATPase (NKA, EC 3. 6. 3. 9), is the classical receptor of cardiac steroids and there is an interest in searching for new NKA modulators targeting other clinical conditions such as cancer (Slingerland et al., New Drugs 2013, 31:1087–1094). We performed a kinetic study focusing digitoxigenin derivatives to study the influence of the carbohydrate moiety at C3 on the kinetics of NKA inhibition. **Methods:** 12 digitoxigenin derivatives were synthesized (Wang et al., ACS Med. Chem. Lett. 2011, 2:264-269) by adding different kinds of osidic groups at C3. The K+-dependent pNPPase reaction was used in order to assess the kinetics of the inhibitory effect of these compounds on NKA, through colorimetric measurement of the p-nitrophenol liberated during the reaction performed at 37°C in a medium containing (in mM): KCl 50, MgCl2 3, p-nitrophenylphoshate (p-NPP) 10, EGTA 1 and Maleate-Tris 20 (pH 7. 4). The absorbance (430 nm) was measured in a 96-well plates reader every 15 min until equilibrium (2 h). The association rate (kon) and dissociation rate (koff) constants were obtained by globally fitting the inhibition vs. time curves of 3-5 concentrations of each compound using the following equation:Y=Ymax*(1 - exp(-1*kobs*X)), where: Ymax = Occupancy*Bmax; Occupancy = L/(L+Kd); Kobs = Kon*L+Koff; L = L(nM)*1e-9; Kd = Koff/Kon and L = the compound concentration. **Results:** We showed that the addition of a rhamnosyl residue at C3 of digitoxigenin reduced the Kd by 4. 16 times and that this was driven by a decrease of the koff (3. 6x) and not by an increase of the kon (1. 2x). However, when two rhamnosyl were added at C3, the Kd was increased by 17x and was driven by a decrease of the kon (28x) and not by a koff increase (1. 6x). The addition of three digitoxoses at C3 (digitoxin vs. digitoxigenin) did not alter the Kd (difference of only 1. 5x) but altered the kinetics, by decreasing both koff (4. 5x) and kon (3. 0x). **Conclusion:** 1. Using K+-pNPPase activity, we were able to estimate the kinetics of new NKA inhibitors in a simple, fast and cheap way. We believe that this methodology can contribute to a better characterization of cardiotonic steroids. 2. We showed that changes in the number and chemical of osidic groups at C3 were able to affect the Kd by changing kon, koff or both in different ways. Our results suggest that the affinity difference related to the C3 substituent is not restricted to the koff alone. **FINANCIAL SUPPORT:** FAPERJ, CNPq, CAPES. ANIMAL RESEARCH ETHICAL COMMITTEE: no needed.

13. Pharmacology Education and Technology

13.001 **Interactions Between Drugs and Food/Nutrients: Report of this Practice of Extension Education in the Context of Remote Teaching**. Montes GC[1], Campos WVA[2], Rossi BA[2], Barbosa CD[2], Ferreira CCD[2], Carmo PL[2] [1]UERJ, Rio de Janeiro, Brazil, [2]UFRJ-Macaé, Macaé, Brazil

Introduction: Drugs can interact with food/nutrients, and this content is little explored in undergraduate studies or in clinical practice in different areas of health. The objective of this work is to describe the experience of the extension action developed by the project "Interactions between food/nutrients and drugs: dissemination of this knowledge", from the Multidisciplinary Center of the Federal University of Rio de Janeiro (UFRJ)- Macaé. **Methods:** Two editions of the online course were offered to academics and health professionals about interactions between food/nutrients and drugs. The course was designed and taught by the project team, including two professors and four undergraduate students of Nutrition, Medicine and Chemistry graduation courses of UFRJ, offered in remote format through the Google Meet digital platform and divided into: organism

systems/pharmacological classes, mechanisms of interactions between drugs and foods/nutrients, in addition to possible recommendations found in the existing scientific literature. The dissemination of the course was carried out on electronic platforms, including the project page on Instagram (@ifan. proex), and registrations made by email. Interested parties answered a registration questionnaire on Google Forms, in which it was mandatory to read and agree to the Terms of Conduct for Remote Education at UFRJ. Individuals who had not yet taken the discipline of Pharmacology were not invited to the course. The course was taught over a period of two hours. Before the participants received the certificate, they answered another form for quantitative (on a scale of 0-10, participants rated their level of knowledge) and qualitative evaluation (criticism or suggestions), which was anonymous. **Results:** In the 1st edition, we had 22 participants (3 men and 19 women); of which 81. 8% were students and 18. 2% were health professionals. In the 2nd, there were 37 participants (7 men and 30 women); 48. 6% of students and 51. 4% of professionals. Among the participants were people from the following areas: Nutrition, Medicine, Pharmacy and Biomedicine. On a scale of 0-10, participants rated their level of knowledge on the subject at an average of 5. 5 and 5. 8; and after attending the course, it increased to 8. 4 ($P<0.05$) and 7. 5 ($P<0.05$), in the 1st and 2nd editions, respectively. In the 1st post-course evaluation, 86. 4% of people classified the course as excellent, 9. 1% good and 4. 5% fair; in the 2nd edition, 78. 4% classified it as excellent and 21. 6% as good. The participants liked the course, and they could recommend it for other people in the next edition of the course. The public had 90% good aspects of the students' perception of learning after the course. They thought a dynamically presentation, the interaction that they had with the presenters and the easy understanding of the content. The suggestions by the participants at the end of the questionnaire were: creation and implementation of an elective course at undergraduate, do not stop offering the course for professionals and students, to add an approach focused on patients which it is using enteral nutrition, and to make at least in two meetings in the next editions. **Conclusion:** This project allowed students and health professionals to expand their knowledge about drug-food interactions. In addition, the course enabled the students and professors involved to experience the teaching/research/extension tripod, in the context of remote teaching.

13.002 **Undergraduate Medical Students Perception of Team-Based Learning in the Study of Antibiotics Pharmacology**. Morais SA, Cabral MCB, Coelho AM, Januário MJB, Bessa MMM, Lima LAR, Oliveira FFB FAP, Medicina, Araripina, Brazil

Introduction: Teaching Methods focused on memorization and transmission of information are unable to develop fundamental characteristics in students, such as pro-activity, collaboration, critical thinking, teamwork and entrepreneurial vision. In these methods, the student becomes a passive subject of the knowledge process, where the teacher just transfers the content, just like the "banking education". Team Based Learning (TBL) is an active methodology with a collaborative approach, which uses a teaching strategy focused on the student, promoting autonomy and pro-activity, and has become an important alternative pedagogical proposal in the context of the most frequently used teaching methods in medical education. In view of this, the applicability of TBL for pharmacology learning is of paramount importance, since it requires the application of individually acquired knowledge, valuing the responsibility of each student in their work teams, which is consolidated in the acquisition of knowledge by the student. The objective of this study was to identify the level of perception of undergraduate medical students about TBL as methodology for learning the pharmacology of antibiotics. Method: In the curricular unit of Mechanisms of Aggression and Defense, the students of the second period of the medical course of the Faculdade Paraíso Araripina (FAP-Araripina) initially received previous study guides with the theme of pharmacology of antimicrobials that would be developed and carried out the previous study of the activities developed in the classroom. In class, they answered a test individually. After the individual test, the students were divided into small groups to discuss each of the questions and answers that they elected, reaching consensus for the presentation of a single group answer. **Results:** The medical students, who participated in the study, reported that there was significant improvement in the assimilation of the content. They also pointed out that the initial search for the content, before its formal presentation, and the performance of individual tests stimulated them to study previously, contributing to their understanding of the theme studied through TBL. Moreover, they reported that the group discussion reinforced and helped consolidate learning. **Conclusion:** We conclude that the use of TBL promoted better acceptance and assimilation of the pharmacology

content of antibiotics, being a methodology capable of improving the learning process of medical students. Acknowledgments: The authors would like to thank the Faculdade Paraíso Araripina. License number of ethics committee: N/A.

13.003 **Team Basic Learning (TBL) as Collaborative Learning Tool for the Study of Pharmacology of Antibiotics**. Coelho AM, Januário MJB, Cabral MCB, , Morais SA, Bessa MMM, Lima LAR, Oliveira FFB FAP, Medicina, Araripina, Brazil

Introduction: In the undergraduate medical course, the teaching of pharmacology aims to train students for the systematic and continuous study of drugs. The traditional method of teaching remains the basis of Brazilian education, whether at the basic or professional level, where the student have no room to act individually, stimulating the formation of a reactive individual. Thus, in the mid 1970s, Larry Michaelsen created the Team Basic Learning (TBL), a method for American business schools, which aimed to improve and develop collaborative work strategies through constructivist educational methods and techniques, centered on the active process, promoting a critical and reflective view to the student; however, only in 2001 it started to be inserted as a method in the medical course. Objective: This article aims to describe the use of TBL as a collaborative learning tool to study the pharmacology of antimicrobials in a medical school located in the interior of Northeastern Brazil. Method: During the month of November 2021, 44 undergraduate medical students (2nd period) of the Faculdade Paraíso Araripina (FAP-Araripina) underwent a teaching session with the TBL method in the curricular unit of Mechanisms of Aggression and Defense with the theme of pharmacology of antimicrobials (β-lactams). At the end of the session, the students answered a specific questionnaire with four items that addressed different aspects of the method. **Results:** The results showed that 95. 5% of the participants approve the use of the methodology. 88. 6% affirmed that the methodology favored the understanding of the proposed content; 63. 6% claimed that all doubts regarding the content were solved with the discussions of the methodology. Additionally, it was observed that group performance improved significantly ($p<0.01$) when compared to individual performance. **Conclusion:** It was concluded that the team-based methodology brings benefits to the students and makes them more active in class, besides instigating them to seek new knowledge related to the subject, making them more independent in their studies. The methodology additionally promoted attitudes such as adaptability, autonomy, and collaboration. Acknowledgments: The authors would like to thank the Faculdade Paraíso Araripina. License number of ethics committee: N/A

14. Pharmacology: Other

14.001 **Development and Evaluation of the Bioadhesive Properties of Chitosan and Hyaluronic Acid Polyelectrolyte Nanoparticles**. Hirokawa CM[1,2], Passos JS[2], Lopes LB[2] ICB-USP, Dpt of Pharmacology, São Paulo, Brazil [1]FCF-USP, São Paulo, Brazil, 2 ICB-USP, Dpt of Pharmacology, São Paulo, Brazil

Introduction: Polyelectrolytes are polymeric macromolecules that can form nanoparticles (PEC) spontaneously through electrostatic interactions. Considering the simple, efficient and low-cost processes available to obtain these nanoparticles, as well as the possibility to use biocompatible and/or biodegradable molecules for their production, they have been proposed as nanocarriers for various drugs. In this study, we evaluated the influence of composition and process parameters on the characteristics and bioadhesive properties of PECs produced with hyaluronic acid (HA) and chitosan (CS), aiming to encapsulate antitumor drugs for intraductal administration and localized treatment of breast cancer. **Methods:** The PECs were developed by adding the HA solution dropwise to the CS solution under constant stirring. The following process parameters were varied: polymer concentration (0,1 - 0,5mg/mL), homogenization method (magnetic agitation for 0 – 4 hours or probe sonication for 5 minutes) and type of surfactant/cosolvent (propylene glycol (PG) or Tween 80). Size, polydispersity index (PDI) and zeta potential were evaluated with a Zetasizer NanoZS90 instrument. Incorporation of the cytotoxic drugs 5-fluorouracil (5-FU) and paclitaxel (PTX) was assessed. The bioadesive properties were studied by incubating selected PECs with mucin in PBS for 30 min at 37°C, and assessing shifts on the diameter and zeta potential of PECs. **Results:** PECs characteristics were highly influenced by the concentration of HA and CS solutions, with smaller nanoparticles (<200nm) and polydispersivity index (PDI<0. 3) observed with lower concentrations. Probe sonication was capable of reducing the PDI compared to magnetic agitation. However, higher zeta potential values (>30mV), which are often associated with improved stability, were observed when the polyelectrolytes

concentration increased. PG at 20%, but no Tween 80, reduced nanoparticle diameter by 2-fold when HA and CS concentration was 0,5 mg/mL, but had no effect at lower polyelectrolyte concentrations. The optimized formulation was produced with HA and CS at 0,25 mg/mL in the presence of PG at 20% and probe type sonication for 5 min. 5-Fluorouracil and paclitaxel could be incorporated at 0. 75% and 0. 25% (w/w), respectively, without promoting pronounced changes on PEC diameter. Incubation of PECs with mucin resulted in an increased particle diameter (4-fold) and an inversion of zeta potential from positive (+24. 5 ± 2. 7 mV) to negative values (-2. 0 ± 0. 0 mV), which suggest that HA and CS maintained their bioadhesive properties when organized as nanoparticles. **Conclusion:** The polyelectrolyte complexes developed in this study displayed bioadhesive properties and were able to incorporate antitumor drugs without pronounced changes on diameter. Future studies will address their cytotoxic effects. **Financial Support:** FAPESP (2021/12658-7, 2018/13877-1)

14.002 **Transgenic Effect on the Composition of Nutrients from Corn: GMO Vigilance**. Vital AJL[1], Castro LGG[2], Ribeiro AF[1], Barros BAF[1] [1]PUC-MG, [2]UFMG

Introduction: Corn is an important food for the world human population. Also, corn is utilized in fabrication of several dietary sources, including flour, snack, cake, biscuit. Moreover, most of its production is destined for animal feed. The genetic modification of the corn seed aims at its resistance to pests and herbicides, enabling greater productivity, however there is a lack of information about how much these modifications can interfere with its nutritional composition. Thus, the objective of the present study was to analyze the nutritional composition between the different products, to integrate the scientific evidence that can later collaborate with the development of a protocol for the characterization of risk to human health in the face of exposure to organisms genetically modified. **Methods:** A descriptive pilot study was made using samples of Genetically Modified (GM) corn with genes from Agrobacterium tumefaciens, Bacillus thuringiensis and Streptomyces vidrochromogenes, and non-GM corn. Corn samples were tested for different components (total carbohydrate; fiber; total, saturated, mono, poli and trans-fat; total protein; sodium and calories), according to RDC nº 360 de 23. 12. 2003, ANVISA; Methods 045 and 036/IV (Instituto Adolfo Lutz. Métodos físico-químicos para análise de alimentos, 2005); Official Methods of Analysis of AOAC International 20th Edition chapters 9 and 45 (2019), Official Method 984. 13A (2016); and PE FQ 157. The analyses were carried out in the A3Q Laboratory. **Results:** GM corn exhibited (i) total carbohydrate 18% higher; (ii) calories 3. 8% higher; (iii) fiber 55% lower; and (iv) total protein 2. 7% lower than non-GM corn. The quantity of total fat and fraction was not quantifiable. The components values observed in the laboratory analysis were in accordance with the supplier packaging of GM corn. **Conclusion:** It was possible to evidence differences in the macronutrient composition between transgenic and non-transgenic corn, suggesting a lower nutritional value in transgenic foods. However, the pilot study had limitations, among which we can highlight (i) the small amount of samples, which makes an inferential statistical analysis impossible; (ii) the small variety of food products; (iii) the micronutrients were not quantified and, (iv) the conditions of cultivation and/or the environment, storage, transport, used in the production of the food product were not surveyed. Thus, more studies need to be carried out. **Financial Support:** The Financial Support and fellowships were granted from PUC Minas – FIP-27013-1S/2021. Acknowledgements: We thank the PUC Minas for the fellowships awarded. We also thank the course coordinators and employees of the PUC Minas for their assistance.

14.003 **Drug-Drug Interactions in Patients on Covid-19 During the First Wave in Brazil**. Santos JR, Razera A, Marques ACR, Carraro E Unicentro, Dpt of Pharmacy, Guarapuava, Brazil

Introduction: Patients hospitalized with coronavirus disease 2019 (Covid-19) are often older, with comorbidities and polymedicated. Thus, these factors can contribute to the concomitant use of multiple drugs, which increases the risk of drug-drug interactions (DDIs) be able to take to therapeutic failure and increased toxicity [1]. In that regard, this study aimed to analyze the possible drug-drug interactions (pDDIs) of patients with Covid-19 in order to provide subsidies to the improvement of pharmaceutical interventions and improvements in the pharmacotherapy of these patients. **Methods:** This is a cross- sectional, retrospective, descriptive, and analytical study, carried out through consultation of medical records evaluated between March and November 2020. Data collection was carried out at Hospital de Caridade São Vicente de Paulo (HCSVP) in Guarapuava, Paraná. The drugs were categorized according to the anatomical therapeutic chemical (ATC) classification system [2]. The pDDIs were checked with the online resource "drugs. com"[3]. **Results:** The results show that n=84 patients were

included in the study, of which n=37 (44%) were female. The age of the subjects ranged from 25 to 94 and the mean was age 57 years. Considering all the patients, n=14 (16. 7%) died during this study period. Before hospital admission, patients used to use an average of 2 drugs. However, after hospital admission the average consumption of drugs increased to 4. 6. In this bias, total medication administration per patient at the end was on average 6. 3 medications. Polymedication was present in n=69 (82. 1%) patients. The amount of 483 pDDIs were detected in n=67 (79. 7%) patients and involved 113 different medications. Analyzing the potential of pDDIs, it was observed that n=51 (10. 5%) in severe, followed by n=321 (66. 5%) moderate and other n=111 (23%) were mild. As per ATC, most of the detected pDDIs were related to general anti-infective classes for systemic use (n=132. 5/27. 4%), active in cardiovascular system (n=110/ 22. 7%), blood and hematopoietic organs (n=67. 5/ 13. 9%), systemic hormonal preparations, excluding sex hormones and insulins (n=58. 5/ 12. 1%) and alimentary tract and metabolism (n=37. 5/ 7. 7%). The 5 most recurrent pDDIs in the study were: ceftriaxone + heparin (n=34/ 7%), heparin + losartan (n=17/3%), dexamethasone + losartan (n=9/ 1. 9%), azithromycin + hydroxychloroquine (n=8/ 1. 6%), piperacillin + heparin (n=7/ 1. 5%). It is worth noting that about 88% of the pDDIs in the study were caused by 10 drugs, these being: heparin (n=94/ 19. 5%), azithromycin (n=52/ 10. 8%), hydrocortisone (n=50/ 10. 4%), dexamethasone (n=49/ 10.1%), losartan (n=45/ 9. 3%), ceftriaxone (n=40/ 8. 3%), metformin (n=29/ 6%), furosemide (n=27/ 5. 6%), spironolactone (n=23/4. 8%), and ciprofloxacin (n=19/ 3. 9%). Overall, pDDIs were related to increased chance of synergism, antagonism, or toxicity. **Conclusion:** It is concluded that patients with Covid-19 have a high prevalence of pDDIs, probably due to the predominance of polymedication, despite the minority presenting pDDIs in a severe form. Acknowledgements: CNPq. License number of ethics committee: Human Research Ethics Committee of UNICENTRO (CAAE28847719. 0. 0000. 0106). **References:** [1]CANTUDO-CUENCA, M. D. et al. Drug-drug interactions between treatment specific pharmacotherapy and concomitant medication in patients with COVID-19 in the first wave in Spain. Scientific reports, v. 11, p. 1-8, 2021. [2]https://www. whocc. no/atc_ddd_index/. Accessed on: mar. 2022. [3]https://www. drugs. com/drug_interactions. html. Access on:mar. 2022.

14.004 **Pathophysiological Mechanism of Primary Dysmenorrhea involves Enlargement of the Uterine Myometrium and Oxidative Stress**. Souza PPS, Lacerda Júnior FF, Barros BC, Almeida Filho EJB, Ferreira PB, Silva AS, Silva BA UFPB

Introduction: Primary dysmenorrhea (DisP) is defined as severe pelvic pain, which can become disabling, which affects most women of childbearing age (ITANI, et al., KorJourofFamMed., p. 101. 2022). Thus, we aimed to evaluate, after previous implementation in our Lab of the DisP induction model, changes in histomorphometric parameters and oxidative stress in uterus and ovary of virgin Wistar rats. **Methods:** The rats were randomly divided into a control group (CG), a group in which primary dysmenorrhea was induced (DisP) and a group with dysmenorrhea that received the standard drugs ibuprofen (IBU) and scopolamine + dipyrone (Esco+Dip). For the induction of DisP, diethylstilbestrol (i. p) was injected into the rats once a day, for 10 consecutive days, (2. 5 mg/kg) on the 1st (first) and 10th (tenth) days and 1 mg/kg of the 2nd (second) day to 9th (ninth) day. For histological analysis, after euthanasia, samples of the uterus and ovaries of each rat were isolated and fixed in a 10% buffered formaldehyde solution, dehydrated with graduated concentrations of ethanol, embedded in paraffin, sectioned in a microtome and stained with hematoxylin and eosin. For the analysis of oxidative stress after euthanasia, the uterine horns and ovaries were isolated and stored at -20°C, for the quantification of malondialdehyde (MDA) by the method described by Ohkawa; ohishi; Yagi (1979) and to quantify the total antioxidant capacity (CAT) the DPPH method described by Brand-Williams was used; Cuvelier; Berset (1995). **Results:** in the histological analysis of the uterus, it was observed that in the myometrial layer in the DisP group there was an increase (582 ± 11. 5) when compared to the CG (289. 2 ± 3. 8 µm2) and that the treatment with standard drugs did not reverse this data IBU (528. 8 ± 20. 2 µm2) and Esc + Dip (586. 2 ± 4. 6 µm2). In the analysis of oxidative stress, an increase in the concentration of MDA in the uterus was observed in the DisP (6. 0 ± 0.1%) groups when compared to the CG (1. 9 ± 0. 2%) and IBU (5, 3 ± 0. 3%) and Esc+Dip (4. 9 ± 0. 2%) did not reverse this change. Regarding CAT, it was observed that there was a decrease in CAT in the uterus of the DisP group (82. 2 ± 2. 9%) when compared to the CG (94. 8 ± 1. 2%) and the standard treatments did not reverse this decrease of IBU (77. 5 ± 4. 0%) and Esc + Dip (80. 5 ± 3. 1%). In the histological evaluation of the ovary, it was observed that there was no change in the presentation of secondary follicles present in this organ. In the analysis

of oxidative stress, it was observed that there was an increase in MDA levels in the DisP group (5. 4 ± 0. 2%) when compared to the GC (1. 5 ± 0.1%) and that the treatments did not reverse this increase in IBU (5. 4 ± 0. 6%) and Esc+Dip (5. 9 ± 0. 7%). In the CAT analysis, it was observed that there was a decrease in the ovaries of the DisP group (37. 9 ± 2. 3%) when compared to the CG (59. 5 ± 1. 3%) and that the treatments did not reverse this decrease in IBU (40.1 ± 1. 0%) and Esc+Dip (39. 7 ± 7. 1%). **Conclusion:** In view of this, it is concluded that the model listed for induction of DisP is leading to uterine histological changes as well as increased oxidative stress and decreased antioxidant capacity in the uterus and ovary, demonstrating the involvement of oxidative stress in the pathogenesis of DisP and the Standard drugs listed for this study did not reverse the parameters evaluated. I would like to thank the Federal University of Paraíba and the PPgPNSB/UFPB for their **Financial Support**. CEUA/UFPB (No. 2240150621 and 188601052).

14.005 **ATB346, a Hybrid H_2S Donor, Enhances Time for Blood Vessel Occlusion in Brain of Mice**. Dias KT, Muscara MN, Rodrigues SFP ICB-USP, Dept of Pharmacology

Introduction: Coagulation is an important physiological process that ensures hemostasis in situations that can harm the individual. This process needs to be carefully balanced to avoid disseminated thrombus formation. Thrombosis is one of the principal causes of mortality and morbidity in the world as it is related to fatal and frequent diseases such as thrombotic stroke and acute myocardial infarction (AMI). There are two types of thrombosis, arterial and venous. Antithrombotic drugs are effective in both thrombosis; however, the main side effect is hemorrhage, which can be fatal. Therefore, it is necessary to discover safer antithrombotic drugs. Physiological hemostasis can be influenced by gasotransmitters, including hydrogen sulfide (H2S). To control the administered concentration of H2S, donors were created to act as potential therapeutic agents, these include ATB-346. ATB-346 is a H2S donor coupled to naproxen that longer and rapidly reduces the activity of COX, an important pro-inflammatory enzyme, with no concomitant gastrointestinal side effects, which is usually observed when naproxen is used alone. However, despite of inflammation and coagulation share common activation steps, it is not known whether these H2S donors exert any vascular protective action on thrombus formation. **Methods:** To verify whether ATB-346 (90 µmol/kg, orally) interfere in the thrombus formation in vivo, pial cerebral blood vessels of male C57BL/6 mice (CEUA protocol #2355221121) were used and thrombus formation was formed in situ by a combined action of light and the fluorescein dye (FITC), damaging endothelial cells. As controls, equimolar naproxen or thiobenzamide – the H2S donor part of ATB-346 – were injected alone, as well as vehicle (1% DMSO) or saline. Initial time for thrombus formation and time of blood vessel occlusion were measured along with the prothrombin (PT) and partial thromboplastin times (PTT), using commercially available kits, and macroscopic gastric injury. RESULTS. The ATB-346-treated group showed an increase in total vessel occlusion time compared to the control groups (422. 1 ± 91. 8 sec and 1,097 ± 134. 0 sec, control group and ATB-346-treated group, respectively, N=8.). There was no statistical difference in the analysis of PT and PTT and ATB-346 caused no gastric injury. **Conclusion:** Treatment with ATB-346 can enhance time for vessel occlusion, without changing PT and PTT or causing any gastric injury, showing itself as a potential treatment for thrombosis. Funding support: CAPES (#88887. 627123/2021-00; FAPESP #2020/07212-7).

14.006 **Maternal Microbiota or Early Life Microbiota Dysbiosis Induces Neurodevelopmental and Behavioral Impairments Associated with Psychiatric Disorders**. Hassib L[1], Campos AC[2], Ferreira FR[3], [1] FMRP-USP, Dept of Mental Health, Ribeirão Preto, Brazil; [2]FMRP-USP, Dept of Pharmacology, Ribeirão Preto, Brazil, [2]Fiocruz

Introduction: Gut microbiota alterations have a significant role in Major Depressive Disorder (MDD) neurobiology. The bidirectional interactions between the host microbiome and the Central Nervous System are described as Gut-Brain-Microbiota (GBM) axis, in which stress is a noteworthy modulatory factor, inclusive in the microbiota profile. Although the mechanisms through GBM interactions that may contribute to the development of MDD are the focus of many notable works, the temporal window in which they can lead to behavioral alterations needs further elucidation since only part of individuals exposed to stressful situations develops disorders. Therefore, our group investigated if exposure to maternal microbiota alteration through the gestational period can cause behavioral deficiencies and gene expression alterations. **Methods:** Swiss pregnant mice previously treated with antibiotics to deplete their microbiota received for 28 days, by gavage, the suspension of feces from animals submitted to Chronic Unpredictable Stress (CUS) protocol, or from healthy

mice from control. We randomly split the offspring males into two groups to grow, one for 21 days, and another for 55 days. After growing, they passed through behavioral tasks, we dissected and stored their prefrontal cortex and hippocampus for analysis and collected their feces for microbiota profiling. **Results:** The 21 days mice born from mothers that received CUS donor microbiota showed a lower number of risk assessment behaviors in the elevated plus-maze test, a longer immobility time in the tail suspension test, and performed a smaller number of facial grooming during the sucrose spray test compared to the control group. The 55 days mice born from mothers that received CUS donor's microbiota had higher latency to start eating in the novelty suppressed feeding test and to do the first facial grooming in the sucrose spray test, in which they also did a smaller number of facial grooming compared to the control animals. Both groups showed alterations in genes related to neurodevelopment expressions, such as Synapsin-1, Oligodendrocyte Transcription Factor 1, and SOX 2 **Conclusion:** Both 21 and 55-day-old offspring from mice that received CUS donor microbiota during pregnancy had behavioral and gene expression impairments associated with depressive-like symptoms. Together these results show that the alteration of the maternal microbiota during pregnancy may influence the offspring's development, with behavioral impairments that continue until adulthood. **Financial Support:** CAPES, CNPQApproval by animal research ethical committees: CEUA: L-001/17

14.007 **Nebivolol Mitigates Endothelial Dysfunction in a Model of Preeclampsia**. Bueno Pereira TO, Bertozzi-Matheus M, Nunes PR, Rocha ALV, Sandrim VC IBB-Unesp-Botucatu, Dept of Biophysics and Pharmacology, Botucatu, Brazil

Introduction: Preeclampsia (PE) is characterized by placental ischemia and the release of vasoactive factors into the maternal bloodstream leading to generalized endothelial dysfunction. Decreased nitric oxide (NO) bioavailability and increased reactive oxygen species (ROS) are key points for the repercussions of the disorder besides potentiating the oxidative stress state. Regarding this, nebivolol is a molecule that shows vasodilating and antioxidant properties via β3 adrenergic receptor agonist, by activating endothelial nitric oxide synthase (eNOS) and consequently increasing NO bioavailability, as well as reducing oxidative stress. Here, we evaluated the nebivolol effect on the NO production, via β3 adrenergic receptor, in human umbilical vein endothelial cells (HUVEC) as well as superoxide production and total antioxidant capacity of these cells. **Methods:** HUVECs were incubated with 10% pooled plasma (n=10) from preeclamptic pregnant women and then were treated in the presence or absence of nebivolol (10μM), L-name (eNOS inhibitor) (100 μM), L-748,337 (β3 antagonist) (3 μM), to determine, through fluorescent probes, NO and ROS levels. The total antioxidant capacity was measured through Ferric Reducing Antioxidant Power Assay (FRAP) and the Griess reagent was assessed by a nitrite measurement kit. **Results:** Endothelial cells exposed to plasma from PE patients showed reduced levels of NO, and nebivolol was able to increase these levels through eNOS and β3 adrenergic receptor-dependent as identified in the group incubated with eNOS inhibitor and β3 antagonist. Regarding superoxide production, PE group showed higher levels and nebivolol was effective to decrease them. Conversely, plasma from PE and nebivolol treatment did not change the total antioxidant capacity. **Conclusion:** The results demonstrated that nebivolol enhances NO production through eNOS activation and β3 adrenergic receptors in this model and modulates superoxide release. The understanding of these mechanisms, using this strategy model, may offer, in the future, alternatives for the management and possible treatment of the disease. **Financial Support:** Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), grant numbers 2019/07230-8 and 2021/01945-5. The approval by human research ethics committees: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee of the Faculty of Medicine of Ribeirão Preto, Brazil (CAAE 37738620. 0. 0000. 5440 approved on 19 October 2020 FMRP–USP).

14.008 **Cardiac Alterations in Hepatic Steatosis: Role of the Age-Rage Pathway**. Rodrigues KL[1], Silva VVD[1], Pereira ENGS[1], Silvares RR[1], Linhares DOC[1], Flores EEI[1], Araujo BP[1], Ramos IP[2], Daliry A[1] [1]IOC-Fiocruz, Lab of Cardiovascular Investigation, Rio de Janeiro, RJ, Brazil, [2]UFRJ, National Center of Structural Biology and Bio-imaging, Rio de Janeiro, Brazil

Introduction: Nonalcoholic fatty liver disease (NAFLD) affects 20-30% of the adult population worldwide. Studies suggest an important causal relationship between liver changes and cardiovascular damage, which is the leading cause of death in patients with NAFLD. Currently, the role of advanced glycation end products (AGEs) in the etiology of cardiovascular disease and NAFLD is under debate. AGEs are proteins that are altered by reducing

sugars in a non-enzymatic manner. AGEs are formed throughout life but increase in situations of oxidative stress and hyperglycemia and can cause tissue damage due to the activation of its receptor, RAGE. However, the mechanisms leading to cardiac dysfunction in NAFLD are not yet known. Therefore, the aim of our study was to determine the role of the AGE-RAGE pathway in cardiac dysfunction in a preclinical model of NAFLD. Methods: C57BL6 mice were fed a high-fat, high-carbohydrate diet (HFHC) to induce NAFLD or a normocaloric diet (CTL) for 36 weeks. At the end of the protocol, animal weight, biochemical markers, severity of steatosis and presence of fibrosis, levels of AGEs and cardiac oxidative damage, and cardiac function were assessed in all groups. The Animal Welfare Committee of the Oswaldo Cruz Foundation approved all experiments protocols (license L-0012/18 A1), which were performed following the principles for the care and use of laboratory animals. Results The NAFLD-induced mice had higher body weight and more severe steatosis and fibrosis than CTL mice. Regarding cardiac function, the HFHC group showed worse cardiac function assessed by stroke volume, ejection fraction, and cardioprotective index compared with the CTL group. In addition, mice with NAFLD had increased serum and cardiac AGE levels and increased oxidative stress in cardiac tissue. In the person analysis, a negative correlation between cardiac parameters and the presence of steatosis/fibrosis and the level of AGEs was also observed. Conclusion: We conclude that the degree of steatosis and fibrosis together with the AGE-RAGE pathway may partially explain cardiac complications associated with NAFLD. Supported by FAPERJ, CNPq, and FIOCRUZ.

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