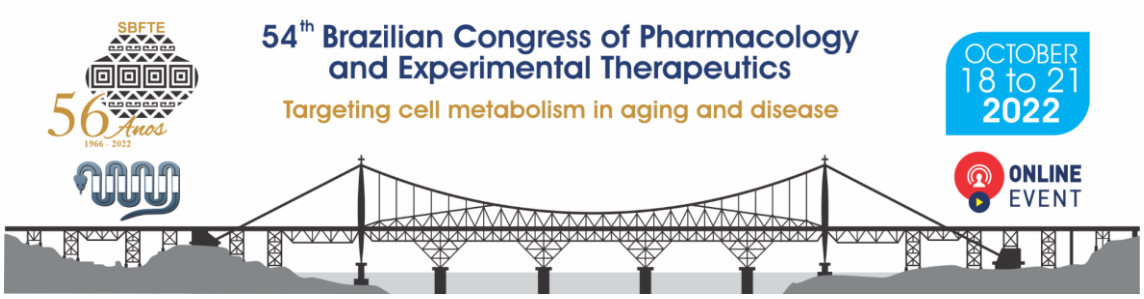

PRÊMIO JOSÉ RIBEIRO DO VALLE – 2022

O prêmio José Ribeiro do Valle, oferecido a cada ano pela SBFTE, visa identificar a cada ano os melhores trabalhos científicos desenvolvidos por jovens investigadores na área da Farmacologia. Entre os trabalhos inscritos para esta vigésima terceira edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 54º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, no Formato Online.O resultado foi o seguinte:

Primeiro prêmio

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

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.

Segundo prêmio

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

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.

Menção Honrosa

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

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

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

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