12. Hit, lead, drug candidate

François Noël, November 2019

As pharmacology is an essential discipline in the process of discovering and developing new drugs and medicines (Drews, 2000), it seems important to define some of the terms commonly used in this process. Considering that pharmacology and medicinal/pharmaceutical chemistry are essential and partner disciplines in this endeavor, there should be concern for adopting definitions that are accepted by both fields. Accordingly, we will discuss the definitions of the terms hit, lead compound, and drug candidate, which are widely used in the international specialist literature. From the standpoint of translating these terms into Brazilian Portuguese, we suggest the adoption of the terms *substância ativa* (hit), *protótipo* (lead compound), and *candidato a fármaco* (drug candidate).

Although there is broad agreement on the definitions of these terms, there are still considerable differences among companies and research groups involved in new drug discovery. As IUPHAR does not address this issue in its nomenclature recommendations (Neubig et al., 2003), we begin by referring to the definitions proposed by IUPAC (Buckle et al., 2013), which are quite similar to those adopted in high-quality reference articles on the subject (Bleicher et al., 2003; Hughes et al., 2011; Lombardino & Lowe III, 2004). According to the Glossary of Terms Used in Medicinal Chemistry (Buckle et al., 2013), a **HIT** produces reproducible activity above a predefined threshold (for example, some limit in terms of IC_{50} values) in a biological assay (such as a binding or enzyme inhibition assay) and has an established structural identity. Such substances generally arise from high-throughput screening (HTS) or other relatively large-scale primary assays (such as high-content assays in cell culture). Hits initially identified in a screening process are rarely marketable drugs, as they usually display only moderate affinity for the target, lack the desired selectivity, and do not possess adequate pharmacokinetic properties.

By contrast, a **LEAD COMPOUND** is a substance (or a series of substances) that meets predefined minimum criteria enabling further optimization of structure and activity (lead optimization). Typically, a lead compound demonstrates appropriate activity and selectivity, a tractable structure-activity relationship, and has its activity confirmed in a relevant cellular assay. It is worth noting that some authors consider that a substance should only be called a lead if it shows efficacy in an animal model of the target disease. Thus, it would be more appropriate to speak of "hit identification" and "lead discovery", since the transition from one to the other (hit-to-lead development) is a rational process involving the active participation of chemists and pharmacologists aimed at improving activity, for example after establishing structure-activity relationships to guide structural modifications. Some authors even argue that the term *"drug discovery"* should be replaced by *"drug invention"* to emphasize this aspect.

As the term "drug candidate" is not defined in the IUPAC glossary, we refer here to the definition proposed by Hefti (2008): an appropriate **DRUG CANDIDATE** intended to enter clinical testing is expected to bind selectively to the receptor site on the target to produce the desired functional response, to have adequate bioavailability and distribution to elicit the intended responses in animals and humans, and to have undergone formal toxicological evaluation in animals.

The transition period between a lead compound and a drug candidate is often referred to as the chaos zone, problem-solving period, or valley of death in the drug discovery and development process (Hefti, 2008).

References

Bleicher K.H., Böhm H.J., Müller K., Alanine A.I. Hit and lead generation: beyond high-throughput screening. *Nat. Rev. Drug Discov*. 2:369-378, 2003.

Buckle D.R., Erhardt P.W., Ganellin C.R., Kobayashi T., Perun T.J., Proudfoot J., Senn-Bilfinger J. Glossary of terms used in medicinal chemistry. Part II (IUPAC Recommendations 2013) *Pure Appl. Chem*. 85(8):1725-1758, 2013.

Drews J. Drug Discovery: a historical perspective. *Science* 287:1960-1964, 2000.

Hefti F.F. Requirements for a lead compound to become a clinical candidate. *BMC Neuroscience* 9 (Suppl 3):S7, 2008.

Hughes J.P., Rees S., Kalindjian S.B., Philpott K.L. Principles of early drug discovery. *Br. J. Pharmacol.* 162(6):1239- 1249, 2011.

Lombardino J.G., Lowe III J.A. The role of the medicinal chemist in drug research - then and now. *Nat. Rev. Drug Discov*. 3:853-862, 2004.

Neubig R.R., Spedding M., Kenakin T., Christopoulos A. International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. XXXVIII. Update on Terms and Symbols in Quantitative Pharmacology. *Pharmacol. Rev*. 55:597-606, 2003.