9. Selectivity vs. Specificity - Multi-target vs. Promiscuous Drugs

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Although there is no doubt about the difference between **selectivity** and **specificity** in pharmacology, misuse of these terms can still be found. For this reason, it seemed worthwhile to draw attention to this fundamental issue, which is crucial both for the appropriate use of a substance as a tool (e.g., for characterizing a signaling pathway) and for the selection of drug candidates within a drug development project.

DEFINITIONS

Here we adopt the definitions provided by Terry Kenakin (2014), one of the world's leading references in the quantitative study of drug-receptor interactions:

- **Selectivity:** the difference in activity that a given biologically active molecule has for two or more processes. Thus, the difference in activity is always relative rather than absolute; with sufficiently high dose/concentration, activation of the other process(es) will occur.

- **Specificity:** can be considered an extreme form of selectivity, in which no increase in the concentration of the molecule will be sufficient to activate the other process(es).

AND IN PRACTICE?

In a very pragmatic sense, specificity can be viewed as an extreme, almost utopian, case of selectivity. Accordingly, we may state that *"no drug produces a single, specific effect: drugs are merely selective, rather than specific, in their actions"* (Von Zastrow, 2012). Terry Kenakin (2014) goes further by stating that *"the term specificity is often used incorrectly because high concentrations have not been tested to define what is likely to be merely a case of selectivity"*.

HOW CAN THE SELECTIVITY OF A DRUG BE ASSESSED QUANTITATIVELY?

It is generally based on the relative affinity for the target receptor and for the "off-target" receptor, using the following ratio: $\boldsymbol{K_i}$ **(off-target) /** $\boldsymbol{K_i}$ **(target)** (Bowes et al., 2012), where K_i is the equilibrium dissociation constant of the drug for the receptor, measured in binding (competition) experiments and therefore the inverse of affinity. The same practice is recommended for the study of enzyme inhibitors during drug development (Copeland, 2005): *"The ratio of the dissociation constant (K_i) for an off-target enzyme over the dissociation constant for the target enzyme provides the best measure of selectivity for any substance"*.

Alternatively, it may be even more relevant to perform an integrated risk assessment, as suggested by regulatory agencies (ICH S7B). In this case, selectivity is quantified based on *in vitro* and *in vivo* data using the ratio between the IC_{50} value for the off-target in vitro and the maximum plasma concentration of the free fraction of the drug (Cmax) after administration of an effective dose (Bowes et al., 2012; Muller and Milton, 2012): $\mathbf{IC_{50}}$ **(off-target) /** $\mathbf{C_{max}}$.

WHAT LEVEL OF SELECTIVITY CAN BE CONSIDERED GOOD OR DESIRABLE?

The criteria depend on the nature of the off-target and therefore on the risk associated with its inhibition (or activation). A factor of at least 100-fold (K_i (off-target) / K_i (target)) may be considered sufficient for inhibition of hERG, one of the most dangerous off-targets, since inhibition of this K^+ channel is responsible for cardiac arrhythmias (StarDrop User Guide v5.5). For the same off-target (hERG), a selectivity of at least 30-fold may be considered reasonably safe when using the second criterion (IC_{50} (off-target) / C_{max}) (Muller and Milton, 2012).

On the other hand, one must also consider the risk-benefit balance, as done by the Food and Drug Administration when reviewing applications for marketing authorization. Thus, stricter criteria can be applied to treatments for less severe conditions than for diseases with a very poor prognosis if left untreated, such as AIDS and cancer.

MULTI-TARGET VS. PROMISCUOUS DRUGS

Pharmacological promiscuity can be defined as the property of a substance to display pharmacological activity at multiple targets. In this context, targets classically include both therapeutic targets and off-targets. Consequently, promiscuous drugs, sometimes referred to as "dirty" drugs, are generally undesirable, and pharmacological promiscuity is viewed as a potential source of adverse effects that compromises safety. As such, it is not desired in drug development projects (at least those "classic" ones focused on the "one drug-one target" paradigm coined by Paul Ehrlich). One way to quantify pharmacological promiscuity is to calculate the percentage of off-targets at which a substance shows more than 30% activity when tested at a concentration of 10 µM. If one wishes to restrict the analysis to cases of greater relevance, only off-targets at which the substance shows at least 90% activity can be considered (Peters et al., 2009).

By contrast, there is a growing view that modulating multiple targets may increase the chances of success in multifactorial diseases, such as psychiatric disorders, cancer, AIDS, and cardiovascular diseases (Roth et al., 2004; Lu et al., 2012). Such drugs are referred to as **multi-target drugs**.

References

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