A Quick Guide for Projects that Require Medicinal Chemistry

Small molecular weight compounds often require medicinal chemistry optimization to increase potency, but also to achieve physical properties that are suitable for *in vivo* testing. Since such optimizations are costly, candidate compounds must fulfil certain criteria to ensure that drug candidates can be produced within project timelines and budget.

Terminology

ID - identification

Hit vs Lead

A **hit** is a molecule that comes directly from either high-throughput-screening or virtual screening. Drug discovery is more likely to be successful if **the IC_{50} of a hit in a biochemical assay is <10 μM and/or the EC_{50} in a cellular assay is <5 μM**. Weaker compounds often lack structure activity relationships because of solubility limitations!

A **lead** is a compound that has been modified by medicinal chemists and shows a clear structure-activity relationship. Such compounds have been evaluated for solubility, permeability, and metabolism.

Virtual Screening

Virtual screening is an attractive technology for hit identification. However, it is important to understand that virtual screening software can only *estimate* the affinity of a compound for a protein target, which explains why hit rates are usually below 20%.[1] As a consequence **validation of virtual screening hits in a biochemical or biophysical assay is important**.

Compound Structure

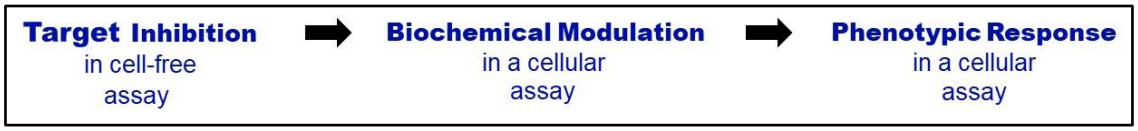
A hit or a lead compound **should not come from a compound class that has known liabilities**. A variety of scaffolds are well known for pan-assay interference[2] and cationic compounds often cause phospholipidosis.[3] Also avoid scaffolds that are known to be **multi-kinase inhibitors**, since selectivity will be very difficult to achieve and developing multi-kinase inhibitors is a challenge.

Knowing the Target

Target identification is becoming more important for drug discovery since the knowledge of biological mechanisms facilitates biomarker development. Knowing the target will also simplify the optimization of a compound and aid in the demonstration of its biological activity.

Assays

Modern drug discovery progresses compounds through three different types of assays, as shown below.[4] It is possible to avoid a cell-free assay, however such projects must use chemical biology techniques to demonstrate the biochemical modulation of a target in a cellular assay.



Selectivity

Selectivity is an important criterion to judge the attractiveness of a compound for drug discovery. **Unselective compounds often have potent cellular activity because multiple targets are inhibited** (this is especially true for kinase inhibitors). Multi-target inhibitors pose more challenges for drug development since unselective **compounds are more likely to show toxicity**.

Toxicity Assays

Physical properties must be optimized **before** compounds are assessed for toxicological liabilities. AMES, COMET, hERG and general cell toxicity assays are not informative if the compounds are not soluble at the tested concentrations. Do note also that cell toxicity data is more meaningful if several different cell lines are evaluated!

Tool Compounds

Tool compounds (also called chemical probes) are often produced to study the biological consequences of modulating a target in a cellular assay. Such compounds may not have all the necessary properties of a development compound, but they are often shaped by chemistry to answer specific biological questions (target engagement, selectivity, location in the cell etc.).

The following principles apply for tool compounds:[5]
A quality chemical probe should have: (1) sufficient potency and selectivity to confidently associate its *in vitro* profile with its cellular activity; (2) sufficient chemical and physical property data (e.g. permeability, stability) to ensure the quality of its cellular data; (3)

sufficient mechanistic data to confidently link its on-target effects in cellular assays with its phenotype.

References

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2. Tummino et al., *Science*, **2021**, 10.1126/science.abi4708
3. Baell et al., *J. Med. Chem*., **2010**, 53, 2719–2740
4. Copeland et al., *Cell Chem. Biol.*, **2018**, 25, 128-134
5. Frye S.V., *Nat. Chem. Biol*., **2010**, 6, 159-161

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