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# Chemical Probe Development to Produce Biomedicine

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## INTRODUCTION

A probe is a single-stranded sequence of DNA or RNA used to search for its complementary sequence in a sample genome. The importance of high-quality chemical probes has gained increased recognition in recent years, as they play a central role in understanding complex biological mechanisms and diseases, as well as in the drug discovery process. There are numerous excellent publications discussing the various aspects of chemical probe development and use. A recent chemical probe paper highlighting the promise and perils of chemical probes. Here we highlight some key takeaways from seminal chemical probe publications and discuss the value of chemical probes, criteria for building good chemical probes, including the importance of target engagement assays, as well as resources for identifying and using high quality chemical probes.

## DESCRIPTION

In addition to the central role of chemical probes in target validation, chemical probes are often used at later stages of drug discovery to help determine the clinical translatability of the target. At this later stage, probes are used in preclinical *in vivo* studies to aid the design of future clinical testing/monitoring. For example, chemical probes may be used to understand *in vivo* pharmacodynamics or identify biomarkers needed for clinical testing. This typically involves development of more specialized probes that have drug-like properties and fit the experimental need. Chemical probes need to possess specific properties to be useful for their intended purpose of addressing the role(s) of a protein target in complex biological contexts. Chemical probes must have high affinity for the intended target protein, good cellular potency, excellent selectivity over closely related target proteins and a known chemical structure and mode of inhibition. Guidance for some of these parameters is provided in the literature, such as <100 nM potency in a biochemical assay, <1 µM cellular potency and >30-fold selectivity over closely related proteins. The development of high-quality chemical probes with these properties requires extensive efforts that employ multiple methods. Some of these are outlined in the figure below, and include chemistry to make and optimize the probes, screening assays to identify potential probe candidates, structural studies to evaluate the binding mode of the chemical probe candidates and cell-based assays to show the probe engages the target in cells and has an effect on a cellular phenotype. One method utilized during chemical probe development warrants special attention.

## CONCLUSION

This is verifying target engagement in a cell-based assay, or the confirming that the chemical probe binds to the intended target in cells. The critical reason for measuring target engagement during chemical probe development was summarized nicely by Simon and colleagues. This is important as *in vitro* assays are frequently performed with only the protein domain of interest, rather than the full-length protein. The authors further advocated that the most valuable target engagement assays are those that: Report directly on the interaction between the chemical probe and target protein, rather than a distal measurement; and measure probe selectivity or the interaction of the probe with other related target proteins. Among the leaders in chemical probe development are scientists at the Structural Genomics Consortium (SGC), a not-for-profit, public-private partnership formed to aid in precompetitive drug discovery.

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