Retooling chemical probes

Increased transparency and consistency in reporting well-validated chemical probes will further enhance the impact of this exciting and rapidly advancing area of chemical biology.

In 2007, scientists from Sirtris Pharmaceuticals along with academic collaborators reported the identification of a series of compounds that activated SIRT1 *in vitro* and led to beneficial effects in mouse models of type II diabetes (*Nature* **450**, 712–716, 2007). It is widely believed that based at least in part on the discovery of SIRT1 activator compounds, GSK acquired Sirtris for $720 million in 2008 (*Nat. Biotechnol.* **26**, 595, 2008). Recently, a study from scientists at Pfizer has concluded that, in the absence of a fluorophore-modified peptide substrate used in the original assays, the reported SIRT1 activators did not activate SIRT1 *in vitro*. Further, the study reports that the compounds had many off-target activities and did not have the reported *in vivo* efficacy (*J. Biol. Chem*., published online 8 January 2010, doi:10.1074/jbc.M109.088682). Beyond any potential scientific implications, this paper has raised speculations in the blogosphere on the wisdom of the GSK acquisition of Sirtris (http://pipeline.corante.com/archives/2010/01/15/sirtuin_scenarios.php). Regardless of the ultimate resolution of this particular case, the story illustrates the high scientific and financial stakes that can rest on investigations of the *in vitro* and *in vivo* mechanisms of action of small molecules. In this light, the significant strides that chemical biologists are making in discovering high-quality chemical probes and in developing improved methods for characterizing the biological activities of small molecules are clearly not esoteric pursuits. In this issue, we feature Commentary and Review Articles that capture opinions and advances at the frontiers of chemical probe research. We also are announcing new formats for reporting small-molecule screening data and chemical probe information with the aim of increasing the transparency and utility of the data.

Potent, selective and cell-permeable small molecules that perturb a biological target in a dose-dependent manner can be used to dynamically 'probe' the role of the target in biology. However, the successful application of these 'tool compounds' remains challenging. Frye (Commentary, p. 159) proposes guidelines for high-quality chemical probes that can confidently be used to reach biological conclusions. Despite the extensive academic and industrial efforts focused on discovering kinase inhibitors, Knapp and colleagues (Commentary, p. 166) reveal a lack of inhibitors for a surprisingly large fraction of the human kinome. The authors highlight the immediate impact that chemical probes for these functionally unannotated kinases could have on drug discovery efforts. With an increased focus in the academic community on obtaining probes rather than drugs, constraints that make a compound 'drug-like' may no longer apply. In reconsidering small-molecule discovery from the probe perspective, Kodadek (Commentary, p. 162) puts forth the case for emphasizing simple chemistry, binding screens and covalent inhibitors to maximize the impact that 'probe hunters' have on biology. Collectively, these Commentaries highlight some ongoing discussions and emerging directions in the field.

Over the past few years there has been significant progress in expanding the targets and mechanisms of chemical probes, including in two areas that are reviewed in this issue. First, antibiotics targeting the bacterial ribosome have enabled important advances in understanding bacterial translation, yet relatively few analogous chemical tools were available for probing eukaryotic gene expression systems. Yoshida and colleagues (Review, p. 189) describe recent advances in identifying inhibitors of eukaryotic splicing and translation that are poised to impact our understanding of this fundamental aspect of biology. Second, the identification of small-molecule activators has recently become an important complement to the traditional focus on discovering inhibitors. Zorn and Wells (Review, p. 179) describe four mechanisms through which known activators work and discuss methods for identifying these "gain-of-function" probes.

Given their central role in discovering and developing new chemical probes, chemical biologists need to champion rigorous characterization and transparent reporting of chemical screens and chemical probe information. Because reporting of high-throughput small molecule screens varies widely, we have followed the community's lead (*Nat. Chem. Biol.* **3**, 438–441, 2007) and created a standardized system for reporting screening data in *Nature Chemical Biology* papers. Going forward, where applicable, we will ask authors to include an 'HTS Table' (for example, please see Supplementary Table 2 within Kokel *et al.*, p. 231) that provides readers with a concise summary of the screen. We believe that this step towards consistent reporting of screening data will be straightforward for authors to provide and will benefit the field.

As highlighted previously (*Nat. Chem. Biol.* **5**, 441–447, 2009 and *Biochem. J.* **425**, 53–54, 2010) and in this issue (p. 159 and p. 162), careful characterization of chemical probes is essential to ensure the rigor of biological conclusions. To increase the accessibility of information on tool compounds, we will publish a table summarizing the relevant *in vitro*, cellular and (if available) *in vivo* results for new chemical probes described within the journal. This 'Chemical Probe Table', which will be provided by authors and verified by referees, will be made freely available on the journal website and associated with the online version of the paper. Please see http://www.nature.com/nchembio/chemical_probes for an example from Bradner *et al.* (Article, p. 238). We hope these open-access summaries will provide a valuable community resource that encourages the informed use of probes.

With an increasing number of investigators discovering and using chemical probes, we have seen a steady rise in submissions in this area. As a result, selecting which papers to consider for publication has become increasingly challenging. With the aim of continuing to publish high-impact and well-validated chemical probe studies, we particularly seek papers that report high-quality probes of previously intractable targets, provide evidence for novel mechanisms of activation or inhibition, or gain significant new mechanistic insight into biology through the use of tool compounds. We also welcome submission of important new methods for discovering or characterizing small-molecule probes and their targets. We look forward to continuing to publish the highest impact chemical probe research—reported with increased consistency and transparency—to support the efforts of chemical biologists to expand the 'probeable genome'. ■