Probing questions

Chemical probes are proven tools for biological research and early-stage drug development, but how can chemical biologists make them more useful to the broader scientific community?

Chemical probes, small molecules that specifically bind and potently modulate the activity of a discrete cellular target, are archetypal tools of the trade for chemical biologists. Quality chemical probes are high-value reagents for biological discovery that are orthogonal to many molecular biology and genetic approaches and permit the precise molecular-level interrogation of biological targets and their associated pathways (*Nat. Chem. Biol.* **1**, 64–66, 2005). Furthermore, chemical probes bridge basic and translational research in a unique way by providing potent pharmacological tools for validating clinical target candidates (*Nat. Chem. Biol.* **9**, 195–199, 2013) and, at the same time, offering chemical starting points that can be further optimized by medicinal chemistry for drug development.

Past successes in chemical probe development have underscored the utility of high-quality chemical probes in basic and biomedical research (*Nat. Chem. Biol.* **6**, 159–161, 2010; *Chem. Biol.* **17**, 561–577, 2010). Yet chemical biologists need to provide ongoing leadership to ensure more effective use of these probes by the scientific community. As highlighted in several articles in the current issue, chemical biologists need to sustain their traditional role as collaborative developers of high-quality chemical probes, but they must also expand their remit to become innovators in under-probed biological systems, advocates for chemical probe quality standards and mentors for less experienced users of these powerful but specialized research tools.

Chemical probe efforts over the past decade have targeted numerous protein classes and biological pathways. For example, protein kinases (*Nat. Chem. Biol.* **9**, 3–6, 2013), G protein–coupled receptors (*Nat. Struct. Mol. Biol.* **22**, 362–369, 2015) and proteostasis pathways (*Nat. Chem. Biol.* **10**, 870–874, 2014) have received substantial attention in recent years. In a Commentary in this issue (p. 542), Schapira and colleagues focus on the enabling potential that chemical probes will have for investigations of the epigenome. In fact, significant progress is already being made in this area, reflected in recent reports of high-quality chemical probes for several classes of chromatin-targeted proteins.

The cell provides an expansive landscape of undercharted biological space awaiting exploration with chemical probes; in the coming years, tools directed against these new targets are likely to have significant impacts in basic and translational research. For instance, will potent chemical modulators of plant signaling pathways have real-world agricultural applications? Could we conceive of new chemical probes that specifically disrupt protein-protein interactions in membranes or in macromolecular complexes involved in diverse cellular processes such as transcription, RNA processing, translation, respiration or biosynthesis? Perhaps it is time to move beyond proteins and develop chemical probes that target other important cellular biomolecules, including nucleic acids and carbohydrates? Conversations between current developers and potential users can help point to yet other systems where probes would be particularly desirable.

To effectively channel the community's enthusiasm for new chemical probes for more diverse target classes, researchers must be cognizant of several important realities. First, existing high-quality chemical probes have typically been developed in a time- and cost-intensive practice involving cross-disciplinary teams of scientists with expertise spanning traditional academic and industrial roles. Thus, researchers who are serious about probe development need to be open to broader collaborations that provide the infrastructure, resources and scientific know-how required for success. Second, chemical probe developers need to help create and administer standards to ensure that new chemical probes deliver robust and reproducible biological results. This requires that all participants in the probe development pipeline become familiar with relevant experimental reporting standards to ensure that their data support a broader network of scientists. As an illustration of these contingencies, a Correspondence by Tropsha (p. 535) highlights the critical need for experimentalists involved in chemical screening to think carefully about the cheminformatic endpoints of their studies.

This call for greater communication and adherence to chemical probe standards during all stages of chemical probe development and usage is the centerpiece of a Commentary in this issue (Edwards, p. 536) by an experienced group of academic and industrial scientists. The authors review examples of high-quality probes that have yielded key biological, and in some cases clinical, insights. In parallel, they present cases from the literature that report misleading results derived from experiments using probes of lesser quality or, alternatively, using high-quality probes improperly. On the basis of this historical analysis and their combined expertise in chemical probe development and in mentoring colleagues and collaborators outside the chemical biology community on the proper use of chemical probes, the team offers specific recommendations to expand the reach of chemical probes.

Edwards and colleagues call for greater rigor and accountability not only in the development and application of chemical probes, but also during peer review. They urge all scientists involved in the evaluation of grant proposals and scientific manuscripts that make use of chemical probes to ensure that they meet basic quality requirements. To support this, the authors put forward a set of questions that define standards for reporting high-quality chemical probes (see Box 1, p. 540). Many of these considerations have been on our list of editorial criteria for evaluating chemical probe papers at *Nature Chemical Biology* for a number of years, and we strongly encourage other journals and funding agencies to adopt these standards as they evaluate submissions focused on chemical probe development or application.

The authors (p. 536) also recognize that guidelines are not always enough and have created an open community resource, the Chemical Probes Portal (http://www.chemicalprobes.org/), to aggregate and disseminate expert knowledge on chemical probes. Researchers will be able find the best current chemical probe for a given target alongside relevant compound data and application guidelines for its use. This dynamic site will be maintained by the founders, but the site's utility and impact will ultimately be determined by its community of users. The chemical probe aficionados at *Nature Chemical Biology* will certainly participate, and we hope that you will join us in making the Chemical Probes Portal a valuable resource to support chemical probe efforts in the future! ■