nature chemical biology

Frontiers in drug discovery

Integrating chemistry and biology in the search for the next generation of therapeutics.

The 'traditional' view of drug discovery involves a linear process of identifying and validating a target, generating a lead molecule, optimizing its properties and then proceeding to preclinical and clinical studies. In this scheme, the biologists take the lead in identifying and validating a target. The chemists subsequently look for potent small-molecule inhibitors, most often through optimization of lead compounds from high-throughput screening. In this issue we highlight how this linear process of drug discovery has been twisted about through a closer integration of chemistry and biology along the path to creating the next generation of therapeutic agents.

Basic advances at the interface of chemistry and biology, such as RNAi and high-throughput compound screening in living organisms, have created an important foundation that can be used in the search for new therapeutics. In his Commentary, Tomi Sawyer (p. 646) calls for a move toward 'smart drug discovery', in which teams of chemists and biologists take advantage of the new information and tools available to more rationally develop interventions for targeting the complex biology of diseases such as diabetes and neurological disorders. In a Review article, Ian Collins and Paul Workman (p. 689) describe how the integration of chemistry and biology can be used specifically in the development of cancer therapeutics. They envision a drug discovery process in which chemical biology and structural biology have the central role.

Two Perspective articles in this issue remind us of biology as a resource for small-molecule drug discovery and development. Interest in natural products has substantially declined as high-throughput screening has emerged as the major source of drug leads. William Fenical and Paul Jensen (p. 666) highlight the rich chemical diversity that has been found in marine bacteria and the important place of natural products in drug discovery. As a drug candidate advances, an efficient synthetic route is critical for producing the large amounts of a small molecule needed for preclinical and clinical trials. However, for complex small molecules, producing even small amounts can be difficult or impossible. Using artemisinin and Taxol as examples, Michelle Chang and Jay Keasling (p. 674) describe the recent advances in metabolically engineering bacteria and yeast to produce synthetically intractable drugs.

Alternatives to small-molecule drugs are becoming increasingly important in treating diseases. For instance, in oncology, antibodies have made a significant impact over the last decade. Although biology clearly plays a central role in generating biological therapeutics, two articles in this issue highlight the roles chemistry can play in tinkering with these biological molecules. Sachdev Sidhu and Frederic Fellouse (p. 682) describe advances in generating antibodies *in vitro* and the potential role of protein engineering in producing therapeutic antibodies that rival the diversity and function of those created by the immune system. Since its discovery in 1998, RNAi is now recognized as a widespread regulator of *in vivo* protein expression. Bumcrot *et al.* (p. 711) describe the progress towards generating therapeutic RNAi and the recent results from clinical trials as this new biological drug is poised to enter the clinic. Chemical modifications have been shown to be critical for improving the pharmacological properties of RNA, emphasizing the importance of closely combining chemistry and biology for generating new therapeutic molecules.

Beyond emphasizing the importance of a synergy between chemistry and biology in drug discovery, several articles in this issue highlight the important roles of both academic and industrial scientists in creating new drugs. RNAi is a good example of a basic scientific advance that has rapidly led to a new pharmaceutical approach. In many cases, more explicit academic-industrial collaborations have been instrumental in generating drugs. In a Commentary, Nathanael Gray (p. 649) describes some successes forged through academic-industrial partnerships and illustrates areas in which academic and industrial scientists are able to make important contributions to the drug discovery process. For some diseases, including many that are a significant global health burden, the limited potential financial return has prevented the pharmaceutical industry from taking an interest in developing needed medicines. Adam Renslo and James McKerrow (p. 701) describe how the recent formation of consortia of academic and industrial scientists, driven in large part by increased philanthropic funding, is making progress toward filling the gap in the pipeline of antiparasitic drugs.

What role does chemical biology have in drug discovery? It is important to note that not all chemical biologists are engaged in drug discovery. Many are focused on making basic advances in understanding the molecular workings of chemistry and biology. For instance, in a News and Views article in this issue (p. 663), Stephen Michnick highlights a new gene expression profiling method for investigating the global effects of small molecules on cells. Advances such as these provide fundamental scientific insights that can have practical applications in drug discovery.

As the content of this issue clearly highlights, scientists at the interface of chemistry and biology have been instrumental in directly developing new paradigms in drug discovery. With the move toward integrating chemistry and biology, it is perhaps not surprising to see that chemical biologists are in a unique position to contribute to this multidisciplinary drug discovery enterprise. Advances in drug discovery that define new approaches to drug discovery or generate new biochemical or biological understanding have particularly far-reaching effects. We are pleased to spotlight the significant breakthroughs being made by chemical biologists in the search for new drugs. ■