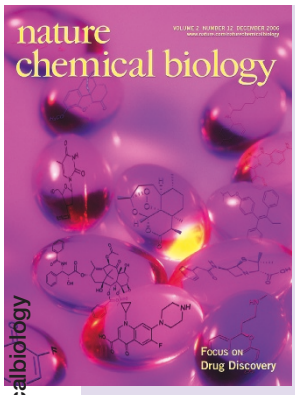


FOCUS ON DRUG DISCOVERY

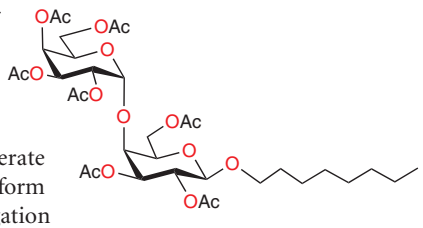
With the dramatic increase in genomic and proteomic information, as well as increasingly powerful biological and chemical tools for probing *in vivo* biology, scientists looking to develop new drugs have many new resources at their disposal. Tomi Sawyer [**Commentary, p. 646**] addresses the opportunity to translate these advances into 'smart' drug discovery. As highlighted by Nathanael Gray [**Commentary, p. 649**], collaborations that capitalize on the scientific strengths of academic and industrial research in these new technologies offer one important way to successfully advance drug discovery.

Chemically complex small molecules have the potential to be highly specific and potent drugs. However, as addressed in several pieces in this issue, this increased complexity presents correspondingly greater challenges during many stages of the drug discovery process. Although natural products from soil bacteria have traditionally been an important source for identifying drug leads, alternative sources are now needed to reinvigorate natural product–based drug discovery efforts. Fenical and Jensen [**Perspective, p. 666**] put forth the case for marine bacteria as a valuable new source of diverse chemical structures. Another approach to identifying complex small-molecule drug leads is fragment-based drug discovery, in which simple, low-affinity inhibitors are attached together to generate more complex and potent inhibitors. By dissecting a known β-lactamase inhibitor, Babaoglu and Shoichet find that the simple assumption of modular construction in assembling fragments does not always hold true [**Letters, p. 720; News & Views, p. 658**]. Chang and Keasling [**Perspective, p. 674**] outline recent progress in the use of bacteria and yeast as factories to produce isoprenoid drugs, thereby addressing the important challenge of industrial-scale production of natural products.

Developing new therapeutics for unmet medical needs continues to be an important focus of drug discovery efforts. Collins and Workman [**Review, p. 689**] discuss the bottlenecks in developing new cancer therapeutics and propose an integration of chemistry and biology to decrease the time from target identification to having a finished drug. A continuing challenge is developing treatments for illnesses that are a public health burden but are not being pursued by pharmaceutical companies. Renslo and McKerrow [**Review, p. 701**] discuss recent progress in antiparasitic medicines, which has been catalyzed by increased philanthropic funding and the formation of academic-industrial consortia. An interview with Stuart Levy, director of the Center for Adaptation Genetics and Drug Resistance at Tufts University and president of the Alliance for the Prudent Use of Antibiotics, [**Elements, p. 655**] highlights the challenges of maintaining a steady supply of effective therapies for bacterial infections, and a discussion with Marlene Haffner, director of the US Food and Drug Administration's Office of Orphan Products Development, [**Elements, p. 657**] addresses the challenges in developing drugs for rare diseases.

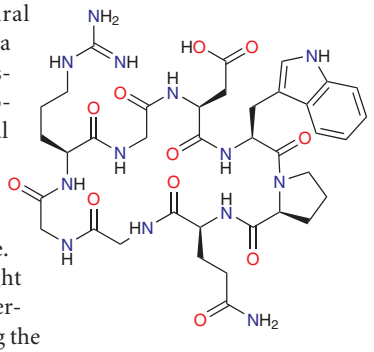
Alternatives to small-molecule therapeutics have been making progress in clinical trials and in the clinic. Monoclonal antibodies have made a significant medical impact, particularly in oncology. Sidhu and Fellouse [**Perspective, p. 682**] discuss antibodies generated *in vitro* as a potential new source of therapeutic antibodies. RNAi represents a potential new class of therapeutic molecules, and Bumcrot *et al.* [**Review, p. 711**] discuss efforts to advance RNAi into the clinic. *JK*

Sugar connections



Making complex oligosaccharides remains a considerable synthetic challenge, and the development of more facile ways to generate oligosaccharides in pure form would aid in the investigation of the biological roles of glycosylation. Lairson *et al.* now demonstrate the use of glycosyltransferases to generate a variety of disaccharides. In contrast to the expected stringent substrate specificity, the LgtC α(1-4)-galactosyltransferase was able to transfer a variety of non-natural substrates to either an equatorial or axial hydroxyl on the acceptor sugar. Using a 'substrate engineering' approach in which alkyl or aryl substituents were attached to the acceptor sugar, the enzyme was directed to catalyze the formation of α(1-2), α(1-3) and α(1-4) linkages. The production of single regioisomers at catalytically useful rates represents an important step in oligosaccharide biosynthesis. [**Letters, p. 724; News & Views, p. 659**] *JK*

Libraries made to order



Some peptide-based natural products are encoded by a genetic sequence and translated like proteins at the ribosome. As a result, potential mechanisms to incorporate structural diversity into these classes of compounds are limited by the genetic code. Donia *et al.* now provide insight into one mechanism for diversity generation by investigating the DNA encoding the patellamides, a group of modified cyclic peptides. They discovered small, hypervariable cassettes within a multienzyme biosynthetic pathway that are similarly expressed and processed to create a library of compounds. Hypothesizing that the associated tailoring enzymes must already tolerate great diversity in their substrates, the authors further demonstrated that a new compound could be produced by genetically reprogramming one of the cassettes. This discovery provides clues to the evolution of the patellamides and a new biosynthetic tool for the production of cyclized peptides. [**Letters, p. 729; News & Views, p. 661**] *CG*

In This Issue written by Catherine Goodman and Joanne Kotz