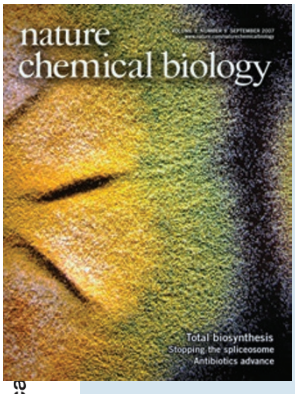
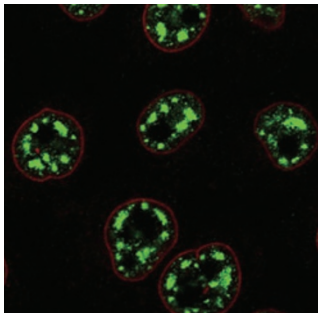


Biosynthesis *in vitro*

Compared to metabolic engineering, reconstituting biosynthetic pathways *in vitro* offers potential advantages, such as better-defined conditions for natural product synthesis. In this issue, Cheng *et al.* report the total *in vitro* synthesis of enterocin from benzoic acid and malonyl coenzyme A starter units. The reconstitution, which proceeded in ~25% overall yield, involves an aromatic polyketide synthase pathway that includes 12 purified proteins, the formation of 7 chiral centers, and a Favorskii-like rearrangement. Also in this issue, Balibar *et al.* report the full *in vitro* biosynthesis of the bisindole alkaloid fungal natural product terrequinone A, which is formed through a mixture of nonribosomal peptide synthesis and isoprenoid biosynthesis pathways. The *in vitro* reconstitution of this five-protein pathway revealed a number of interesting components, including a unique thioesterase domain that catalyzes carbon-carbon bond formation and a single prenyltransferase that catalyzes two successive prenylation reactions. *In vitro* biosynthesis of these natural products has set the stage for the increased mechanistic understanding of these intriguing enzymatic transformations, as well as providing an opportunity for biosynthetic engineering of these natural product pathways. [**Brief Communications, p. 557; Articles, p. 584; News & Views, p.531**] *JK*

Splicing stopped



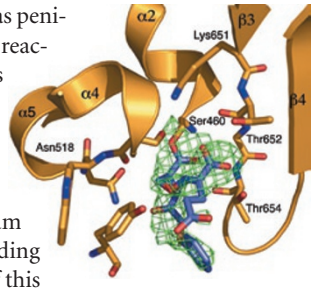
The spliceosome, which carries out the splicing of pre-mRNA to translatable mRNA, is a complex biological machine composed of several distinct ribonucleoprotein subunits, termed U1–U6. Although many details of splicing are understood, the full determination of the role of each subunit within and external to the splicing machinery remains to be done. Now two natural products, both previously isolated from bacterial sources and identified as potential anticancer compounds, have been shown to inhibit the spliceosome, and in particular to target SF3b, a portion of the U2 subunit. Both Kotake *et al.*, working with pladienolides B and D, and Kaida *et al.*, investigating FR901464 and its derivatives, observed an inhibition of the splicing of several transcripts as well as a reorganization of the intracellular location of spliceosomes. The study by Kaida *et al.* goes on to demonstrate a role for the spliceosome in retaining unspliced RNA in the nucleus, and suggests one potential route by which cell death may be occurring in response to these compounds. These studies not only provide chemical probes for determining spliceosome assembly and function but also point to a potential new mechanistic target for drug design. [**Letters, p. 570; Articles, p.576; News & Views, p. 533**] *CG*

Written by Catherine Goodman & Joanne Kotz

One sugar to rule them all

Glycolipids serve as important stimulators of the immune system, but detailing key molecules involved in immune responses has been challenging because researchers are often limited to membrane extracts or other potentially impure natural sources. In particular, bacterial glycosphingolipids are known to activate natural killer T cells, but it has been unclear whether the activation is caused by one or more of the glycosylated substrates. Long *et al.* now use a highly convergent synthetic scheme to prepare four of these complex compounds, ranging from mono- to tetrasubstituted glycolipids. They find that, of the pure compounds, only the monosubstituted lipid activates T cells, a result that can be explained by their observation that the more complex glycolipids are not processed by lysosomal glycosidases. This study highlights the complexity of natural sources and underscores the importance of examining individual molecules in determining biological function. [Letters, p. 559] *CG*

Alternative antibiotics



The most common antibiotics, such as penicillin, contain a β-lactam ring as their reactive motif. Extensive resistance to this chemical functionality, however, has long since prompted the search for antibiotics that employ novel architectures. Lactivicin, a natural product that does not contain a β-lactam ring, is able to inhibit penicillin-binding protein (PBP), but the mechanism of this inhibition, and whether the molecule bypasses β-lactam resistance, are not known. Macheboeuf *et al.* now demonstrate that lactivicin is an effective antibiotic against isolated β-lactam–resistant strains. Crystal structures of inhibitor-protein complexes reveal a remarkable similarity between the bound conformation of these and traditional β-lactam–based inhibitors, and further indicate that inhibition is likely to proceed in a two-step process, with the final, covalently bound molecule being stabilized by the oxyanion hole. This study highlights the unique structural organization of lactivicin that facilitates enzyme inhibition and points toward the development of future antibiotics. [**Letters, p. 565**] *CG*

Antibiotic alternatives

The threat of antibiotic resistance continues to increase, and resistance to the few new classes of antibiotics has rapidly emerged. As a result, there is a need to move beyond traditional approaches to antibiotics. In this issue, two review articles describe alternative paradigms for developing therapeutics to treat bacterial infections. Antibiotics have typically targeted cellular pathways that are essential for bacterial viability. Clatworthy *et al.* describe progress toward developing antibiotics that inhibit proteins required for infection but not for growth. Besides expanding the scope of potential antibiotic targets, inhibiting nonessential proteins may reduce the rate at which resistance develops. In an alternate strategy for reducing resistance, Smith and Romesberg discuss advances in understanding the pathways involved in bacterial acquisition of resistance and the potential to prolong the life of antibiotics by inhibiting these adaptation mechanisms. [Review, p. 541; Review, p. 549] *JK*