IN THIS ISSUE

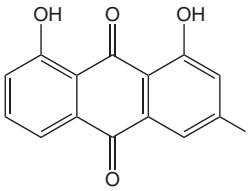
COVER STORY

The activation of the G protein–coupled receptor β2-adrenergic receptor (β_2-AR) is accompanied by at least one conformational intermediate and potentially more than one molecular switch, including an 'ionic lock' that holds together two of the transmembrane domains until receptor activation and a 'rotamer toggle switch' that modulates helix conformation around a conserved proline kink. By disrupting the ionic lock with a range of full and partial agonists, Yao *et al*. showed that the ionic lock and the rotamer toggle switch independently activate distinct regions of β_2-AR, with both switches being required for full receptor activation. Therefore, depending on what molecule is used to activate the receptor, its output is tuned by unique combinations of switches. **[Letters, p. 417; News & Views, p. 395]** *MB*

S1P signaling revealed

Lipids are frequently viewed as passive components of biological membranes that define cellular and organellar boundaries. However, ongoing research has shown that in addition to this, lipids are actively engaged in cellular processes. Sphingosine-1-phosphate (S1P) is known to regulate immune cells, but the molecular details of its actions have been obscured by its involvement in numerous signaling pathways. In this issue, Sanna *et al.* describe a synthetic analog, called W146, that is an S1P antagonist of the $S1P_1$ receptor subtype. W146 was constructed by replacing the phosphate group of S1P with a phosphonate linkage. The hydrolytic stability of W146 under physiological conditions allowed the authors to provide *in vivo* evidence that links antagonism of $S1P_1$ with enhanced leakage of plasma proteins from the blood and greater migration of lymphocytes into the bloodstream from primary tissues. **Articles, p. 434; News & Views, p. 396]** *TLS*

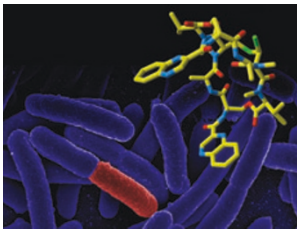
Which way to form?



The polyketide chrysophanol is a common defensive anthraquinone compound made in diverse organisms including leaf beetles, fungi and flowers. Bringmann *et al.* now show that chrysophanol is also made in the soil bacterium *Nocardia*. Because most polyketide biosynthetic pathways are confined to either prokaryotes or eukaryotes, chrysophanol is unique in its wide distribution and can thus be used to examine biosynthesis across kingdoms. By monitoring the incorporation pattern of ^{13}C-labeled acetate, the authors found that of four different possible synthetic modes for generation of the tricyclic core structure, fungi and plants use the so-called "F" mode that has been defined for fungi, whereas the bacterium uses a new "S'" mode. These results point toward the existence of divergent synthetic pathways to the same polyketide across biological kingdoms. [Letters, p. 429] *MB*

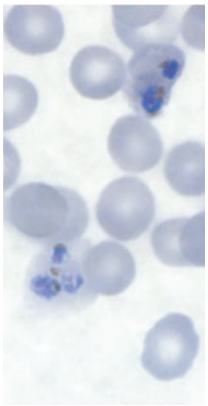
In This Issue written by Mirella Bucci, Kaspar Mossman and Terry L. Sheppard

An antibiotic factory



Expanding the scope of cellular biochemistry has been an important aim for chemical biologists. Manipulation of an enzymatic assembly line at the genetic level offers an attractive way for biosynthetic engineers to reprogram the metabolic machinery of a cell. Unfortunately, certain organisms known to produce chemically interesting natural products can be difficult to manipulate genetically or in cell culture. Watanabe *et al.* now report a method that allows the transplantation of a non-native biosynthetic pathway into *Escherichia coli*. The authors demonstrated that *E. coli* could be engineered to synthesize echinomycin, a nonribosomal peptide, by heterologous expression of the biosynthetic pathway. These engineered bacterial strains also provided a tool for testing biosynthetic mechanisms: the authors showed that Ecm18 catalyzes an unusual transformation of a disulfide bond to a methyl thioacetal, which is found in echinomycin. **[Letters, p. 423; News & Views, p. 398]** *TLS*

Malaria pipeline redirected



As a result of infection with *Plasmodium falciparum*, the malaria parasite, heme molecules from the blood of victims become crystallized, causing destruction of red blood cells. Some antimalarials, such as chloroquine, inhibit this heme crystallization step. Chong *et al.* examined the ability of over 2,600 known compounds in advanced stages of development for their ability to inhibit growth of *P. falciparum*. This medium-throughput screen yielded several compounds with antimicrobial and antimalarial properties, including the antihistamine drug astemizole. Astemizole inhibited heme crystallization and reduced parasitemia in mouse malaria models by a mechanism that seems to be distinct from that of chloroquine, indicating that it could be useful against the chloroquine-resistant malaria strains that are prevalent in malaria-endemic countries. [Brief Communications, p. 415] *MB*

The machinery of iron regulation

Iron concentration and metabolism are controlled in mammalian cells by iron regulatory proteins 1 and 2 (IRP1 and IRP2), which bind to iron-responsive elements (IREs) in the mRNAs of ferritin and the transferrin receptor. Rouault reviews the relationship between IRP structure and IRE binding, the function of an iron-sulfur switch in IRP1, and how dissolved oxygen explains why IRP2 dominates physiological iron regulation, even though IRP1 and IRP2 originated from a duplicated gene. **[Perspective, p. 406]** *KM*