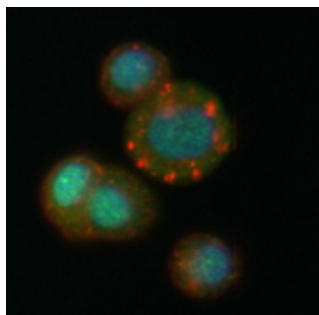


## Riboswitch that Senses the Tetrahydrofolate

PAGE 681

The ongoing discovery of numerous bacterial riboswitch classes that sense metabolites and control gene expression is revealing the extent to which modern organisms entrust RNA to carry out important chemical sensing and regulation tasks. Breaker and coworkers now report the discovery of riboswitches that sense the ubiquitous coenzyme tetrahydrofolate (THF). This coenzyme is used by many protein enzymes involved in single-carbon metabolism, including those critical in fundamental pathways such as nucleotide and amino acid biosynthesis.



## Chemoproteomics Leads to Hsp90

PAGE 686

A chemoproteomics-based drug discovery approach was employed by Fadden et al. to identify inhibitors of the purine binding proteome. The methodology couples a sepharose affinity resin, mass-spectrometry-based protein identification, and a focused chemical library. Tissue lysates were screened to identify over 1500 ligand-purine protein interactions. In particular, novel inhibitors of Hsp90 were identified, and the potential of the method is demonstrated by the ability to optimize one of the hits to a drug candidate for clinical testing.

## Exploring the Epigenetics Space

PAGE 695

Among a myriad of posttranslational modifications of chromatin, histone lysine methylation and demethylation catalyzed by protein lysine methyltransferases (PKMTs) and demethylases (PKDMs), respectively, have received significant attention because of their essential function in many biological processes including gene expression and transcriptional regulation, heterochromatin formation, and X-chromosome inactivation. To better enable chemical exploration of these enzymes, Wigle et al. have developed a novel and highly quantitative microfluidic capillary electrophoresis assay to permit full mechanistic studies of these enzymes and to demonstrate its ability to rigorously characterize their inhibition.

## Modules in PKS Communication

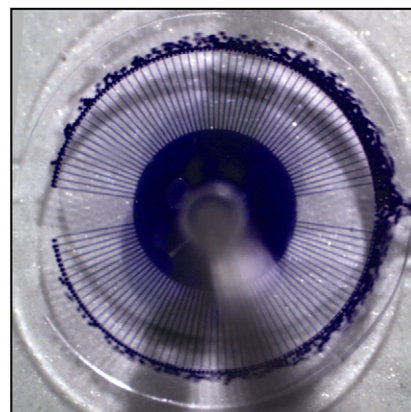
PAGE 705

Modular polyketide synthases (PKSs) are molecular scale assembly lines which generate natural products via the successive action of sets, or “modules,” of catalytic domains. During the construction process, polyketide chains remain attached to small, noncatalytic domains called acyl carrier proteins (ACPs). Thus, the details of how ACPs interact with the enzymatic domains are central to understanding these important biosynthetic factories. Using a multidisciplinary approach, Tran et al. have investigated how a model polyketide-ACP domain communicates with its thioesterase partner. These experiments reveal a fundamental mechanistic difference between PKSs and a second class of modular enzymes, the nonribosomal peptide synthetases (NSPSs).

## Evolving RNA Enzymes in Microfluidic Compartments

PAGE 717

Chemists and biologists make use of water-in-oil emulsions as a means to generate artificial “cellular” compartments that can be used to study molecules in isolation. The emulsions usually are prepared in mayonnaise-like fashion by whipping together water and oil phases, although this results in water droplets that are highly variable in size. Employing microfluidic technology, it now is possible to generate “perfect” mayonnaise, consisting of tens of millions of uniformly sized droplets. As shown by Paegel and Joyce, such droplets were used to carry out compartmentalized molecular evolution of a population of RNA enzymes that developed resistance to inhibition by an aminoglycoside antibiotic.



## Laulimalide-Microtubule Binding Mode

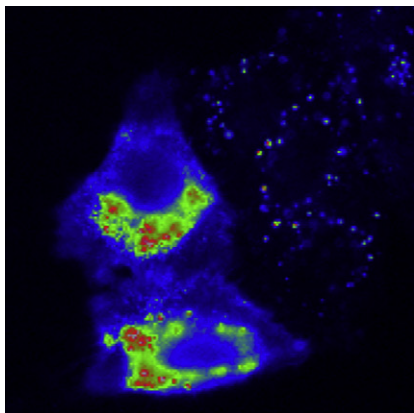
PAGE 725

This study by Bennett et al. defines the location of a fourth distinct ligand binding site within  $\alpha/\beta$ -tubulin, an important anticancer protein target. The laulimalide site joins the ranks of the colchicine, vinca, and taxol binding sites, bearing properties that directly couple into microtubule stability. However, the laulimalide site is unique in its exposure to the outside surface of the microtubule. The binding mode shows the penetration of the ligand side chain into a deep, narrow cavity through a conformation akin to a “striking cobra.” This mode helps define a pharmacophore model and reveals the importance of the C1-C15 axis in the macrocycle.

## Cell Penetrating Peptides Goes for the Kill

PAGE 735

Cell-penetrating peptides (CPPs) that traverse the extracellular cell membrane can deliver bioactive agents to inaccessible intracellular targets. Moreover, CPPs with intrinsic biological activities possess utility for the more direct modulation of cellular function. Here, Jones et al. show that CPP sequences identified within the Cytochrome c protein (Cyt c) induced tumor cell apoptosis, thus mimicking the role of Cyt c as a key regulator of programmed cell death. One such peptide, Cyt c77-101, was selected to incorporate additional target-specific peptidyl motifs designed to interrupt the function of pores within the nuclear membrane. These studies further identified a chimeric CPP with significantly enhanced cytotoxic potency.



## More FRETing: Reversibly Photoswitchable RFP

PAGE 745

Subach et al. have developed the first reversibly photoswitchable red fluorescent protein, named rsTagRFP. During illumination of rsTagRFP with light, it changes its color in daylight from pink to yellow and vice versa. Due to this feature, rsTagRFP, in a combination with yellow fluorescent protein EYFP, can be used for regulation of a Förster resonance energy transfer (FRET). The FRET between rsTagRFP and EYFP disappears as a result of a prolonged illumination with yellow light, and it appears again after a short pulse of blue light. The authors have demonstrated this photoswitchable FRET in live cells for determination and validation of protein-protein interactions.

## Riboswitch Sensing B12 Metabolism

PAGE 756

Detecting the abundance of a small molecule of interest within living cells presents a significant challenge. In the study by Fowler et al. (pp. 756–765), RNA regulatory elements known as riboswitches are assessed for their ability to carry out this task within the bacterial organism *E. coli*. Highly sensitive and specific sensors were constructed that detect coenzyme B12, a factor required in specialized types of metabolism. The sensors were successfully employed to monitor the metabolism and transport of coenzyme B12, demonstrating their utility in biological research. This work highlights the possibility of using riboswitch sensors to easily monitor a wide range of cellular metabolites and processes.

## Impaired HIV-1 infection by Rigidifying Membrane Domains

PAGE 766

HIV-1 assembles the receptors and lipids it needs for host-viral membrane fusion by co-opting the lateral organization of the plasma membrane. This “smart” HIV-1 infection strategy can also be its Achilles’ heel, however, as it offers a way to interfere with virus entry into the cell. Vieira et al. show that inhibitors of dihydroceramide desaturase increase rigidity of biological membranes and reduce HIV-1 infection.

## Acyl Carrier Protein One Step at a Time

PAGE 776

Despite its well-studied role as a carrier protein, there are no examples of type II fatty acid ACP structures with bound intermediates other than fully saturated fatty acid chains. Access to ACPs with bound moieties from a full cycle of fatty acid biosynthesis is complicated by the need for synthesis of the individual intermediates and successful loading onto the ACP. Płoskoń et al. present five high-resolution NMR structures of the *S. coelicolor* FAS ACP over a full round of the fatty acid cycle and examine how the ACP responds to the chemical nature of the attached intermediate.

