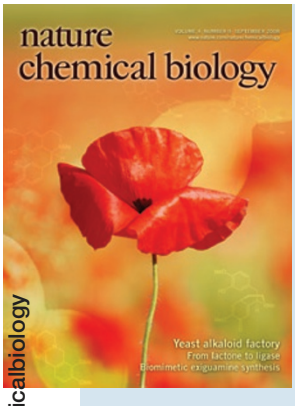
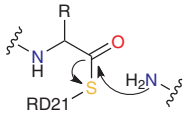
IN THIS ISSUE



Fine-tuning alkaloid production

The benzylisoquinoline alkaloids (BIAs) are a diverse group of plant metabolites that have a wide range of pharmacological activities; however, obtaining useful amounts of these compounds from natural sources has been difficult, and their molecular complexity has precluded chemical synthesis. To gain access to these structures, Hawkins and Smolke sought to reconstruct the BIA biosynthetic pathway in yeast. Using three enzymes from two plant species, they engineered yeast to produce the BIA pathway branch point intermediate reticuline from the commercially available norlaudanosoline. To optimize BIA enzyme expression levels, they used a titration strategy that allowed the concentration of each enzyme to be 'tuned' independently. After optimization, the authors demonstrated the broad potential of their yeast strains by expressing additional enzymes (including a human cytochrome P450) to synthesize several downstream BIA metabolites. [**Articles, p. 564; News & Views, p. 524**] *KS*

Will the real enzyme please stand up?



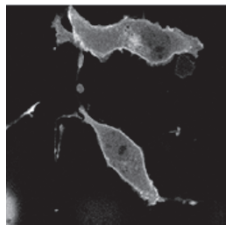
Activity-based probes are powerful tools for profiling the presence of or perturbations to enzyme classes within whole cells. Proteases are particularly well suited for this method, as the general enzyme mechanism is known but the specific function of each protein is less clear. To gain insight into the proteases in *Arabidopsis thaliana*, Wang *et al.* developed a series of β-lactone probes that target six known papain-like cysteine proteases (PLCPs) and related proteases. Surprisingly, application of these probes resulted in labeling of several proteins with no resemblance to proteases. Further investigation identified RD21, a known PLCP, as a transpeptidase capable of ligating the ring-opened lactone (and other substrates) onto the N termini of other proteins. The existence and identity of any endogenous substrates of this reaction remain to be discovered. [**Articles, p. 557; News & Views, p. 525**] *CG*

An orphan receptor gets an agonist

The nuclear orphan receptor Nur77 is a transcription factor with roles in apoptosis and glucose homeostasis. Though it contains a ligand binding domain, no physiological ligands for Nur77 are known. Zhan *et al.* now identify the bacterially derived octaketide cytosporone B (Csn-B) as a selective agonist of Nur77. Molecular modeling and biophysical studies provided evidence that Csn-B binds the Nur77 ligand binding domain. Cell-based and *in vivo* experiments showed that Csn-B increases Nur77's transcriptional activation activity; one of the upregulated genes was Nur77 itself, which indicates the existence of a positive autoregulatory loop. Finally, the authors showed that Csn-B increases expression of genes encoding gluconeogenesis enzymes, induces apoptosis in certain human cancer cells and reduces xenograft tumor growth in mice. In the absence of an endogenous ligand, Csn-B should be a valuable probe for further investigating Nur77 function. [**Articles, p. 548**] *KS*

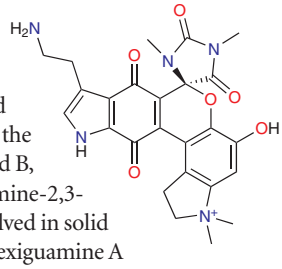
Written by Catherine Goodman, Kenneth Sercy & Terry L. Sheppard

Rafting on the Akt pathway



Membrane rafts are thought to be localized patches of the membrane enriched inlipids such as sphingolipids and cholesterol, but their biological function and even their existence remains controversial. Lasserre *et al.* use fluorescence correlation spectroscopy to demonstrate the dependence of raft nanodomain formation on the biosynthesis of the putative component lipids. Inhibition of raft lipid biosynthesis also specifically inhibited signaling in the phosphoinositide-3 kinase/Akt pathway, but not in the closely linked Ras/MAPK pathway. Additional biochemical and fluorescence experiments showed that this inhibition is caused by the lack of Akt recruitment to the membrane, which is similarly caused by an interruption in the localized accumulation of PIP_3, the ligand for the Akt pleckstrin homology (PH) domain. Because the Akt-PIP_3 complex mixed efficiently with other raft components, but PIP_3 alone should not, these results raise the intriguing possibility that PH-PIP_3 interactions serve the dual role of targeting Akt to the membrane and promoting nanodomain formation. [**Articles, p. 538**] *CG*

Synthesis *au naturel*



Biomimetic synthesis approaches take inspiration from natural biosynthetic pathways, but use the methodologies of organic chemistry to generate the targeted natural product. Volgraf *et al.* now report the biomimetic synthesis of exiguamine A and B, two potent alkaloid inhibitors of indoleamine-2,3-dioxygenase enzymes, which may be involved in solid tumor survival. The synthetic strategy to exiguamine A starts from three proposed biosynthetic starting materials: tryptophan, *N*,*N*-dimethylhydantoin and dopamine. The key step involves an oxidative catecholamine cyclization cascade, triggered by Ag(II) oxide, producing exiguamine A in 46% yield. Under certain conditions, the cyclization reaction also yields exiguamine B, an oxidized analog of exiguamine A that the authors separately identified as a natural product from the sponge *Neopetrosia exigua*. The synthetic route may offer new insights into how exiguamine alkaloids are synthesized in sponges and creates potential therapeutic opportunities based on these natural products. [**Brief Communication, p. 535**] *KS*

We're in the money!

Scientists face increasing challenges in obtaining funding for their research. Chemical biologists, who are working in a relatively new and still rapidly developing interfacial area, encounter even greater challenges in this effort [Editorial, p. 509]. In this issue, we feature a collection of articles that offer perspectives on the funding of chemical biology research across the globe. Colón and colleagues [Commentary, p. 511] discuss the challenges of funding interdisciplinary fields such as chemical biology at the US National Science Foundation. Jiang *et al.* highlight the development of a targeted chemical biology funding initiative in China [Commentary, p. 515]. McGovern discusses the role of private foundations in financial support of chemical biology [Commentary, p. 519]. Finally, we highlight ERA-Chemistry, a new initiative designed to facilitate cooperative funding of chemical research across Europe [Elements, p. 523]. *TLS*