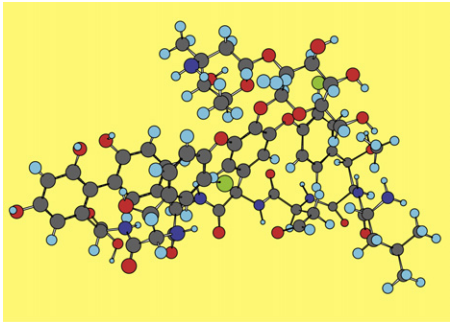
In This Issue

Halogenation Strategies in Natural Product Biosynthesis



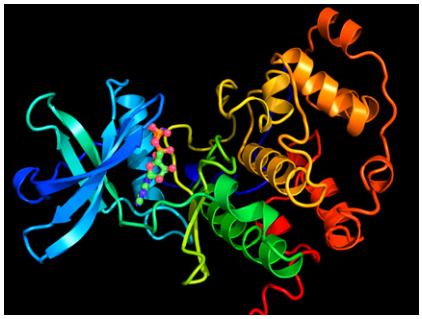
PAGE 99

The 19th century can be considered to be the period when halogen elements came out of age. During those hundred years all currently known halogens, except astatine, were recognized as bona fide elements, and their properties were catalogued. The realization that Nature widely employs halogens for production of thousands of diverse natural products came somewhat later. These days, halogenated natural products are being exploited as powerful anticancer agents and antibiotics. In this issue, Neumann et al. review the accumulating information about the enzymes employed in production of halogenated natural products. (Figure shows vancomycin, a halogenated natural product).

Dual Mode of Human Protein Kinase CK2 Inhibitor Binding

PAGE 111

Protein kinases are enzymes extensively involved in transmitting signals and thus controlling myriads of cellular processes. A Ser/Thr kinase, CK2, participates in apoptosis suppression, cell survival, and tumor genesis. CK2 is a tetramer and consists of two catalytic subunits (CK2α) attached to a dimer of noncatalytic subunits (CK2β). To probe details of CK2 activity, a number of specific inhibitors has been developed. Raaf et al. now describe an intriguing dual binding mode of a known CK2 inhibitor, DRB. Their structural work reveals that one molecule DRB binds to the canonical ATP-cleft of human CK2α, as expected, and another DRB molecule binds to an additional allosteric site, disrupting CK2α/CK2β interaction.



NRPS with Stereospecificity for D-Alanine

PAGE 118

Blackleg fungus, *Leptosphaeria maculans*, is a plant pathogen, a causative agent for one of the most serious diseases of canola, blackleg disease. Potent antifungal compounds are fusaricidin-type, lipopeptide antibiotics produced by a Gram-positive bacterium, *Paenibacillus polymyxa*, which are able to inhibit blackleg fungus growth. Li and Jensen have now cloned and characterized the entire fusaricidin gene-cluster from *P. polymyxa* PKB1, showing the presence of six functional modules, all containing domains typical for nonribosomal peptide synthetases (NRPSs): an adenylation (A), a thiolation (T), and a condensation (C) domain. Surprisingly, detailed investigation of substrate specificity revealed that the peptide synthetase that makes fusaricidin can directly incorporate a D-amino acid. This unusual capability may be of value in future combinatorial biosynthesis studies aimed at production of new types of bioactive peptides.

CLIPping Colors onto Proteins

PAGE 128

Monitoring complex cellular processes can be achieved by imaging protein behavior using a suitable spectroscopic readout. Routinely, the protein of interest is fused to a tag that can be covalently modified by a chemical probe inside of the living cell, thus allowing direct observation. Taking this a step further, to enable simultaneous observation of two proteins, Gautier et al. introduce CLIP-tag, an engineered mutant of the human O^6-alkylguanine-DNA alkyltransferase, evolved to react specifically with O^2-benzylcytosine (BC) derivatives. Since the substrate specificity of CLIP-tag is orthogonal to that of the parent SNAP-tag, the two tags can be used together to distinguish two different proteins in a single cell. Using this approach, the authors used simultaneous multicolor pulse-chase labeling to visualize old and new copies of two different proteins in the same sample.

Seeing Red: Prodiginine Biosynthesis

PAGE 137

Bioactive tripyrrole red-pigments, prodiginines, produced by both Gram-positive and Gram-negative bacteria, are of substantial interest due to their reported antibacterial, antifungal, antiprotozoal, antimalarial, immunosuppressive, and antitumor activities. The biosynthesis of prodiginines is proposed to be a bifurcated process involving the condensation of a bipyrrole containing moiety with a monopyrrole (2-undecylpyrrole (UP)). Mo et al. establish that UP is the key intermediate for the production of undecylprodiginine and its cyclized derivative, streptorubin B, in *Streptomyces coelicolor*. They show that the production of a UP precursor, dodecanoic acid, requires redirection of the fatty acid biosynthetic process, demonstrating that UP pathway enzymes assume the role of enzymes from fatty acid biosynthesis pathway. It is suggested that clear functional separation of two distinct pathways is achieved through acyl carrier protein (ACP) specificity.

Do You Know What Your Cytochrome P450 Does?

PAGE 149

Cytochrome P450s (P450s) are a large family of ubiquitous monooxygenases found in all lineages of life. Although some effort has gone into the identification and classification of the thousands of P450s known to exist in nature, much work still needs to be done to determine their potential substrates and the products generated by this versatile class of enzymes. Here, Kruse et al. report development of an in vivo plant-screening platform that allows for the analysis of potential substrate/P450 interactions. This platform utilizing sensitive analytical chemistry techniques demonstrates the ability to identify novel adducts of therapeutic compounds.

Open the Angucycline Biosynthetic Black Box

PAGE 157

The formation of the angucycline core is typically followed by a series of flavoprotein-catalyzed oxidations that are found to be inseparable in vivo and thus referred to as a "biosynthetic black box." Kallio et al. now focus on the enzymology of some of the key steps behind this "biosynthetic black box" and the structural diversity of angucyclines. They reconstitute the operation of flavoprotein-catalyzed oxidation cascade in vitro and demonstrate that the successful and effective primary product formation required tight synchronization between successive steps in the catalytic sequence. Interestingly, the proposed model for the reaction sequence involves a quinone methide intermediate. (Photo of a section of 96-well plate illustrating enzyme assisted oxygenation courtesy of Kallio et al.)

Small Molecule Activators for Ser/Thr Phosphatase PP-1

PAGE 167

The activity of enzymes is controlled in many ways, including binding to drugs or drug-like ligands. Such small molecule modulators continue to play a particularly important role in controlling the action of many enzymes, both as pharmaceutical agents and as probes for basic cell biology studies. The vast majority of modulators in this category are inhibitors, but activators would be equally as interesting in some cases. Accordingly, Tappan and Chamberlin report here the rational design of the first drug-like molecule that activates the important Ser/Thr phosphatase PP-1, thus complementing the large number of known inhibitors of this enzyme.

Now Presenting Kirromycin Biosynthesis Gene Cluster

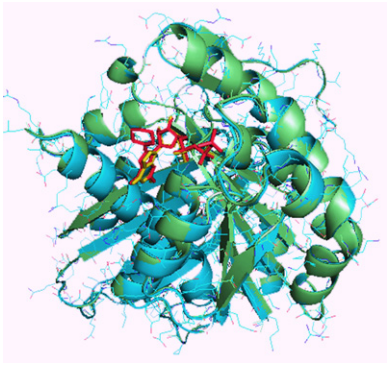
PAGE 175

Kirromycin, produced by *Streptomyces collinus* Tu 365, is a potent antibiotic that inhibits bacterial protein biosynthesis by interaction with elongation factor Tu. In this work, Weber and colleagues describe the isolation, sequencing, and characterization of the kirromycin biosynthesis gene cluster. Kirromycin is synthesized by a hybrid nonribosomal peptide synthetase (NRPS)/type I polyketide synthase mechanism (PKS I) that includes PKS-modules which contain internal acyl transferase domains and also modules which rely on discrete acyl transferase enzymes. Isotope feeding studies revealed that β-alanine is the building block of the pyridone moiety of kirromycin.

FtsZ and Tubulin Nucleotide Binding Sites are Different

PAGE 189

The cytoskeletal proteins FtsZ and tubulin play a pivotal role in prokaryotic cell division and eukaryotic chromosome segregation, respectively. Selective inhibitors of the GTP-dependent polymerization of FtsZ could constitute a new class of antibiotics, while several inhibitors of tubulin are widely used in anti-proliferative therapy. In this work, Läppchen et al. designed and characterized GTP-derived, selective inhibitors of FtsZ. Unexpectedly, the GTP analogs had an opposite effect on the polymerization of tubulin. Their data suggest surprising differences between the intersubunit active sites of both proteins and call for a reevaluation of the current models of the FtsZ protofilament interface. (Figure credit: Läppchen et al.)



 ©2008 Elsevier Ltd All rights reserved