In This Issue

In Review: Regenerative Chemical Biology

PAGE 413

There is great interest in the therapeutic potential of cell-based therapies, referred to as regenerative medicine, which generally encompass the use of embryonic stem cells and reprogrammed adult cells with embryonic stem cells-like properties, called induced pluripotent stem cells. However, key issues such as optimal strategies for cellular reprogramming and directed differentiation to ensure efficacy and safety of regenerative therapy have not been resolved. In this review, Ao et al. discuss these challenges and the innovative uses of synthetic chemicals to tackle them. The emerging study of regenerative chemical biology has far-reaching impact on the future of regenerative medicine.

Engineering Improved Selectivity towards Malarial Parasites

PAGE 425

A number of structurally less complex and more stable analogs of pactamycin have been generated by Lu et al. from genetically engineered strains of *Streptomyces pactum*. The compounds show potent antimalarial activity but, in contrast to pactamycin, have significantly reduced antibacterial activity and cytotoxicity against mammalian cells. The results suggest that distinct ribosomal binding selectivity or new mechanism(s) of action may be involved in their plasmodial growth inhibition, which may lead to a new direction in the discovery and development of drugs against malaria and other life-threatening protozoal infections.

Resistant Smoothened Conquered

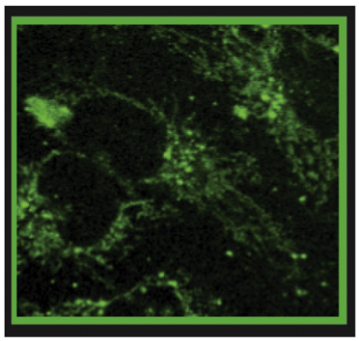
PAGE 432

Small-molecule antagonists for Smoothened (Smo) have been developed and achieved promising preclinical efficacy in cancers. However, tumor relapse was quickly developed due to a drug-resistant mutation on SMO. Here Tao et al. report two Smo antagonists that bind to distinct sites and inhibit both wild-type and mutant Smo. These findings provide an insight of the ligand binding sites of Smo and a basis for the development of potential therapeutics for tumors with drug-resistant Smo mutations.

Supramolecular Templating in Kirromycin Biosynthesis

PAGE 438

In the biosynthesis of complex polyketides, acyltransferase domains (ATs) are key determinants of structural diversity. Their specificity and position in polyketide synthases (PKSs) usually controls the location and structure of building blocks in polyketides. Many bioactive polyketides, however, are generated by trans-AT PKSs lacking internal AT domains. They were previously believed to employ mainly malonyl-specific free-standing ATs. Here, Musiol et al. report a mechanism of structural diversification in which the *trans*-AT KirCII regiospecifically incorporates the unusual extender unit ethylmalonyl-CoA in kirromycin polyketide biosynthesis.



Rerouted to Mitochondria: Path to Cancer Defeat

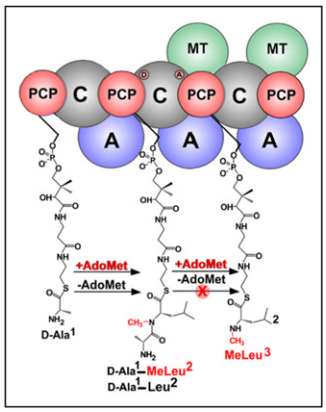
PAGE 445

Chlorambucil is a clinically used leukemia drug that alkylates nuclear DNA. However, resistance against the drug has been noted, limiting its effectiveness. Fonseca et al. investigated whether redirecting chlorambucil from the nucleus to another cellular organelle that also contains DNA, the mitochondria, would allow retention of activity and circumvention of resistance. This was achieved using a peptide-based delivery system that is mitochondria specific. Indeed, evasion of resistance and a significant increase in chlorambucil activity was observed in clinical samples. This is the first successful delivery of an alkylating agent to mitochondria.

Multidrug Efflux Pump: Putting the Pieces Together

PAGE 454

Drug resistance presents an ever-increasing threat to public health and encompasses all major microbial pathogens and antimicrobial drugs. Some pathogens have acquired resistance to multiple antibiotics (multidrug resistance) and cause infections that are effectively untreatable. The high multidrug resistance of Gram-negative pathogens is based on activities of multicomponent drug efflux transporters. The study by Tikhonovsa et al. describes the reconstitution of the multidrug efflux pump AcrAB-TolC that functions in the context of two membranes of *E. coli*. The kinetic analyses identified a possible "bottleneck" in the assembly of the tripartite complex that could be targeted for development of effective inhibitors of AcrAB-TolC assembly.



Cyclosporin A N-methylation

PAGE 464

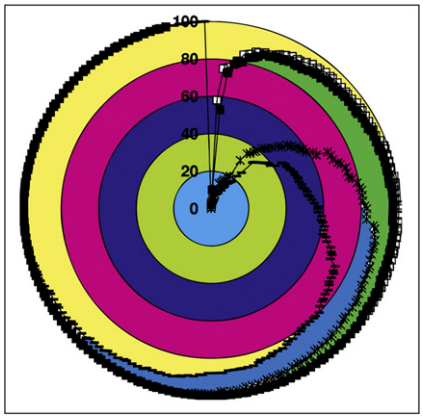
The N-methylation of enzyme-bound intermediates is of general importance in the synthesis of many peptide and depsipeptide antibiotics. The N-methylation of specific amide positions in the backbone of cyclosporine A is critical for the efficient progression of peptide assembly to the mature undecapeptidyl stage. Velkov et al. establish that desmethylation of even a single amide appears to destabilize the main conformation of cyclosporine A. Given the mechanistic similarities across nonribosomal peptide synthetase (NRPS), these findings provide a biochemical model for N-methylation processes of NRPS in general.

In This Issue

Impairing Prostate Cancer Pathogenesis

PAGE 476

Cancer cells depend on different metabolic pathways from normal cells to support their malignant behavior. Mapping these metabolic pathways may uncover biochemical mechanisms that support tumorigenesis and identify new drug targets. The serine hydrolase KIAA1363 is highly elevated in aggressive cancer cells, where it regulates ether lipid metabolism. Here, Chang et al. have created a potent, selective, and in vivo-active inhibitor of KIAA1363. This compound, termed JW480, reduces ether lipids in cancer cells and impairs their migration, invasion, and in vivo tumor growth. These studies support a protumorigenic function for KIAA1363 and report a versatile inhibitor for pharmacological characterization of this enzyme.



Cross-Reactivity within Wnt/β-Catenin Signaling

PAGE 485

Verkaar et al. describe the screening of a small-molecule compound library for inhibitors of Wnt/β-catenin signaling, an important pathway in embryonic development, adult stem cell maintenance, and disease. The authors demonstrate that two clinically evaluated p38 MAPK inhibitors inhibit Wnt/β-catenin signaling by cross-reacting with casein kinase 1δ and ε. These compounds may be repositioned as drugs for β-catenin-dependent disease, such as colon cancer. In addition, casein kinase 1δ and ε are key regulators of the mammalian circadian clock. Therefore, the inhibitors may potentially alleviate misalignment of the internal clock, as experienced during jet lag, depression, and seasonal affective disorder.

Real-Time Imaging of Histones

PAGE 495

Histone acetylation is one important epigenetic mark whose information is read by bromodomain-containing proteins. Modulation of histone acetylation has also emerged as a promising drug-target for anticancer therapy. In this study, Ito et al. developed a novel probe, Histac-K12, that enables visualization of histone H4K12 acetylation in living cells. Using this probe, the authors could monitor changes in histone acetylation in vivo upon treatment with various histone deacetylase inhibitors and observe the ability of a compound to inhibit the bromodomain binding to acetylated H4K12. Thus, Histac-K12 is useful for spatiotemporal analysis of histone H4K12 acetylation in living cells and anticancer drug development.

Linking Chemistry and Genetics Cyanobactin Family

PAGE 508

Cyanobactins comprise one of the major ribosomal peptide natural product families and are widespread in cyanobacteria. Donia and Schmidt developed and applied a phylogenetic model to understand the gene chemistry relationship in this family and to discover new pathways and compounds. A tyrosine *O*-prenylating gene cluster and natural products from Spirulina health supplements are described.

Rationally Designing Catalysts for Natural Products

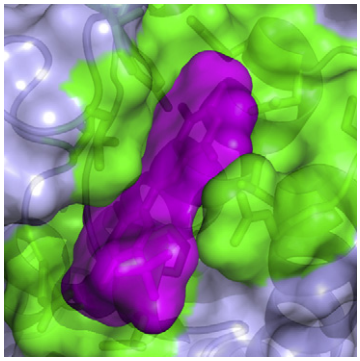
PAGE 520

Nature provides a great source of pharmaceuticals, but before a natural product potentially becomes a therapeutic agent, properties influencing the pharmacological or pharmacokinetic qualities might have to be improved. By protein engineering, Härle et al. rationally designed LanGT2, an O-glycosyltransferase, towards an enzyme able to catalyze sugar attachment by a C-glycosidic bond. The resulting structural difference might not influence the bioactivity but raises substantially the stability. The achievement in overcoming natural limitations by protein engineering might document a general strategy in gaining further chemical diversity in the field of combinatorial biosynthesis and opens space in creating valuable drugs.

Preventing p53 from Causing Serious Damage

PAGE 531

Excessive activity of the master transcription regulator p53 activity during myocardial ischemia causes irreversible cellular injury and cardiomyocyte death. In this study, Borah et al. discovered a small molecule named ischemin that blocks p53 recruitment of transcriptional cofactor CBP, thus preventing stress-induced apoptosis in ischemic cardiomyocytes.



Gliotoxin Biosynthesis in *Aspergillus fumigatus*

PAGE 542

Gliotoxin, a sulfur-contained molecule, is produced by the opportunistic human pathogen *Aspergillus fumigatus* and is known to play an important role in organism virulence. Amazingly, for over 70 years, the biological mechanism for the introduction of sulfur atoms into gliotoxin has remained undiscovered. Here, Davis et al. demonstrate that an enzyme normally involved in detoxification plays a key role in gliotoxin biosynthesis via the sulfurization of a gliotoxin biosynthetic intermediate in *A. fumigatus*. The data also suggest that an acyl imine intermediate structure is present during gliotoxin biosynthesis, and this has significant implications for biocatalysis using fungal enzymes.