In This Issue

Don't Forget a Chaperone

PAGE 1521

Fabry disease patients show a deficiency in the activity of the lysosomal enzyme α-galactosidase (α-GAL or α-Gal A). One proposed treatment for Fabry disease is pharmacological chaperone therapy, where a small molecule stabilizes the α-GAL protein, leading to increased enzymatic activity. Guce et al. show that the pharmacological chaperones 1-deoxygalactonojirimycin (DGJ) and galactose stabilize α-GAL and reveal a biochemical basis for pharmacological chaperone therapy applicable to other protein misfolding diseases.

Overproducing Salinosporamide A

PAGE 1527

The chlorinated natural product salinosporamide A is a potent 20S proteasome inhibitor currently in clinical trials as an anticancer agent. To deepen understanding of salinosporamide biosynthesis, Lechner et al. investigated the function of a pathway-specific regulatory gene, *salR2*, and observed a selective effect on the production of chloroethylmalonyl-CoA. The ectopic overexpression of SalR2 under constitutive promoter control was the key to selectively double the production yield of salinosporamide A without increasing the production levels of its minor analogs, suggesting a unique mode of regulation of a biosynthetic precursor in polyketide assembly.

TB Lipid Analysis Goes Big

PAGE 1537

Although tuberculosis remains a leading cause of death, detection of the causative mycobacterium in patients remains slow and insensitive. Here Layre et al. report a mass spectrometry system for rapidly detecting the diverse lipid molecules in mycobacteria that cause tuberculosis and databases that categorize the many lipid molecules in the cell wall. This system rapidly compares molecular content of any two bacteria and allows the study of environmental and genetic effects. Additionally, improved platform for lipid profiling enables rapid determination of the nature of the bacterium within a given patient.

DUBs Dirty Dozen

PAGE 1550

Intracellular fate of numerous proteins is regulated by ubiquitination, whereby small protein, ubiquitin (Ub), or Ub chains are attached to the target. Additionally, cells have large number of deubiquitinating enzymes (DUBs), which hydrolyze Ub linkages. DUBs are a diverse family of enzymes, and Faesen et al. analyzed a dozen of enzymes more narrowly classified as Ubiquitin-specific proteases (USPs) in order to deconvolute effect of regulatory domains and establish Ub chain preference. The study provides insight in the biochemical behavior in the USP family and validates chemical tools that will be useful in characterizing other DUBs.

RaPID Means Business

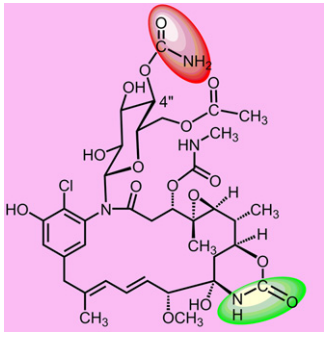
PAGE 1562

Naturally occurring peptides often possess macrocyclic and *N*-methylated backbone. These features grant them properties suitable for drug development. Because such peptides are generally found as natural products, it is still a formidable challenge in constructing novel libraries for screening bioactive molecules. Yamagishi et al. describe RaPID, a system for synthesizing a de novo library of "natural product-like" macrocyclic *N*-methyl-peptides using translation machinery, coupled with an in vitro display. This system allows for rapid selection of strong binders against therapeutic targets, as illustrated by selection of anti-E6AP macrocyclic *N*-methyl-peptides that strongly inhibit polyubiquitination of proteins.

Dual Carbamoylations on Ansamitocin

PAGE 1571

Li et al. describe an interesting ansamitocinoside with carbamoyl substitution at the C-4 hydroxyl group of the N-β-D-glucosyl moiety, which they identified from the ansamitocin producer *Actinosynnema pretiosum*. The carbamoylation of the glucosyl moiety was attributed to carbamoyltransferase gene *asm21* gene product Asm21. This enzyme displayed preference for 18-O-methyl-19-chloroproansamitocin as a substrate for macrolactam C-7 carbamoylation. However, Asm21 exhibited higher catalytic efficiency towards the glucosyl moiety. This work highlights curious enzymatic activity of an *O*-carbamoyltransferase performing dual action on both a polyketide backbone and a glycosyl moiety during ansamitocin biosynthesis.



No More Proinvasive Crosstalk

PAGE 1581

Block the messenger! The tumor microenvironment is now acknowledged as a key regulator of cancer progression. Jung et al. apply forward chemical genetics to the problem and discover heat shock protein 90 (Hsp90) as a potential drug target to modulate cell communication within this microenvironment. This led to the characterization of triazine compound S06 as a promising drug candidate for blocking Hsp90 function and cancer invasion.

A Map of the Antibiotic Resistance Kinome

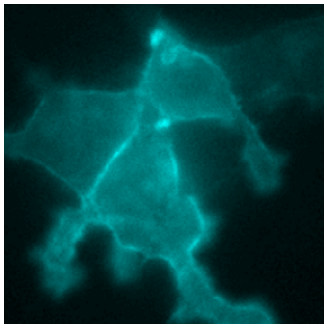
PAGE 1591

To map the resistance kinase chemical space, Shakya et al. conducted a screen of 14 antibiotic resistance kinases against 80 protein kinase inhibitors. This screen identified molecules with varied inhibition profiles, proving that protein kinase inhibitors offer privileged scaffolds with the potential to block antibiotic resistance. For example, the flavonol quercetin inhibited a number of resistance kinases in vitro and in vivo. The authors show that protein kinase inhibitors can be repurposed to block antibiotic resistance, providing leads for codrug design.

Pulling a Plug on Malarial Parasite

PAGE 1602

Much like a resistor in an electric circuit, a class of tetracyclic benzothiazepines, described here by Dong et al., blocks the flow of reduction equivalents through the mitochondrial electron transport chain in the malaria parasite by specific inhibition of cytochrome bc1. Using a transgenic parasite strain engineered to bypass the requirement of this otherwise essential mitochondrial machinery, in combination with resistance selection and genetic mapping, the authors revealed the targeted pathway and pinpointed the molecular target of this previously unexplored family of antimalarial compounds.



$Ca2^+$ Signaling Enters Synthetic Biosystems

PAGE 1611

Synthetic biosystems have been engineered to enable control of metazoan cell morphology, migration, and death. These systems possess signal specificity but lack flexibility in choice of input signal. To exploit the potential of $Ca2^+$ signaling, Mills and Truong designed RhoA chimeras that enable reversible, $Ca2^+$-dependent control over RhoA morphology and RhoA-dependent migration. The $Ca2^+$-activated RhoA chimera demonstrated distinct activation patterns based on the spatial and temporal characteristics of the input $Ca2^+$ signal. Engineering synthetic biological systems with input versatility and tunable spatiotemporal responses are key motivations for further application of $Ca2^+$ signaling in this field.

Glycolipids Wake Natural Killer T Cells Up

PAGE 1620

Natural killer T (NKT) cells are a unique lymphocyte population that recognizes glycolipids presented by CD1d. The first antigen described, the glycosphingolipid α-galactosyl ceramide (αGalCer), was derived from a marine sponge and is a potential anticancer agent whose activity depends upon IFNγ secretion. Structural variants of αGalCer are currently under development. Tyznik et al. synthesized different analogs with an altered sphingoid base or fatty acid, based on glycosphingolipids found in various sponges. These elicit an increased proinflammatory immune response characterized by high and sustained serum levels of IFNγ and may be useful for cancer treatment. Immunology and structural data suggest increased lipid-CD1d stability in vivo may be responsible for the enhanced secretion of IFNγ.

VEGF-VEGFR Interface As a Clear Target

PAGE 1631

Combined in silico-in vitro screening studies were carried out over the vascular endothelial growth factor (VEGF)-VEGF receptor (VEGFR) system, one of the flattest protein-protein interfaces available and a validated target for anti-angiogenic treatments. The approach allowed Gaitier et al. to identify several low molecular weight compounds that bind to the receptor, inhibit the binding of VEGF, and thus block a very challenging protein-protein interface.

New Cluster for New Polymyxin B-Type Antibiotics

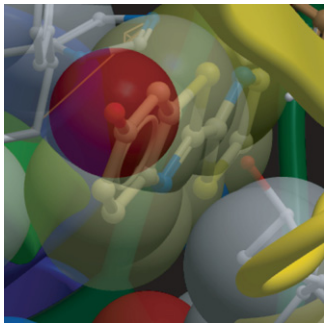
PAGE 1640

Polymyxins are peptide antibiotics active against many species of drug-resistant Gram-negative bacteria. Shaheen et al. sequenced the gene cluster for polymyxin biosynthesis from *Paenibacillus polymyxa* PKB1. The cluster codes for a peptide synthetase complex responsible for making the polymyxin and two transporter proteins for moving the polymyxin out of the cell. Further analysis confirmed that *P. polymyxa* PKB1 produces two novel forms of polymyxin B, which may have altered activity or toxicity properties compared to the original antibiotic.

Aminoluciferins Shine Bright

PAGE 1649

Firefly luciferase-catalyzed light emission from D-luciferin is widely used as a reporter of gene expression and enzymatic activity both in vitro and in vivo. Despite the power of bioluminescence for imaging and drug discovery, light emission from firefly luciferase is fundamentally limited by the physical properties of the D-luciferin substrate. Harwood et al. have previously synthesized aminoluciferin analogs that exhibit light emission at longer wavelengths than D-luciferin and have increased affinity for luciferase. Here, the authors describe mutant luciferases that exhibit improved and selective light output with aminoluciferins in both lysed and live mammalian cells.



Mending a Broken Heart

PAGE 1658

Ni et al. have discovered compounds able to induce cardiac cell generation and selectively promote cardiomyocyte formation without affecting other tissue and organ development. The authors name the compounds Cardionogens and show that they act as antagonists of Wnt signaling pathway. The finding demonstrates the benefits of a whole organism-based chemical screen and may open exciting avenues for developing new therapeutics to replenish cardiac cells in diseased hearts.

