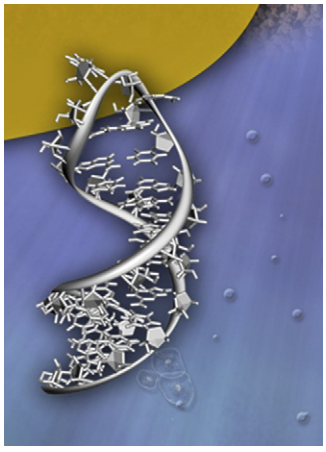
In This Issue

In Review: Influenza A Virus Hemagglutinin-Glycan Receptor Interactions

PAGE 803

The variety of biological processes is mediated by protein-glycan interactions, including the host-pathogen communication. In this case, pathogens have evolved various strategies to recognize host cell surface glycans. This review by Shriver et al. now focuses on the binding of influenza A hemagglutinin (HA) to specific sialylated glycans on the human cell surface as an illustrative example of protein-glycan interactions and discusses strategies used to extract valuable biochemical, structural, and functional information that can be generalized for other protein-glycan systems. This can be effectively achieved by combining a *top-down* approach, based on the available structural information, with a *bottom-up* approach, based on data mining and informatics. The review highlights the synergistic value of combining new technologies for glycomics with computational modeling to extend our understanding of protein-glycan interactions.

Living it Up in the "RNA WORLD"



PAGE 815

The most straightforward version of the "RNA World" hypothesis assumes that RNA was the initial polymer responsible for life. The capability of all living systems to grow exponentially implies that significant selective pressure to evolve new metabolic pathways would have existed as prebiotic supplies of complex nutrients were consumed. Here Lau and Unrau show that a promiscuous ribozyme selected for its ability to promote Schiff base chemistry with ribose can also mediate nucleotide synthesis without a single change to its sequence. This catalytic flexibility supports the assumption that ribo-organisms could have rapidly evolved new metabolic functionalities early in the history of evolution. (Figure credit: Lau and Unrau.)

Fitness Test for Staph Challengers

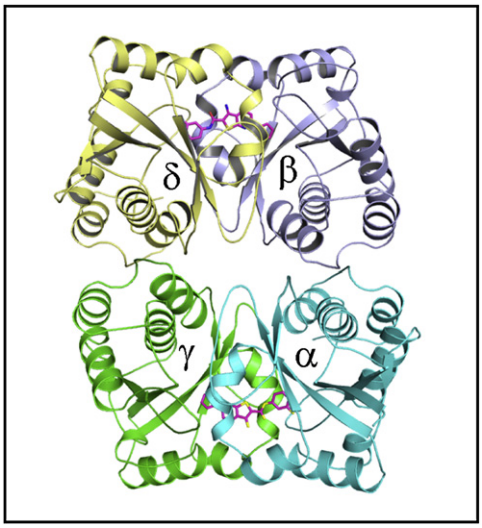
PAGE 826

The need to discover new antibacterial drugs is a pressing world-wide problem exasperated by the difficulty in finding attractive new chemical leads that work through target-specific mechanisms in the whole cell. The study by Donald et al. describes a chemical genetics platform developed in the bacterial pathogen *Staphylococcus aureus* that produces information-rich strain sensitivity profiles that reflect a compound's whole-cell mechanism of action (MOA). The platform has broad applications for the field of antibacterial drug discovery, including MOA determination for newly discovered antibacterial agents, the identification of novel drug targets, and the elucidation of reporter strains for pathway-specific screens.

MRSA Meets Its Match

PAGE 837

As noted in the related report by Donald et al., combating bacterial infections by using currently available antibiotics is becoming increasingly challenging in light of the emergence of drug resistance among the pathogens. Here, Huber et al. describe a chemical biology approach to identify small molecules that display intrinsic antibacterial activity and uniquely potentiate the effects of β-lactam antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA). Mechanism-of-action studies demonstrate that two structurally related agents identified from the screen inhibit cell wall biosynthesis and likely act through SAV1754, an essential protein that the authors propose functions as a peptidoglycan flippase required for cell wall assembly. These results suggest that SAV1754 inhibitors may possess therapeutic potential alone or in combination with β-lactams to restore MRSA efficacy.

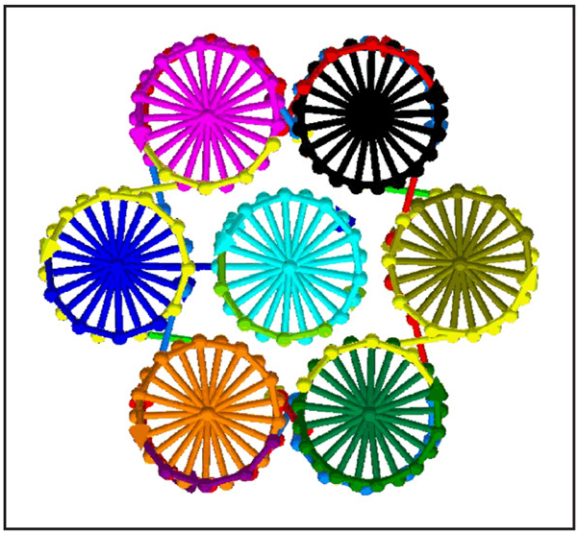


NAD Biosynthesis Under Attack

PAGE 849

Biosynthesis of NAD cofactor is one of the most conserved pathways in bacterial pathogens, and several downstream NAD biosynthetic enzymes are promising drug targets. In this work, Sorci et al. validate nicotinate mononucleotide adenylyltransferase of the NadD family as a target for broad-spectrum antimicrobial development by combining comparative genomics with a structure-based approach. Small-molecule inhibitors targeting NadD from divergent bacteria were identified and shown to bind in the area of active site, have on-target antibacterial activity, and have no side-effects on functionally equivalent human enzymes. (Figure credit: Sorci et al.)

DNA Nanorod Slips into Cavity



PAGE 862

The control of the structure of matter is a key goal of nanoscience, and DNA is an exciting molecule for control because it forms programmable intermolecular interactions. Today, there is great interest in the organization of one-dimensional rod-like species. Candidates include biological microfilaments or microtubules as well as carbon nanotubes or other inorganic nanotubes. The idea behind the work by Wang et al. is that a DNA sheath can be used to organize its contents by interacting with a two-dimensional DNA surface; e.g., a DNA crystal or an origami tile. The authors have prototyped this approach by encapsulating a DNA double helix within a DNA sheath. (Figure credit: Wang et al.)

Biomarkers for Celiac Sprue

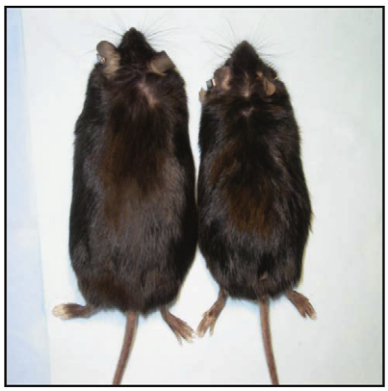
PAGE 868

New tools are needed for managing celiac sprue, a life-long immune disease of the small intestine caused by dietary gluten. In order to tackle this issue, Bethune et al. designed gluten peptide analogs that retain key properties of their pathogenic counterparts but that are noninflammatory. In vitro and animal studies demonstrated the utility of these analogs as biomarkers for detecting intestinal permeability changes as well as glutenase-catalyzed gastric detoxification of gluten. Accordingly, controlled clinical studies are warranted to evaluate the use of these peptide biomarkers in diagnostic and therapeutic applications for celiac sprue and other diseases of genetic or infectious origin in which the gut barrier is impaired.

Fatostatin: Of Mice and Diets

PAGE 882

Sterol regulatory element binding proteins (SREBPs) are transcription factors important in lipogenesis. The study by Kamisuki et al. reports a small synthetic molecule (fatostatin) that impairs the activation of SREBPs, thereby decreasing the transcription of lipogenic genes. Experiments suggest that fatostatin inhibits the ER-Golgi translocation of SREBPs through binding to their escort protein, the SREBP cleavage-activating protein (SCAP), at a distinct site from the sterol-binding domain. Fatostatin blocked increases in body weight, blood glucose, and hepatic fat accumulation in obese *ob*/*ob* mice, even under uncontrolled food intake. Fatostatin may serve as a tool for gaining further insights into the regulation of SREBP. (Figure from Kamisuki et al.)



From the Sea of Papua New Guinea

PAGE 893

Cyanobacteria have emerged as exceptionally rich sources of toxins, drug leads, and pharmacological tool compounds. Using a neuropharmacological screening assay to guide the process, a new type of natural product was isolated: a Papua New Guinea assemblage of two marine cyanobacteria, as reported by Pereira et al. in this issue of the journal. The isolated compound, hoiamide A, derives from an interesting integration of modified amino acid and polyketide synthase fragments, and extensive NMR was used to define its complete 3-dimensional structure. Hoiamide A potently inhibits batrachotoxin binding to voltage-gated sodium channels (VGSC) via partial agonism at site 2 and could potentially be used as a probe of VGSC function.

