In This Issue

Fungal Fighter: Improving Nature's Way

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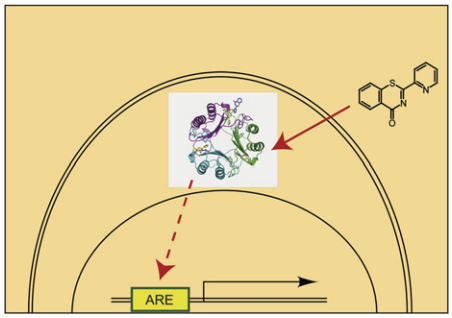
Natural products are often large, synthetically intractable molecules, yet frequently offer surprising inroads into previously unexplored chemical space for enzyme inhibitors. This work by Rush et al. shows how, aided by detailed structural information, the large natural product chitinase inhibitor argifin can be dissected down to a tiny 9 atom active fragment that can then be used as a scaffold to develop micromolar inhibitors for a chitinase from the opportunistic pathogen *Aspergillus fumigatus*.

BTZO-1 Reveals MIF's ARE Secret



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Macrophage migration inhibitory factor (MIF), a ubiquitous protein, is a critical upstream regulator of the innate and acquired immune response; however, its precise function in the majority of cells is not known. Here, Kimura et al. clarify a mechanism of function of MIF using a small molecule compound BTZO-1. BTZO-1, by interacting with MIF, activates the antioxidant response element (ARE) of glutathione S-transferase Ya subunit (GST Ya) gene, and protects cardiomyocytes from oxidative insults. Stimulation of MIF-mediated ARE activation by BTZO-1 derivatives may serve as a strategy for the treatment of heart diseases.

Through CYPome to New Fatty Acid Hydroxylase

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Cytochrome P450 enzymes are a superfamily of heme monooxygenases that play important physiological roles in the biosynthesis of secondary metabolites and antibiotics, as well as in fatty acid oxidation. Sorangium cellulosum So ce56, a producer of important secondary metabolites, is equipped with 21 putative P450 genes. Khatria et al. perform a bioinformatic analysis of the P450s and reveal 9 novel bacterial P450 families. Since fatty acids play a pivotal role during its complex life cycle, potential fatty acid hydroxylases were identified. This represents the initial report of two autologous and one heterologous electron transfer paths for the subterminal hydroxylation of saturated fatty acids by CYP109D1.

Computer Power to Engineer

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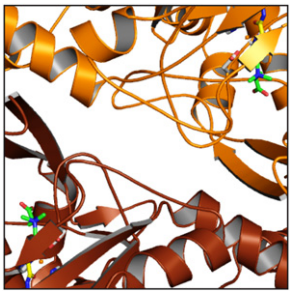
Engineered biosynthetic pathways have potential to produce high-value molecules from inexpensive feedstocks, but a key limitation is engineering enzymes with high activity and specificity. Here, Lippow et al. developed a method for combining structure-based computational protein design with library-based enzyme screening. The key advance is to take advantage of interresidue correlations favored by the design by encoding these amino-acid combinations (as well as single-position preferences) into the library. This approach improves screening efficiency by at least two orders of magnitude for engineering a novel glucose 6-oxidase enzyme, and these defined-sequence libraries will most likely be broadly applicable in protein engineering.

BBOX Inhibited!



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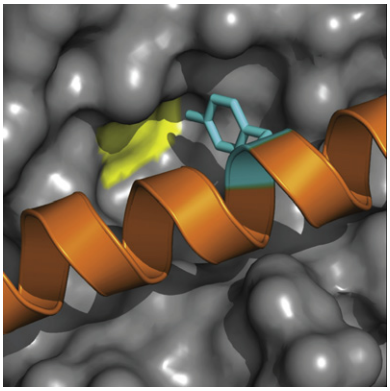
The final step in carnitine biosynthesis is catalyzed by γ-butyrobetaine (γBB) hydroxylase (BBOX), an iron/2-oxoglutarate (2OG) dependent oxygenase. BBOX is inhibited by trimethylhydrazine-propionate (THP), a clinically used compound. Leung et al. report structural and mechanistic studies on human BBOX and its reaction with THP. The results provide a basis for development of improved BBOX inhibitors and may inspire the discovery of new rearrangement reactions.

BCL-2 Family Interactome Gets Stapled



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Defining protein interactions forms the basis for discovery of biological pathways, disease mechanisms, and opportunities for therapeutic intervention. To harness the robust binding affinity and selectivity of structured peptides for interactome discovery, Braun et al. engineered photoreactive stapled BH3 peptide helices that covalently capture their physiologic BCL-2 family targets. The cross-linking α helices covalently trap both static and dynamic protein interactors and enable rapid identification of interaction sites, providing a critical link between interactome discovery and targeted drug design.

Of Nucleosomes and Cisplatin

PAGE 1334

Todd and Lippard explore the effects of cisplatin binding to DNA at the nucleosome level to incorporate key features of the eukaryotic nuclear environment. Site-specifically platinated nucleosomes carrying a 1,3-*cis*-{Pt(NH3)2}2+-d(GpTpG) intrastrand cross-link were investigated using X-ray crystallography, in vitro nucleosome mobility assays, and in vitro transcription experiments. The results from these studies provide new information about the effects of cisplatin binding to nuclear DNA and enhance our understanding of the mechanism of transcription inhibition by platinum anticancer compounds.

LDL Receptor Gets a Small RNA Hit

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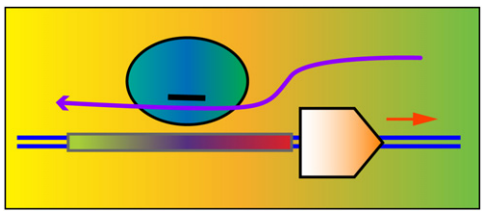

Low-density lipoprotein receptor (LDLR) is a cell-surface receptor that regulates cholesterol levels. Increased levels of LDLR would reduce cholesterol levels and help treat hypercholesterolemia. Here Matsui et al. show that duplex RNAs complementary to the promoter of LDLR activate expression of LDLR and increase the display of LDLR on the surface of liver cells. Activation can be achieved by chemically modified duplex RNAs. Promoter-targeted duplex RNAs can overcome repression of LDLR expression by 25-hydroxycholesterol and do not interfere with activation of LDLR expression by lovastatin. These data demonstrate that small RNAs can activate LDLR expression and affect LDLR function.

Mycobacterial Galactan Biogenesis Drawn to a Halt

PAGE 1356

UDP-galactofuranose is a substrate for UDP-galactopyranose mutase and galactofuranosyltransferases, two enzymes present in many pathogenic organisms but absent from mammals. In particular, these enzymes are involved in the biosynthesis of a polymer essential for the survival of the causative agent of tuberculosis. Peltier et al. describe here the synthesis of derivatives of UDP-Galf modified at C-5 and C-6 using a chemoenzymatic route. In cell-free assays, these compounds prevented the formation of mycobacterial galactan via the production of short ''dead-end'' intermediates. Such compounds may ultimately facilitate the future development of new therapeutic agents against tuberculosis.

