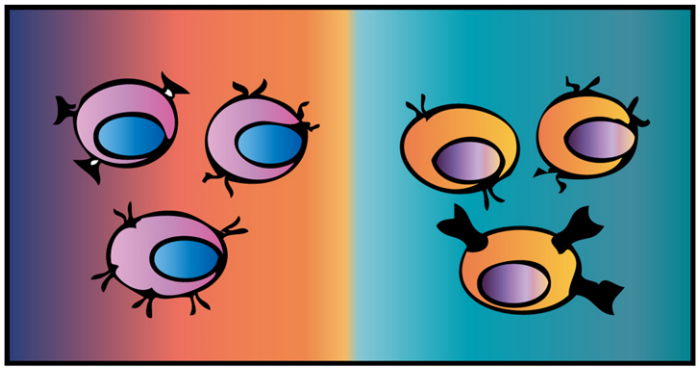
In This Issue

Fighting against Oneself



PAGE 1133

Ideally, treatments for autoimmune disorders would specifically target the autoantigen-recognizing B and T cells that drive the disease. However, this is not possible and current therapies either shut down the immune response globally, with serious consequences, or simply treat the associated inflammatory symptoms. Here, Gocke et al. present a combinatorial library screening strategy that allows for the isolation of compounds that target autoantigen-recognizing T cells with high specificity. The authors show that a compound derived from a screen targeted to murine autoimmune T cells that drive a multiple sclerosis-like disease can be selectively inactivated. This technology provides proof of principle for the development of therapeutic reagents that attack undesirable immune cells with unprecedented specificity.

E1 Elimination from Green to Red

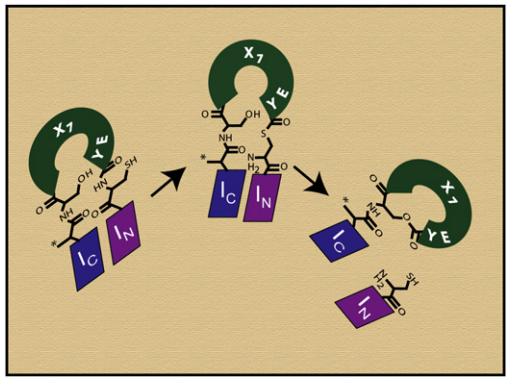
PAGE 1140

Photoconvertible fluorescent proteins change their emissions from green to red when exposed to ultraviolet light. This process occurs via a β-elimination reaction that causes cleavage of the Nα-Cα bond of a histidine residue and subsequent extension of a π-conjugated system. By comparing green and red states of an engineered photoconvertible fluorescent protein, KikGR, and analyzing the crystal structures of each, Tsutsui et al. discovered rotation along the Cα-Cβ bond of the histidine following cleavage of the Nα-Cα bond. The structural rearrangement enhances overall understanding of the mechanisms for the photoconversion that couples processes of photoexcitation and β-elimination reactions within a protein cavity.

"Lariat" Peptide Inhibitors of Protein Function

PAGE 1148

Reverse genetic approaches, although extremely useful, are difficult to perform on a large scale and in diploid organisms. Barreto et al. now describe development of technology for generating "lariat" peptide inhibitors. Lariats consist of a lactone-cyclized peptide "noose" with a covalently attached peptide "handle." The versatile handle provides lariats with many advantages over "head-to-tail" cyclized peptides. For example, functional domains can be inserted into the handle that allows combinatorial libraries of lariats to be screened using genetic assays. Affinity tags and fluorophores can also be attached to the handle during chemical synthesis. Further, the small size of lariats allows their structures to be easily solved and makes them useful as drugs or drug leads.



SMIFH2 Puts a Stop to Actin Assembly

PAGE 1158

Actin filament assembly stimulated by formins is critical for cells. However, the contributions of multiple formin isoforms for different processes in a variety of cell types are unclear. Here, Rizvi et al. describe the identification and characterization of a small molecule inhibitor of formin-mediated actin assembly. SMIFH2 targets formins from evolutionarily diverse organisms including yeast, nematode worm, and mice. SMIFH2 blocks both formin-mediated actin filament nucleation and elongation and disrupts formin-dependent actin structures in fission yeast and mammalian cells. Therefore, SMIFH2 may be a useful drug for elucidating formin-mediated processes in a range of organisms.

Autofluorescent Proteins at Sea

PAGE 1169

Despite their ubiquitous use as experimental tools in cell biology and invertebrate organisms, fluorescent proteins have seen only limited use for whole-body imaging in animals. This is partly because existing fluorescent proteins are inefficiently excited at the red wavelengths of the optical window away from hemoglobin absorbance. Lin et al. report the development of a monomeric far-red fluorescent protein named mNeptune that can excited in the optical window. A detailed structural characterization also reveals the chemical mechanism by which mNeptune achieves its red-shifted excitation spectrum.

Building the Bridge of Bacterial Destruction

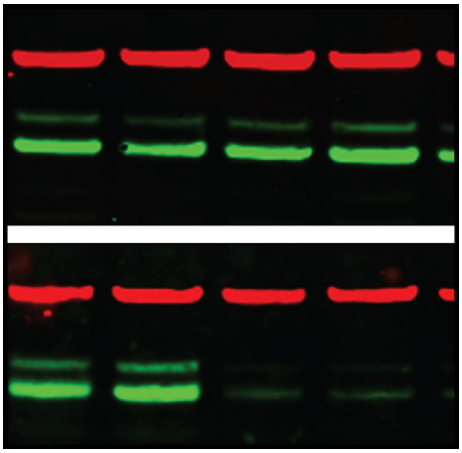
PAGE 1180

Hygromycin A (HA) is an antibacterial compound isolated from *Streptomyces* that acts via inhibiting protein synthesis and depends on the presence of a methylenedioxy bridged-aminocyclitol moiety. Palaniappan et al. now investigate roles that gene products of HA gene cluster play in the process of HA biosynthesis. The authors show that Hyg18 and Hyg25 are dispensable for HA biosynthesis but contribute to antibiotic yields. On the other hand, Hyg8 and Hyg17 are essential for HA biosynthesis. Specifically, they establish that Hyg6 is a methyltransferase acting on the aminocyclitol and suggest that hyg7 gene product, homologous to a metallo-dependant hydrolases, catalyzes oxidative cyclization step of methylenedioxy bridge formation. The authors argue that the existence and function of Hyg7 implies a unique enzymatic strategy for biosynthesis of these unusual bridge moieties.

Across the Membrane and into the Signaling Cascade

PAGE 1190

A negatively charged phospholipid, phosphatidylinositol, occurs in cells in a variety of phosphorylated forms that are called phosphoinositides. These lipid molecules with varying numbers of phospho groups play important roles in cell and lipid signaling and membrane trafficking. The work by Laketa et al. demonstrates that membrane-permeable phosphoinositide derivatives including a novel phosphoinositide analog with a phosphate on the 6-OH position are suitable for rapidly activating intracellular signaling events downstream of PI3K, such as Akt, MAPkinase, and p70S6 kinase. This makes them important tools to investigate the contribution of phosphoinositide signaling in living cells. This is demonstrated by the initiation and modulation of complex PI3K-dependent processes such as neurite outgrowth of PC12 cells.



Polyketide Synthases Start Your Engines

PAGE 1197

Hedamycin is an antitumor polyketide antibiotic with unusual biosynthetic features. In this work, Khosla et al. demonstrate that initiation of hedamycin biosynthesis requires interplay between type I and type II polyketide synthases. The role of individual protein components from the different synthase types was investigated through in vitro and in vivo experiments, and the resulting insights were parlayed into the engineered biosynthesis of new "unnatural" natural products.

