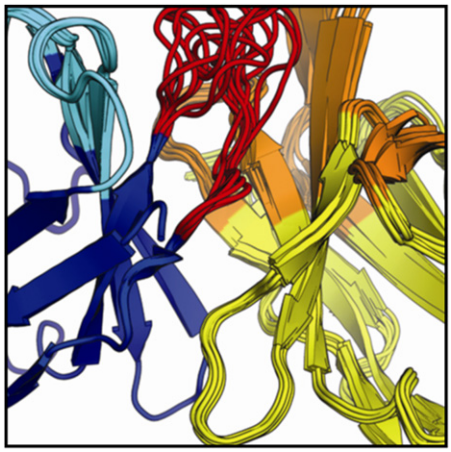
In This Issue

Fluorination of Thiostrepton

PAGE 443

Quinaldic acid formation requires an unusual rearrangement of the indole part of L-tryptophan to give a quinoline ketone, further conversion of which into an enantiomerically pure *S*-alcohol is catalyzed by a stereospecific oxidoreductase. Duan et al. elucidate this chemistry and facilitate new thiopeptide generation, as shown by regiospecific fluorination of thiostrepton with improved antibacterial activity.



Supercharged Antibodies

PAGE 449

Mutation of surface residues to charged amino acids increases resistance to aggregation and can enable reversible unfolding. Miklos et al. develop a protocol that "supercharges" proteins while considering the energetic implications of each mutation. Using a homology model, a single-chain variable fragment antibody was designed that has a markedly enhanced resistance to thermal inactivation and displays an unanticipated improvement in affinity. Such supercharged antibodies should prove useful for assays in resource-limited settings and for developing reagents with improved shelf lives.

Nerve Agent Detoxification

PAGE 456

Chemical warfare agents such as the G-type nerve gases (G-agents) are highly toxic compounds. Currently available treatments of nerve agent intoxication are of limited effectiveness. Using accelerated protein evolution techniques on the enzyme serum paraoxonase 1, Goldsmith et al. have developed broad-spectrum variants of the enzyme that can rapidly degrade the four major G-agents. Their greatly enhanced efficacy is coupled with a complete reversal of stereospecificity resulting in preference for the toxic enantiomers of the chiral G-agents, rendering them highly suitable for both prophylaxis and postexposure treatment of nerve agent intoxication.

Specific Inhibitors of USP7/HAUSP

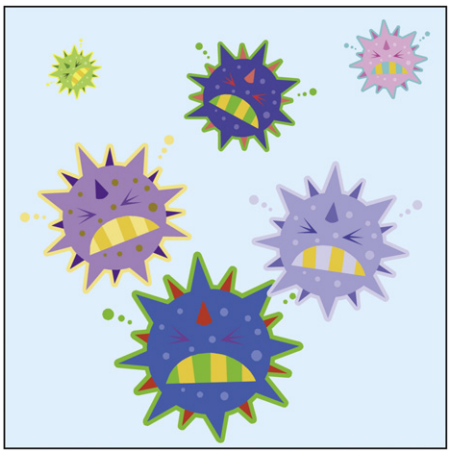
PAGE 467

The human USP7 deubiquitinating enzyme appears as novel strategic target for cancer therapy since it regulates many proteins involved in cell cycle as well as tumor suppressors and oncogenes. Reverdy et al. identified small-molecule inhibitors of USP7 and demonstrated USP7 inhibitor occupancy and selectivity in cancer cell lines. These active-site-targeting inhibitors regulate the level of several USP7 substrates and thus recapitulated the USP7 knockdown phenotype. These results provide proof of principle that USP7 inhibitors may be valuable therapeutics for cancer, and the discovery of such molecules offers valuable tools for studying deubiquitination.

Parasites in an Artificial Cell under Control

PAGE 478

One of the fundamental biological functions, translation-coupled replication of genetic information, was constructed from well-defined components but ran into problems. Now, Bansho et al. report that the appearance of parasitic replicators is a critical problem for the replication system and successfully overcome this problem by encapsulating the reaction into microcompartments. The results demonstrate that a mechanism for repression of parasitic replicators is required to achieve a long-lasting genome replication system, providing important insights for the possible design of an artificial cell.



Blocking Inflammation through DOCK2

PAGE 488

Tissue infiltration of activated lymphocytes is a hallmark of transplant rejection and organ-specific autoimmune diseases. DOCK2 plays a key role in migration and activation of lymphocytes, and its deficiency prevents rejection of cardiac allografts and development of autoimmune diabetes in mouse models. Therefore, DOCK2 may serve as a molecular target for controlling immune-related disorders. Here, Nishikimi et al. have identified CPYPP as a small-molecule inhibitor of DOCK2. When lymphocytes were treated with CPYPP, both chemotactic response and T cell activation were markedly suppressed. These findings provide basis for development of the DOCK2-targeting immunosuppressant.

Transporting Mycolic Acids

PAGE 498

Mycolic acids are key components of the cell wall of *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), and play an important role in virulence. While the biosynthesis of these characteristic fatty acids has been well studied, components of the transport machinery for mycolic acids remained unknown. The study by Varela et al. demonstrates that MmpL3, a large membrane-associated mycobacterial protein, is involved in the transport of mycolic acids in the form of a glycolipid, trehalose monomycolate. The gene encoding MmpL3 is also essential for growth highlighting its potential as a new drug target.

Phototswitchable LOV

PAGE 507

Photocontrol of functional peptides is a powerful tool for spatial and temporal control of cell signaling events. Lungu et al. use genetically encoded light-sensitive AsLOV2 domain to reversibly photomodulate the affinity of two peptides for their binding partners. These peptides were embedded into the Jα helix of the AsLOV2 domain while maintaining AsLOV2 structure in the dark, but allowing for binding to effector proteins in the light. Caged versions of the ipaA and SsrA peptides, LOV-ipaA and LOV-SsrA, bind their targets with enhanced affinity in the light, thus enabling light-dependent photoactivatable gene transcription in yeast.

Knocking Down HPV

PAGE 518

The human papillomavirus (HPV) oncoprotein E7, as well as other viral oncoproteins, bind to and inactivate the retinoblastoma protein pRb. This inactivation can lead to a number of diseases, ranging from benign warts to cancers of the cervix and other organs. Consequently, it is of interest to target this protein-protein interaction with small molecules. Here, Fera et al. describe the development of a class of small molecule compounds that inhibit E7-pRb interaction and are selectively cytotoxic in HPV-positive cells. These compounds provide a promising scaffold for the development of therapies to treat HPV-mediated pathologies.

Inhibiting c-Fes

PAGE 529

The c-Fes protein-tyrosine kinase regulates cellular differentiation, the innate immune response, and vasculogenesis. Here Hellwig et al. report the identification of kinase inhibitors with potent activity against c-Fes both in vitro and in cell-based assays, one of which is the anaplastic lymphoma kinase inhibitor TAE684. The authors solve a crystal structure of TAE684 in complex with the c-Fes SH2-kinase domain unit and find excellent shape complementarity with the ATP-binding pocket and a key role for the gatekeeper methionine in inhibitor binding. TAE684 and other nanomolar inhibitors identified in this study were used to establish a new role for c-Fes in osteoclast differentiation from macrophages, identifying Fes as a potential drug target in osteoporosis.