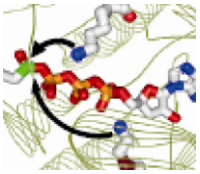
In This Issue

Targeting Sec Translocase Traffic Jam with Motor Inhibitors

PAGE 685

New antibiotic targets are currently being explored in the search for new therapies to combat infections caused by multidrug resistant bacteria. In this review, Segers and Anné provide an overview of research efforts on the discovery of small-molecule inhibitors of SecA, a central component of the bacterial secretory pathway. Recent advances regarding the structure and function of SecA and their potential impact on antibacterial drug discovery are discussed, suggesting that although the SecA active site is not an ideal drug target, it might be possible to develop inhibitors to disrupt the interaction of SecA with its various protein ligands.



In Situ Kinase Profiling

PAGE 699

Here, Patricelli et al. show that profiling of native kinases in cell or tissue lysates using active-site-directed probes enables comprehensive determination of inhibitor potency and selectivity in a species-independent manner. They observe strong correlation between probe-based IC_{50} values and in vivo efficacy for several kinase inhibitors and demonstrate the predictive power of probe-based studies. Moreover, differences in inhibitor potency for recombinant and native enzymes are presented that highlight the value of native kinase profiling in drug discovery efforts, which together with observations of inhibitor-induced kinase activation, further demonstrate the value of kinase probes directed to active sites.

Plasmodium: Welcome to the SUMO Game

PAGE 711

Small ubiquitin-related modifier (SUMO) is implicated in the regulation of numerous biological processes, including transcription, protein localization, and cell cycle control. In *Plasmodium falciparum*, the parasite that causes human malaria, the functional significance of SUMO modification is unclear. Here, Ponder et al. describe the expression and characterization of an active SUMO regulatory protease of *P. falciparum*, PfSENP1. Subsequent screening of a small molecule library identified a compound that inhibited PfSENP1 and induced parasite death, indicating that PfSENP1 may be a viable drug target. These inhibitors are likely to be valuable tools for studying SUMOylation in parasites and other eukaryotic systems.

New Probes for SENPs

PAGE 722

A commonly used yet poorly understood mechanism for posttranslation regulation of proteins is the addition of a small ubiquitin-like modifer (SUMO) protein tag. Recent efforts have begun to uncover the repertoire of proteins that are regulated through SUMOylation. However, SUMO modification is dynamic, making it difficult to monitor the temporal aspects of this posttranslational process. Here, Albrow et al. describe the design and synthesis of small molecule inhibitors of the human SUMO-specific proteases (SENPs) that can be used to block SUMO removal from substrates, thus allowing more comprehensive studies of SUMOylation pathways in the cell.

Rhodopsin Photoactivation: Less (Isomerization) Than Meets the Eye

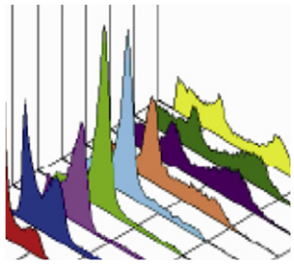
PAGE 733

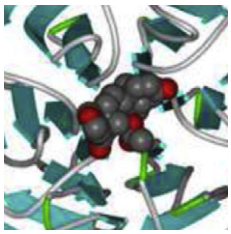
Light absorbed by the N-retinylidene chromophore of the visual receptor rhodopsin triggers electron motion along the chromophore. The conserved, highly polarizable amino acid residues surrounding the chromophore capture light absorption by translating the electron motion into protein conformational change essential for rhodopsin activation. Using a rhodopsin from *Chlamydomonas,* Foster el al. show that completely nonisomerizable chromophores retain full photoactivation of rhodopsin. This electronic activation mechanism is applicable to all rhodopsins, as they all have N-retinylidene chromophores that are located in a trough of highly polarizable amino acid residues. Notably, related GPCRs for pharmaceutical ligands share a similar electron motion mechanism.

TOP(2) Inhibition: New Approach to Cancer Therapy

PAGE 743

Identifying the molecular target of uncharacterized bioactive small molecules is a crucial step in drug development and chemical genetic studies. Using their recently developed proteomic profiling approach, Kawatani et al. identify the target of BNS-22, which has antiproliferative activity against human cancer cells, as DNA topoisomerase II (TOP2) and show that it acts as a catalytic inhibitor in a cell system. This study identified a new structural class of TOP2 inhibitors that can be used to treat cancers with high levels of DNA repair, which currently compromise the therapeutic effects of DNA-damaging agents.





Attacking Oxidative Stress on All Fronts

PAGE 752

Oxidative stress is a recognized mediator of many neurological conditions including stroke, spinal cord injury, Parkinson's disease, and Alzheimer's disease, but there is also growing recognition that "oxidative stress" cannot be therapeutically defeated with a single antioxidant scavenger. An alternative approach is to induce a broad range of genes capable of neutralizing the deleterious effects of many oxidants. Here, Smirnova et al. describe a novel reporter assay, ideally suited for high throughput screening, to identify direct activators of Nrf-2 transcription factor, a master regulator of the antioxidant defense response, which allowed them to find nonoxidant activators.

Role of Protein Homeostasis in Gaucher's Disease

PAGE 766

Lysosomal storage diseases are caused by aberrant accumulation of metabolites in the lysosomes. Gaucher's disease is the most common among these diseases and is characterized by mutations in the gene encoding for lysosomal glucocerebrosidase (GC) that destabilize native folding and lead to rapid degradation. Here, Wang et al. demonstrate that treatment of diseased fibroblasts with the L-type Ca^{2+} channel blocker lacidipine results in increased folding, cellular trafficking, and activity of mutated GC variants. They propose a novel mechanism for protein homeostasis that combines modulation of cellular folding and Ca^{2+} homeostasis, while at the same time protecting from induction of apoptosis.

Targeting SOC in Huntington's Disease

PAGE 777

Huntington's disease (HD) is a neurodegenerative disorder caused by a polyglutamine expansion within the Huntingtin (Htt) protein. Using a phenotypic screen, Wu et al. identified a class of quinazoline-derived compounds that delayed progression of a motor phenotype in transgenic *Drosophila* HD flies. They found that these compounds act by inhibiting store-operated calcium entry (SOC) pathway in HD neurons. The authors conclude that the neuronal SOC pathway constitutes a novel target for HD treatment and that the identified compounds represent a novel class of therapeutic agents for treatment of HD and possibly other neurodegenerative disorders.

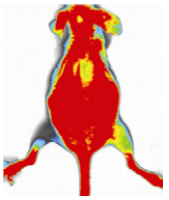
Anamorsin and Mia40: Trapped in the Mitochondria Together

PAGE 794

Here, Banci et al. structurally characterize human anamorsin, implicated in cytosolic Fe/S cluster biogenesis, and show that it binds a [2Fe–2S] cluster. Anamorsin is found to be a novel substrate of Mia40, an oxidoreductase involved in protein trapping in the mitochondrial intermembrane space (IMS). It catalyzes the formation of disulfides in a twin CX_2C motif of anamorsin. Import of anamorsin in the IMS, together with the observation of an intermolecular disulfide-bonded Mia40-anamorsin intermediate, suggest that these interactions exist in mitochondria and that anamorsin plays a role in the cytosolic Fe/S cluster biogenesis, once it is imported in the IMS.

Measuring In Vivo Protein Half-Life

PAGE 805



The rate of turnover of proteins critically influences many biological functions, yet methods have so far been lacking to assess this parameter in vivo. Here, Bojkowska et al. demonstrate that pulse chase labeling of proteins fused to a SNAP-tag, a mutant of human O6-alkylguanine-DNA alkyltransferase, can be exploited to measure the in vivo half-life of proteins in living animals, thereby opening new perspectives for studying in vivo protein function.

