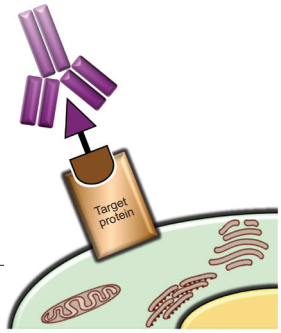
In this ISSUE

acs chemical biology



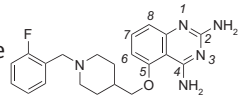
Bifunctional Small Molecules

Much effort is focused on finding small molecules that inhibit interactions between proteins, for such worthy causes as drug discovery and biological exploration. However, manipulating biological processes by *promoting* protein–protein interactions also has both investigative and clinical applications. Bifunctional small molecules are compounds that contain two protein-binding moieties and are thus capable of bringing two proteins close together. Corson *et al.* (p 677) review recent developments in the design and application of bifunctional small molecules.

With their many varying structures and designs, bifunctional small molecules have been used to induce cell signaling events as well as to redirect the localization, promote the proteolysis, or alter the activity of specific proteins. With the ultimate goal of using bifunctional molecules for therapeutic purposes, three classes of bifunctional small molecules developed to date are discussed according to their potential for development in whole organisms.

Incapacitating a Decapper

Discovery of small molecules capable of modulating gene expression is a promising therapeutic approach for the many diseases that are affected by transcriptional regulation. The severity of the devastating motor neuron disease spinal muscular atrophy, which is caused by inactivation of the gene encoding the survival motor neuron protein (SMN), can be reduced upon expression of a duplicate gene SMN2. Indeed, C5-substituted quinazolines can increase SMN2 gene expression, and now Singh *et al.* (p 711) provide intriguing insight into their mechanism of action.



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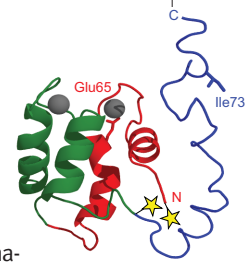
Using protein microarrays and a radiolabeled C5-quinazoline probe, the authors identified the quinazoline target as the nuclear shuttling protein scavenger decapping enzyme (DcpS), a modulator of messenger RNA structure and RNA metabolism.

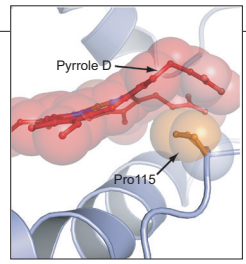
A New Kind of Protein Folding



Biosensors are molecular devices that produce signals in response to a particular substance or event, such as the interaction between a protein and its ligand. Indeed, biosensors have been created from proteins that undergo large conformational changes upon ligand binding. However, this strategy is limited to those proteins that actually do undergo large conformational changes upon ligand binding, a relatively small group. Stratton *et al.* (p 723) describe a new approach to creating biosensors using a concept termed alternate frame folding (AFF).

AFF provides a method for engineering ligand-dependent conformational change into diverse proteins. This clever approach works by duplicating a portion of the protein to produce a second "frame" of folding, essentially creating two mutually exclusive ligand-binding conformations. Strategic insertion of fluorescent tags, either small-molecule fluorophores or genetically encoded fluorescent proteins, enables detection of ligand binding through FRET.

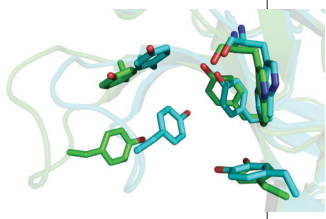
Functional Distortion



Hemoproteins, which include large protein superfamilies such as the globins and the cytochrome P-450s, engage in diverse chemical reactions, and this facilitates their ability to perform a wide range of functions. When bound to a protein, the otherwise planar heme group is distorted, and this distortion is believed to be important for function. Using X-ray crystallography and protein mutagenesis, Olea *et al.* (p 703 and Point of View p 673) investigate the significance of heme distortion in an H-NOX domain from *Thermoanaerobacter tengcongensis* (*Tt* H-Nox), which harbors a highly distorted heme group.

Because interactions between the heme group and a key proline residue appear to be responsible for the large distortion observed in *Tt* H-Nox, the proline was mutated to an alanine. In addition to adopting a reduced heme distortion, the mutant domain exhibited an increased affinity for oxygen, a decreased reduction potential, and a significant conformational change.

An Addictive Approach



Nicotinic acetylcholine receptors (nAChRs) are drug targets for various conditions, including nicotine addiction, neuromuscular disorders, and neurological diseases. Drug candidates targeting nAChRs are typically agonists or competitive antagonists that bind the receptor and either promote or prevent its gating activity, that is, its ability to function as an ion channel. Cation–π interactions at nAChR transmitter binding sites have been implicated in nAChR function, and now Tantama and Licht (p 693) combine computational and experimental methods to explore the link between cation–π interactions and agonist and antagonist activity.

Calculation of cation–π interaction binding energies between benzene and a series of small organic cations, along with experimental evaluation of binding affinities and gating efficiencies, revealed a strong correlation between calculated binding energy and gating efficiency, but not binding affinity.

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