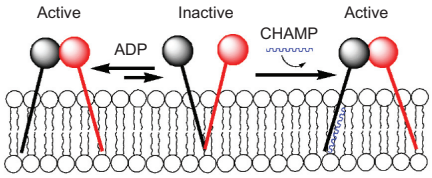
In this ISSUE

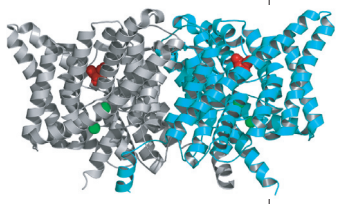
acs chemical biology

Taking Aim at Membrane Proteins

Integral membrane proteins are key components in signal transduction pathways. As such, studying the transmembrane domains of these proteins is necessary to understand how signals pass through biological membranes. Also, targeting these domains often allows cellular activities to be modulated in diseased states. Slivka *et al.* (p 402) review recent approaches to developing rationally designed exogenous peptides that recognize transmembrane domains.



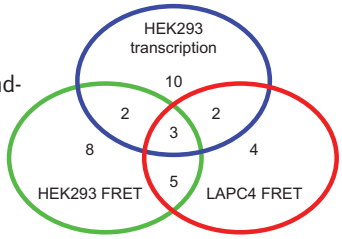
CLC Inhibitors That Click!



Anion-transport proteins, including members of the CLC chloride channel family, are involved in numerous physiological processes. However, the study of CLC chloride-transport proteins has been hindered, in part, by the lack of potent and selective inhibitors. These small molecules could be used to dissect the mechanism of inhibition and also in the design of therapeutics for treating diseases connected to altered chloride transport. Matulef *et al.* (p 419 and Point of View p 399) present the most potent inhibitors of CLC chloride-transport proteins discovered.

While examining the nonspecific, anion-transport inhibitor 4,4-diisothiocyanatostilbene-2,2′-disulfonic acid (DIDS), the authors discovered that the polythiourea hydrolysis products were more potent than the parent isothiocyanate. Interestingly, although DIDS has been used for several decades to study anion-transport proteins, the authors now show that inhibition might in fact be caused by the DIDS-derived polythioureas.

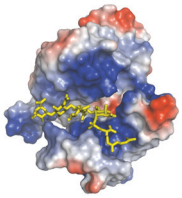
Thinking Outside the Active Site



The androgen receptor (AR) is a transcription factor that undergoes a conformational change upon binding of the natural ligand dihydrotestosterone. Ligand binding occurs prior to nuclear localization and participation in gene activation. In humans, AR is involved in a number of physiological processes. For example, male pattern baldness and prostate enlargement are two conditions linked to AR signaling. Current treatment options aim to prevent ligand binding to AR, and screening for inhibitors of this receptor usually employs transcription-based reporters. However, these are susceptible to nonspecific effects. Now, Jones and Diamond describe a highly specific FRET-based assay linked to conformational changes in AR (p 412).

Using this assay, the authors identify compounds not previously known to inhibit AR. They then demonstrate the efficacy of these compounds in secondary assays. None of the inhibitors tested interfered with ligand binding, an indication of a noncompetitive mechanism. This assay illustrates the efficacy of using a conformation-based screening scheme in identifying inhibitors that might otherwise go unnoticed.

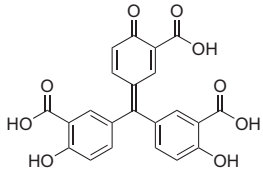
Building a Better Antibiotic



Peptidoglycan is an essential constituent of the bacterial cell wall. Because peptidoglycan is not found in eukaryotes, many current antibiotics target the synthesis of this polymer. Peptidoglycan glycosyltransferases (PGTs), enzymes that catalyze chain formation, are targets of the natural-product antibiotics moenomycins. Recently, the crystal structures of PGT from two organisms with moenomycin A bound to the active site have been resolved. Yuan *et al.* (p 429) present the crystal structure of PGT bound to an active truncated moenomycin A analog at 2.3 Å resolution.

Using the truncated analog neryl-moenomycin A, the authors find that only a small segment of the ligand is involved in critical contacts inside the active site of PGT. Site-directed mutagenesis studies reveal that six conserved active site residues are potentially involved in enzymatic activity. The authors use these data to present a minimal ligand with biological activity, and this should be useful in the design of potent PGT inhibitors.

Protein–DNA Interactions See the Light



One way to gain insight on the metabolism of cells is by perturbing the protein–DNA interactions involved in many essential cellular processes. Small molecules that specifically modulate a number of these interactions are particularly desirable because these compounds often lead to new drugs. However, there are few reliable methodologies for identifying disruptors of protein–DNA interactions that can be used in screening large compound libraries. Chan *et al.* (p 437) describe a platform for the detection of protein–DNA interactions that fills this void.

The authors use photonic crystal biosensors to detect shifts in the wavelength of reflected light upon binding of a protein to an immobilized DNA oligomer. Photonic crystal biosensors can be used for the detection of both sequence-dependent and sequence-independent DNA binding. In addition, the authors discover a novel inhibitor of a protein–DNA interaction using this technology.

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