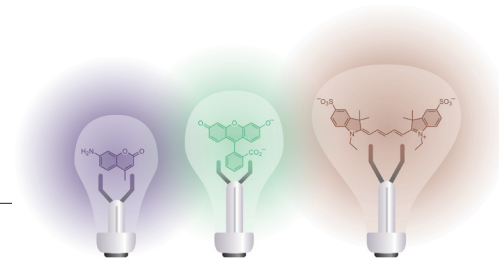
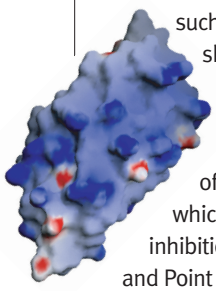
ACS chemical biology

In this ISSUE



Designing a Protein to Thwart Cancer

The chaperone heat shock protein 90 (Hsp90) is essential for the proper folding of many proteins associated with cancers. As a consequence, inhibitors of Hsp90 such as geldanamycin analogues show potential in cancer therapy. Unfortunately, a side effect of many of these drugs is that they promote the production of another chaperone, Hsp70, which offsets the outcome of Hsp90 inhibition. Cortajarena *et al.* (p 161 and Point of View p 140) design a protein module that specifically binds to Hsp90 with great affinity.



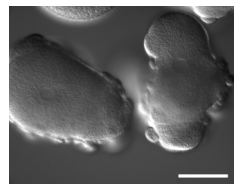
Starting from a stable scaffold, the authors grafted residues to enhance binding. They then solved the X-ray crystal structure of this protein bound to its Hsp90 target. By analyzing this information, the authors further increased the specificity and affinity of their protein toward Hsp90. Because this engineered protein binds better than the natural Hsp90 binding domain, it can inhibit chaperone activity. Introducing this designed module into cells results in the marked reduction of levels of a protein associated with cancer that requires Hsp90 function for proper folding. In addition, this new module could also be used as a tool to study protein folding in normal and cancer cells.

A One-Stop Source for Fluorescent Molecules

Fluorescent small molecules are widely used as environmental and cellular dyes and as substrates and labels for biological macromolecules. The design of a fluorescent small molecule is based on the fluorophore (which imparts fluorescence) and on the functional groups needed for the specific target under investigation. Choosing the right fluorescent compound is often a laborious task because of the large number of possible molecules that are available commercially and through chemical synthesis in the lab. The good news is that a plethora of functional groups are attached to a few core fluorophores. Lavis and Raines (p 142) discuss the chemical properties of the core fluorophores used in biological research.

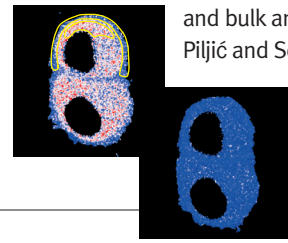
A Chemical that Disrupts Cell Division

Bisphenol A (BPA) is a man-made compound found in a number of synthetic products such as polycarbonate plastics, resins, and adhesives. Previously, it had been suggested that BPA interferes with cell division. However, details of how exactly BPA disrupts this process at a molecular level had yet to be revealed. George *et al.* (p 167) describe a novel process for identifying cellular targets of BPA. Using this approach, the authors showed that this compound binds to tubulin and stimulates microtubule assembly *in vitro*. In addition, the authors found that treating embryonic or somatic cells with BPA led to mistakes in mitotic spindle assembly and to the formation of multipolar spindles.



A Time and a Place to FRET

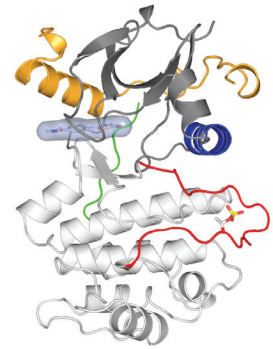
FRET is used to study interactions in many intracellular processes. However, a serious limitation of current FRET approaches is that most of them only allow the study of one process in a cell at a time. Studying different cellular processes is currently possible by taking a large number of variable measurements or by extrapolating from separate single experiments. Neither approach is ideal because many cellular processes have well-defined spatial and temporal characteristics. Information on timing is hard to glean from separate experiments, and bulk analysis yields little meaningful data on cellular localization. Piljić and Schultz (p 156) describe, for the first time, the simultaneous quantitative measurement of events within a single cell using multiple ratiometric FRET sensors. The utility of this new technology is demonstrated by monitoring three events triggered by different levels of calcium.



Stop that Kinase!

Certain enzymes known as aurora kinases regulate important events during mitosis. Abnormal regulation of the genes encoding these proteins has been implicated in cancer cells. So, to study the normal function of aurora kinases, it would be useful to have small molecules that are selective inhibitors of these enzymes. Such small molecules might also be helpful in designing potent therapeutics for treating cancer. Andersen *et al.* (p 180) describe the discovery and detailed characterization of inhibitors that specifically target Aurora kinases.

The authors discovered the selectivity of an aminothiazole to Aurora kinases by screening against a panel of kinase enzymes. Using this aminothiazole as a lead, the authors synthesized a fluorescent derivative, which enabled them to study the mechanism of binding in greater detail. A comprehensive study of structure–activity relationships yielded improved selective inhibitors of Aurora kinases. Elucidation of the crystal structure of an Aurora kinase with an inhibitor explains the selectivity and the mode of inhibition of these compounds. Finally, the authors characterized the activity of these inhibitors in *Xenopus* egg extract and in cells.



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