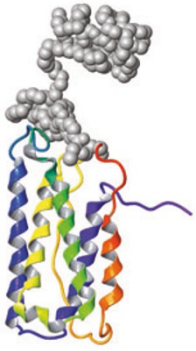
IN THIS ISSUE

COVER STORY

In the laboratory, drugs are optimized for their effect on a known target. However, in practice drugs often interact with unintended targets, which may lead to side effects. Michnick, Westwick and co-workers have now developed an assay for uncovering these off-target effects and 'hidden' phenotypes. By using protein-fragment complementation, the authors were able to monitor the effects of small molecules on a wide range of cellular processes. By screening 107 known drugs for their effects on cells, the authors found that chemically or therapeutically related molecules had similar effects on both intended and unintended cellular-signaling pathways. The clustering analysis also suggested that four drugs had an unknown antiproliferative phenotype; this was then confirmed biochemically, revealing the power of this assay for uncovering unexpected drug actions. **[Articles, p. 329; News & Views, p. 295]** *JK*

PEGging disulfides



Because disulfide bonds are so structurally important for proteins, scientists have traditionally considered them to be resistant to chemical modification. Shaunak and colleagues have now modified the disulfide bonds of several proteins without significantly decreasing their activity. They used unique chemistry to modify the disulfide bonds in various therapeutic proteins, including interferon α-2b (IFN). The first step was to introduce a three-carbon bridge between internal sulfur atoms of IFN. The carbon bridge then served as a scaffold for introducing PEG. The addition of PEG stabilizes the protein while allowing it to retain its activity, making it potentially useful for hepatitis C therapy. [Brief Communications, p. 312] *MB*

Screening membrane proteins in minutes

Screening membrane proteins for altered function or for small-molecule binding has traditionally been a slow and tedious process. Holden, Bayley and colleagues have now developed a method for rapidly screening membrane proteins. In this method, a glass probe is touched to an *Escherichia coli* colony that is overexpressing the protein of interest. Surprisingly, when the probe is then touched to a planar bilayer, a functional protein is inserted and can be assayed by single-channel recording. This approach was demonstrated for a K^+ channel and a β-barrel protein pore. One hundred individual mutants of the two-component pore leukocidin were successfully screened in just a few hours for combinations that bound to a small-molecule pore blocker. The ease of functionally screening membrane proteins promises to open up new possibilities for proteomic approaches to studying membrane proteins. **[Letters, p. 314; News & Views, p. 298]** *JK*

In this Issue written by Mirella Bucci and Joanne Kotz.

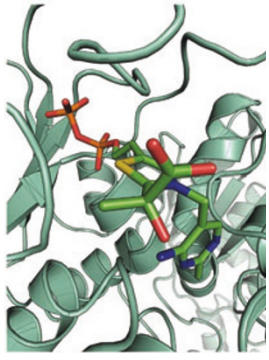
Natural products link death and cancer

Naphthalene and *para*-dichlorobenzene (PDCB) are carcinogenic compounds found in mothballs and air fresheners. Kokel, Xue and colleagues report that the compounds' carcinogenicity could be due to their ability to inhibit cell death. They found that naphthalene and PDCB can inhibit apoptosis in *Caenorhabditis elegans*, leading to a developmental delay and a reduced brood size. They also show that 1,4-naphthoquinone, a naphthalene metabolite, can inactivate caspases *in vitro* by oxidizing the active site cysteine residue. Naphthalene and PDCB are the first small-molecule inhibitors of apoptosis identified in *C. elegans*, and this discovery lends support to the idea that a decrease in cell death can lead to carcinogenesis. **[Letters, p. 338]** *MB*

A model for Huntington disease onset

Huntington disease is a neurodegenerative disorder caused by an expansion of polyglutamines (polyQ) in the first exon of the *huntingtin* gene. Huntingtin proteins containing long polyQ expansions are prone to aggregation, which is thought to be the major contributor to the onset of disease. Because of this, the age of onset of Huntington disease is indirectly proportional to the length of the polyQ expansion. Colby, Wittrup and colleagues used probabilistic mathematical modeling to develop and test an equation that connects the molecular mechanism of early aggregate formation (nucleation) to the stochastic formation of aggregates within cells. The kinetics of aggregate formation in cells suggest that the nucleation event is the rate-limiting step to aggregate formation and that nucleation also correlates with the age of onset of the disease. One strategy for delaying disease onset, then, is to reduce the level of mutant huntingtin being expressed so as to minimize nucleation of aggregates. [Articles, p. 319; News & Views, p. 297] *MB*

Photogenic thiamin diphosphate



Pyruvate oxidase is a thiamin diphosphate (ThDP) enzyme whose catalytic cycle goes through several intermediates. The cycle begins with the formation of a tetrahedral adduct (2-lactyl-ThDP) with the substrate pyruvate and ends with a reduced 2-acetyl-ThDP. Wille, Tittmann and colleagues were able to follow each ThDP intermediate using NMR. They could then adjust the reaction conditions to trap three of the intermediates for cryocrystallography. Their extensive X-ray structural data suggests a coupling between electron transfer and a phosphate-linked acyl transfer, making this the first description of a radical-based phosphate transfer in an enzyme. **[Letters, p. 324; News & Views, p. 294]** *MB*