line carried a different DNA sequence, and the researchers engineered the mice such that DNA sequences that were *bona fide* enhancers could be identified on the basis of their ability to turn on expression of a reporter gene (**Fig. 1**).

Using this strategy, the researches identified many new enhancers, with approximately half of the sequences they tested in mice functioning as actual enhancers. Pennacchio cautions, though, that this strategy does have certain limitations, and may be biased toward identifying particular classes of enhancers: "We have currently focused on an extreme version of human genome noncoding conservation and these elements are not randomly distributed. Rather they are highly clustered and biased toward transcription factors and other key developmental genes (likely due to the extreme constraint on the regulation of genes important in vertebrate body plan development)". Additionally, enhancers that are active in an adult, but not during embryonic development, would be missed because the enhancer activity screen is only performed at an embryonic time point.

Nonetheless, this approach has proven to be very effective at enhancer identification. In fact, since their initial study, the researchers have continued their efforts to identify new enhancers and are doing so at an impressive rate. Pennacchio explains, "In this study, in our first pass, we tested ~170 elements in about a year and are now testing closer to 500 per year. With an enhancer identification success rate of ~50%, we are quickly surpassing the cumulative number of enhancers identified by all investigators to date."

Jesse Potash

RESEARCH PAPERS

Pennacchio, L.A. *et al. In vivo* enhancer analysis of human conserved non-coding sequences. *Nature* **444**, 499–502 (2006).

than with small-molecule inhibition. "The advantage of the small-molecule inhibitor is that you can get a quick picture of what the acute effects are of inactivating an enzyme," explains Cravatt, whereas "the shRNA approach gives you a steady-state picture of what an inactivated enzyme looks like over many days," which will certainly be important for evaluating potential drug targets. Additionally, mice injected with shKIAA1363 cancer cells showed reduced tumor growth compared to those injected with control cancer cells.

This powerful approach allowed the researchers to place KIAA1363 at a central node in an ether lipid signaling network. "This paper really shows, I think for the first time, that one can go into a complex biological model like a human cancer cell and annotate a disease-relevant protein using purely systems biology methods. We didn't have to recombinantly express or purify the enzyme at all to figure any of this stuff out," says Cravatt. As opposed to the more classical 'test-tube' enzyme characterization, Cravatt explains, "being able to do these experiments in living systems is really valuable because it allows you to circumvent potential *in vitro* artifacts related to what an enzyme can do versus what it really does do."

Allison Doerr

RESEARCH PAPERS

Chiang, K.P. *et al.* An enzyme that regulates ether lipid signaling pathways in cancer annotated by multidimensional profiling. *Chem. Biol.* **13**, 1041–1050 (2006).

NEWS IN BRIEF

IMAGING AND VISUALIZATION

Welcoming an improved blue fluorescent protein

Though a rainbow of genetically encodable fluorescent proteins are available for biological imaging applications, existing blue fluorescent protein (BFP) variants were rather dim, had low quantum yields and underwent rapid photobleaching. By repacking the BFP core to make the chromophore more rigid, Mena *et al.* have developed a new BFP named Azurite with greatly improved properties for biological imaging in both bacterial and mammalian systems.

Mena, M.A. *et al. Nat. Biotechnol.*; published online 19 November 2006.

PROTEOMICS

A quantitative picture of the synaptic vesicle

Using a battery of proteomics, biophysical, imaging and modeling technologies, Takamori *et al.* have constructed the first detailed, quantitative model of a trafficking organelle—the synaptic vesicle. They determined its size, density and mass, its full protein and lipid composition, and the copy numbers of major constituents. This complete model sets the stage for future quantitative trafficking studies.

Takamori, S. *et al. Cell* **127**, 831–846 (2006).

STEM CELLS

Small-molecule stem-cell maintenance

There is currently much to learn about the molecular cues that cause embryonic stem cells (ESCs) to remain in an undifferentiated state. Normally, when ESCs are grown *in vitro*, feeder cells are used to help them remain undifferentiated. Using high-throughput screening of chemical libraries, Chen *et al.* identified a new small molecule that can be used to maintain mouse ESCs in an undifferentiated state, even in the absence of feeder cells.

Chen, S. *et al. Proc. Natl. Acad. Sci. USA* **103**, 17266–17271 (2006).

SPECTROSCOPY

Elementary insights into an enzyme mechanism

Using a combination of colloidal probe atomic force microscopy and a quartz crystal microbalance, Suzuki *et al.* obtained an extremely detailed picture of the specific elementary interactions taking place in an enzymatic reaction. For the first time, they were able to investigate the complex interactions between the heptaprenyl disphosphate synthase enzyme subunits, a cofactor and a substrate.

Suzuki, T. *et al. J. Am. Chem. Soc.* **128**, 15209–15214 (2006).

PROTEIN BIOCHEMISTRY

A method for selective sulfation

Tyrosine sulfation is a common post-translational modification found in eukaryotic proteins, yet tools to probe the biological function of this modification have been lacking. Liu and Schultz now describe a method for the selective, recombinant incorporation of sulfotyrosines into proteins by an orthogonal tRNA–aminoacyl-tRNA synthetase pair assigned to the amber nonsense codon. They expressed sulfo-hirudin in *Escherichia coli*, which previously could not be made using recombinant methods.

Liu, C.C. & Schultz, P.G. *Nat. Biotechnol.* **24**, 1436–1440 (2006).