

## METHODS IN BRIEF

## CHEMICAL BIOLOGY

## Targeting deubiquitinating enzymes

Ubiquitin (Ub) is conjugated to proteins via an E1→E2→E3 enzyme cascade, a process reversed by deubiquitinating enzymes (DUBs). There are 58 known human Ub-specific proteases (USPs), representing half of the known DUBs. Ernst *et al.* report a strategy for developing highly potent, specific inhibitors of USPs, which can also be expanded to other DUBs and E2 and E3 enzymes. All USPs share a common ubiquitin-binding fold, but because Ub binds to USPs with low affinity and a large binding area, the researchers reasoned that they could make Ub mutants with enhanced affinity for specific USPs. Using a phage-display selection strategy, they identified Ub variants that served as specific inhibitors of four USPs, which they confirmed by crystallography. This strategy will allow the development of a useful suite of tools to study the Ub system in greater detail.

Ernst, A. *et al. Science* **339**, 590–595 (2013).

## STEM CELLS

## Reprogramming by derepression

There are now several reports of methods to convert non-neuronal cells, such as fibroblasts, into neurons. Such methods typically involve the ectopic expression of combinations of transcription factors, with or without small molecules. MicroRNAs are known to play a role as well. Xue *et al.* now report a new twist in this tale: the researchers showed that reducing levels of the polypyrimidine tract-binding (PTB) protein, a process that occurs during brain development, can also do the job. Knockdown of PTB with short hairpin RNA converts mouse embryonic fibroblasts and neural progenitor cells to functional neurons and can also differentiate and transdifferentiate human cells to neuron-like cells. This reprogramming is proposed to occur in part through a newly discovered role of PTB, in which it functions with microRNAs to repress neuronal genes.

Xue, Y. *et al. Cell* **152**, 82–96 (2013).

## MODEL ORGANISMS

## Worm behavioral motifs

In the examination of subtle behavioral phenotypes, manual scoring has several drawbacks. Automated methods are increasingly being applied to mitigate these problems: predefined patterns can be rapidly and reproducibly identified by computer algorithms in both static images and video of many model organisms. Brown *et al.* show with *Caenorhabditis elegans* that behavior can also be automatically analyzed without any predefinition, solely on the basis of the patterns present in the data. Starting with video data of about 300 mutant worm strains, the researchers identified recurring behavioral motifs that could be strung together into a profile describing the phenotype of a given strain. Phenotypic profiles can be further compared between strains to generate hypotheses about gene function.

Brown, A.E.X. *et al. Proc. Natl. Acad. Sci. USA* **110**, 791–796 (2013).

## GENE EXPRESSION

## Genome-wide enhancer maps

An active enhancer resides in open chromatin and is marked by histones with specific post-translational modifications (H3K4me1 or H3K27ac). Genome-wide screens for both of these features exist, but they cannot quantify enhancer activity. To do so, Arnold *et al.* developed self-transcribing active regulatory region sequencing (STARR-seq), which takes advantage of the fact that enhancers function independently of their positions relative to a promoter. The researchers cloned randomly sheared genomic DNA from *Drosophila melanogaster* behind a minimal promoter, expecting the enhancers to regulate their own transcription. They transfected S2 cells with these fragments and then sequenced their RNA. The level of enrichment of every fragment correlated with its strength as an enhancer. Interestingly, 30% of strong enhancers were in closed chromatin, indicating that they were not active in the particular cells tested.

Arnold, C.D. *et al. Science* published online (17 January 2013).