METHODS IN BRIEF

CHEMICAL BIOLOGY

Targeting the undruggable proteome

Small molecules are useful for studying protein function, but the vast majority of human proteins lack specific probes. Backus *et al.* report a covalent screening approach allowing one to target these 'undruggable' proteins by treating cells with compounds containing a cysteine-reactive group and blocking other, unreacted cysteines in the proteome with a broadly reactive molecule containing a click chemistry group. Biotin tags labeled with either light or heavy stable isotopes are then clicked onto experimental and dimethylsulfoxide-treated control samples, respectively, to enrich proteins on streptavidin beads before digestion and analysis by quantitative liquid chromatography–mass spectrometry. This process reveals cysteine residues that were bound specifically by the cysteine-reactive compounds. The authors identified covalent ligands for more than 700 cysteines in the proteome, including many for previously undruggable proteins.

Backus, K.M. *et al. Nature* **534**, 570–574 (2016).

MICROBIOLOGY

Profiling rare mutations in bacteria

Spontaneous mutations underlie the diversity of bacteria, but because the per-generation mutation rate is several orders of magnitude lower than the error rates of high-throughput sequencers, it is challenging to detect these mutations accurately. To find such rare mutations in a genomic region of interest, Jee *et al.* designed maximum-depth sequencing (MDS), a strategy that involves the use of a barcoded primer for linear amplification of the target region followed by the addition of a second barcode during subsequent exponential PCR. The researchers profiled the mutation rate of *Escherichia coli* at six target regions and found that it differs by at least an order of magnitude. Their data allowed them to investigate the relationships among transcription, translation and mutation rate and to characterize the types of mutations induced by antibiotics.

Jee, J. *et al. Nature* **534**, 693–696 (2016).

STEM CELLS

Chemical reprogramming to heart cells

Although the conversion of human somatic cells to cardiomyocyte (CM)-like cells has been reported previously, existing methods involve at least one exogenously expressed gene. Recent work from Cao *et al*. describes chemical induction of CM-like cells from human foreskin or lung fibroblasts. After an iterative screening process based in part on prior knowledge, the researchers identified a cocktail of nine small molecules that, in combination with growth factors, result in 6–7% of treated cells expressing the CM marker cardiac troponin T. The resulting ciCMs (chemically induced CM-like cells) are similar molecularly and functionally to human pluripotent stem cell–derived CMs. Furthermore, *in vitro* treatment of fibroblasts with the nine-chemical cocktail yielded cells that resembled CMs when transplanted *in vivo* into the infarcted heart of an immunodeficient mouse.

Cao, N. *et al. Science* **352**, 1216–1220 (2016).

IMAGING

Toward tagging every human protein with GFP

Over ten years ago, Erin O'Shea and colleagues tagged 75% of the yeast proteome with GFP, allowing for image-based analysis of protein localization on a global scale. Now, Leonetti *et al*. describe a CRISPR/Cas9-based method that will facilitate GFP tagging of the roughly 20,000 proteins encoded in the human genome. In their method, purified Cas9 and a desired single guide RNA are electroporated into cells along with a double-stranded DNA that encodes a short fragment of GFP and flanking sequence homologous to the target region. Cas9 editing at the desired target site leads to integration of this DNA and tagging of the protein of interest. The cells themselves stably express the complementary portion of GFP, allowing for formation of fluorescent GFP on the tagged protein. Using this strategy, the team successfully tagged 48 human genes.

Leonetti, M.D. *et al. Proc. Natl. Acad. Sci. USA* **113**, E3501–E3508 (2016).