METHODS IN BRIEF

CHEMICAL BIOLOGY

Inhibition with BOLT

Small-molecule probes are important tools for studying protein function in cells. Identifying potent and specific inhibitors, however, remains a tedious and challenging process. Tsai *et al.* present bioorthogonal ligand tethering (BOLT), a broadly applicable method to selectively and reversibly inhibit proteins. In BOLT, an unnatural amino acid functionalized with a reactive bioorthogonal group is installed on a protein; a ligand for the protein is attached to another bioorthogonal group that reacts with the unnatural amino acid to create a covalent bond. In this manner, the proximity effect allows a ligand with low selectivity for the protein of interest to rapidly bind to that protein, as the authors demonstrate by selectively inhibiting MEK1 and MEK2 in live cells. A photoswitch can also be integrated in the ligand construct, allowing protein activity to be turned on and off with light.

Tsai, Y.-H. *et al. Nat. Chem.* doi:10.1038/nchem.2253 (18 May 2015).

EPIGENETICS

Chromatin accessibility in single cells

The accessibility of chromatin to regulatory proteins provides an important layer of gene expression control, and it varies between tissues. Cusanovich *et al.* now establish genome-wide accessibility mapping in single cells and use combinatorial indexing to profile large numbers of cells. The researchers add barcode sequence–bearing transposase, which preferentially inserts into accessible regions, to uniquely label single permeabilized nuclei deposited in individual wells of 96-well plates. Nuclei are then pooled, redistributed into new wells and lysed, and their contents are amplified with a second barcode and sequenced. The method allows mixed human cell lines to be distinguished by their accessibility landscapes. By pooling nearly 15,000 cells from different experiments, the authors detected ~96% of sites found by bulk-population DNase I hypersensitivity sequencing. The method can detect heterogeneity within a single cell type or distinguish different cell types on the basis of relatively shallow sequencing.

Cusanovich, D.A. *et al. Science* **348**, 910–914 (2015).

STRUCTURAL BIOLOGY

RNA structure by solid-state NMR

RNAs can be tough to crystallize owing to their conformational flexibility, and large RNA complexes are difficult to study by standard solution nuclear magnetic resonance (NMR) spectroscopy. Marchanka *et al.* show that RNA structure can be successfully characterized at high resolution by solid-state NMR (ssNMR) spectroscopy. Although methods for proteins are fairly well established, a challenge particular to RNAs arises from poor chemical-shift dispersion of ribose NMR resonances, which makes resonance assignment difficult. The authors developed a nucleotide labeling scheme for resolving spectral overlap and describe an experimental ssNMR protocol for structure determination. They solved the structure of the 26-mer C/D RNA from *Pyrococcus furiosus* in complex with the protein L7Ae; the method should be particularly useful for solving intractable ribonucleoprotein complex structures.

Marchanka, A. *et al. Nat. Commun.* **6**, 7024 (2015).

CELL BIOLOGY

A high-throughput platform for studying chemotaxis

Eukaryotic cells can sense and move in response to chemical gradients in their environment in a process known as chemotaxis. Despite active research into the sensing mechanism, it remains poorly understood. Collins *et al.* describe a high-throughput approach for studying sensing and chemotaxis that is based on uniform chemical gradients in individual wells of a microwell plate, which are generated by treating agar-embedded photocaged compounds with a gradient of light. Cells grown in the wells are imaged before and after gradient formation, and their trajectories are measured. Automated analyses were developed and applied to study hundreds of cells per well. Using this approach, the authors tested the phenotypic effects of knockdown by 285 short interfering RNAs, leading to new findings regarding proteins that affect the speed and direction of cell movement.

Collins, S.R. *et al. Mol. Sys. Biol.* **11**, 804 (2015).