METHODS IN BRIEF

MICROBIOLOGY

Genome editing in bacteria

To fend off intruding viruses and plasmids, bacteria use CRISPR (clusters of regularly interspaced short palindromic repeat) RNAs to guide foreign nucleic acids to a silencing effector complex. Jinek *et al.* show that in the case of CRISPR effector Cas9, two distinct small RNAs direct the complex to specifically bind and cleave DNA. The authors recognized that the blunt-ended cut created by Cas9 could in principle be used to selectively edit any genome, much as with other gene-targeting nucleases. Yet the system does not require protein engineering, instead needing only Cas9 and one hybrid RNA molecule containing a targeting sequence, making it easy to generate unique RNA-guided nucleases for nearly any locus. They demonstrated the method by producing lesions *in vitro* in plasmid-encoded GFP.

Jinek, M. *et al. Science* **337**, 816–821 (2012).

CHEMICAL BIOLOGY

Expanding the fly's genetic code

Genetic code expansion methods allow unnatural amino acids carrying useful labels such as fluorophores, cross-linkers or reactive chemical handles to be site-specifically incorporated into proteins in cells and organisms. To date, approaches have been developed for *Escherichia coli*, yeast, mammalian cells and even Caenorhabdi*tis elegans*. Bianco *et al.* now describe an amber suppressor aminoacyl-tRNA synthetase/$tRNA_{CUA}$ pair that allows site-specific unnatural amino acid incorporation into proteins in *Drosophila melanogaster*. They showed that the approach worked efficiently in both fly embryos and adult flies, in various tissues and even in a subset of cells within a tissue. The approach should facilitate experiments to probe protein function in the fly such as studying signaling kinetics or mapping transient protein interactions.

Bianco, A. *et al. Nat. Chem. Biol.* **8**, 748–750 (2012).

CHEMICAL BIOLOGY

Mass-barcoded cells

In mass cytometry, metal ions conjugated to binding reagents are used for molecular labeling and are read out by inductively coupled plasma mass spectrometry. The technique has dramatically increased the number of cellular parameters that can be detected in a sample (34 simultaneous measurements, compared to 12 for fluorescence). Bodenmiller *et al.* now demonstrate mass-tag cellular barcoding (MCB) to increase the throughput of this technique via multiplexing. They use binary combinations of seven lanthanide metal ions to multiplex samples from an entire 96-well plate. They apply MCB to detect multiple cell-surface and intracellular components of signaling pathways in human peripheral blood mononuclear cells over time, in multiple donors and in the presence or absence of a panel of inhibitors at several doses.

Bodenmiller, B. *et al. Nat. Biotechnol.* advance online publication (19 August 2012).

EPIGENETICS

Functional variants from chromatin changes

The majority of genetic variation falls outside of coding sequences, in regions where it can be especially challenging to predict whether a given variant has functional consequences for the cell. To find functional clues, Smith *et al.* use formaldehyde-assisted isolation of regulatory elements (FAIRE), which involves cross-linking DNA to histones and then enriching for histone-depleted regions that are likely to be involved in transcription. Their strategy scans for distorted allele ratios at heterozygous loci between FAIRE-enriched and unenriched control samples. Using lymphoblastoid cell lines and commercial chips for genotyping cardiovascular genes, the researchers discovered a variant with a highly distorted allelic ratio that suggests an effect on gene regulation. They confirmed that the allele is associated with plasma cholesterol levels.

Smith, A.J.P. *et al. PloS Genet.* **8**, e1002908 (2012).

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