TOOLS IN BRIEF

SYNTHETIC BIOLOGY

Programming transcription

In a cell's intricately regulated gene expression network, transcription factors (TFs) call the shots. If we fully understood how TFs operate, not only would we understand gene regulation but we could also use this understanding to engineer gene circuits for biotechnology purposes. Khalil *et al.* took a step in this direction. They constructed synthetic TFs consisting of a zinc-finger domain that binds a user-specified sequence within an engineered promoter, an activation domain that recruits the transcription machinery and a protein-protein interaction domain that interacts with other TFs. The researchers created a library of such TFs and engineered cooperative transcriptional systems in yeast that use the multimerization of weak TFs to fine-tune expression levels. These modular complexes are more like their natural counterparts, and the synthetic recapitulation of transcriptional regulation will allow insights into how a cell regulates its transcription.

Khalil, A.S. *et al. Cell* **150**, 647–658 (2012).

MOLECULAR ENGINEERING

Improved TALE tools

The DNA binding domains of transcription activator–like effector (TALE) proteins from *Xanthomonas* are very promising for precise genomic targeting of various enzymatic activities. TALE DNA-binding domains consist of multiple 34-amino-acid repeats, each binding to a single nucleotide. Binding specificity is determined by amino acids 12 and 13, called the repeat variable diresidue (RVD), within each repeat. The TALE toolbox is still being developed. Cong *et al.* conducted a systematic transcription-activation screen to identify an RVD, Asn-His, that recognizes guanine in the target DNA with higher specificity and activity than currently used RVDs. In a separate screen of six transcription repressor domains from multiple species, they identified the mammalian SID domain as an effective repressor of endogenous gene expression when fused to a TALE.

Cong, L. *et al. Nat. Comm.* **3**, 968 (2012).

MASS SPECTROMETRY

Towards single-molecule mass spectrometry

Mass spectrometry is the workhorse of the proteomics field, but it is not a single-molecule technique. However, a fundamentally different technology, in the form of nanoelectromechanical systems (NEMS) resonators, is being developed as a kind of single-molecule mass spectrometer. NEMS resonators detect molecular mass with extremely high sensitivity, as the adsorption of a molecule to the resonator causes a jump in the resonant frequency that is proportional to the mass of the molecule. Hanay *et al.* now show that the NEMS technology can detect the mass of arriving molecules, including gold nanoparticles and human IgM antibodies, in real time as they adsorb to the NEMS resonator. The ability to detect single proteins in real time may eventually open up the possibility of single-cell proteome profiling.

Hanay, M.S. *et al. Nat. Nanotechnol.* **7**, 602–608 (2012).

NEUROSCIENCE

More optogenetic mouse lines

Light-sensitive microbial proteins are frequently used for manipulating the electrical activity of genetically defined cells in the brain and observing how such perturbations affect an animal's behavior. Several labs have generated transgenic mouse lines that express the light-sensitive proteins in a cell type–specific manner, but obtaining sufficiently high expression levels of the proteins in the desired cells for activity control has not been trivial. Working around this problem, Tanaka *et al.* have now generated a line of transgenic mice that expresses a highly light-sensitive version of channelrhodopsin-2 under the control of the *tTA* promoter. To obtain sufficiently high and reliable levels of the light-sensitive protein, the group inserted the transgene as a knock-in into the locus of the β-actin gene. These mice expand the existing repertoire of transgenic lines for optogenetic control that are based on bacterial artificial chromosome transgenics or the Cre-*loxP* system.

Tanaka, K.F. *et al. Cell Rep.* **2**, 397–406 (2012).