IN BRIEF

MICROSCOPY

Whole-brain imaging with ExLLSM

Gao, R. et al. *Science* **363**, eaau8302 (2019).

Expansion microscopy (ExM) has made a splash in the imaging world by allowing super-resolution imaging with conventional microscopes. ExM enlarges and clears samples, and is compatible with multiple probes for imaging of diverse targets. Gao et al. have now combined ExM with lattice light-sheet microscopy (LLSM) for super-resolution structural imaging of the brain. LLSM allows for fast, high-resolution, volumetric imaging with relatively low light doses. With this combination, which they term ExLLSM, the researchers obtained detailed images of the cortical column of the mouse brain, as well as the entire *Drosophila* brain. The researchers also developed bespoke tools to handle the huge amount of generated image data and reconstruct final image volumes from as many as 25,000 tiled subvolumes in each of multiple colors. *RS*

https://doi.org/10.1038/s41592-019-0336-8

BIOPHYSICS

Solid-state nanopores read DNA

Liu, K. et al. *Nat. Commun.* **10**, 3 (2019).

Nanopore sequencing allows the reading of individual, long DNA molecules, but the protein-based nanopores currently used for nucleotide-level resolution are only one form of nanopore. The need to embed them in a lipid bilayer and their larger structure are drawbacks that could be addressed with solid-state pores. Liu et al. focus on thin MoS_2 pores and show that they can detect topological alterations in DNA. The researchers created a DNA molecule with a single-strand segment sandwiched between two double-stranded ends. They measured the change in current as the DNA translocated through the 3-nm pore and saw that while only 10% of events were complete translocations of the entire molecule, the different strand topologies could be distinguished. When they probed a single-strand DNA with a small barcoded oligo hybridized close to one end, the current trace clearly distinguished the barcoded region. The authors see potential utility of these thin solid-state pores as biomarker sensors; the pores could also be used to probe whether DNA of unknown sequence pairs with known barcodes. *NR*

https://doi.org/10.1038/s41592-019-0337-7

GENETICS

A light-dependent Flp recombinase

Jung, H. et al. *Nat. Commun.* **10**, 314 (2019).

Inducible Cre variants are widely used tools in the mouse for controlling gene expression in a spatiotemporal manner. Jung et al. report a photoactivatable Flp recombinase (PA-Flp) that can be used as an alternative to or in combination with Cre. The researchers identified a suitable split site within Flp. They then combined the split Flp with the Magnet system, which leads to reconstitution upon blue light illumination. The researchers optimized the tool in cell culture and then applied PA-Flp in the mouse brain to precisely control the expression of a reporter gene. Furthermore, they combined PA-Flp with a Flp-dependent Cre construct to control the expression of a small hairpin RNA targeting a calcium channel in GABAergic neurons in the medial septum. This treatment resulted in increased object-exploration behavior in the mice. Although not yet explored, PA-Flp could be used for further spatial and temporal refinement of Cre-dependent gene expression. *NV*

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CHEMICAL BIOLOGY

A trap for intermediate enzyme complexes

Huguenin-Dezot, N. et al. *Nature* **565**, 112–117 (2019).

Many enzymatic reactions, including those of serine hydrolases and cysteine proteases, proceed via the formation of an unstable acyl-enzyme intermediate. Because these intermediates exist in fleeting states, they are hard to study structurally, which prevents mechanistic analysis. Huguenin-Dezot et al. describe a trapping strategy for stabilizing such intermediate enzyme states. By using genetic code expansion methods, they incorporate the unnatural amino acid DAP (2,3-diaminopropionic acid) into an enzyme of interest, in place of the catalytic serine or cysteine residue. DAP acts as a nucleophile, forming an amide bond with the enzyme substrate, and effectively trapping the acyl-enzyme intermediate. The trapped intermediate states are more amenable to structure determination, such as by X-ray crystallography. The authors applied this approach to study the mechanism by which valinomycin synthetase oligomerizes and cyclizes its tetradepsipetidyl substrate to produce the natural product valinomycin. *AD*

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