NEUROSCIENCE

Multifunctional miniature microscopy

Senarathna, J. et al. *Nat. Commun.* **10**, 99 (2019).

Current miniature microscopes are limited to either fluorescence or hemodynamic imaging. Senarathna et al. developed a multi-contrast miniature microscope that is capable of imaging fluorescence signals, intrinsic optical signals, and laser speckle contrast at a resolution of 5 µm. Thus, it is possible to visualize neuronal activity, changes in cerebral blood volume, and cerebral blood flow with the same device. The microscope's effective weight is 3 g, which is well tolerated by freely moving mice. The researchers applied the miniature microscope to visualize the responses to auditory stimuli in freely behaving mice. Furthermore, the researchers combined their multi-modal imaging with EEG recordings in mice awaking from anesthesia. Finally, they monitored the progression of a fluorescently labeled tumor and its effect on the vasculature. This work highlights the power of multi-modal imaging in freely behaving animals. *NV*

https://doi.org/10.1038/s41592-019-0340-z

GENOMICS

Inhibiting CRISPR

Nakamura, M. et al. *Nat. Commun.* **10**, 194 (2019).
Li, B. et al. *Cell Rep.* **25**, 3262–3272 (2018).

To make genome-editing applications more specific, it is desirable to fine-tune the temporal window during which CRISPR nucleases are active and to find ways to terminate their activity. Two research groups explored different ways to inhibit various functions of Cas proteins. Nakamura et al. characterized five anti-CRISPR (Acr) proteins for their inhibitory effects on Cas9 during gene activation and repression. They found AcrIIA4 to be the most potent inhibitor. Its expression protects a cell against CRISPR activity, which the authors say can be used as a prophylactic option if gene editing is to be limited in a population of organisms. Li et al. focused on Cas12a and found that a DNA oligonucleotide with phosphorothioate modifications potently inhibited the cleavage activity of Cas12a. They showed that the oligo forms a ternary complex with the guide RNA and Cas12a and prevents binding of the complex to the target DNA. Synthetic oligos and naturally occurring Acr proteins provide complementary ways to fine-tune CRISPR activities. *NR*

https://doi.org/10.1038/s41592-019-0341-y

MICROSCOPY

Sound sculpts light

Chamanzar, M. et al. *Nat. Commun.* **10**, 92 (2019).

A major challenge of optical imaging is that most biological tissues scatter light, which in many cases precludes light delivery beyond a few millimeters. Chamanzar et al. have developed a unique approach for steering and confining light within scattering samples by using ultrasound. This approach works because the applied acoustic waves change the local density and therefore the refractive index within the sample. The researchers demonstrated the use of acousto-optic confinement to generate optical waveguides by creating regions of high refractive index flanked by low-index regions. They further showed that the method can steer light through 240-µm-thick mouse brain slices. The promise of this approach is that it can be used to form desired light patterns within tissues, for advanced deep tissue imaging applications. *RS*

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PROTEOMICS

An FDR metric for top-down proteomics

LeDuc, R. D. et al. *Mol. Cell. Proteomics* https://doi.org/10.1074/mcp.RA118.000993 (2019).

Most proteomic analyses are carried out using a 'bottom-up' strategy, in which the proteome sample is digested into peptides. Mass spectrometry analysis of such peptides is powerful and straightforward, but valuable biological information about sequence variants and combinatorial post-translational modifications can be lost upon digestion. In contrast, the 'top-down' approach avoids digestion and instead analyzes intact proteoforms, but multiple technical challenges have prevented its deployment in large-scale proteome analyses. One particular impediment has been the absence of a method for determining the false discovery rate (FDR), for assessing the accuracy of the results. LeDuc et al. present a statistical approach for calculating accurate FDR at the four different molecular levels of identification: proteoform–spectral match, protein, isoform, and proteoform. The authors benchmarked their approach by analyzing known proteoforms, and they provide a tool, TDCD_FDR_Calculator, which should help enhance the quality of top-down results. *AD*

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