IN BRIEF

GENOMICS

RNA editing with endogenous ADARs

Merkle, T. et al. *Nat. Biotechnol.* **37**, 133–138 (2019).

Making changes in the genome after double-strand breaks in the DNA bears the risk of unintended mutations. Making changes by editing RNA, in contrast, involves no such breaks and is thus considered a safer method. Merkle et al. improve site-directed RNA editing by no longer relying on overexpression of the enzyme needed to introduce a base change, adenosine deaminase acting on RNA (ADAR), and instead recruiting endogenous enzymes. Their RESTORE method recruits the ADAR via a bipartite antisense oligo (ASO): an optimized hairpin binds to the enzyme, and a single-stranded sequence with chemical modifications binds the complementary RNA sequence of interest. The researchers show editing of several endogenous transcripts in cultured cell lines and disease-relevant loci in human primary cells. Off-target analysis by RNA-seq demonstrated high specificity of editing. While this work focuses on ADAR1, ASOs could be further modified to recruit other ADAR isoforms. *NR*

https://doi.org/10.1038/s41592-019-0380-4

PROTEOMICS

Template-free visual proteomics

Xu, M. et al. *Structure* https://doi.org/10.1016/j.str.2019.01.005 (2019).

Cryo-electron tomography (cryo-ET) potentially offers a powerful way to map macromolecular complexes in cells frozen in a close-to-native state. Identifying and locating complexes in the crowded environment of a cell is challenging, however. Most current methods use known structures as templates for mapping complexes, but this approach is inherently limited and cannot be applied to unknown structures. Xu et al. report a template-free method that they call "multi-pattern pursuit" and that applies a pattern-generation, selection, and alignment approach to map the locations of complexes in cellular tomograms without using information from known structures. The researchers tested their method using simulated, crowded mixtures of complexes, and also applied it to discover patterns in three different experimental cellular tomograms of whole bacteria. Though still at a proof-of-principle stage, the method shows promise for 'visual proteomics' investigations of single cells. *AD*

https://doi.org/10.1038/s41592-019-0382-2

NEUROSCIENCE

Mapping the marmoset brain

Lin, M. K. et al. *eLife* **8**, e40042 (2019).

Connectivity maps of the brain serve as a template for functional and behavioral studies, as exemplified by the maps available for the mouse brain. Lin et al. now outline a histological and computational pipeline for generating such a connectivity map for the marmoset brain. Marmosets are New World monkeys that are attractive as models because of their social behaviors, their small brain size, and the availability of molecular tools. The standardized workflow for mapping the marmoset brain involves in vivo magnetic resonance imaging (MRI) of the brain, injections of anterograde and retrograde tracers into multiple brain regions in a grid-like pattern, ex vivo MRI, and cryo-sectioning of the brain. The brain sections are then subjected to various staining procedures followed by imaging. The acquired images are registered to each other and to a reference brain atlas. The whole pipeline takes about one month for a single brain. The researchers expect that at the current processing rate, the connectivity map for the marmoset brain will be completed by 2024, although collaborative efforts would speed this up. *NV*

https://doi.org/10.1038/s41592-019-0381-3

MICROSCOPY

On algorithmic resolution

Cohen, E. A. K. et al. *Nat. Commun.* **10**, 793 (2019).

Single-molecule localization microscopy methods such as photoactivated localization microscopy (PALM) and stochastic optical reconstruction microscopy (STORM) rely on image-processing algorithms that identify the positions of individual fluorescent emitters in a given frame en route to full image reconstruction. The resolution of these images is intricately linked to algorithm performance, yet no approaches have been available to evaluate the resolving capabilities of such al gorithms. Cohen et al. addressed this challenge by using spatial statistics to explore the impact of algorithm performance on resolution. They found that achievable resolution varies widely among the tools tested, with some being much larger than diffraction-limited resolution. They also show that these differences can affect downstream analysis, such as the quantitative analysis of protein clustering. However, they show that incorporation of the known algorithmic resolution can be used to correct clustering analysis for accurate results. *RS*

https://doi.org/10.1038/s41592-019-0383-1