IN BRIEF

CHEMICAL BIOLOGY

Reversible covalent inhibitor target search

Senkane, K. et al. *Angew. Chem.* https://doi.org/10.1002/ange.201905829 (2019).

Small molecules and drugs that target active-site residues can be useful in clinical and biological applications. One class of small molecules is reversible covalent inhibitors, which allow sustained target engagement but entail lower immunogenicity risks and fewer off-target effects than irreversible covalent inhibitors. Senkane et al. describe a mass-spectrometry-based method for proteome-wide evaluation of reversible inhibitor targets. The method integrates gel filtration (GF) and activity-based protein profiling to evaluate cysteine residues for reversible and irreversible interactions with α-cyanoacrylamide fragments across the human proteome. The GF step after addition of the electrophile essentially reverses the interaction where it is not permanent, and a comparison of all targets versus post-GF targets reveals the reversible candidates. The experiment showed broad potential with proteins from several classes. In spite of the limitations, such as the fact that certain proteins may unfold during the GF stage, a comprehensive mapping of entire proteomes using a variety of electrophiles has promise for drug development. *AS*

https://doi.org/10.1038/s41592-019-0516-6

SENSORS AND PROBES

Bright labeling with MoonTag

Boersma, S. et al. *Cell* **178**, 1–15 (2019).

The SunTag has gained popularity in microscopy, especially with researchers imaging single molecules, because it allows numerous copies of GFP to be recruited to a protein of interest for bright signals. Boersma et al. have now developed MoonTag, a tag that is analogous to the SunTag but fully orthogonal. The MoonTag has two components: multiple copies of a 15-amino-acid peptide (gp41 peptide) and the gp41 nanobody fused to either a red fluorescent protein or HaloTag bound to a fluorescent dye. The protein of interest is tagged with multiple copies of the gp41 peptide, which, when translated, recruits the fluorescently tagged gp41 nanobody. The researchers used both tags to study heterogeneity in translation-start-site selection in mammalian cells, where they found that alternative-start-site selection and out-of-frame translation are likely to be widespread phenomena for many mRNAs. *RS*

https://doi.org/10.1038/s41592-019-0517-5

STEM CELLS

hPSCs on a diet

Cornacchia, D. et al. *Cell Stem Cell* **25**, 120–136 (2019).

Human pluripotent stem cells (hPSCs) can be described as naive or primed, corresponding to pre- or post-implantation epiblast tissue, respectively. These distinct states differ in their transcription factor profile, with genes such as *KLF4*, *ESRRB*, *TFE3* and *STELLA* (*DPPA3*) being upregulated in naive hPSCs. However, the boundaries are fluid, and intermediate states are possible. Cornacchia et al. now report that such an intermediate state is induced when hPSCs are maintained in the chemically defined E8 culture medium. E8 hPSCs express some but not all of the markers of naive pluripotency, and they more closely resemble naive hPSCs than primed hPSCs. An important feature of the E8 medium is its lack of lipids, and the researchers found that it is indeed lipid deprivation that induces the naive-to-primed intermediate state. Furthermore, these cells are characterized by an inhibited ERK pathway, a feature they share with naive hPSCs. As E8 hPSCs represent an intermediate developmental stage between naive and primed hPSCs, they may help shed light on the cellular and molecular changes during the implantation process. *NV*

https://doi.org/10.1038/s41592-019-0518-4

GENOMICS

Multi-omics single-cell analysis

Rooijers, K. et al. *Nat. Biotechnol.* **37**, 766–772 (2019).

A plethora of methods have shed light on the molecular features in a single cell, from its transcriptome to its 3D genome structure, and to DNA and histone modifications. Combinatorial approaches have refined the characterization of heterogeneity in single cells even further by linking chromatin features to gene expression in the same cell. Rooijers et al. now add scDam&T-seq, a multi-omics method that queries sites of DNA–protein interaction and gene expression. They combine the overexpression of a bacterial adenine methyltransferase (Dam), which methylates adenine in GATC motifs, with single-cell RNA-seq. Importantly, linear amplification allows the simultaneous processing of the m^6A-labeled genome and mRNA in vitro transcription. The researchers used scDam&T-seq, expressing either free Dam or Dam fused to lamin, to compare the effects of open chromatin and chromatin associated with the nuclear lamina on gene expression. They also probed the effect of chromatin interacting with a polycomb-group protein on gene expression. *NR*

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