TOOLS IN BRIEF

GENOMICS

Big Papi uncovers genetic interactions

Genes form complex networks that underlie development and maintenance of an organism but go awry in disease. To probe pairwise genetic interactions in human cells, Najm *et al.* use Cas9 proteins from two bacterial species together with their optimized single guide RNAs. This dual Cas9 system, Big Papi (paired *aureus* and *pygogenes* for interactions) ensures that no recombination occurs between the two sgRNAs and has high on-target efficiency. The researchers tested for synthetic lethal interactions between 25 genes, targeted by three sgRNAs each, in six cell lines. They also probed the network of 32 proapoptotic and antiapoptotic genes. In addition, they applied Big Papi to overexpress 38 oncogenes with SpCas9–VPR while knocking out 45 tumor suppressor genes with SaCas9, and thus to screen with orthogonal activities.

Najm, F.J. *et al. Nat. Biotechnol.* http://dx.doi.org/10.1038/nbt.4048 (2017).

IMAGING

A colorful series of bioorthogonal probes

Bioorthogonal probes are ideal for fluorescence imaging in living cells via click chemistry. These probes are fluorescent conjugates, in which tetrazine (Tz) often serves as both the bioorthogonal reactive group and the fluorescence quencher. These probes can be 'clicked' to target compounds harboring a *trans*-cyclooctene group. However, the fluorophore component as well as the linker can influence the reactivity of the probes, which is problematic for multiplexed imaging. Lee *et al.* generate a series of Tz conjugates based on Seoul-Fluor that cover a broad range of emission wavelengths and still have similar reactivity. The emission wavelength of Seoul-Fluor can simply be tuned by adding side groups to the fluorophore. The authors demonstrate the application of their probes by imaging microtubules in fixed cells and mitochondria in live cells.

Lee, Y. *et al. JACS* https://doi.org/10.1021/jacs.7b10433 (2017).

STEM CELLS

Biobanking breast cancers

The derivation of cancer cell lines from a wide diversity of patients has been critical for the study of disease mechanisms and drug susceptibility. Sachs *et al.* now extend the idea of a living biobank to cancer organoids, three-dimensional self-organizing cultures derived from adult stem cells. The researchers optimized a growth medium containing a number of niche factors for long-term culture of breast cancer organoids and generated an initial set of over 100 mammary epithelial organoid cultures, representing a wide range of breast cancer subtypes from primary and metastatic tumors. Cultures were characterized by histology, genomic sequencing and gene expression profiling; and they showed physiologically relevant responses when subjected to a high-throughput drug screen targeting the *HER2* pathway. The biobank will be an important and expanding resource for the cancer research community.

Sachs, N. *et al. Cell* https://doi.org/10.1016/j.cell.2017.11.010 (2017).

PROTEOMICS

Cell-type-specific proteomics in the *in vivo* mouse brain

Orthogonal tRNA synthetase-tRNA pairs have been used to tag proteins during translation in a variety of contexts ranging from microbes to cell culture and flies. Krogager *et al.* have adapted the pyrrolysyl-tRNA synthetase-$tRNA_{CAU}$ system to analyze proteomes in the mouse brain in a cell-type-specific manner. The researchers deliver the tool with adeno-associated viruses (AAVs) and achieve cell-type specificity by using neuronal or glial promoters for tRNA synthetase expression. They also generated a Cre-dependent version of the AAV to allow further restriction of the expression pattern. After labeling of the nascent proteome, the tagged proteins can be either visualized or enriched and analyzed by mass spectrometry. The researchers applied their approach to analyze the proteome of neurons in the mouse striatum.

Krogager, T.P. *et al. Nat. Biotechnol.* http://dx.doi.org/10.1038/nbt.4056 (2017).

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