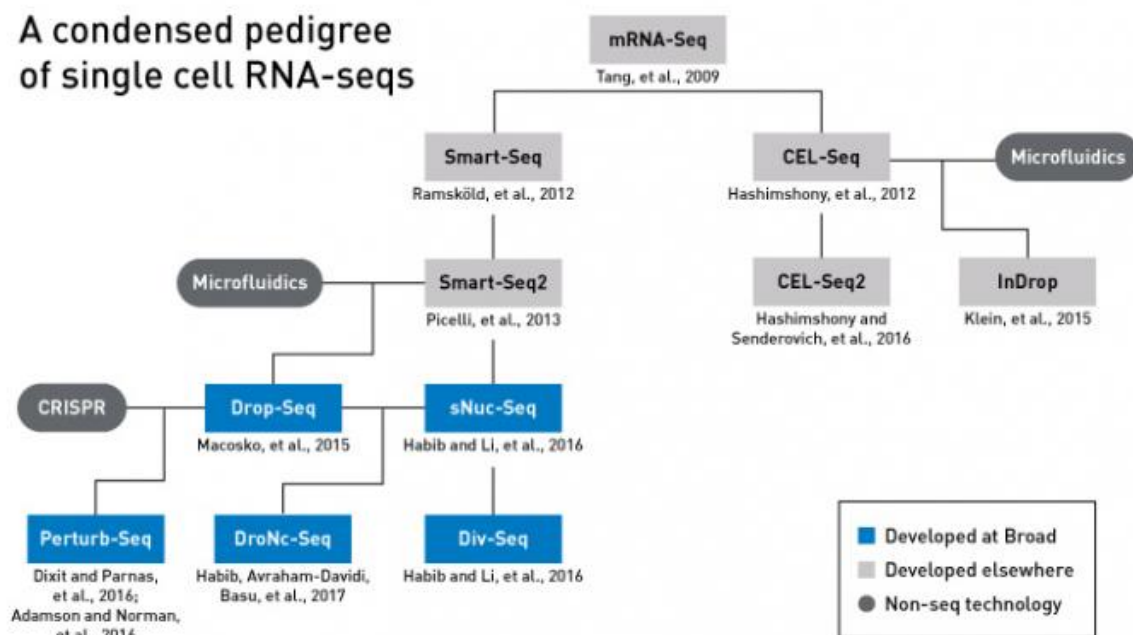


Single-nucleus RNA sequencing, droplet by droplet

August 28 2017



This family tree captures just a sampling of single-cell and single-nucleus RNA sequencing technologies that have burst onto the scene over the last eight years. Credit: Susannah M. Hamilton and Tom Ulrich, Broad Communications

Last year Broad researchers described a single-nucleus RNA sequencing method called sNuc-Seq. This system enabled researchers to study the gene expression profiles of difficult-to-isolate cell types as well as cells

from archived tissues. Now a Broad-led team has overcome a key stumbling block to sNuc-Seq's widespread use: scale.

In a paper published in *Nature Methods*, postdoctoral fellows Naomi Habib, Inbal Avraham-Davidi, and Anindita Basu; core institute members Feng Zhang and Aviv Regev; and their colleagues reveal DroNc-Seq, a single-cell expression profiling technique that merges sNuc-Seq with microfluidics, allowing massively parallel measurement of gene expression in structurally-complicated tissues.

Researchers struggled in the past to study expression in neurons and other cells from complex tissues, like the brain, at the single-cell level. This was because the procedures for isolating the cells affected their RNA content and did not always accurately capture the true proportions of the cell types present in a sample. Moreover, the procedures did not work for frozen archived tissues. sNuc-Seq bypassed those problems by using individual nuclei extracted from cells as a starting point instead.

sNuc-Seq, however, is a low-throughput technology, using 96- or 384-well plates to collect and run samples. To scale the method up to the level needed in order to efficiently study thousands of nuclei at a time, the team turned to microfluidics. Their inspiration: Drop-Seq, a single-cell RNA-seq (scRNAseq) technique that encapsulates single cells together with DNA barcoded-beads in microdroplets to greatly accelerate expression profiling experiments and reduce cost.

To test the new method's accuracy and speed, the team successfully benchmarked DroNc-Seq against Drop-Seq, sNuc-Seq, and other lower throughput scRNAseq methods using a mouse cell line and mouse brain [tissue](#). They also applied it to human brain tissue collected by the Genotype-Tissue Expression (GTEx) Project, finding that they could a) identify expression signatures unique to neurons, glial [cells](#), and other [cell types](#) in the brain (including rare types), and b) differentiate between

closely related cell subtypes.

DroNc-Seq's robustness and accuracy suggest it could be a valuable addition to the stable of technologies being used as part of the Human Cell Atlas and other scRNAseq-based efforts.

More information: "Massively parallel single-nucleus RNA-seq with DroNc-seq," *Nature Methods* (2017). [DOI: 10.1038/nmeth.4407](https://doi.org/10.1038/nmeth.4407)

Provided by Broad Institute of MIT and Harvard

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