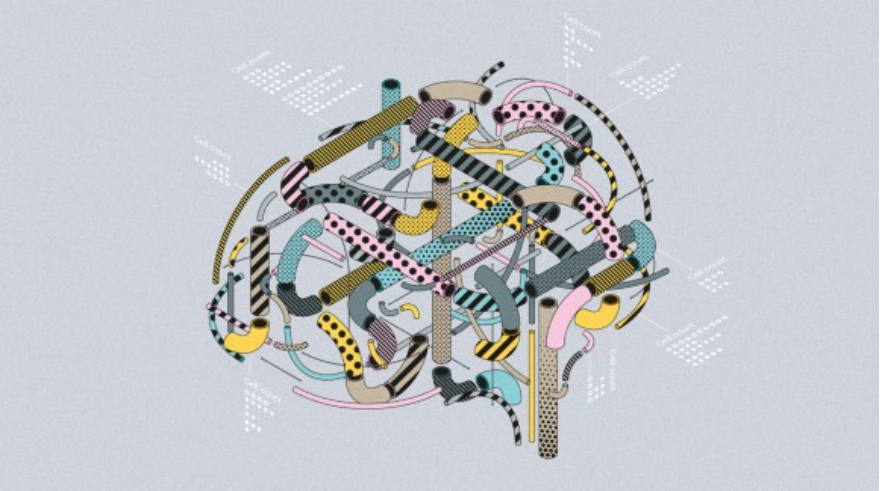
Single Cell Transcriptomics

Newsletter October 2021

Thematic release

BICCN just published 27 papers across the Nature Portfolio on mammalian primary motor cortical cell type identities on a molecular level. This incredible work includes analyses of more than 2.2 million cell transcriptomes as well as about 1 million cell epigenomes. The samples originate from marmoset and human brains, and comparative analyses across species are included. All data are freely available through the NIH's BRAIN consortium.

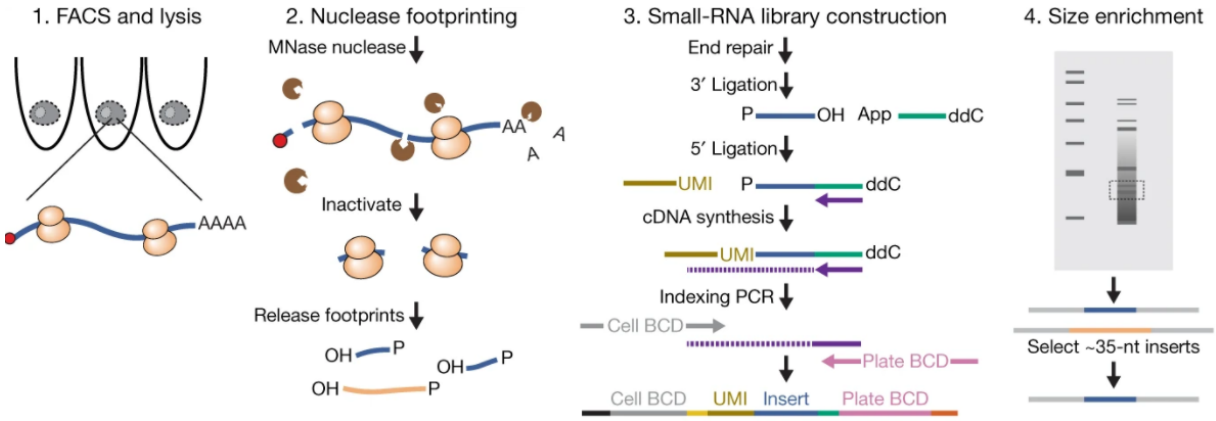


BRAIN Initiative Cell Census Network—Motor Cortex

Papers 1-3

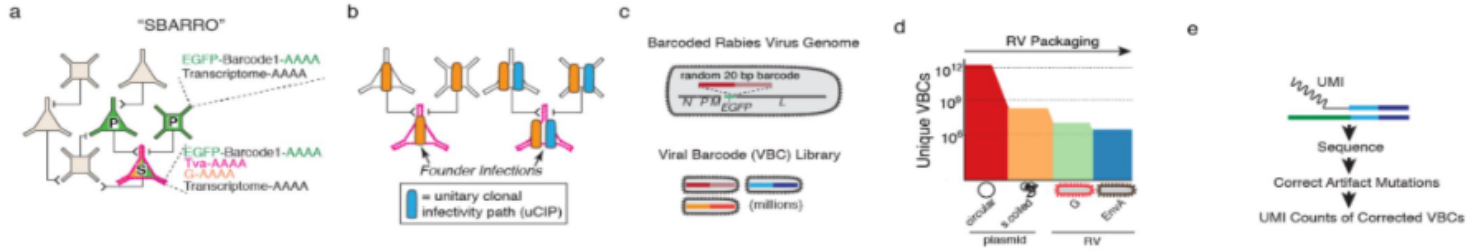
The first papers of this month's newsletter describes novel single-cell techniques. The first paper by VanInsberghe *et al*. describes Ribo-seq that enables ribosome profiling in single cells at a single-codon resolution. They demonstrate how Ribo-seq is scalable to thousands of cells in a single experiment. Further, the authors highlight how Ribo-seq is transgene-free and does not require the expression of an exogenous fusion protein. The authors anticipate that this method will see broad application, particularly in highly dynamic systems such as development, in which rare and short-lived populations are impossible to measure with existing techniques.

VanInsberghe, M *et al.* Single-cell Ribo-seq reveals cell cycle-dependent translational pausing, *Nature*, 2021



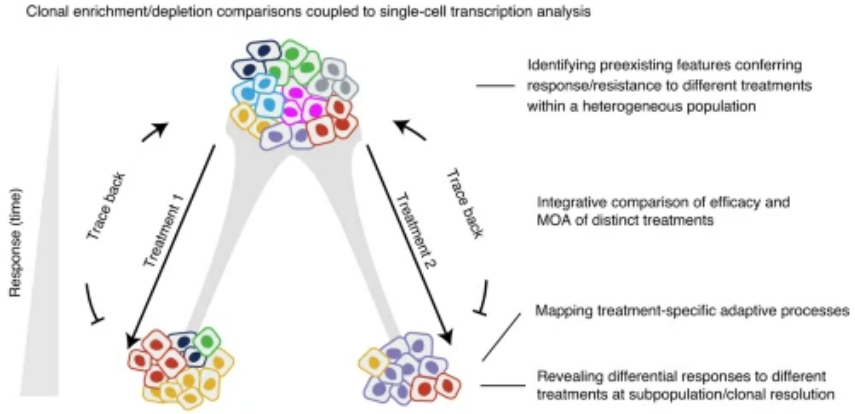
In the second paper, Saunders and colleagues introduce SBARRO (Synaptic Barcode Analysis by Retrograde Rabies ReadOut), a method that uses single-cell RNA sequencing to reveal directional, monosynaptic relationships based on the paths of a barcoded rabies virus from its "starter" postsynaptic cell to that cell's presynaptic partners. The authors show the scalability of their method by investigating mouse brain cells *in vitro*, and that the molecular identity of the starter cell predicts the number and types of cells that synapses onto it. Taken together, SBARRO offers new opportunities to map the synaptic organization of neural circuits in health and disease.

Saunders, A. *et al.* **Ascertaining cells' synaptic connections and RNA expression simultaneously with massively barcoded rabies virus libraries**, *BiorXiv,* 2021



The third paper from Chang *et al*. describes the development of tracking differential clonal response by scRNA-seq (TraCe-seq). TraCe-seq is a method that captures at clonal resolution the origin, fate and differential early adaptive transcriptional programs of cells in a complex population in response to distinct treatments. Chang and colleagues show the applicability of TraCe-seq by tracing cells that respond and persist after exposure to different therapies in lung cancer cells. In conclusion, TraCe-seq is an approach to study how preexisting transcriptional programs affect treatment responses.

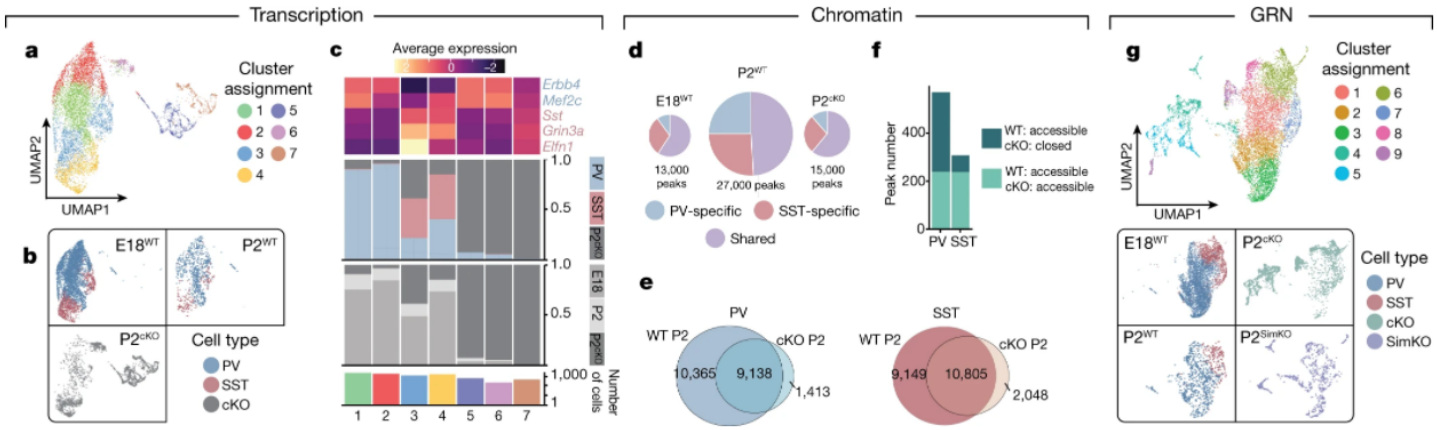
Chang, M. et al. Identifying transcriptional programs underlying cancer drug response with TraCe-seq, *Nature Biotechnology*, 2021



Paper 4

Next, we turn our focus towards interneuron development. Specifically, Allaway *et al*. focuses on PV and SST interneurons and how developmental changes in transcription and chromatin structure enable these cells to acquire distinct identities in the mouse cortex. They construct cell-type-specific gene regulatory networks to observe how PV and SST positive cells initiate distinct programs upon settling within the cortex. Doing so, they reveal how a common molecular program diverges to enable these neuronal subtypes to acquire highly specialized properties by adulthood. Their methods provide a framework for examining the emergence of cellular diversity, as well as for quantifying and predicting the effect of candidate genes on cell-type-specific development.

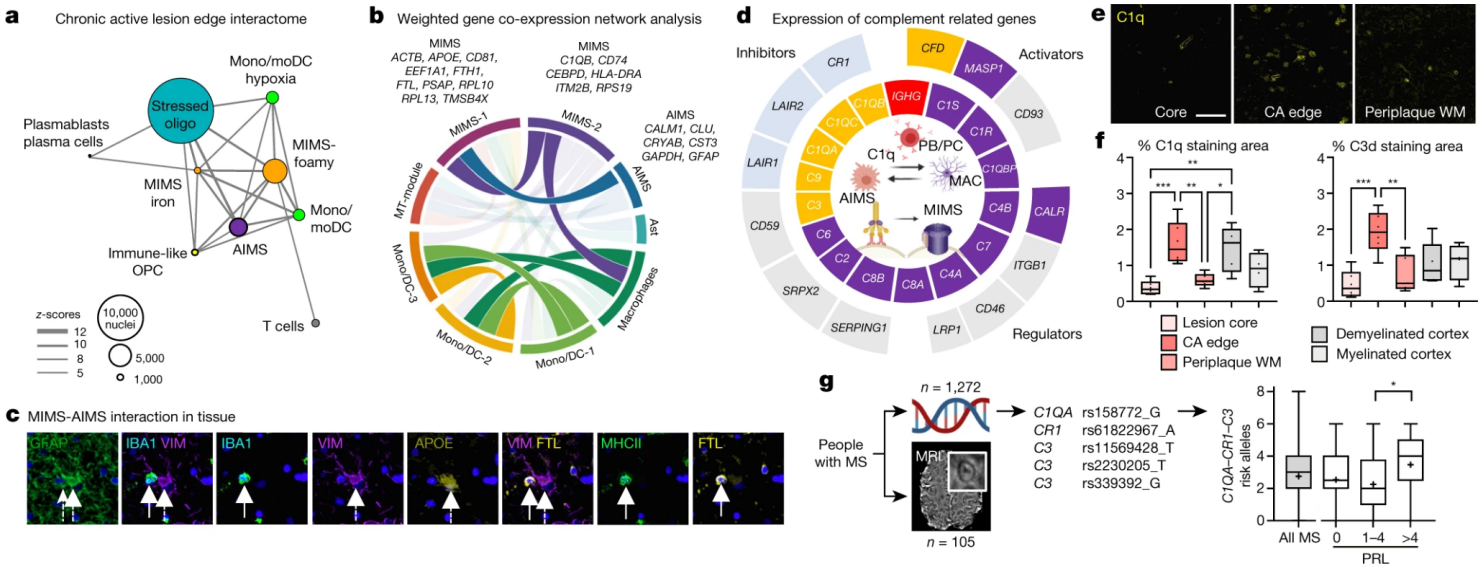
Allaway, K. et al. Genetic and epigenetic coordination of cortical interneuron development, *Nature*, 2021



Paper 5

The last paper concerns multiple sclerosis and the interplay between lymphocytes of the peripheral immune system and brain immune cells. In order to do this, Absinta and colleagues used MRI-informed single-nucleus RNA sequencing to profile the edge of demyelinated white matter lesions at various stages of inflammation. Doing so, they identify microglial and astrocytic phenotypes that demonstrate neurodegenerative programming. Interestingly, the transcriptional profile of the disease-specific microglia phenotype overlaps with that of microglia in other neurodegenerative diseases, suggesting that primary and secondary neurodegeneration share common mechanisms and could benefit from similar therapeutic approaches. Specifically, the authors identify complement component 1q (C1q) as a critical mediator of activation of the disease-specific microglia which they validate in MS tissue and *in vitro* in mice EAE models. They conclude that C1q inhibition is a potential therapeutic avenue to address chronic white matter inflammation, which could be monitored by longitudinal assessment of its dynamic biomarker, paramagnetic rim lesions, using advanced MRI methods.

Absinta, M. et al. A lymphocyte–microglia–astrocyte axis in chronic active multiple sclerosis, *Nature*, 2021



New papers from Danish researchers

- ➔ VeTra: a tool for trajectory inference based on RNA velocity. Guangzheng Weng, Junil Kim, Kyoung Jae Won. *Bioinformatics*, 2021
- ➔ Identification of vulnerable interneuron subtypes in 15q13.3 microdeletion syndrome using single-cell transcriptomics Susmita Malwade, Janina Gasthaus, Carmelo Bellardita, Matej Andelic, Borna Moric, Irina Korshunova, Ole Kiehn, Navneet A. Vasistha, Konstantin Khodosevich. *Biological Psychiatry*, 2021
- ➔ A TALE/HOX code unlocks WNT signalling response towards paraxial mesoderm. Mariani, L., Guo, X., Menezes, N. A., Drozd, A. M., Çakal, S. D., Wang, Q., and Ferretti, E. *Nature Communications*, 2021.

Conferences

Single Cell Analyses (Virtual) | CSHL 10th-12th November 2021

Next Single Cell Seminar

Date: 29th October 2021, Maersk Tower top floor, 7.15.92

9:00 – 10:00

Peter Kharchenko, PhD, Harvard Medical School

Analysis of multi-cellular expression programs from inter-individual variation

If you would like to announce anything single cell related, being it job announcement, event, your published paper, technology development etc., please contact us.

Contact: rasmus.rydbirk@bric.ku.dk