Single Cell Transcriptomics

Newsletter October 2020

Collection 1

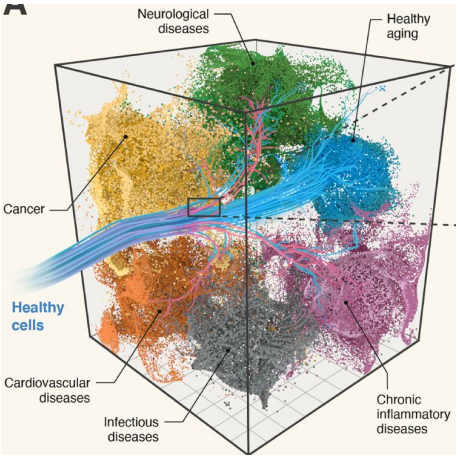
GTEx Consortium. The Genotype-Tissue Expression Project, *Science, 2020.*

On Sep 10, the Genotype-Tissue Expression (GTEx) Consortium published results of their third and final phase, which consist of 14 (!) top-notch papers. Among others, they investigated impact of sex on gene expression, showing that effect is highly tissue-specific, investigated association of QTLs to various traits, showed effect of some rare genetic variants on gene expression and developed a method to improve genotype-phenotype mapping by using transcriptome data. Even though the project does not go to the level of single cells, they provide unique insights about effects of genetics and gene expression on tissue and cell type levels.

Paper 2

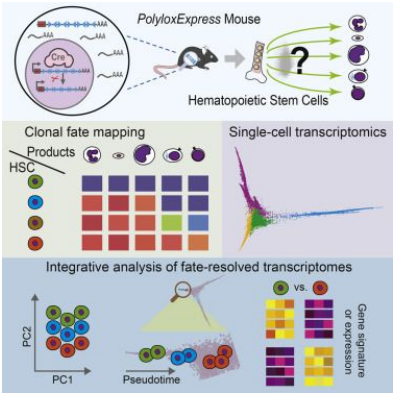
Rajewsky N, *et al*. LifeTime and improving European healthcare through cell-based interceptive medicine, *Nature, 2020*

In 2018, the LifeTime initiative was organized with the aim to track, understand and target human cells during the onset and progression of complex diseases. And this paper outlines LifeTime's vision and key aspects of their Strategic Research Agenda towards establishing cell-based interceptive medicine. The authors promise a big step towards early detection and interception of complex diseases, which should also allow to select the most effective therapeutic strategy for a patient. Advancing this direction requires development of new protocols, as well as computational methods for working with these modalities. There also will be a large coordination effort to obtain large-scale patient data in form of both biological samples and electronic health records. The paper also provides some details on implementation of such a huge project, including questions about infrastructure, ethical and legal issues, interaction with industry, as well as impact on medicine and healthcare.



Paper 3

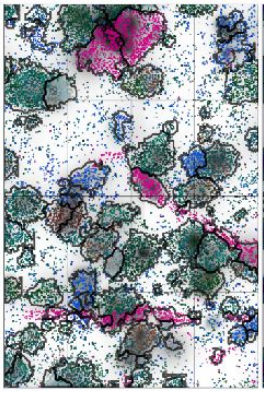
Pei W, et al. [Resolving Fates and Single-Cell Transcriptomes of Hematopoietic Stem Cell Clones by PolyloxExpress Barcoding](), *Cell Stem Cell, 2020*



Pei and colleagues developed an endogenous RNA barcoding system, *PolyloxExpress*, that allows joint readout of barcodes and transcriptomes in individual cells developing under physiological conditions. The authors used *PolyloxExpress* to study fates (via comparison of barcodes in hematopoietic stem cells and mature lineages) and transcriptomes (via scRNA-seq and barcode matching) of individual HSC clones in mice. To reveal HSC fates, four mice were analyzed between 7 and 20 weeks after birth. Using scRNA-seq data from all analyzed HSCs (22,565 cells) they performed extensive comparison of differentiation-inactive, myelo-erythroid-restricted, and multilineage HSCs.

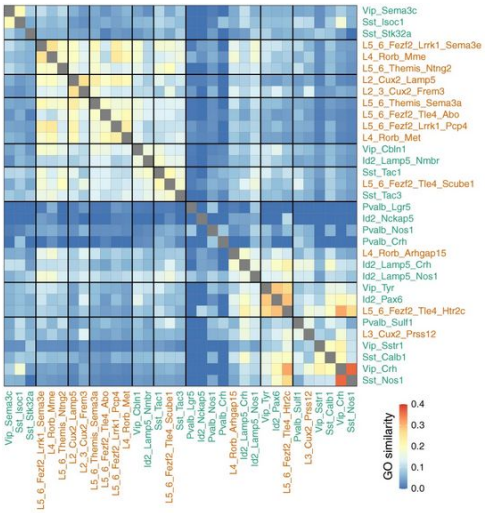
Papers from Khodosevich Lab

Petukhov V, Soldatov RA, Khodosevich K, Kharchenko PV. [Bayesian segmentation of spatially resolved transcriptomics data](), *biorXiv, 2020*



A whole bunch of single-molecule spatially-resolved protocols (such as sm-FISH or *in-situ* sequencing) was published the last two years. They allow to count millions of individual RNA-molecules for hundreds of genes. However, assigning these molecules to the cells of their origin is a big problem. Some solutions based on segmentation of DAPI or poly-A stains exist, but their quality is rather low. To deal with it we developed a tool for pre-processing and analysis of spatial data, called Baysor. Using Bayesian Mixture Models, it allows to infer cell assignment from transcript data alone, without requiring additional experiments. However, if provided, Baysor can also utilize an existing segmentation as a prior to increase the quality of the results.
We also introduced the concept of Neighborhood Composition Vectors, which allows to apply scRNA-seq pipelines to spatial data without performing cell segmentation. Finally, we described a Markov Random Field framework for labeling spatial data, which was then applied to filtration of background molecules and to transfer annotation from scRNA-seq data. Baysor performs well across most of the existing protocols, including MERFISH, osm-FISH, ISS and STARmap. It recovers up to twice the number of cells, compared to the staining-based segmentation methods, while also reducing expression contamination!

Pfisterer U, Petukhov V, Demharter S, Meichsner J, *et. al.* [Identification of epilepsy-associated neuronal subtypes and gene expression underlying epileptogenesis](), *Nature Communications, 2020*



This is a comparative study for Temporal Lobe Epilepsy, where we produced and analyzed scRNA-seq data from temporal cortex of 10 control and 9 epileptic individuals (>110k cells in total). We developed a method for prioritizing cell types based on their expression changes and show L5-6_Fezf2 and L2-3_Cux2 subtypes of principal neurons are affected the most. Then, we performed functional annotation of changes and showed that cell types can be grouped based on similarity of the affected Gene Ontology pathways, which suggests coordination of expression across types. Next, we focused on three pathways that were known to be associated with overexcitation (Glutamate receptor signaling, Action potential and AMPA glutamate complex). We showed that most genes, disregulated in these pathways are affected through all six layers. Finally, we used smFISH for validation of CKAMP44, GRIA1 and GRIN3A genes, showing indeed significant changes between the control and epilepsy.

Next Single Cell Seminar

Date: 30th Oct 2020, Location: Zoom

09:00-10:00

Roman Romanov, Medical University of Vienna, Austria - Design logic of molecular and spatial cellular attributes during hypothalamus development

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

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