DANISH SINGLE-CELL NETWORK NEWSLETTER

FEBRUARY - 2023

THIS MONTH'S HIGHLIGHTS:

ASGARD is A Single-cell Guided Pipeline to Aid Repurposing of Drugs

He, B., Xiao, Y., Liang, H. et al.

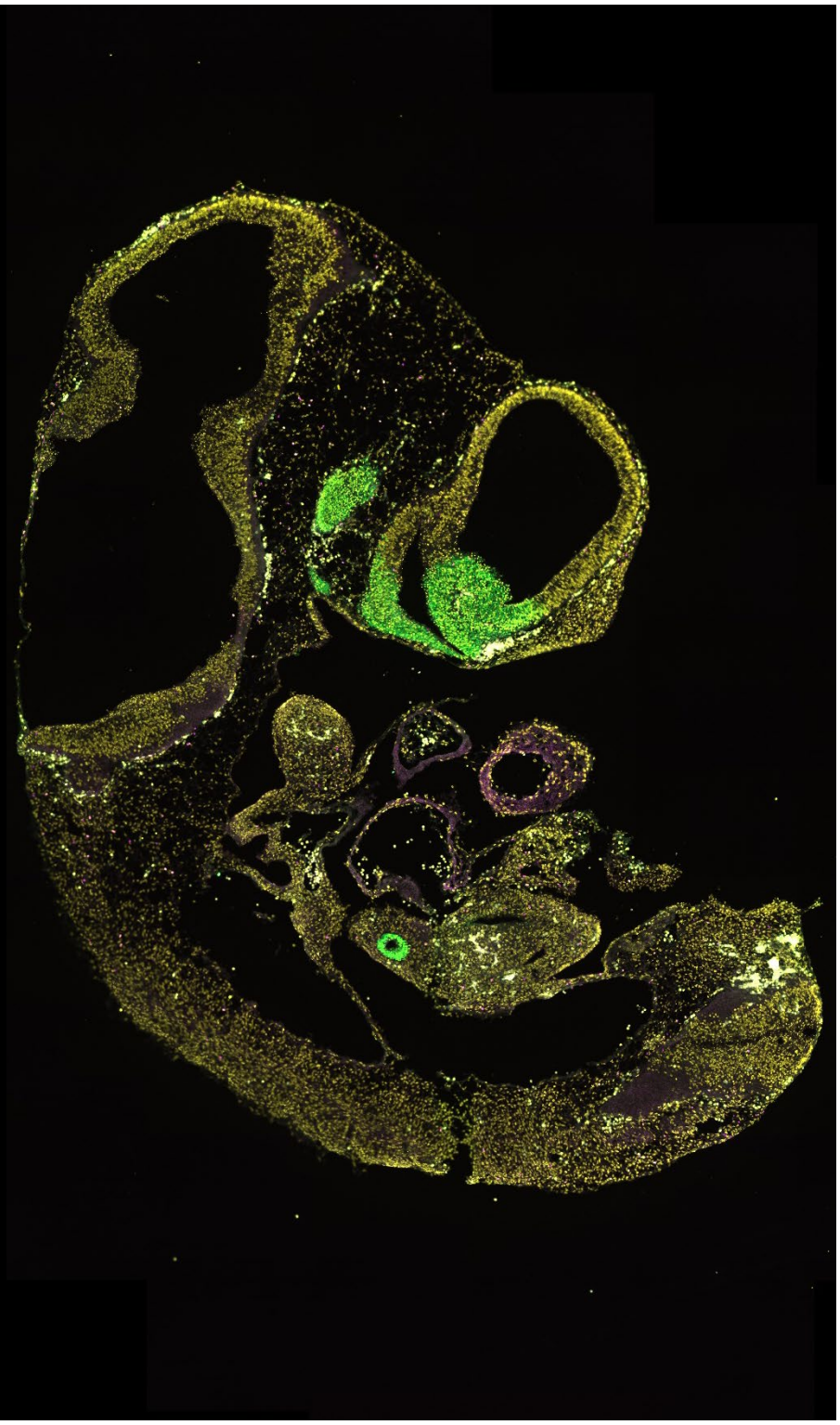
Dissecting cell identity via network inference and in silico gene perturbation

Kamimoto, K., Stringa, B., Hoffmann, C.M. et al.

Mitochondrial single-cell ATAC-seq for high-throughput multi-omic detection of mitochondrial genotypes and chromatin accessibility

Lareau, C.A., Liu, V., Muus, C. et al..

COVER IMAGE
Author: Laura Wolbeck, University of Copenhagen
Title: sagittal E10.5 mouse embryo (2023)



UNIVERSITY OF COPENHAGEN

UPCOMING EVENT

3rd Danish Single Cell Meeting:
Biotechnology and Application to Biology

https://singlecell.ku.dk/3rd-danish-single-cell-meeting-biotechnology-and-application-to-biology/

Time and place: April 26th-27th 2023; Natural History Museum of Denmark, Øster Voldgade 5-7, 1350 Copenhagen (dinner & postersession at Mærsk Tower, Blegdamsvej 3B, 2200 København)

Deadline for registration: 26stMarch

ASGARD is A Single-cell Guided Pipeline to Aid Repurposing of Drugs

He, B., Xiao, Y., Liang, H. *et al. Nat Commun* (2023). https://doi.org/10.1038/s41467-023-36637-3

The researchers of the first paper developed ASGARD - A Single-cell Guided Pipeline to Aid Repurposing of Drugs. This tool should improve patient-tailored precision medicine by recommending a drug while considering intercellular heterogeneity within each patient. ASGARD uses single-cell RNA sequencing data to define a drug score that considers all cell-types to account for intercellular heterogeneity within patients and it performs considerably better than two bulk-cell-based drug repurposing methods (CLUE and DrInsight) and other single-cell-based repurposing methods. (Alakwaa's and Guo's). By applying the drug response prediction technique TRANSACT to patient samples with Triple-Negative-Breast-Cancer, the researchers confirmed the efficacy of ASGARD. The outcomes demonstrated that a significant number of highly ranked drugs are either currently undergoing clinical trials or have already been approved by the Food and Drug Administration for the treatment of corresponding diseases. Overall ASGARD has the potential to unlock the full potential of single-cell RNA sequencing technology for precision medicine and help clinicians make more informed decisions about which drugs to use to treat their patients.

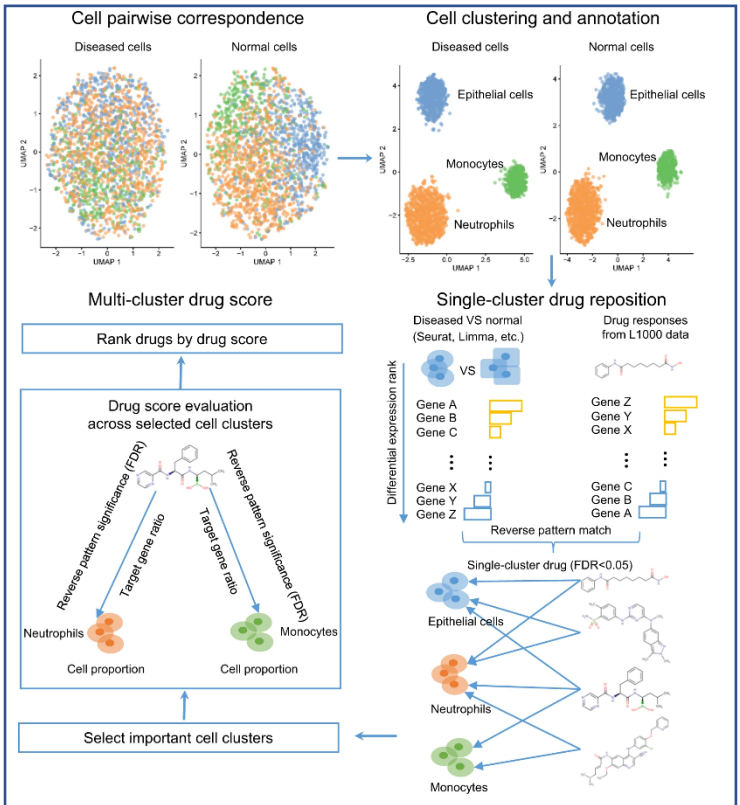


Figure 1. The workflow of the ASGARD drug repurposing pipeline. *Every cell cluster in the diseased sample is paired to that in the control sample using "anchor" genes that are consistently expressed between diseased and control cells. To identify drugs for each single cluster, ASGARD uses the consistently differentially expressed genes as inputs to identify drugs that can significantly reverse the pattern of DE genes. To identify drugs for multiple clusters, ASGARD defines a drug score to evaluate the drug efficacy across multiple cell clusters selected by the user.*

Dissecting cell identity via network inference and in silico gene perturbation

Kamimoto, K., Stringa, B., Hoffmann, C.M. *et al. Nature* (2023). https://doi.org/10.1038/s41586-022-05688-9

In the second paper researchers have used gene-regulatory networks (GRNs) inferred from single-cell multi-omics data to simulate changes in cell identity resulting from in silico transcription factor perturbations. This machine-learning-based approach, called CellOracle, was applied to established models of mouse and human hematopoiesis and zebrafish embryogenesis and accurately modeled changes in phenotype resulting from transcription factor perturbation. In developing zebrafish they could simulate and experimentally validate a previously unreported phenotype that results from the loss of noto, an established notochord regulator. Additionally, they identified an axial mesoderm regulator, lhx1a. The limitations of the method include the inability to analyze cell states that do not exist in the input scRNA-seq data and TF simulation limitations due to input data availability and quality. The researchers note that the approach could be used to simulate TF overexpression and predict previously unreported phenotypes. Overall, the results demonstrate that CellOracle can be used to analyze the regulation of cell identity by transcription factors, providing mechanistic insights into development and differentiation.

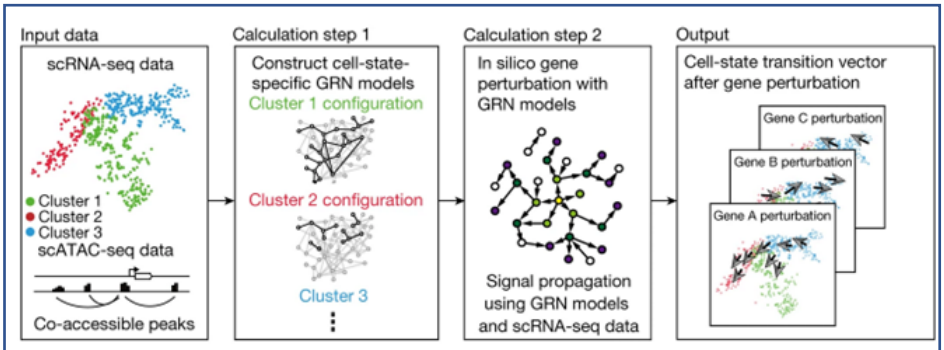


Figure 2. Simulation of cell-state transitions in response to TF perturbation. *Using scRNA-seq and scATAC-seq data as input, CellOracle builds custom transcriptional GRNs. Then, cell-state specific GRNs are generated using accessible promoter and enhancer peaks from scATAC-seq data combined with scRNA-seq data. Upon in silico TF pertrubation CellOracle simulates the change in cell state and projects the results onto the cell trajectory map.*

Mitochondrial single-cell ATAC-seq for high-throughput multi-omic detection of mitochondrial genotypes and chromatin accessibility

Lareau, C.A., Liu, V., Muus, C. *et al. Nat Protoc* (2023). https://doi.org/10.1038/s41596-022-00795-3

The authors of the third paper have introduced a new method named 'mitochondrial single-cell assay for transposase-accessible chromatin with sequencing' (mtscATAC-seq) that can simultaneously profile mitochondrial DNA (mtDNA) variant heteroplasmy and accessible chromatin variation in individual cells. The natural sequence variation in mtDNA can be utilized as natural genetic markers for tracing lineages and clones within human cells. Therefore, this technique allows

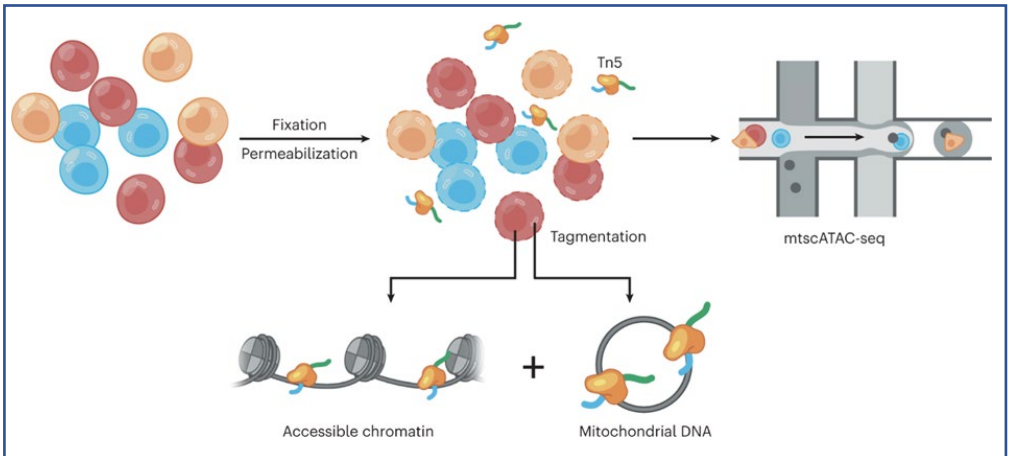


Figure 3. mtscATAC-seq experimental workflow*. First, whole cells are fixed before mild lysis and permeabilization to keep mtDNA within their host cells. Permeabilization enables Tn5 transposase to have access to mtDNA and nuclear chromatin. After transposition the cells are loaded onto the Chromium Next GEM Single Cell ATAC platform of 10x Genomics to achieve single-cell compartmentalization and library generation.*

mapping of clonal relationships between cells in human tissues and studying important aspects of mitochondrial genetics. The authors have provided a step-by-step guide for using mtscATAC-seq, including several workflows for processing cells and performing flow cytometry on primary hematopoietic cells. They have also discussed quality control measures for both experimental and computational data and suggested ways to extend the technique to other mammalian tissues. The authors emphasize that mtscATAC-seq is a versatile tool for multi-omic discovery and can be used to infer clonal relationships among native ex vivo-derived human cells, which is not possible using genetic engineering-based clonal tracing approaches.

Next Single Cell Seminar

Time and place: to be announced

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

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