3.1 Machine Learnings from HCA
Dr Sarah Teichman
http://www.teichlab.org/

Human Genome Project

- Understanding how it is possible to encoding a multitude of cell types from a single genome?
    - Subset of genes that have been switched on/off defining the shape and functions of the cell types
- Cell mapping
    - "We need a programme of making maps of cells, and maps of how cells talk to each other… **The CellMap project, for which we don't need a model organism, will be one of the things to occupy us for the next few decades**" – Sydney Brenners 2002
        - No measurement to quantify single cell
    - 2016
        - Aviv Regev (Broad Institute)
- Human Cell Atlas
    - To create a comprehensive reference map of the types and properties of all human cells, the fundamental unit of life, as a basis for understanding, diagnosing, monitoring, and treating health and disease
    - Joining the initiative
        - https://www.humancellatlas.org/join-hca/
        - 2,414 members, 1,200 institutes, 79 countries
        - Multi-disciplinary

Resolution revolution: single cell genomics, spatial transcriptomics

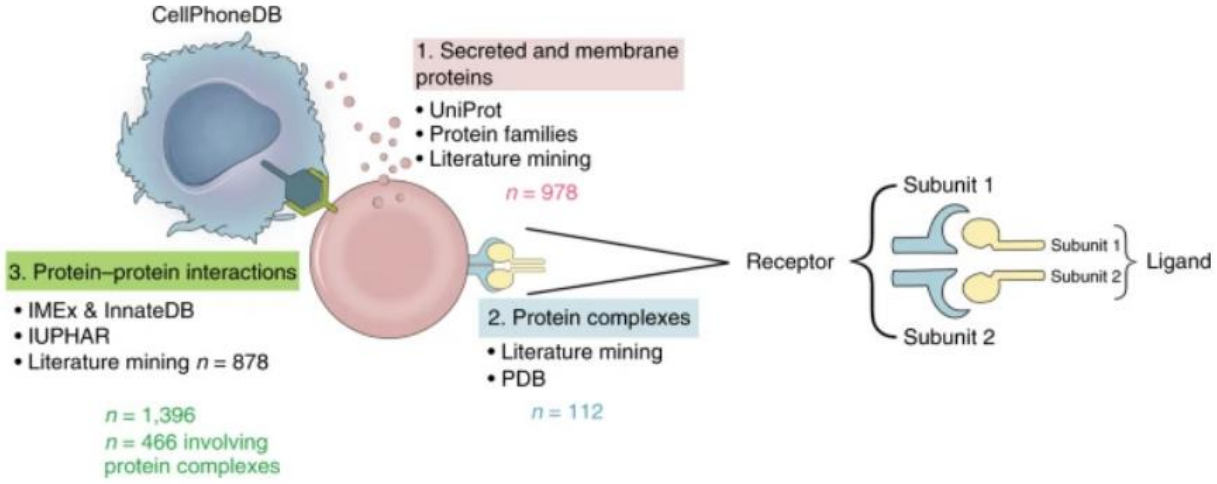
- Combining sc genomics and spatial transcriptomics
    - WIth AI and ML
- Cell mapping at scale during development, physiology & disease
- Example projects from Teichmann lab
    - Maternal-fetal interface
        - Vento-tormo Nature 2018
            - https://www.nature.com/articles/s41586-018-0698-6
    - Immune development
        - Popescu Nature 2019
            - https://www.nature.com/articles/s41586-019-1652-y
        - Park Science 2020
            - https://www.science.org/doi/10.1126/science.aay3224
        - Jardine Nature 2021
            - https://www.nature.com/articles/s41586-021-03929-x
        - Suo, Dann Science, 2022
            - https://www.science.org/doi/10.1126/science.abo0510
    - Lung

        - Vieira Braga Nat Med 2019
            - https://www.nature.com/articles/s41591-019-0468-5
        - Madissoon, Oliver bioRxiv 2022
            - https://www.biorxiv.org/content/10.1101/2021.11.26.470108v1
    - Gut
        - James Nat Immunol 2020
            - https://www.nature.com/articles/s41590-020-0602-z
        - Elmentaite Dev Cell 2020
            - https://linkinghub.elsevier.com/retrieve/pii/S1534-5807(20)30886-8
        - Elmentaite Nature 2021
            - https://www.nature.com/articles/s41586-021-03852-1
    - Heart & skeletal muscle
        - Litvinukova Nature 2020
            - https://www.nature.com/articles/s41586-020-2797-4
        - Kedlian bioRxiv 2022
            - https://www.biorxiv.org/content/10.1101/2022.05.24.493094v1
    - Cross-tissue immunity
        - Dominguez-conde, Xu, Jarvis Science 2022
            - https://www.science.org/doi/10.1126/science.abl5197?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Computational tool overview

- Fundamental tools to understanding the cell
    - CellTypist: suspension cell
        - https://www.celltypist.org/
    - Cell2location: mapping tissue architecture
        - Integrating with spatial data
        - https://cell2location.readthedocs.io/en/latest/
    - CellphoneDB: Inferring cell-cell interactions
        - https://www.nature.com/articles/s41596-020-0292-x
    - Drug2cell:
        - Drug target exploration
- CellTypist
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7612735/
    - Precise and rapid annotation of single cell data
    - > 100 Immune cell type and states
        - One model encompassing all tissues
- Cell2location
    - https://cell2location.readthedocs.io/en/latest/
    - https://www.nature.com/articles/s41587-021-01139-4
- CellPhoneDB
    - https://www.nature.com/articles/s41596-020-0292-x

Fig. 1: Overview of the database.



(1) Secreted and membrane proteins stored in protein_input; (2) protein complexes stored in complex_input; and (3) protein–protein interactions stored in interaction_input. Information aggregated within www.CellPhoneDB.org. CellPhoneDB stores a total of 978 proteins: 501 are secreted proteins and 585 are membrane proteins. These proteins are involved in 1,396 interactions; out of all proteins stored in CellPhoneDB, 466 are heteromers. There are 474 interactions that involve secreted proteins and 490 interactions that involve only membrane proteins. There are a total of 250 interactions that involve integrins. Adapted with permission from CellPhoneDB.org.

- Drug2cell
    - Based on ChEMBL
    - Finding drugs that act on cells
        - Clinically approved compounds wrt their targets predicted by transcriptomics
    - Manuscript under preparation
    - ChEMBL + Single-cell/nuclei RNAseq -> Filter drugs -> Drug scores -> Find drugs/ cells -> find target molecules

CellTypist

- What are the cell states across organs?
- What features are context-specific?
    - Is the related to the positioning of the data
- Categorizing the distributed immune system
    - 12 donors, ~330k immune cells from lymph nodes, blood samples, bone marrows, liver, thymus, lung, muscle, kidney, and gut
        - scRNA-seq or scVDJ-seq data
        - Generating scRNA-seq
    - With label curation and model training for CellTypist
        - Annotate cell in generated scRNA-seq data

- From knowledge-driven to data-driven
    - Knowledge and data are negatively correlated
        - More data, less knowledge
        - Less data, more knowledge required
    - Knowledge is required for manual annotation
    - Data is required for automatic annotation
    - AI/ML models
        - cross-tissue database and server integration?
        - Interpretable pipeline for label projection?
- Classical machine learning vs deep learning
    - High performance can be achieved with canonical machine learning methods
        - **A comparison of automatic cell identification methods for single-cell RNA sequencing data**
            - https://genomebiology.biomedcentral.com/articles/10.1186/s13059-019-1795-z
        - **Deep learning does not outperform classical machine learning for cell-type annotation**
            - https://www.biorxiv.org/content/10.1101/653907v2.full
    - Notably logistic regression models
        - **Molecular Diversity of Midbrain Development in Mouse, Human, and Stem Cells**
            - https://www.cell.com/cell/fulltext/S0092-8674(16)31309-5?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416313095%3Fshowall%3Dtrue
        - **Single-Cell Sequencing of Developing Human Gut Reveals Transcriptional Links to Childhood Crohn's Disease**
            - https://www.cell.com/developmental-cell/fulltext/S1534-5807(20)30886-8?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1534580720308868%3Fshowall%3Dtrue
- Optimisation
    - Mini-batch training
        - Bypass memory overload and decrease execution time
        - 1,000 random cells as a training batch
        - 100 mini-batches per epoch * 10 epochs
    - Stochastic gradient descent learning
        - Fast convergence for large datasets
        - Allow for online training (incorporating future new datasets)
- Cell type distribution across the body
    - Big picture of enrichment of specific cell types of specific tissues
    - https://www.science.org/doi/10.1126/science.abl5197

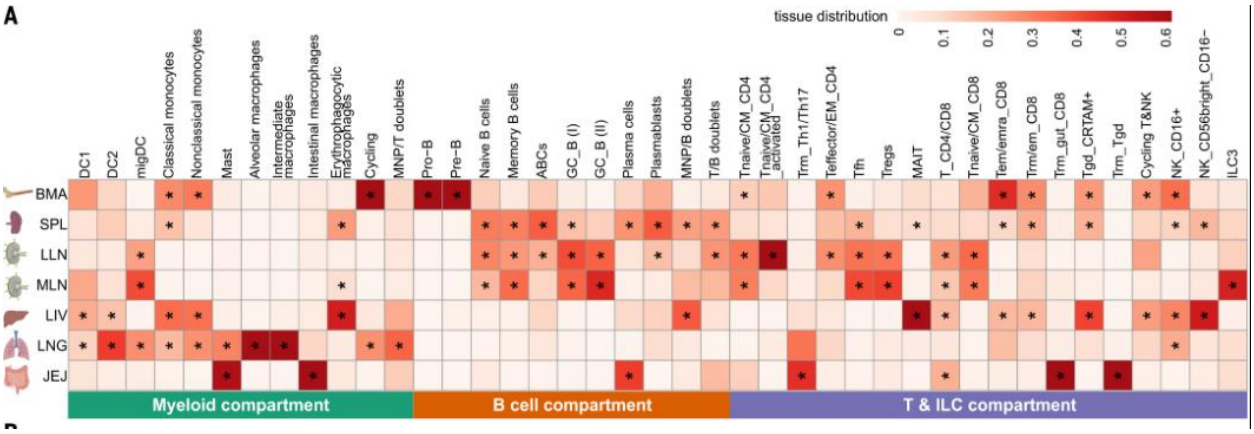
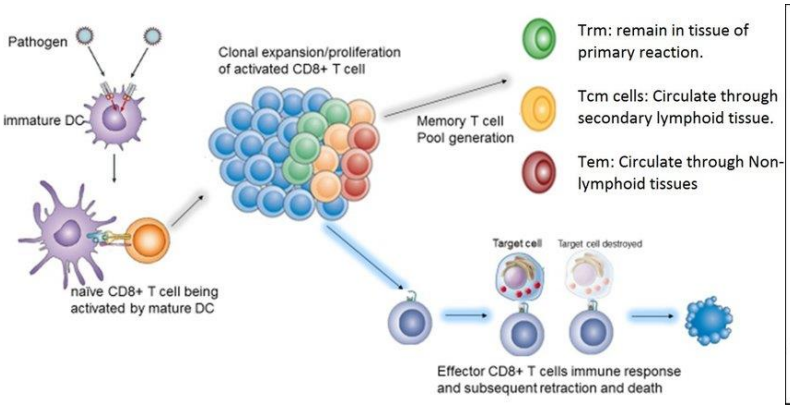
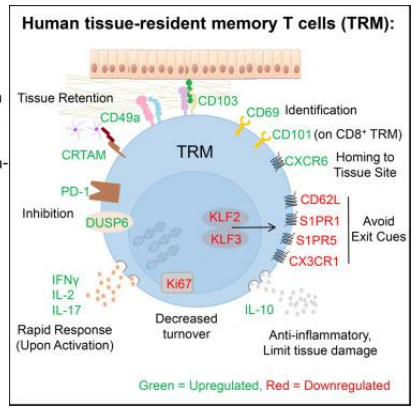


Fig. 5. A cross-tissue updatable reference of immune cell types and cell states.

(**A**) Heatmap showing the distribution of manually curated cell types across selected tissues. Cell numbers are normalized within each tissue and later calculated as proportions across tissues. Asterisks mark significant enrichment in a given tissue relative to the remaining tissues (Poisson regression stratified by donors, $P < 0.05$ after BH correction). (**B**) Workflow for the iterative update of CellTypist through the periodic incorporation of curated cell type labels.

- Further insights into in vivo CD8+ T cell memory formation
    - Lower expression: migration to lymph node
    - Unbiased analysis with further understanding of the biology





- Summary
    - Cross tissue adult immunity
    - Integration of immune system across body
    - CellTypist: cell type encyclopedia
    - Towards an integrated Human Cell Atlas

Focus on the Heart: tissue microenvironments and drug targets

- Mapping how cells fit into the tissue microenvironment
- Expansion of the atlas:
    - V2 capturing other anatomical position to V1
        - Higher RA, PV, aorta…
- Understanding rare diseases
    - Atrial fibrillation
    - Aortopathies

    - Mitral valve prolapse
    - Coronary artery disease
    - Brugada syndrome
- Discovering spatial microenvironment
    - Visium slide -> Automated (cell2location) and structural (manual) annotation harmaonized -> identifying factors which refine manual automation -> CellPhone v3 + GPCR-DB
    - Understanding the electric conduction that flows from the pacemaker cells in the heart through all the cardiac walls of chambers

- Cell2Location telling us centric node
- Detailed understanding of where the spontaneously farms is
    - Cellular molecular level
    - Peripheral structure of particular cell populations
- Epicardium & fibrotic myocardial niches
    - Immune shielding around the edge of the heart
    - Fibrotic area associated to aging
        - Secretion of collagen
        - Activated, next to vessel
        - TGF and BMP signalling
- Pacemaker cells
    - Cardiac conduction system
    - Semi-nerounal and semi-muscular fibres
    - Singel cell analysis of pacemaker cells
    - Identifying SAN-region pacemaker cells
        - Unbiased clustering approaches
        - Working cardiac myocytes and Pacemaker cell separation
            - Low sodium channel SCN5A expression and high calcium channel CACNA1D expression
        - How are the ion channels affected by drugs?
            - Subclasses of drugs frequently targeted:
                - Which drug having an effect on these ion channels? Thus side effects on the heart?
                    - ChEMBL
                        - https://www.ebi.ac.uk/chembl/
                    - Integration with ChEMBL – Drug2Cell
    - Drug target exploration with drug2cell
        - Identification of diabetic drugs which targets pacemaker cells
            - GLP1 analogues Perampanel targeting GLP1R and GRIA3 in pacemaker cells
        - Up to 6 beats per minute
            - Might be via the autonomic nervous system
            - This analysis pinpoints specifically– hypothesis generation
                - Homeostatic perturbation at autonomic nervous system

        - Brainstem and cord/ higher CNS centers
- Summary
    - Define cell type composition
    - Discover tissue microenvironments
    - Map drug targets

Q&A

- Data harmonisation, cleaning are mostly addressed not manually
- Classical ML vs DL
    - DL usually in normalization, integration tasks rather than hypothesis generation and elucidating mechanisms in single cell field
    - Gain for deep learning
        - Possibly in the future
        - Interpretability will be a major potential pitfall – obscure variables from DL
- CellTypist
    - Continuous improvement
    - Accuracy higher for immune area compared to stromal cells
        - Dependent of effort and data availability
- Single cell data direction
    - Multi-modal directions
- Single omics in understanding systemic impact
    - Cross-tissue integration, spatial microenvironment, cell-cell communication
    - Stitching cardiac conduction system
        - Has been performed
        - Understanding the overall system
    - Fetal trophoblast cells communicating with maternal feature
- Important skillsL
    - Python and R
    - Data handling and analysis
    - Framework
    - Asking questions on the data rather than new method development
        - Then going into complicated projects and questions