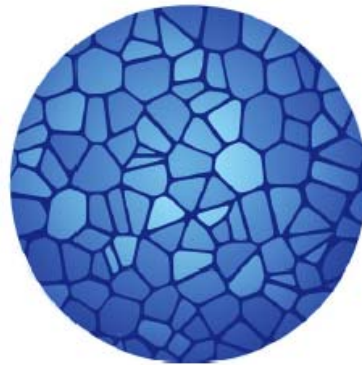


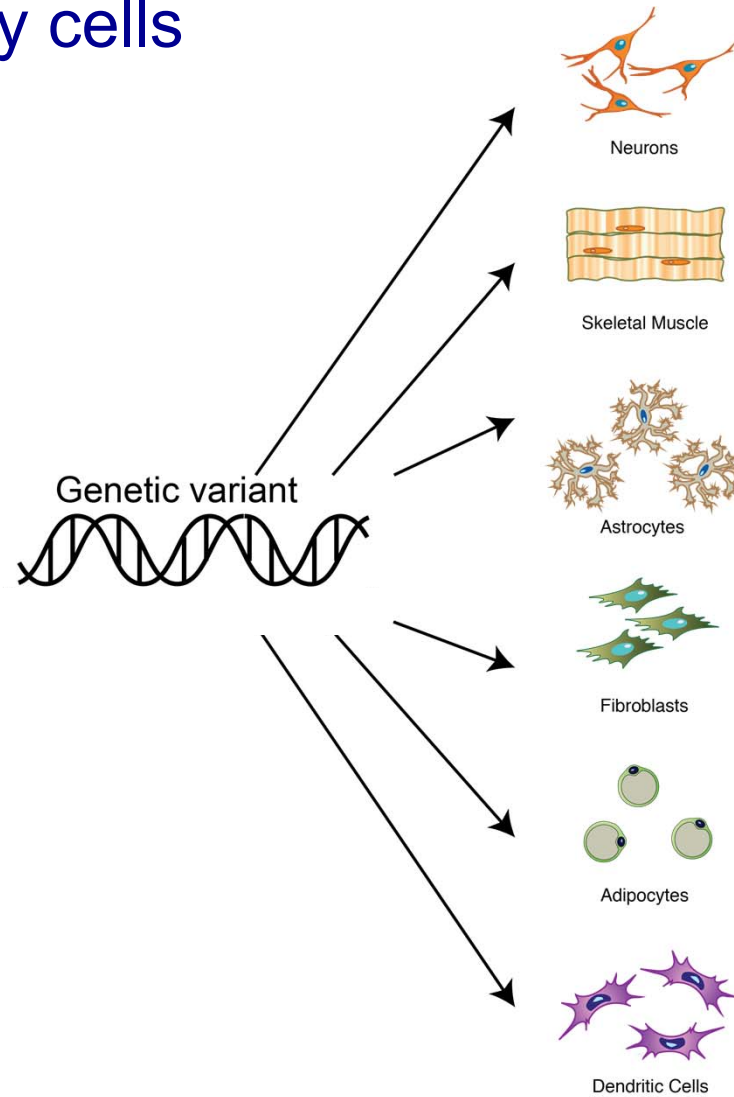
Human Cell Atlas & Genotype-Phenotype Relationships



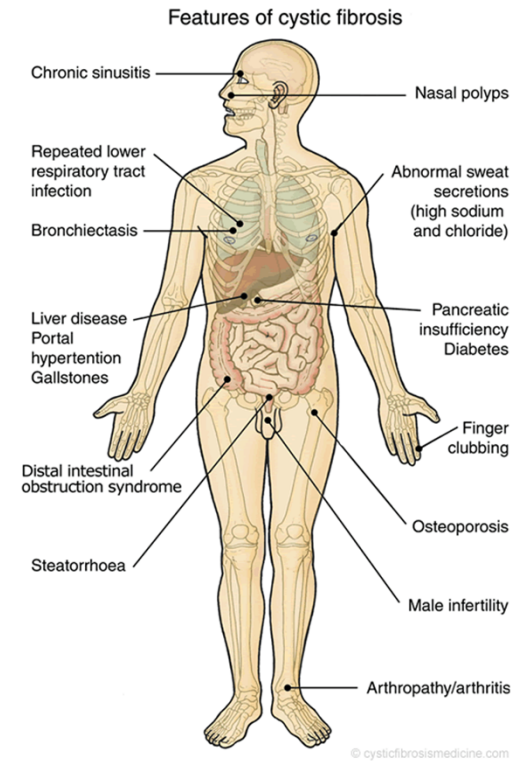
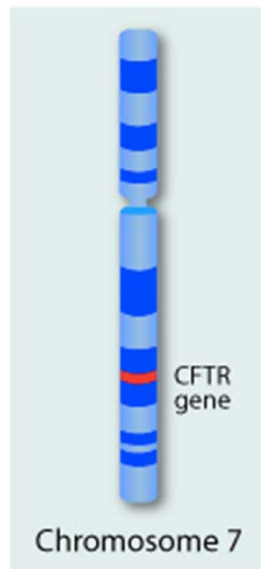
Sarah Teichmann

Wellcome Sanger Institute
Cambridge, UK

One genome, many cells

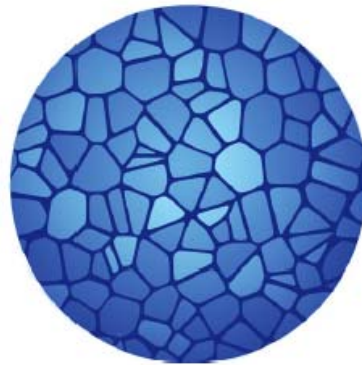


Personalised medicine

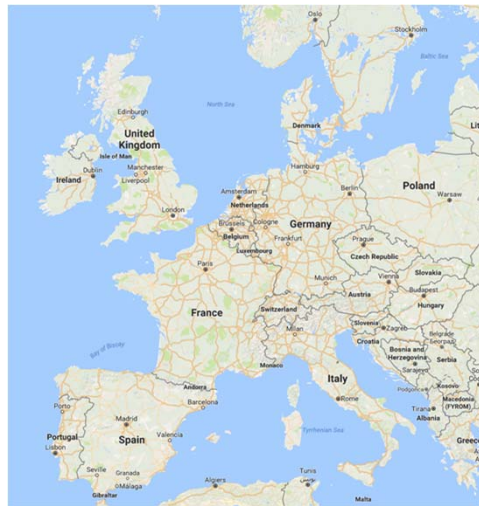


Human Cell Atlas: Mission

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



“Google maps” for the human body

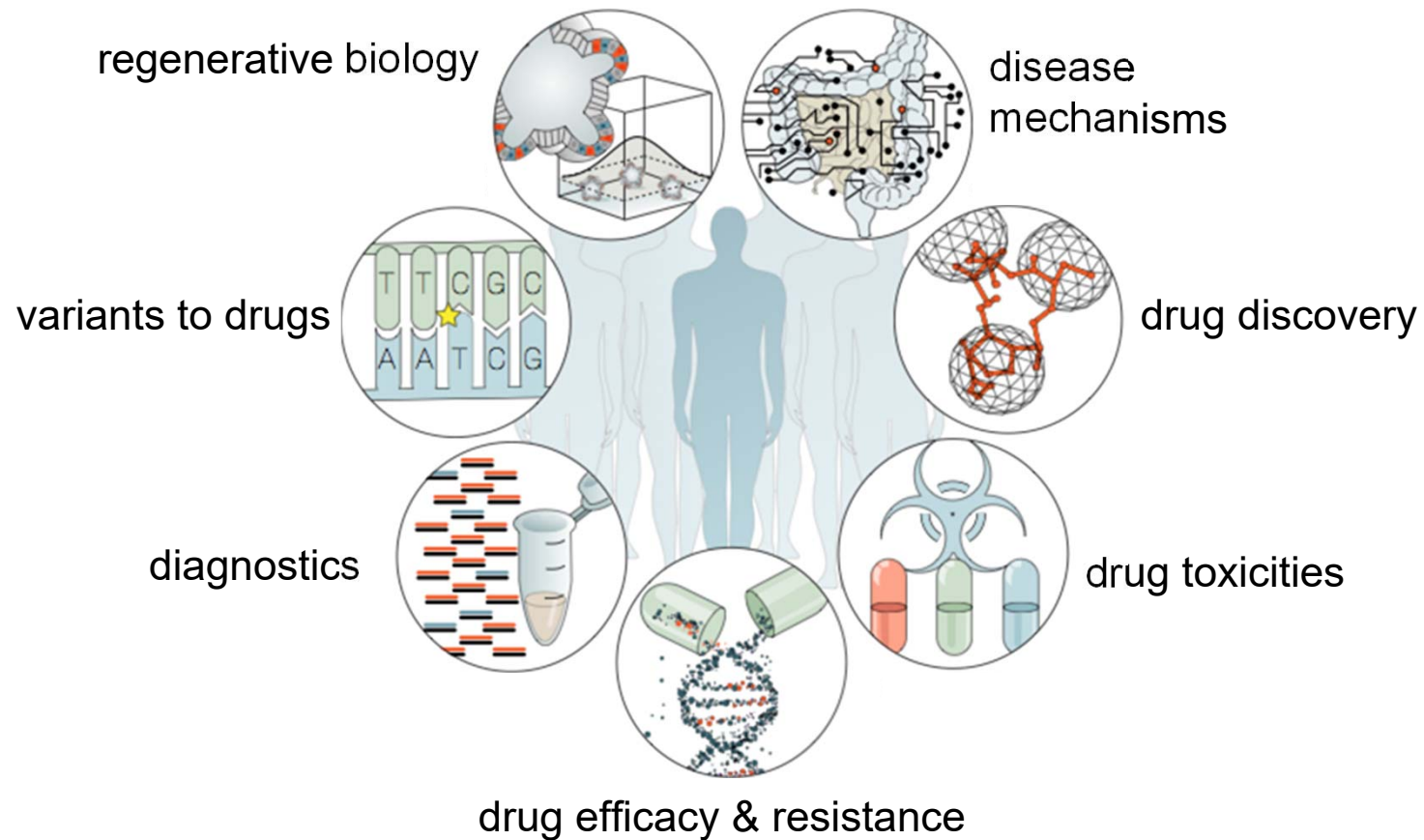


versus



single cell genomics + spatial transcriptomics
to define cells in tissues

Why a human cell atlas?



A periodic table of our cells

01
Br
Brain

01
G
Gut

01
Lu
Lung

01
S
Skin

01
L
Liver

01
B
Bone

01
K
Kidney

01
Dev
Development

01
H
Heart

01
Rep
Reprod.

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

01
Heart

01
Muscle

01
Development

01
Brain

01
Eye

01
Gut

01
Lung

01
Skin

01
Liver

01
Kidney

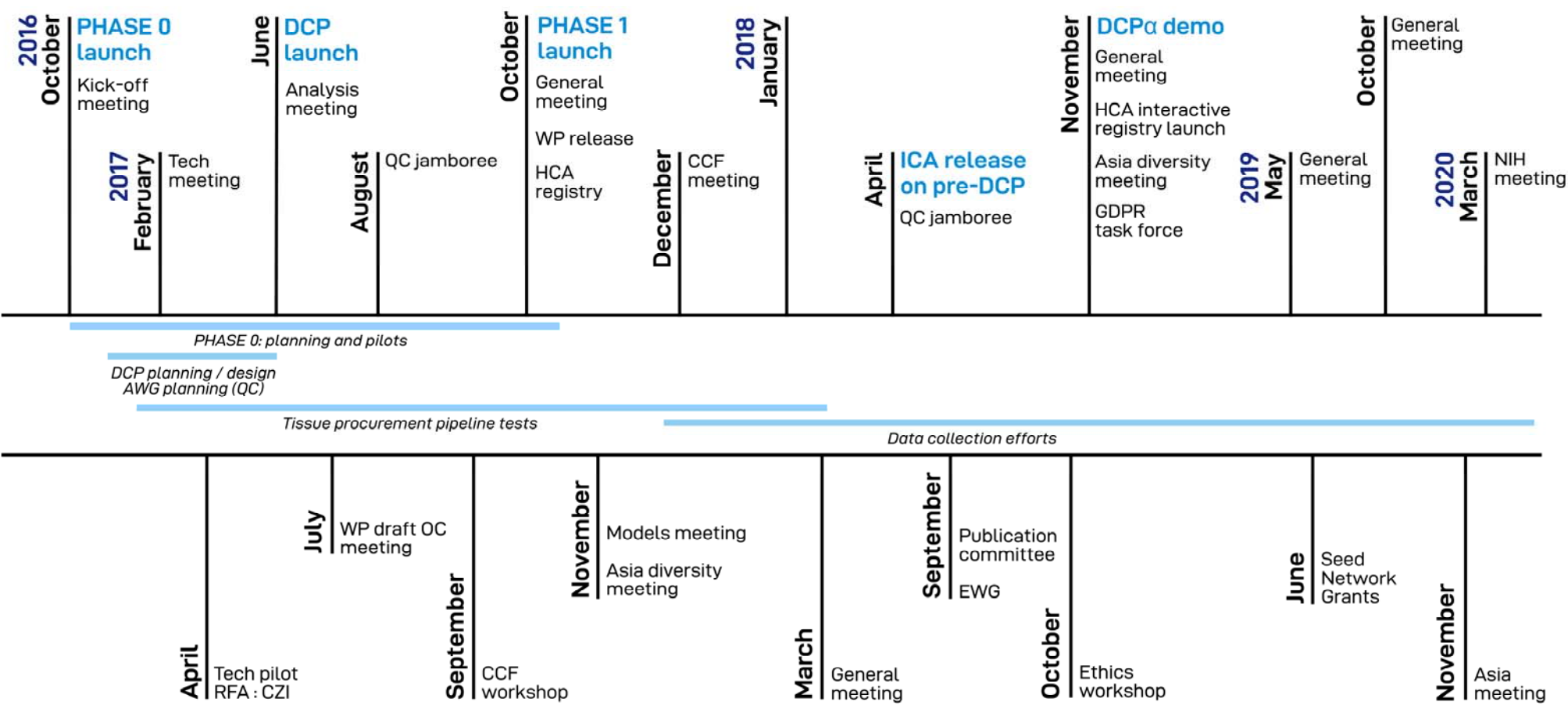
01
Heart

01
Muscle

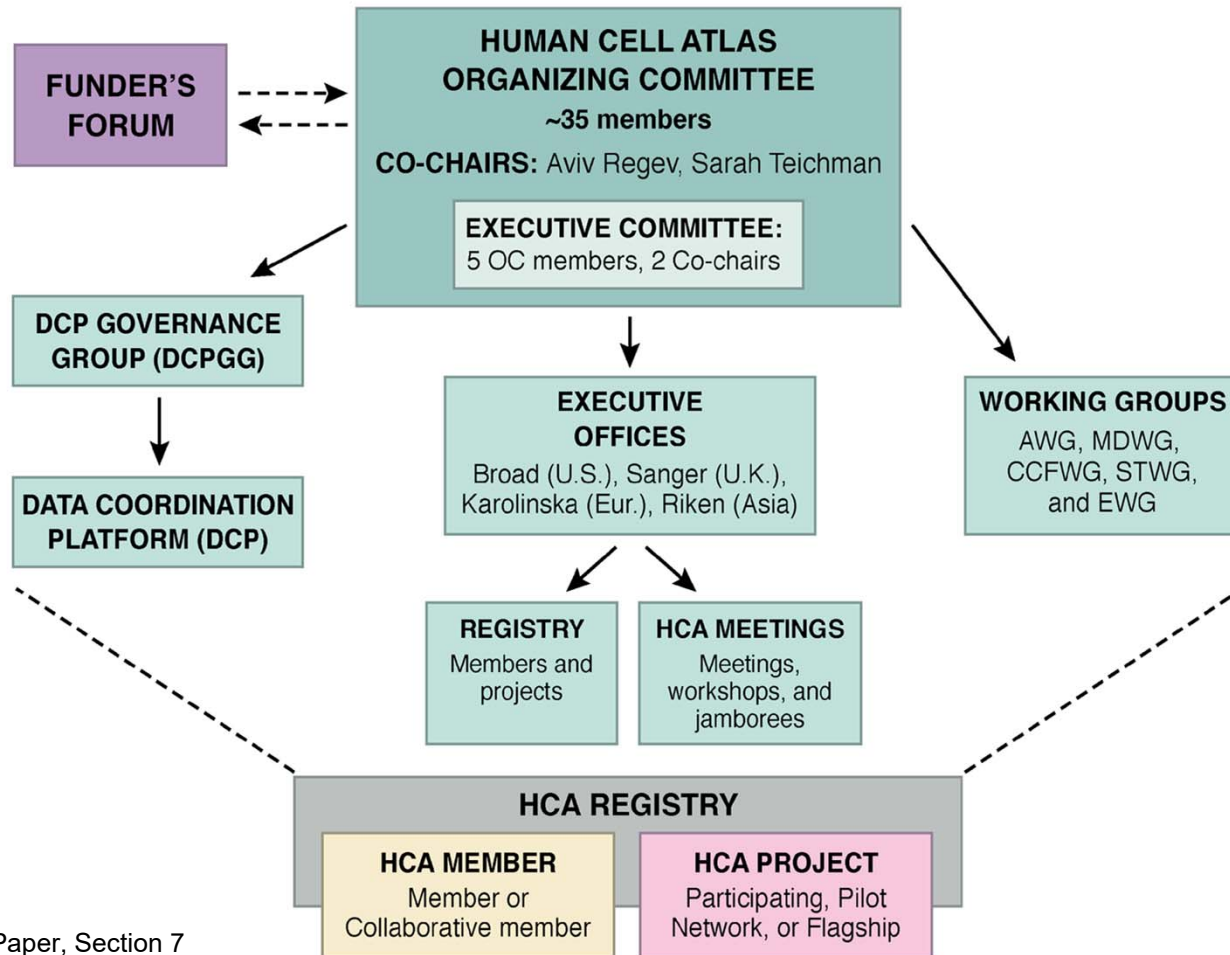
01
Development

</

HCA Timeline: 2016 - present



HCA Consortium Governance



HCA membership: global and rapidly growing

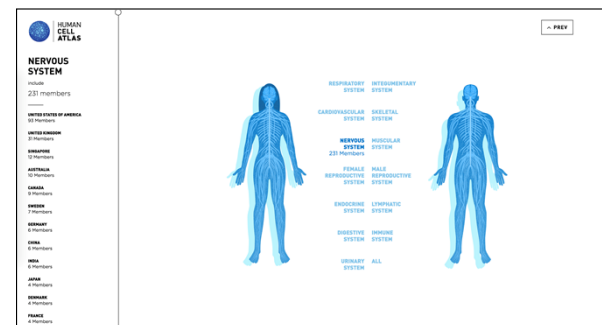
1398 Members, 62 Countries, 896 Institutes

Japan: 36 Members, 22 Institutes



1398 members, 558 PI

14 organs/systems: e.g. nervous system; 231 members



www.humancellatlas.org/joinhca

Technological advances: Single cell and spatial genomics



Bulk genomics



Single cell genomics



Spatial (*in situ*)

An evolving technology landscape

DNA and epigenome

- ✓ Single cell genomes (WES, WGS)
- ✓ Single cell epigenomics (HiC, ChIP, ATAC, mC)

RNA

- ✓ Full length (mRNA, total RNA)
- ✓ 5' and 3' end counting

Proteins

- ✓ Multi-parameter flow
- ✓ Mass cytometry

'multi-omics'

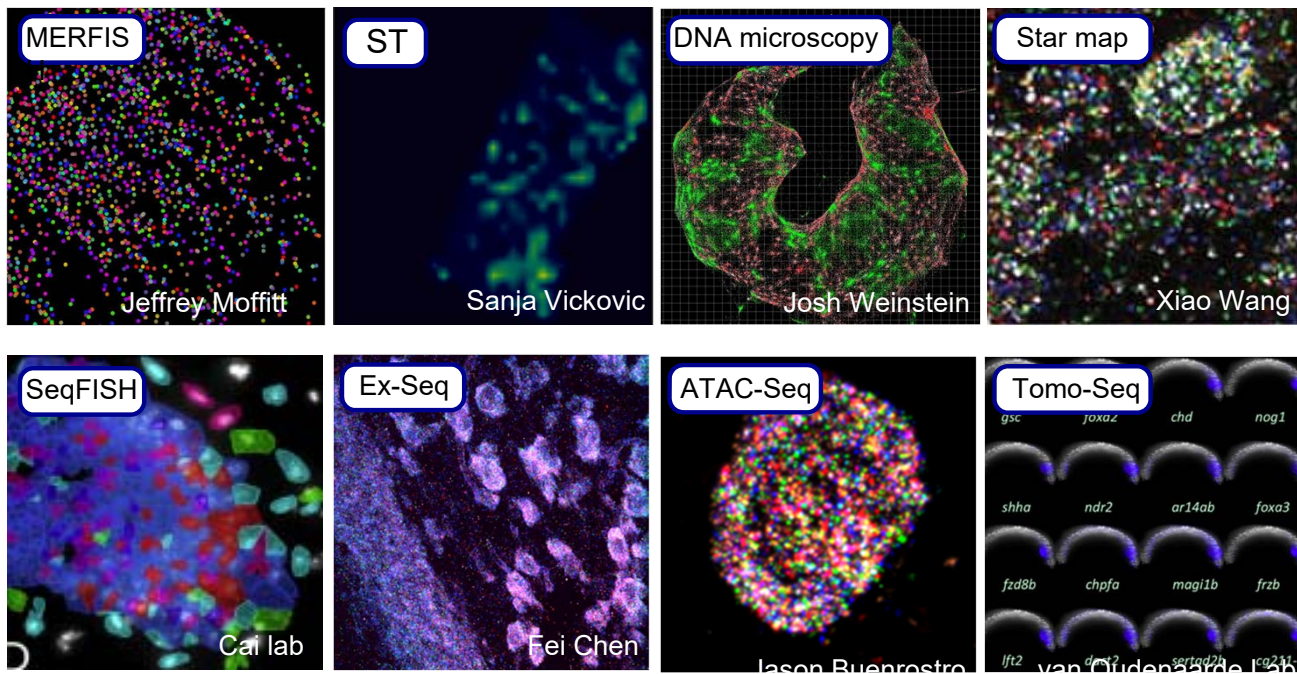
- ✓ DNA+RNA (G+T)
- ✓ RNA+protein (T+P)
- ✓ Epigenome + RNA

Spatial

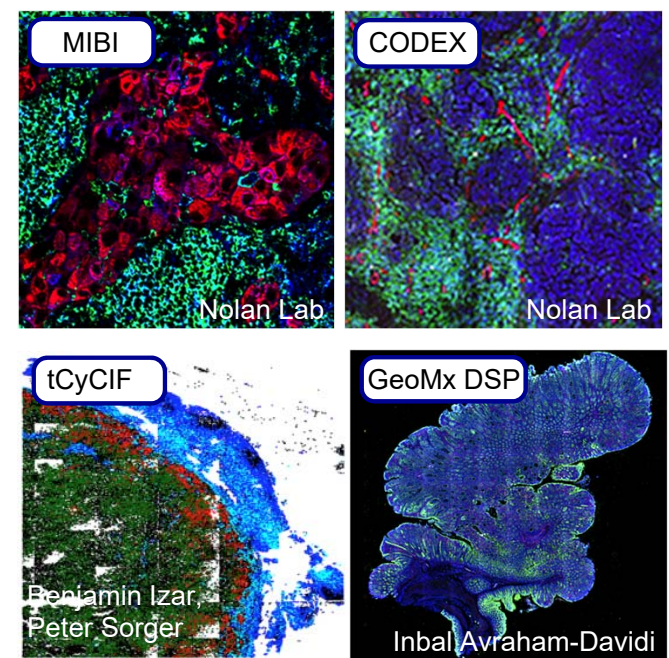
- ✓ Proteins (IMC, MIBI)
- ✓ Multiplex FISH (Seq-FISH, MERFISH)
- ✓ In situ RNA-Seq (e.g., Spatial Transcriptomics)

Rapidly expanding toolbox for spatial analysis

RNA



Protein



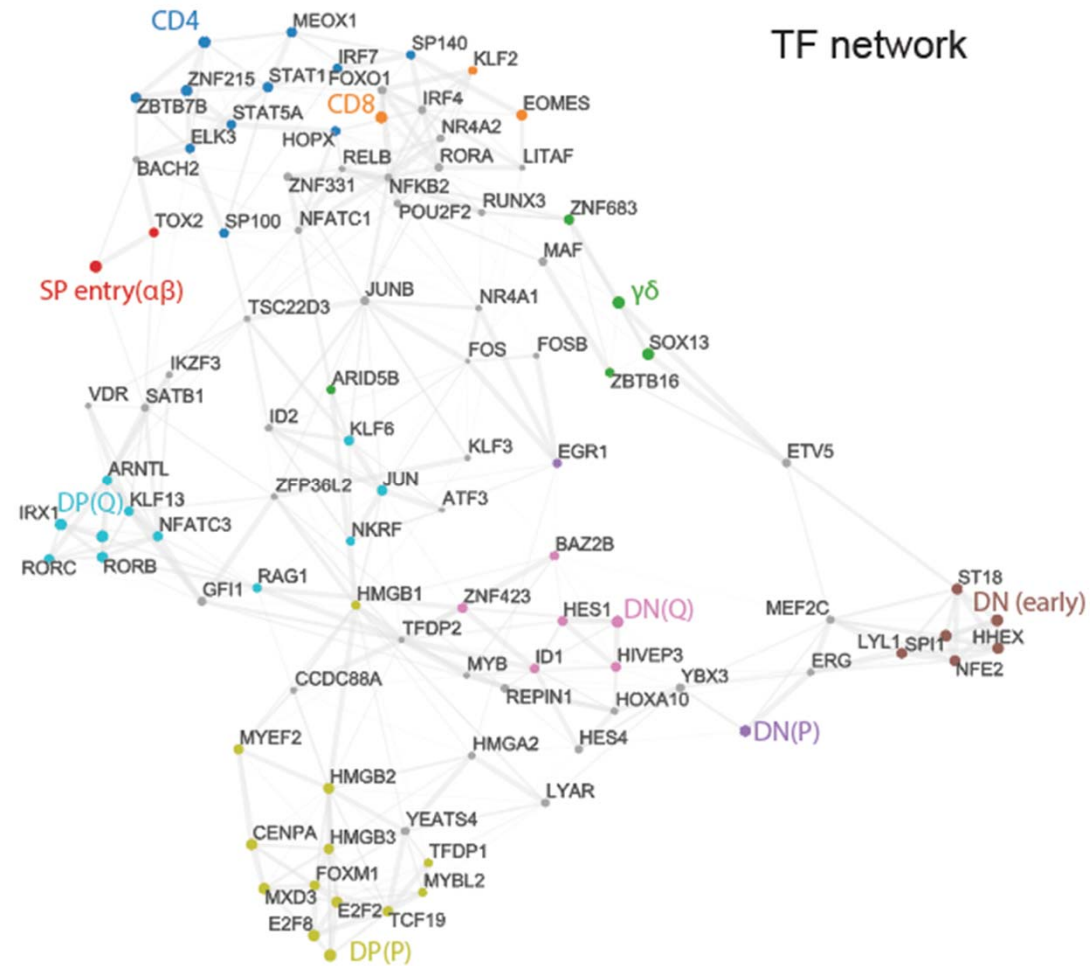
Credit: L. Gaffney, A. Regev

HCA Map of Gene Expression Across the Lifespan & Genetic Associations

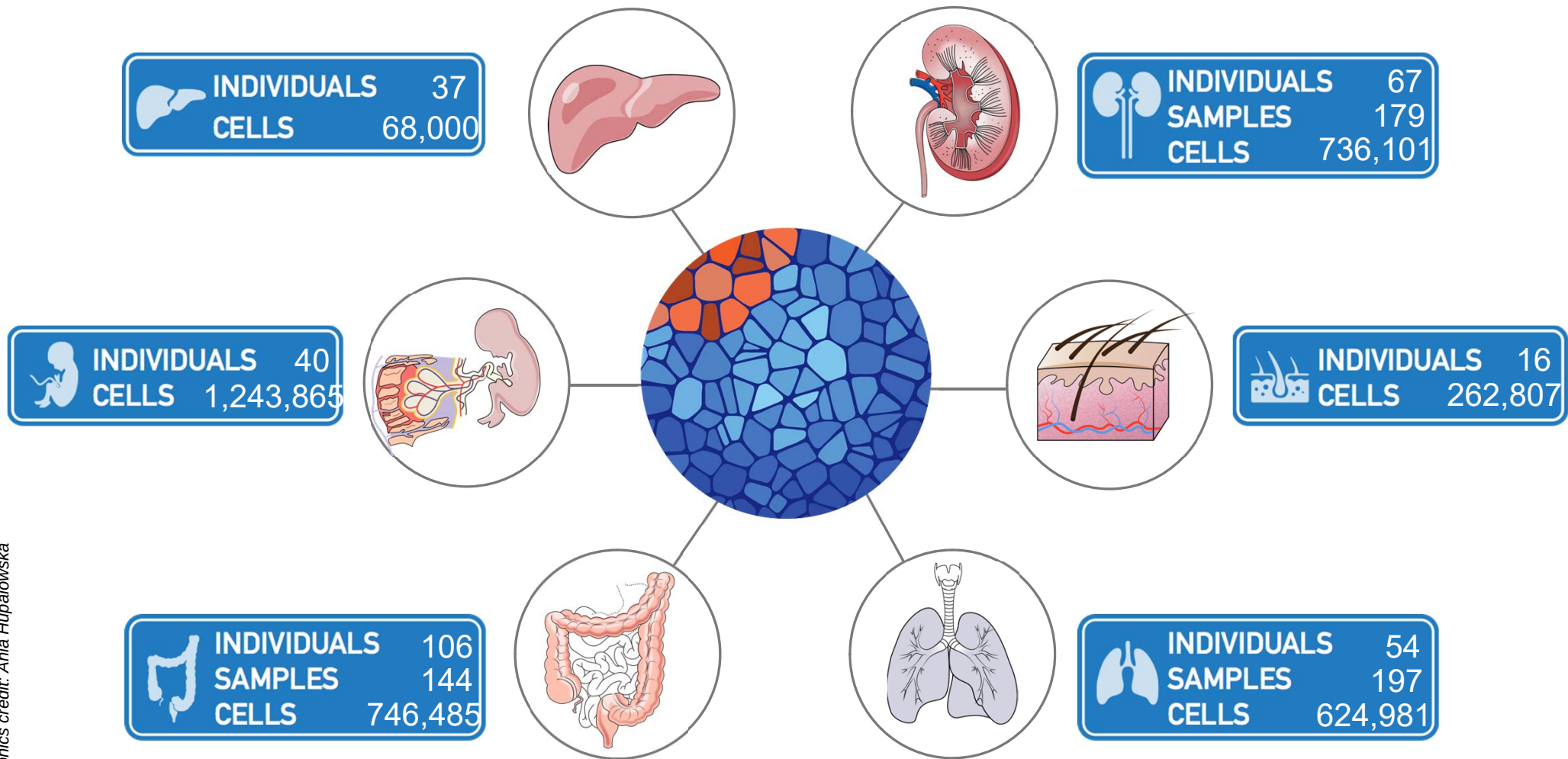
- Basis for interpretation of rare disease genes & GWAS loci
- Non-coding variants – Epigenetics
- Cell-type specific eQTLs (deconvolution of bulk data)
- Single cell eQTLs

=> ATLAS WILL BE CRITICAL FOR TARGETING EDITING & MAKING RIGHT EDITED CELLS

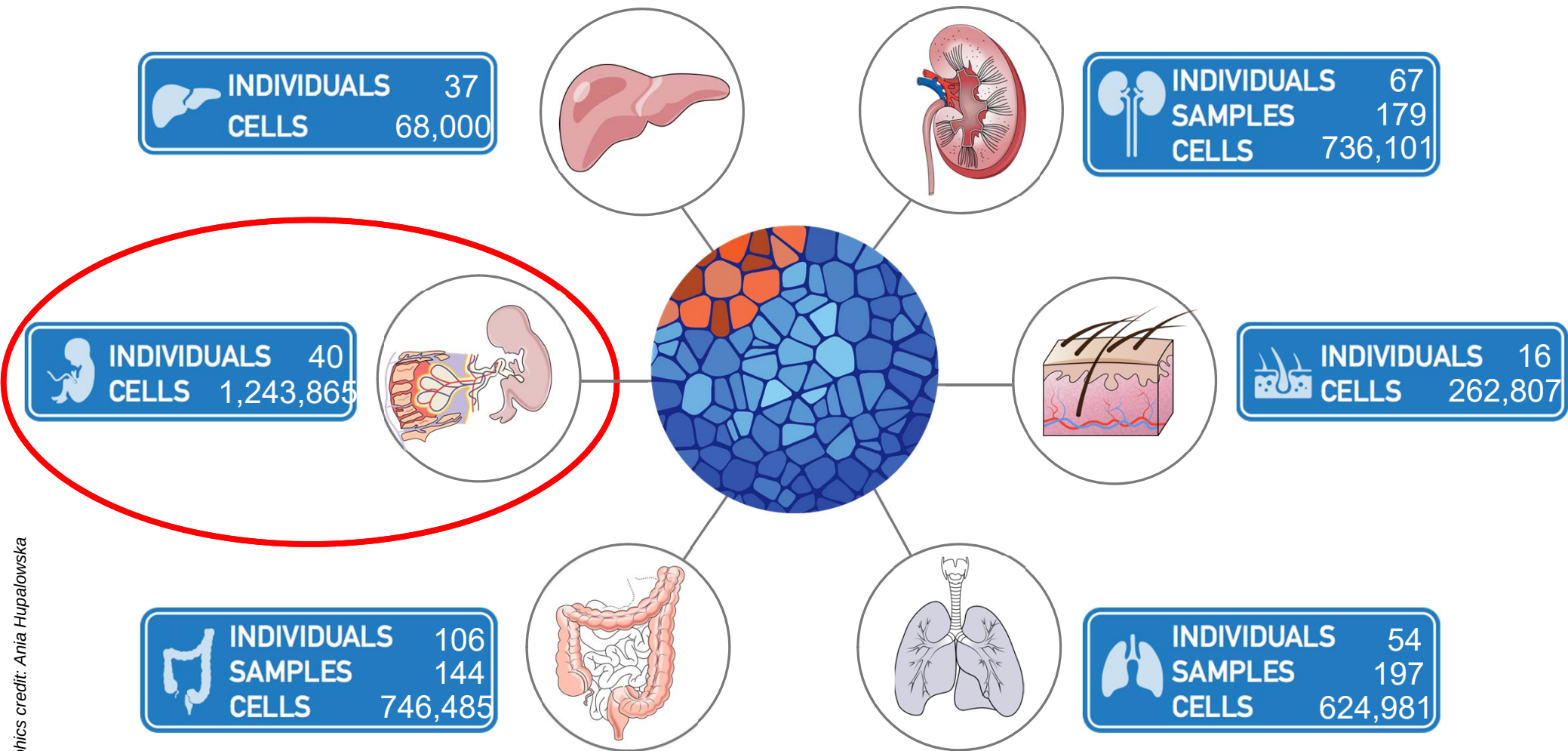
Gene-gene correlations and regulatory networks

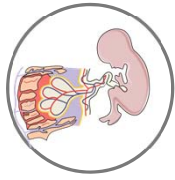


Views from the Atlases



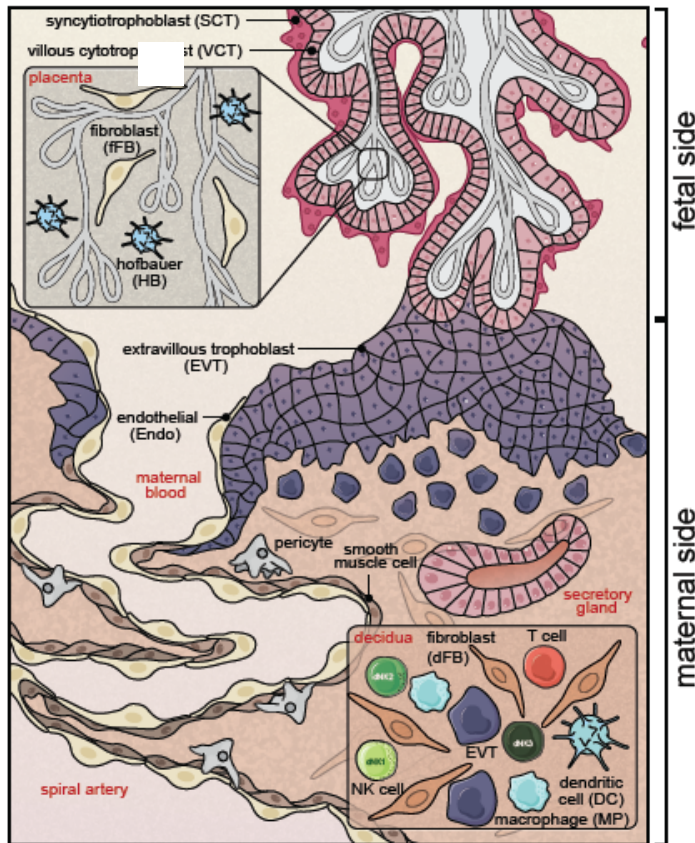
Views from the Atlases





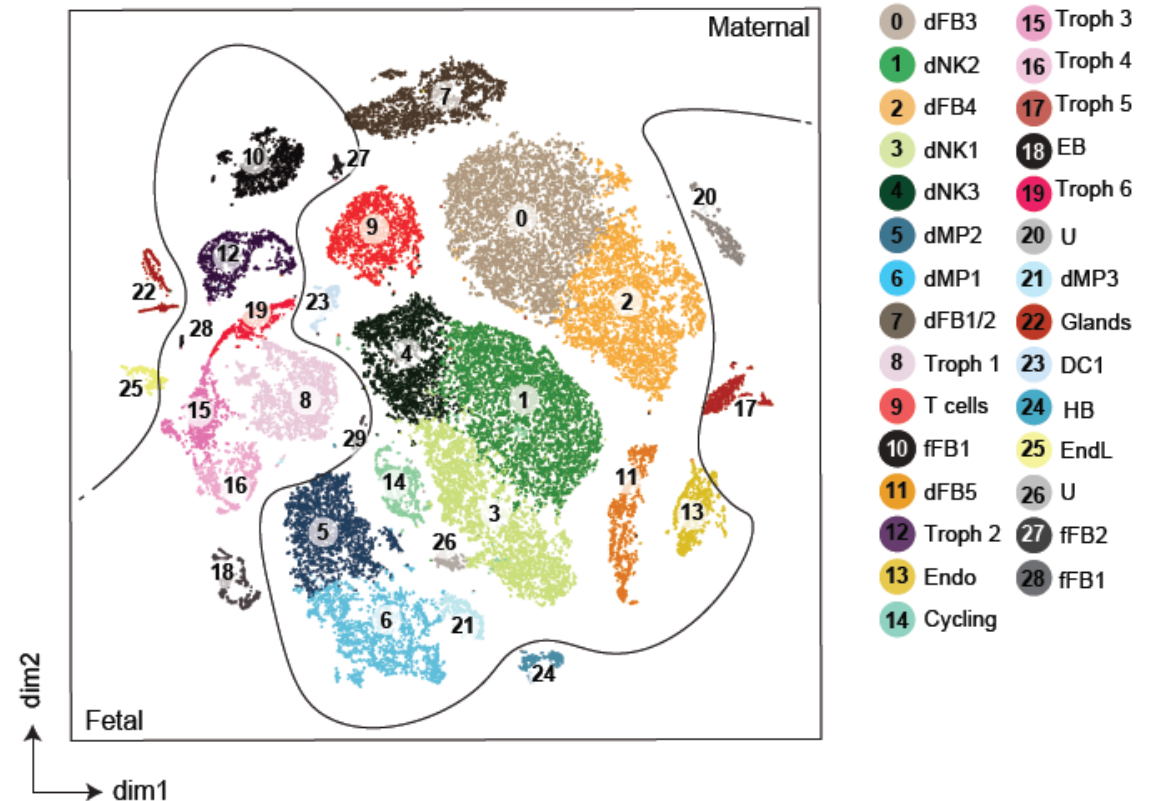
Developmental Cell Atlas 1.0

d

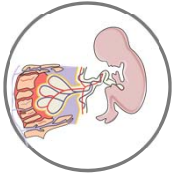


e

Maternal-fetal interface (2 placentas, 4 deciduas)
droplets (n > 45000)

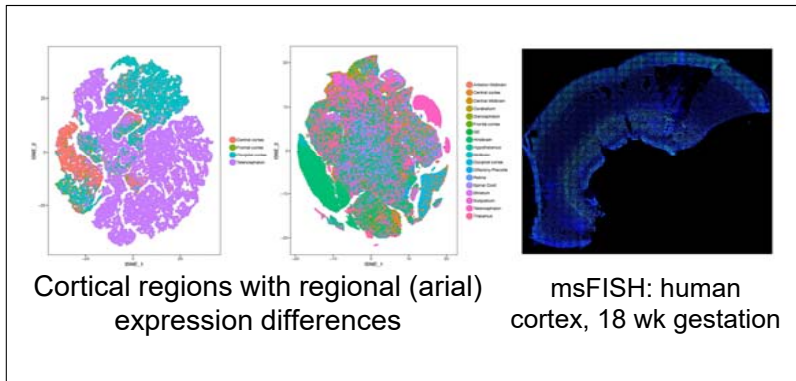


Novel cell types at the maternal/fetal interface



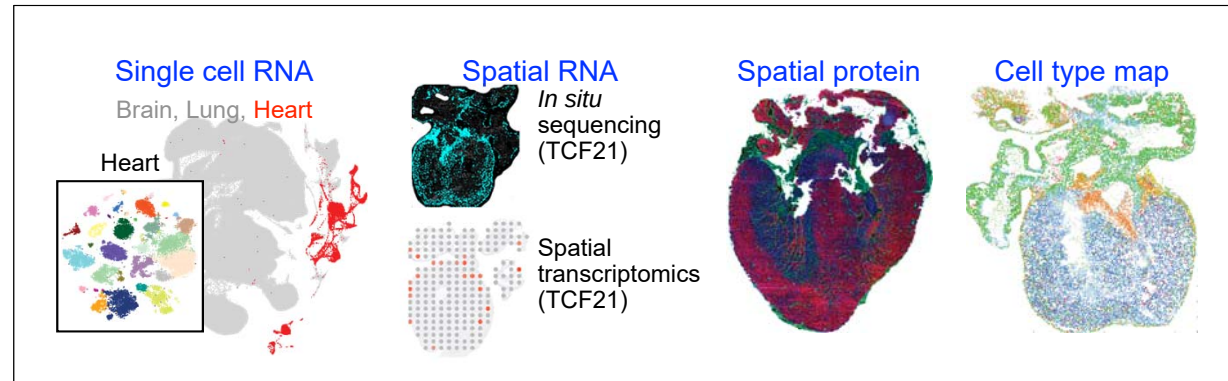
Developmental Cell Atlas 1.0

Fetal brain



Kriegstein lab

Fetal brain, heart and lung

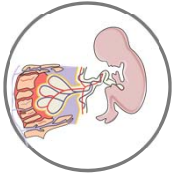


Linnarsson, Lundeberg, Lundberg, Nilsson, Sundström, Samakovlis labs

➔ Swedish and French Dev consortia

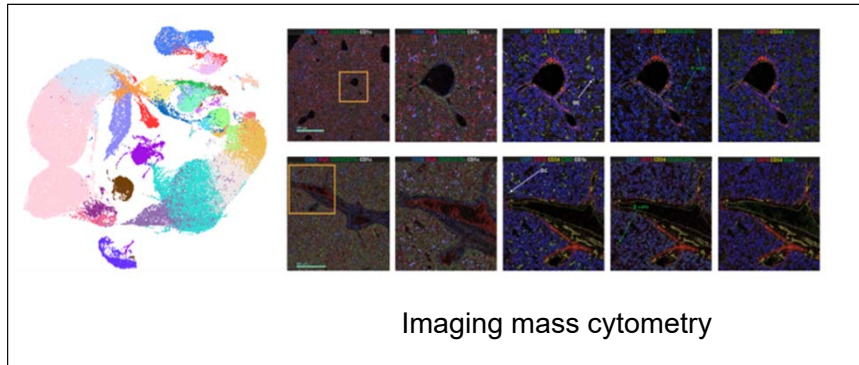
Support: NIH BRAIN Initiative, Knut and Alice Wallenberg Foundation, and Erling Persson Family Foundation

Slide adaptation courtesy of Linnarsson, Kriegstein



Developmental Cell Atlas 1.0

Fetal liver haematopoiesis

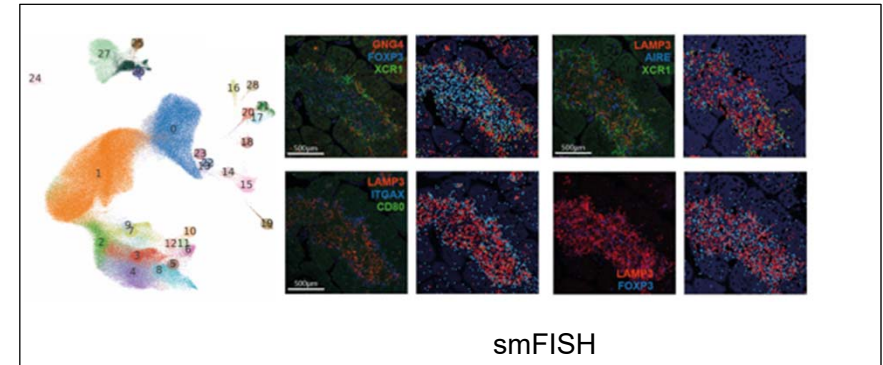


Popescu *et al.*, *Nature*, in press

Haniffa, Behjati, Teichmann Labs

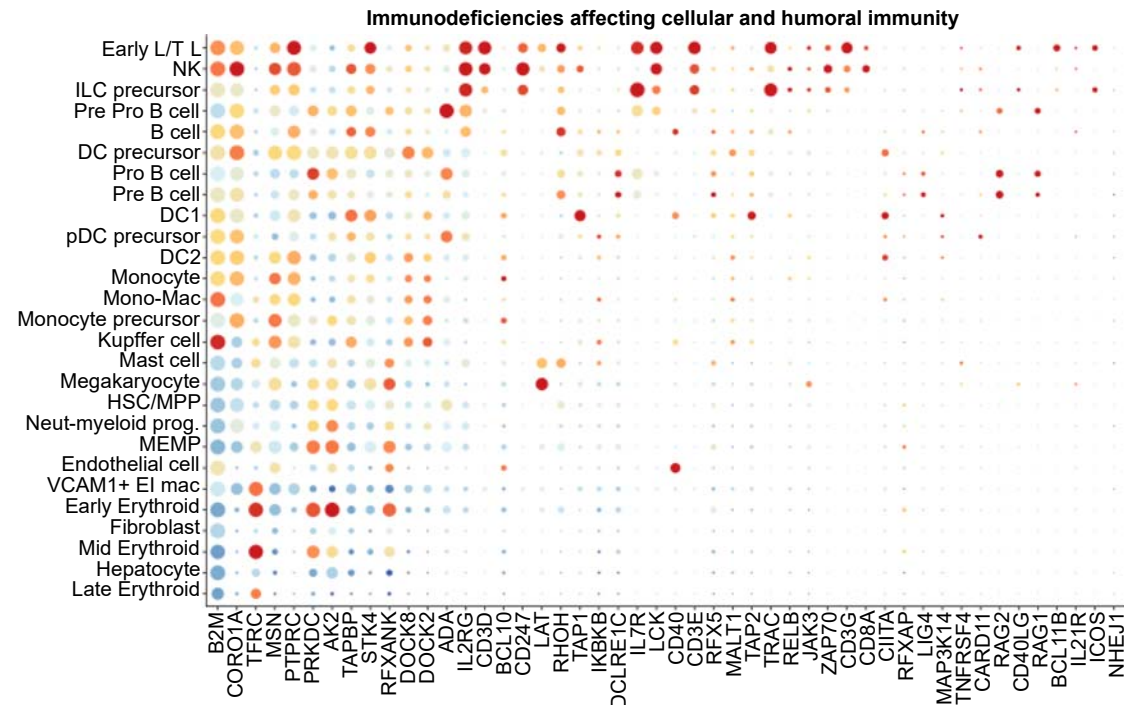


Fetal thymus



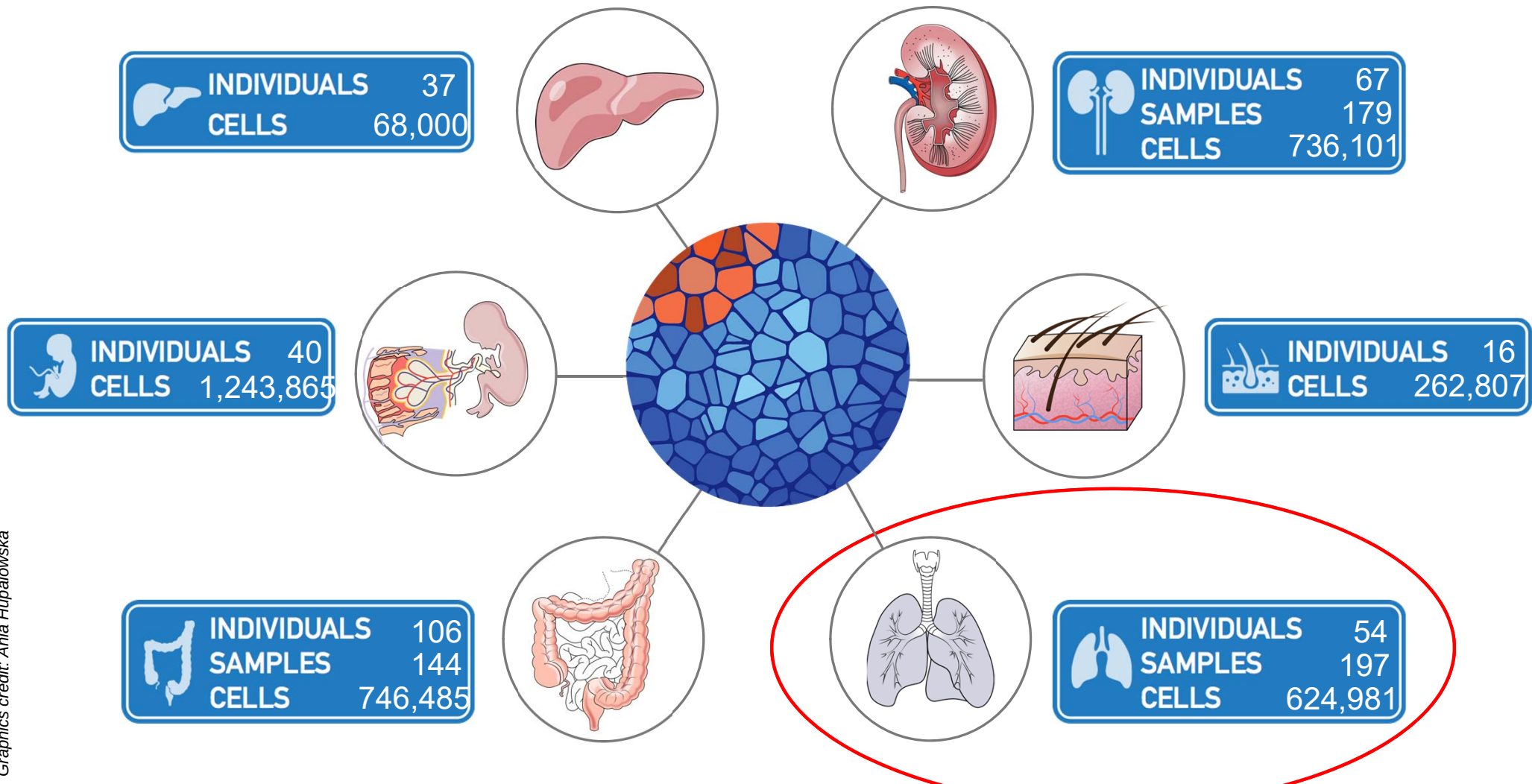
Slide adaptation courtesy of Haniffa

Expression of Rare Disease Genes During Fetal Liver Haematopoiesis



=> TARGETS for EDITING & information on OFF-TARGET effects

Views from the Atlases

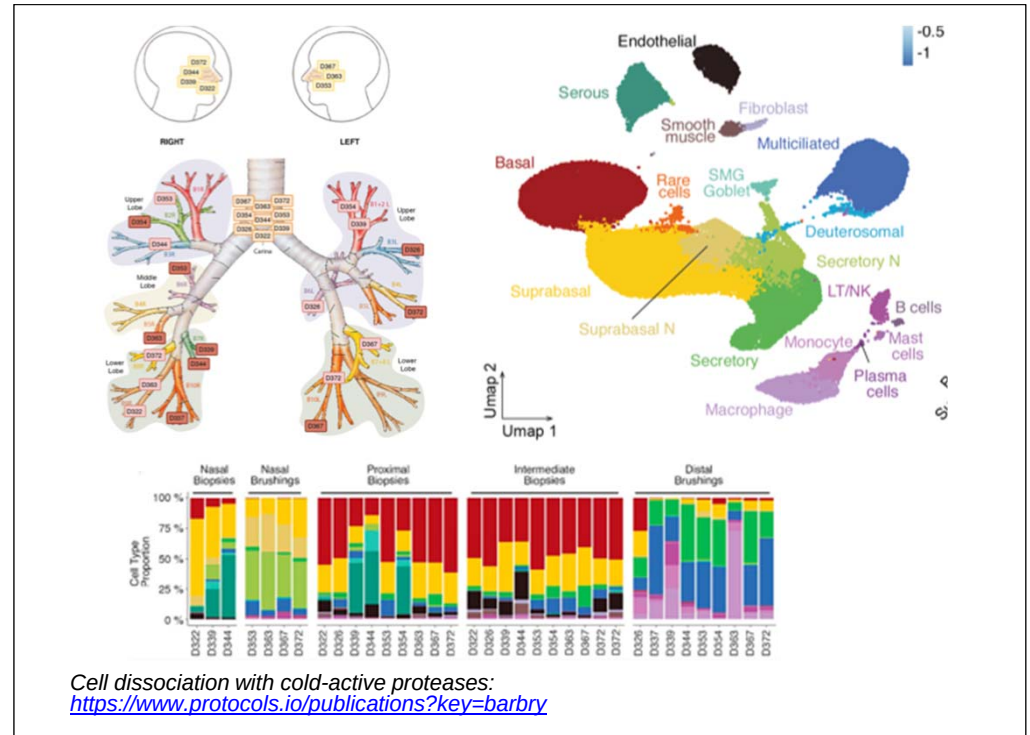
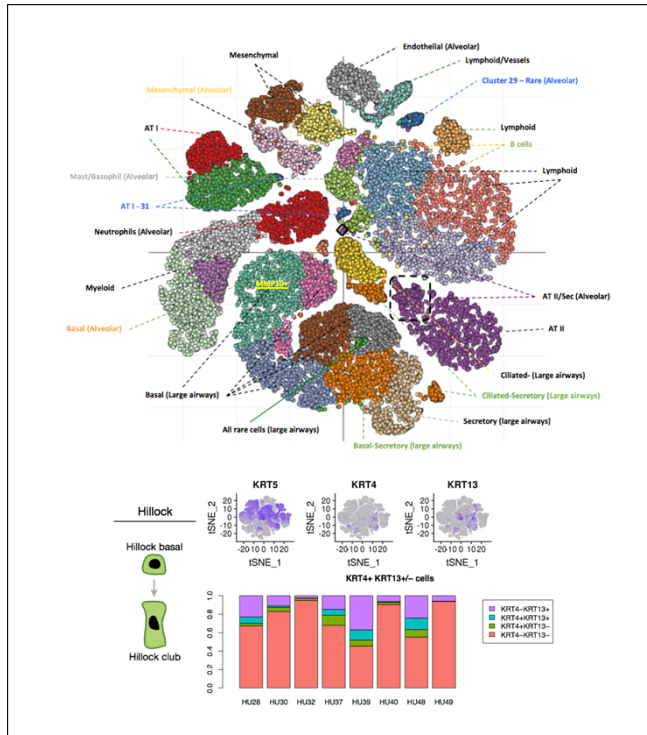




Lung Cell Atlas 1.0

Human branching tree
Rajagopal & Regev labs

Human airway wall, proximal/distal axis
Barbry lab

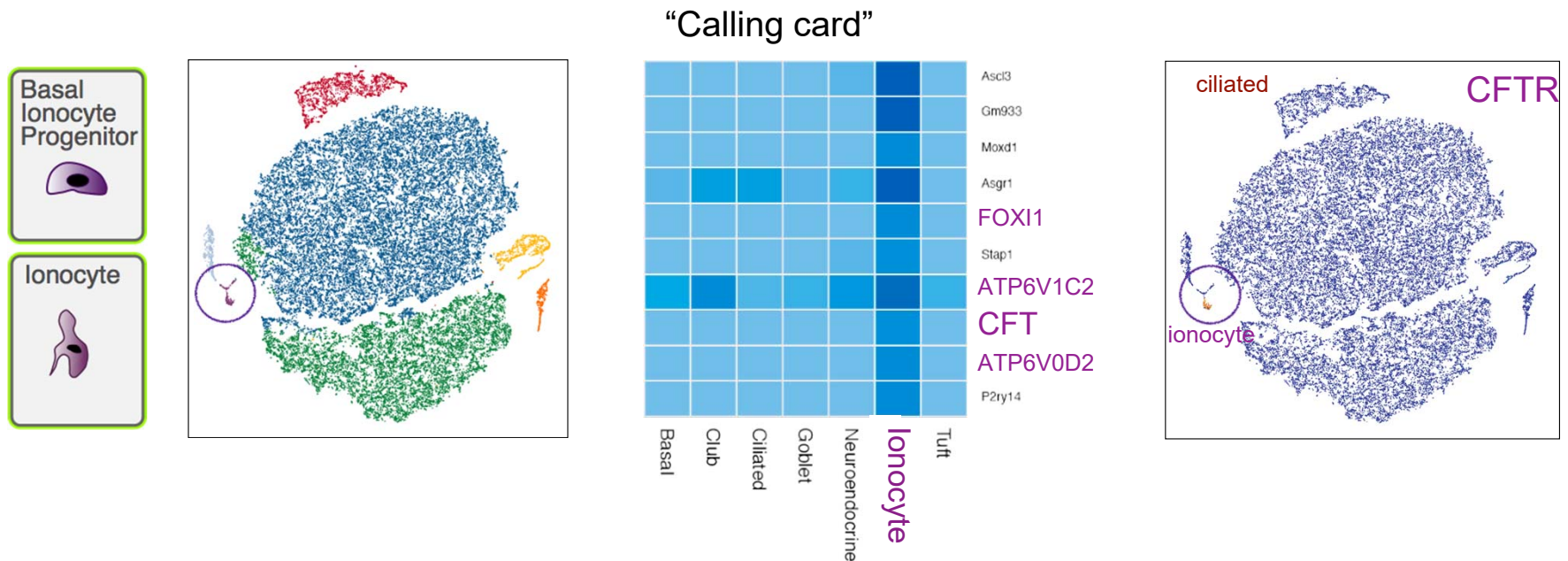


Cell dissociation with cold-active proteases:
<https://www.protocols.io/publications?key=barbry>

Support: Menton Foundation, Univesité Côte D'Azur,
France Genomique, CNRS, Chan Zuckerberg Initiative

Slide adaptation courtesy of Jay Rajagopal and Pascal Barbry

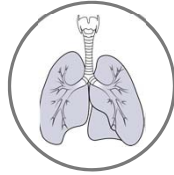
New rare ionocytes are major CFTR expressing cells



CFTR was thought to be expressed by the abundant **ciliated** cells at low levels
=> CARE NEEDED EVEN FOR SOMATIC CELL GENE EDITING

Montoro, Haber, Biton *et al Nature* 2018

Graphics credit: Daniel Montoro, Adam Haber, Moshe Biton, Aviv Regev, Jay Rajagopal

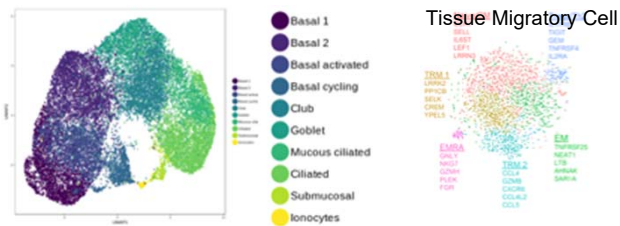


Lung Cell Atlas 1.0

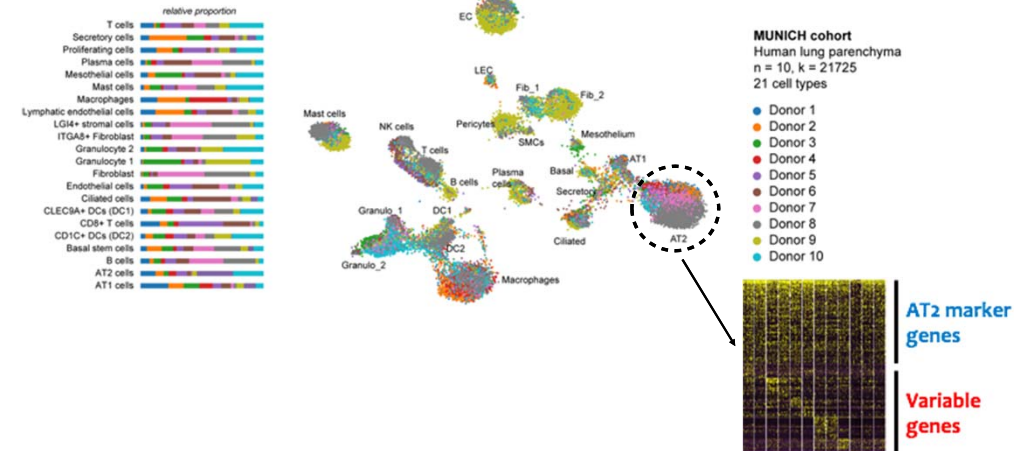
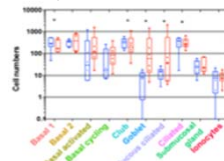
Human airway wall/parenchyma
Nawijn & Teichmann labs

Human lung parenchyma:
Inter individual variance within cell type
Schiller & Theis labs

Novel tissue resident CD4 T cell subset:



Unique disease-associated airway epithelial cell state:
Mucous Ciliated Cell



Support: German Center for Lung Research (DZL), Helmholtz Association, Single Cell Omics Germany, LifeTime, Chan Zuckerberg Initiative, CU Anschutz

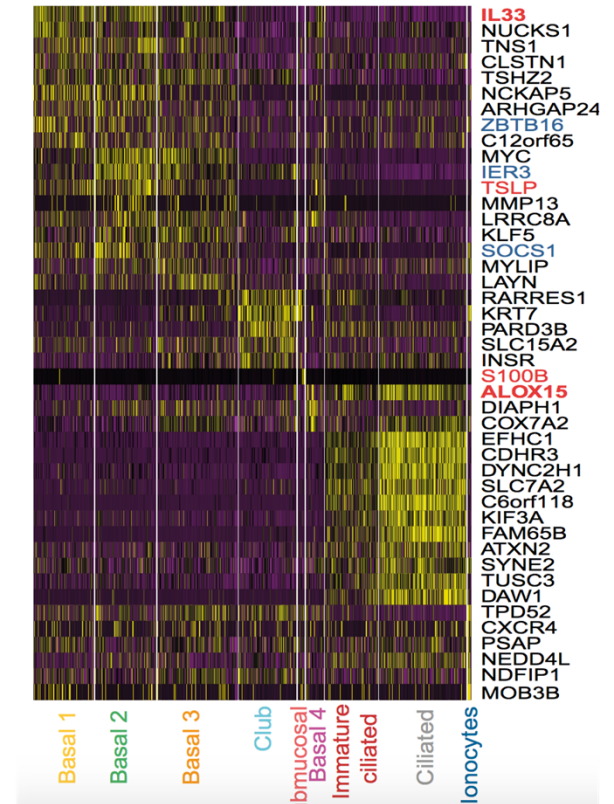
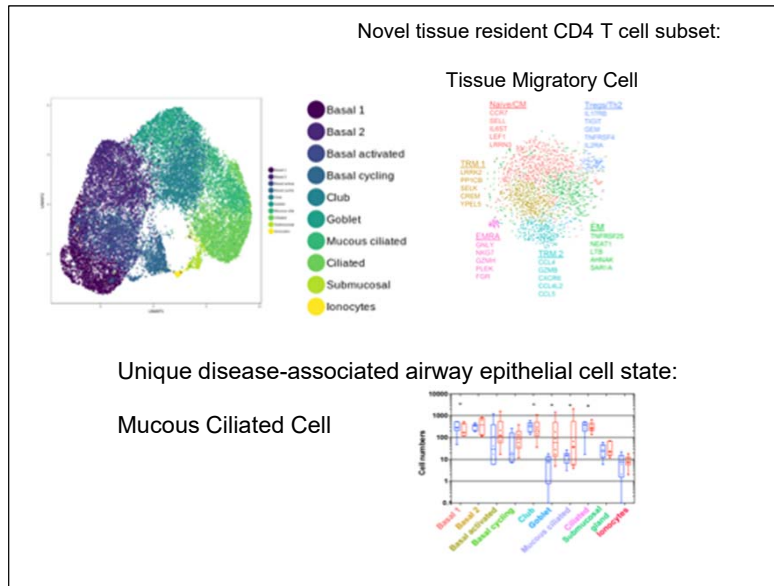
Slide adaptation courtesy of Martijn Nawijn, Sasha Micharin, Herbert Shiller, Fabian Theis



Lung Cell Atlas 1.0

Human airway wall/parenchyma
Nawijn & Teichmann labs

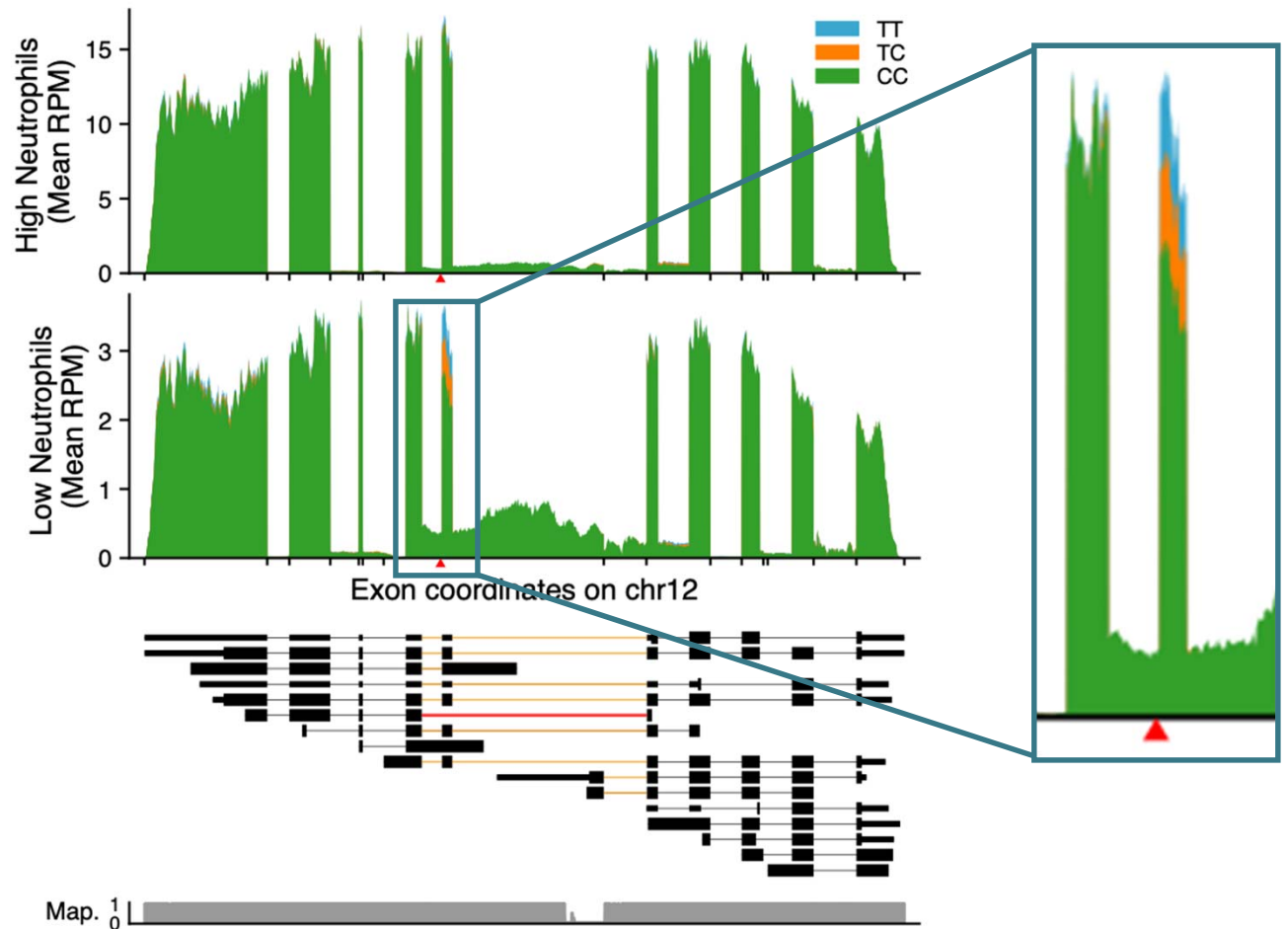
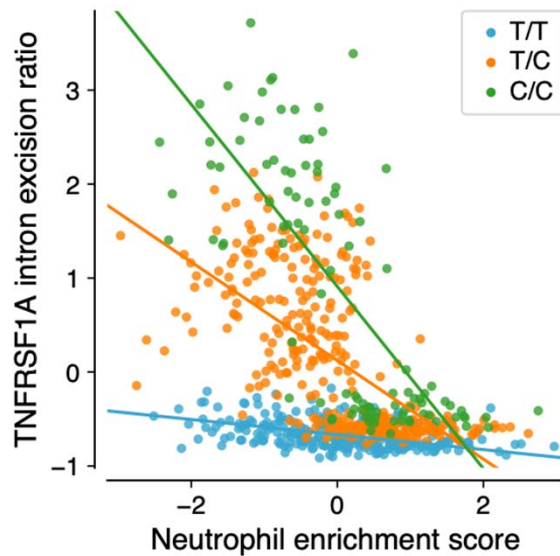
Asthma GWAS genes are expressed in a cell-type specific manner



Support: German Center for Lung Research (DZL), Helmholtz Association, Single Cell Omics Germany, LifeTime, Chan Zuckerberg Initiative, CU Anschutz

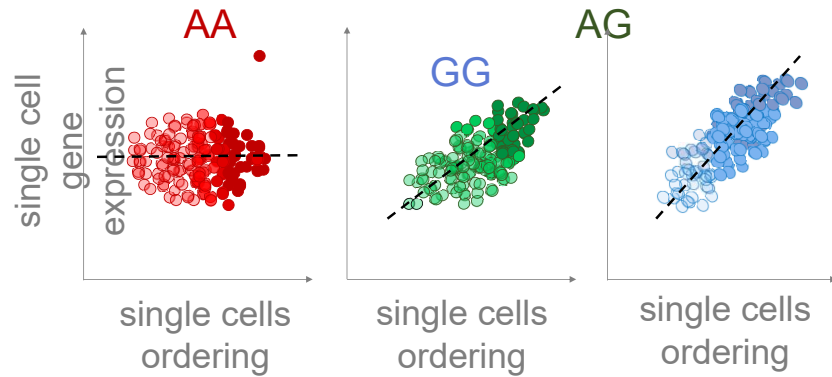
Vieira Braga *et al*, *Nature Medicine*, 2019

GTEx Cell type interaction QTLs: splicing example

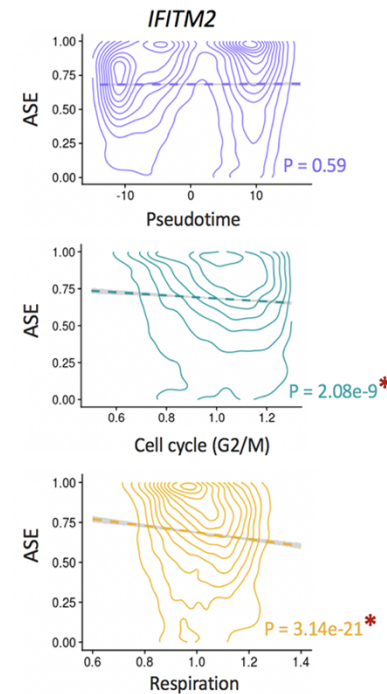
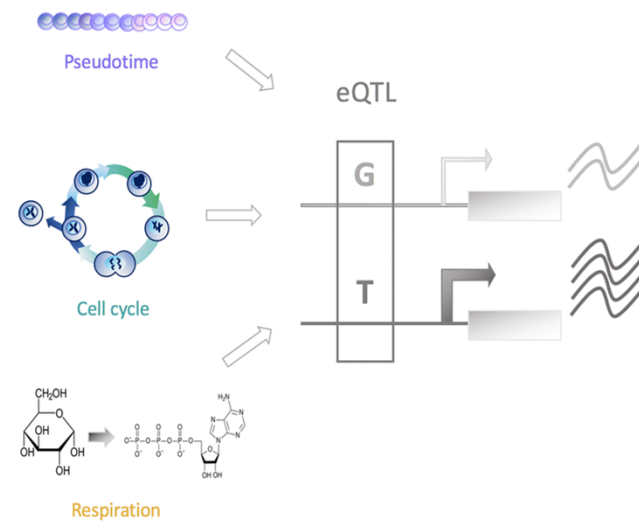


Francois Aguet, Sarah Kim-Hellmuth, Kristin Ardlie

Single cell interaction eQTLs



ASE interaction eQTLs with cell states



Credits: Ana Cuomo, Oliver Stegle

SUMMARY

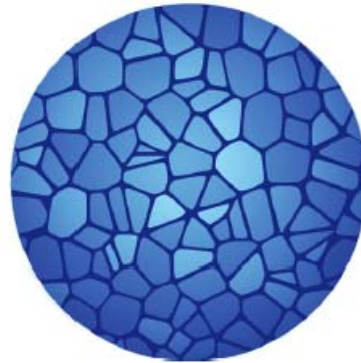
- **HCA data on gene expression at cellular resolution**
= important framework for editing considerations
- **Developmental expression: mostly first - second trimester, less third trimester and paediatric**
- **Cell-type specific editing: challenging but safer?**

THANK YOU

Broad Institute:

Aviv Regev

Jane Lee
Orit Rozenblatt-Rosen
Jenny Rood
Ania Hupalowska



Wellcome Sanger Institute:

Tracey Andrew
Kerstin Meyer
Sarah Aldridge

All HCA Members