

# Single-cell multiomics: from reference atlases to human diseases

Human Cell Atlas Latin America

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Web: <https://mereulab.org>



**Josep Carreras**  
LEUKAEMIA  
Research Institute



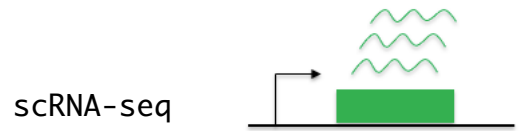
@eli\_mereu



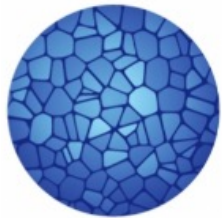
<https://github.com/mereulab>

# Characterizing complex tissues at molecular and cellular level

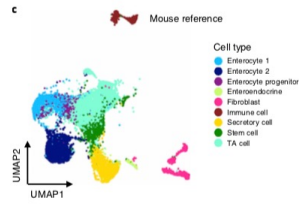
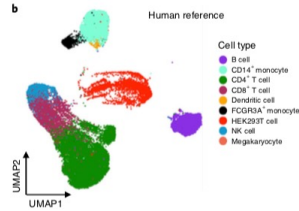
Molecular and spatial reference maps of normal tissues



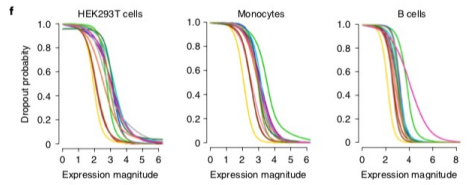
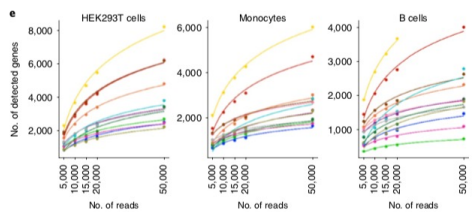
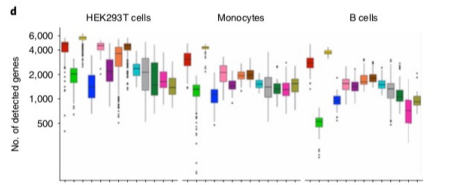
**HUMAN CELL ATLAS**



- CEL-seq2
- MARS-seq
- Quartz-seq2
- gmcSCR-seq
- Smart-seq2
- C1HT-small
- C1HT-medium
- Chromium
- Chromium (sn)
- ddSEQ
- Drop-seq
- ICELL8
- inDrop



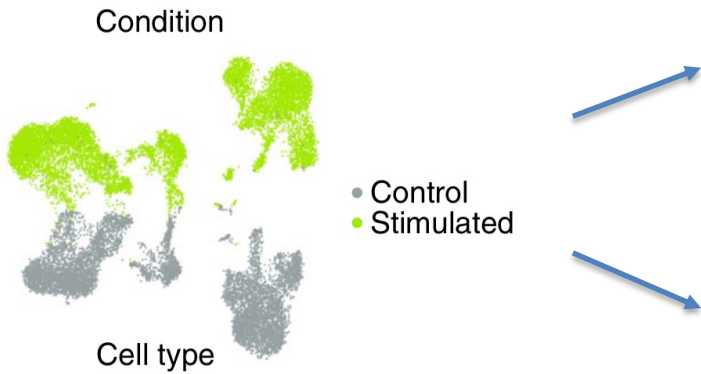
## Technology Benchmarking



Mereu, Nat. Biotech (2020)

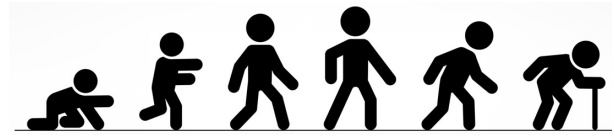
# Targeting inflammation in ageing and human diseases

Perturbed/Diseased states

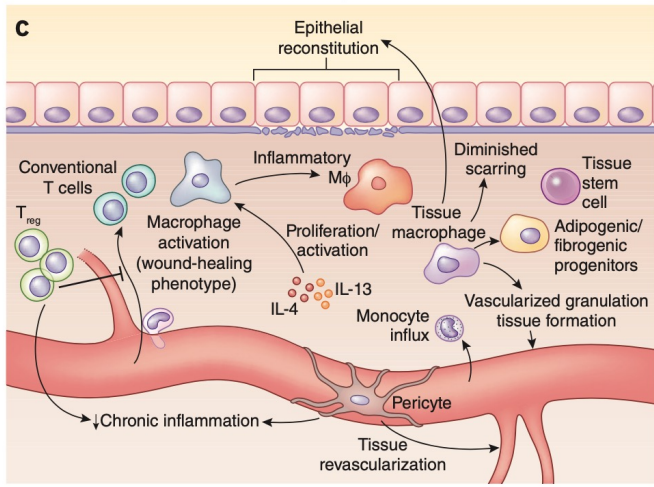


Adapted from scGEN, Lotfollahi et al, Nat. Methods. 2020

Ageing

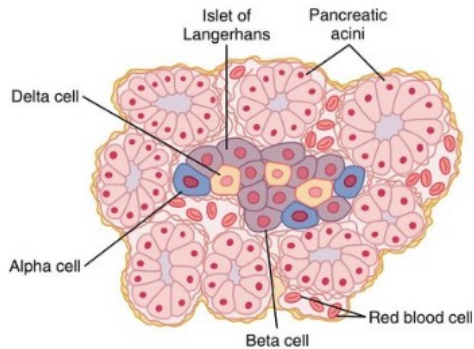
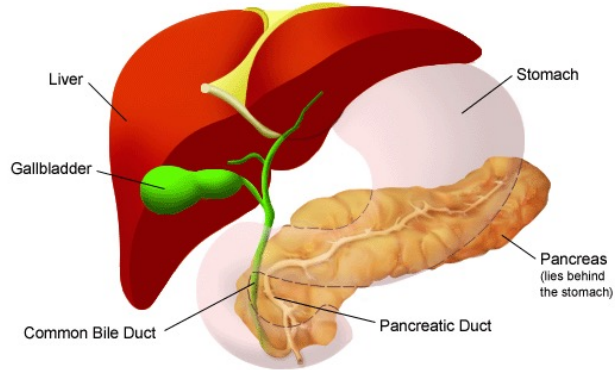


## Tissue-level inflammation and regeneration



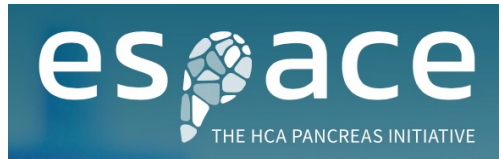
Forbes & Rosenthal, Nat. Medicine (2014)

# 1. The Human Pancreas Atlas: why is it important?



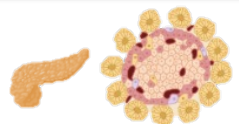
- The pancreas is a vital organ consisting of:
  - *Exocrine: 95% of cells*
  - *Endocrine: 5% of cells*
- Dual function:
  - the secretion of enzymes for the digestive system.
  - the regulation of several hormones (e.g. insulin)
- Several human diseases are associated with the pancreas, including:
  - *Pancreatic Adenocarcinoma*
  - *Diabetes Mellitus*
- Difficult to study due to its high autolytic activity, resulting in the rapid degradation of cells upon pancreatic resection.

# 1. The ESPACE consortium is the European HCA Pancreas initiative



# A single-cell multiomics atlas of the Human Pancreas

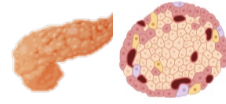
ESPACE- Comprehensive molecular characterization of the Human Pancreas



Fetal samples  
(4-13 wpc)

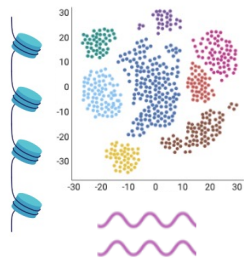


Adult samples  
Focus on Exocrine cells

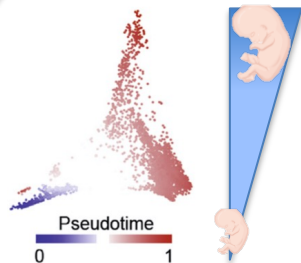


Diseased samples  
Focus on endocrine cells

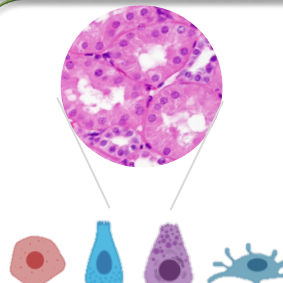
Transcriptomics/Epigenomics



Cell-type Development



Micropathology characterization

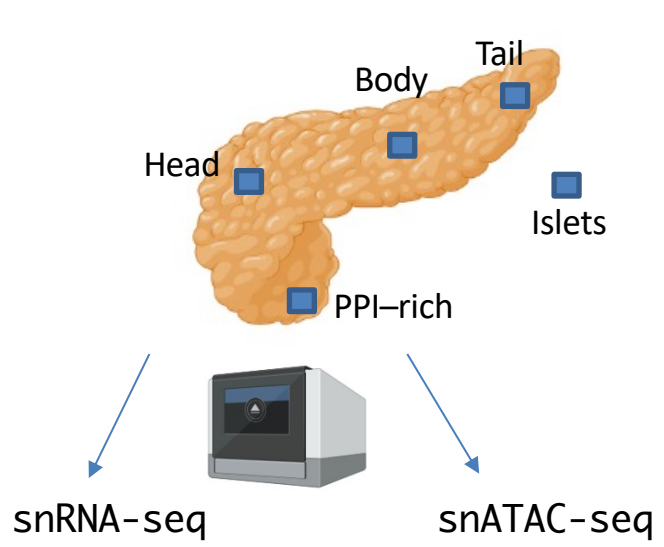


Our deep characterization includes:

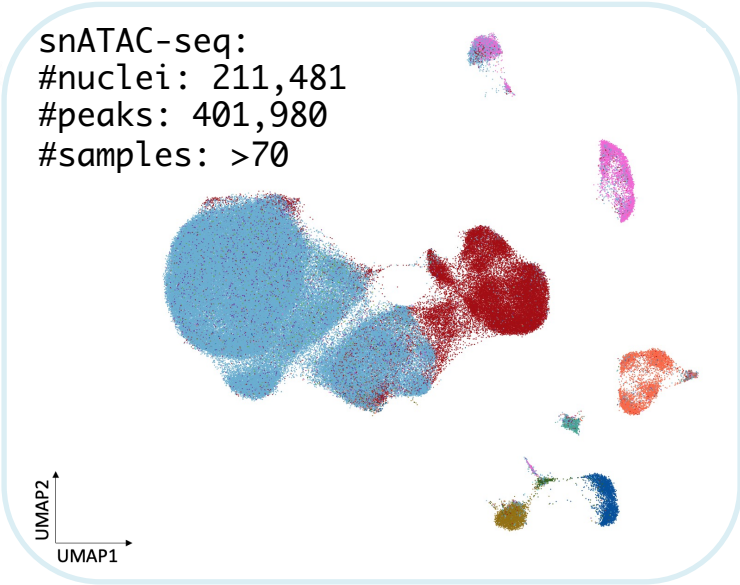
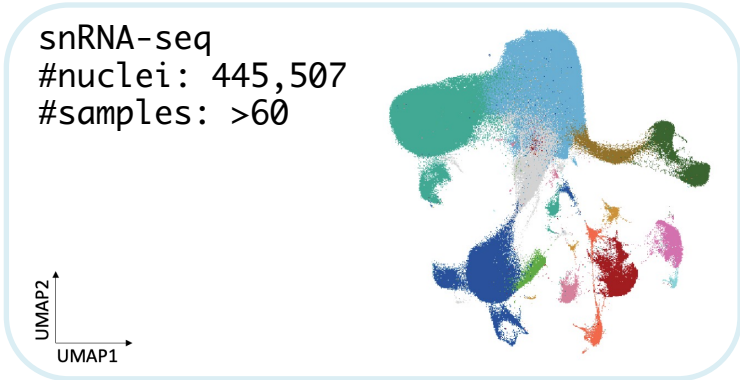
- snRNA-seq
- scATAC-seq
- VASA-seq – full length
- Spatial proteomics by CODEX and ISS



# 1. The transcriptomic and epigenomic human pancreas atlas



- Cell types
- Acinar-s
  - Acinar-i
  - Ductal
  - Undefined
  - Fibroblasts
  - Alpha
  - Beta
  - Endothelial
  - Macrophage
  - Immune
  - Ductal\_MUC5+
  - Lymphocytes
  - Lymphatic Endothelium
  - Schwann
  - Delta

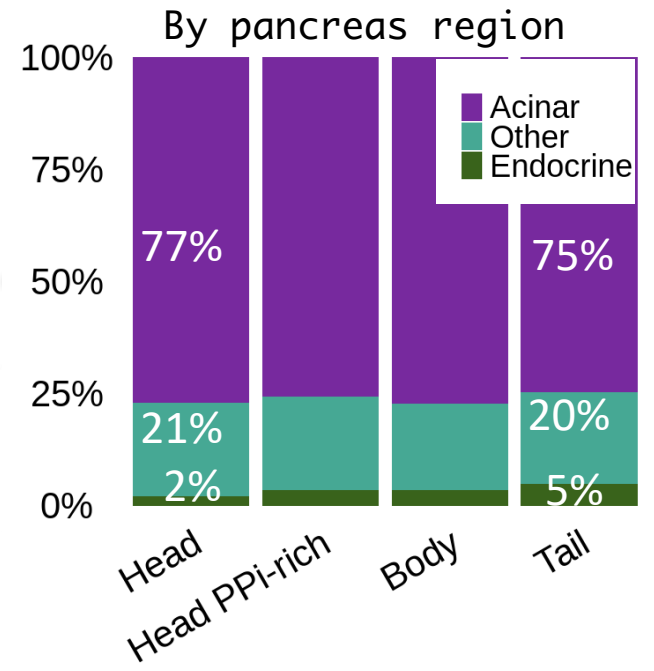
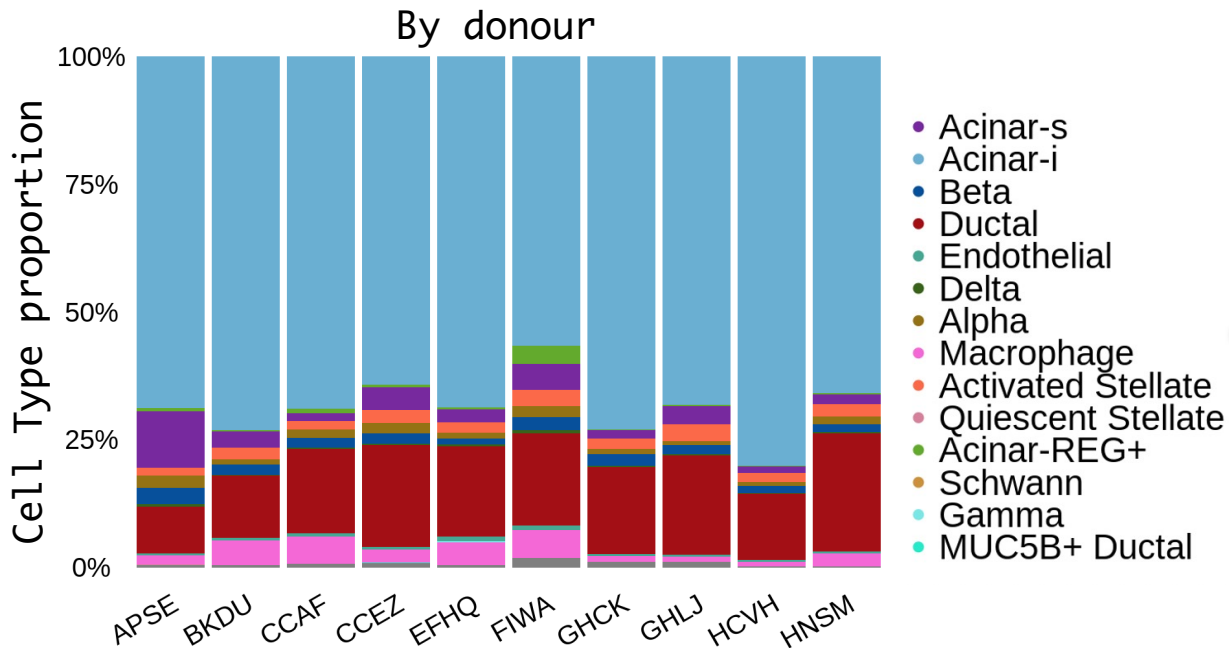


# Roadmap towards a Human Pancreas Atlas

1. Reads quality checks and mapping to generate the gene/peak count matrix
2. Characterize, merge and filter peaks in snATAC-seq
3. Filtering of low-quality cells
4. Integrating samples
5. Ambient RNA removal
6. Technical doublet removal in both RNA/ATAC
7. Consensus cell-type annotations
8. ....Downstream analysis ..

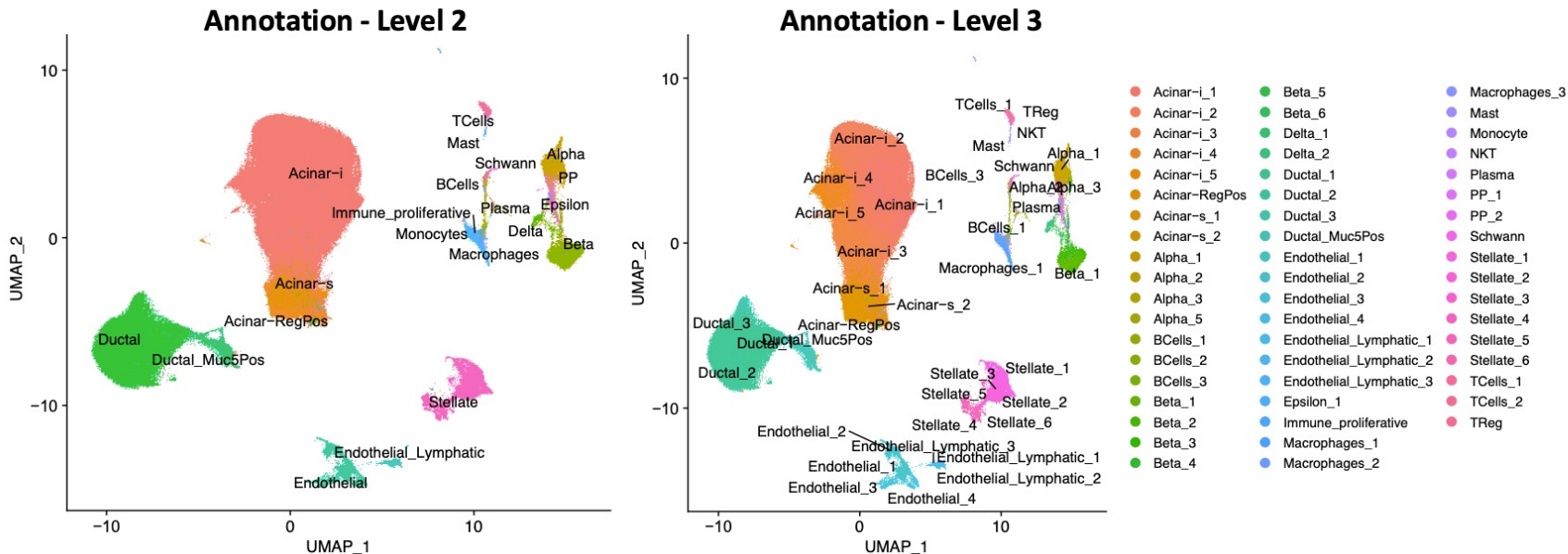


# Cell-type composition of the healthy human pancreas (scATAC data)



# Generating a comprehensive cell-type reference dataset

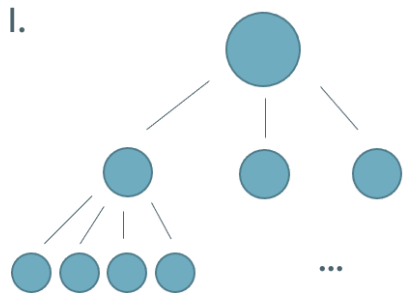
Total: 445.507 cells – 16 donors – 64 samples



# Generating a comprehensive cell-type reference dataset

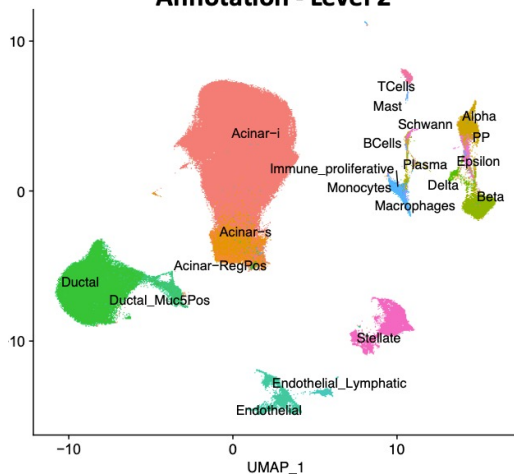
Total: 445.507 cells – 16 donors – 64 samples

## Clustering Strategy

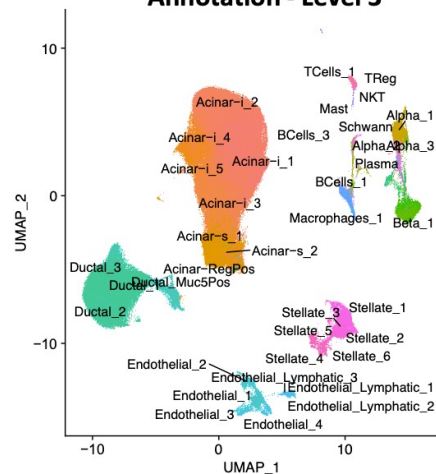


- Integrate once
- Subset and recalculate clusters

## Annotation - Level 2



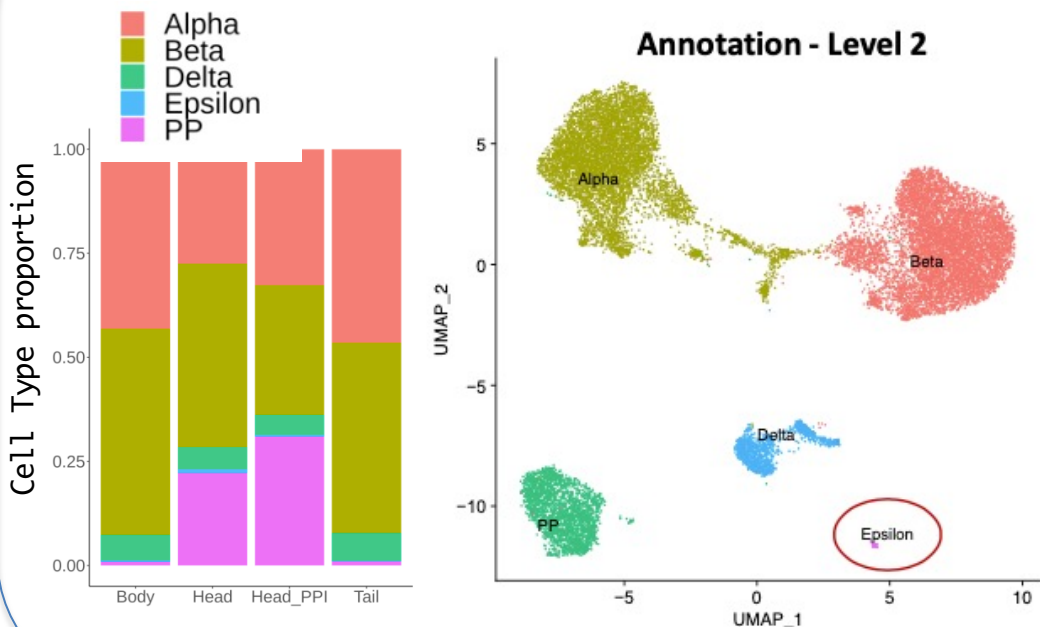
## Annotation - Level 3



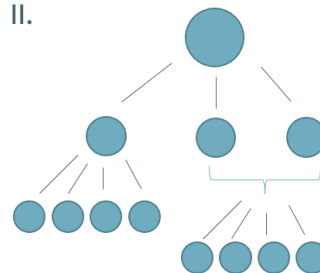
# Generating a comprehensive cell-type reference dataset

## Endocrine cells

Total: 18.171 cells – 16 donors – 64 samples



II.

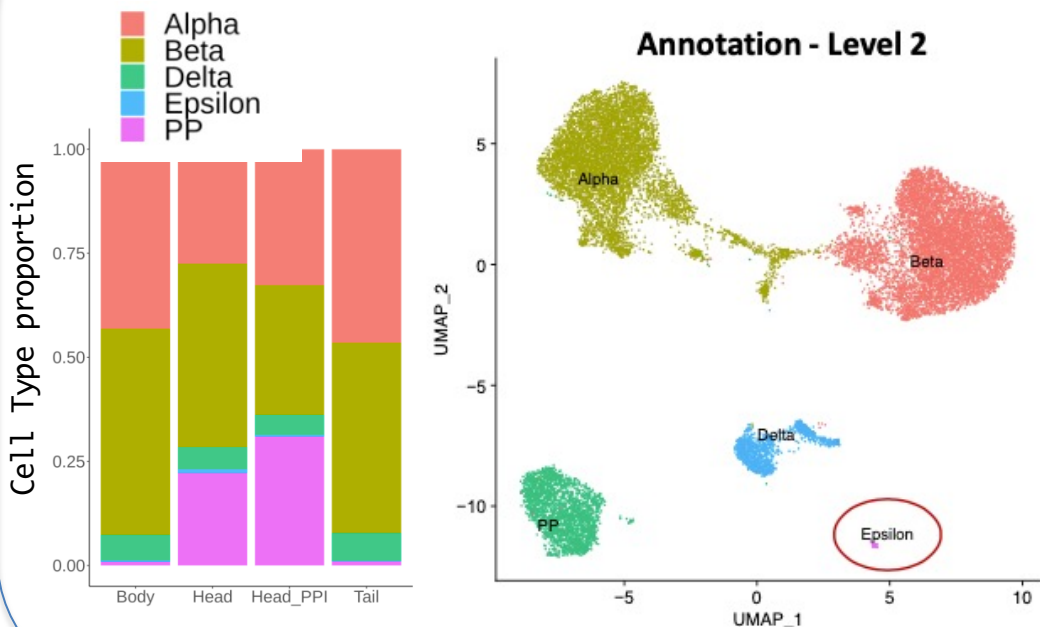


- Integrate at each step
- Subset and recalculate integration and clusters

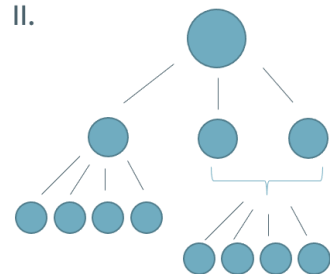
# Generating a comprehensive cell-type reference dataset

## Endocrine cells

Total: 18.171 cells – 16 donors – 64 samples



II.

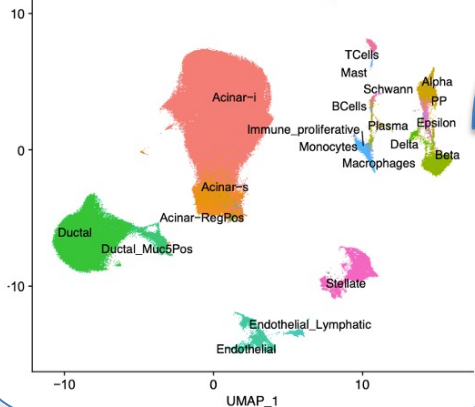


- Integrate at each step
- Subset and recalculate integration and clusters

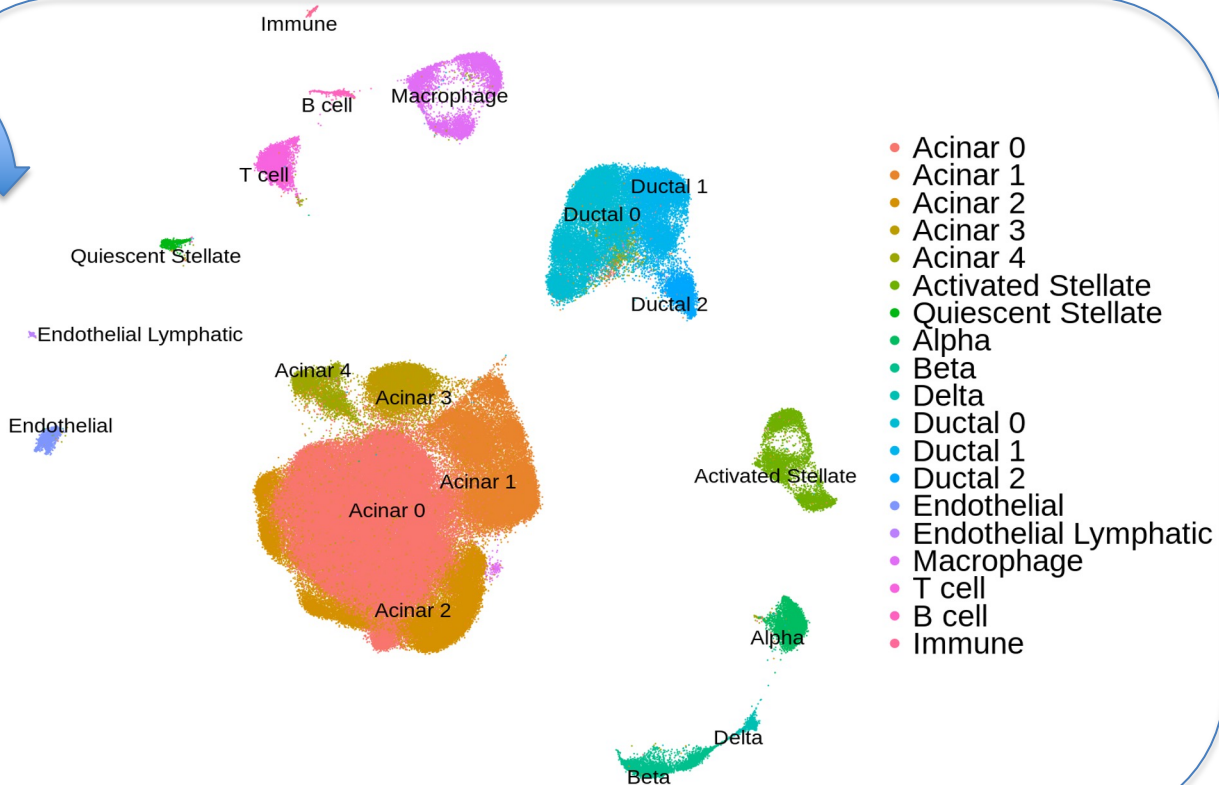
# Integration with scATAC-data through label transferring

snRNA

Annotation - Level 2



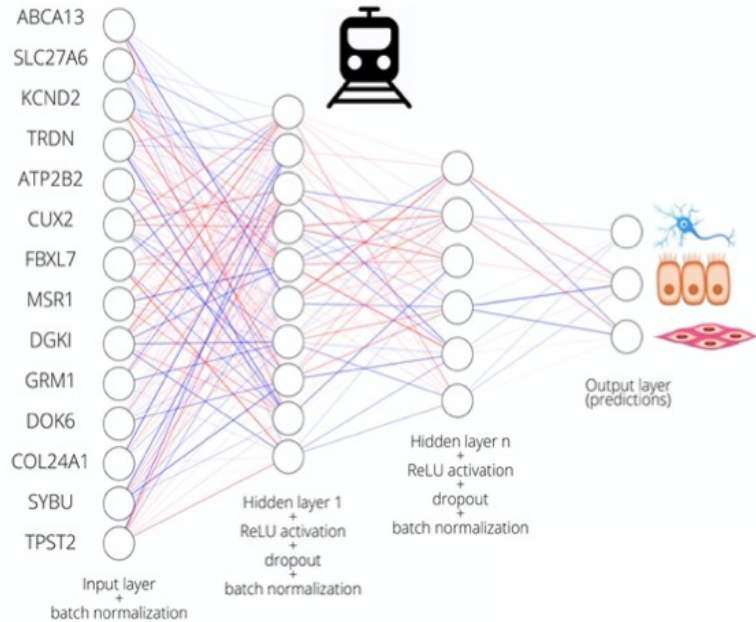
snATAC





# Harmonizing cell annotations across samples, regions and modalities

## the\_model



deepScore

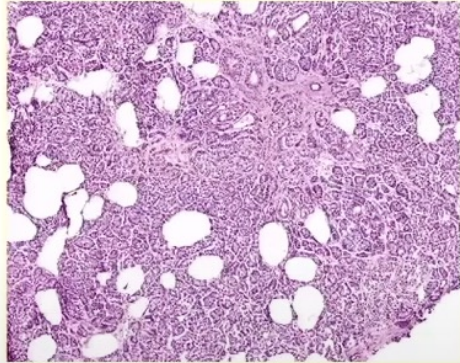
- User-friendly and fast
- Multi-language (R/Python)
- Multi-modal count data



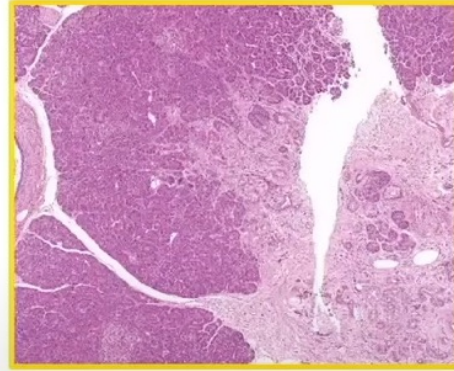
**/Fig4. Multi-language metro map of the main different platforms and packages that DeepScore integrates.**

# Pancreatic lesions affects healthy pancreas

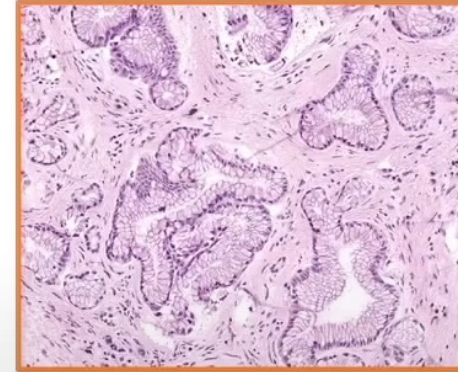
Lipomatosis



Fibrosis



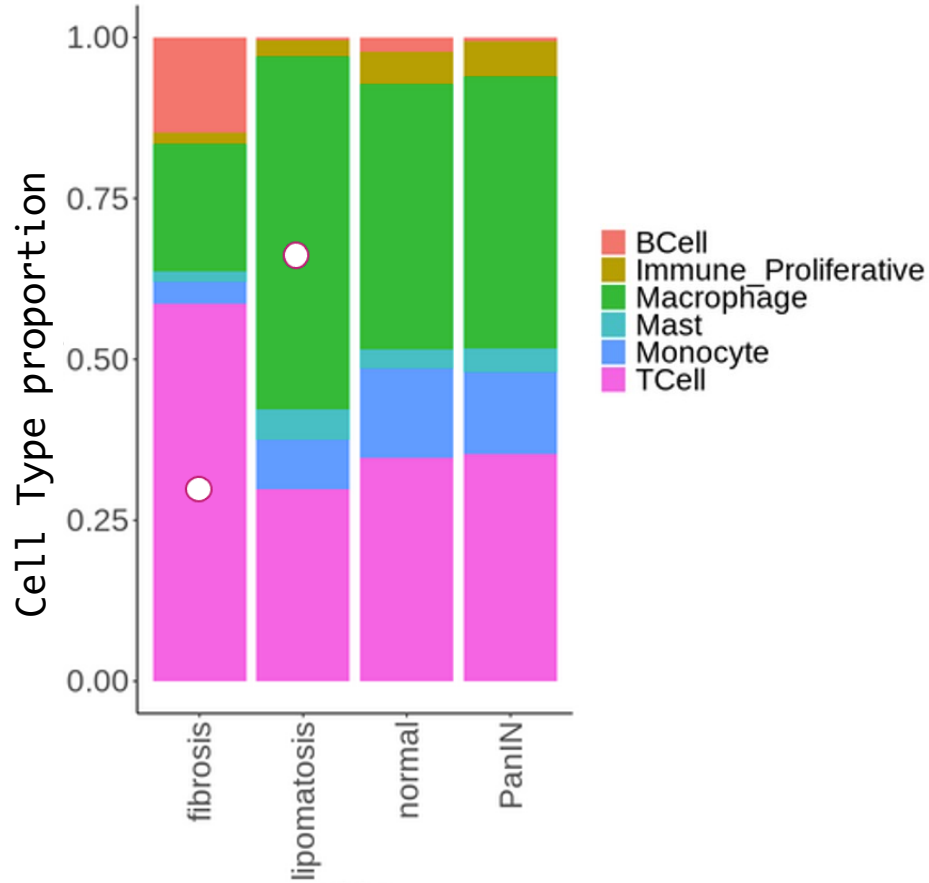
PanIN



(Pancreatic  
Intrahepatic  
Neoplasia)

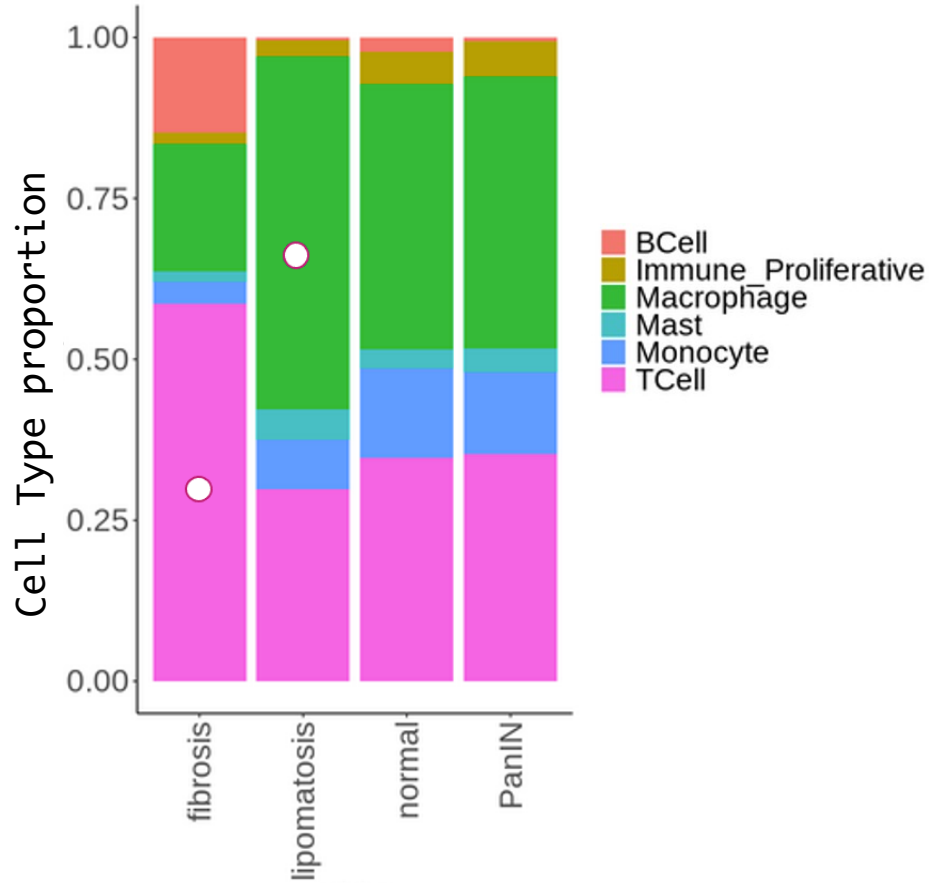
Donor	Normal	Lipomatosis	Fibrosis	PanIN
Healthy	36	17	17	6
Pancreatectomy	5		1	
T2D	3		2	

# Cell-type composition changes in micropathologies



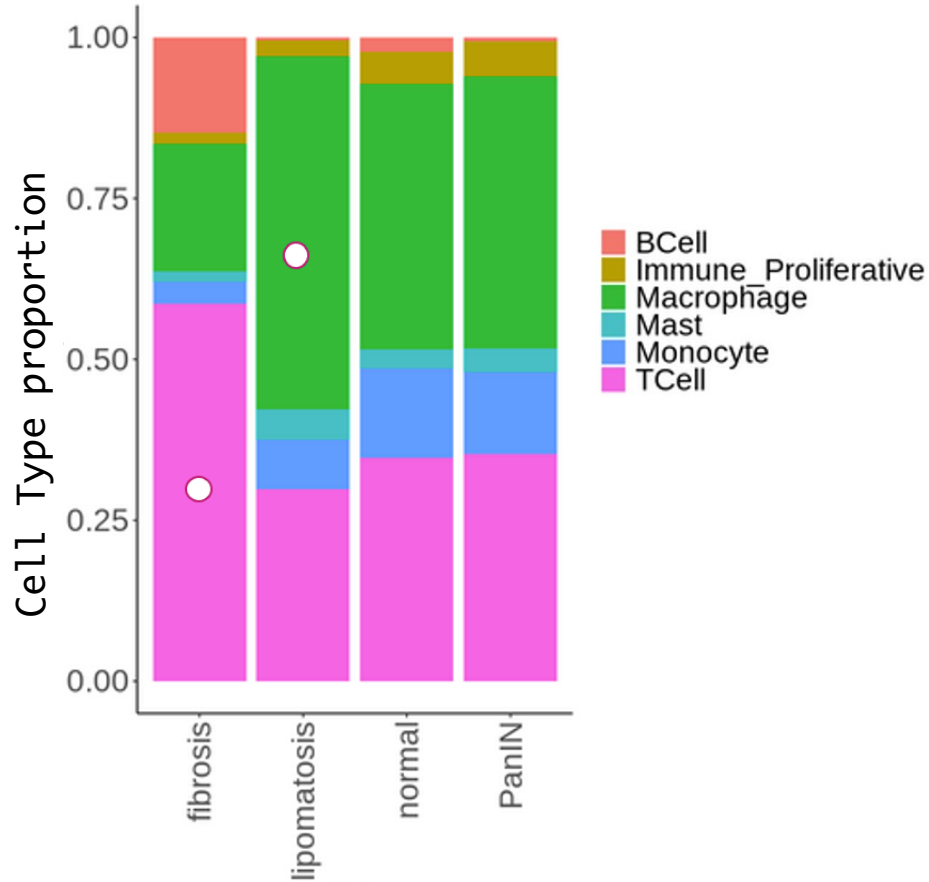
- Higher abundance of macrophages in lipomatosis

# Cell-type composition changes in micropathologies



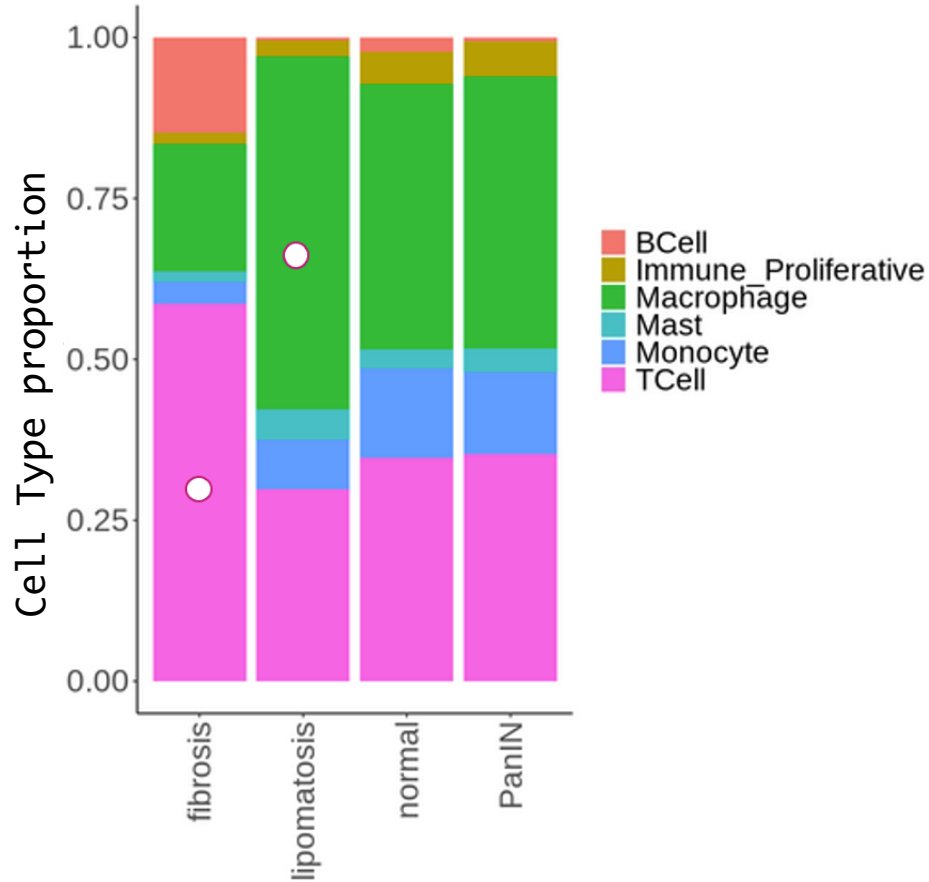
- Higher abundance of macrophages in lipomatosis
- Higher abundance of lymphocytes in fibrotic samples

# Cell-type composition changes in micropathologies



- Higher abundance of macrophages in lipomatosis
- Higher abundance of lymphocytes in fibrotic samples
- No changes in composition for PanIN

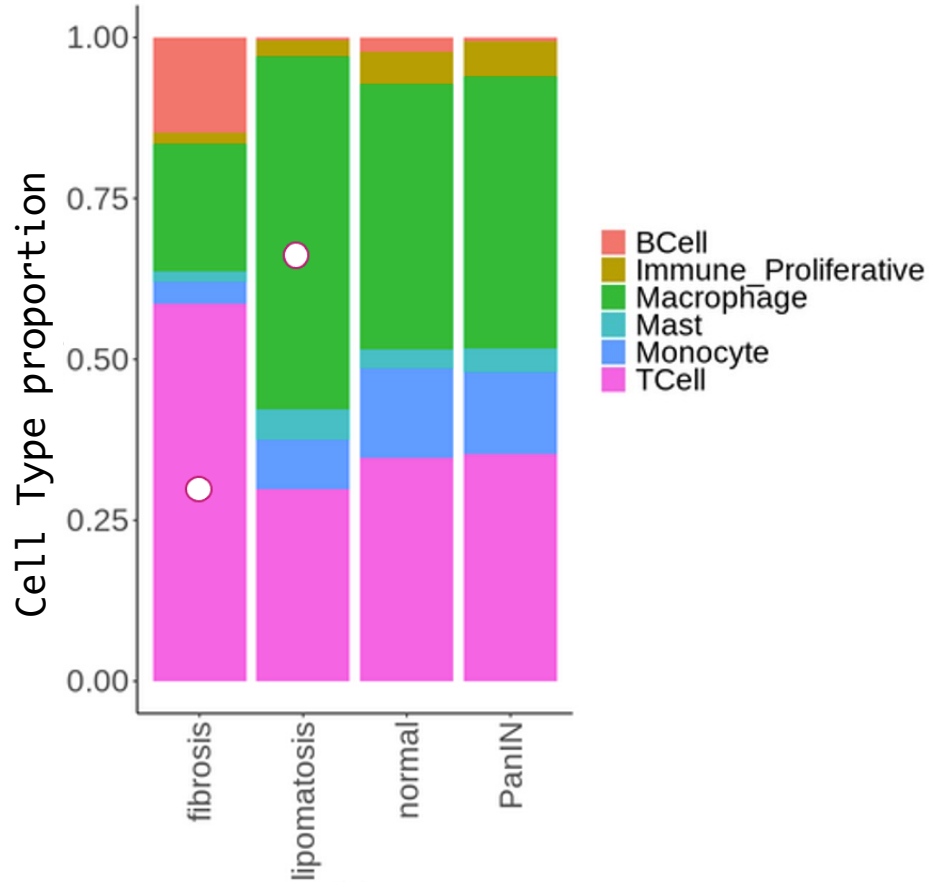
# Cell-type composition changes in micropathologies



- Higher abundance of macrophages in lipomatosis
- Higher abundance of lymphocytes in fibrotic samples
- No changes in composition for PanIN (integration with PDAC will serve to reconstruct the early stages of PDAC initiation)

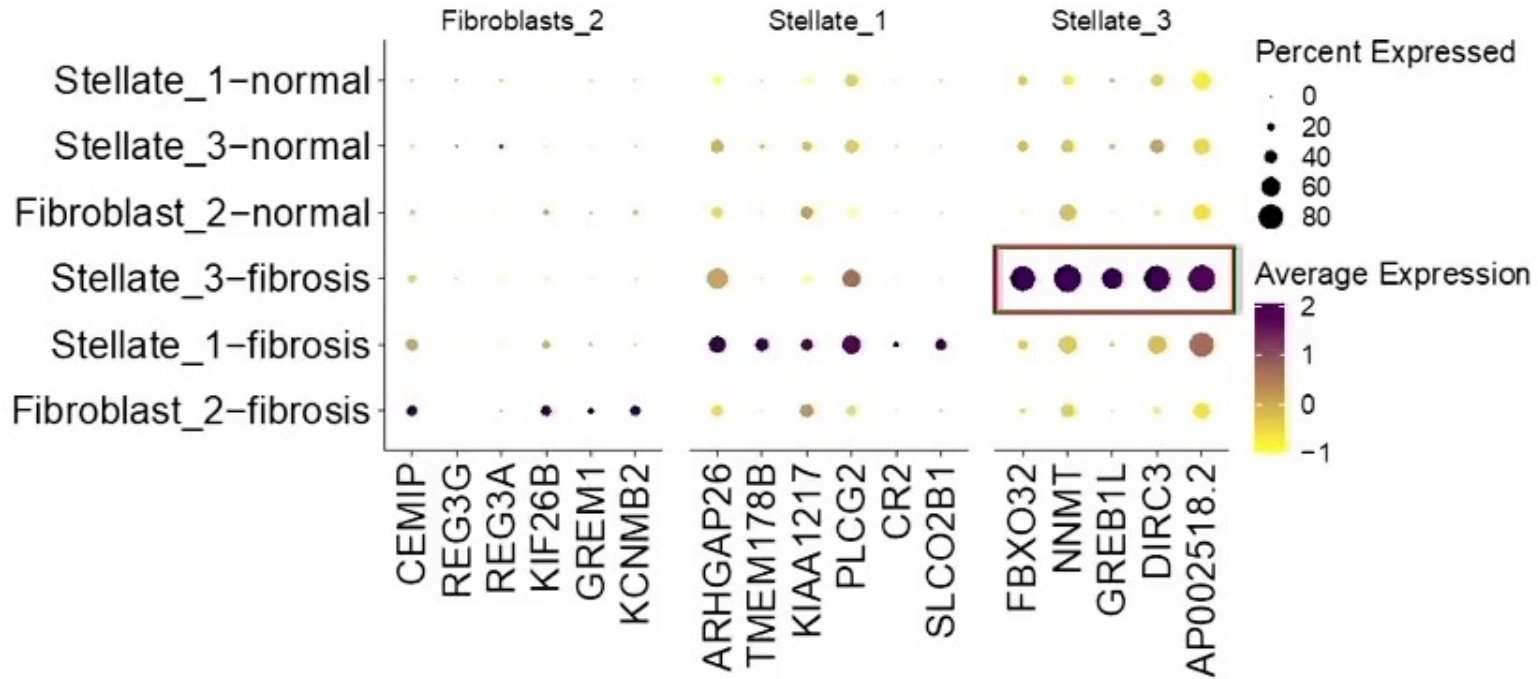


# Cell-type composition changes in micropathologies

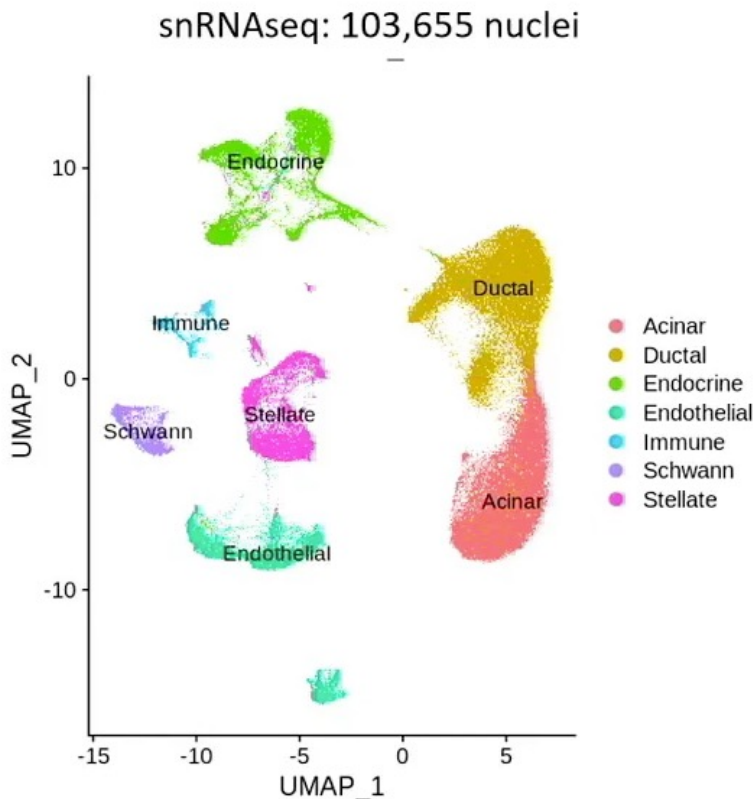


- Higher abundance of macrophages in lipomatosis
- Higher abundance of lymphocytes in fibrotic samples
- No changes in composition for PanIN (integration with PDAC will serve to reconstruct the early stages of PDAC initiation)

# Transcriptional and epigenetic changes in micropathologies

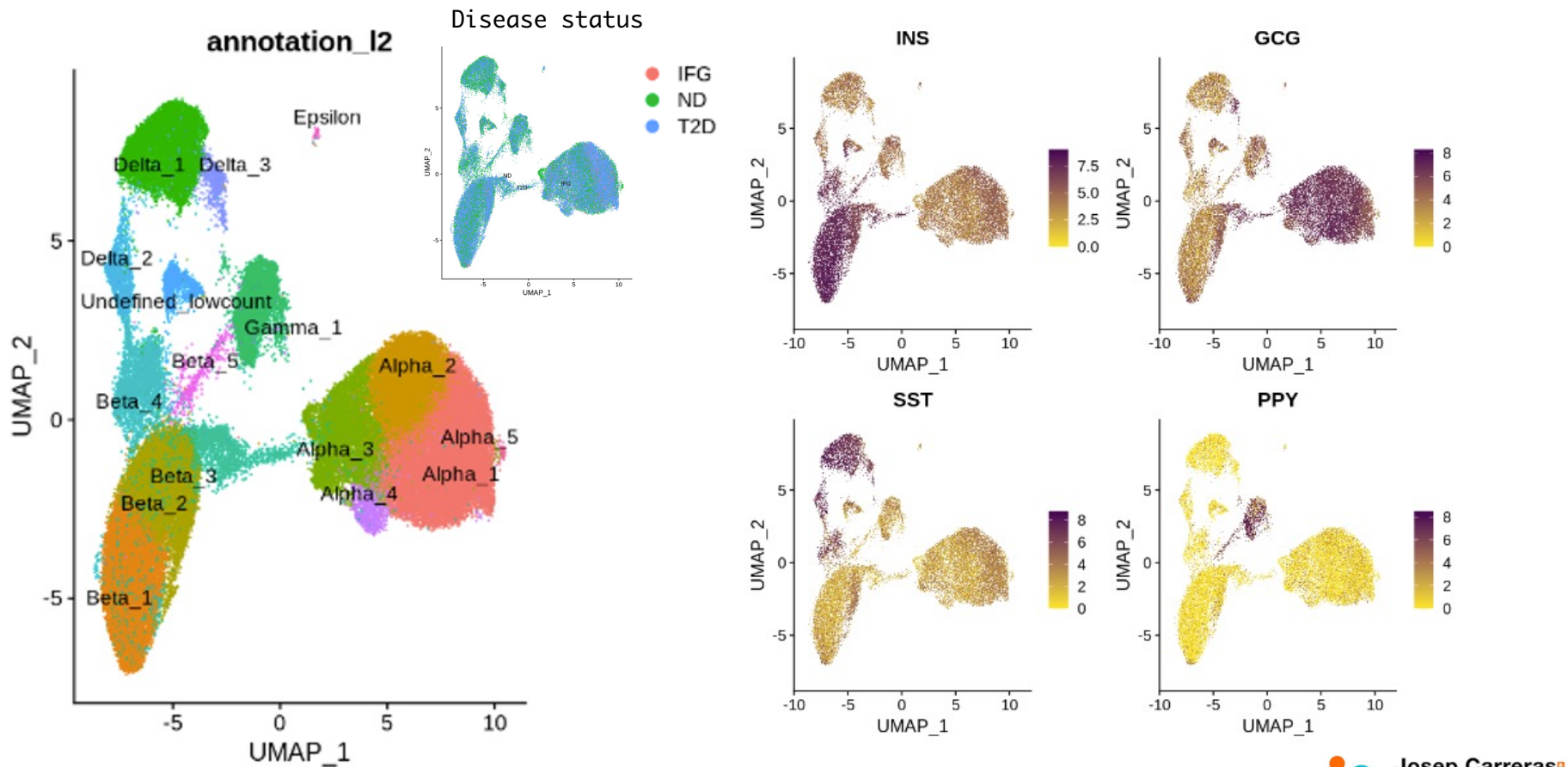


# Temporal single-cell analysis of fetal samples shed light on pancreas development



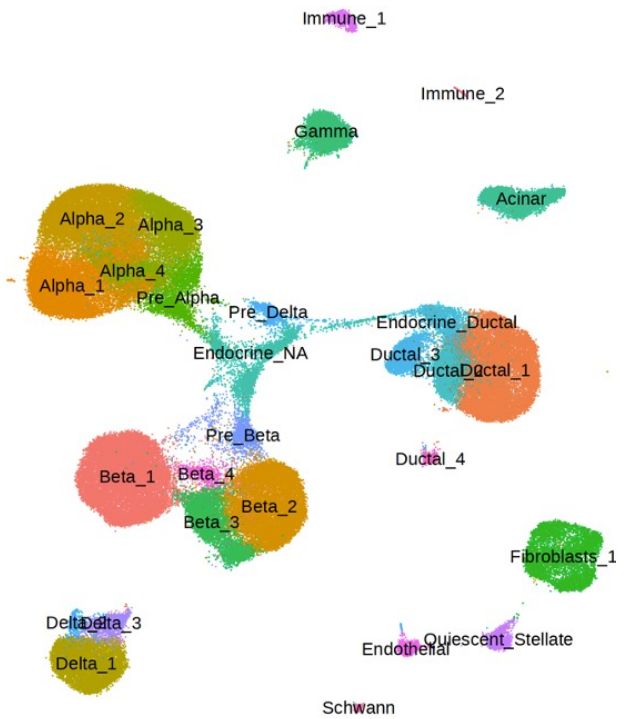
- Characterization of pancreatic cell-type progenitors
- Particularly relevant in understanding human pancreatic disorders and regenerative medicine

# Characterization of the endocrine cells in health and T2 diabetes

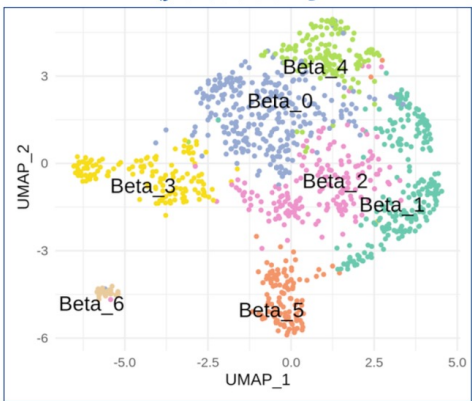


# Changes in chromatin accessibility at different levels of glucose

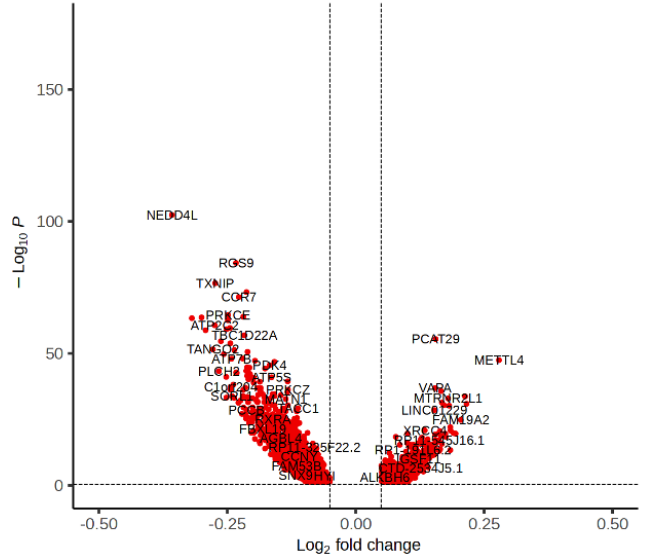
Level 4 – Cell substates



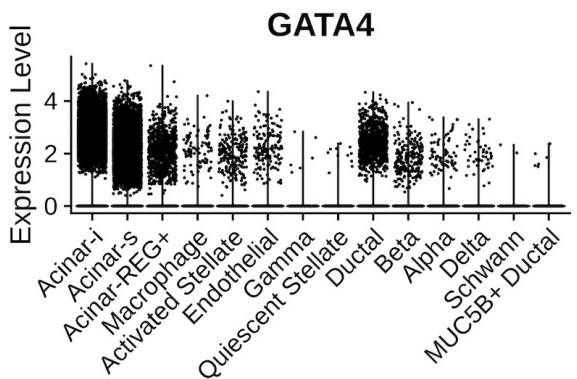
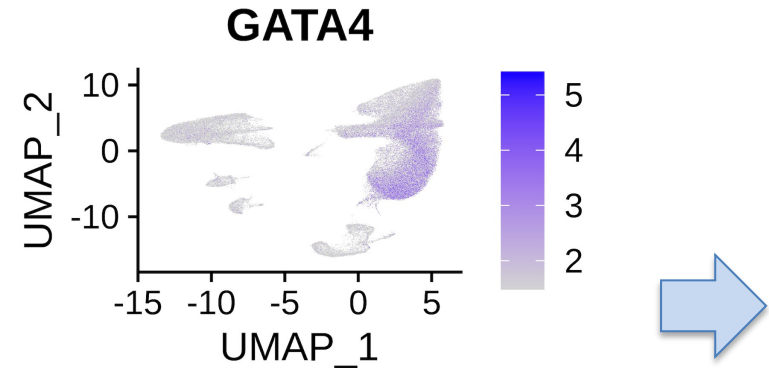
Beta cells



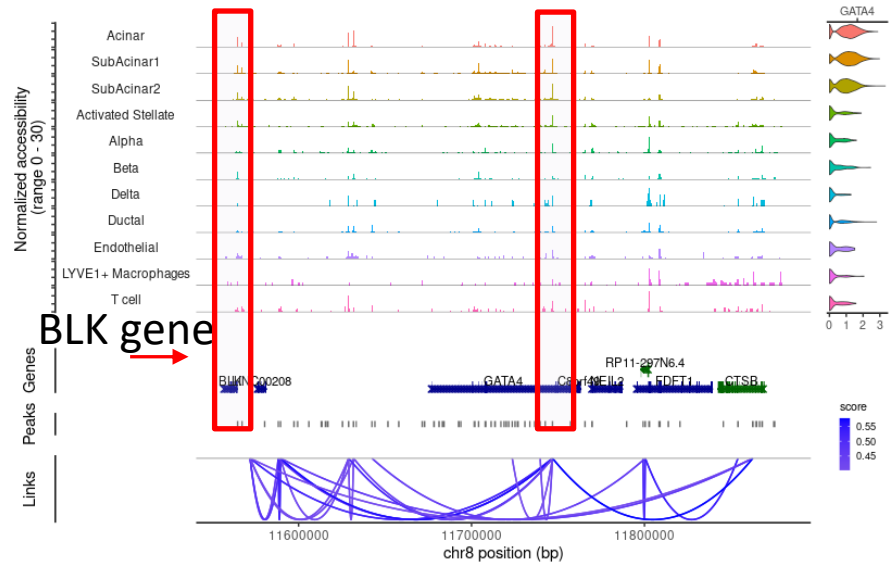
Changes in chromatin accessibility in Beta cells related to glucose levels



# Linking regulatory DNA elements to their target genes by co-accessibility networks



## GATA4 (Acinar development)



BLK: The gene encodes a protein that stimulates insulin synthesis and secretion in response to glucose and enhances the expression of several beta-cell transcription factors.

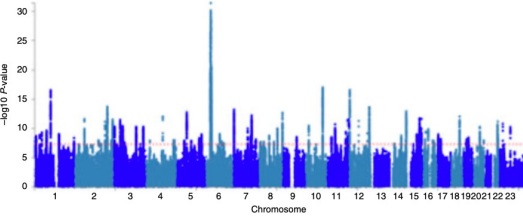




# Integrating GWAS signals with peaks to obtain genetic mapping of cell-type specificity for complex traits and diseases (ONGOING..)

Many risk variants for common diseases fall within accessible genomic regions in disease-relevant tissues or cell types

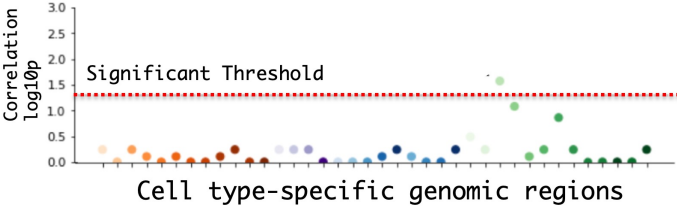
GWAS



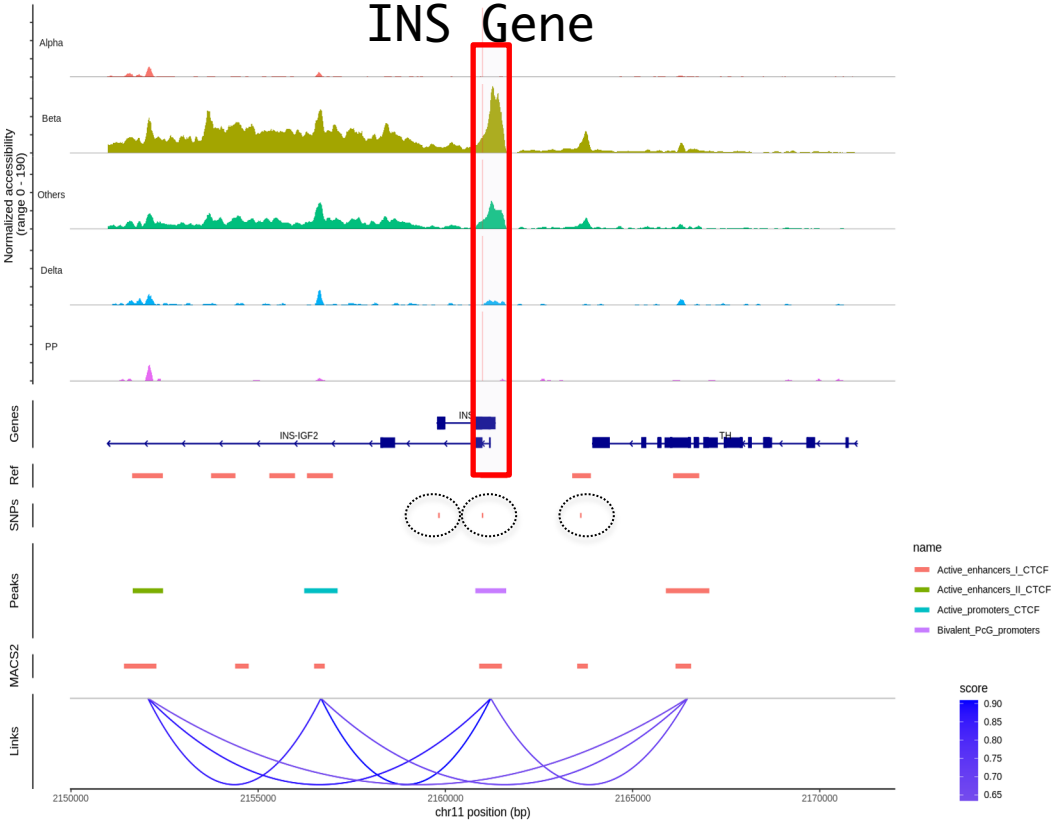
SNPs



Pancreas-associated phenotypes



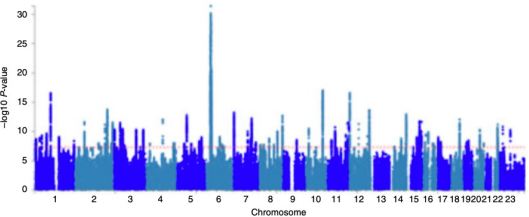
INS Gene



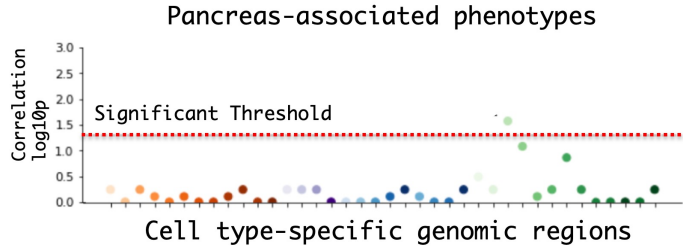
# Fetal development of pancreatic cells to understand cell

Many risk variants for common diseases fall within accessible genomic regions in disease-relevant tissues or cell types

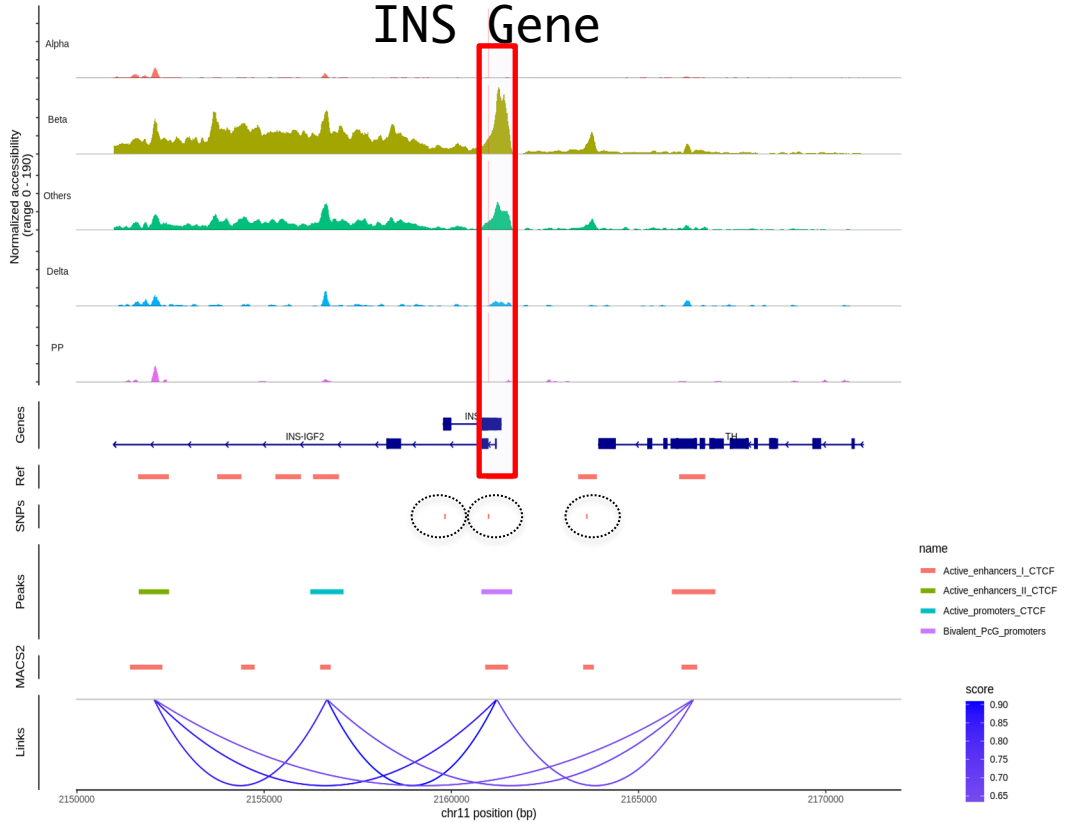
GWAS



SNPs



INS Gene



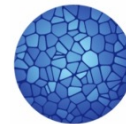
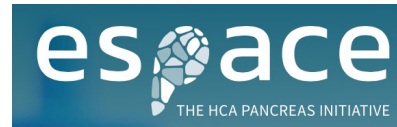
# Acknowledgements



## Cellular Systems Genomics Group

Aina Rill  
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Anton Popov  
Mario Acera  
Marta Casado

**Computational Postdoc WANTED!!**



**Josep Carreras**  
LEUKAEMIA  
Research Institute