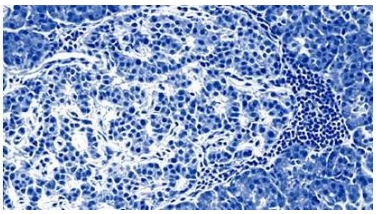
nPOD
Network for Pancreatic Organ Donors with Diabetes



# Single cell resolution analysis of the human pancreatic ductal progenitor cell niche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## PURPOSE

To analyze the human ductal progenitor cell niche at single cell resolution

## METHODS

FACS-sorting of ALK3$^{bright+}$ cells from human pancreatic samples, corresponding to the pancreatic ductal tree. Principal Component Analysis and Clustering. Validation. Sorting and transplantation into immunodeficient mice.

## SUMMARY OF RESULTS

We have described multipotent progenitor-like cells within the major pancreatic ducts (MPDs) of the human pancreas. They express PDX1, its surrogate surface marker P2RY1, and the BMP receptor 1A (BMPR1A)/Activin-like Kinase 3 (ALK3), but not carbonic anhydrase II (CAII). Here we report the single cell RNA sequencing (scRNAseq) of ALK3$^{bright+}$-sorted ductal cells, a fraction that harbors BMP-responsive progenitor-like cells.

## CONCLUSIONS

Our analysis unveiled the existence of multiple sub-populations along two major axes, one that encompasses a gradient of ductal cell differentiation stages and another featuring cells with transitional phenotypes towards acinar tissue. A third potential ducto-endocrine axis is revealed upon integration of the ALK3$^{bright+}$ dataset with a single-cell whole-pancreas transcriptome. When transplanted into immunodeficient mice, P2RY1$^{+}$/ALK3$^{bright+}$ populations (enriched in PDX1$^{+}$/ALK3$^{+}$/CAII$^{-}$ cells) differentiate into all pancreatic lineages, including functional β-cells. This process is accelerated when hosts are treated systemically with an ALK3 agonist. We found PDX1$^{+}$/ALK3$^{+}$/CAII$^{-}$ progenitor-like cells in the MPDs of type 1/2 diabetes donors, regardless of the duration of the disease. Our findings open the door to the pharmacological activation of progenitor cells *in situ*.