Canadian Cystic Fibrosis Conference

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CFRD – Research Insights

Presenter: Rebecca L. Hull-Meichle

Cystic Fibrosis Canada | Fibrose kystique Canada

w/o limits

Dr. Dorothy H. Andersen

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CYSTIC FIBROSIS OF THE PANCREAS AND ITS RELATION TO CELIAC DISEASE

A CLINICAL AND PATHOLOGIC STUDY

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NEW YORK

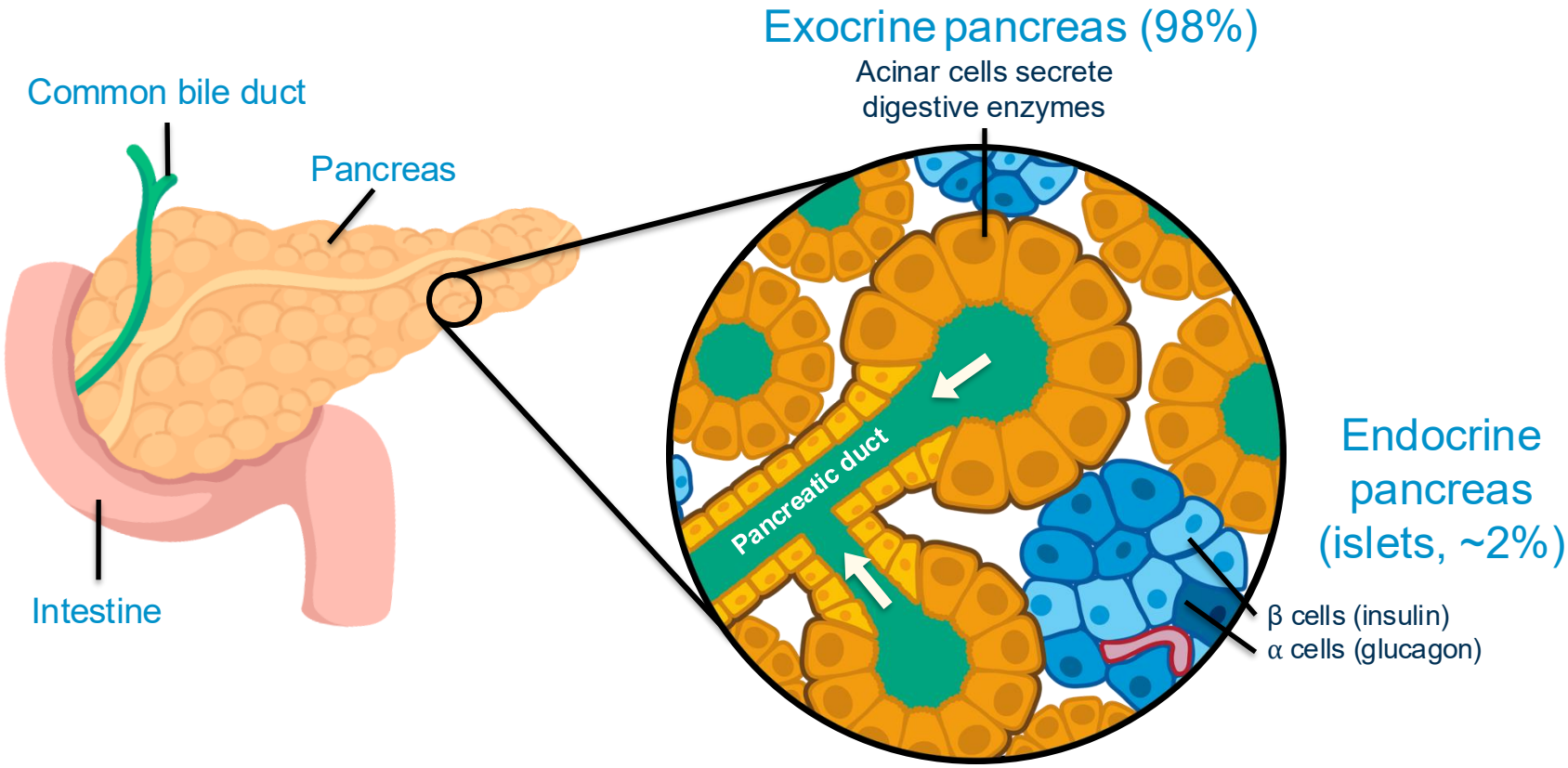
TABLE 1.—*Summary of Cases of Cystic Fibrosis of the Pancreas in Which Postmortem Examination Was Done*

Case No.	Author	Age at Onset: Difficulty in Feeding	Age at Onset: Cough	Age at Death	Sex	Predominant Clinical Symptoms	Postmortem Observations: Cause of Death	Postmortem Observations: Data on Pancreas	Postmortem Observations: Other Data
				Group I.—Infants Dying Before the Age of One Week					
1	Landsteiner, 1905....	Birth	—	5 days	F	Vomiting; failure to pass meconium	Meconium ileus; peritonitis (Staph. aureus)	Cystic fibrosis; duct of Wirsung patent	Uric acid infarcts of kidney
2	Kornblith and Otani, 1929	Birth	—	5 days	F	Vomiting; failure to pass meconium	Meconium ileus; ulcers of ileum and colon; peritonitis	Cystic fibrosis; stenosis of duct of Wirsung	Meckel's diverticulum; atelectasis of lungs; uric acid infarcts of kidney
3 (I)	Andersen, 1938.....	Birth	—	4 days	M	Vomiting; failure to pass meconium	Band across lumen of ileum with obstruction; peritonitis	Cystic fibrosis	Meckel's diverticulum, uric acid infarcts in kidneys
4 (II)	Andersen, 1938.....	Birth	—	6 days	F	Vomiting; prematurity	Multiple atresia of ileum; volvulus; peritonitis (Str. haemolyticus	Cystic fibrosis	Aspiration of gastric contents
5 (III)	Andersen, 1938.....	Birth	—	6 days	F	Failure to pass meconium; distended abdomen	Atresia of jejunum; fetal peritonitis	Cystic fibrosis	Congenital malformations of heart; jaundice of liver; atresia of cystic duct; congenital atelectasis of lungs
				Group II.—Infants Dying Between the Ages of One Week and Six Months					
6	Blackfan and Wolbach, case 2, 1933	Birth	Birth	5 wk.	M	Infection of respiratory tract	Bronchopneumonia; bronchiectasis	Cystic fibrosis	Keratinizing metaplasia in trachea; hemosiderosis of liver and spleen
7 (IV)	Andersen, 1938.....	Neonatal	7 wk.	8 wk.	F	Feeding problem; failure to gain	Purulent bronchitis; bronchopneumonia with abscesses (Staph. aureus)	Cystic fibrosis	Otitis media (Staph. aureus)
8	Passini, 1919, case 2..	Neonatal	?	2 mo.	F	Poor development; large stools	Bronchopneumonia; empyema	Cystic fibrosis; loss of islands	
9 (V)	Andersen, 1938.....	?	6 wk.	2½ mo.	F	Failure to gain; cough	Bronchiectasis; purulent bronchitis; lobular pneumonia (Staph. aureus)	Cystic fibrosis; atresia of Wirsung's duct ?	Atresia of cystic duct; atrophy of gallbladder; cysts of cystic duct and gallbladder; congenital strictures of ureter; congenital malformation of aorta
10 (VI)	Andersen, 1938.....	Neonatal	5 wk.	2½ mo.	M	Failure to gain; cough	Purulent bronchitis (Staph. aureus); [illegible]monia	Cystic fibrosis; atresia of Wirsung's duct (?)	Congenital strictures of ureter; fatty liver; hemosiderosis of liver and spleen

Screenshot

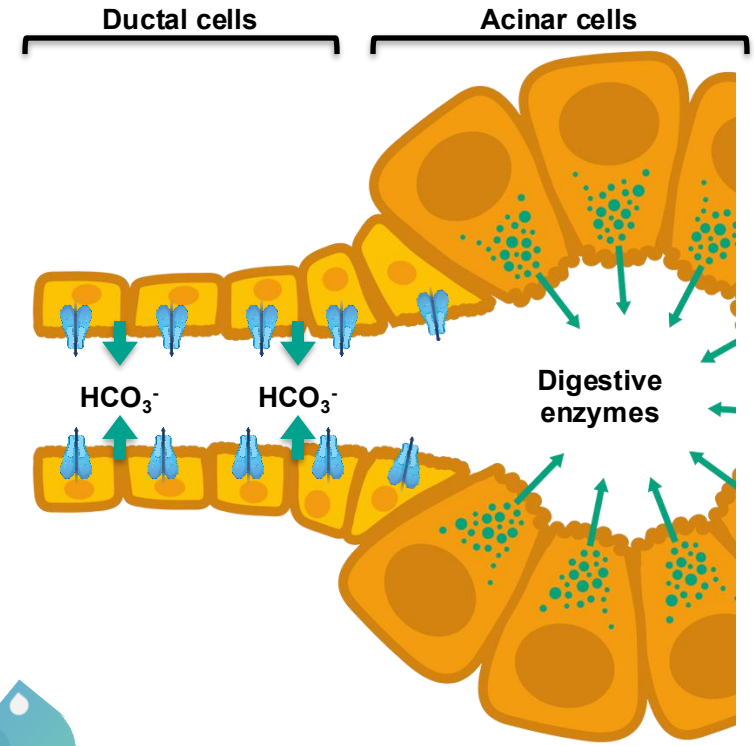
Andersen DH: Am J Dis Child 56:344-399, 1938

Overview of the pancreas

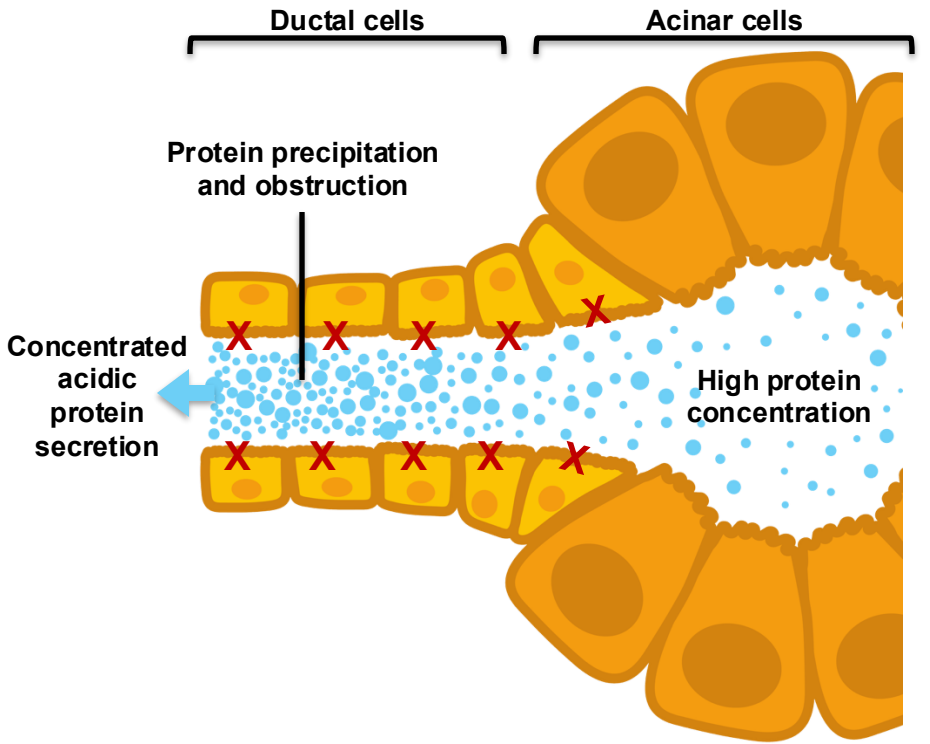


Impact of non-functional CFTR in the pancreas

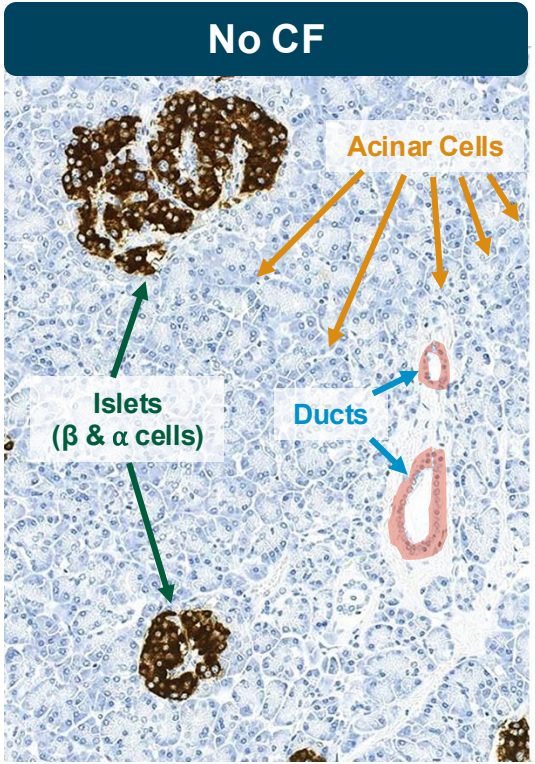
NORMAL



CYSTIC FIBROSIS

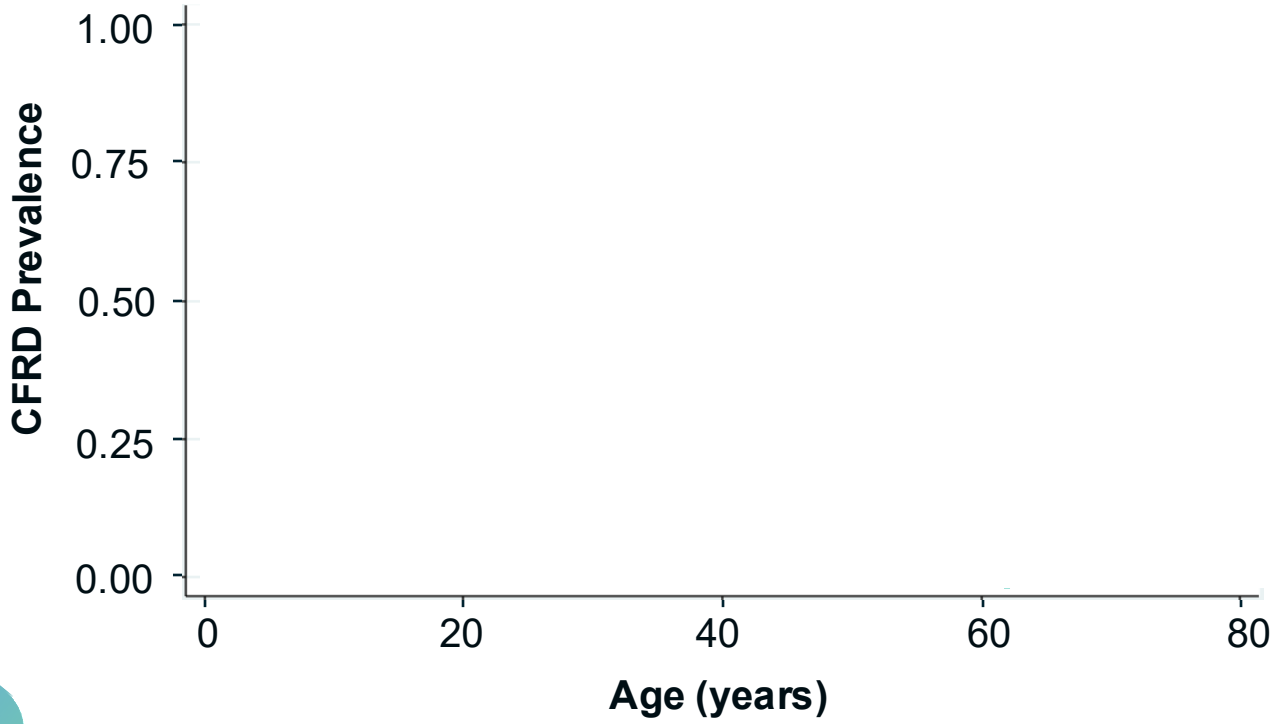


Pancreas Pathology in Cystic Fibrosis



Adapted from Norris et al: J Endocrinol 2019, PMID: 30759072

Diabetes rates increase with age in people with CFTR mutations of varying severity



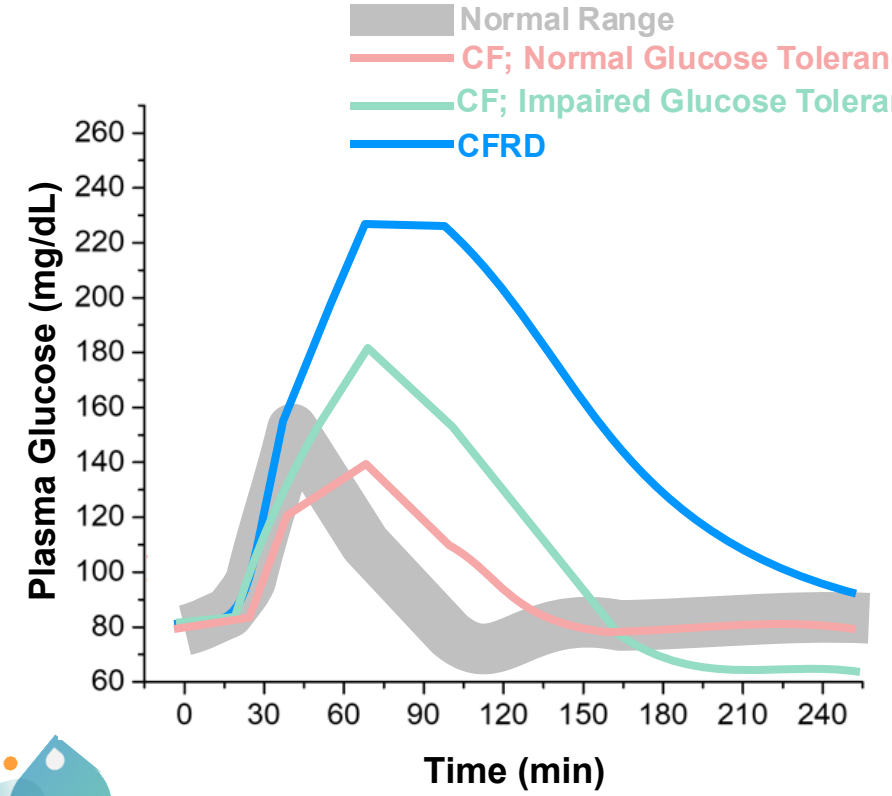
Scott Blackman

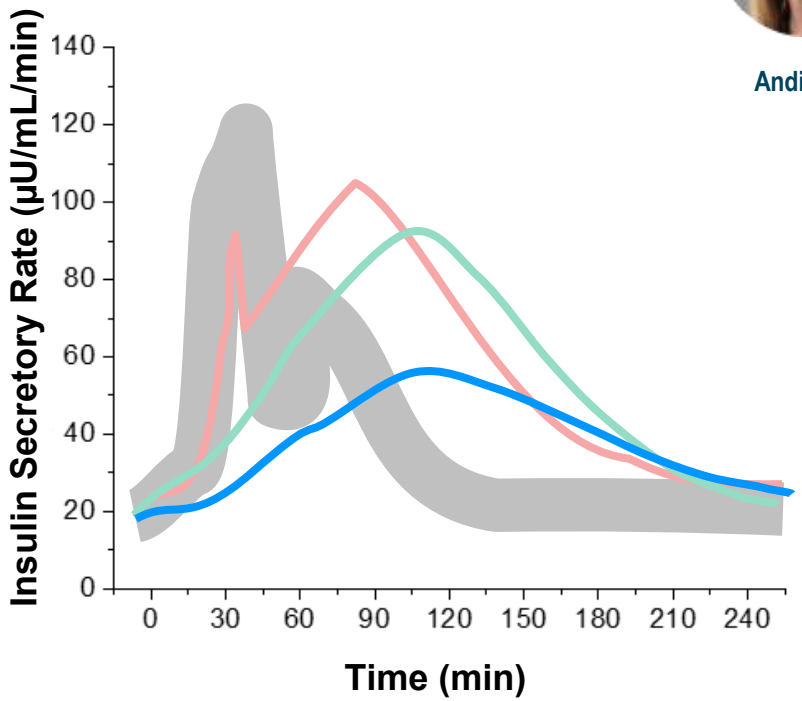
Note: data are pre-modulators

Clinical and Functional Translation of CFTR

Progressive insulin secretory defect and loss of early-phase insulin secretion in CF

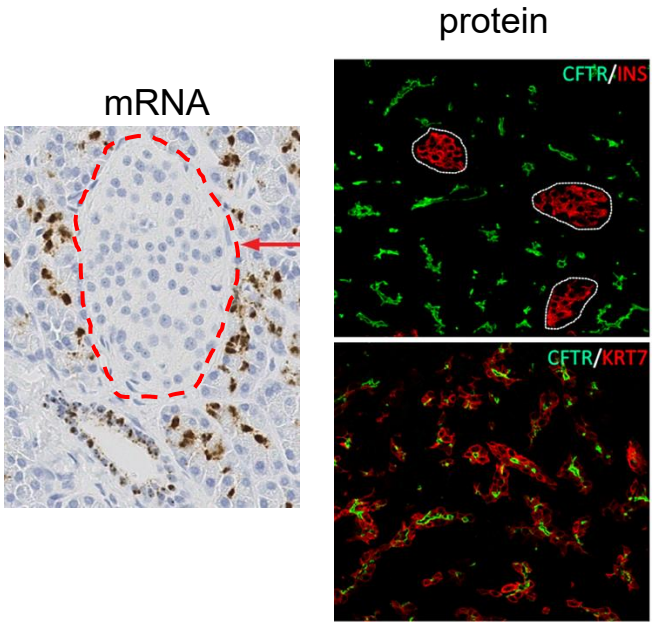
Andi Kelly





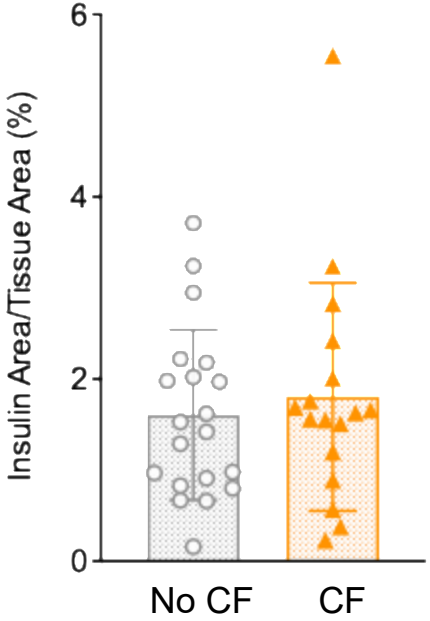
The islet β-cell is relatively spared in CF

β-cell CFTR synthesis



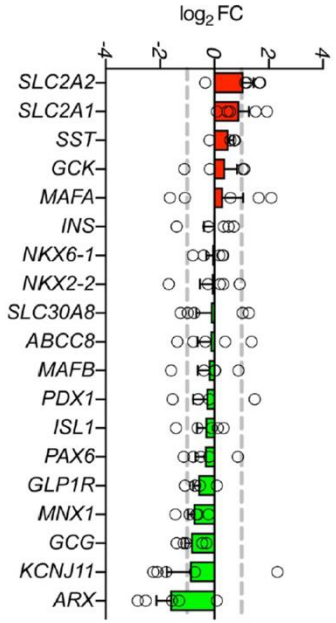
White MJ et al: JCEM, 2019; PMID: 31748811

β-cell abundance



Hull RL et al: Diabetes Care, 2018; PMID: 29437698

Islet "genes"



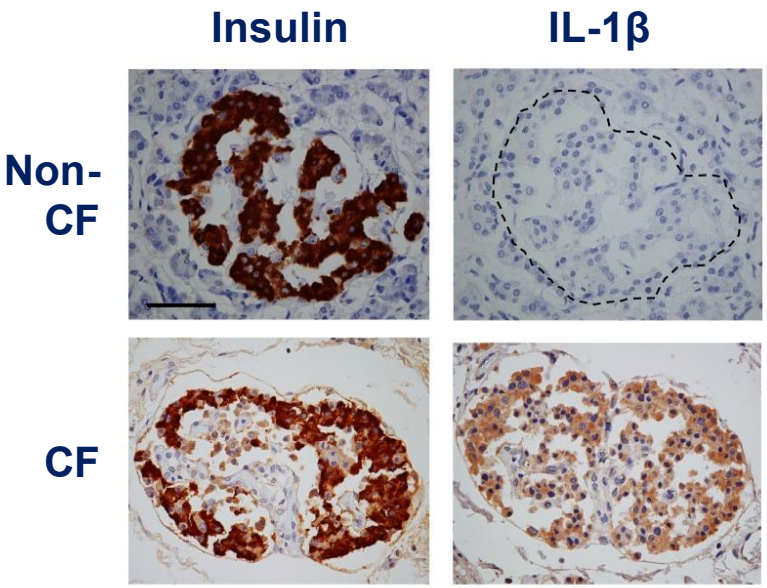
Hart NJ et al: JCI Insight, 2018; PMID 29669939

CF islets show very high levels of inflammation

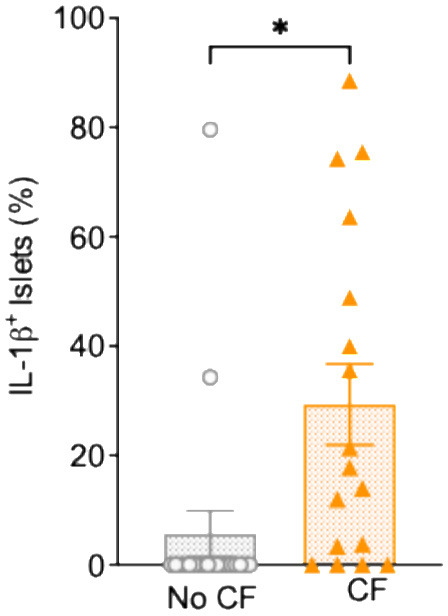

Bonnie Ramsey

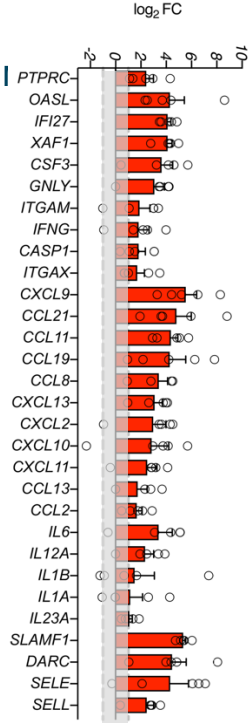

Ron Gibson


Deutsch



Hull RL et al: Diabetes Care 41:823-830, 2018





Hart NJ et al: JCI Insight 3:98240, 2018

Comprehensive analysis of the CF pancreas


Kyle Gaulton


Hannah Mummey

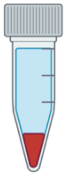

Sierra Corbin


Jacinta Lucero


Allen Wang

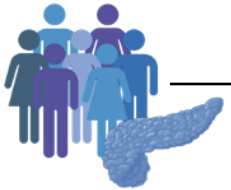

Aga D'Antonio -Chronowoska

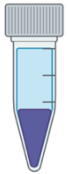
CF/CFRD
(n=9)

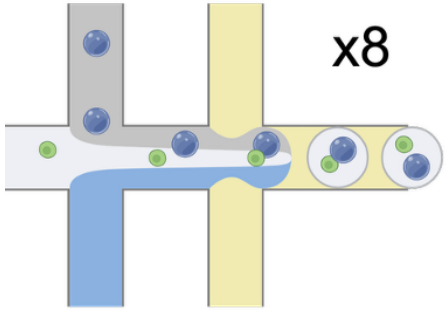


Isolate nuclei

No CF/
No diabetes
(n=10)





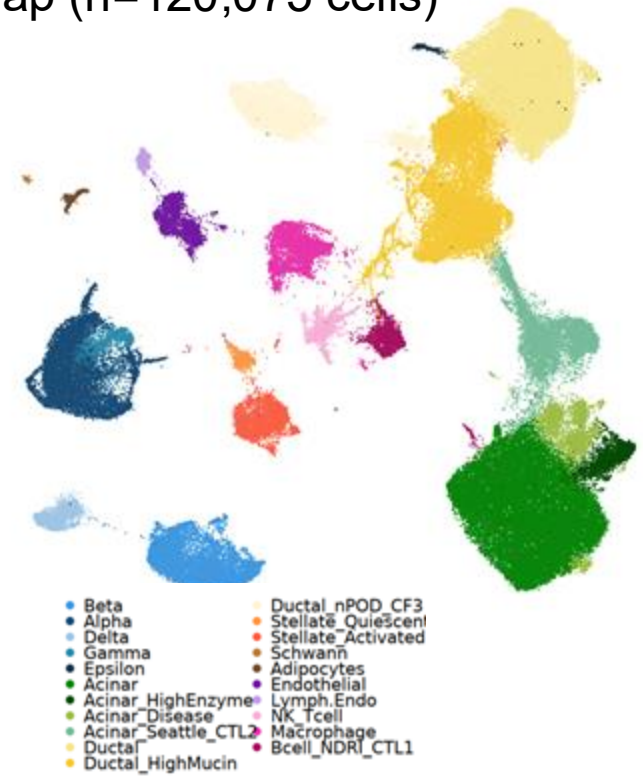


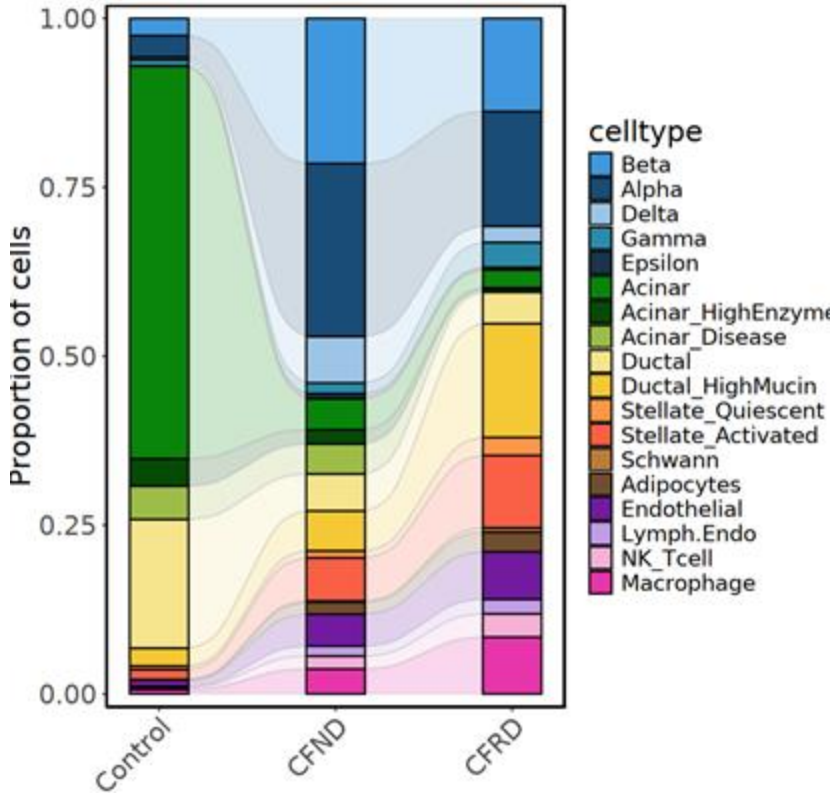
Sequence all pooled nuclei across 8 lanes using 10x Multiome

Assign cells to original donor using genotype

Single nuclear RNAseq – initial results

Cell map (n=120,075 cells)



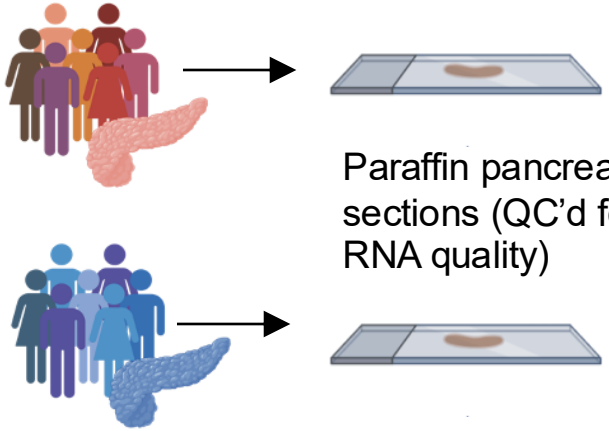


Comprehensive analysis of the CF pancreas

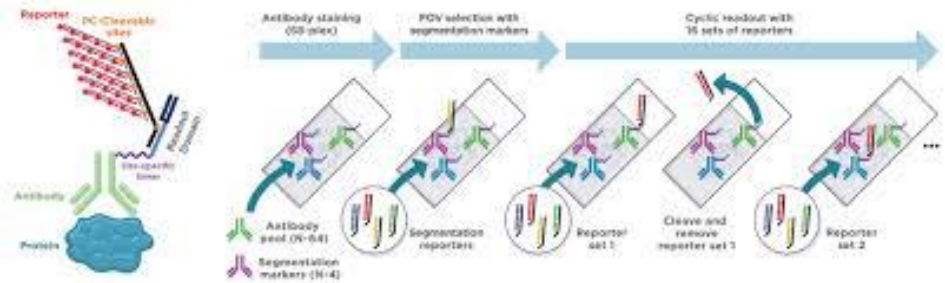
Hannah Mummey

CF/CFRD (n=6)

No CF/ No diabetes (n=6)

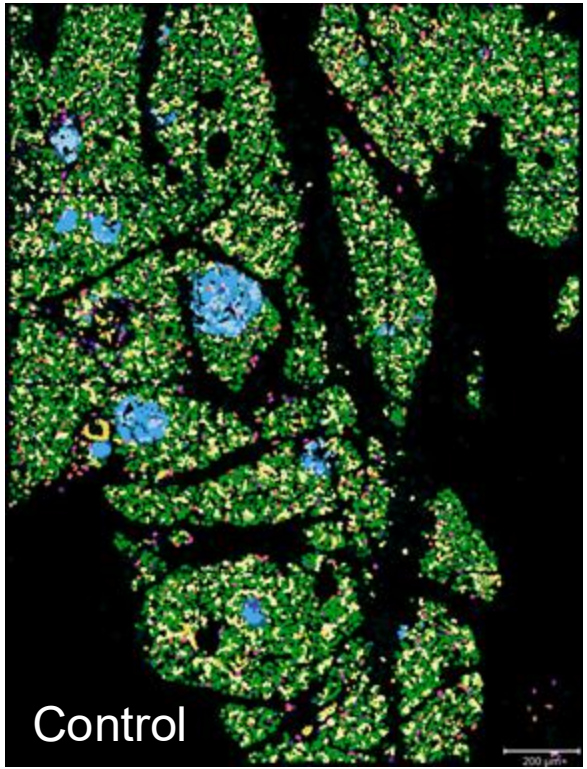


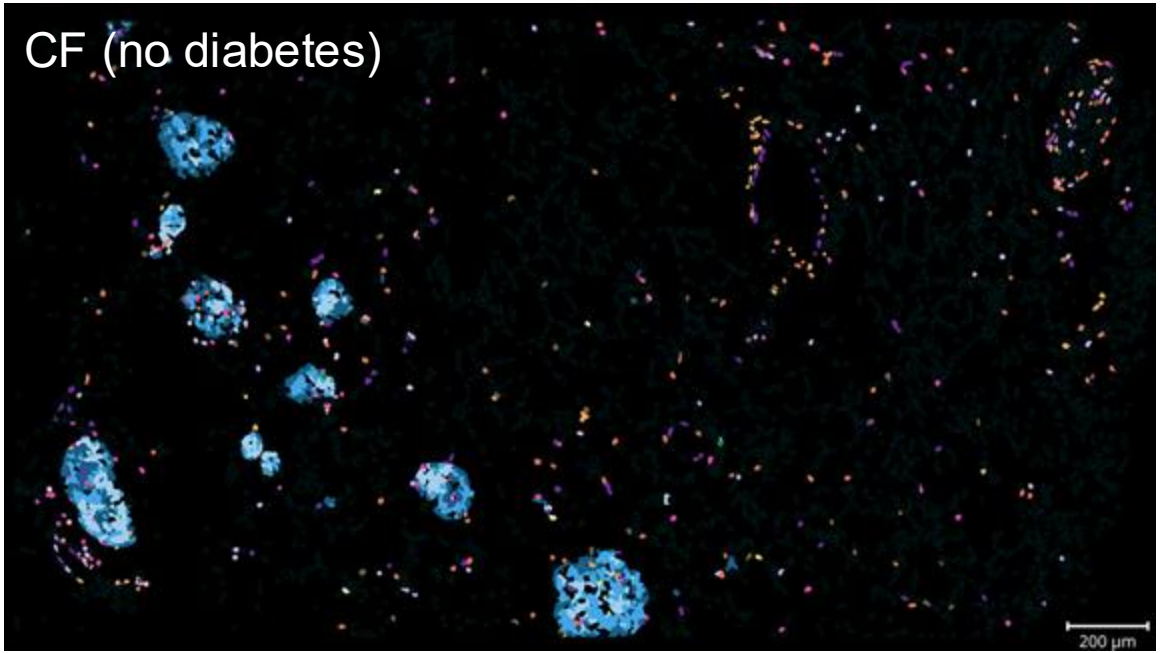
Paraffin pancreas sections (QC'd for RNA quality)



Nanostring CosMx Single Cell Spatial Profiling (1000 gene panel)

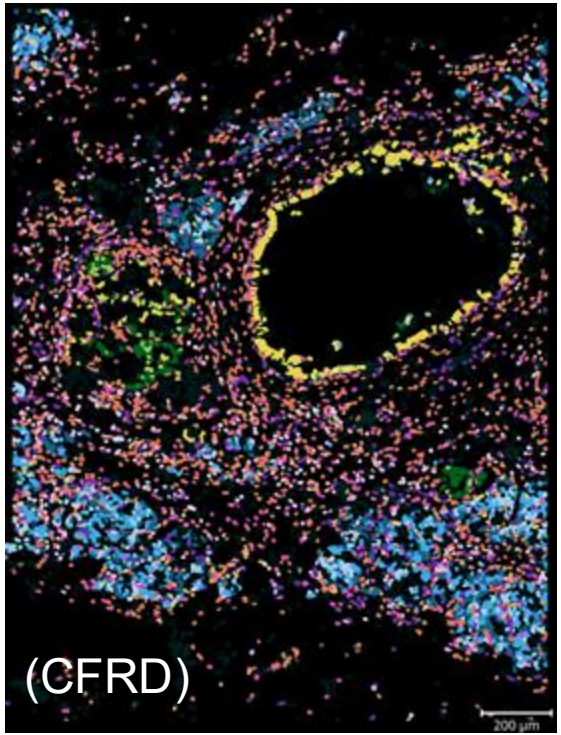
Example images from spatial profiling





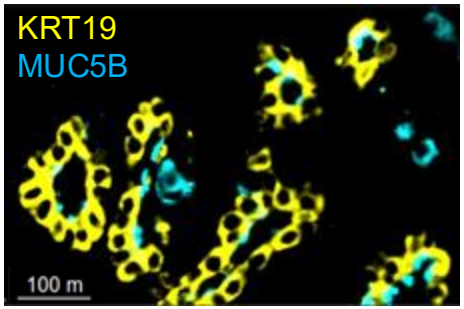
Next Steps – validation and exploratory analyses

RNA (spatial profiling)

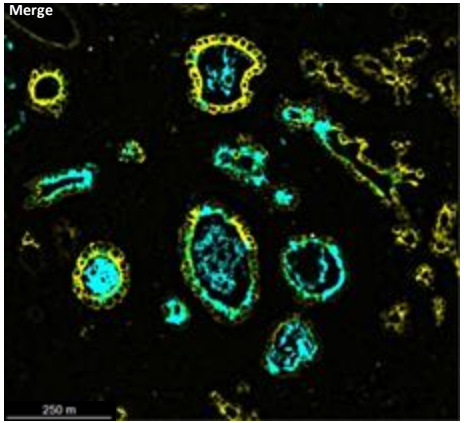


Protein (Immunostaining)

No CF



CF (<1yo)



Victoria Johnston

Summary

- Diabetes is a common complication of CF and is likely to increase in prevalence as the CF population ages
- Insulin deficiency is common in CF, but the beta cell itself is relatively unaffected
- Multiple cell types within the islet (and pancreas) exhibit abnormalities in abundance, arrangement and phenotype in CF
- Ongoing work to better understand these abnormalities will help develop improved treatment options for people with CFRD

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UCSD:

Kyle Gaulton

Hannah Mummey

Sierra Corban

Allen Wang

Aga D'Antonio-Chronowska

Jacinta Lucero

UW/SCH:

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Ron Gibson

Sharon McNamara

Gail Deutsch

Sakeneh Zraika

U Toronto:

Herbert Gaisano

Patients & Families

nPOD Network for Pancreatic Organ Donors with Diabetes

Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

ADI ISLETCORE

UW Medicine UNIVERSITY of WASHINGTON

@RebeccaLHull

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CYSTIC FIBROSIS FOUNDATION®

Canada Excellence Research Chairs

Chaires d'excellence en recherche du Canada

NIH National Institute of Diabetes and Digestive and Kidney Diseases

University Hospital Foundation

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Thank You.