Solving a pediatric dilemma: Drug-induced pancreatitis (DIP)

Sohail Husain, MD

Associate Professor of Pediatrics

Children's Hospital of Pittsburgh and the University of Pittsburgh

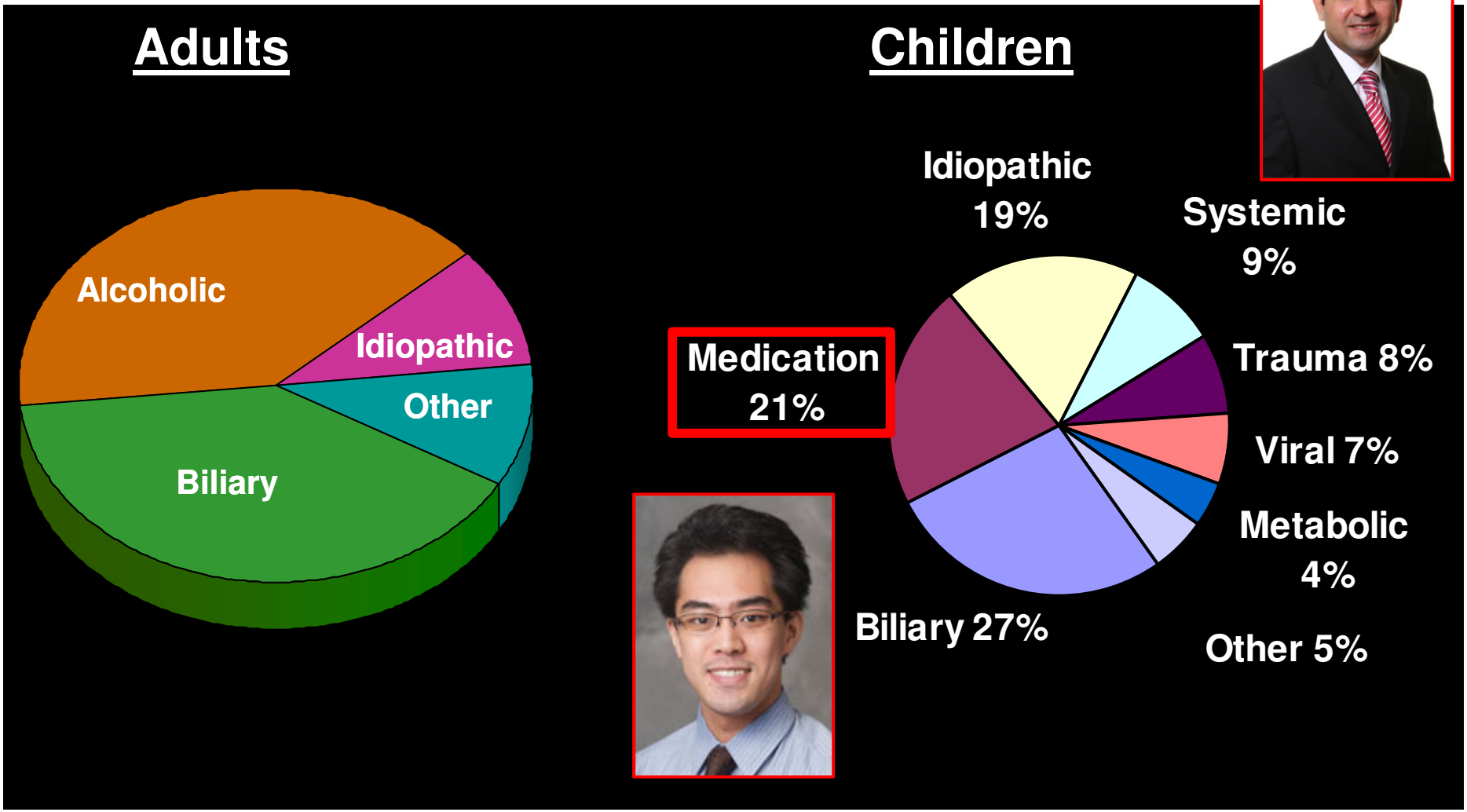
*In the past 12 months, I have had **no relevant financial relationships** with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.*

Learning objectives

- Recognize the problem of drug-induced pancreatitis (DIP)
- Discuss insight into novel mechanisms underlying DIP
- Understand how to devise strategies to prevent DIP

<u>Bridging</u> the gap between basic science and clinical application

Etiologies of Acute Pancreatitis



AGA, 2006

*Park A, *Latif SU, JPGN, 2009

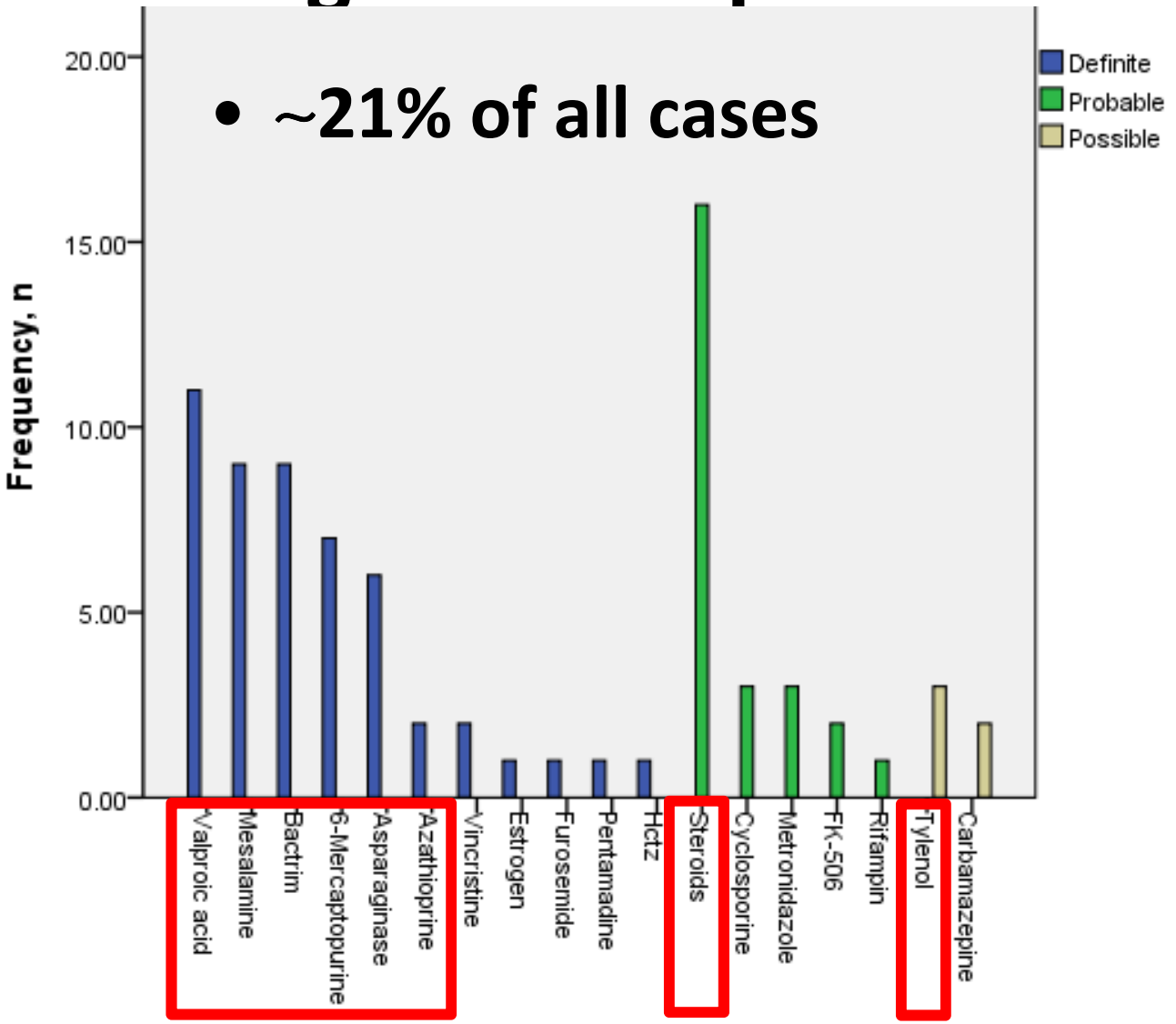
What qualifies as DIP?

Category	Reasonable temporal sequence	Follows a known response pattern	Could not be explained by other factors	Relieved by cessation of the drug	Recurs after a repeat challenge
Definite	✕	✕	✕	✕	✕
Probable	✕	✕	✕	✕	
Possible	✕	✕			

Karch and Lasagna, Adverse drug reactions, JAMA, 1974

Problem of drug-induced pancreatitis

- ~21% of all cases



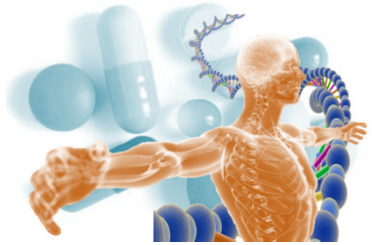
Bai HX, JPGN, 2011

Pressing questions about DIP

- Why do some patients develop DIP?
- Can we identify patients who are at risk before they receive the drug and prevent DIP?
- Can DIP instruct us about pancreatic physiology and disease?

Concomitant etiologies identified in childhood cases of drug-associated pancreatitis

IBD pharmacogenomics



- Pancreatitis and IBD in children (comprehensive review)
  - Medications are likely the major contributor to this association

Heap etal., Nat Genetics, 2014

- A class II HLA haplotype
  - Heterozygotes had a 9% risk of developing pancreatitis with thiopurines
  - Homozygotes had a 17% risk

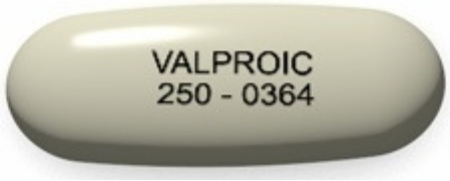
- **Not there yet in making clinical changes to care with just this info.**

- But likely with another one or a few additional genetic or environmental discoveries?

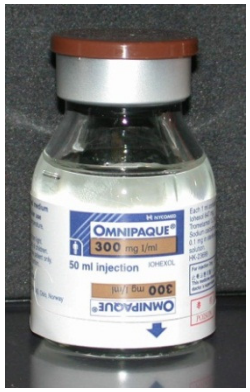
- **Computational risk modeling**

Two short stories about unraveling the mechanism of DIP and one worthy of mention

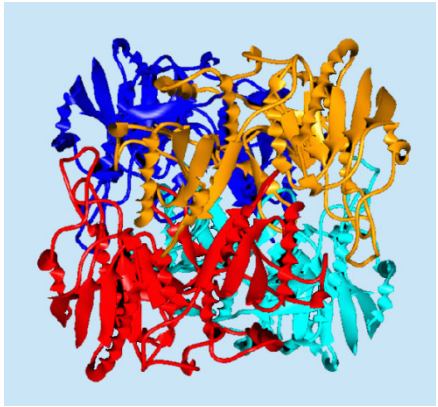
- #1 Valproic acid



- #2 Radiocontrast

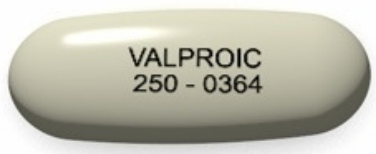


- Asparaginase



Story #1: Valproic acid (VPA)-associated pancreatitis

- "Worst case of acute pancreatitis I saw as a fellow"



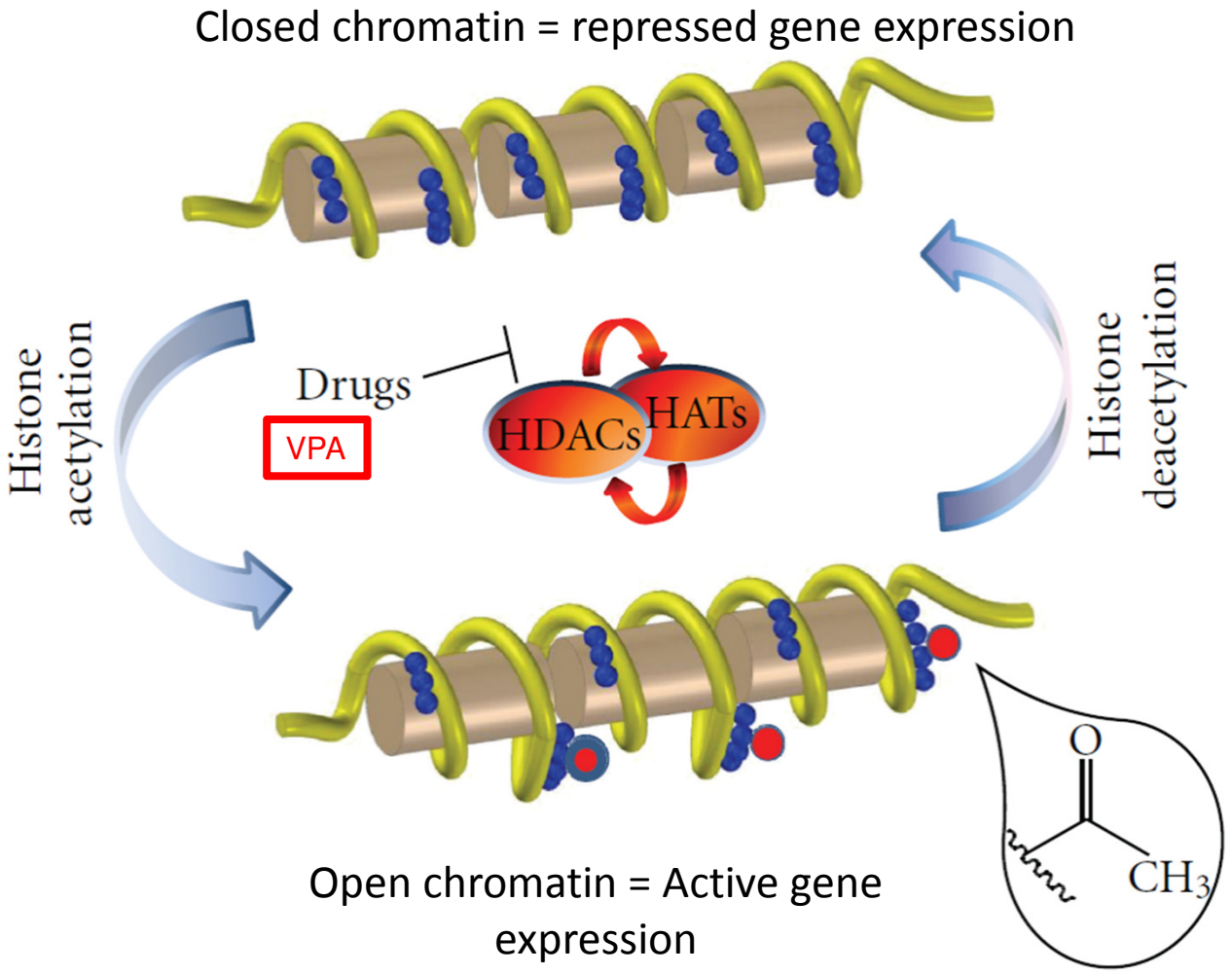
- 5 yo dev. delayed child with epilepsy, taking VPA for 6 months

How does VPA predispose some patients to pancreatitis?

- VPA by itself doesn't cause pancreatitis

- VPA is an histone deacetylase inhibitor (HDACi)

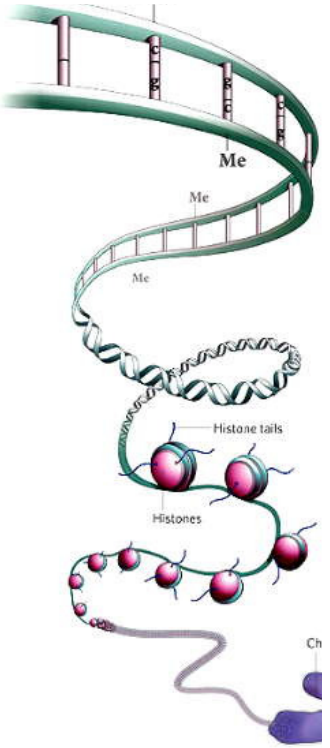
HDACs remove acetyl groups from histone tails, resulting in chromatin compaction and gene repression

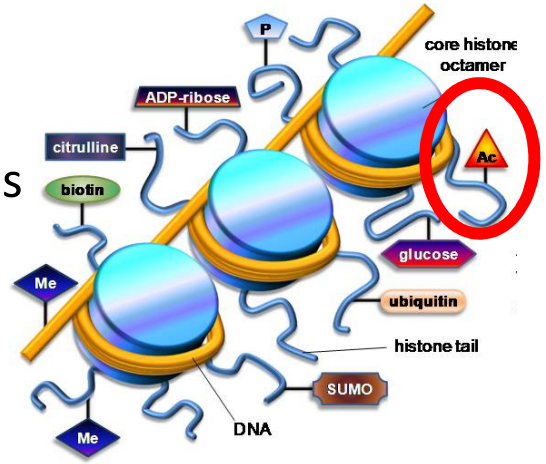


Peserico, A., Journal of Biomedicine and Biotechnology, 2011

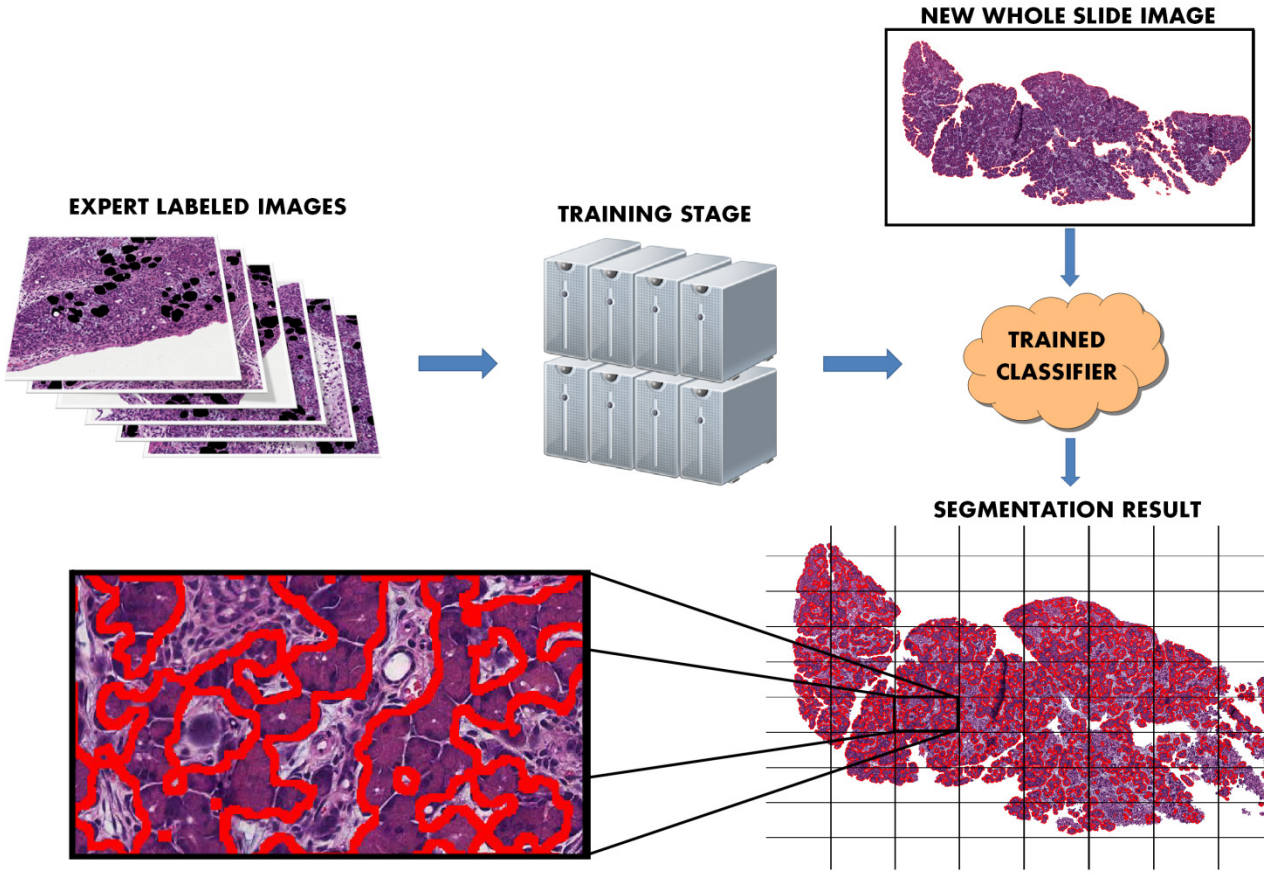
HDACs, epigenetics, pancreatitis, and pancreatic recovery

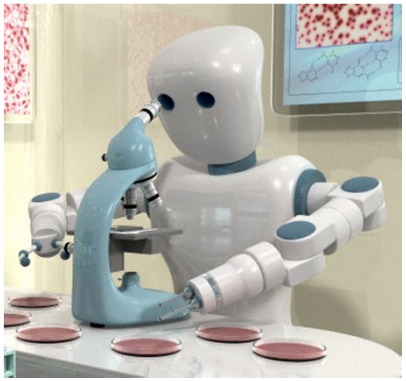
- **Epigenetics** is the study of the molecules that determine when, where, and how much of our DNA is used
- HDACs are a major epigenetic regulator through modifying histones
- HDACs are upregulated during pancreatic development
- Elements of pancreatic development recap. during pancreatic recovery
- **Hypothesis**: HDACs are crucial for activating the programs necessary for pancreatic recovery and regeneration after pancreatic injury





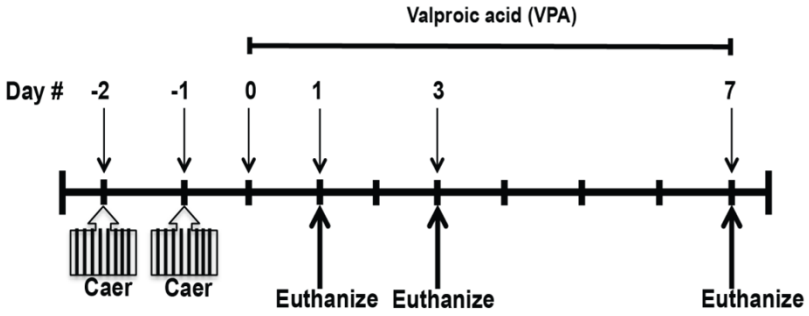
Devised a machine learning tool to quantify pancreatic acinar content

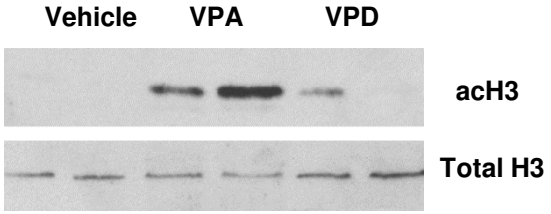


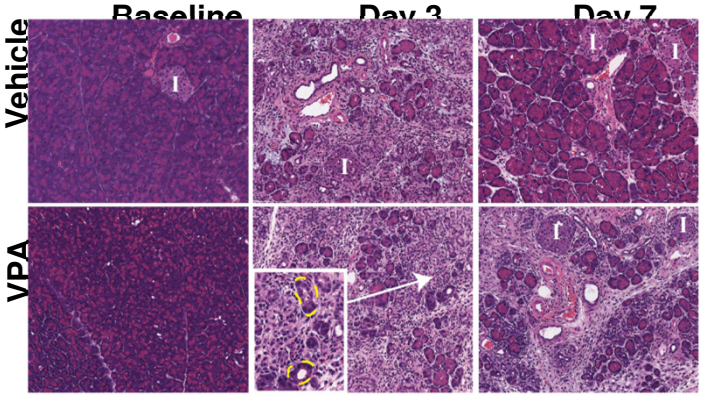


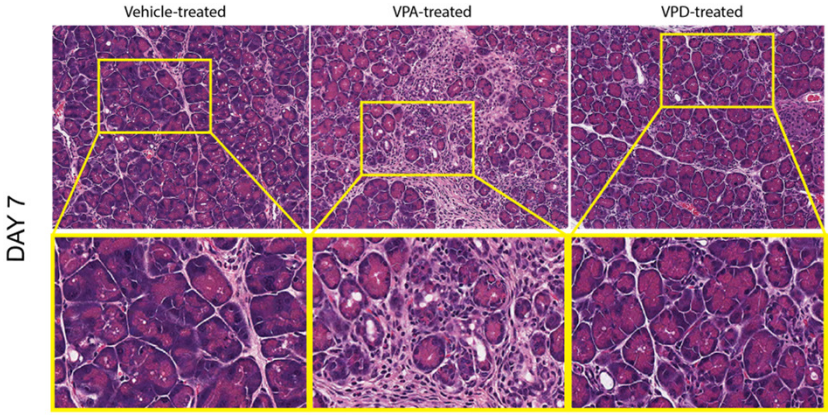
Amy Davis, MD

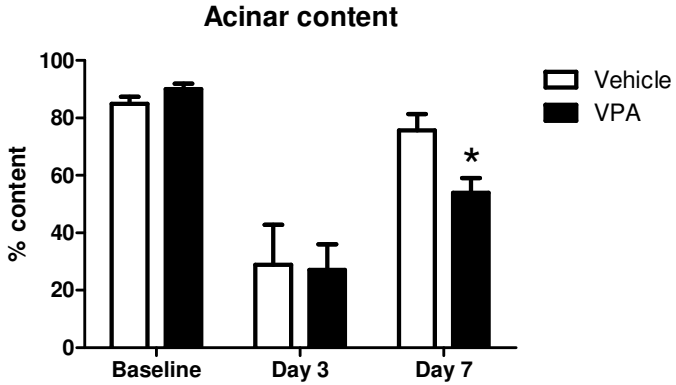
Valproic acid (VPA) limits pancreatic recovery following injury

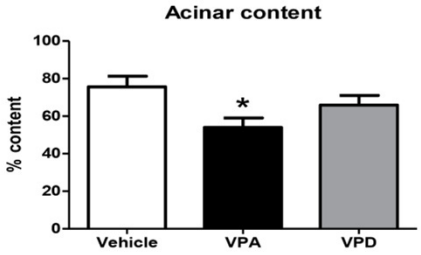




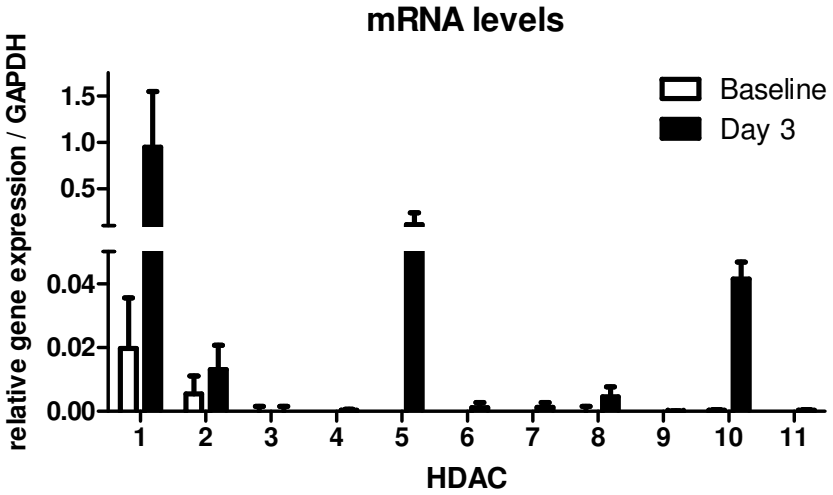


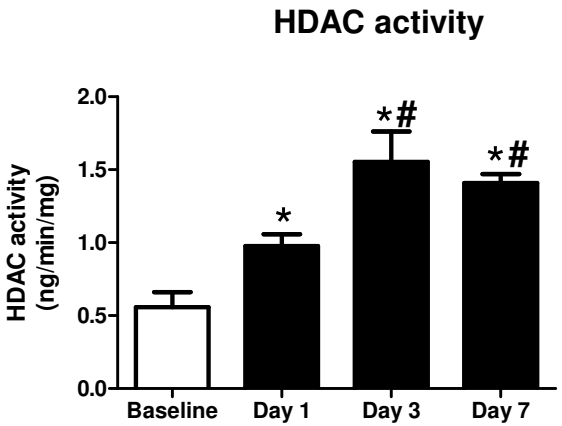


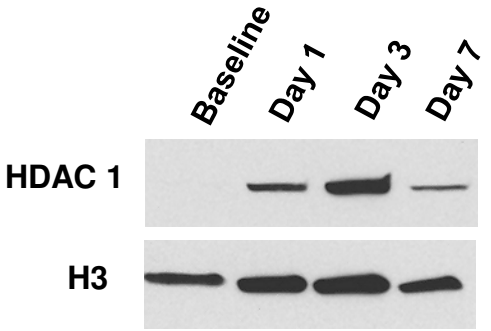


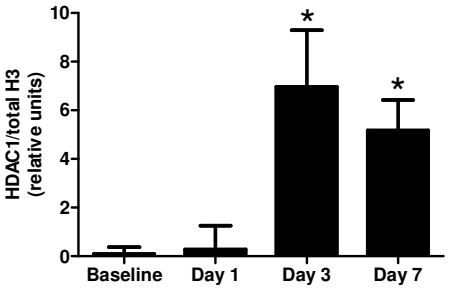


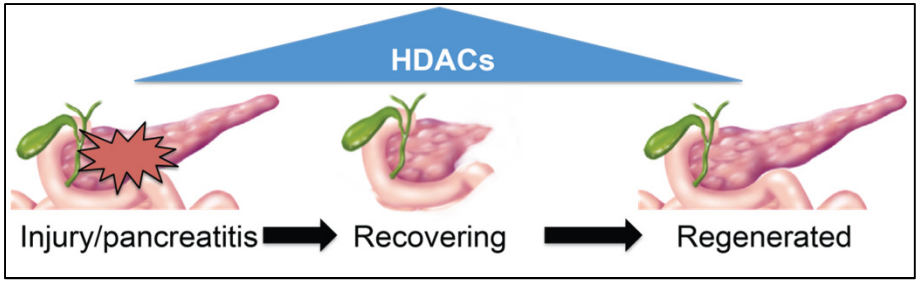
HDACs are upregulated within the pancreas during recovery following injury



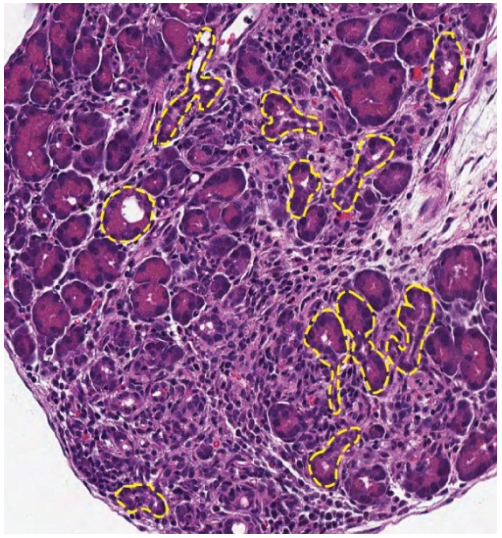


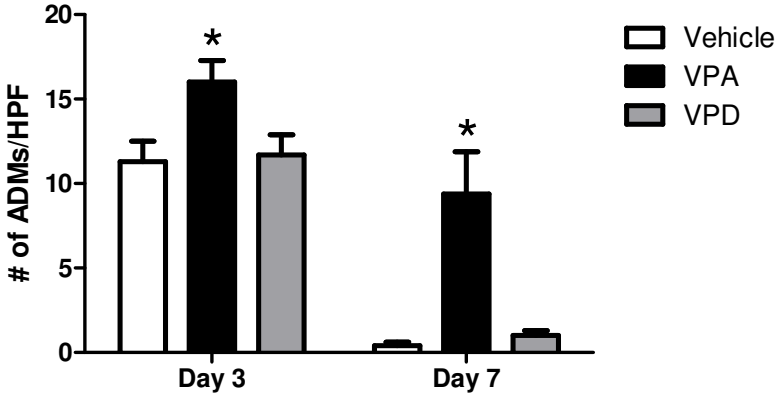


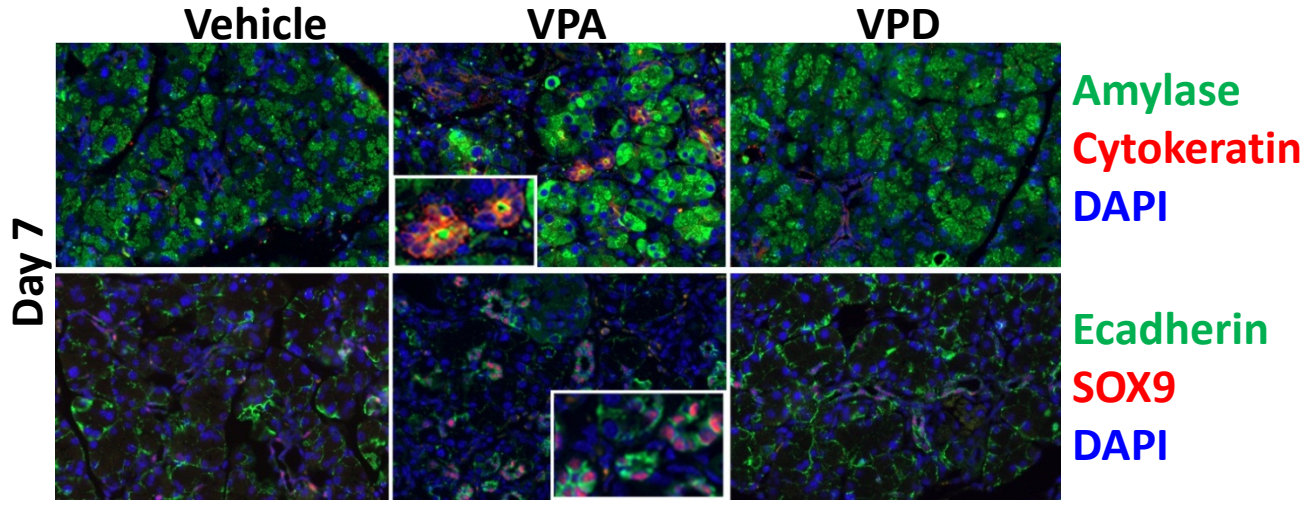




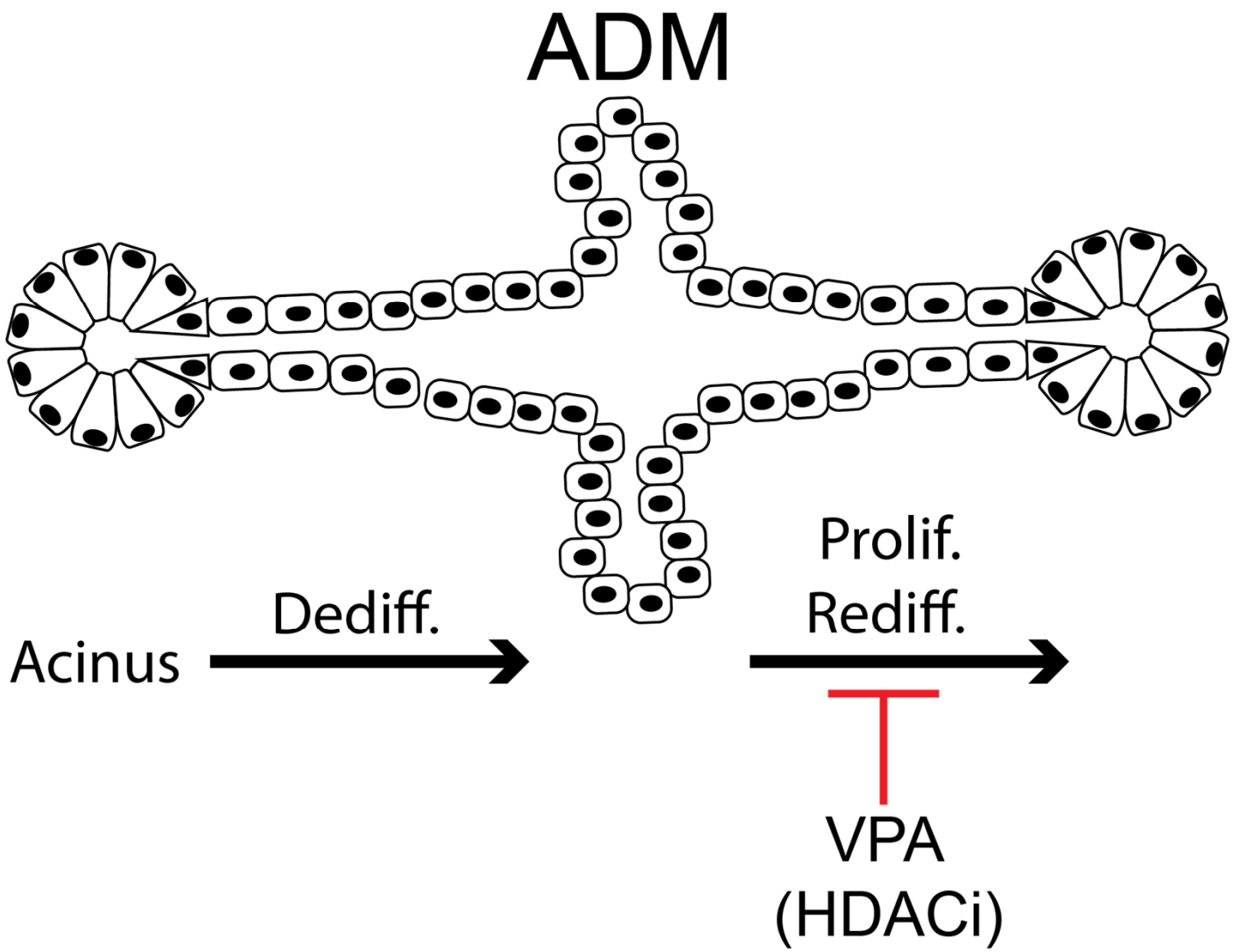
HDACi with VPA causes the persistence of regenerative acinar to ductal metaplastic complexes (ADMs) during pancreatic recovery





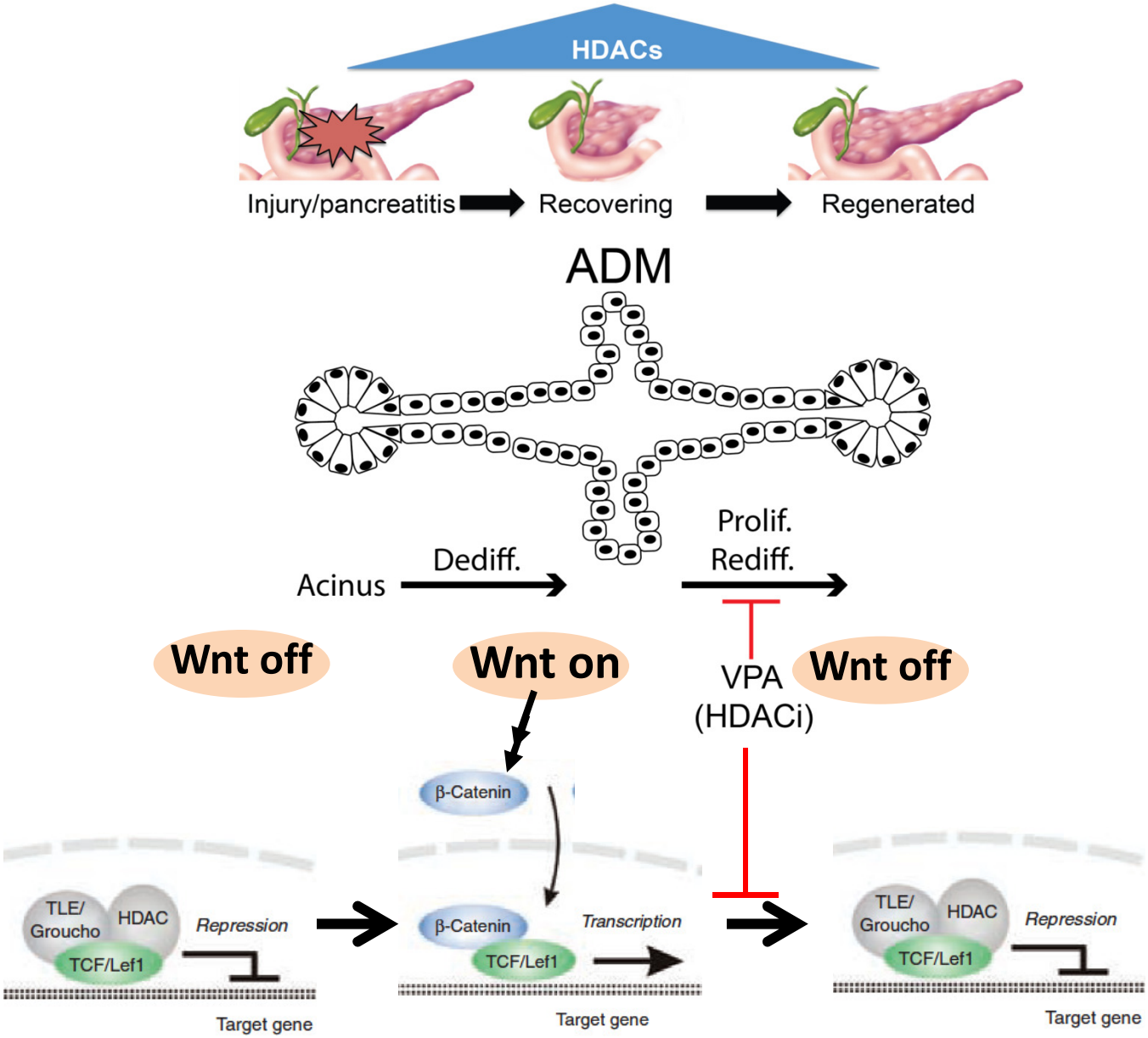


HDACi with VPA causes the persistence of regenerative acinar to ductal metaplastic complexes (ADMs) during pancreatic recovery

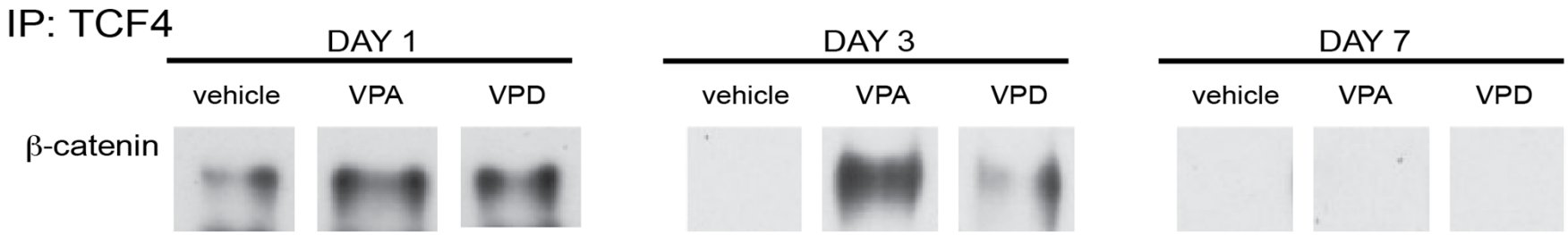


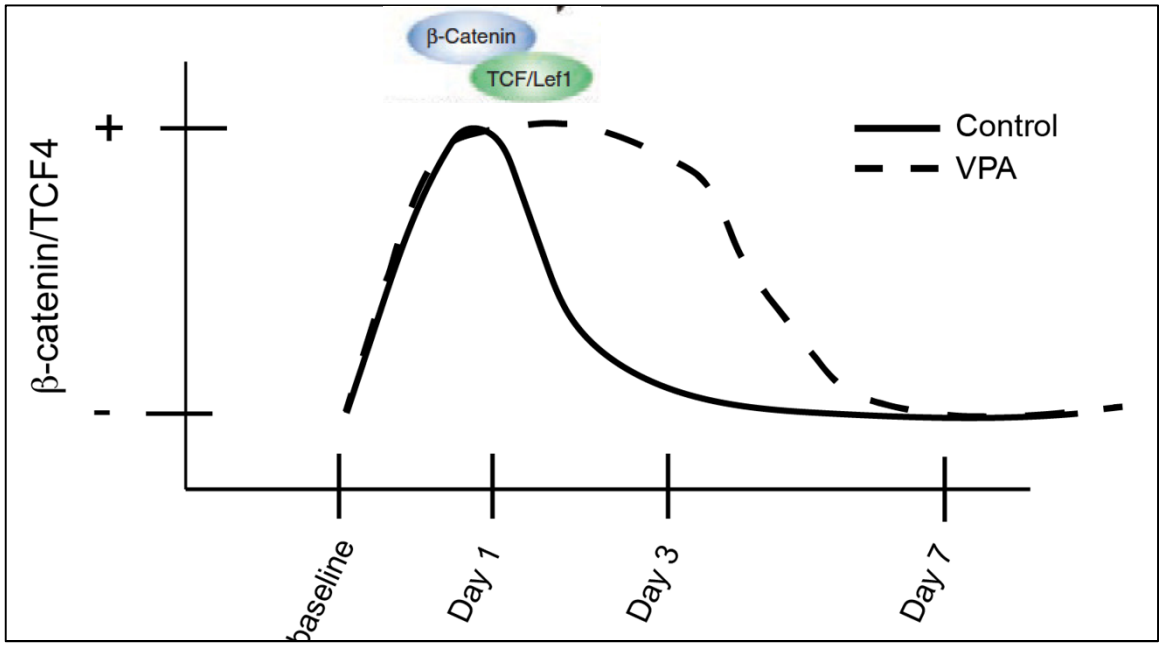
What is the mechanism by which HDACs allow pancreatic recovery to run to completion?

Hypothesis

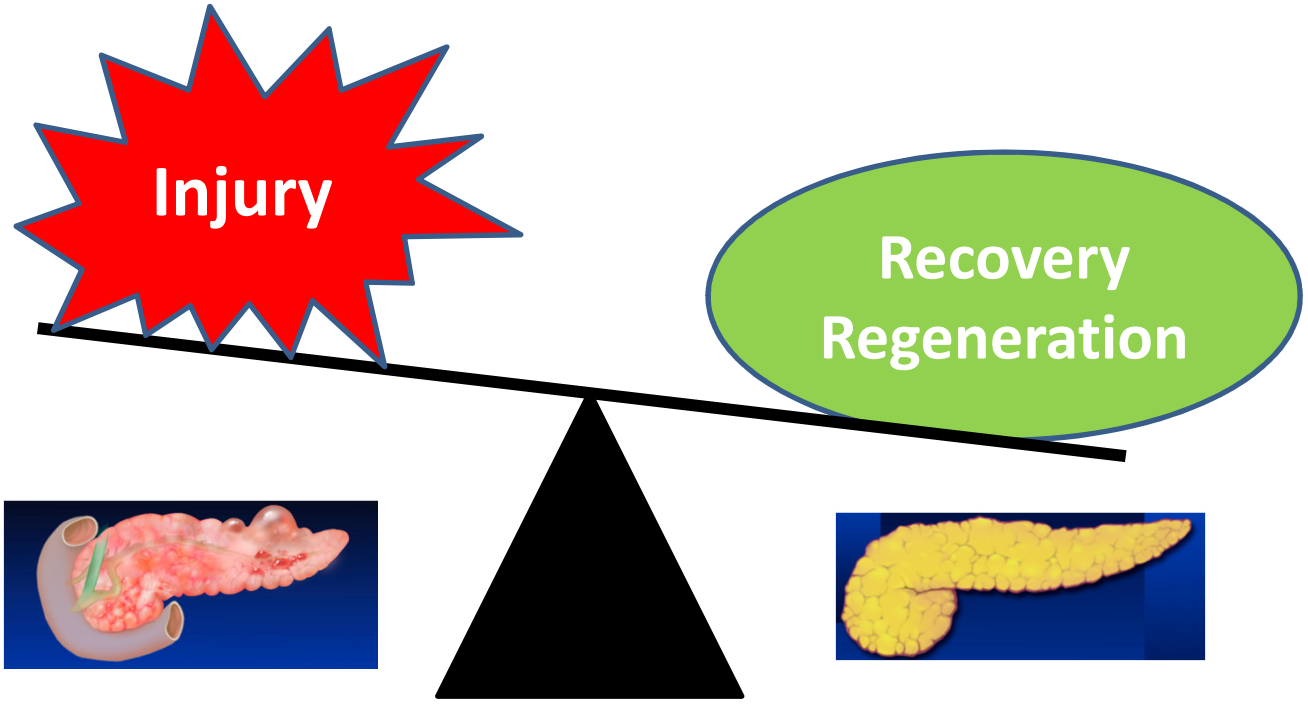

HDACs
Injury/pancreatitis
Recovering
Regenerated
ADM
Acinus
Dediff.
Prolif.
Rediff.
Wnt off
Wnt on
VPA
(HDACi)
Wnt off
β-Catenin
TLE/
Groucho
HDAC
TCF/Lef1
Repression
Target gene
β-Catenin
TCF/Lef1
Transcription
Target gene
TLE/
Groucho
HDAC
TCF/Lef1
Repression
Target gene

HDACs facilitate the repression of β-catenin signaling in the pancreas

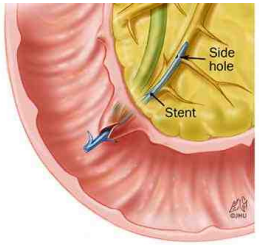




VPA-associated pancreatitis:
Opened up a new paradigm to examine whether epigenetic processes that enhance recovery during pancreatic injury can tip the balance in pancreatic health



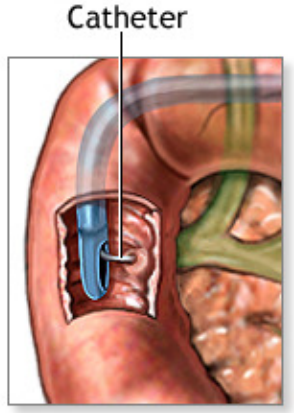
Story #2: Radiocontrast, ERCP, Ca2+, and post-ERCP pancreatitis (PEP)

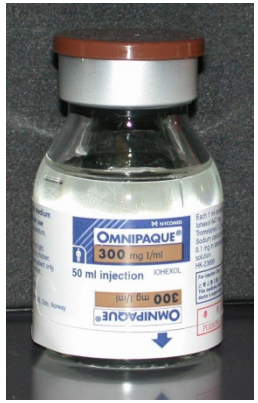


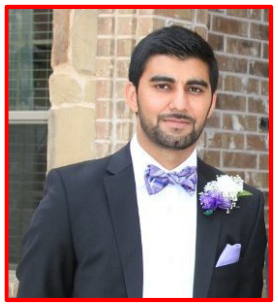
- "Sohail, it's interesting that patients taking Cn inhibitors don't seem to develop PEP."
  –Dr. Priya Jamidar, Yale

- PEP is still a problem
- Over a quarter million ERCPs performed in the US; a bulk of them by community GIs

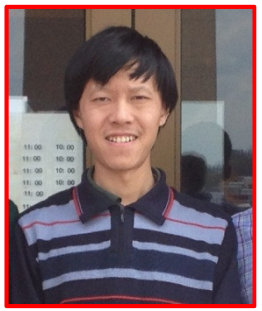
- **What is the pathophysiology of PEP?**



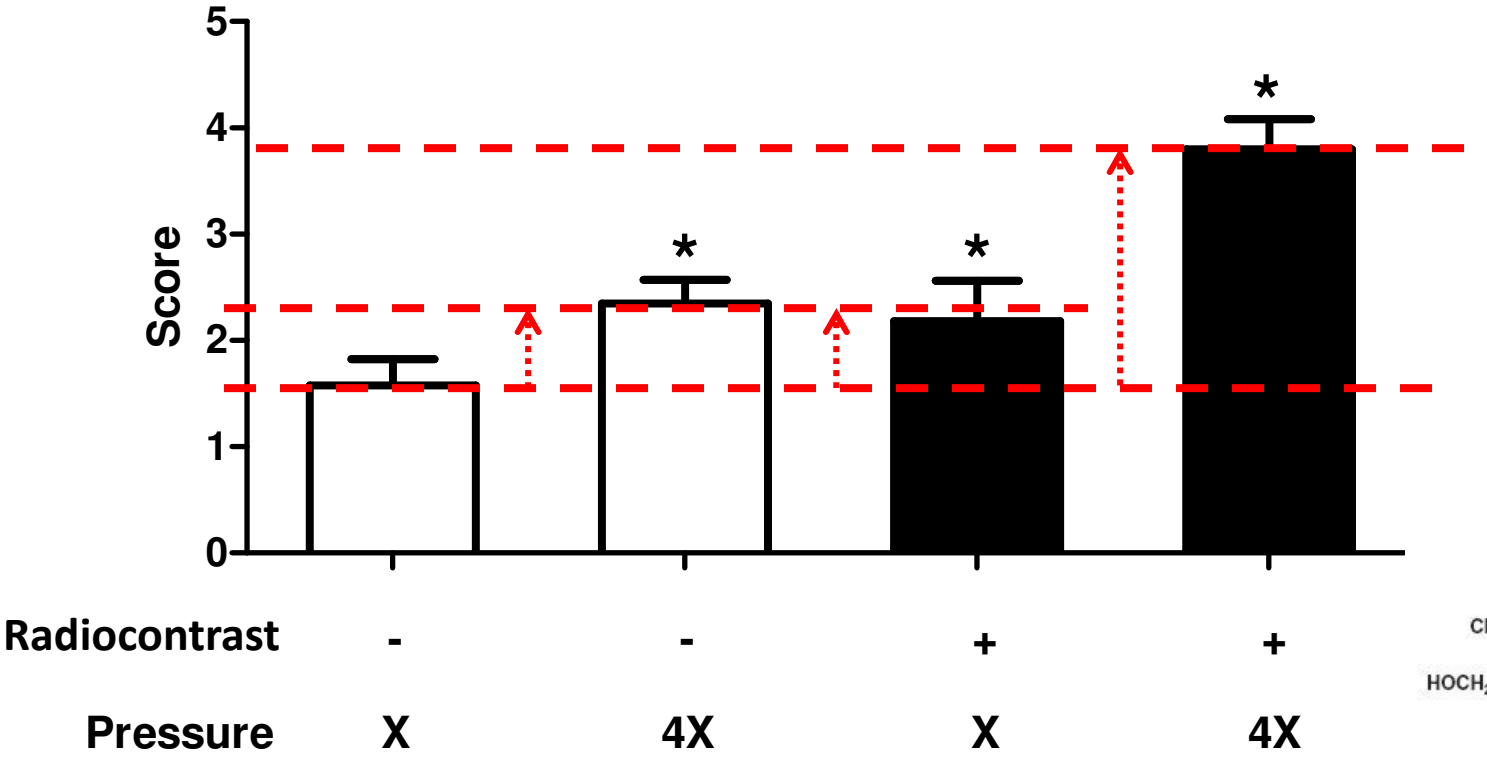


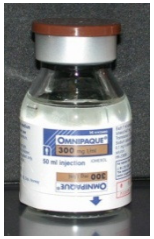


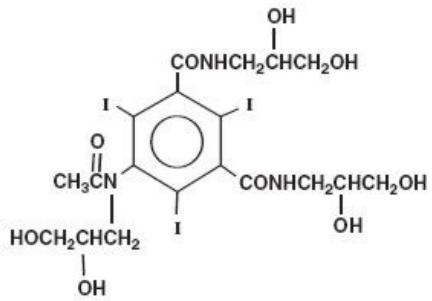
PEP = pressure + radiocontrast (RC)



Histological Severity



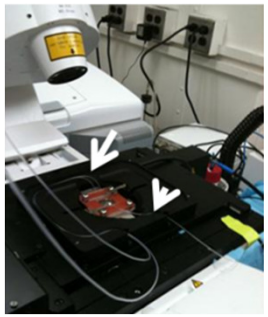


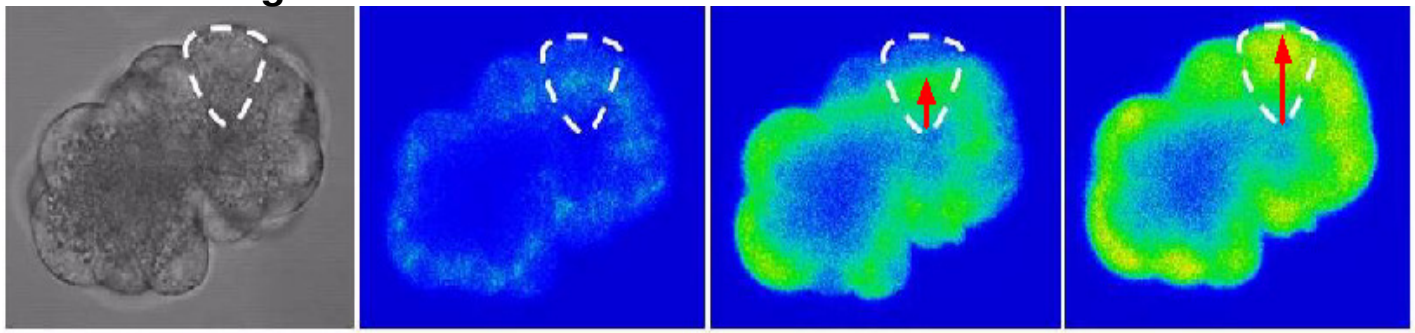


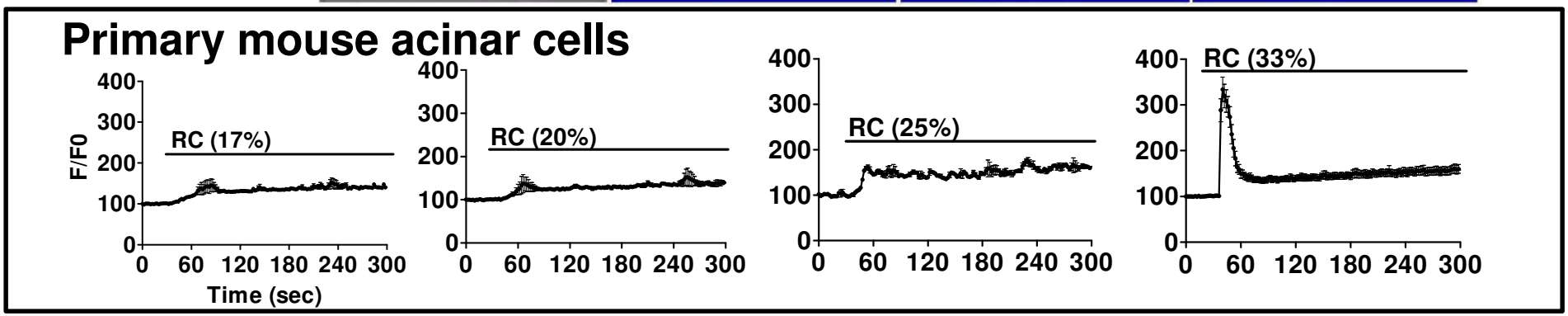
- Clues to Ca^{2+}: Pressure = Ca^{2+}; RC ≈ Ca^{2+} (renal)

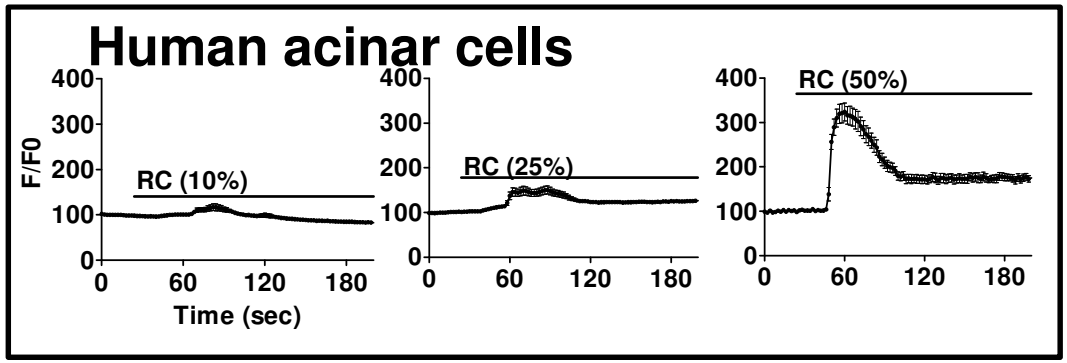
Jin, Gastro, 2015

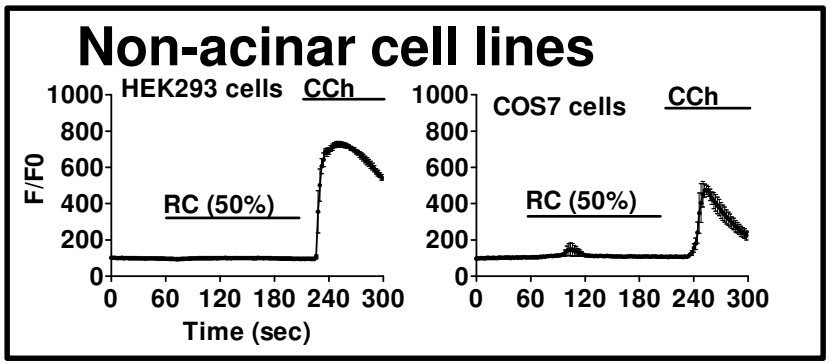
Radiocontrast (RC) selectively induces acinar cell Ca^{2+} signals





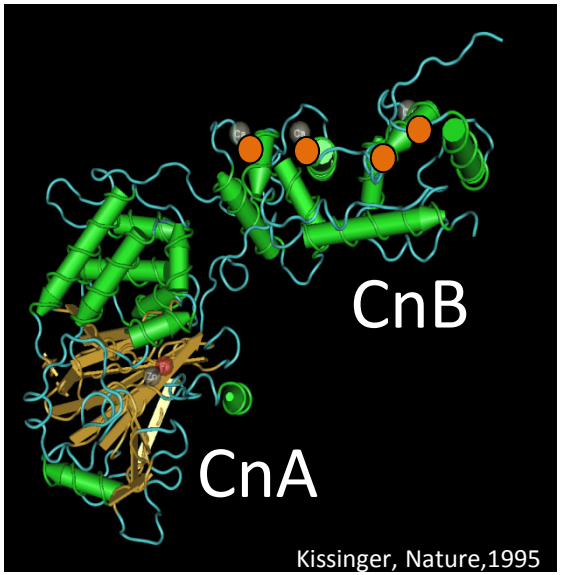


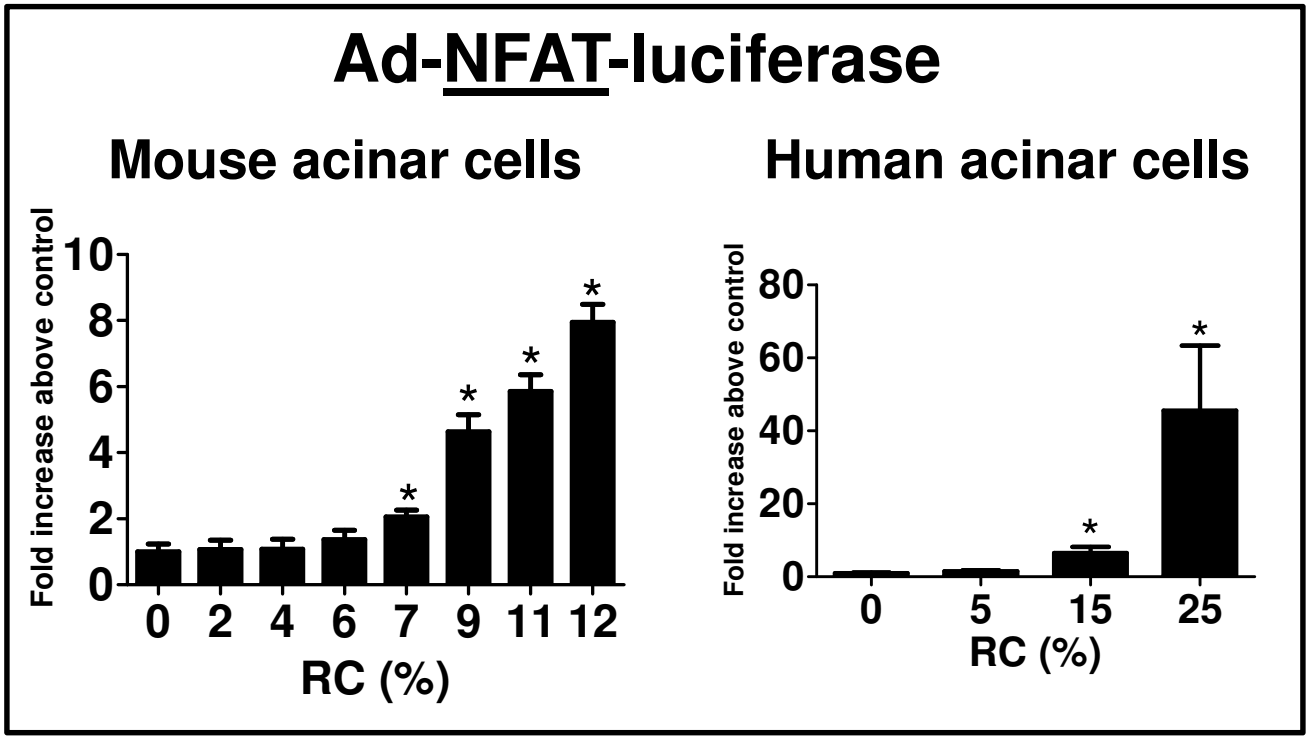




Jin, Gastro, 2015

A target of the RC-induced Ca^{2+} is the Ca^{2+}-activated phosphatase calcineurin (Cn)



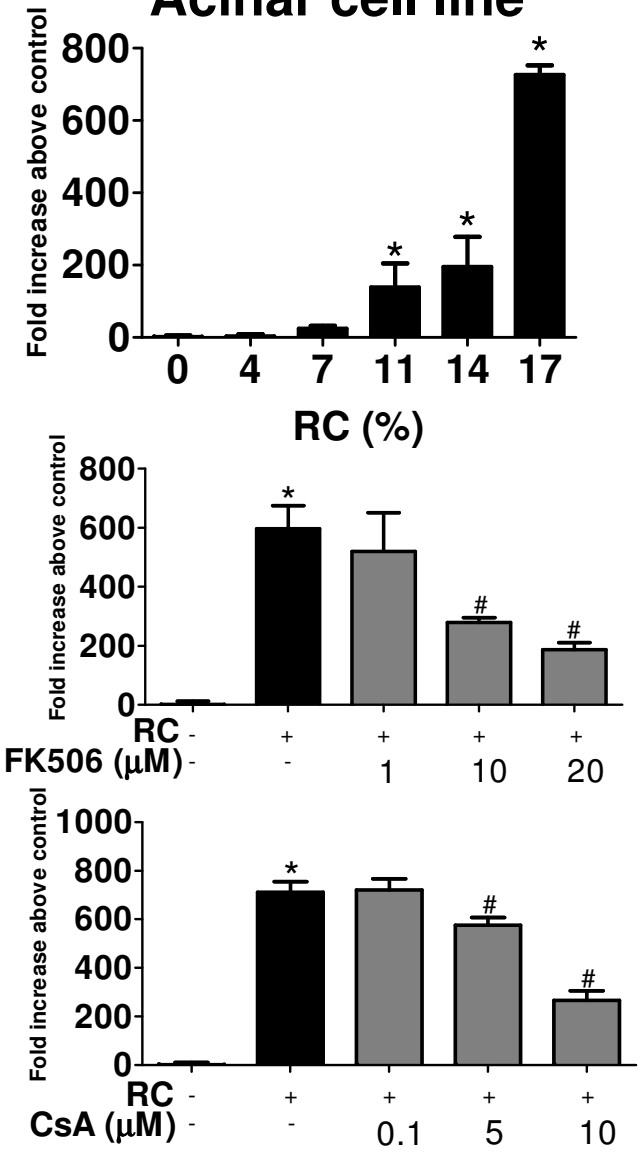


Jin, Gastro, 2015

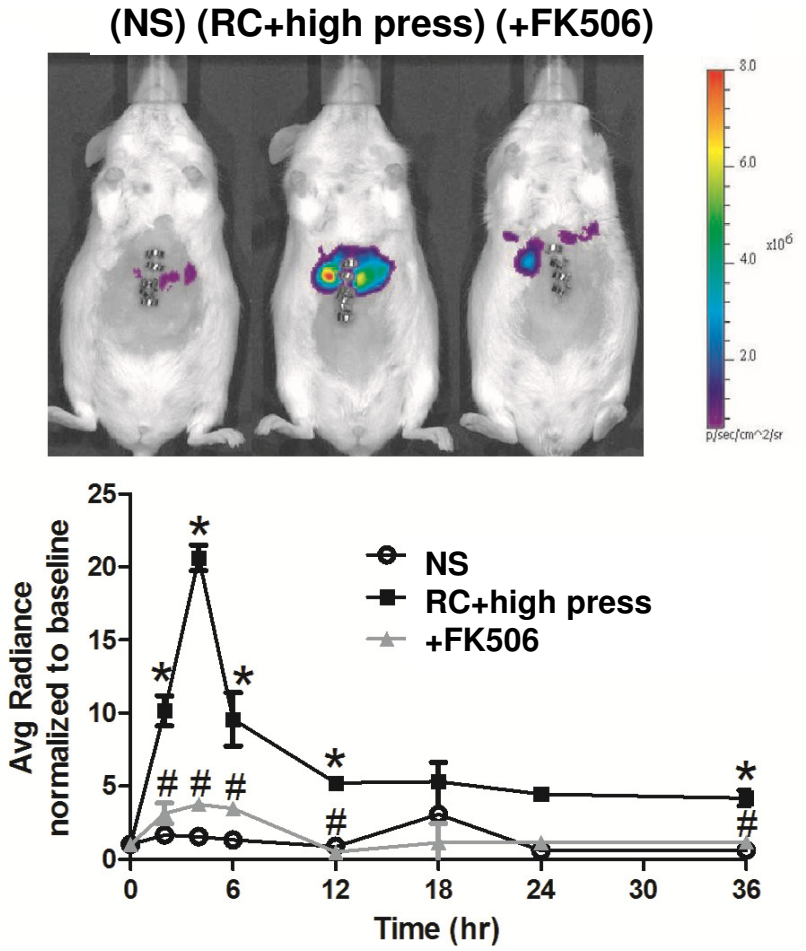
RC-induced NF-kB activation is Cn-dependent

Ad-NF-kB-luciferase

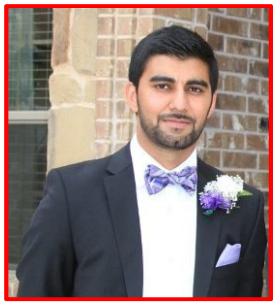
Acinar cell line



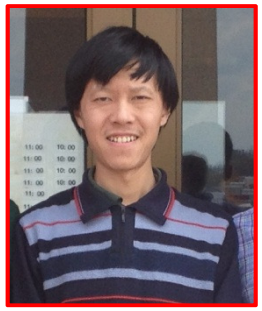
AAV6-NF-kB-luciferase

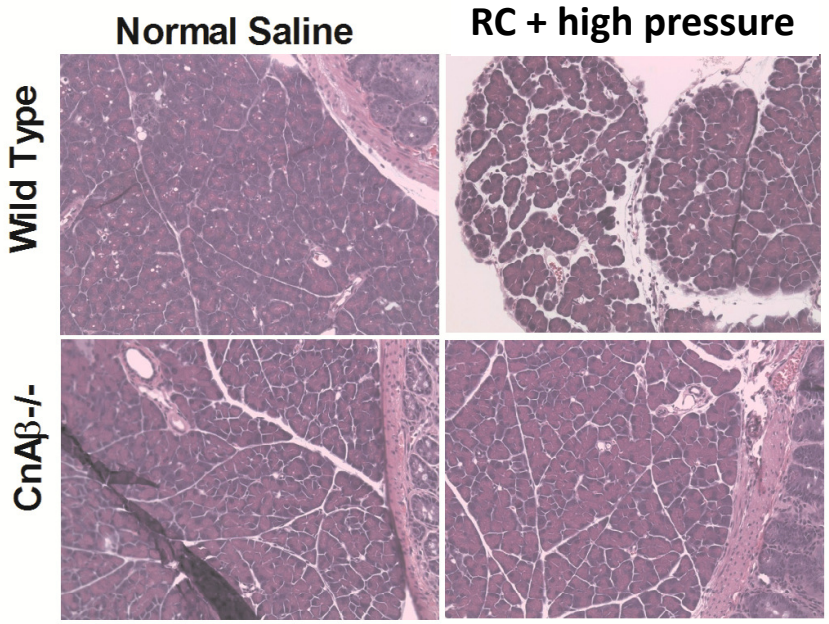


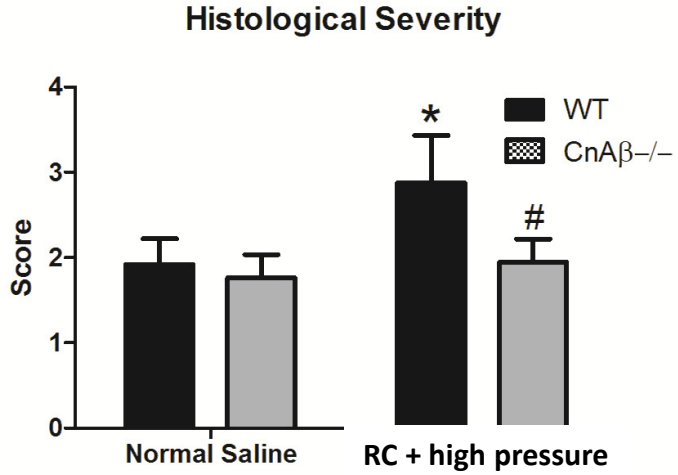
Jin, Gastro, 2015



CnAb$^{-/-}$-deficient mice protected against PEP







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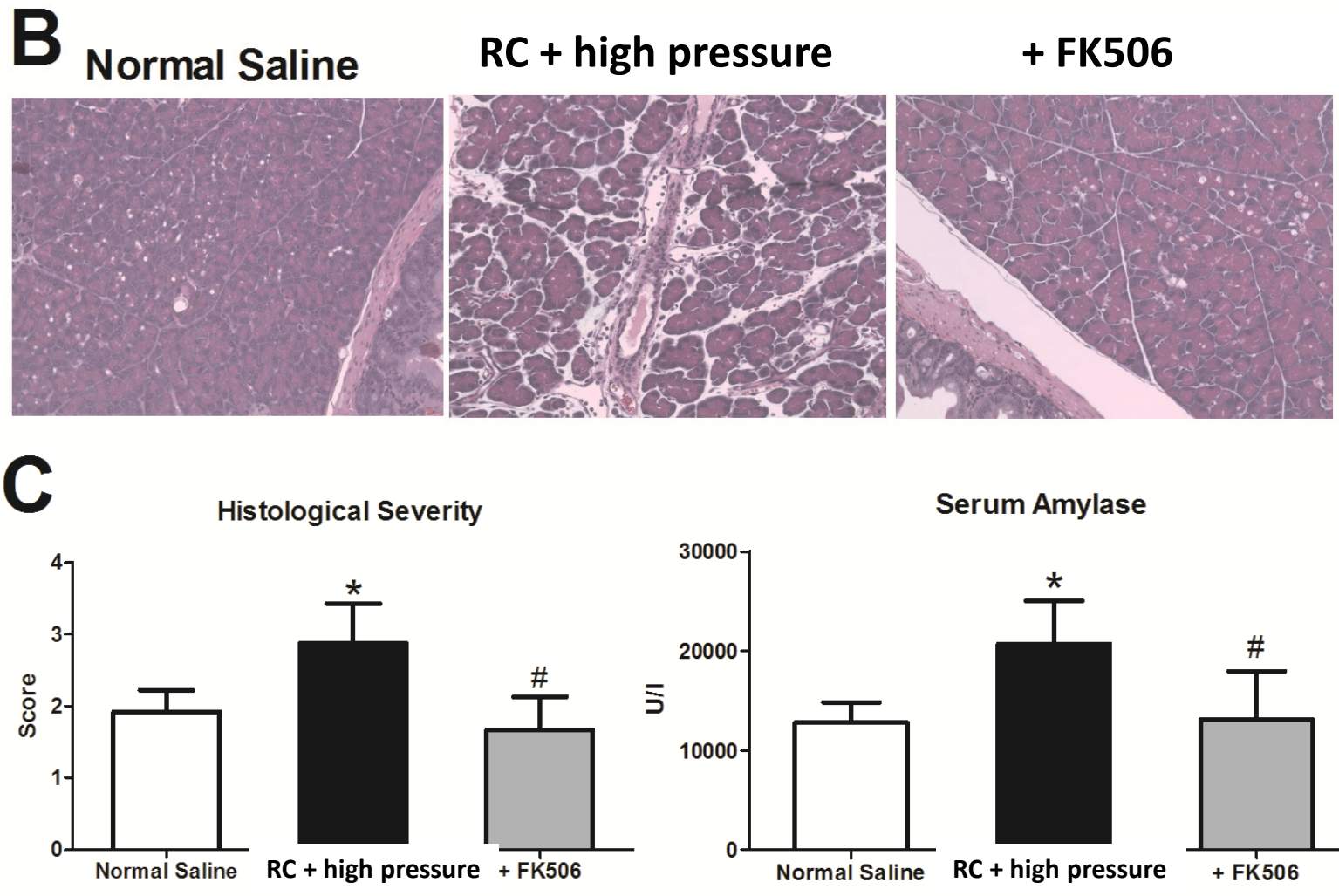
In vivo

Cn mediates PEP: Cn inhibitors



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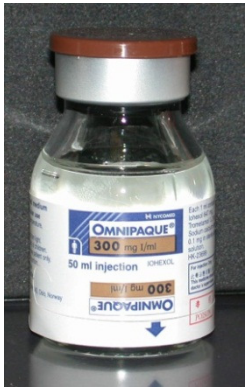
Summary: RC on Ca^{2+}/Cn in PEP



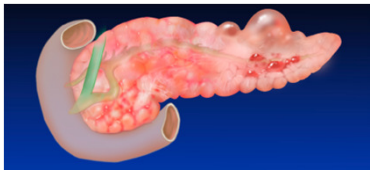
- Ca^{2+}/Cn are critical mediators of pancreatic injury
- Ca^{2+}/Cn pathways appear to mediate RC-induced injury and PEP
- These pathways can be harnessed as pancreatitis therapies

Current questions

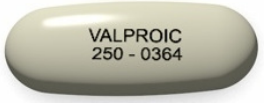
- How does RC exposure to the pancreas induce Ca^{2+} and Cn?
- How does Cn activation by RC induce NF-κB and pancreatic injury?
- Are pancreatic acinar cells a critical site of Cn activation during *in vivo* PEP?
- Would targeted *in vivo* delivery of Cn inhibitors to the pancreas prevent PEP?

Summary of drug-induced pancreatitis (DIP)

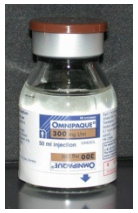
- DIP is a major pediatric dilemma



- VPA predisposes to pancreatitis by inhibiting HDACs and the redifferentiation programs during pancreatic recovery



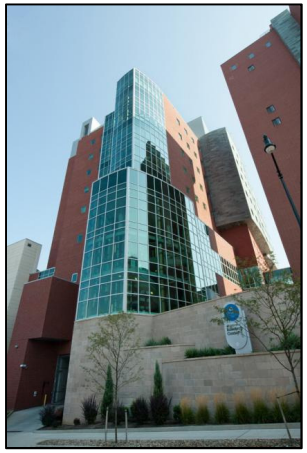
- RC exposure is a risk factor for PEP through inducing pancreatic Ca^{2+} and Cn



- Understanding the mechanisms underlying DIP will be crucial for preventative and therapeutic strategies

We will need to cross more bridges between science and medicine

Acknowledgments: Building bridges



Current Lab Members

- Shunqian Jin
- Abrahim Orabi
- John Eisses
- Tanveer Javed
- Kristy Boggs
- Fateema Turay
- Judy-April Oparaji

Former Members

- Tianming Le
- Swati Sah
- Sheharyar Sarwar
- Katie Lemon
- Zachary Dionise
- Kamaldeen Muili

Mark Lowe

Farzad Esni
Angela Criscimanna

Maching Learning Group
Gustavo K. Rohde
John Ozolek
Amy W. Davis
Burak Tosun

(Paul) Satdarshan Monga

NIH National Institute of Diabetes and Digestive and Kidney Diseases

INSPPIRE

The National Pancreas Foundation

Pitt/Children's Joint Pancreatic Research Group