
A novel rectal formulation to prevent the iatrogenic complication of post-ERCP pancreatitis: PrevPanc

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Project Team: Prevpanc

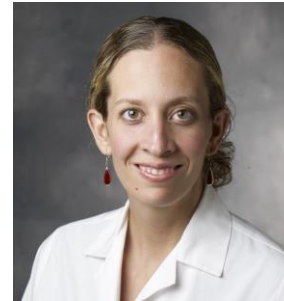


Sohail Z Husain, MD

Team Lead

Stanford Professor and Chief,
Pediatric Gastroenterology

Signal transduction in pancreatitis
20 years of experience at Stanford,
Pitt, Yale



Monique Barakat, MD, PhD

Co-Lead

Stanford Assistant Professor,
Pediatric and Adult
Gastroenterology,
Associate Director of Endoscopy

Physician-scientist
Performs ERCP

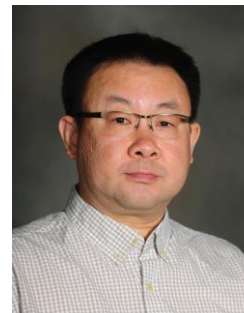


Sameena Sharif, PhD

Project Manager, RPI
(a Division of Premier Research)

President, RPI

20+ years of experience in
managing complex drug
development, from startup to
clinical trials



Mang Yu, PhD

Senior Scientist, Husain Lab

21 years of experience in pre-
clinical research at Stanford

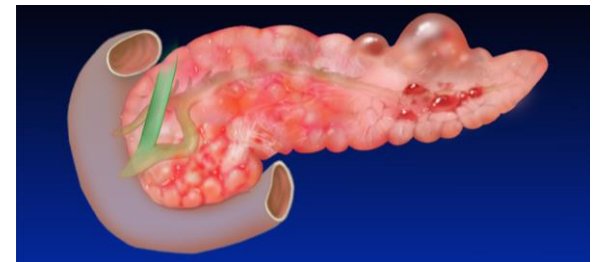
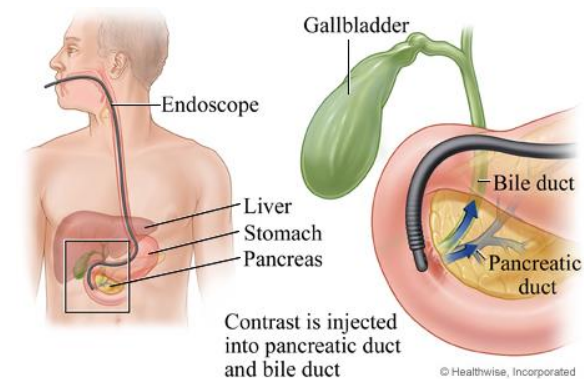
Rieko Yajima, PhD (SPARK Advisor)



SPARK
AT STANFORD

Background: The problem of post-ERCP pancreatitis (PEP)

- An ERCP (endoscopic retrograde cholangiopancreatography)
 - Radiocontrast dye is injected into the bile or pancreatic ducts through an endoscope
 - Common procedure—Over half million ERCPs annually in the US, and on the rise
- The **problem** is that 5-15% of patients develop the iatrogenic complication of **post-ERCP pancreatitis (PEP)**
 - Inflammation of the pancreas
 - Painful, life-threatening, life-altering
 - Costly
 - Reduces procedure quality metrics, and results in lawsuits
 - Post-ERCP pancreatitis higher in low volume ERCP community centers (the majority of ERCP centers)



Unmet need: Current standards of care for PEP prophylaxis are inadequate

- **Rectal indomethacin** (administered for high complex ERCPs, off label use, efficacy is debated)
- **Aggressive IV hydration** (time-consuming, contraindicated with heart or renal failure)
- **Pancreatic duct stenting** (risk of complications, repeat ERCP may be necessary for stent removal)
- There is an **unmet need** to devise better preventative for post-ERCP pancreatitis

Overview of the technology: We discovered that a crucial pathway for PEP is through the calcineurin pathway

In our pre-clinical studies,

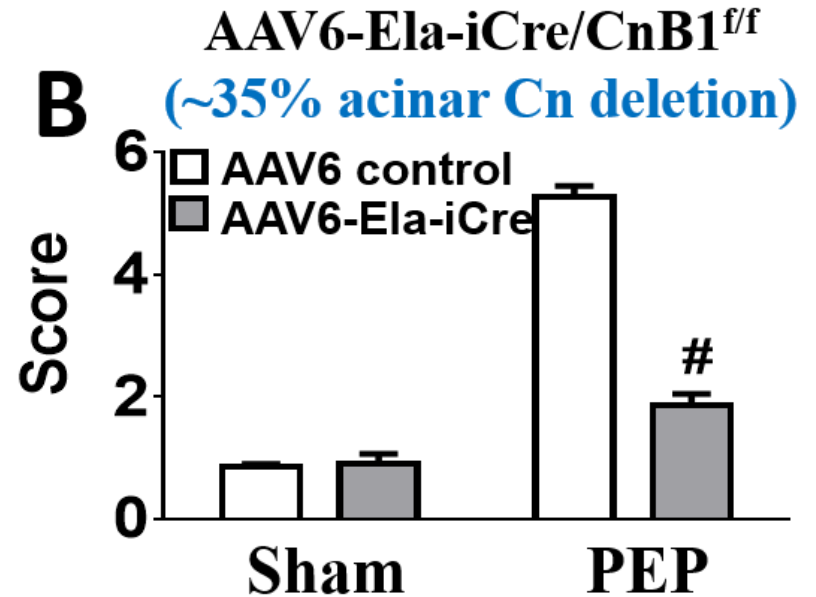
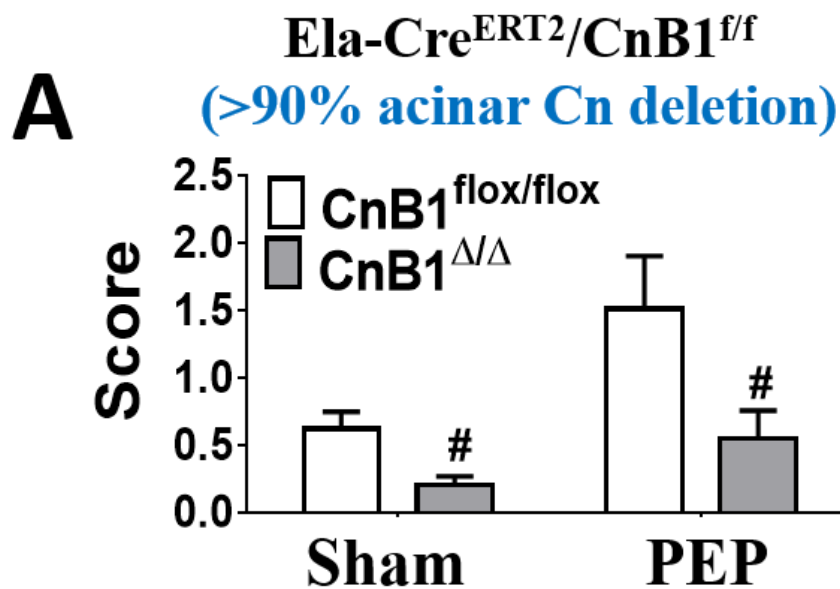
- Calcineurin inhibition or deletion blocked the pathological signals that propagate PEP (AJP 2007, AJP 2012; JBC 2013 (1); JBC 2013 (2), Gastroenterology 2015, CMGH 2017, Gastroenterology 2018)
- The calcineurin inhibitor effect is independent of the mechanism of action of the standard of care therapy using indomethacin (NSAID)
- Some level of systemic calcineurin inhibition is necessary to be more comprehensively effective for pancreatitis, such as to prevent the complication of lung damage (Gastroenterology 2020)

In clinical studies,

- Serendipitous use of PO calcineurin inhibitors reduced post-ERCP pancreatitis
- Serendipitous use PO tacrolimus and rectal indomethacin provided additive benefit

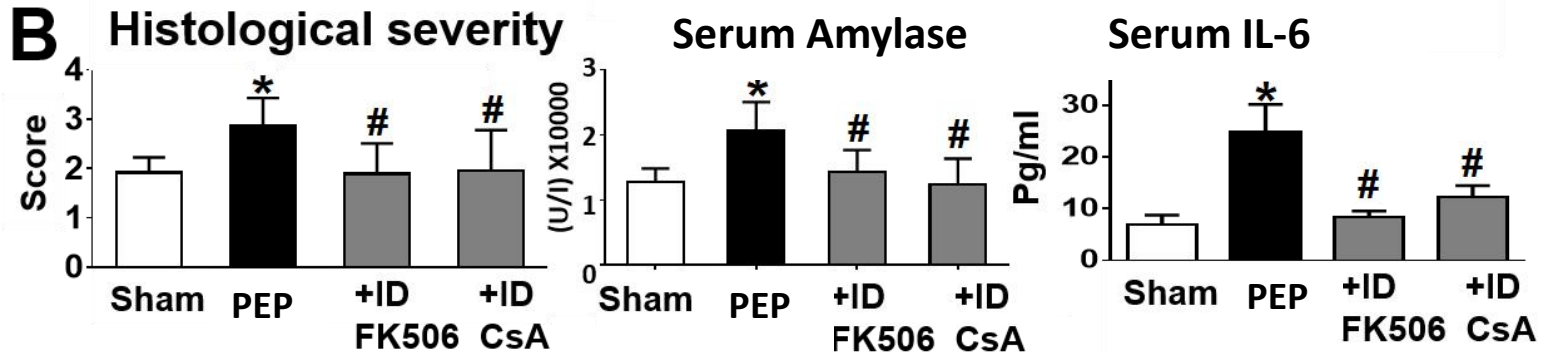
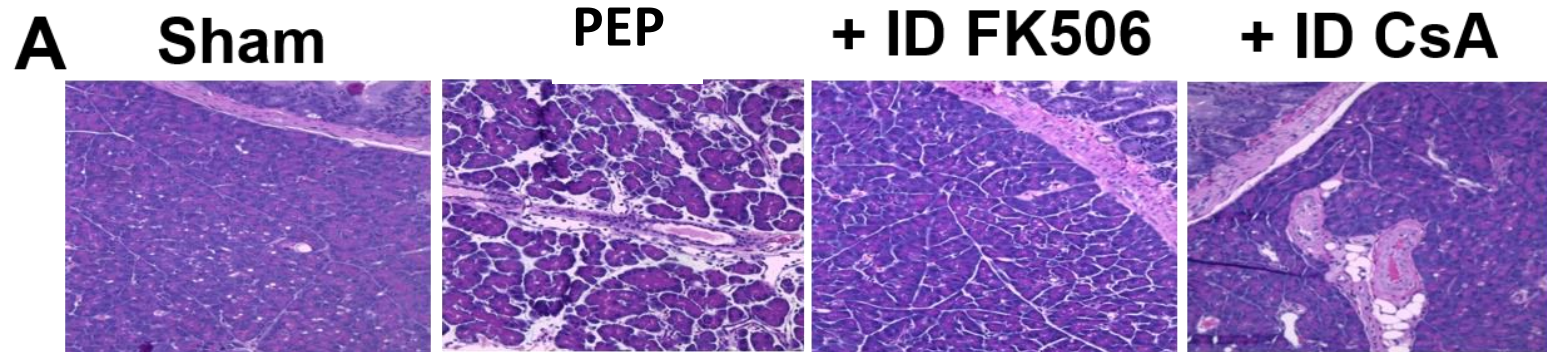
(our unpublished data; KJIM, 2020; CGH 2020)

Both near complete and partial knockouts of calcineurin prevent PEP



Orabi, CMGH 2017

Administration of calcineurin inhibitors prevents PEP



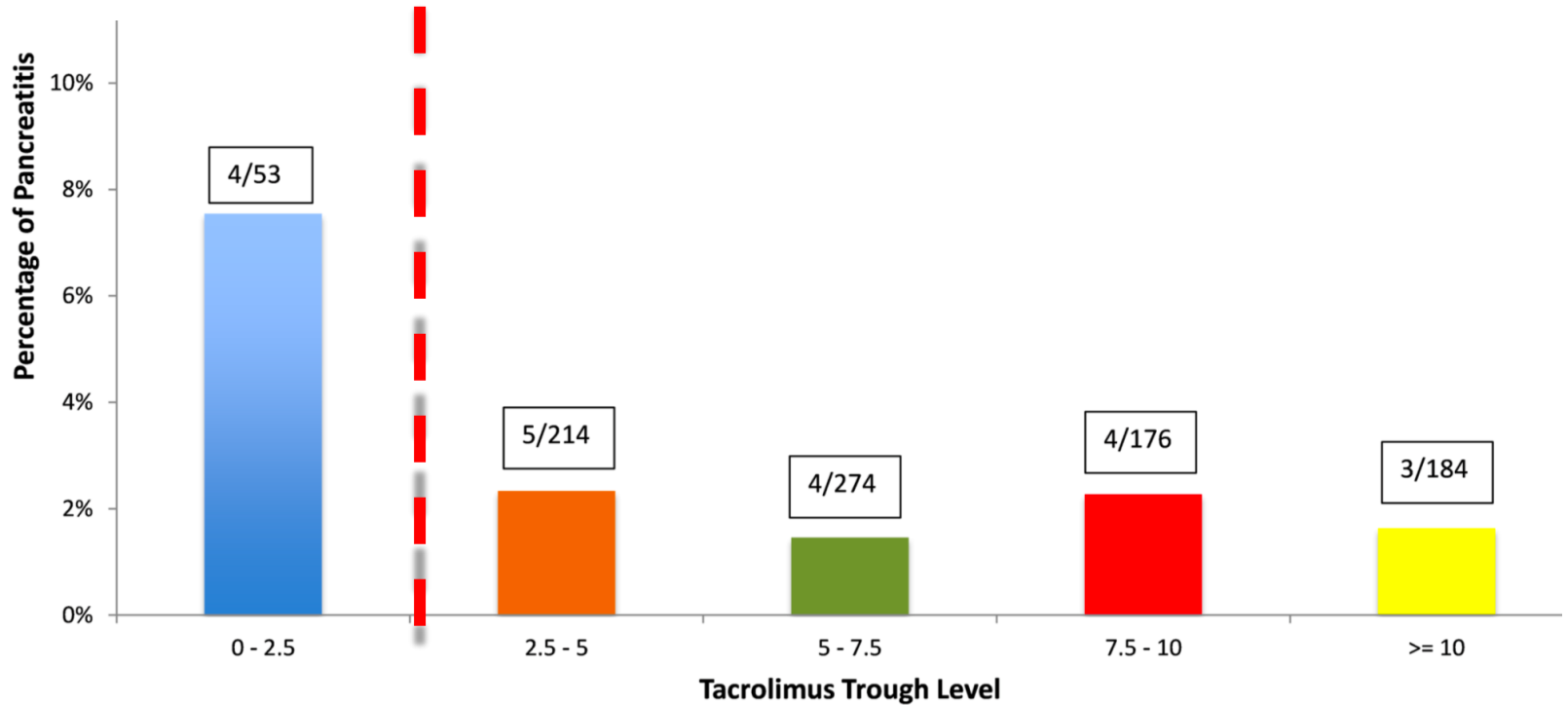
Orabi, CMGH 2017

Clinical evidence for a reduction in post-ERCP pancreatitis (PEP) among tacrolimus users

Study	PEP without tacrolimus	PEP with tacrolimus	PEP reduction	Significance
Oparaji & Sah, our unpub data (Pittsburgh)	13.2%	6.9%	48%	P<0.02
Harshavardhan, DDW, 2017 (South India)	16.1%	6.8%	58%	P<0.001
Oh, Korean J Int Med, 2020 (South Korea)	4.8%	0.7%	85%	P<0.01
Thiruvengadam, CGH, 2020	3%	0.3%	91%	P<0.001

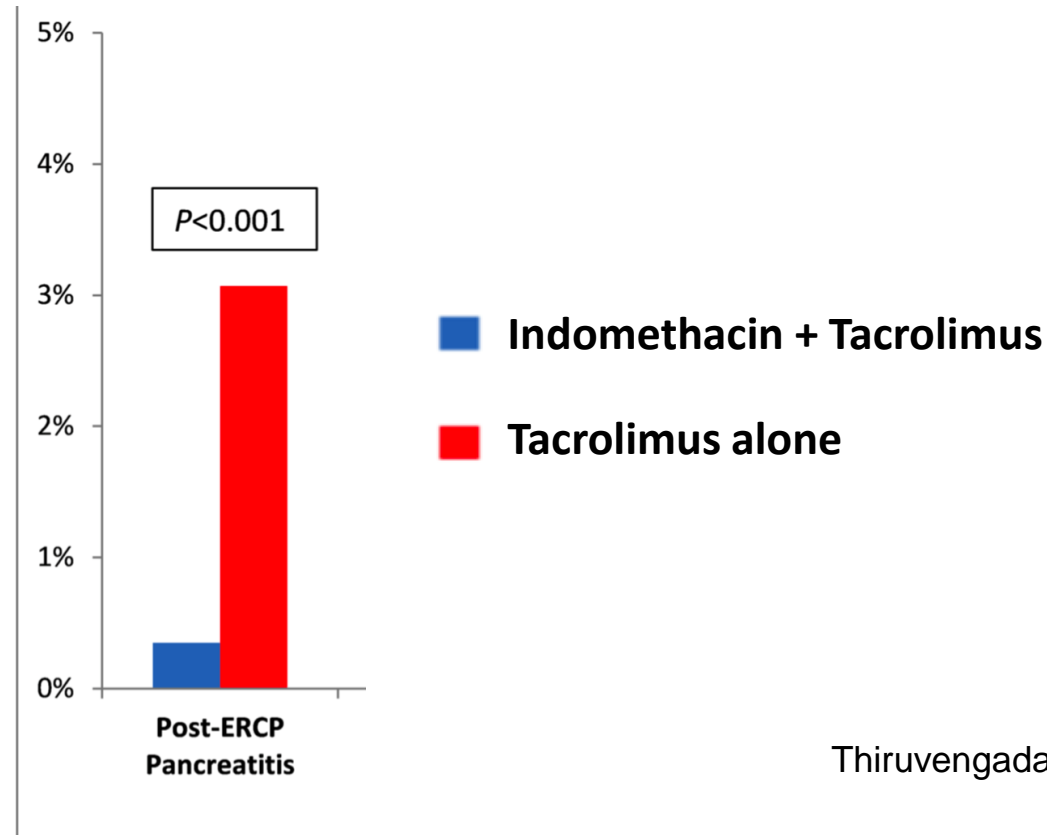
Anecdotal reports from several other sites.

Patients who had blood tacrolimus levels above a certain low threshold were protected against PEP



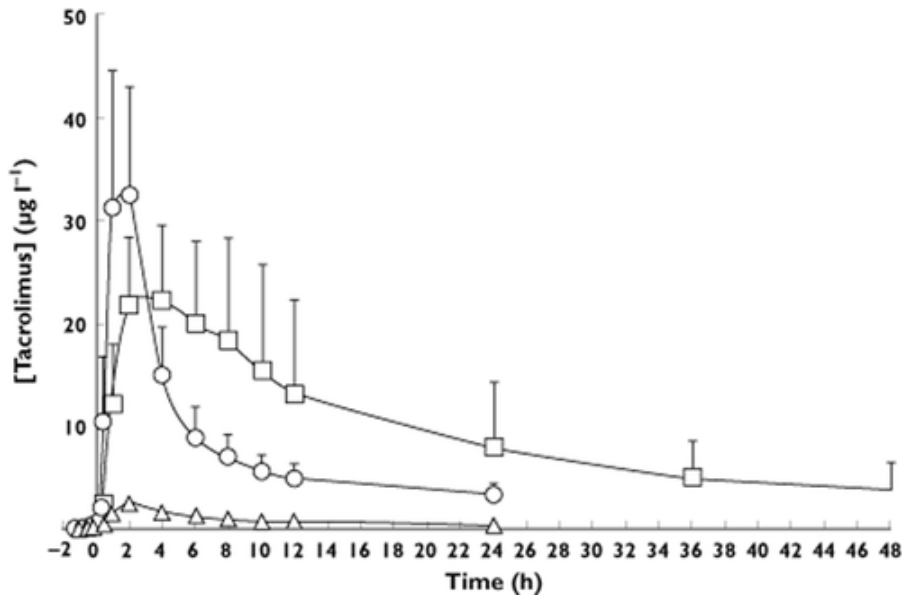
Thiruvengadam, CGH, 2020

Serendipitous use of both PO tacrolimus and rectal indomethacin provided additive benefit in preventing PEP

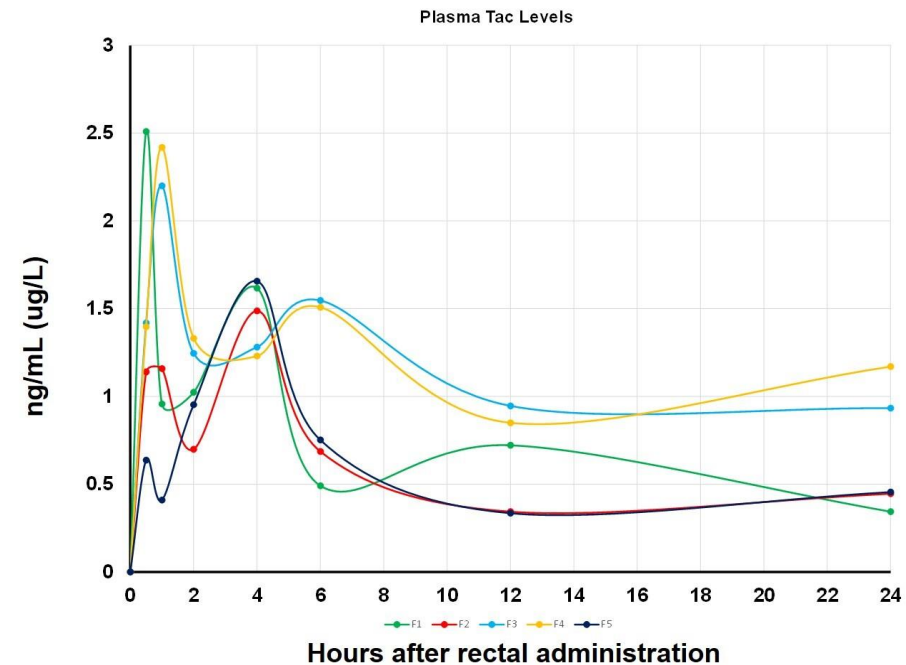


Thiruvengadam, CGH, 2020

The rectal route of administration of the CN inhibitor tacrolimus leads to long, sustained systemic levels



B J Pharm, 2014



Mang, 2021

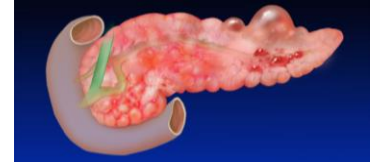
We came up with PrevPanc: A novel rectally administered combination formula of calcineurin inhibitor and NSAIDs, that is given simultaneous in a single preparation, to optimally prevent PEP

- Combine NSAIDs, with indomethacin as the prototypic NSAID and current standard of care
- With the calcineurin inhibitor FK506 (tacrolimus), based on our laboratory proof of concept and the recent retrospective associations
- In a rectal preparation, provides longer-sustained systemic release, while enriching the pancreatic circulation

Competitive advantage of PrevPanc over the current PEP prophylaxis

- Less time-consuming and safer than pancreatic duct stenting (risk of complications, repeat procedure) and IV hydration (often contraindicated)
- Twice as effective as rectal indomethacin alone (>75% vs 35-40%)
- Ready-to-use, minimally invasive formulation (rectal administration)
 - Does not add time to the busy endoscopy flow
 - The rectal route is an already familiar mode of administration (because of rectal indomethacin)
- Cost-savings, due to the reduced hospitalization and morbidity

Value proposition



- **For therapeutic endoscopists** who perform ERCPs
 - Most are community hospital-based and fear litigation and peer-review due to ERCP complications
- **Who deal with the procedure-related complication of post-ERCP pancreatitis (PEP)**
- Our **value proposition** is that this novel formulation is a ready to use, superior substitute for other modalities of pancreatitis prophylaxis, and it will **provide** improved ERCP quality metrics, a cost savings, due to reduced hospitalization and morbidity, and a reduced fear of malpractice by preventing PEP by over 75%, on top of the current PEP preventatives
- **Unlike** the current, cumbersome preventatives, this novel formulation is safer, twice as effective, noninvasive, easier to use, and it saves on precious endoscopy time

Major Progress

- Non-dilutive funding from a Department of Defense CDMRP Technology Award (\$4.4M) for IND-enabling studies
- Utility patent filed in March 2021
 - Stanford plans to market the IP
- Identified a regulatory CRO, RPI
 - Also provides project management and pharmacology expertise
- Performed a gap analysis

Opportunities identified from the gap analysis

- Clearer path to IND filing and next steps
- ODD filing
- IP enforceability
 - Formulation and manufacturing
- Timeline (confidential)
 - PreVPanc anticipates clinic readiness by Q4, 2021
 - Direct to Phase II trial will take ~1 year

Savings to the health care system

- Practice loss due to PEP
 - 80% have mild pancreatitis (-30K loss per hosp)
 - 20% have severe pancreatitis (-100K loss per hosp)



Hospital center scenario per year

- 1000 ERCPs performed, 5% risk of ERCP pancreatitis
= 50 cases of ERCP pancreatitis
- Practice loss for ERCP pancreatitis/yr **-\$2.2M loss per year**
- The novel rectal calcineurin inhibitor/indomethacin formulation will reduce practice loss by 75% and save \$1.65M per center

Patentability claims for rectal formulation

- **Subject matter**

- Novel combination of two FDA-approved drug categories in a novel route of administration (Indomethacin + Tacrolimus)

- **2 major novelties**

- Mode of **rectal** administration

- Sustained delivery of drug levels and enriched in the pancreas due to flow through the portal venous system
- Rectal administration obviates the problem with administering the drugs to patients who are NPO prior to ERCP due to the anesthesia.

- **Timing** of administration just prior to ERCP

- May provide additional benefit