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

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Sameena Sharif, PhD
Mang Yu, PhD
Rieko Yajima, PhD

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Outline

- The team
- The problem of post-ERCP pancreatitis (PEP)
- Overview of the technology
- Patent status
- Pre-clinical development and IND filing timeline

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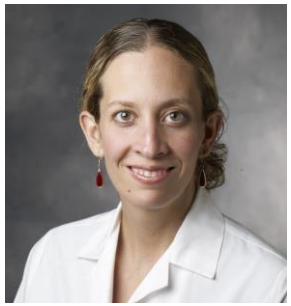
Project Team: Prevpanc

Sohail Z Husain, MD
Team Lead

Stanford Professor and Chief, Pediatric Gastroenterology

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



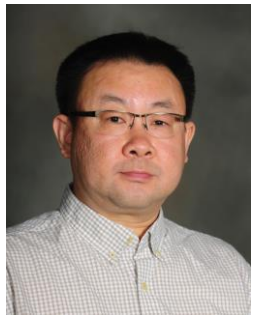
Monique Barakat, MD, PhD
Co-Lead
Stanford Assistant Professor, Pediatric and Adult Gastroenterology,
Associate Director of Endoscopy

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

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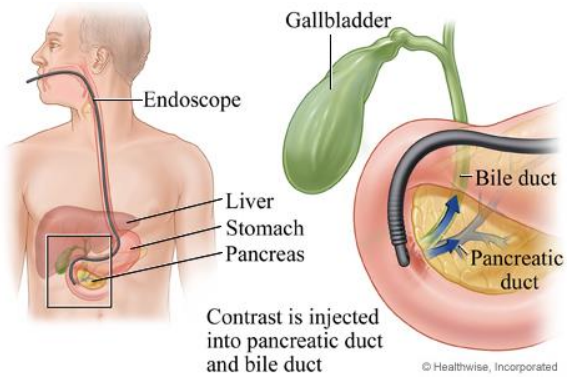
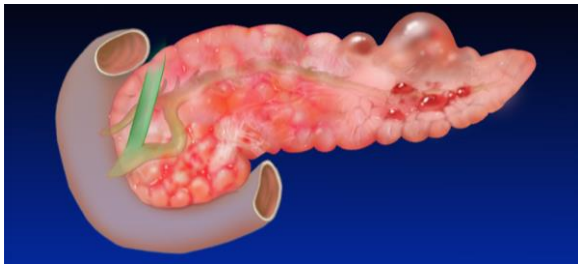
Background: The problem of post-ERCP pancreatitis (PEP)

- 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)



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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

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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)

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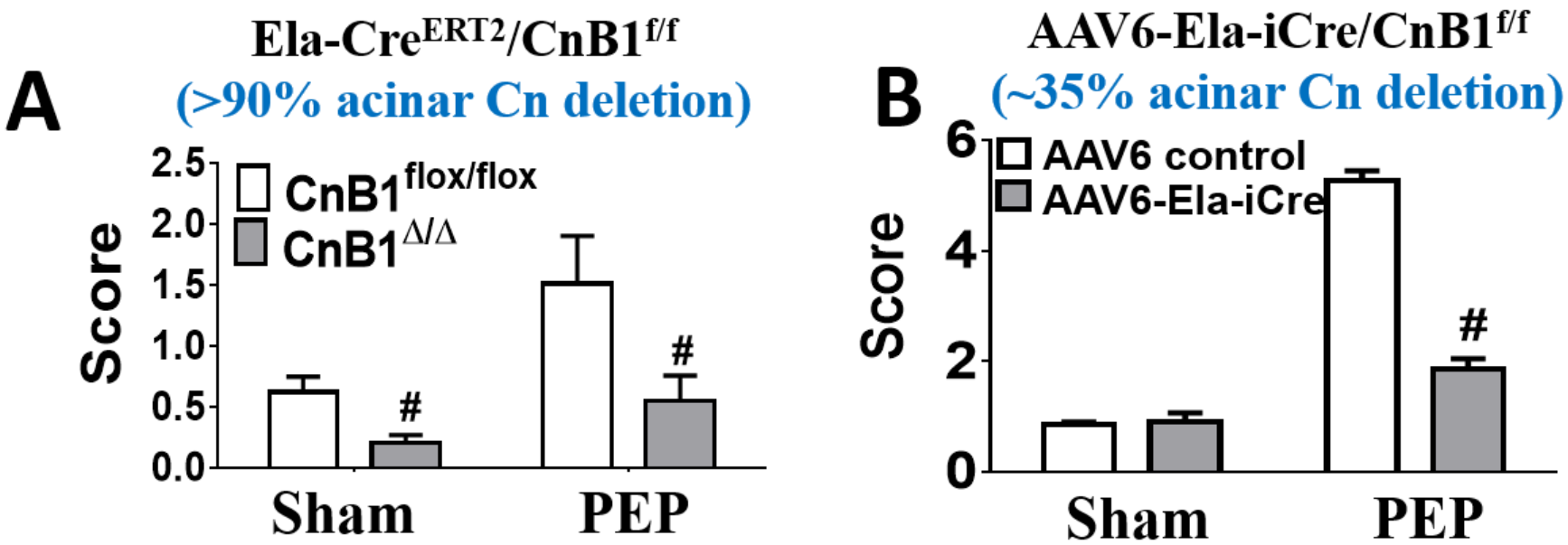
Both near complete and partial knockouts of calcineurin prevent PEP



Orabi, CMGH 2017

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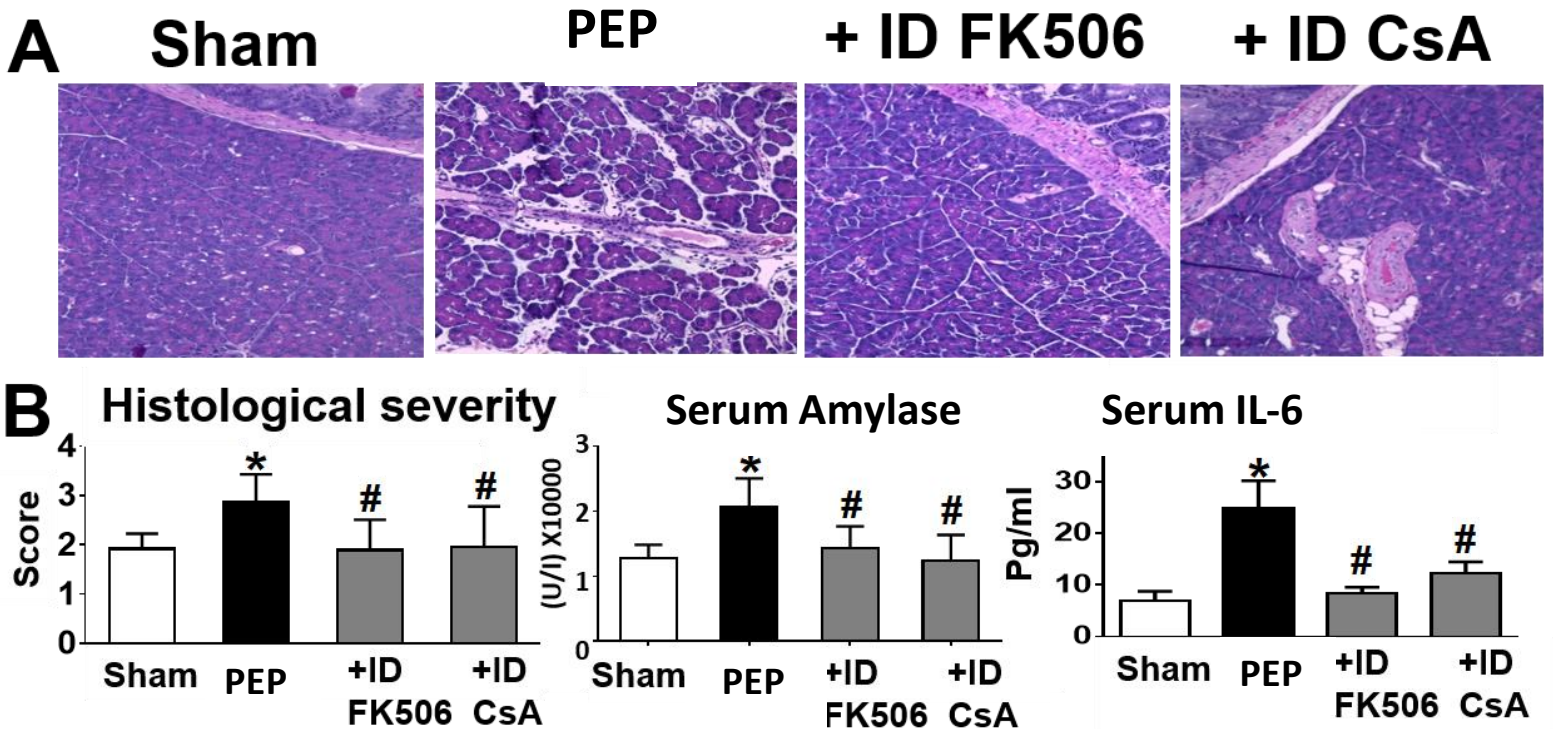
Administration of calcineurin inhibitors prevents PEP



Orabi, CMGH 2017

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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.				

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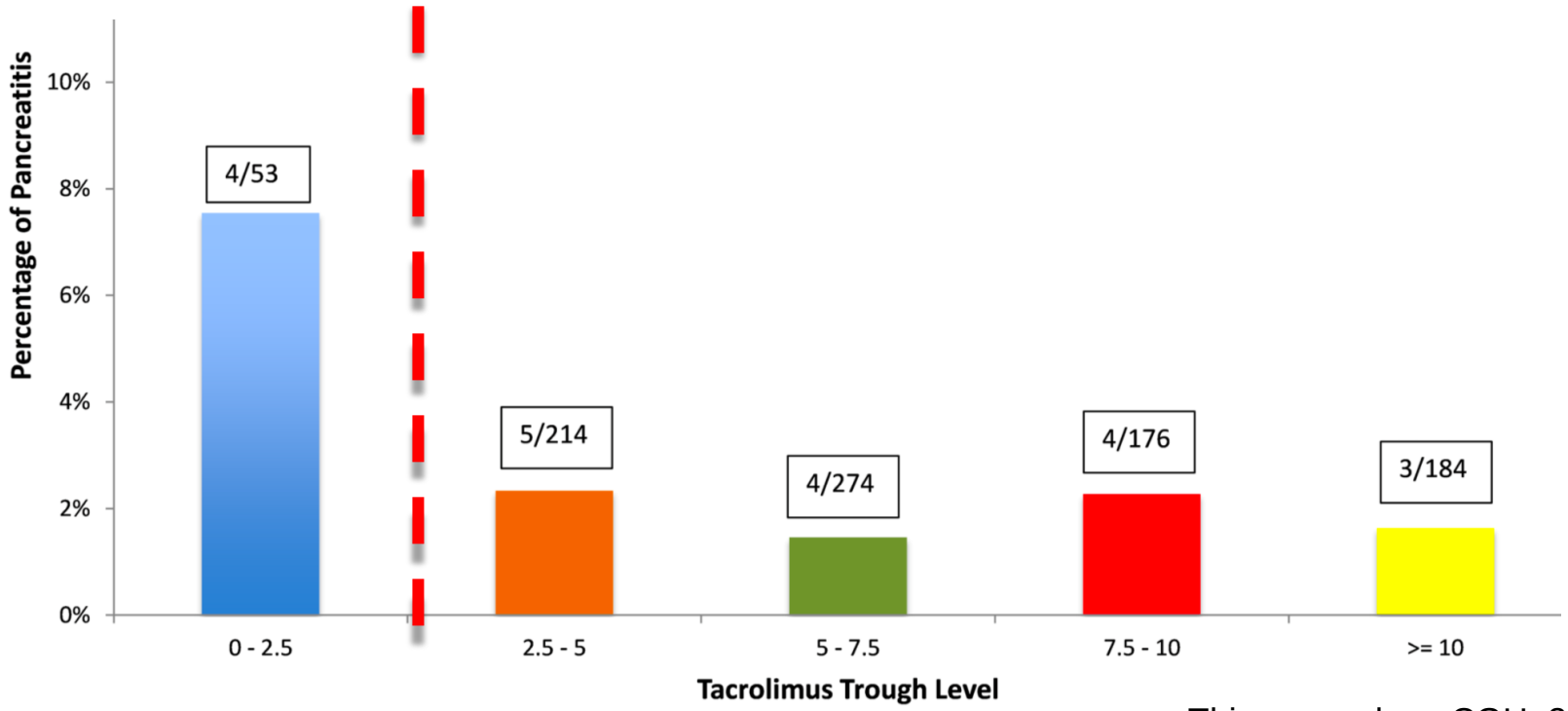
Patients who had blood tacrolimus levels above a certain low threshold were protected against PEP



Thiruvengadam, CGH, 2020

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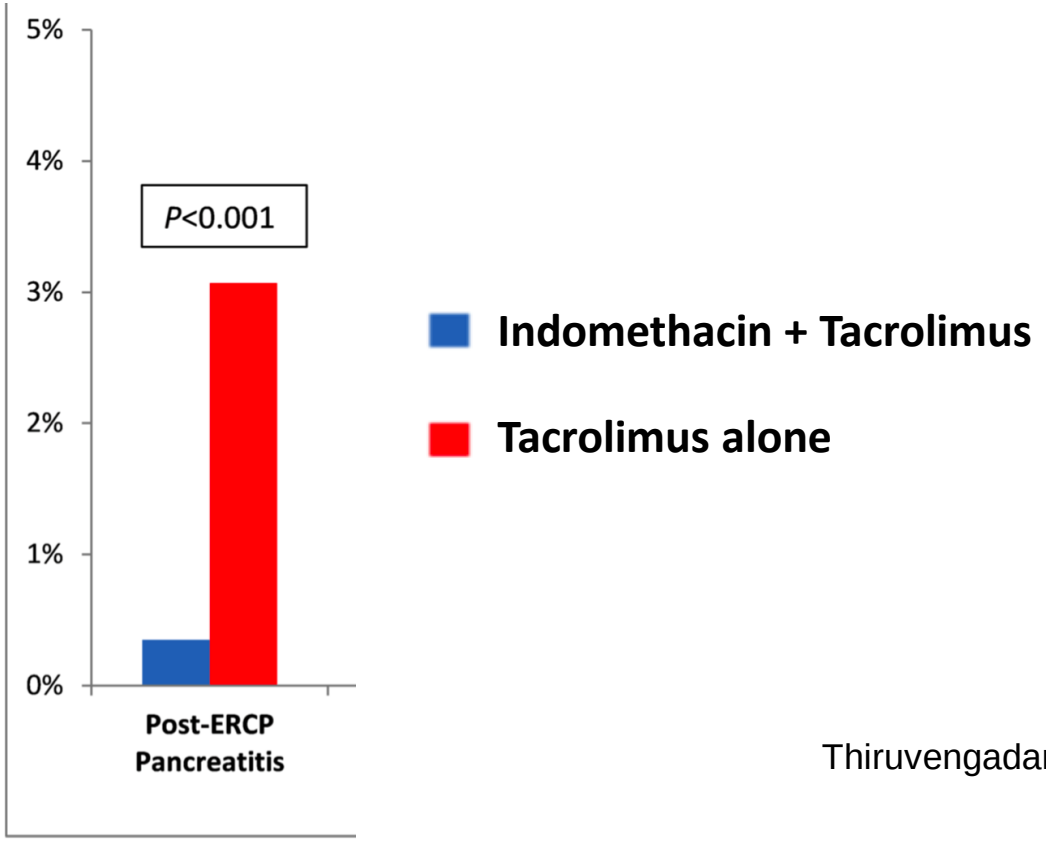
Serendipitous use of both PO tacrolimus and rectal indomethacin provided additive benefit in preventing PEP



Thiruvengadam, CGH, 2020

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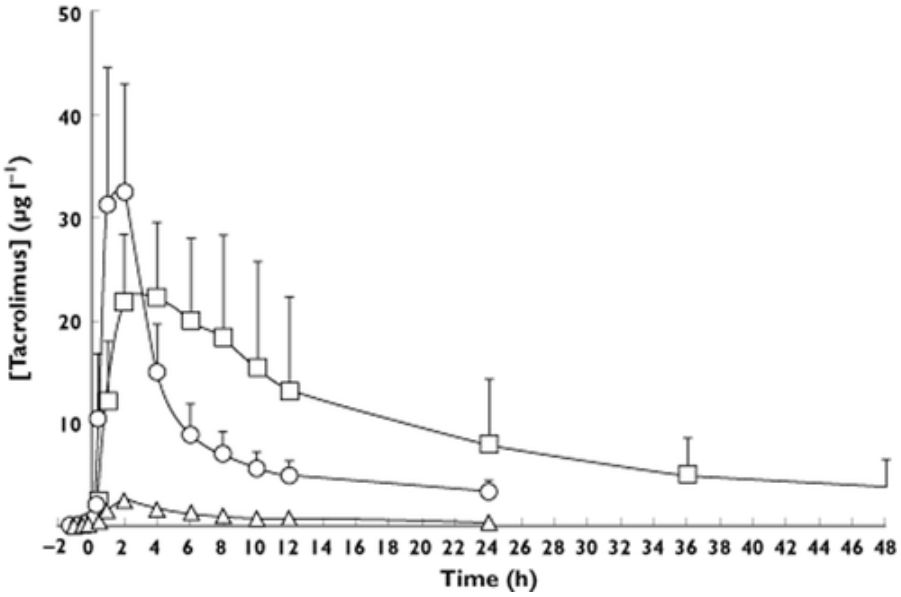
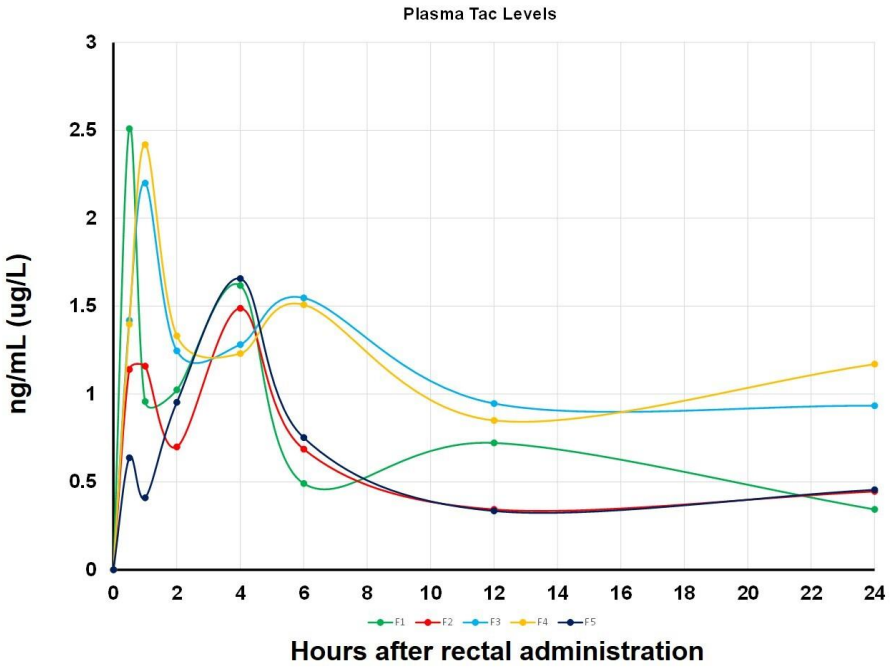
The rectal route of administration of the CN inhibitor tacrolimus leads to long, sustained systemic levels



B J Pharm, 2014



Mang, 2021

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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

- **Combination of** the calcineurin inhibitor FK506 (**tacrolimus**), based on our laboratory proof of concept and the recent retrospective associations, **with**

- NSAIDs, specifically **indomethacin** as the prototypic NSAID and current standard of care

- **In a rectal preparation**, provides longer-sustained systemic release, while enriching the pancreatic circulation

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Competitive advantage of PrevPanc over the current PEP prophylaxis

- Targets two key inflammatory pathways, both the early calcineurin and the later NSAID-responsive inflammatory pathways, for greatly increased efficacy over indomethacin alone
- 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

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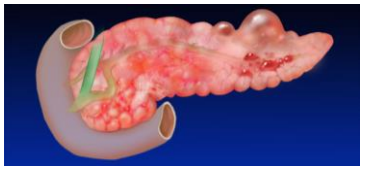
Value proposition



- **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

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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)

<u>Hospital center scenario per year</u>

- 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

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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

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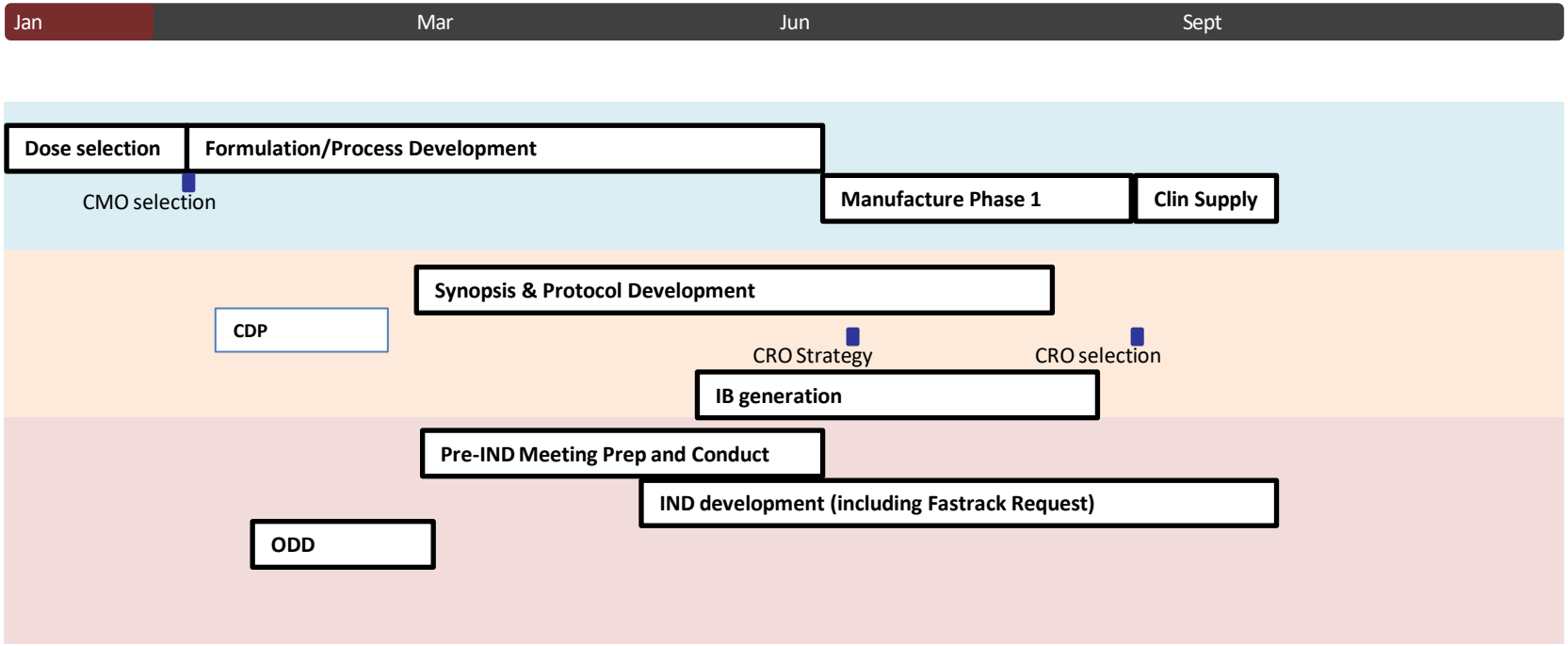
Our timeline



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Overview of the plan for testing efficacy

- Primary outcome: PEP rate
- Selective enrollment of patients at high risk for PEP
- Standard two-arm superiority trial, with equal allocation, without interim analyses
- Statistical Analysis: Two-sample test of proportions (one sided)

Phase	PEP rate (SOC arm)	Est PEP rate (experimental arm)	Power	Sample Size per arm (no drop-out)	Sample Size per arm (with 5% drop-out)
II	10%	2.5%	0.80	128	135

Assuming PEP rate for the experimental arm is estimated to be 2.5%, while 10% for the standard-of-care arm, under one-sided alpha error of 0.05, equal allocation between the two arms and a drop-out rate of no more than 5%, then **N=135 subjects/arm** will yield a power of 80%.

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