PROCEED to Chronic Pancreatitis

(Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies)

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Lecture Outline

• RAP – CP Natural History

• Research Opportunities and Gaps: Discovery

• Future Directions: Validation, Clinical Implementation
Natural history of RAP - CP results in progressive fibrosis and loss of function

Recurrent Acute Pancreatitis

• ≥2 episodes of AP with resolution of symptomatic and imaging abnormalities between episodes
• Occurs in ~20% of AP patients
• RAP is the strongest risk factor for progression to CP
  – HR of 4.57 (95% CI 3.40-6.14)

### Progression from AP to CP: Population studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Sample size</th>
<th>Follow up (years)</th>
<th>Etiology</th>
<th>CP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>1985-90</td>
<td>9579</td>
<td>5</td>
<td>All</td>
<td>6</td>
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<tr>
<td>Germany</td>
<td>1997-2004</td>
<td>532</td>
<td>7.8 (median)</td>
<td>All</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol</td>
<td>13</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Idiopathic</td>
<td>None</td>
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<tr>
<td>Japan</td>
<td>1987</td>
<td>714*</td>
<td>13 (min.)</td>
<td>All</td>
<td>15</td>
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<td>Alcohol</td>
<td>26</td>
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<td></td>
<td></td>
<td>Idiopathic</td>
<td>13</td>
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<tr>
<td>Denmark</td>
<td>1977-82</td>
<td>352</td>
<td>Until 2008</td>
<td>All</td>
<td>24</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-alcohol</td>
<td>20</td>
</tr>
<tr>
<td>USA</td>
<td>1996-2005</td>
<td>6010</td>
<td>~4</td>
<td>All</td>
<td>6</td>
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<td>Alcohol</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-alcohol</td>
<td>4</td>
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</tbody>
</table>

Conceptual framework – CP

Window of Opportunity

Inflammatory markers

Fibrosis markers

AP

Diabetes

Pain

Steatorrhea

Surgery

AP

AP

AP

Pain

AP

AP

Mechanistic Definition

A. “At Risk”
- Susceptibility factors (asymptomatic)

B. “AP-RAP”
- SAPE, then RAP
- CP biomarkers
- susceptibility to recurrence

C. “Early CP”
- Injury or stress

D. “Established CP”
- Immune dysregulation
- Acinar dysfunction
- Islet dysfunction
- Pathologic pain
- Metaplasia

E. “End Stage CP”
- Fibrosis/sclerosis
- Exocrine Insufficiency
- DM (T3c)
- Pain Syndrome
- PDAC

Therapeutic approaches

Progression pathways

Symptomatic and supportive treatment

Years → Days → Months → Months to Years → Remainder of life

- Biomarker Discover / Development
- Yellow Zone – RAP, “Early CP”

Whitcomb, DC, et al., Pancreatology 2016
Research Gaps and Opportunities

• Improve and accurate assessment of maldigestion and EPI.

• Establish simpler, less invasive tools to measure acinar and ductal cell function from more easily obtained biological specimens such as urine or blood to screen for pancreatic disease.

• Develop RAP and CP biomarkers that can be used to better define the stage, determine prognosis, assess severity, and stratify patients for medical or surgical intervention using the mechanistic definition framework.

• Develop enzyme products requiring fewer pills and with better compliance and potency.

Research Gaps and Opportunities

• Develop long-term primary acinar and ductal epithelial cell culture models.

• Explore co-culture models (eg, acinar-duct, duct-islet, acinar- islet) to identify factors that regulate exocrine cell function and restitution.

• Define mechanisms by which gene mutations/variants cause pancreatic inflammation, ductal cell malfunction, and acinar cell loss.

• Design novel therapies that target restoring pancreatic acinar cells and/or manipulate ductal cells (ie, gene and cell-based therapies, CRISPR/Cas9, CFTR correctors and potentiators).

• Develop experiments to determine the critical age and time for intervention to reestablish appropriate stem cell niches for cell-based therapies in diseases that damage the exocrine pancreas.

Uc A., Pancreas 2016.
RFA-DK- 14-027/28: Consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer

Stanford U.
Baylor U.
U.Texas - M.D. Anderson
Cedars Sinai LA
Ohio State U
U.Pittsburgh
U.Iowa
Indiana U
Mayo C
U.Florida
Kaiser F, UCSF
Stanford U.
Cedars Sinai LA
U.Texas - M.D. Anderson
Baylor U.
**PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies**

**Rationale and Study Design for PROCEED From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer**

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on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)
Adult CP_RAP Scope of Work
Four (4) Primary Objectives

1. **Establish** a model longitudinal research cohort
2. **Estimate** the risk of disease related complications
3. **Validate** predictive and diagnostic candidate biomarkers
4. **Develop** a biorepository platform to perform genetic and mechanistic studies
Adult CP_RAP Scope of Work

- Bio/Immune markers (cross-sectional, prospective)
- Genetic Studies (susceptibility, progression, complications)
- Islet Testing (CP w or w/o DM, T2 DM, PDAC)
- RCTs
- Longitudinal Cohort (Controls, Suspected CP, Definite CP)
- Metabolic studies
- Ancillary Studies (Epidemiologic analysis on longitudinal Data)
- Microbiome Analysis
- Develop Standardized criteria Imaging, etc.
Progressive chronic pancreatitis

Early markers

Late markers

Imaging / Biospecimens

Green Zone

Yellow Zone

Red Zone

Healthy

Mild

Moderate

Severe

Proteins, RNA, DNA, cytokines, miRNA, lipids, microbiome

Minimal Change

Diagnostic Window

At Risk

AP-RAP

Early CP

Established CP

End Stage CP

Susceptibility factors

SAPE, then RAP

CP biomarkers

Immunedysregulation

Acinar dysfunction

Islet dysfunction

Pathologic pain

Metaplasia

Fibrosis/sclerosis

Exocrine Insufficiency

DM (T3c)
Pain Syndrome

PDAC

Years

Days

Months

Months to Years

Remainder of life

PROCEED STUDY
# Adult Cohort Definitions

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CONTROLS</th>
<th>Suspected Chronic Pancreatitis</th>
<th>Recurrent Acute Pancreatitis</th>
<th>Chronic Pancreatitis</th>
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</thead>
<tbody>
<tr>
<td><strong>Minimal Inclusion Criteria</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Longitudinal Follow-up</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Outcomes</td>
<td>N/A</td>
<td>RAP Chronic Pancreatitis</td>
<td>Chronic Pancreatitis</td>
<td>Chronic Pancreatitis</td>
</tr>
<tr>
<td>Sample Size</td>
<td>100 (50)*</td>
<td>250 (100)</td>
<td>660 (330)</td>
<td>660 (45)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>No symptoms</td>
<td>Pancreatic Type Pain</td>
<td>Recurrent Acute Pancreatitis (2 or more AP attacks)</td>
<td>AP (one or more) and/or Chronic pain</td>
</tr>
<tr>
<td>TIGAR-O CP Risk factors</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Cambridge Imaging Grade (MRI/CT)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Grade I - II</td>
</tr>
<tr>
<td>EUS Score</td>
<td>0 - 2</td>
<td>0 - 2</td>
<td>0 - 2</td>
<td>≥3</td>
</tr>
<tr>
<td>Histology</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Fibrosis (Ammann 1-6) and either inflammation and/or acinar cell loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥5</td>
</tr>
</tbody>
</table>

Exocrine Insufficiency Type 3cDM Cancer

RAP ± Chronic pain or No symptoms

Grade III - IV AND/OR Calcifications

Fibrosis (Ammann 7-12) and Inflammation and Acinar cell loss
Standard Operating Procedures for Biospecimen Collection, Processing, and Storage

From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

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and Darwin L. Conwell, MD,† on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

(Pancreas 2018;47: 1213–1221)
PROCEED Cohort Study
Prospective collection

- **Controls (250)**
- **Acute Pancreatitis (660)**
- **Chronic Pancreatitis (660)**

- Case Report forms
  - Patient, physician
- Labs
- Imaging: CT and MRI/MRCP and DEXA
- Endoscopic Ultrasound
- Biospecimens
  - Urine
  - Blood
  - Saliva
  - stool
PROCEED Cohort Study

Sub-cohort | Yellow (suspected CP) | Red (definite CP)
---|---|---
Endpoint | Progression to definite CP | PDAC, new-onset DM
Longitudinal data | AP/RAP, biomarkers, morphology, pain/symptoms, endocrine/exocrine pancreatic insufficiency |
Biomarker in Chronic Pancreatitis (BioChiP) Study: Urine & Pancreas Fluid and Magnetic Resonance Imaging as a Non-Invasive Method for the Assessment of Pancreatic Fibrosis (MINIMAP)
New Strategy

Reduced sample needs: 3% of the original volume!

Reduced processing time: Complete processing in 8 hrs!

No compromise in protein identifications!

150 µl urine → MStern blot → DIA LC-MS
(2) *Candidate* Urine Biomarker Proteins have also been identified: **U-BioCHiP Panel**

**Figure 6.** Random Forest-based classification of quantitative maps of urine samples from CP patients (bicarbonate <75 meq/L, red dots) and controls (bicarbonate >80meq/L, blue dots) identifies CLIP2 and ATAD2 as best classifiers. Xy-scatter plot for these two proteins. Green arrowheads indicate misclassified urine samples based on separation indicated by grey line.

\[ \text{AUC} = 0.89 \]
Endoscopic (ePFT) Collection of Pancreas Fluid
A “Bridge” to Translational Research

Pancreatic fluid collection

Time (min) 0 15 30 45 60

Secretin injection

Paulo JA et al., Pancreas. 2010
Paulo JA et al., Electropheresis 2010
Paulo JA et al., Proteomics Clin Appl. 2010
Paulo JA et al., J Immunol Methods. 2011
Hart PA et al., Am J Gastro 2016

www.epft.net
Candidate Pancreas Fluid Biomarker Proteins have been identified for CP: P-BioChiP Panel

Figure 4. Random Forest-based classification of pancreatic fluid proteomes associated with CP patients and controls (NP). A) Scatter plots of the members of the protein panel with the best classification performance. B) Resulting ROC curve with an AUC of 0.89. C) Principal Component Analysis of the 18 pancreatic fluid specimens based on the 5 protein biomarker panel; red: CP; blue: NP. Green arrowheads indicate misclassified samples.

AUC = 0.89
Conclusion:

1. PJ PGE2 concentrations are elevated in CP and MCCP
2. PJ PGE2 concentration may be useful diagnostically
3. In addition, our findings support the concept that COX-2 inhibition might modify disease progression at early stages.

PAIR STUDY -preliminary data

AUC = 0.89

Abu Dayyeh, BK et., Clin Transl Gastro 2015
Magnetic Resonance Imaging as a Non-Invasive Method for the Assessment of Pancreatic Fibrosis (MINIMAP)

Evan L. Fogel, M.D. and Temel Tirkes, MD
Indiana University Hospital
Indianapolis, Indiana
Magnetic Resonance Imaging as a Non-Invasive Method for the Assessment of Pancreatic Fibrosis (MINIMAP)
T1 mapping
Diffusion-Weighted Imaging

- Measures free motion of water molecules within the tissues
- More time-consuming: 5-7 minutes to perform
Secretin-stimulated MRCP

- Time: 10-12 minutes
- Provides information about ductal anatomy as well as exocrine volume, function of the pancreas

2D thick slab MRCP before secretin

Increased caliber of pancreatic duct, 2min after secretin

Return to baseline of PD 15 minutes after secretin, with increased duodenal fluid
Chronic Pancreatitis Risk Score

*MRI + PE-1 + Nausea (0-6)

Low = 0 pts
No pancreatic Disease (10%)

Interm = 2 pts
Equivocal (50%)

High = 4-6 pts
Chronic Panc (>85%)

Non-invasive
-urine
-UBioChiP

Invasive
-pancreas fluid
-PBioChiP

OSU_protein
Urine Biomarker

PGE2
Pancreas fluid Biomarker

*Note - MRI rules out PDAC
Probability of CP (%):
0 pts(10), 2 (50), 4(86), 6 (92)
OSU protein AUROC =0.878
Conceptual framework – CP

Conclusion

• PROCEED - Prospective Longitudinal Cohort

  – Natural History of RAP to CP

  – Natural History of CP and sequelae

  – Framework for Biomarker Discovery and Validation

  – Multicenter Collaboration