Request for Renewal of a Trans-NIH RFA Initiative: Chronic Pancreatitis, Diabetes and Pancreatic Cancer Consortium

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Purpose

The Consortium was established to gain insight into the pathophysiology of chronic pancreatitis and its sequela: chronic pain, pancreatic insufficiency, T3cDM and the diabetes/pancreatic cancer association.
Ancillary Studies

- NOD is a high-risk cohort for PDAC
- Minority populations at increased risk of PDAC in NOD
- Immune Profiling in Patients with Pancreatitis and PDAC Associated DM
- Investigating NMU roles in Type 3c DM associated with CP and PDAC

**Type 3cDM** – diabetes caused by disease of the exocrine pancreas (e.g. CP, PDAC)

**CPDPC Consortium Infrastructure**

- NIDDK Supported Research
- NCI Supported Research

**Consortium Steering Committee**

- Funding 60% NIDDK + 40% NCI
Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Consortium

**Consortium has 4 large projects** –

Chronic Pancreatitis – PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED)

Pediatric Pancreatitis – INternational Study Group of Pediatric Pancreatitis: In search for a cure (INSPPIRE)

Type 3c Diabetes – Evaluation of a Mixed Meal Test for Diagnosis and characterization of Pancreatic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis (DETECT)

**New-Onset Diabetes** (NOD)
CPDPC Ancillary Studies

- Small exploratory studies (short/intermediate term)
- Hypothesis driven
- Utilize existing consortium resources
- Future validation in prospective cohorts

Examples –
- Immune Profiling in Patients with RAP, CP and PDAC Associated DM
- Investigating NMU (Neuromedin U) roles in Type 3c DM associated with CP and PDAC
New-onset diabetics, age 50-85, are at elevated risk of pancreatic ductal adenocarcinoma (PDAC):

- Cumulative incidence rate over 3 years – 0.85%*
- 6-8 fold higher risk of being diagnosed with PDAC within 3 years of developing diabetes
- 25-40% of patients with PDAC develop diabetes between 6 and 24 months prior to PDAC diagnosis

*Gastroenterology 2005;129:504.
New-Onset Diabetes (NOD) Project

A cohort of 8,000 NOD patients will be recruited with goals:

1. Estimating the probability of PDAC in a cohort of new onset diabetes
2. Establishing a biobank of clinically annotated biospecimens, to establish a reference set of specimens for pre-diagnostic PDAC and other diabetics
3. Performing validation studies of promising biomarkers for identification of occult PDAC
4. Provide a platform to develop future interventional and screening protocols for early diagnosis

- Early detection of PDAC will require asymptomatic subjects in a high-risk population
- New-Onset Diabetes (NOD) is a high-risk population
Timeline

9/2015
CPDPC Funded

2016
Site PIs Funded
CPDPC WGs Formed
Cohort Studies planned
Protocols developed
IRB documents prepared

NCORP Outreach
Concept proposed
Protocol reviewed
Submitted to cIRB

9/2017
NCI Supplemental Funds –
CPDPC and NCORP

NCORP Approval

9/2018
CPDPC Site IRB approvals
NOD algorithm developed

10/2018
Sites Activated

12/2018
First Patients Recruited

IRB Applications across CPDPC/NCORP harmonized
Participating Sites

**CPDPC Sites (4000 patients)**
- Baylor College of Medicine
- Cedar Sinai
- Indiana University
- Kaiser Permanente Southern California
- Mayo Clinic
- Ohio State University
- Stanford University
- University of Florida
- University of Pittsburgh

**Estimated recruitment rates:**
- 2-3 patients / week / site
- 10-12 patients / month / site
- 9 sites = 90-100 patients / month
- One year = 1000-1200 patients

**NCORP Sites (4000 patients)**
- Kaiser Permanente Northern California
- St. Joseph’s Mercy

**Additional Sites**
- Geisinger
- Intermountain
- LSU Health Sciences Center
- HSHS St. Vincent Hospital
Accrual Challenge

- Beginning in 2018, NOD Study accrual faced several difficulties:
  - Delays in IRB approval
  - Lack of multi-lingual consent forms (e.g. Spanish)

- Recruitment pace is improving and appears promising based on the current numbers and projection for the future.
Addressing the Accrual Challenge

- High volume sites are being identified and prioritized for greater responsibility

- Patient incentives to improve participation

- Appropriate language translations for patient consent forms
Increasing Recruitment

- High volume sites (e.g. KPSC / KPNC / Geisinger)
- Multi-lingual consent forms (e.g. Spanish)
- Satellite sites
- Eligibility criteria (one elevated A1c level [≥6.5])

<table>
<thead>
<tr>
<th>6 Month Data</th>
<th>TOTAL KPSC Region</th>
<th>KPSC Region (20-30 Miles of Pasadena Facility)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total # Patients</td>
<td>Total # Patients</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3698</td>
<td>1583</td>
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</tbody>
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Reasonable expectation – patient pool increases by 7-8 fold
- Including Spanish speakers
- Eliminating confirmatory blood test
Renewal of CPDPC Consortium

Goals

- Maintain infrastructure and core facilities
- Provide a platform for clinically relevant studies using the biospecimens and cohorts accrued during the first grant cycle
- Complete enrollment and collection of biospecimens in the prospective cohort studies
- Follow-up to assess clinical outcomes
Proposed NCI Budget

- $2.3M / year for supporting infrastructure: $1.8M for 9 U01 grants for Clinical Centers and $500K for 1 U01 grant for Coordinating Center (institutional/personnel costs)

- $11.5M TOTAL for 5 years
Thank you.

Questions?

www.cancer.gov

www.cancer.gov/espanol
CPDPC Generation of Projects and Ideas

- SC identifies, deliberates and decides on projects
- Projects are additionally vetted by experts outside the consortium
- Initial funding ($270K Direct Costs) supports personnel, infrastructure, and institutional costs to participate in the consortium
- Initial funding does not include the funding for consortium-wide projects
- Projects are funded by Administrative Supplements from NCI and NIDDK
Types of Diabetes

- Type 1 Diabetes mellitus: 9.2%
- Type 2 Diabetes mellitus: 67.7%
- Type 3c Diabetes mellitus: 23.1%

Type 3c Diabetes

- Chronic Pancreatitis: 79%
- Hereditary Hemochromatosis: 8%
- Pancreatic Cancer: 7%
- Status post Pancreatic Resection: 2%
- Cystic Fibrosis: 4%

Ancillary Studies Related to NOD

- NOD is a high-risk cohort for PDAC *Gastroenterology* 2018;3:730.

- Minority populations at increased risk of PDAC in NOD (Multi-ethnic cohort) *JNCI* 2018 Jun 18

- Fasting Blood Glucose Starts Rising 30-36 months before PDAC Diagnosis *Gastroenterology* 2018;155;490.

- Model enriches NOD for PDAC: The ENDPAC score *Gastroenterology* 2018;3:730-39
Significance of PDAC Early Detection

Compelling needs for PDAC

▪ A strategy to detect PDAC at a potentially curable stage
▪ A means to identify high-risk groups for preventive interventions

Principal challenges to developing an early detection program for sporadic PDAC:

▪ Lack of an identified high risk group for sporadic PDAC
▪ Limited availability of high quality biospecimens from pre-symptomatic subjects
▪ Dearth of biomarkers of early PDAC
▪ Inability of imaging techniques to identify early PDAC
▪ Inadequate information about progression rates of preneoplastic lesions → under- and over-treatment
New-Onset Diabetes (NOD) Cohort Assembly: Principles

- Identify NOD in primary care settings
  - DM in PDAC is not usually managed by endocrinologists
- Identify NOD as close to its onset as possible
  - Median interval between meeting criteria for DM and PDAC diagnosis is ~13 months
  - 64% of DM-associated PDAC occur within 1 year of DM onset
- Use standardized biochemical criteria for diagnosis rather than physician diagnosis
  - Physician diagnosis could be delayed by months to years
New-Onset Diabetes and Hyperglycemia – Precede PDAC Diagnosis

Predicted duration of invasive PDAC before diagnosis (Sojourn time)

Lead time: 30-36 months

Mean FBG (mg/dl)

Cases (n=219)

Controls (n=440)

Hyperglycemia

Diabetes

PDAC diagnosis

Time to Diagnosis (months)
Risk of PDAC in New-Onset Diabetes – 6-8 fold Higher

Eligibility Criteria

No Elevated blood sugar
- Fasting blood glucose (<126 mg/dl)
- Glycosylated hemoglobin (HbA1c) (<6.5%)
- Random blood glucose (≤200 mg/dl)

Single Elevated blood sugar
- Fasting blood glucose (≥126 mg/dl)
- Glycosylated hemoglobin (HbA1c) (≥6.5%)
- Random blood glucose (≥200 mg/dl)

18 months

Confirmatory blood test

3 months

Consent Patient
Biospecimen Collection

NOD Cohort Timeline

Baseline
Required:
- Blood
- Patient Questionnaire
- CRF (capture EMR data)

1 year (±3 mo.)
Required:
- Blood
- FU CRF

2 year (±3 mo.)
Required:
- Blood
- FU CRF

3 year (±3 mo.)
Required:
- FU CRF
  (PDAC endpoint)

6 months
(±2 mo.)
Only blood collection

Required Visit:
- Blood
- FU CRF