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)
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 Diabetes (NOD) Background

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

NCORP Approval
Protocol reviewed
Submitted to cIRB

9/2017
NCI Supplemental Funds –
CPDPC and NCORP

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])

### Total KPSC Region

<table>
<thead>
<tr>
<th>6 Month Data</th>
<th>TOTAL Patients</th>
<th>KPSC Region (20-30 Miles of Pasadena Facility)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>3698</td>
<td></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**

- **CP (Chronic Pancreatitis)**: 79%
- **PDAC (Pancreatic Cancer)**: 8%
- **Hereditary Hemochromatosis**: 2%
- **Status post Pancreatic Resection**: 4%
- **Cystic Fibrosis**: 7%

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

Gastroenterology 2018;155;490
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
NOD Cohort Timeline

Baseline

- Blood
- Patient Questionnaire
- CRF (capture EMR data)

1 year (±3 mo.)

- Blood
- FU CRF

2 year (±3 mo.)

- Blood
- FU CRF

3 year (±3 mo.)

- FU CRF (PDAC endpoint)

Required Visit:
- Blood
- FU CRF

6 months (±2 mo.)

Only blood collection