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

Joint RFA Initiative: NIDDK, NCI and NIAAA

June 23-24, 2014
Participating Institutes

National Cancer Institute

Division of Cancer Prevention
- Jo Ann Rinaudo, Ph.D.
- Sudhir Srivastava, Ph.D., M.P.H.

Division of Cancer Control and Population Sciences
- Mukesh Verma, Ph.D.

Division of Cancer Biology

Division of Cancer Treatment and Diagnosis
Participating Institutes

National Institute of Diabetes and Digestive and Kidney Diseases
Division of Digestive Diseases and Nutrition
- Jose Serrano, MD, Ph.D.
- Dana K Andersen, M.D.
- Stephen James, M.D.

National Institute on Alcohol Abuse and Alcoholism
Division of Metabolism and Health Effects
- Gary J. Murray, Ph.D.
Background
Chronic Pancreatitis

- Progressive, debilitating and incurable disease
- Fibrosis leads to loss of both endocrine and exocrine pancreatic function
  - Resulting in nutritional and metabolic disease – diabetes
- Risk of **pancreatic carcinoma** increases with duration of disease

Unclear what factors are involved in the initiation of chronic pancreatitis, progression to severe fibrosis, and transformation into pancreatic cancer.
### Risk of Pancreatic Ductal Adenocarcinoma (PDAC)

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Risk Factor</th>
<th>OR, Confidence Interval*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Smoking</td>
<td>1.75 CI 1.61-1.87</td>
<td>Iodice 2008</td>
</tr>
<tr>
<td></td>
<td>Alcohol (&gt;4 drinks/day)</td>
<td>1.5</td>
<td>Lucenteforte 2012</td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td>Chlorinated hydrocarbons</td>
<td>1.4-4.4</td>
<td>Andreotti, 2012</td>
</tr>
<tr>
<td></td>
<td>Polycyclic aromatic hydrocarbons (PAH)</td>
<td>1.5</td>
<td>Andreotti, 2012</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>n-nitroso containing foods</td>
<td>1.27 CI 1.09-1.48</td>
<td>Risch, 2012</td>
</tr>
<tr>
<td></td>
<td>saturated fat / animal fat</td>
<td>1.5</td>
<td>Sanchez, 2012</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td>Pancreatitis</td>
<td>5.1 CI 3.5-7.3</td>
<td>Raimondi, 2010</td>
</tr>
<tr>
<td></td>
<td>- Chronic pancreatitis</td>
<td>13.3 CI 6.1-28.9</td>
<td>Raimondi, 2010</td>
</tr>
<tr>
<td></td>
<td>- Hereditary pancreatitis</td>
<td>69.9 CI 56.4-84.4</td>
<td>Raimondi, 2010</td>
</tr>
<tr>
<td></td>
<td>Allergies</td>
<td>0.5</td>
<td>Olson 2012</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>1.5</td>
<td>Li 2012</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>1.3</td>
<td>Bracci, 2012</td>
</tr>
<tr>
<td></td>
<td>ABO blood group</td>
<td>1.65 CI 1.30-2.09</td>
<td>Risch, 2012</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>BRCA2</td>
<td>3.5 CI 1.87-6.58</td>
<td>Klein 2012</td>
</tr>
<tr>
<td></td>
<td>STK11/LKB1</td>
<td>132 CI 44-261</td>
<td>Klein 2012</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>Familial**</td>
<td>Jones, 2012</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>12-38</td>
<td>Klein 2012</td>
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<tr>
<td></td>
<td>CFTR</td>
<td>5.3-6.6</td>
<td>Raimondi 2009</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td>Familial**</td>
<td>Raimondi 2009</td>
</tr>
<tr>
<td></td>
<td>APC</td>
<td>4.46 CI 1.2-11.4</td>
<td>Raimondi 2009</td>
</tr>
<tr>
<td></td>
<td>Mismatch repair genes</td>
<td>0 – 8.6</td>
<td>Klein 2012</td>
</tr>
<tr>
<td></td>
<td>PALLD</td>
<td>Familial**</td>
<td>Pogue-Geile 2006</td>
</tr>
<tr>
<td></td>
<td>1q32.1</td>
<td>0.77 CI 0.71-0.84</td>
<td>Petersen 2010</td>
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<tr>
<td></td>
<td>13q22.1</td>
<td>1.26 CI 1.18-1.35</td>
<td>Petersen 2010</td>
</tr>
</tbody>
</table>
## Risk of Pancreatic Ductal Adenocarcinoma

### At-Risk Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard Ratio (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pancreatitis (CP)</td>
<td>5 – 13</td>
</tr>
<tr>
<td>Hereditary Pancreatitis</td>
<td>56 – 84</td>
</tr>
<tr>
<td>3 Affected First Degree Family Members</td>
<td>17</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus (T2DM)</td>
<td>1.5 – 2.0</td>
</tr>
<tr>
<td>T2DM + CP</td>
<td>12 - 33</td>
</tr>
<tr>
<td>Type 3c Diabetes Mellitus (T3cDM)</td>
<td>?</td>
</tr>
</tbody>
</table>

Pancreas Initiative – NCI BSA June 23-24, 2014
Distribution of Type 1, 2 and 3c Diabetes
Potential Causes of Type 3c Diabetes

- **T2DM** 80%
- **T1DM** 12%
- **T3cDM** 8%

- **Pancreatic neoplasia** 9%
- **Hemochromatosis** 8%
- **Pancreatic resection** 3%
- **Cystic fibrosis** 4%
- **Chronic pancreatitis** 76%

*Curr Opin Endocrinol Diabetes Obes 2013, 20:81.*
Diabetes and Cancer

- Diabetes increases risk for cancer

- 75% of pancreatic cancer patients have diabetes\(^1\)

- 50% of diabetes associated with cancer is secondary or T\(_3\)cDM (pancreatogenic) \(^1\)

- In 20% of pancreatic cancer patients, the onset of diabetes occurs when patients are asymptomatic for cancer\(^2\)

- Potential high risk group for screening

\(^1\)Curr Opin Endocrinol Diabetes Obes 2013, 20:81.

\(^2\)Panreatology 2012, 12:156.
Scientific Discussion for Unmet Clinical Needs

- NIDDK (June 2012) and NIDDK/NCI (June 2013) sponsored workshops to discuss:
  - Type 3c Diabetes Mellitus (T3cDM) and risk of pancreatic cancer
  - Basic and translational studies in the area of chronic pancreatitis
  - Risk factors which link chronic pancreatitis, diabetes, and pancreatic cancer
  - Strategies and therapeutic targets to reduce the burden of disease

- NCI’s Scientific Framework for Pancreatic Ductal Adenocarcinoma, February 2014

  “The NCI will continue to work with NIDDK to develop new funding opportunities for studying the diabetes-PDAC connection.”
NCI Strategic Goals

- **Identify patients at high risk** for developing pancreatic cancer
- **Develop methods** (e.g. *in vitro* diagnostic and/or imaging) to:
  - Detect early stage pancreatic cancer
  - Detect *Pancreatic intraepithelial lesions* (PanINs)
  - Distinguish low vs. high risk *intraductal papillary mucinous neoplasms* (IPMNs)
  - Distinguish low vs. high risk *mucinous cystic adenomas*
- **Determine the relationship** between T3cDM and pancreatic cancer
Organizational Structure of the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer

**Governance:**
- Steering Committee & NIH Staff

- **IC repository for bio-specimens**
- **Specialized imaging, genetic and molecular profiling labs**

**Data Coordinating Center**

**Clinical centers (Adult and Pediatric)**
Research Objectives:

Identify fibrosis markers in patients with acute or recurrent pancreatitis who progress to chronic pancreatitis.

Detect and quantify pancreatic fibrosis and pancreatic cancer.

Trials to determine efficacy of treatment strategies to improve symptoms and outcome (anti-fibrosis for (early) chronic pancreatitis; metformin for prevention of diabetes and pancreatic cancer in patients with chronic pancreatitis.

Determine which combination(s) of genetic and/or environmental factors give rise to pancreatic cancer.
Research Objectives:

Epidemiological studies to establish the incidence and prevalence of Type 3c diabetes (T3cDM).

Studies to establish the risks of acute/chronic pancreatitis and pancreatic cancer in patients with Type 2 (T2DM) diabetes treated with incretin-based therapy.

Studies of “high risk” patients to evaluate genomic, proteomic, and hormonal markers of early pancreatic cancer.

Conduct pilot surveillance studies and generation of survivorship registries; and identification of factors that may contribute to disparity in incidence of pancreatic cancer among populations.
Examples of Deliverables from Consortium:

- Recruitment: 1200 patients (3-4 patients/month x 48 months x 8 sites)
- Longitudinal assessment of progression
  - Identify markers for fibrosis progression to chronic pancreatitis and cancer
  - Develop methods to detect pancreatic fibrosis and evaluate T3cDM as a possible biomarker of pancreatic cancer
  - Epidemiological survey for risk factors
- Serial samples
  - Plasma, serum, DNA
  - Stool, urine
  - Duodenal / pancreatic aspirates
  - Diagnostic biopsies, pancreatic resections
  - Imaging – EUS, secretin–MRCP

Pancreas Initiative – NCI BSA June 23-24, 2014
Rationale for RFA

This RFA is addresses specific high priority needs not adequately met by any other programs at NIDDK, NCI or NIAAA.

The proposed clinical research network will provide the resources (patients and biospecimens) and collaborative opportunities necessary for achieving theses goals in pancreatic disease research.
Rationale for Consortium and Cooperative Agreement Award

- Uniform data collection, protocols, and analyses
- Common Data Elements (CDEs) for serial sample collection and clinical annotation
- Reproducibility of data collection including verification and auditing
- Central management of IRB, MTA and protocols

A consortium of centers will aide in the recruitment of sufficient patients, in the collection of bio-specimens, and will help ensure the sharing of these resources. No single site has resources to achieve these goals.

The cooperative agreement mechanism will allow NIH program staff to guide and support the research to facilitate meeting the IC goals.
U01 Funding Budget

Anticipated Number of Awards:
- 7-9 clinical centers and 1 Data Coordinating Center

Length of Award in Years:
- 5

Repository Data and Bio-specimen repository:
- Consortium and NIDDK repository

Funding Requested:
- NIDDK: $3.5 million/year (Approved NIDDK Council for FY15)
- NCI: $2 million/year
- NIAAA: $0.5-1 million/year
Thank you!

Questions?