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The Agenda for Accelerating Pancreatic Research

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This issue of *Pancreas* contains several articles that document the work of the most recent National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop on “Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis: Knowledge Gaps and Research Opportunities,” (Fig. 1) as well as articles that describe the work of The Consortium for the Study of Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) (Fig. 2). These programs are related to each other, and represent a sustained effort to advance the understanding and treatment of pancreatic diseases.

For the past six years, the Division of Digestive Diseases and Nutrition at NIDDK has sponsored multiple workshops which brought together experts from a spectrum of disciplines to identify the research needed to advance our understanding and treatment of pancreatic disease. These included workshops on the mechanisms of the etiology, inflammation and repair processes in acute and chronic pancreatitis,¹ the relationships of pancreatitis and diabetes as risks and consequences of pancreatic cancer,² the role of total pancreatectomy with islet auto-transplantation for the treatment of refractory chronic pancreatitis,³ the role of new technological developments in bioimaging and bioengineering for the identification of useful biomarkers of pancreatic disease,⁴ the pathobiology and obstacles for further progress in chronic pancreatitis,⁵ advances in endoscopic ultrasound for the diagnosis and treatment of pancreatic disease,⁶ and the interface of pancreatic cancer with diabetes, obesity, and inflammation.⁷ These workshops have helped to create several multidisciplinary networks of investigators who are unraveling the complex mechanisms of both benign and malignant pancreatic disease. Most importantly, the current workshop now engages the Food and Drug Administration in developing a path forward for the treatment of pancreatitis, and in assisting with the guidance for future drug trials in acute, recurrent acute, and chronic pancreatitis. The articles in this issue related to the “Accelerating the Drug

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Delivery Pipeline for Acute and Chronic Pancreatitis: Knowledge Gaps and Research Opportunities” workshop represent a significant effort by several working groups to develop a roadmap needed to quicken the progress in addressing the unmet medical needs to improve outcomes in patients with pancreatitis diseases.

Since 2013 each workshop summary has been published in *Pancreas*, and some have been co-published in other journals to reach an even wider audience. The recommendations outlined in the summaries have provided strong bases for several investigator-initiated research grants which have received NIDDK funding. Although basic research in pancreatic disease has received support, clinicians appreciate the fact that few studies have expanded our ability to diagnose pancreatic diseases at an early enough timepoint to alter the course of disease, or to provide effective medical treatment. The need for clinical translational studies has been a common priority cited in all the workshops, and led directly to the support for the CPDPC.

THE FORMATION OF THE CPDPC

With an unexpectedly strong response and attendance at the 2013 workshop on “Pancreatitis-Diabetes-Pancreatic Cancer” there was general appreciation at NIDDK and the National Cancer Institute (NCI) that the role of pre-malignant diseases and risk factors needed to be examined within the domain of clinical studies.² An additional incentive for action was provided by grass roots efforts to improve outcomes in pancreatic cancer patients which resulted in the Recalcitrant Cancer Act passed by the US Congress in 2012 and signed by President Obama in 2013. The coalescence of these events led to the recognition that only with large scale human cohort studies could the complex relationships between chronic pancreatitis and diabetes and pancreatic cancer be deciphered and mechanistically investigated especially considering that diabetes acts both as a risk factor and as a product (and harbinger) of pancreatic cancer. These areas of unmet need and the mandate to develop new strategies for early detection and prevention of pancreatic cancer served as a focus for the support for Requests for Applications (RFAs) for a consortium of clinical centers and a coordinating center (<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-027.html>, <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-028.html>) issued in 2014 in a unique collaborative sponsorship by NIDDK and NCI, and is further described in the article by Serrano et al.⁸

The consortium took on the name of The Consortium for the Study of Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). The overriding objectives of CPDPC are to pursue clinical research in children and adults to determine the natural history and mechanism by which acute, recurrent and chronic pancreatitis and pancreatogenic or Type 3c Diabetes Mellitus (T3cDM) predict and promote pancreatic cancer.^{9–11}

THE PROGRESS OF THE CPDPC

There has been significant progress within the CPDPC consortium through the efforts of its working groups and committees. The main goals of the CPDPC are to establish large prospective cohorts of deeply phenotyped patients, with a robust collection of biospecimens

for analysis by clinicians and investigators in the future. The cohort studies have been developed by the working groups of the Consortium, and include both adult and pediatric patients with proven chronic pancreatitis, suspected or possible chronic pancreatitis, and acute relapsing pancreatitis. These cohorts INSPPIRE2 (INternational Study Group of Pediatric Pancreatitis: In Search for a Cure) developed by the chronic pancreatitis and acute relapsing pancreatitis (CP-ARP) Pediatrics Working Group¹² and PROCEED (PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies) developed by the CP-ARP Adult Working Group¹³ are actively recruiting subjects, and these specimens and cohorts will form the platform for future studies defining etiology, diagnostic criteria, natural history, prevention of progression, and individualized therapy in chronic and acute relapsing pancreatitis. A very large cohort of patients at increased risk of pancreatic cancer, those with new onset diabetes above the age of 50 (the New-Onset Diabetes [NOD] cohort), developed by the Diabetes and Pancreatic Ductal Adenocarcinoma (DM-PDAC) Working Group¹⁴ is now also recruiting through the CPDPC and other collaborators, with comprehensive collection of biospecimens and follow-up to provide the infrastructure for identification of biomarkers of very early stage, pre-symptomatic pancreatic cancer. As this cancer presents late and remains highly lethal, this work may finally allow strategies for early detection. Finally, a large cross-sectional study (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis [DETECT]) developed by the Type 3c diabetes mellitus (T3cDM) Working Group is identifying the mechanisms and diagnostic criteria for diabetes associated with chronic pancreatitis and pancreatic cancer, to provide insights into the complex relationships among these three conditions.¹⁵ Each of these working groups are currently also pursuing numerous parallel ancillary studies, including studies of etiology, diagnostic criteria, biospecimen handling and collection, mechanistic studies, and intervention trials. The efforts of these working groups, described in the accompanying papers in this issue of *Pancreas*, will ultimately provide a rich and unique resource for the entire community of clinicians, investigators, and patients so motivated and dedicated to progress in finding solutions for benign and malignant pancreatic diseases.

PARTNERS IN THE AGENDA

The product of the NIDDK workshops and the progress of the CPDPC have been greatly facilitated by several partners, including the National Pancreas Foundation, the Kenner Family Research Fund, and the Pancreatic Cancer Action Network. Further, organizations such as the American Pancreatic Association and PancreasFest have provided a venue for updates and workshops devoted to these efforts. Finally, the support of the journal *Pancreas*, through its editor-in-chief, Vay Liang W. Go, MD, has been an especially valuable partner and promoter of this collaborative effort. We are grateful to all our partners for their support.

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Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis:

Knowledge Gaps and Research Opportunities

FIGURE 1.
“Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis: Knowledge Gaps and Research Opportunities” workshop.

FIGURE 2.

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