Scientific Framework for

Pancreatic Ductal Adenocarcinoma (PDAC)

National Cancer Institute

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Scientific Framework for Pancreatic Ductal Carcinoma

Executive Summary

Significant scientific progress has been made in the last decade in understanding the biology and natural history of pancreatic ductal adenocarcinoma (PDAC); major clinical advances, however, have not occurred. Although PDAC shares some of the characteristics of other solid malignancies, such as mutations affecting common signaling pathways, tumor heterogeneity, development of invasive malignancy from precursor lesions, inherited forms of the disease, and common environmental risk factors, there are unique obstacles that have made progress against PDAC difficult. These include: diagnosis at a late stage in the disease because of a lack of specific symptoms or biomarkers to facilitate early diagnosis, and the anatomical location of the pancreas; metastatic spread when the primary tumor is too small to detect by current methods; dynamic interaction of the tumor with stromal cells creating dense fibrous tissue around the tumor that contributes to therapeutic resistance; and the small percentage of patients for whom curative surgery is a feasible option.

The Recalcitrant Cancer Research Act of 2012 (Public Law 112-239, §1083) calls upon the National Cancer Institute (NCI) to "develop scientific frameworks" that will assist in making "progress against recalcitrant or deadly cancers." PDAC is a recalcitrant cancer as defined by its five-year relative survival rate of less than 5 percent that translates into the loss of almost 40,000 lives per year. Consensus within the scientific community regarding the limited early diagnostic or therapeutic approaches for patients with PDAC has provided a stimulus for the evaluation of new and missed opportunities that could now be applied to the existing portfolio of PDAC research in order to make more substantial progress.

The current state of knowledge in PDAC research, including epidemiology, risk assessment, pathology, screening, early detection, and therapeutic research was evaluated by an expert panel of extramural scientists that helped the NCI identify and prioritize new scientific ideas, technologies, and resources that might advance the field and improve the outlook both for patients with PDAC and for individuals at high risk of developing the disease. Four investigational initiatives developed by this group of experts were recommended for consideration by the NCI to incorporate within the existing research portfolio for PDAC: (1) development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus of recent onset; (2) evaluation of longitudinal screening protocols, concomitant with the development of new molecular and imaging biomarkers, for patients at high risk for PDAC (because of genetic factors or the presence of mucinous pancreatic cysts) who could be candidates for early surgical intervention; (3) implementation of new immunotherapy approaches based on a deeper understanding of how PDAC interacts with its potentially immunosuppressive microenvironment; and (4) development of new treatment strategies that interfere with *RAS* oncogene-dependent signaling pathways.

Plans for implementation of these recommended initiatives, within the context of NCI's current research framework for PDAC, have been developed. In addition, an overall process for evaluating progress and providing oversight for the NCI's PDAC research portfolio is in place to meet the goals of the Recalcitrant Cancer Research Act of 2012.

Introduction

The Recalcitrant Cancer Research Act of 2012 (Public Law 112-239 §1083) defines recalcitrant cancers as those cancers with a five-year survival rate below 50 percent. The Act requires the NCI to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20% and cause more than 30,000 deaths per year in the United States and to develop a scientific framework for the conduct or support of research for each of these cancers.

This report, prepared by the NCI, National Institutes of Health (NIH), for submission to Congress and posting on the Department of Health and Human Services (DHHS) website, focuses on the NCI's scientific framework for pancreatic ductal adenocarcinoma (PDAC). This report fulfills the provision of the Act that the NCI develop a scientific framework for the first of two identified recalcitrant cancers within 18 months of enactment (by July 2, 2014). The scientific framework will be sent to Congress and made available publicly on the website within 30 days of completion. A separate report from a workshop held at the NCI on October 23 and 24, 2012, that was attended by the NCI Director and other Federal and non-Federal experts, and that was conducted to assist with the expansion of the NCI's existing scientific framework for PDAC, is attached as an appendix.

Background

Pancreatic cancers are a group of heterogeneous diseases of both the endocrine and exocrine pancreas. PDAC, an exocrine tumor, represents over 90% of all pancreatic malignancies[1]. Endocrine tumors of the pancreas, such as those that arise from pancreatic islets, represent 3-5% of pancreatic neoplasms; endocrine tumors are a distinct class of cancers that must be differentiated both pathologically and clinically from PDAC. Although PDAC is a relatively rare tumor (2% of all cancer cases), it is the fourth leading cause of cancer death in the United States with an average survival time after diagnosis of less than one year. The incidence of PDAC increases with age, with a median age of 71 years at diagnosis. It has been estimated that there will be 45,220 new cases of PDAC in the U.S. in 2013 with 38,460 deaths from PDAC in the same period; the incidence of PDAC has been rising slowly from 1982 to 2008 (http://www.cancer.gov/researchandfunding/reports/pancreatic-research-progress.pdf). The average lifetime risk for developing PDAC is about 1/78 for both men and women[2]. Globally, 70% of all pancreatic cancer cases occur in people living in advanced economies, with over 270,000 deaths per year worldwide[3]. Approximately 10% of PDACs occur in families with a history of PDAC[4]; some occur in association with other cancers or diseases, but most do not occur in association with a defined syndrome[5]. The overwhelming majority of PDAC cases are sporadic, that is, occurring without a history of the disease in first degree relatives.

Although much is known about the evolution of PDAC from its earliest non-malignant precursor lesions, PDAC cases are most often diagnosed at late stages: about 30% of patients have locally advanced disease and over 50% have metastases at distant sites when the disease is first diagnosed. Early detection has been problematic because of the absence of specific symptoms, the insufficiency of serological biomarkers with appropriate sensitivity and specificity, the lack of a clinically practical diagnostic examination for the disease, and the retroperitoneal position of the pancreas. Unlike many other malignant diseases, the metastatic spread of PDAC is thought to begin when the primary tumor is approximately 10 mm in size, when results of routine non-invasive imaging are often equivocal or negative[5]. Currently,

surgery (pancreaticoduodenectomy) provides the only possible curative therapy for PDAC; but less than 20% of patients are suitable candidates for this difficult procedure because the disease has already spread. Overall, surgery produces long-term, disease-free survival in only 3-4% of all individuals presenting with this disease—generally in patients with "early" PDAC (i.e., tumors $\leq$ 20 mm) and without tumor involvement in the surgical margins at resection. Evidence comparing stage of disease with outcome following surgery suggests that death rates for PDAC would be reduced if the disease could be diagnosed at an earlier stage[6,7]. Since genomic sequencing data from primary and metastatic PDACs indicate that it takes approximately 17 years for PDAC to progress from the tumor-initiating cell to the development of metastatic disease[8], it would appear that there is ample time to diagnose and intervene, if diagnostic barriers to earlier detection could be overcome.

Summary of the Literature and Recent Advances

Biology and Genetics:

PDACs arise from a ductal cell lineage or from acinar cells that undergo acinar-to-ductal metaplasia[9]. Pancreatic intraepithelial neoplasms (PanINs) are the most common precursors to PDAC, and are often found associated with areas of focal pancreatic inflammation. Certain cystic lesions of the pancreas are also premalignant: pancreatic intraductal papillary mucinous neoplasms (IPMNs) are found equally in men or women in their 60s and often communicate directly with the main pancreatic duct; mucinous cystic neoplasms (MCNs), which are overwhelmingly found in women in their late 40s[10], are often solitary cystic lesions in the body or tail of the pancreas. Virtually all PanINs, even the earliest type, PanIN-1, harbor KRAS mutations. Mutant KRAS alleles show increased expression as PanIN-1 evolves to intermediate PanIN-2, and then to the carcinoma *in situ* lesion, PanIN-3[11,12]. The few precursor lesions that do not contain mutant KRAS often have mutations in other genes in the KRAS signaling pathway, such as those in BRAF[13]. Loss of CDKN2A, a tumor suppressor, is also found in some early PanINs. It is now thought that a KRAS mutation is necessary, but not sufficient, to drive PanINs to PDAC[12,14]. Recent studies, however, have shown that in mutant KRAS-driven PDACs, KRAS is required at all states of pancreatic carcinogenesis and for subsequent tumor maintenance[15,16]. KRAS is mutated in approximately 95% of all PDACs—the highest percentage of all solid malignancies[1].

Besides mutated KRAS and the loss of CDKN2A (often referred to by the protein it encodes, $p16^{INK4a}$), genetic alterations have been found in tumor suppressor genes SMAD4 (also termed DPC4) and TP53. A more detailed genomic analysis of a large number of PDACs has uncovered an average of 63 genetic alterations, mostly point mutations, which affect up to 12 different signaling pathways or processes[17]. These include alterations in apoptosis pathways, hedgehog signaling, regulation of invasion, and signaling via KRAS, TGF-β, and Wnt or Notch. The expression of sonic hedgehog protein (a ligand of the hedgehog pathway) in both early and late PDAC lesions has been implicated as a chemoattractant in the desmoplastic response (a host stromal response resulting in the proliferation of fibrotic tissue with an altered extracellular matrix and a pronounced hypovascularity)[18].

Risk Assessment and Screening:

Risk assessment studies have been performed associating germline susceptibility genes with the development of PDAC. Many of these case-control studies were performed using registries of families with a strong history of pancreatic cancer. Individuals in these families can have up to a 13-fold increase in risk. Mutations in the following germline genes appear to have a role in susceptibility to PDAC although most do not have a high penetrance: BRCA2, STK11, PALB2, ATM, and CDKN2A[19-21]. In addition, mutations in PRSS1 and SPINK1 are associated with susceptibility for hereditary pancreatitis, which greatly increases the risk for PDAC. Other hereditary diseases and syndromes have also been shown to increase risk for PDAC; individuals with these syndromes often harbor mutations in the genes that confer risk for PDAC. Studies of the gene alterations in high risk individuals could also be important in informing studies of sporadic PDAC and lead to a better understanding of the etiology of the disease.

Among the known non-genetic risk factors are: tobacco use; age; obesity; chronic pancreatitis, including hereditary pancreatitis; and diabetes, both long-term type 2 diabetes and especially new-onset diabetes, which may be an early consequence of PDAC itself[3,20].

It has become clear that early detection of small resectable lesions, particularly pre-neoplastic lesions such as PanINs (2 and 3) and IPMNs or MCNs is the best hope for increasing the overall survival in this disease, since locally advanced and metastatic PDACs are relatively insensitive to chemotherapy or radiation therapy, and surgical resection is often followed by relapses. So far, no serum or tumor-based biomarkers or biomarker panels have been discovered that are both sensitive and specific enough for accurate early detection. CA19.9 is the most commonly used tumor biomarker for monitoring therapeutic progress in PDAC, but the lack of specificity of the assay is a concern, and CA19.9 therefore cannot be used for early detection. Progress in this area will have to come from new diagnostic discoveries—perhaps employing circulating tumor cells, tumor-derived DNA, autoantibodies, miRNA profiles, cytokines and chemokines, and from specific genetic, epigenetic, or proteomic signatures. Advances in non-invasive imaging technology that can detect tumors or pre-cancerous pancreatic lesions as small as 0.5 mm will also be needed. Invasive imaging such as endoscopic ultrasound can detect most pancreatic cysts[22,23], and targeted imaging agents have been shown to detect PanIN-3 lesions[24]. These methods of detection are expensive and cannot be used for routine screening, but could be employed in high risk individuals.

One approach is to focus screening efforts on the groups of asymptomatic individuals who have been shown to have a higher risk of PDAC than the general population: those with hereditary risk factors, environmental risk factors, or other diseases that increase the odds of developing PDAC. The risk relationship between long-standing type 2 diabetes and PDAC, based on epidemiological evidence, is well-known as is the increased risk of PDAC in patients with newly-diagnosed diabetes; the relative risk estimate for patients diagnosed with diabetes at least five years prior to a diagnosis of PDAC is 2.0 (95% confidence interval, 1.2 to 3.2)[25]. As reviewed in the Workshop Report: *Pancreatic Cancer: Scanning the Horizon for Focused Interventions* (Appendix 1), recent evidence suggests that screening for PDAC in patients with specific subtypes of diabetes, such as those newly diagnosed, and particularly in association with other risk factors (such as genetic predisposition or tobacco use), may be a particularly fruitful approach to early detection[26-28].

Models of PDAC:

The development of new, clinically-relevant treatment approaches for PDAC can benefit greatly from testing in appropriate animal models—ones that display the evolution of PDAC from the earliest lesion to frank PDAC, both morphologically and genetically, and demonstrate the hallmark features of the disease: intratumoral heterogeneity, dense desmoplasia, and early spontaneous metastases. Mouse xenografts using cultured PDAC cells are minimally useful because, although they often retain the key genetic alterations in signaling pathways of PDAC, they lack the early carcinogenic stages of the disease (when treatment might be most effective), do not exhibit a natural disease progression, and are missing the immunological and other stromal components of the tumor-host interaction normally seen in the human disease. Mutant KRAS-driven genetically engineered mouse models (GEMMs) that recapitulate key aspects of human PDAC, including non-invasive precursor lesions, have now become some of the most important tools for the study of PDAC development and invasion, as well as preclinical testing of novel therapeutic approaches[29-32]. The introduction of additional altered genes that are important in progression from early lesions to invasive PDAC has enabled the construction of specific models that faithfully follow the development of PDAC from PanINs or pancreatic cysts. It has recently been shown, using these models, that canonical Wnt/β catenin pathway activation can encode pancreatic carcinogenesis as early as the PanIN stage[33]. One caveat in the use of these models is that the altered KRAS allele, KRASG12D, is activated during embryogenic pancreatic development, which is probably not an event likely to occur in patients who later develop PDAC[31]. Nonetheless, the Pdx1-Cre;KrasG12D and the PTF1a+/Cre; KrasG12D models show a spectrum of PanINs and/or pancreatic cysts, long latency, late onset of PDAC, and frequent metastases, and can be further manipulated to speed disease progression.

Therapy and Resistance:

For over a decade, gemcitabine or gemcitabine in combination with other chemotherapy agents has been the standard of care for advanced PDAC[34]. In 2011, FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-FU) was shown to provide a modest increase in overall survival, although the toxicity was greater[35]. The addition of molecularly targeted therapies has been evaluated; to date, only erlotinib, targeting the EGF receptor, has demonstrated a modest, albeit statistically significant, response rate in combination with gemcitabine[36,37]. The recent elucidation of alterations in the various signaling pathways in PDAC and in pancreatic cancer stem-like cells may lead to the testing of new agents and combinations in the future, and to defining the patient populations that might benefit from targeted systemic therapy.

Resistance to therapy is a characteristic feature of PDAC, and the extent of resistance is greater than in many other human tumors. This could be due to inefficient drug delivery, intrinsic and acquired resistance of the tumor, tumor hypoxia, or the insensitivity of cancer stem-like cells to currently used agents. It is thought that the dense desmoplasia produced by the dynamic interaction of stromal cells with the tumor, and which constitutes 90% of the tumor volume, creates a barrier to systemic drug delivery and penetration[38]. Novel approaches employing newly-developed biological molecules, discussed in the next section, may provide a means to overcome therapeutic resistance in patients with PDAC.

NCI's Current Research and Framework for PDAC

The NCI supports major, ongoing efforts to advance the scientific understanding of the cause(s) of PDAC, to develop new tools for early diagnosis, and to devise more effective therapeutic interventions. These existing research programs, (described in the 2011 National Cancer Institute Action Plan for Pancreatic Cancer http://www.cancer.gov/researchandfunding/reports/pancreatic-research-progress.pdf), formed the scientific foundation from which new areas of emphasis were developed by the recent PDAC workshop (Appendix 1).

Basic PDAC Biology:

The NCI currently supports research programs dedicated to advancing progress in understanding the basic biology of PDAC. These programs involve studies to further elucidate the biology of the normal pancreas, including interdisciplinary approaches to understand islet cell development and function, the characterization of signaling pathways suspected to play a role in the development of PDAC, and large-scale genomic studies, including those of The Cancer Genome Atlas, that are developing a detailed understanding of the molecular underpinnings of PDAC development and evolution. Studies of the interactions between the microenvironment within which PDACs develop and host factors, such as the response of the immune system to inflammatory stress, are attempting to understand the biological alterations that play an essential role in the progression of early PanIN lesions to PDAC.

Risk, Prevention, Screening, and Diagnosis:

The NCI provides resources for epidemiologic studies, including those involving several case-control and cohort consortia, to determine the role of environmental and genetic factors on the risk of developing PDAC. These investigations examine the influence of smoking, obesity, and physical activity on PDAC development. Several studies are also evaluating the potential of dietary factors to prevent or modify the initiation and progression of PDAC.

Efforts to develop new diagnostic markers in serum for the early detection of PDAC are ongoing. Improving the capabilities of several different imaging techniques to enhance their sensitivity, enabling the detection of pre-neoplastic pancreatic cysts and small tumors that would both be amenable to complete surgical resection, is also a priority. Diagnostic and screening studies are being pursued both in laboratory models and through the expansion of registries for patients and families at high risk of developing PDAC.

Treatment:

Because of the ineffectiveness of most current therapies, the NCI is investing in a wide range of approaches to improve the treatment of PDAC. These approaches are being pursued both in preclinical model systems and in clinical trials. Emphasis has been placed on understanding whether specific signaling pathways can be targeted for therapeutic benefit in PDAC. In particular, studies attempting to interfere with the dense stromal reaction that interferes with the delivery of therapeutic agents to both PDAC cells and the surrounding microenvironment (including new nanoparticle drug formulations) hold the promise of overcoming resistance to currently-available agents[39-42].

In addition to drugs targeting specific molecular pathways, biological therapies are under study. Biological treatments being evaluated in animal models and patients include: vaccines (incorporating highly immunogenic tumor-specific antigenic targets); monoclonal antibodies and other direct targeting agents such as immunotoxins; adoptive cellular therapies, particularly in patients with resectable tumors; various gene therapy methodologies; and oncolytic viruses (replicative competent viruses with selective tropisms for tumors but not normal cells)[43-45]. One biological approach currently supported by the NCI that is of major interest has been the adoptive transfer of genetically modified T lymphocytes that express a chimeric antigen receptor (CAR), an approach that has demonstrated significant therapeutic benefit in preclinical models of PDAC[46].

Patients with PDAC often experience debilitating symptoms that markedly diminish their quality of life. The degree of pain, fatigue, or anorexia that commonly accompanies PDAC often prevents the administration of standard treatment or participation in clinical trials. Thus, ongoing efforts to understand the etiology of and to develop treatment for fatigue and cachexia are important components of NCI-supported clinical research in the area of symptom management.

Training:

NCI has recognized the need for a dedicated workforce to conduct pancreatic cancer research across a wide range of investigational topics. Research training in the area of PDAC has grown substantially over the past decade and now supports investigators in pre-doctoral and post-doctoral positions, as well as independent early-career scientists and clinical trialists. NCI-supported scientists are being trained to investigate the biology, epidemiology, and genetics of PDAC and other malignancies, as well as combined modality approaches to treatment and the development of clinical trials with targeted agents, and the signal transduction pathways involved in drug resistance for these diseases.

Support for PDAC Research by NCI: Grants, Contracts and Cooperative Agreements:

To support this ongoing research framework, the NCI invested $105 million in fiscal year 2012 for pancreatic cancer research, a 5-fold increase since 2000 ($20 million; Figure 1). This investment includes funding in the form of grants, cooperative agreements, and contracts to extramural scientists and trainees (93%) and to NCI intramural investigators (7%) involved in basic, pre-clinical, translational, and clinical pancreatic cancer research. Awards have been made to support traditional investigator-initiated R01 research, Program Project Grants, Cancer Center Support Grants, Specialized Programs of Research Excellence (SPOREs), and other P50 grants, exploratory/development grants, small business awards, training and fellowship grants, cooperative agreements, intramural research, and other funding mechanisms (Figure 2).

The number of investigators supported by R01 grants for pancreatic cancer research has also increased since 2000 (Figure 3). Realizing that it is important to attract to the field new investigators (those who have never obtained a substantial NIH independent research award) and early stage investigators (new investigators who are, in addition, within 10 years of completing a terminal degree or a medical residency), the NCI has made an effort to fund these

investigators who are embarking on a career in pancreatic cancer research. Figure 4 shows the number of extramural scientists who received pancreatic cancer research funding, utilizing all mechanisms, from the NCI in 2012. Although the majority of the grants were awarded to experienced investigators, a significant number of grants were awarded to new and early stage investigators, and most of these grants had 100% relevance to pancreatic cancer. As one might expect, the total number of dollars awarded to new and early stage investigators studying PDAC is considerably less than that awarded to experienced investigators because many of the new awardees obtain fellowship, training, and exploratory grants, which have lower cost caps. Table 1 contains a list of the funding mechanisms and numbers of grants awarded to the next generation of researchers who are working on PDAC and supported by the NCI. The full data can be reviewed using the following link: http://tiny.cc/deyv7w

If one considers NCI's total investment per year in research relevant to PDAC, the amount is much greater than $105 million because many areas of study that are central to PDAC research—the KRAS signaling pathway (and its interaction with and activation of other pathways), genetic risk factors and somatic mutations, tumor suppressor genes, immune responses to solid tumors, diagnostic and screening technology development, combination therapeutic strategies including drug discovery and development—are shared with studies of other types of cancers and are supported by numerous NCI grants and contracts as well.

Research Resources:

Beyond grants, the NCI has many resources all of which are available to researchers working on PDAC and many other relevant cancers. Over 100 scientific resources are available to qualified scientists. The resource topics include: animals and animal models; drug and biological drug development, manufacturing, screening, and repositories; epidemiology and statistics; human and animal specimen collection and distribution; scientific computing; and family registries and cancer genetics (https://resresources.nci.nih.gov). Specific areas of interest to pancreatic cancer research are: **The Cancer Genome Atlas (TCGA)** program which generates comprehensive profiles of gene expression, epigenetic modifications, copy-number variation, and somatic mutations in tumors together with matched normal DNA sequence information and provides a platform for researchers to search, download, and analyze data sets generated by TCGA; the **Early Detection Research Network (EDRN),** a network of laboratories and centers (Biomarker Developmental Laboratories; Biomarker Reference Laboratories; Clinical Validation Centers; Data Management and Coordinating Center) whose goal is to accelerate the translation of biomarkers into clinical applications and to evaluate new ways of testing cancer in its earliest stages; the **Clinical Proteomic Tumor Analysis Consortium (CPTAC)** which systematically identifies proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public; the **Mouse Models of Human Cancers Consortium (MMHCC)** which derives and characterizes mouse models, and generates resources, information and innovative approaches to the application of mouse models in cancer research; the **NCI Clinical Trials Network (NCTN)** which conducts definitive, randomized, late phase clinical treatment trials and advanced imaging trials across a broad range of diseases and diverse patient populations as part of the NCI's overall clinical research program for adults and children with cancer. The **Specialized Programs of Research Excellence (SPOREs)** is a grant program in translational research that uses a team science, multidisciplinary approach to focus on specific organ site cancers. There are currently three pancreatic cancer SPOREs and

one gastrointestinal SPORE that has pancreatic cancer-related projects. An additional two SPOREs are supporting approaches to the targeting of KRAS. Each of these grants is required to have a biospecimen/pathology CORE (to collect, analyze, store, and annotate specimens) which in addition to supporting the research in the grant has the obligation to share specimens with the scientific community. SPOREs also provide opportunity for collaboration, including international collaboration, through the Developmental Research Program in each grant. Examples of SPORE research resources and projects related to pancreatic cancer can be found using these links: http://trp.cancer.gov/spores/pancreatic.htm; http://trp.cancer.gov/spores/gi.htm.

For investigators studying PDAC, another resource is the **International Cancer Research Partnership (ICRP)**. The ICRP, established in 2000, is an alliance of public and private cancer research funding organizations from around the world working together to enhance global collaboration and strategic coordination of research. Members who fund pancreatic cancer research include the NCI, Pancreatic Cancer Action Network, Canadian Cancer Research Alliance, Dutch Cancer Society, National Pancreas Foundation, National Cancer Research Institute, American Institute for Cancer Research, American Cancer Society, and Institut National du Cancer. All of the partners code their research portfolios according to a Common Scientific Outline, a classification system that groups research into seven areas: biology; etiology; early detection, diagnosis, and prognosis; treatment; cancer control, survivorship, and outcomes research; and scientific model systems. The pooled data is incorporated into a shared database that researchers can search to identify potential collaborators and avoid duplication of efforts (https://www.icrpartnership.org).

Evaluation and Expansion of the Scientific Framework for PDAC Research

NCI's research framework for PDAC was examined during a multidisciplinary workshop convened to develop a forward-looking scientific approach for this recalcitrant disease. The workshop report, *Pancreas Cancer: Scanning the Horizon for Focused Interventions*, was presented to and accepted by the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) at the March 2013 meeting, and is available in Appendix 1 and on the internet at**:** http://deainfo.nci.nih.gov/advisory/ctac/workgroup/ctacsupmat.htm.

Research Initiatives Proposed:

Four initiatives to expand PDAC research were recommended by the workshop:

1. Understanding the biological relationship between PDAC and diabetes mellitus
2. Evaluating longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors
3. Studying new therapeutic strategies in immunotherapy
4. Developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways

Relationships between PDAC and diabetes mellitus (DM)

Clinical and genetic epidemiological studies have identified an association between DM of recent diagnosis and a subsequent diagnosis of pancreatic cancer[28]. About half of all PDAC

patients have DM at the time of diagnosis, and half of those patients have experienced the onset of DM within the prior 3 years. Yet, only 1% of recent-onset DM patients will develop PDAC within 3 years[28]. Progress in the early detection of PDAC will therefore require a more detailed understanding of the clinical and biological characteristics of the population of patients who subsequently develop or have undiagnosed PDAC in the setting of newly diagnosed diabetes. It will be essential to define specific risk factors to make screening efforts cost-effective by focusing on these individuals. It also will be important to understand whether other risk factors for the development of PDAC (such as exposure to tobacco smoke) interact with diabetes to increase the risk of PDAC. This is especially true for individuals with type 3c diabetes (diabetes secondary to pancreatic diseases) with coexisting chronic pancreatitis, in whom the risk of PDAC is increased 30-fold. Research efforts should determine whether risk factors of sufficient specificity can be defined to justify a coordinated early detection program in these patient groups.

Screening protocols for biomarkers for early detection of PDAC and its precursors

The goal of early detection strategies is to identify patients with the earliest-stage pancreatic cancers, who have the best chance of cure, and those individuals who are at highest risk, i.e., individuals who have precursor lesions that are likely to evolve into PDAC. Two groups of patients with precursor lesions, defined by pathologic or radiologic criteria, are those with type 3 highly dysplastic PanINs or cystic neoplasms of the pancreas--either IPMN or MCN. These patient populations overlap with the population of individuals who have germline mutations in specific genes that predispose to PDAC (such as *BRCA2, LKB1,* etc.) as well as families with multiple first-degree relatives who have developed PDAC. Genetically-defined patient populations also frequently harbor high-grade PanINs or small mucinous cysts that serve as pathologic precursors to invasive pancreatic cancer[47]. However, estimating the true extent of these lesions in the entire population has proven difficult; thus, the major diagnostic challenge is to develop more accurate and sensitive methods of imaging and more accurate and sensitive methods to identify the molecular alterations that characterize these lesions to improve early detection. This research effort should evaluate longitudinal screening protocols for patients at high risk of developing PDAC because of their genetic background or the presence of mucinous pancreatic cysts. These screening protocols, especially those that could collect specimens from early lesions, fluid from cysts, circulating tumor cells, or DNA from serum may help in the development of new molecular or imaging biomarkers that could be used in the selection of patients for early surgical intervention.

Immunotherapy approaches

The intrinsic cellular heterogeneity and genetic instability[48] of PDACs as well as the lack of understanding of the complex interrelationships among tumor cells, stromal cells, and immune cells characteristic of this malignancy have contributed in the past to the slow progress in developing effective systemic therapies for this disease[49]. In addition, the dense desmoplastic reaction itself, with its extensive deposition of extracellular matrix, is thought to act as a physical barrier and a great challenge to therapeutic success. It has recently been shown in a PDAC GEMM that mutational activation of KRAS triggers the production, by PDAC precursor lesions, of the growth factor GM-CSF, which promotes the expansion of Gr-1+ CD11B+ myeloid cells as part of the inflammatory reaction[50,51]. These immature myeloid cells (also known as myeloid suppressor cells) suppress CD8+ T cell antitumor immunity. Breakthroughs in targeting stromal cells, in reversing immunosuppression, and in the use of immune

checkpoint blockade agents, vaccines, and T cell-based immunotherapies, alone or in combination, have created opportunities for progress against PDAC.

RAS-specific therapeutics

Advanced PDAC is resistant to treatment with cytotoxic agents as well as the molecularly targeted drugs that have been tested to date. One of the reasons for this is the high frequency of an activating mutation in KRAS—the oncogenic driver of PDAC—which has been notoriously difficult to target with drugs. After more than 30 years of research into RAS and its role in pancreatic (and other) cancers, it has become evident that targeting this oncogene requires new approaches. These should include research efforts to develop new treatments employing recently discovered techniques in chemical biology supporting the discovery of molecules that interfere with *RAS*-oncogene-dependent signaling pathways. Since *KRAS* mutations are common in PDAC and many other malignancies, endeavors to target KRAS provide an opportunity to make inroads into establishing new therapies that might be widely applicable to the treatment of PDAC as well as other cancers.

Plans for Implementation of Recommended Initiatives

Coordinated Research Initiatives:

In response to the recommendations from the workshop, NCI has developed plans to pursue the four proposed research initiatives and has taken action on some of these. In general, the recommended research initiatives fall into one of four general categories: 1) developing a better scientific understanding at the molecular epidemiologic level of how specific predisposing factors, such as recently-developed diabetes or familial predisposition to PDAC, lead to the onset of this disease; 2) enhancing research into the discovery of biomarkers to identify PDAC precursor lesions that might be amenable to early treatment; 3) utilizing recent advances in cancer immunology to develop new immunotherapies for PDAC; and 4) pursuing new therapeutic approaches to mutant forms of the RAS oncogene that are present in the majority of patients with PDAC.

Relationship between PDAC and diabetes mellitus

The workshop established that some patients with new-onset DM constitute a high to moderate risk group for PDAC and that some of these patients might already have early stage PDAC which might be amenable to resection and cure. The use of familial pancreatic cancer registries would be a starting point for studies and screening. Mining data from health maintenance organizations could be used to establish new cohorts for imaging studies. Additional annotations about obesity and smoking might refine the population for screening.

In June 2013, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NCI, together with the Pancreatic Cancer Action Network, sponsored a two-day interdisciplinary meeting: *NIDDK-NCI Pancreatitis-Diabetes-Pancreatic Cancer Workshop,* as an initial step toward understanding the clinical and biological relationships between chronic pancreatitis (CP), PDAC and DM (http://www.niddk.nih.gov/news/events-calendar/Pages/niddknci-workshop-on-pancreatitisdiabetespancreatic-cancer.aspx). The purpose of the workshop was to explore the known and suspected mechanisms for the increased risk for PDAC associated with chronic pancreatitis (CP) and DM; to identify the prevalence of type 3c DM (T3cDM; diabetes associated with diseases of the pancreas) in the overall DM

population; to assess strategies to differentiate T3cDM from Type 2 DM (T2DM); to review the effects of anti-diabetic therapy on the development of PDAC; and to explore possible PDAC surveillance methods for T2DM and T3cDM patients. Sessions included: Overview of the Problem; Chronic Pancreatitis as a Risk Factor for PDAC; Diabetes as a Risk Factor of PDAC; Pancreatogenic (Type 3c) Diabetes; Genomic Associations of CP, DM, and PDAC; and Surveillance of High-risk Populations and Early Detection of PDAC. Participants defined high-priority strategies that need to be pursued in the areas of mechanisms, biomarkers, and refinement of risk. One important area that needs resolution is the controversy over whether relatively new diabetes drugs that are agonists for the glucagon-like peptide 1 (GLP-1) receptor (expressed in pancreatic duct cells) or inhibitors of dipeptidyl peptidase-4 (DPP-4) cause pancreatitis, development of PanINs, and PDAC. Data on both sides of the argument were presented, but no consensus was established[52-55]. Discussion also included the potential beneficial role of metformin in reducing or preventing PDAC recurrence[56].

Recommendations for next steps: The NCI/NIDDK workshop attendees recommended that the NCI and NIDDK publish the meeting proceedings and develop a funding opportunity announcement (FOA) for expanding research in all the areas considered critical.

Biomarkers for Early Detection of PDAC and Its Precursors

There is consensus that the discovery of biomarkers that can identify early lesions (PanINs 2 and 3, and mucinous pancreatic cysts) and perhaps serve as therapeutic targets is a critical goal in advancing progress in PDAC since diagnosis of pre-invasive or even small cancers can improve resectability, prognosis after resection, and survival. To date, there are no biomarkers or panels of biomarkers that are sensitive and specific enough for diagnosis of PDAC in its early stages. Cysts can be detected by current imaging techniques, but many cysts are benign and wholesale surgery is not recommended because of morbidity and cost considerations. One group of investigators has shown a significant difference between the expression and glycosylation of specific proteins in cysts with high malignant potential and cysts with low malignant potential, and has suggested that these molecules could serve as biomarkers for the diagnosis of high risk pancreatic cysts[57,58].

Armed with new information about activated molecular pathways, technological advances in screening strategies and non-invasive imaging, investigators are now poised to discover novel methods of detecting early lesions[59].

Work is in progress in several laboratories on refining the standard assay for the carbohydrate antigen, CA19-9, by measuring CA19-9 on specific protein carriers; the pattern of expression on these carriers has been shown to discriminate PDAC from pancreatitis[60]. However, the ideal biomarker should also be able to detect pre-invasive cancers or precursor lesions. Proteomic techniques are also being used in to identify serum proteins and peptides that indicate premalignant PanINs. Many of the studies in early biomarkers for PDAC are collaborative and supported by cooperative agreements through EDRN.

Other areas of investigation are the use of novel imaging techniques, miRNAs, circulating tumor cells, circulating DNA, autoantibodies, and methylated DNA as early detection biomarkers[6,61-63].

Recommendations for next steps: For further progress in the development of early detection biomarkers, it will be essential to optimize screening protocols, to improve enrollment of high risk populations in screening studies, and, crucially, to demonstrate that screening can improve the outcome of patients. A potentially useful approach to enhancing screening research is to prospectively harvest and analyze tissue from patients with PanIN-2 and -3 lesions during resection, and from cyst fluid from those undergoing endoscopic ultrasound and fine needle aspiration. Through the issuance of a Program Announcement over the next twelve months, focusing on the development of novel methods to obtain and interrogate pancreatic tissues containing pre-neoplastic lesions, the NCI will actively stimulate studies in this area.

Immunotherapy

Recent advances in cellular and molecular immunology have led to a detailed understanding of the induction and regulation of the immune response to cancer, including the complex network of signaling and checkpoint pathways involved; to a comprehension of the dynamic processes involved in the interaction between tumor and the cells of its microenvironment, including the action of soluble mediators that aid or inhibit the immune response; and to the recognition that most human cancers have the potential to respond to immunomodulation therapy either as single agent therapy or in combination with other agents. Data provide evidence that many early-stage tumors induce an immune response, but an immunosuppressive environment that inhibits an anti-tumor response is often quickly established. Yet, promotion of T-cell-dependent antitumor immunity can result in tumor regressions in patients with metastatic pancreatic as well as other types of cancer[21].

The availability of new immune response modifiers, including FDA-approved agents that can modify interactions between tumor cells and the surrounding stromal cells, provides opportunities to accelerate research in the development of effective pancreatic cancer immunotherapies. Genetically engineered immunocompetent mouse models of spontaneous pancreatic cancer that closely mimic the human disease, including the development of early lesions (i.e., PanINs and mucinous cystic neoplasms) and the generation of dense desmoplasia, have permitted more relevant ways to test new therapies than do transplantable tumor models[64].

Much of the NCI-supported research in immunotherapy of pancreatic cancer has been in the area of therapeutic vaccines. It has been postulated that the best chance for these vaccines to have an anti-tumor impact on pancreatic cancer would be in the post-surgical (minimal disease) setting. The optimal strategy would be to create a vaccine against unique pancreatic tumor antigens/neoantigens that play key roles in cancer growth and progression. Although the NCI is funding investigators to discover, characterize, and validate such antigens, only a few have been discovered so far. Therefore, allogeneic whole cell vaccines that have been engineered to secrete GM-CSF, a growth factor for dendritic cells, have been used in pre-clinical and clinical studies, predominantly[65-67]. Current trials have added ipilimumab, an FDA-approved antagonistic monoclonal antibody against CTLA4, which is a T cell receptor that when it engages its ligands, CD80 and CD86, downregulates the immune response[68,69].

The detection in paraffin-embedded pancreatic cancer specimens of PD-L1 (also known as B7-H1), another negative regulator of T cell responses, and the availability of antagonistic anti-PD-L1 monoclonal antibodies, have created further opportunities for combining vaccines with immune checkpoint inhibitors[70].

A CD40 agonistic antibody, which stimulates antigen-presenting cells, has been tested in combination with gemcitabine in a clinical trial of pancreatic cancer patients and is being followed up with additional studies[71,72]. Concomitant laboratory studies have demonstrated that this antibody drives both T cell-dependent and T cell-independent mechanisms of action and is thought, in pancreatic cancer, to cause stromal involution and re-education of tumor-associated (suppressive) macrophages.

An industry-sponsored series of studies that has now reached a Phase 3 trial is testing algenpantucel-L, an allogeneic whole cell pancreatic cancer vaccine that has been genetically modified, together with gemcitabine or gemcitabine plus 5-fluorouracil chemoradiation, in surgically resected pancreatic cancer patients [ClinicalTrials.gov identifier: NCT01072981.][73]

In September 2013, the Center of Excellence in Immunology at the NCI's intramural Center for Cancer Research sponsored a two-day conference on "Inflammation, Microbiota, and Cancer." This conference discussed many aspects of cell-cell and cell-mediator interactions that are important to immunotherapy of pancreatic cancer.

Examples of NCI funded projects with high relevance to the immunotherapy of pancreatic cancer can be found using the following link: http://tiny.cc/fngu7w.

Recommendations for next steps: Progress in pancreatic cancer immunotherapy will include not only the support of grants dealing with the discovery and validation of new immunotherapy targets, and the rational combination of immune modifiers in preclinical and clinical studies, but the production of immune-modulatory molecules (such as anti-CD40) at the NCI's Frederick National Laboratory for Cancer Research (FNLCR) to facilitate the initiation of early phase PDAC trials in the area of immunotherapy. For these clinical studies, the Cancer Immunotherapy Trials Network (CITN), which employs the collective expertise of expert academic immunologists together with the NCI, and foundation and industrial partners, will design and conduct cancer therapy trials with the most promising immunotherapy agents in PDAC patients.

RAS-Specific Therapeutics

Many common cancers are driven by mutant forms of RAS, including 95% of PDAC, 45% of colorectal cancers, and 35% of lung adenocarcinomas. Although there have been many attempts at targeting cancer cells driven by KRAS, successful strategies so far have been elusive. Recent discoveries provide opportunities to make progress on this front. These include new information on signaling pathways and complexes based on recent advances in cell biology, protein engineering, the use of RNA interference for target identification in synthetic lethality screens, technological advances in conducting structural analyses, and the generation of genetically engineered mouse models that are more relevant to the human disease[74].

NCI has mounted a large-scale program on RAS at the FNLCR, an HHS Federally Funded Research and Development Center that provides unique capabilities, resources, and approaches to conduct research and development, such as expertise in basic research, applied research and development capacity, clinical research including correlative studies, Good Manufacturing Practice (cGMP), and animal model facilities and experience.

In early 2013, a series of meetings were held with experts in the RAS field to discuss appropriate projects to pursue. Five projects were defined as having high priority[75]:

1. Pursuing allele specific compounds for those RAS alleles most prevalent in human cancer (e.g., KRAS G12D and G12V in pancreatic cancer)
2. Developing KRAS selective binding compounds for KRAS ablation without allele specificity
3. Developing imaging methods and screens to identify and disrupt KRAS complexes in cells and to monitor their disruption
4. Mapping the surface of KRAS cancer cells and identifying epitopes that could be targeted by immunotherapy and proteins that could be targeted for drug delivery by nanoparticles
5. Developing and conducting next-generation synthetic lethality screens and engineering mice to facilitate these screens

The first two projects involve structural and biological approaches to attack RAS directly. The third project, disrupting KRAS complexes within cells, presents new opportunities for drug discovery. The fourth project will define the landscape of proteins on the surface membranes of mutant KRAS cells and facilitate the development of direct antibody-mediated interventions, immune-based therapies—such as adoptive transfer of T cells engineered to attack tumor antigens, and nanoparticle-mediated drug delivery. The fifth project will conduct synthetic lethality screens, including those in 3D cell cultures and animals, in order to discover combinations of proteins that mutant KRAS cells require for survival. Results from this project could lead to the development of new combinations of targeted therapies. Studies will also be performed in other areas of RAS biology, related to both HRAS and NRAS—variants that are relevant to other forms of human cancer. However, much of the entire effort will be specifically directed at KRAS, the form of mutant RAS found in approximately 95% of PDAC patients.

These five projects, which were unanimously approved by the NCI Board of Scientific Advisors and the National Cancer Advisory Board at their joint meeting in June 2013, will be conducted within a "RAS community," by a hub and spoke model, with scientific leaders, core facilities and critical technologies and materials provided by the Advanced Technologies Research Facility at the FNLCR "hub"; and a distributed research effort by a community of investigators at academic institutions, pharmaceutical and biotechnical companies, and the NCI intramural research program as the "spokes."

Recommendations for next steps: Progress, as the project relates to advances in pancreatic cancer, will be measured by periodic reports, publications, and presentations. Some of these will report on the creation of the tools necessary to support the activities of the five projects. These include methods for solving the structures of mutant proteins complexed with relevant effectors and regulators; determining the significance of other types of modifications to RAS proteins, including acetylation and ubiquitination; identifying compounds that disrupt RAS dimers or other aspects of RAS superstructures; developing a comprehensive map of surface proteins on specific RAS cancers; and developing synthetic lethal screens *in vitro* and *in vivo*. Other reports will cover the generation and validation of data, using these tools, to target mutant RAS cancer cells, and the application of the new methods to the treatment of PDAC in pre-clinical and clinical trials.

Oversight and Benchmarks for Progress

The NCI has regularly reviewed its portfolio of PDAC research, at least since 2000, when the NCI convened the Pancreatic Cancer Progress Review Group (PCPRG), a multidisciplinary committee of scientists, clinicians, and advocates; the PCPRG reviewed the field of PDAC research and made prioritized recommendations concerning promising directions for future scientific investment in this disease [National Cancer Institute. Pancreatic Cancer: An Agenda for Action. Report of the Pancreatic Cancer Progress Review Group. NIH Publication No. 01-4940. Bethesda (MD): NCI; 2001. http://planning.cancer.gov/library/2001pancreatic.pdf]. This effort was followed by the development of a strategic plan to enhance PDAC research [National Cancer Institute. Strategic Plan for Addressing the Recommendations of the Pancreatic Cancer Progress Review Group. Bethesda (MD): NCI, 2002. http://planning.cancer.gov/library/pancreatic.pdf]. The clinical trials portfolio in the area of PDAC was examined during a Clinical Trials Planning meeting of NCI's Pancreatic Cancer Task Force (2008); this workshop defined future directions for NCI-supported clinical trials in pancreatic cancer based on input from academic, industry, community, and advocacy experts[76].

To assess the ongoing investment of the NCI in PDAC research, the Pancreatic Cancer Action Planning Group (PCAPG) was formed in 2010; its recommendations and the subsequent implementation plan established the current framework for NCI's PDAC research program [National Cancer Institute. Pancreatic Cancer: A Summary of NCI's Portfolio and Highlights of Recent Research Progress. Bethesda (MD): NCI; 2010. http://www.cancer.gov/researchandfunding/reports/pancreatic-research-progress.pdf]. This report was followed by an "action plan" in 2011 [National Cancer Institute. National Cancer Institute Investment in Pancreatic Cancer Research: Action Plan for Fiscal Year 2011]. http://www.cancer.gov/researchandfunding/reports/pancreatic-action-plan.pdf]. The NCI's PCAPG continues to meet on a regular basis; most recently, it was responsible for developing the joint NCI/NIDDK workshop on the role of diabetes mellitus in PDAC described in a preceding section of this report. The PCAPG will continue to monitor the progress of the initiatives for expanded research proposed at the *Scanning the Horizon* workshop.

Conclusion

The workshop, *Pancreatic Cancer: Scanning the Horizon for Focused Interventions*, provided the NCI with expert advice regarding how to extend its existing extensive repertoire of PDAC research, with the goal of making further progress against PDAC, a disease whose incidence continues to slowly increase, and for which no breakthroughs leading to improved patient survival have occurred. The workshop recommended expanding research in specific areas in ways that could advance the field and open up possibilities for better outcomes.

The NCI has made a significant investment in pancreatic cancer research and will continue to support research in the field, particularly in the four areas that the workshop attendees designated as of high priority for expansion:

- Understanding the relationship between PDAC and diabetes
- Evaluating longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors
- Studying new therapeutic strategies in immunotherapy

- Developing new treatment approaches that interfere with *RAS*-oncogene-dependent signaling pathways

Reports to the Clinical Trials and Translational Research Advisory Committee (CTAC) at regular intervals will inform the public of progress in this difficult disease and fulfill a requirement of the Recalcitrant Cancer Research Act. To implement the specific recommendations proposed in this report:

- The NCI will continue to work with NIDDK to develop new funding opportunities for studying the diabetes—PDAC connection
- The NCI's Cancer Therapy Evaluation Program will facilitate testing combinations of molecularly targeted drugs and biological agents from different companies in a broad range of clinical trials for patients with PDAC that include immunotherapeutic studies
- The NCI will oversee funded grant programs supporting PDAC research and monitor progress in the priority areas, including the development of new biomarkers for patients with mucinous cystic diseases of the pancreas and individuals with a familial predisposition to PDAC
- The NCI will continue its commitment of considerable resources to the RAS project, which includes a five-pronged approach to tackling an oncogene highly relevant to PDAC

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Links:

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Addenda

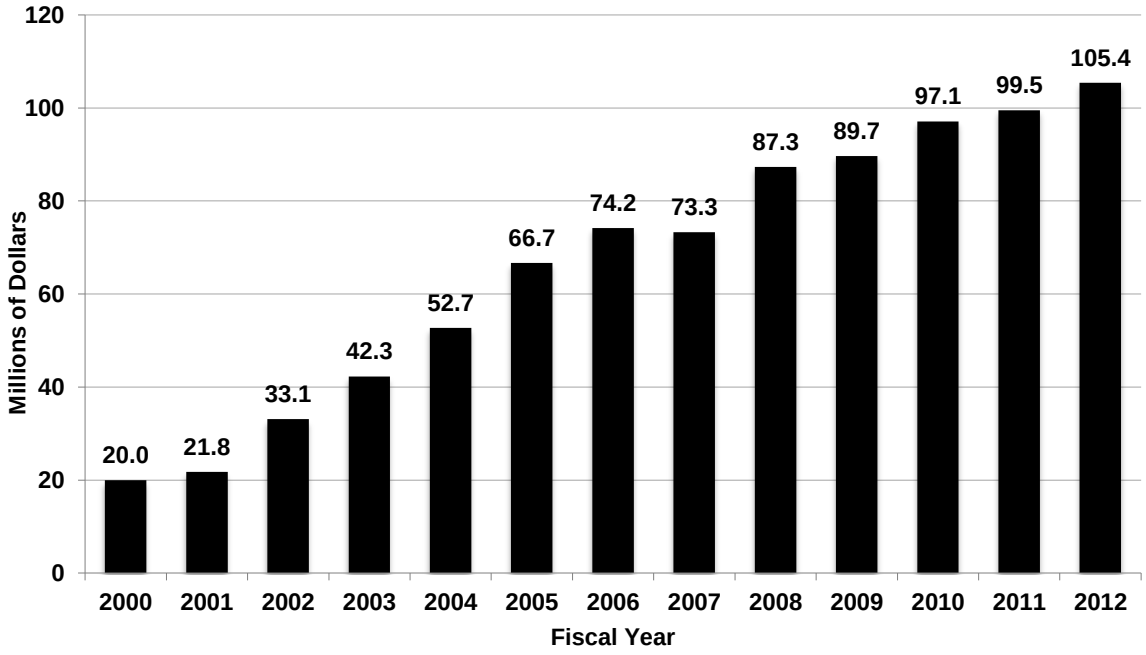

Figure 1: Trends in NCI Funding for Pancreatic Cancer, FY2000–FY2012

For Figures 1-3: NCI grants, other extramural funding mechanisms, and intramural research projects are indexed for a variety of research categories and organ sites. Each category, such as pancreatic cancer research, is assigned, following a review of the entire application by professional staff, a "percent relevance" based on the portion of the funding relevant to the category. A funding mechanism may be 100 percent relevant to multiple categories, and the sum of the percent relevance assignments may exceed 100 percent.

For Figure 1, the dollars invested per year for pancreatic cancer research, was arrived at by multiplying the award for each grant, cooperative agreement, contract, and intramural project funded in that year by its percent relevance and then combining the numbers for a total.

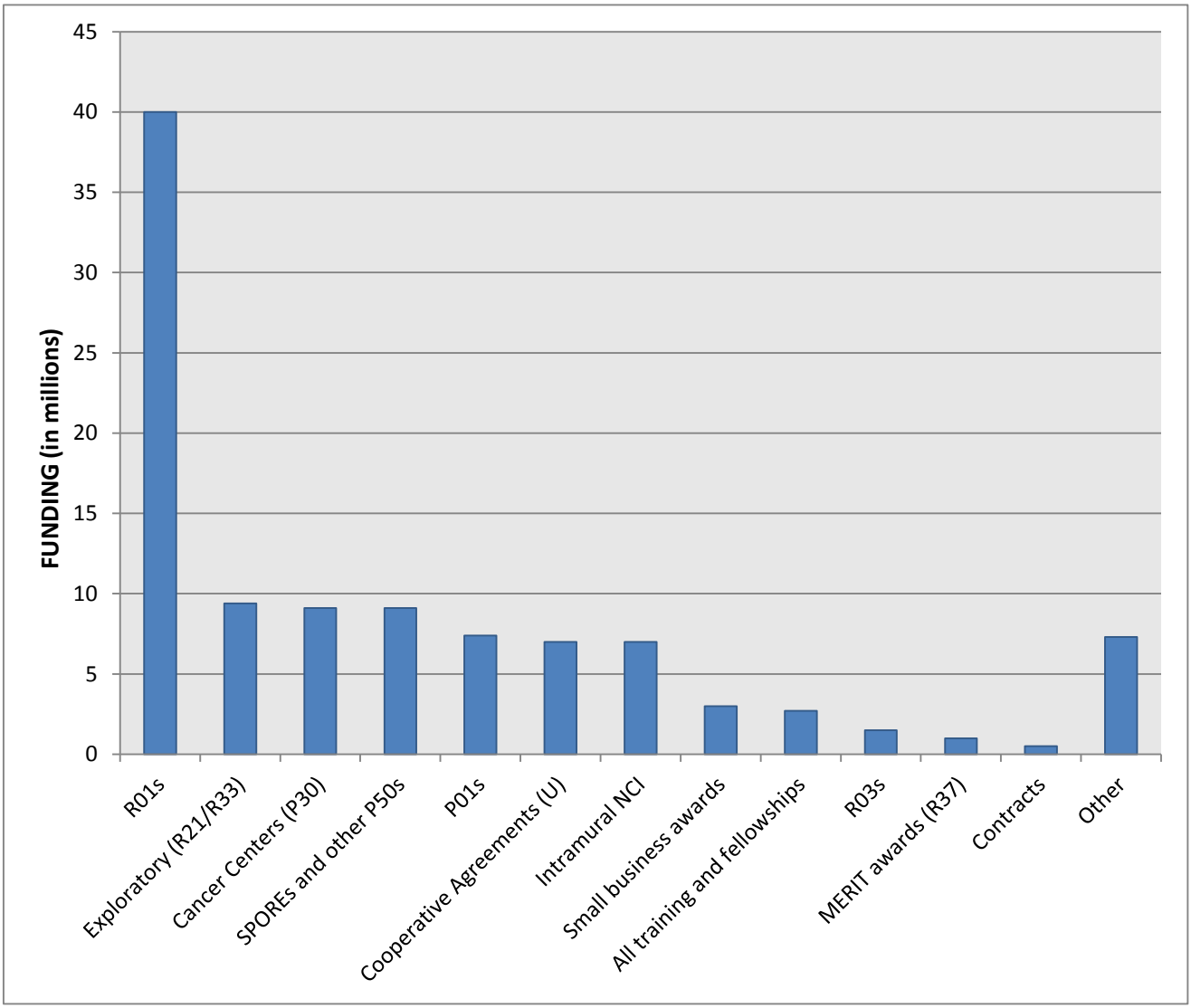

Figure 2: NCI Mechanisms of Funding Pancreatic Cancer Research in FY2012

Source: NCI Office of Budget and Finance

Individual NCI funding mechanisms were evaluated for the dollar amount of NCI investment in pancreatic cancer research. The percent relevance to pancreatic cancer and the total funding was calculated as in Figure 1.

http://deainfo.nci.nih.gov/flash/awards.htm

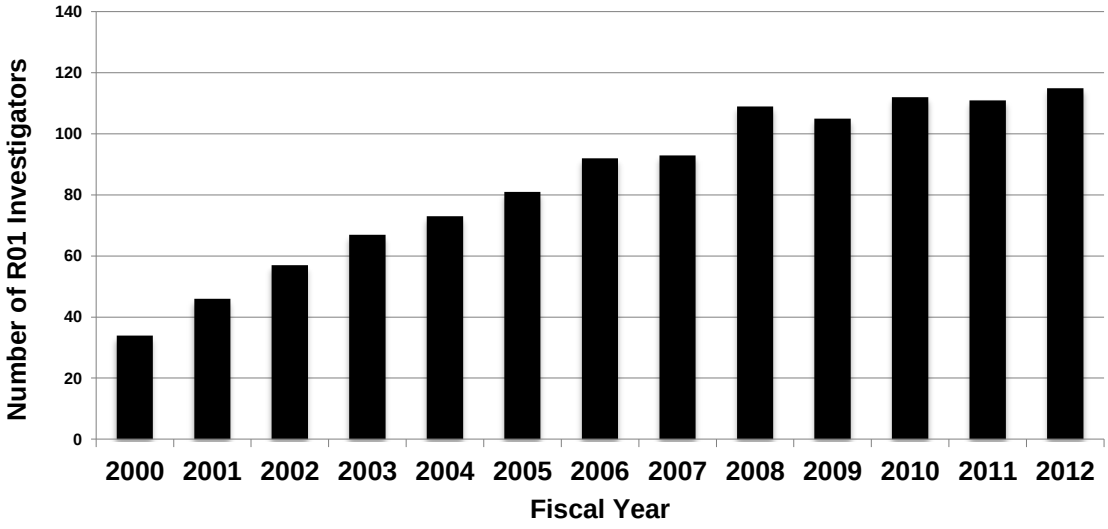

Figure 3: Number of Principal Investigators with at Least One NCI R01 Grant Relevant to Pancreatic Cancer Research, FY2000–FY2012

The investigator-initiated, traditional R01 grant is the predominant mechanism of funding for pancreatic cancer research as seen in Figure 2. The number of individual principal investigators with at least one R01 award that each had at least 25% relevance to pancreatic cancer research (calculated as in Figure 1) was determined for the thirteen-year period, fiscal years 2000 to 2012.

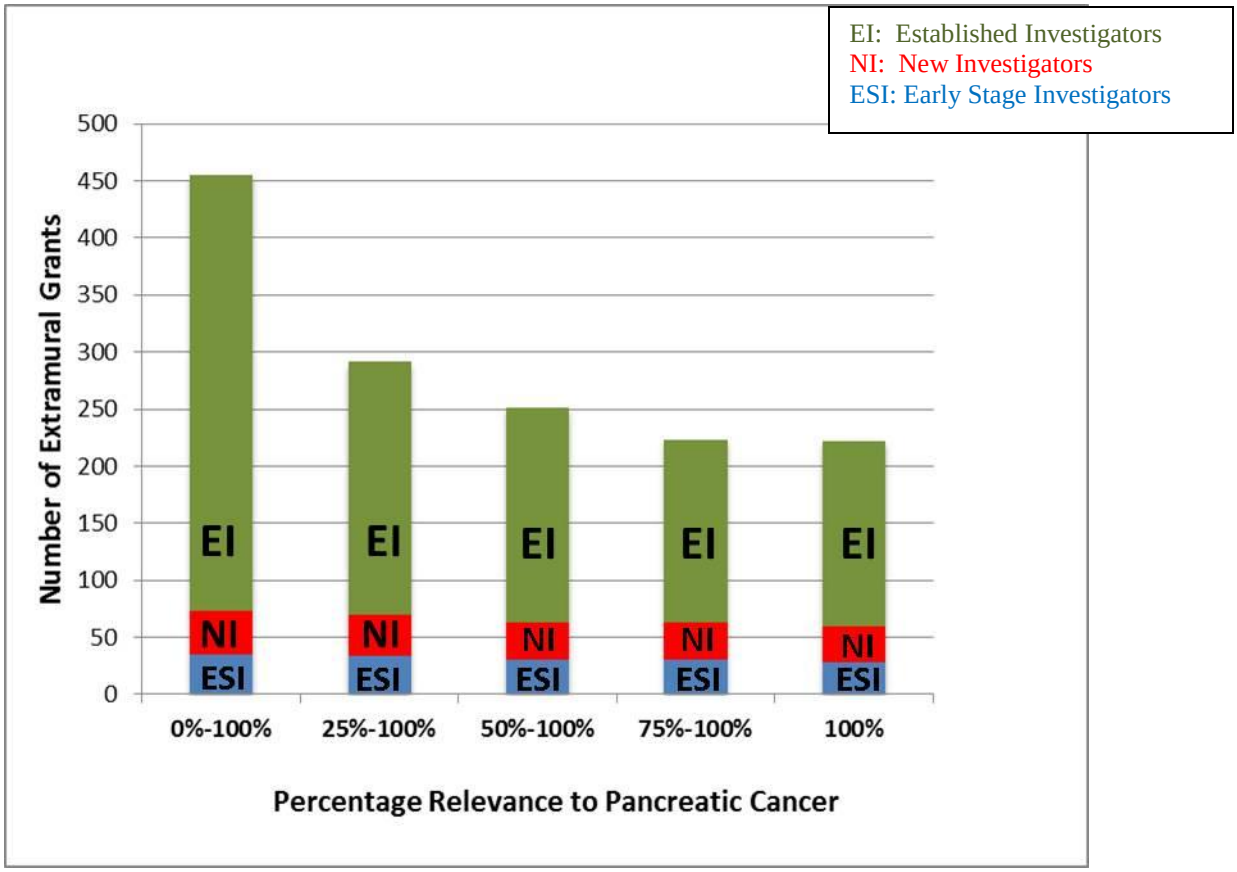

Figure 4: Number of FY2012 Extramural NCI Grants of All Mechanisms in Pancreatic Cancer Research Awarded to Investigators at Different Stages of their Career

Grants utilizing all mechanisms funded in FY2012 with relevance to pancreatic cancer research were identified using the NCI Funded Research Portfolio (http://fundedresearch.cancer.gov/nciportfolio/).

The data were then cross-referenced by **new investigator (NI)** and **early stage investigator (ESI)** person and application eligibility of the contact principal investigator (PI) in the Query/View Reports (QVR) utility of the NIH IMPAC II database. The NIH defines the person and application eligibility of a NI as an NIH research grant applicant who has not yet competed successfully for a substantial, NIH research grant. An ESI is a NI who has completed his or her terminal research degree or medical residency—whichever date is later—within the past 10 years and has not yet been awarded a substantial, competing NIH research grant.

An **established investigator (EI)** is a grant applicant who is not eligible for NI or ESI status. Grants where the PI is an EI are represented by a green bar with EI as the label. Grants where the PI is a NI, but not an ESI, are represented by a red bar with NI as the label. Grants where the PI is an ESI are represented by a blue bar with ESI as the label.

Table 1: NCI Support for Training Relevant to Pancreatic Cancer, FY2012

(At least 25% relevance to pancreatic cancer)

Funding Mechanism	Number of Trainees
F Awards: Ruth L. Kirschstein National Research Service Award Individual Fellowships	**13**
T Awards: Institutional Training Grants	**2**
K Awards: Career Development Awards	**15**
NCI Intramural Program: Center for Cancer Research	**10**
NCI Intramural Program: Division of Cancer Epidemiology and Genetics	**5**

This table lists the various mechanisms the NCI uses for training new scientists, both intramural and extramural, and the number of trainees in pancreatic cancer research in each category for FY2012. The full list of training grants can be obtained at the following link: http://tiny.cc/deyv7w