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D. Summary
A. The Workshop

1. Origin of the Workshop

In August 2012, Dr. Harold Varmus, Director of the National Cancer Institute (NCI), asked Dr. James Abbruzzese, Chairman of NCI’s Clinical Trials and Translational Research Advisory Committee (CTAC), to convene a group of experts in the area of pancreatic ductal adenocarcinoma (PDAC) to discuss recent progress that has been made in understanding the biology, detection, and treatment of PDAC. The group included gastrointestinal, medical, surgical, and radiation oncologists, translational and basic scientists, epidemiologists, patient advocates, and NCI staff; it met in the Washington, DC, area on October 23-24, 2012.

Although significant scientific progress has been made in the last decade to advance understanding of the biology of PDAC, the natural history of the disease in the clinic remains short. (1, 2) The meeting was therefore intended to explore reasons for the continued poor outcomes and to seek new opportunities for making better progress. More specifically, the study group was charged with assessing advances that have recently occurred in PDAC research, especially in epidemiology and risk assessment; pathology, screening, and early detection; and therapeutic research. In addition, it was asked to identify and prioritize new scientific opportunities that could more swiftly advance knowledge about PDAC and improve the outlook for patients with this disease.

Major goals of the meeting were to define new ideas and important unsolved problems in PDAC research and to identify ways to solve those problems; in that sense, it was conducted in the spirit of the NCI Provocative Questions Initiative. In some ways, PDAC is emblematic of malignancies that occur in anatomic locations that are hard to sample technically and also demonstrate a high degree of biological diversity. Furthermore, the limited clinical approaches available to patients with PDAC provide a stimulus for the evaluation of new scientific opportunities that may have been missed.
Findings from the meeting were intended to be shared with the NCI’s National Cancer Advisory Board (NCAB) and CTAC, posted on the NCI website, and used by NCI staff in considering new research opportunities. In response to passage of the Recalcitrant Cancers Act at the end of 2012, this report will also be sent to Congress and the Secretary of the Department of Health and Human Services.

2. Overview of the Program

During the first two introductory sessions, the current state of knowledge was reviewed in the following areas of PDAC research: genetics, mouse models, epidemiology and risk assessment, heritability, cystic neoplasms, screening, multidisciplinary management of potentially resectable disease, and current approaches to medical management. Subsequent breakout sessions were organized around the areas of epidemiology and risk assessment research; pathology, screening, and early detection research; and therapeutic research. The objective of these sessions was to identify opportunities that the NCI could prioritize for focused study.

3. Current Approaches to PDAC

PDAC represents 2% of all cancer cases and is the fourth leading cause of cancer death in the United States (1). The incidence of PDAC increases with age, with a median age of 72 years at diagnosis. Unfortunately, about 30% of patients are found to have locally advanced disease and over 50% have involvement at distant sites at the time PDAC is detected. Surgery is the only curative therapy for PDAC but is indicated for less than 20% of patients and produces long-term, disease-free survival in 3-4% of all individuals presenting with this disease.

Therapeutic approaches for PDAC other than surgery, including postsurgical, adjuvant chemotherapy (with gemcitabine or fluoropyrimidines) or chemoradiotherapy, have modest benefit (3). Furthermore, the overall utility of either single agent or combination chemotherapy for patients with advanced disease is also limited; the mechanisms of resistance of these tumors to both chemotherapy and radiation therapy are complex and not fully understood (4). Thus, novel methods to prevent PDAC, to
detect disease at earlier (even premalignant) stages, and to improve treatment for PDAC are desperately needed.

4. Specific Issues Highlighted at the Workshop

a. Identification of Individuals at High Risk for Developing PDAC

Workshop participants examined a variety of factors that have been found to increase the risk of developing PDAC, including:

Genetic risk: Genetic predisposition can play a significant role in the development of PDAC (5, 6). It has been estimated that 4-10% of patients who develop PDAC have a familial disposition to the disease (defined as having a pair of first-degree relatives diagnosed with PDAC) and that the level of risk increases with the number of affected relatives and with disease onset at less than 50 years of age. Specific germline mutations can be defined in the minority of PDAC families; nonetheless, approximately 20% of individuals with a familial disposition to PDAC demonstrate mutations in the BRCA2, p16, STK11, hMSH2 and hMLH1, and PRSS1 genes that are associated, respectively, with familial breast cancer, the atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, hereditary nonpolyposis colorectal cancer, and hereditary pancreatitis. Recent data from The National Familial Pancreas Cancer Registry reveal that germline mutations in the PALB2 and ATM genes also are associated with an increased risk of pancreatic cancer (7). The development of pancreatic cancer family registries on a broader scale could assist in furthering the identification of individuals with genetic factors that contribute to the development of PDAC.

Behavioral and environmental risk: Smoking tobacco contributes significantly to the development of PDAC (8). Occupational hazards that have been associated with an enhanced risk of developing PDAC include exposure to chlorinated hydrocarbon solvents and heavy metals (9).

Physiological risk: Long-standing chronic pancreatic inflammation as well as inherited genetic anomalies significantly enhance the risk of developing PDAC (10, 11). Although the association between chronic pancreatitis and the development of PDAC has been well known for decades, only
recently have studies clarified how pro-inflammatory cytokines contribute to the progression from premalignant lesion to advanced tumor (12, 13). In addition to chronic pancreatitis, the role of obesity and diabetes mellitus in the development of PDAC has been emphasized; the increase in obesity in the U.S. population and the concomitant increase in associated diabetes mellitus are associated with an enhanced lifetime risk of developing PDAC (14). The strength of the epidemiological data underlying these associations suggests that screening individuals with one or more of these predisposing conditions might lead to the development of a productive diagnostic intervention to detect PDAC in its earliest stages.

Premalignant lesions: It has been observed, because of the routine use of computed tomographic (CT) imaging in the diagnosis of abdominal pain, that cysts of the pancreas are much more common than previously recognized; furthermore, it now appears that certain types of pancreatic cysts (mucinous cystic neoplasms [MCN] and intraductal papillary mucinous neoplasms [IPMN]) are premalignant lesions that, if identified early, are amenable to surgical intervention (15). Cystic lesions often are associated with the most common microscopic (i.e., noncystic) precursor lesions of pancreatic adenocarcinoma—pancreatic intraepithelial neoplasms (PanINs). Thus, it is reasonable to consider whether the detection of preinvasive pancreatic pathologies in either high risk families or individuals with mucinous pancreatic cysts would offer the possibility of preventing the development of PDAC by surgical means.

b. Measures that Might be Taken to Reduce the Risk of PDAC

In light of the increasing appreciation of the populations at risk for developing PDAC, improved screening efforts for these individuals are urgently needed. The workshop participants chose to consider how new cohorts of pancreatic cancer families, as well as individuals with recent-onset diabetes mellitus, might be identified and whether better imaging interventions could be developed to enhance early diagnosis. The development of organizational structures and molecular technologies that could assist in the evaluation of diagnostic and surgical approaches for patients with cystic lesions of the pancreas was also a focus of workshop discussions (cf. Recommended Initiatives, below).
c. Possible Routes to Better Therapies

The limited success of standard chemotherapy and radiotherapy for pancreatic cancer has stimulated interest in new treatment paradigms based on more sophisticated preclinical models and a better understanding of the reasons that current treatment programs fail (16). The participants in the workshop considered the potential for novel therapeutic modalities in this disease (including immunotherapy), as well as how to identify innovative methods to interdict the molecular lesions that have impeded the effectiveness of systemic treatments used for other cancers (3, 4, 17).

B. Updating our Knowledge Base—Major Observations

Workshop participants discussed the major scientific observations made over the recent past that have increased our knowledge of PDAC genetics, biology, and epidemiology, as well as surgical and medical management.

1. Genetics

Genetic alterations in KRAS, CDKN2A, SMAD4, and TP53 in pancreatic adenocarcinomas are well known; however, the clinical significance of these abnormalities, individually or collectively, is only now being characterized (18, 19). With the active implementation of whole-exome sequencing for many tumors, the current problems in PDAC genetics research include the need to overcome the challenge posed by the abundance of stromal cells in pancreatic cancer samples that often obscure the detection of somatic mutations, and the need to comprehend the mechanistic importance of newly described somatic mutations (such as in ARID1A, a gene that plays an important role in regulating the structure of chromatin). A better understanding of how to integrate information about somatic and germline mutations will be required to improve future efforts devoted to the screening of individuals at high risk of developing PDAC.

2. Mouse Models

Many contributions to our understanding of PDAC biology have been provided by genetically engineered mouse models (GEMMs) of this disease (16). In these models, it has been possible to confirm
the role of activating mutations in the KRAS gene, found in over 90% of human PDACs, in the progression of low-grade PanINs to invasive PDACs (20). The first evidence suggesting that PDACs might originate from pancreatic acinar, rather than ductal, cell precursors also was developed from GEMMs (20). These model systems have enhanced our appreciation of the heterogeneity of the tumor microenvironment in PDACs, as well as the role of the inflammatory response in PDAC development (16, 20). Interactions among cancer-associated fibroblasts and immunosuppressive macrophages and myeloid cells contribute to the fibrotic reaction that surrounds most PDACs, supporting cancer cell growth and possibly limiting drug penetration. These models also have provided better tools to study complex immunologic interventions, as well as combinations of targeted biologic molecules, focusing on the interruption of critical signaling pathways known to regulate PDAC growth (such as those controlled by KRAS, p16, or pro-inflammatory cytokines).

3. Epidemiology and Risk Assessment

The clear increase in the age-adjusted incidence of PDAC may be associated with the increased incidence of diabetes mellitus (21-23). Not unexpectedly, the risk of PDAC also is associated with obesity; in particular, with a body mass index (BMI) greater than 35. Recently, epidemiologic studies have focused on the development of PDAC in patients with type 3c (secondary) diabetes, a major subset of diabetes characterized by a severe deficiency of all glucoregulatory hormones. Patients with type 3c diabetes appear to have the highest associated risk of developing PDAC, especially in the setting of coexisting chronic pancreatitis. Type 3c diabetes is also a consequence of PDAC in approximately 30% of patients (22). It is in this setting that the antidiabetic drug, metformin, is being considered for potential use as a PDAC chemopreventive agent (24).

4. Heritable Pancreatic Cancer

Over the past ten years, investigators at Johns Hopkins and a consortium of other institutions have studied 1,500 families in which two first-degree relatives have developed PDAC (25). In these patients, the risk of developing PDAC was increased seven-fold. In addition to the recent discovery of the PALB2
gene in 3% of these families, mutations in \textit{ATM}, a critical partner in the DNA damage repair pathway, also have been discovered. The continuing challenge for the further development of the field of heritable pancreatic cancer is developing a cohort of families of sufficient size to detect new, but rare, germline mutations.

5. Cystic Neoplasms

Cystic neoplasms of the pancreas are common, with an increased prevalence with age and an overall detection rate of 2% among adults undergoing abdominal magnetic resonance imaging (MRI) examinations. Whereas serous cystadenomas are benign abnormalities that do not connect to pancreatic ducts and warrant surgery only if symptomatic, mucinous cystic neoplasms are precursors of PDAC that often occur in the tail of the pancreas, are overtly malignant in 15% of patients, and may require surgical resection (26). Intraductal papillary mucinous neoplasms of the pancreas occur in the head of the organ, are often multifocal, and have a propensity to become malignant. While controversial, at least some surgical series suggest that all patients with this lesion require surgery (27). Because of the rapid increase in the detection of pancreatic cysts over the past decade, detection has outpaced current knowledge of the pathophysiology and natural history of these diseases. There is significant interest in developing better ways to establish the natural history of these abnormalities with sufficient certainty to confidently recommend to patients when surgical removal is required.

6. Screening

Because only 20% of patients with PDAC have resectable disease at the time of diagnosis and less than 5% have pathologically confirmed stage I tumors, there is considerable interest in developing technologies capable of finding high-grade, noninvasive lesions (such as PanIN3 or IPMN with carcinoma in situ) (28-31). However, although there is agreement regarding which currently available methodologies may be useful (MRI and endoscopic ultrasound rather than CT scanning), it is unclear, even in high-risk patients, when screening should be initiated. Consensus about screening does exist regarding the urgent need for better molecular and imaging technologies in this setting.
7. Multidisciplinary Management of Potentially Resectable Disease

Discussants outlined the difficulties in defining patients who will benefit from major surgical resections or from current multidisciplinary treatment strategies (32, 33). A new approach to intraoperative pilot studies was described in which the metabolism of a drug of interest—such as gemcitabine, administered as a single intravenous dose in the operating room—was studied directly in surgically resected PDAC samples as well as in biopsies from surrounding uninvolved pancreatic tissue. For these experiments performed under optimal conditions, substantive incorporation of cytotoxic gemcitabine metabolites was demonstrable in tumor DNA in no more than half the patients. This work clearly underscores the difficulties inherent in developing treatments for PDAC under conditions in which tumor-associated fibrosis appears to exert a major negative effect on drug delivery.

8. Current Approaches to Medical Management

The status of current systemic therapy was described, including the modest but real activity of the combination of 5-FU (5-fluorouracil), leucovorin, irinotecan, and oxaliplatin for patients with advanced PDAC (34, 35). However, it was recommended that, absent evidence for substantive therapeutic efficacy in randomized phase II trials, large investments would be better channeled into the clinical development of predictive molecular markers in earlier-stage studies than into additional phase III investigations (4).

C. Recommended Initiatives

Four options for future research initiatives were recommended by workshop participants:

1. PDAC and Diabetes Mellitus

Patients recently diagnosed with diabetes mellitus, which may be associated with obesity (BMI greater than 35), are at significant risk of developing PDAC. Workshop participants evaluated new experimental approaches to risk assessment and potential interventions to reduce the risk of PDAC, focusing on individuals with new-onset diabetes.

   a. The Challenge
Clinical and genetic epidemiological studies have identified an association between a recent diagnosis of diabetes mellitus and subsequent diagnosis of pancreatic cancer. However, progress in the early detection of PDAC will 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 with coexisting chronic pancreatitis, in whom the risk of PDAC is markedly increased.

b. The Opportunity

Several National Institutes of Health Institutes (for example, the National Institute of Diabetes, Digestive, and Kidney Diseases), as well as major health maintenance organizations and academic health centers, have a specific interest in the clinical course of patients recently diagnosed with diabetes. Existing databases of such patients, often with extensive follow-up information, could be examined to determine more accurately the incidence of PDAC in patients with diabetes.

c. The Recommended Approach

The approach to this research opportunity will require integrating information from these databases about clinical factors, such as smoking and obesity, with emerging data on genetic risk factors for both diseases. Interactions between genetic risk factors for diabetes or obesity, and environmental risk factors (such as tobacco exposure) should be examined. This effort could evaluate whether PDAC emerging in patients recently diagnosed with diabetes differs with respect to treatment response or clinical course compared to patients with or without other known PDAC risk factors. It also would be of interest to understand how diabetes arising in this setting is influenced by underlying genotype as well as behavioral factors. This work would seek to define the population of patients with new-onset diabetes who are likely to harbor early PDAC.
2. Biomarkers for Early Detection of PDAC

a. The Challenge

The goal of early detection strategies is to identify patients with the earliest-stage pancreatic cancers that have the best chance of cure and those most likely to develop pancreatic cancer, i.e., individuals who have precursor neoplasms that are most likely to evolve into pancreatic cancer. Two groups of patients with precursor lesions, defined by pathologic or radiologic criteria, are those with type 3 highly dysplastic pancreatic intraepithelial neoplasms (PanIN3) or mucinous cystic lesions of the pancreas (either intraductal papillary mucinous neoplasms [IPMN] or mucinous cystic neoplasms [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. 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.

b. The Opportunity

Registries of families with pancreatic cancer will be essential to address this challenge. An appreciation of the natural history of mucinous cystic lesions of the pancreas and better staging criteria have also improved therapeutic decision making for such patients. Based on these advances, the opportunity exists to optimize pancreatic cancer screening protocols through the enrollment of a larger proportion of the at-risk patient population in longitudinal natural history studies employing novel imaging and molecular technologies. The development of better pancreatic cancer screening protocols that could detect high-grade dysplasia in patients with cystic neoplasms or early invasive cancers could
form the basis for studies of chemoprevention strategies or early surgical intervention in patients at increased risk of developing PDAC.

c. The Recommended Approach

The approach to developing screening protocols that is likely to benefit patients at high risk of developing PDAC will require a multidisciplinary effort from the pancreatic cancer imaging, surgery, pathology, and epidemiology communities. Mechanisms to support a coordinated program that would enroll and longitudinally follow patients at risk of developing PDAC because of their family history as well as those with mucinous cysts need to be considered. To be effective, such a screening program would likely need to employ novel detection strategies, such as the use of recently described genetic markers of cystic neoplasms (36, 37) in pancreatic cyst fluid obtained during upper gastrointestinal endoscopy. Such studies could help to define patient groups suitable for potentially curative surgical interventions.

3. Immunotherapy

a. The Challenge

The intrinsic cellular heterogeneity of PDACs and the complex interrelationships among tumor cells, stromal cells, and immune cells characteristic of this malignancy have contributed to the lack of progress in developing effective systemic therapies for this disease. Furthermore, until very recently, developing a detailed understanding of the PDAC immunological milieu was not felt to be a scientifically tractable endeavor.

b. The Opportunity

Recent highly encouraging data indicate that promotion of T-cell-dependent antitumor immunity can produce tumor regressions in patients with metastatic pancreatic cancer. Studies in this area have taken advantage of both a greater understanding of the complex immunological signaling networks that are involved in pancreatic cancer growth, as well as the availability of new immunological therapies that can modify interactions between tumor cells and their surrounding stroma. Thus, there is currently a
realistic opportunity to accelerate research into the development of effective immunotherapies for pancreatic cancer.

c. The Recommended Approach

To accelerate clinical and preclinical immunotherapeutic approaches that target pancreatic tumors, additional effort should be directed toward understanding the inflammatory response and mobilizing the immune system against PDAC, since promising preclinical results suggest that modulating the stroma improves the delivery and efficacy of new and currently available small-molecule as well as immunotherapeutic drugs. In the context of such studies, immunological profiling of both the primary pancreatic cancer and the pancreatic cancer microenvironment will advance our understanding of the mechanisms by which new immunological agents are useful in specific patients.

4. RAS-Specific Therapeutics

a. The Challenge

Advanced PDAC is resistant to treatment with cytotoxic agents as well as the molecularly targeted drugs that have been tested to date. The reasons for this are complex but include the high frequency of activating \( KRAS \) codon 12 mutations in PDAC. Furthermore, developing therapeutic agents directed against the mutated \( KRAS \) gene has proven difficult. After more than 30 years of research into RAS and its role in pancreatic (and several other) cancers, it has become evident that targeting this oncogene requires a new approach. However, the fact that \( KRAS \) mutations are common provides an opportunity to develop new therapies that might be widely applicable to the treatment of PDAC.

b. The Opportunity

Despite years of frustration, rapid progress has occurred over the past decade in understanding the intracellular signaling pathways controlled by the \( RAS \) oncogene. Furthermore, innovative chemical approaches to the development of therapeutic agents that target molecules, like RAS, that have previously been thought to be “undruggable” also recently have been developed. Thus, it is timely to consider the use
of novel technologies for the development of drugs that target RAS either directly or through interference with critical RAS-dependent biochemical pathways essential for tumor growth.

c. The Recommended Approach

To develop strategies that neutralize the RAS oncogene, consideration should be given to establishing a consortium of experts in RAS biology and drug development from academia, government, and industry to collaborate on developing new therapeutic molecules against this target. The possibilities for new therapeutic approaches include the use of fragment-based chemical scaffolds to produce compounds that directly bind RAS or RAS ligands, targeted efforts to control interacting RAS-mediated signal transduction pathways, novel applications of synthetic lethality, and new methods to deliver molecules capable of inducing RNA interference.

D. Summary

A workshop of pancreatic cancer experts assessed recent advances in the detection and treatment of pancreatic ductal adenocarcinoma and identified new scientific opportunities for research that might improve the outlook for patients with this disease. Based on an appreciation of our current understanding of PDAC biology and pathophysiology, workshop participants recommended four investigational initiatives for consideration:

1. **PDAC and Diabetes Mellitus:** Development of an in-depth understanding of the clinical and biological relationships between PDAC and recent onset of diabetes mellitus. This research effort should determine whether risk factors of sufficient specificity can be defined to justify a coordinated early detection program in this patient group.

2. **Biomarkers for Early Detection of PDAC and Its Precursors:** Evaluation of longitudinal screening protocols for patients at high risk of developing PDAC because of their genetic background or the presence of mucinous pancreatic cysts that could help to develop new molecular or imaging biomarkers capable of focusing the selection of patients for early surgical intervention.
3. Immunotherapy: Implementation of new therapeutic strategies based on a greater understanding of how PDAC interacts with the immunological environment.

4. RAS-Specific Therapeutics: Development of new treatment approaches utilizing recently discovered techniques in chemical biology that could support the discovery of molecules that interfere with the RAS-oncogene-dependent signaling pathways responsible for many of the pathological characteristics of PDAC.

Overall, workshop participants considered each of these four areas of PDAC research to hold considerable promise for making important contributions to our understanding, and for providing new scientific opportunities for better controlling the disease.
References


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