Strategic Plan for Addressing the Recommendations of the Pancreatic Cancer Progress Review Group

Prepared: September 2002

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Table of Contents

7 Investigate clinically important host-tumor interactions and develop novel therapeutic strategies to address them

Section 3

Risk, Prevention, Screening and Diagnosis

8 Identify genetic and environmental factors and gene-environment interactions that contribute to pancreatic cancer development

9 Develop, implement, and evaluate approaches to prevent pancreatic cancer in high-risk cohorts. Studies should be performed in humans and in animal models of early neoplasia

10 Identify and develop surveillance and diagnosis methods for early detection of pancreatic cancer and its precursors

Section 4

Therapy

11 Facilitate the discovery and drug development of targeted therapeutics

12 Facilitate development of preclinical and minimally invasive clinical techniques to assess targeted therapeutics

13 Accelerate research into the supportive care of patients with pancreatic cancer

Section 5

Communications and Health Care Delivery

14 Identify effective forms of healthcare provider communication with pancreatic cancer patients

15 Identify determinants of message effectiveness in aiding decision making by patients

16 Identify workforce requirements and costs of multidisciplinary clinical trials in pancreatic cancer. Create a Web-based repository to track, update, and categorize information on pancreatic cancer clinical trial costs

17 Determine the effectiveness of current practices in pancreatic cancer care and evaluate new strategies for managing difficult treatment and end-of-life issues

Section 6

Resource Priorities

18 Construct resources to provide access to a range of normal and neoplastic human pancreas samples and all types of biomaterials

19 Construct a relational database containing information on the biological profiles of normal and abnormal pancreas cells. Organize knowledge of signaling pathways into interrelated networks and systems

20 Develop biological sampling techniques that permit analyses of minute quantities of biological samples

21 Develop experimental model systems and establish gene-based model systems in vivo and ex vivo that faithfully recapitulate the complex biology of human pancreatic adenocarcinoma

22 Develop imaging systems for elucidating pancreatic cancer biology and for detecting and monitoring this disease. Develop a Web-based imaging library.

23 Develop new and expanded registries for identification of high-risk patients and kindreds. Develop a survivorship registry. Create consortia of large, aging cohorts for pooled analyses to elucidate causal factors.

24 Develop education materials for healthcare providers and investigators about pancreatic cancer risk assessment, evaluation protocols, and sample collection. Create new education, training, and communication tools for providers with education componen

25 Create technology centers for comprehensively assessing gene and protein expression for use in identifying biologic indicators of the presence and behavior of pancreatic cancer and its precursors

26 Develop mechanisms to facilitate investigator access to novel targeted therapeutic agents for preclinical studies and clinical trials

27 Develop infrastructure for molecular target assessment

28 Improve infrastructure for clinical trials and promote patient participation

29 Develop new models that can be applied and validated in community and academic research settings for analyzing cost to conduct clinical research in pancreatic cancer, assessing communication effectiveness, improving patient decision making, etc.

Appendix A

Pancreatic Cancer Strategic Plan Workgroup

Appendix B

Pancreatic Cancer Strategic Plan

Message From the NCI Director

Pancreatic Cancer, diagnosed in more than 29,000 people every year, is the fifth leading cause of cancer death in the U.S.**.** Most people with pancreatic cancer die within six months. Despite these tragic statistics, pancreatic cancer remains underrepresented in both clinical and basic research compared with other cancer sites. Future success will require a renewed commitment to focused scientific research, a robust infrastructure of supporting resources, and active coordination within the scientific and medical community. In an effort to help identify challenges ahead, the Pancreatic Cancer Progress Review Group (PanC PRG) has produced the first report of recommendations for progress and priorities in the area of pancreatic cancer research.

To address these recommendations, I am pleased to present the following plan detailing the National Cancer Institute's (NCI's) strategies- ongoing, new and proposed-for making progress against this devastating disease. The plan also reflects NCI's commitment to find ways to increase the number of dedicated researchers who will help make the greatest impact on better detection, diagnosis, treatment and prevention research.

I want to thank the PanC PRG and NCI's PanC Working Group for their exceptional efforts in identifying recommendations and strategies. Their expertise and advice will help us close the gaps in NCI's and the Nation's current research effort with sound, productive science. Using this blueprint, NCI will help develop strategies that

- Enhance expertise within the field with training, career development, and resources
- Strengthen our understanding of the biology of pancreatic cancer
- Determine risk factors, develop preventive strategies, and improve detection
- Improve the impact of therapy and advance health services research

Ultimately, this is not just a plan for NCI, but a call to action for the entire cancer research community. It begins the process of building the partnerships and collaborations necessary to successfully implement these strategies. By joining together, I am confident that we will make substantial scientific and medical progress to achieve the one goal that matters most: the reduction and elimination of the burden of pancreatic cancer for all who are in need.

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute

Table 1. New Activities and immediate strategies for pancreatic research

New Activities

Initiatives that NCI has started within the past year to address a priority.

Name	PRG Rec[1]	Page
Funded new Pancreatic Cancer SPOREs	1 2 8	13 16 27
Funded new Pancreatic Cancer mouse models through the Mouse Models of Human Cancer Consortium (MMHCC)	5 12 21	21 38 57
Designated the tumor microenvironment an Extraordinary Opportunity	6	23
Informed investigators of new Pancreatic Cancer funding opportunities for research about clinically important host-tumor interactions	7	25
Held state of the science meeting on management of Pancreatic Cancer symptoms	13	40
Worked with HMO Cancer Research Network to increase palliative care and end of life research	13	40
Developed general educational materials about clinical trials for advocates, patients and healthcare professionals	14 28	43 71
Created an online tutorial for healthcare professionals addressing practical aspects of implementing clinical trials	14 24	43 64
Developed tools for patients and healthcare providers to discuss pain management	14	43
Produced an online training course to inform investigators about the rights and welfare of human research subjects	15	45
Identified a palliative care coordinator to integrate relevant programs across NCI	17	48
Developed Shared Pathology Informatics Network to facilitate data sharing among research institutions	18	51
Established partnership to produce educational materials for healthcare professionals about end of life care	24	64
Funded phase 1 and phase 2 chemoprevention studies for Pancreatic Cancer through RAPID program	26	67

Immediate Strategies[2]

NCI is beginning to implement these strategies.

Name	PRG Rec[1]	Page
Encourage formation of a consortium of family registry studies	8	27
Encourage collaboration between parties with population resources such as the Cancer Genetics Network, Cancer Family Registries, EDRN and SPORES	9	31
Use SBIR/STTR grants for nanotechology research to develop new approaches for using extremely small samples for Pancreatic Cancer early detection	20	55

1 PRG Recommendations: The Pancreatic Cancer PRG made 29 recommendations for future research.

2 Speed of implementation will depend upon the availability of NCI staff to devote appropriate resources to the effort.

Table 2. Short-, medium- and long-term proposed new strategies for pancreatic research

Short-term strategies[3] *NCI is currently developing these strategies further as a first step towards implementation.*			Medium-term strategies[4] *NCI has determined that it will develop these strategies further in the near term.*			Long- term strategies[5]		
Name	**PRG Rec[6]**	**Page**	**Name**	**PRG Rec[6]**	**Page**	**Name**	**PRG Rec[6]**	**Page**
Expand the Transition Career Development Award (K22) to extend funding period and include all scientists	1	13	Fund meritorious Pancreatic Cancer projects that did not receive SPORE grants	1 4 5	13 19 21	Consider noncompetitive renewals (as done for Merit Award renewals) for long term studies	10	32
Establish pay line for pancreatic cancer-relevant research that is 50 percent higher than the overall pay line for NCI research grants.	3	17	Expand the National Research Service Award to increase the number of qualified Pancreatic Cancer mentors	1	13	Expand Rapid Access to Intervention Development (RAID) and Rapid Access to NCI Discovery Resources Program (R*A*N*D)	11 27	35 68
Jointly fund research on normal pancreas biology and pathogenesis of Pancreatic Cancer with NINDDK	4 5 6	19 21 23	Support large case-control studies through the Cancer Research Network in HMOs to improve understanding of Pancreatic Cancer risk factors	8 14 17 23	27 43 48 61	Fund supplements to molecular imaging centers to promote collaborations with drug developers	12	38
Expand cohort-consortium for Pancreatic Cancer	8 10 23	27 32 61	Fund up to 3 grant supplements for tissue acquisition and informatics	11 18	35 51	Develop future funding proposals in cancer symptom management to advance supportive care research	13	40
Identify new markers for Pancreatic Cancer early detection through EDRN and Center for Proteomics	10	32	Foster partnerships with industry to develop promising anti- Pancreatic Cancer compounds	11	35	Create molecular profiling project for Pancreatic Cancer to identify gene expression patterns in normal and tumor cells	23	61
			Provide online educational materials about Pancreatic Cancer	14 15 28	43 45 71	Fund testing of promising therapeutic agents for Pancreatic Cancer	26	67
			Fund competing supplements to develop organotypic models of Pancreatic Cancer	21	57	Support development of Barrett's esophagus GI network and promote extension to include Pancreatic Cancer research	28	71
			Support a database for imaging research	22	59			

3 Actual implementation will depend upon the availability of funds, the receipt of high-quality applications and a final determination that the strategy is feasible and scientifically sound.
4 Further consideration of these strategies will take place over the next several months.
5 While this strategy is important, NCI will not be able to implement it in the near future.

6 PRG Recommendations: The Pancreatic Cancer PRG made 29 recommendations for future research.

Strategic Plan

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In 2001, an estimated 29,200 new cases were diagnosed, and 28,900 people died from the disease. Given the incidence and almost universal fatality of pancreatic cancer, the National Cancer Institute (NCI) believes that substantially increased research efforts are clearly warranted to understand, prevent, and control this disease. Since pancreatic cancer has been understudied in both basic research laboratories and the clinic, greater commitment of resources and scientific expertise is needed to achieve significant improvements in pancreatic cancer diagnosis and management.

The Pancreatic Cancer Progress Review Group (PRG)

In 2000, NCI established a progress review group (PRG) to assess past progress and identify future pancreatic cancer research opportunities. The Pancreatic Cancer Progress Review Group (PANC-PRG) members identified and prioritized opportunities and needs across the continuum of pancreatic cancer research, as well as the scientific resources required to address those needs.

Progress Review Group Overview

- ***Composed of prominent scientists, clinicians, consumer advocates, and industry representatives***
- ***Organized to assess state of knowledge and understanding***
- ***Reviewed grant portfolio and other indicators***
- ***Discussed current initiatives and strategies***
- ***Developed specific recommendations***
- ***Participated in follow-up session to review results and ommendations***

The PANC-PRG was composed of approximately 25 prominent scientists, clinicians, consumer advocates, and industry representatives from the United States (and Canada), representing a wide spectrum of scientific expertise. Members were selected for their ability to broadly identify and prioritize scientific needs and opportunities that are critical to advancing cancer research.

The progress review began in May 2000. The PANC-PRG Roundtable, composed of over 100 scientists, clinicians, and consumer advocates, was held in September 2000. Scientific priorities, related recommendations, and specific resource needs were established and prioritized in sessions on tumor biology, risk/prevention/screening/diagnosis, therapy, and health services research. As similar issues emerged from the breakout sessions, they were organized into 36 crosscutting recommendations, which were documented in the *Pancreatic Cancer PRG Report*. A follow-up meeting with the NCI director was held in July 2001 to discuss the report and provide a framework for addressing the recommendations. The report, follow-up discussions, and an analysis of NCI's existing research initiatives and projects served as key inputs in the development of this strategic plan.

Implementation Approach

In order to develop a comprehensive strategic plan, the NCI Office of Science Planning and Assessment compared the PANC-PRG's recommendations to existing NCI initiatives and projects. It also organized a working group (see roster in appendix A) to review and strengthen the implementation plan, map NCI's projects to the recommendations, and develop strategies for addressing the most important research needs and gaps. Due to funding and other limitations, NCI cannot immediately address all issues raised and recommendations made by the PANC-PRG. Consequently, to make the best use of limited research dollars and to fully utilize NIH's existing infrastructure and funding mechanisms, a strategic plan approach was chosen that:

- Focuses on investigator-initiated research and other mechanisms that provide critical research support,

- Builds on existing broad-based initiatives and leverages existing NCI funding mechanisms,

- Addresses the highest priority areas and gaps between resources and needs.

This implementation plan is organized into six sections representing the principal topic areas in the PRG's report:

- Health of the Field- describing strategies for addressing current research and funding levels for pancreatic cancer and critical issues such as workforce development and training needs, and resource deployment and organization.

- Tumor Biology- achieving a more complete understanding of the normal biology of the pancreas, elucidating the development of pancreatic adenocarcinoma, investigating clinically important host-tumor interactions and develop new therapeutic strategies to address them.

- Risk/Prevention/Screening/Diagnosis- determining risk factors (genetic, environmental and gene-environment interactions), and developing preventive strategies and improved detection technologies for pancreatic cancer.

- Therapy- facilitating the discovery and development of targeted therapeutics, developing and validating preclinical models of human pancreatic cancer, and accelerating research into the supportive care of patients with pancreatic cancer.

- Health Services Research- identifying effective forms of health care provider communication with pancreatic cancer patients, identifying determinants of message effectiveness in aiding decision making by patients, and determining the efficacy of current practices in pancreatic cancer diagnosis and care.

- Resource Priorities- identifying key resources and tools needed for progress in pancreatic cancer research.

For each recommendation within each topic area, the plan provides the following:

- Issues and Challenges: a description of, and justification for, research;

- Ongoing Activities: NCI initiatives that either currently fund pancreatic-specific projects that address the recommendations, or are accepting applications for future funding;

- New Activities: new NCI initiatives started within the past year that address the recommendation;

- Proposed Strategies: initiatives that NCI is exploring as a means to fill gaps in research and address the recommendation.

A table containing all PRG recommendations and relevant NCI initiatives and projects is included as Appendix B. NCI will use this information as a baseline for tracking and monitoring progress over the next 2-3 years.

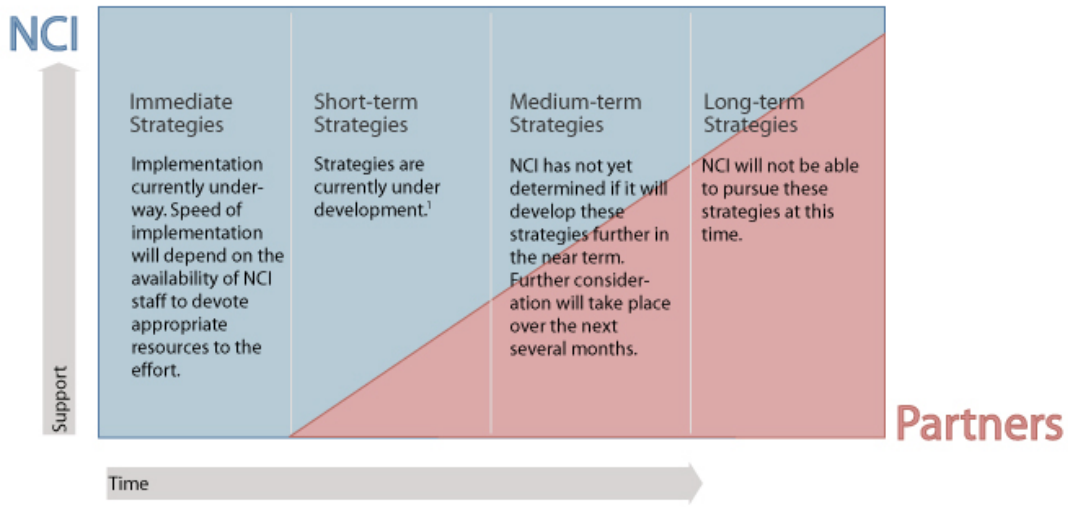
Strategic Plan to Address PRG Recommendations[1]

The NCI will do everything in its power to expedite progress against Pancreatic Cancer The Institute will:

- implement as many of the proposed strategies in this document as it can
- pursue partnerships where they make sense
- encourage and assist other organizations to play a leading role in implementing those strategies that transcend NCI's mandate or resources
- seek collaborations and advice on all fronts as it implements this plan.

For each proposed strategy in this document, the Institute's plan of action is indicated in italics. There are four possible plans of action for each strategy.

Figure 1: Implementation Phases for Proposed Strategies



[1] The ability to implement any new strategy is dependent on: (1) a final determination that the strategy is vital, feasible, and sound; (2) the availability of funds; and (3) the receipt of high-quality applications or proposals.

Section 1
Health of the Field

The PANC-PRG provided a unique opportunity for a wide range of scientists, clinicians, and advocates to help establish an agenda for pancreatic tumor research. This section describes strategies to address current research and funding levels for pancreatic cancer; critical issues, such as personnel development and training needs; and resource deployment and organization.

Pancreatic cancer research currently suffers from a variety of unmet training, career development, and organizational needs, as well as difficulty in obtaining funding. As a result, physician-scientists have demonstrated low levels of enthusiasm for pancreatic cancer research and very few researchers focus on research in this field.

"Pancreatic cancer research currently suffers from a variety of unmet training, career development, and organizational needs. Very few researchers focus on

During the PANC-PRG Roundtable, the lack of a critical mass of personnel and resources dedicated to pancreatic cancer research was often cited. Three overarching, high-impact strategies were identified to augment pancreatic cancer research levels overall and speed progress in addressing the disease:

1. Specialized training programs in pancreatic cancer research,
2. An NIH-based coordinating mechanism for pancreatic cancer research applications, and
3. Centers of excellence for pancreatic cancer care and research.

1 Develop sustained, expanded training and career development efforts in pancreatic cancer research and care

Introduction

Training new investigators and encouraging established investigators to focus on pancreatic cancer is essential to increase the number of researchers focusing on this disease. Although NCI and NIH currently have in place several training mechanisms to support career development in cancer research, specialized training in pancreatic cancer research is critical because multidisciplinary approaches are required at all levels to address the disease. For example, multidisciplinary collaborations are crucial to making progress in risk factor determination, risk reduction, early detection, and treatment.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

Transition Career Development Award provides "protected time" for newly independent investigators to develop and receive support for 3 years for their initial cancer research programs. This award facilitates the transition of investigators from the mentored to the independent stage of their careers in cancer research. One application focused on pancreatic cancer, "Mechanism of Tumor Suppression by p27," has been funded.

Research Training and Career Development Awards for predoctoral candidates, postdoctoral candidates, junior faculty in independent research positions, and established investigators provide a continuum of opportunities as individuals proceed through these four stages of a career track. There were 298 pancreatic grants active in the year 2000.

The following initiatives could potentially address pancreatic cancer:

Cancer Education Grant Program (CEGP) is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will have an impact on reducing cancer incidence, mortality, and morbidity, as well as on improving the quality of life of cancer patients. The CEGP will accept investigator-initiated grant applications that pursue a wide spectrum of objectives. Education grants can focus on education activities before, during, and after the completion of a doctoral-level degree, as long as they address a need that is not fulfilled adequately by any other grant mechanism available at NIH and are dedicated to areas of particular concern to the National Cancer Program. None of the applications funded to date focuses on pancreatic cancer.

NCI Scholars Program supports outstanding new investigators who are beginning their independent research careers. NCI scholars first receive NCI intramural funding mechanism for up to 4 years as they work at the intramural campuses of NCI. Once they continue their careers at an institution of their choice, the NCI scholars receive support through an extramural funding mechanism (K22) for 2 years.

National Research Service Award (NSRA) provides predoctoral training support for doctoral candidates that have successfully completed their comprehensive examinations or the equivalent by the time of award and will be performing dissertation research and training.

New Activities Initiated Within the Past Year

NCI will fund at least three meritorious, peer-reviewed pancreatic cancer-specific **Specialized Programs of Research Excellence (SPOREs)** next year.

- As it did in the early development of the prostate cancer SPOREs, NCI may loosen human endpoint requirements in pancreatic cancer SPORE research projects until the field of translational research in pancreatic cancer matures.
- New pancreatic SPOREs will be encouraged to develop expanded human tissue collections beyond their institutional boundaries. NCI may allow SPOREs to exceed the current budget cap to develop expanded tissue collections, banking activities, and data from high-risk individuals, including family registries.
- Pancreatic SPOREs are expected to use developmental funds to explore new scientific opportunities and encourage new and established investigators to develop their skills in pancreatic cancer research.
- NCI may require all new gastrointestinal SPOREs to include at least one pancreatic cancer project.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Expand the Transition Career Development Award (K22) to all scientists (including basic researchers) pursuing a research project that is at least 50 percent relevant to pancreatic cancer. Fund awards for 5 years instead of 3 years. At the end of the 3rd year or beginning of the 4th year, the applicant will be required to submit an application for research that is 100 percent relevant to pancreatic cancer. The Transition Career Development Award protects the time of junior faculty while they develop their research programs and submit competitive research grant applications. Extending the award from 3 to 5 years and removing the restriction to individuals with an M.D. and prevention and control scientists to include basic scientists will provide more protected time to individuals wishing to pursue careers in pancreatic cancer research, which they will need because the field is so difficult to approach; and open up the award to all basic, clinical, and prevention and control scientists, which will stimulate the entire field.[a]

- Fund highly meritorious projects within unsuccessful pancreatic SPORE or program project applications.[b]

- Expand the NRSA by focusing on institutional awards (T32) rather than individual awards (F32) and on training programs that are conducted in multi-institutional settings. This will help assemble a critical mass of mentors in pancreatic cancer research that represent the basic, clinical, and prevention and control sciences. A few good T32 awards could begin to have an impact on the field and would formalize training programs in pancreatic cancer. [a]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

2 Establish centers of excellence for pancreatic cancer research and care

Introduction

Centers of excellence in pancreatic cancer would optimize both research and patient outcomes and facilitate the diffusion of knowledge into the community. These centers would offer broad clinical expertise, thereby attracting significant patient volume; provide state-of-the-art diagnosis and treatment; and bring together scientific investigators evaluating issues critical to this disease. Organ transplantation and trauma models have improved research and care in those fields by concentrating resources and developing appropriate infrastructures, and these could be used to help improve opportunities for focused pancreatic cancer research.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

- **SPOREs** support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal). Two SPOREs in gastrointestinal cancer at Johns Hopkins University and the University of Nebraska Medical Center focus heavily on pancreatic cancer.

New Activities Initiated within the Past Year

NCI will fund at least three meritorious, peer-reviewed pancreatic cancer-specific **SPOREs** next year.

- As it did in the early development of the prostate cancer SPOREs, NCI may loosen human endpoint requirements in pancreatic cancer SPORE research projects until the field of translational research in pancreatic cancer matures.
- New pancreatic SPOREs will be encouraged to develop expanded human tissue collections beyond their institutional boundaries. NCI may allow SPOREs to exceed the current budget cap to develop expanded tissue collections, banking activities, and data from high-risk individuals, including family registries.
- Pancreatic SPOREs are expected to use developmental funds to explore new scientific opportunities and encourage new and established investigators to develop their skills in pancreatic cancer research.
- NCI may require all new gastrointestinal SPOREs to include at least one pancreatic cancer project.

3 Create an interdisciplinary coordinating mechanism to track pancreatic cancer research applications and monitor funding patterns

Introduction

The PANC-PRG noted that increasing the number of NIH-funded research projects in pancreatic cancer could be accomplished in several ways, such as by establishing an interdisciplinary coordinating mechanism to foster and track pancreatic cancer research applications and progress. The PRG suggested that a coordination committee help direct applications to appropriate study sections for review, foster special funding consideration for new investigators, encourage exception funding for applications meeting identified needs, and coordinate extramural and intramural initiatives.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- The pay line for pancreatic cancer-relevant research will be 50 percent higher than the overall pay line for NCI research grants. Only those applications that are 100 percent relevant to pancreatic cancer will be eligible for this higher exception payline level. To mark an application for consideration, an investigator should cite the PRG Report and include the following language in the Background section of the grant application: The research described in this application is 100 percent relevant to pancreatic cancer.[a]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

Section 2
Tumor Biology

The biology of pancreatic cancer is difficult to study for several reasons. Pancreatic tumors display insidious growth properties—they display few symptoms at early stages and are therefore undiagnosed for long periods of time. The molecular aspects of normal cell differentiation and development of the pancreas are poorly understood. The molecular processes involved in the development of benign and malignant pancreatic diseases are known in part, although the nature and origin of the precursor cells for pancreatic cancer have not been delineated. The relationships between differing clinical presentations of pancreatic cancer, prognosis, and the mechanisms of drug resistance are undefined. The contribution of the tumor's supportive tissue matrix (stroma) and other host factors to patient prognosis has not been studied. Well-characterized tissue of sufficient quality for molecular analysis, particularly for early lesions, is scarce.

"Pancreatic tumors display few symptoms at early stages and are therefore undiagnosed for long periods of time. Molecular aspects of normal cell differentiation and development of the pancreas are poorly understood."

To address the research needs in pancreatic tumor biology, the PANC-PRG identified four priorities:

1. Achieve a more complete understanding of the normal biology of the pancreas,
2. Elucidate the development of pancreatic adenocarcinoma,
3. Study the natural history of the pancreatic cancer stroma and the formation of reactive tissue in the stroma in response to the presence of a tumor (desmoplasia),
4. Investigate clinically important host-tumor interactions and develop new therapeutic strategies to address them.

4 Achieve a more complete understanding of the normal biology of the pancreas

Introduction

New information about pancreatic development has led to insights in nuclear transcription factors and signaling pathways that regulate pancreatic progenitor/precursor cell expansion and differentiation. However, the true cell of origin for pancreatic ductal adenocarcinoma remains unknown. Ductal adenocarcinomas may arise from fully differentiated ductal epithelium, other cell lineages (e.g., acinar cells) by means of transdifferentiation/dedifferentiation, or pluripotent precursor/progenitor cells. A more complete understanding of the normal pancreas at each stage of development is essential for future advances in detecting, preventing, and treating pancreatic cancer.

Developmental biology techniques should prove useful for investigating cell lineage relationships in various animal models of pancreatic cancer and, ultimately, in human disease. Understanding precursor/progenitor cell biology has greatly aided the development of diagnostic and therapeutic tools in leukemias and cancer immunology, so such knowledge is likely to be valuable for improving pancreatic cancer prevention, diagnosis, and treatment. Therefore, a high priority of research should be to isolate, characterize, and propagate cells that initially differentiate into the gland itself. These cells, or their immediate descendants, are likely targets for the various agents that cause pancreatic cancer and may be potential targets for chemoprevention.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

The Cancer Genome Anatomy Project (CGAP) is an interdisciplinary program established to generate the information and technological tools needed to decipher the molecular anatomy of the cancer cell. CGAP's primary goal is to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. All data and material generated through CGAP are made available to the research community without restrictions. Using pancreatic cancer tissue, CGAP scientists have uncovered over 600 expressed genes that may serve as targets for molecular therapies.

The following initiative could potentially address pancreatic cancer:

Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation are intended to stimulate the initiation and/or continued development of high-risk/high-impact technologies that target the sensitive quantitation of the wide spectrum of proteins in human tissues. Investigators are developing technologies for both comprehensive identification and sensitive quantitation of proteins translated and modified in human tumor specimens.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Partner with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to issue a Program Announcement (PAR) to stimulate research on the normal biology of the pancreas and on the pathogenesis of pancreatic cancer. Prior to issuing the PAR, sponsor a workshop on predisposing conditions of the pancreas to foster multidisciplinary collaborations and identify research opportunities and needs in normal biology of the pancreas and pathogenesis of pancreatic cancer. Invite participation of NIDDK and National Institute of Child Health and Human Development (NICHD). [a]

- Fund highly meritorious projects within unsuccessful pancreatic SPORE or program project applications.[b]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

5 Elucidate the pathogenesis of pancreatic adenocarcinoma

Introduction

Current knowledge of the genetics and biology of precursor lesions of pancreatic cancer and their progression to invasive, metastatic disease is incomplete. Significant gaps exist in our understanding of predisposition/modifier genes and how the fundamental genetic alterations affect the signaling pathways that control the cell cycle and differentiation of ductal epithelial cells; how they initiate and induce tumorigenesis, tumor invasion, and metastasis; and how they generate resistance to chemotherapy and radiation. This information is crucial, given the unique biological and clinical characteristics of pancreatic adenocarcinoma.

In addition, genetic changes and expression differences must be correlated with cellular, histologic, and clinical phenotypes to determine whether specific tumor subtypes exist. For example, carcinomas with microsatellite instability may differ from conventional adenocarcinomas in their histologic appearance, prognosis, aggressiveness, and response to cytotoxic drugs. Clearly identifying pancreatic tumor subtypes will improve drug development, intervention selection, and prognosis assessment.

Innate invasive and metastatic potential is a distinctive feature of most pancreatic adenocarcinomas; metastases to the liver almost always develop, even after potentially "curative" surgery that reduces local recurrence. Little is known about the genetic mechanisms and signaling pathways responsible for pancreatic cancer metastasis.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

Innovative Technologies for the Molecular Analysis of Cancer: Phased innovation Award supports the development of technologies for the detection of alterations and instabilities of genomic DNA; measurement of the expression of genes and gene products; analysis and detection of gene and/or cellular products, including post-translational modification, and function of proteins; identification and characterization of exogenous infectious agents in cancer; and assays of the function of major signal transduction networks involved in cancer. One of the applications funded, "Gene expression profiling of known and unknown primary cancers," applies to several cancers, including pancreas, and will define gene expression profiles and determine diagnostic clusters of gene expression.

The Molecular and Cellular Biology of Metastatic Tumor Cells initiative provides funds for preliminary research projects that will form the basis of future R01 applications to investigate metastasis. The intent is to (1) foster collaborative research between investigators with basic molecular and cellular biological and biochemical research experience and those with experience in metastasis research, and (2) increase the number of laboratories and investigators addressing issues of metastasis. One grant, "Function of NFKB in cancer metastasis," is

determining the roles of Rel A gene in pancreatic metastasis and testing inhibitors of Rel A in repressing metastasis in an experimental model.

Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer encourage experienced and new investigators to pursue basic and clinical investigations into the molecular genetics of acute and chronic pancreatitis as well as the "preneoplastic" genetic changes that predispose individuals to adenocarcinoma of the pancreas. Basic studies include the generation of transgenic animal models of pancreatitis that show inherited forms of pancreatitis. Investigators are developing organ-specific transgenic mice that exhibit acute or chronic pancreatitis. Applications are currently funded under this program announcement include:

- The Role of RE1A in Human Adenocarcinoma of the Pancreas
- Genetic Mechanisms in Experimental Pancreatic Cancer
- Discovery of New Secreted Proteins of Pancreatic Cancer
- Interferon Regulatory Factor 2 Functions
- The PanINs of Pancreatitis, Pancreas Cancer and Controls
- Conditional Deletion of DPC4 in Pancreatic Tumorigenesis

The following initiative could potentially address pancreatic cancer:

Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation (see page 19)

New Activities Initiated Within the Past Year

Mouse Models of Human Cancers Consortium investigators are receiving supplements from NCI to further the development of pancreatic cancer mouse models.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Partner with NIDDK to issue a PAR to stimulate research on the normal biology of the pancreas and on the pathogenesis of Pancreatic Cancer. (see page 20)
- Fund highly meritorious projects within unsuccessful pancreatic SPORE or program project applications. [b]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

6 Study the natural history of the pancreatic stroma and desmoplasia

Introduction

The origin and functions of the intense desmoplastic reaction observed in most cases of pancreatic ductal adenocarcinoma is a poorly understood area of pancreatic cancer pathobiology. A number of complex biochemical alterations contribute to this reaction and to the formation of the resulting stroma. Several roles have been hypothesized for the stroma in pancreatic cancer development and maintenance, but a better understanding is needed of the basic mechanisms involved in the development of the stroma, its interaction with pancreatic cancer cells, and its role in the pathogenesis of pancreatic cancer.

The PANC-PRG recommended evaluating the role of the stroma in normal pancreatic tissue, chronic pancreatitis, and pancreatic cancer. The stroma may promote the spread of cancer, block the effectiveness of therapy, and interfere with immune responses to malignant lesions. To assess these possibilities, it is important to determine the origin of the desmoplastic reaction, and whether cancer growth and spread will be arrested if the stroma is altered. In addition, the potential of the stroma to complicate or interfere with diagnostic or surveillance procedures should be investigated.

Ongoing Activities

The following initiative has ongoing projects in pancreatic cancer:

The Molecular and Cellular Biology of Metastatic Tumor Cells initiative (see page 21)

The following initiative could potentially address pancreatic cancer:

Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation (see page 19)

New Activities Initiated Within the Past Year

The tumor microenvironment has been incorporated into the bypass budget as an **Extraordinary Opportunity** area for NCI. Among the initiatives proposed for this Extraordinary Opportunity that may be relevant to this recommendation are proposals to fund:

- Studies to identify the factors used by tumor cells to activate cells in the tumor microenvironment, thereby allowing tumor growth and progression;
- Studies to identify the origin of the cells and factors that comprise the tumor microenvironment; and
- Functional and molecular imaging studies to visualize the physiologic, cellular, and molecular processes in living tissues. These studies should focus on (1) identifying the subtle and important early changes in the molecular biology of tumors and the microenvironment as

-
- tumors become malignant, and (2) monitoring the effects of therapy on tumor cells and the tumor microenvironment.

Proposed Strategies to Address Gaps

- Partner with NIDDK to issue a PAR to stimulate research on the normal biology of the pancreas and on the pathogenesis of pancreatic cancer. (see page 20)

e. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

f. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

g. While these strategies are important, NCI will not be able to implement them in the near term.

NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

7 Investigate clinically important host-tumor interactions and develop novel therapeutic strategies to address them

Introduction

Studies aimed at understanding the immune system's role in controlling tumor progression and the role of angiogenesis and apoptosis mechanisms in pancreatic tumor development, progression, and metastasis are underrepresented in the literature. Even less emphasis has been placed on understanding the mechanisms by which pancreatic cancer induces constitutional symptoms such as cachexia, a problem that appears to contribute significantly to the rapid demise of patients with this disease. Investigating these research areas offers opportunities to define new targets for the treatment and control of pancreatic cancer, and for improved patient performance status and quality of life. Developing therapeutic strategies to address host-tumor interactions would be accelerated by developing and testing novel vaccine approaches and evaluating the effects of angiogenesis inhibitors in animal tumor models that more closely resemble human pancreatic cancer.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

Phased Application Awards in Cancer Prognosis and Prediction evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy. This will provide tools to improve clinical decisionmaking in the care of cancer patients.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials foster collaborations and interactions between basic researchers, private industry, and clinical investigators to perform translational research on promising predictive and prognostic markers. These studies focus on correlations between biologic features of tissue specimens collected from the NCI Clinical Trials Cooperative Groups or other large multi-institutional clinical trials and patient outcomes. The markers will be assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. No projects under this initiative currently focus on pancreatic cancer.

New Activities Initiated Within the Past Year

Enhance promotion of Phased Application Awards and Correlative Studies to Cooperative Groups and SPOREs, and inform their investigators of extra funding for pancreatic cancer research.

Section 3
Risk, Prevention, Screening and Diagnosis

Pancreatic cancer patients seldom exhibit disease-specific symptoms until the cancer reaches an advanced stage, and tumors 1-2 cm in size often have already spread beyond the local area of the primary tumor. For these reasons, determining risk factors (genetic, environmental, and gene-environment interactions), and developing preventive strategies and improved detection technologies are critically important. The three most important research priorities are to:

"Determining risk factors - genetic, environmental and gene-environment interactions- and developing preventive strategies and improved detection technologies are critically important in pancreatic cancer."

- Identify genetic factors, environmental factors, and gene-environment interactions that contribute to pancreatic cancer development.

- Develop, implement, and evaluate approaches to prevent pancreatic cancer in high-risk cohorts (e.g., familial pancreatic cancer, hereditary pancreatitis, older age). Studies should be performed in humans and in animal models of early neoplasia (e.g., PanIN-3).

- Identify and develop surveillance and early detection methods for diagnosis of pancreatic cancer and its precursors.

8 Identify genetic and environmental factors and gene-environment interactions that contribute to pancreatic cancer development

Introduction

Intensive research efforts have led to the discovery of a number of rare genes and environmental factors that contribute to human pancreatic cancer. However, more common genes, genetic polymorphisms, and specific risk factors have yet to be identified, and gene-environment interactions must be investigated to understand their significance.

Many barriers have limited progress in identifying pancreatic cancer genes and risk factors. The lack of early disease markers, the late onset of disease-specific symptoms, the shortage of high-quality biological samples from affected and linked family members, and the limited number of pancreatic cancer families included in research protocols hinder efforts to pinpoint pancreatic cancer genes by linkage analysis. Thus, many of the genetic defects underlying familial pancreatic cancer and hereditary pancreatitis still are unknown.

Obtaining appropriate biological specimens continues to be a critical problem for investigations of genetic and environmental factors, and gene-environment interactions. The absence of samples readily available for high-volume/high-throughput analyses in epidemiologic studies has limited the potential impact of such correlative laboratory studies. In addition, the rapidly fatal nature of the disease and the small number of patients that normally are accrued in any one geographic area make cooperative studies and data pooling essential to progress.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

The Early Detection Research Network (EDRN) identifies and evaluates biomarkers and technologies for earlier detection and risk assessment. EDRN is a national network of academic and industry investigators with expertise in laboratory and clinical sciences, biostatistics, informatics, and public health. Research is funded through EDRN's 18 Biomarkers Developmental Laboratories, three Biomarkers Validation Laboratories, eight Clinical/Epidemiology Centers, and the Data Management and Coordinating Center. Two grants are partially focused on pancreatic cancer: "Cancer Risk Detection by Mutational Load Distribution" and "EDRN: The Hereditary Cancer Clinical Center."

SPOREs support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal). Two SPOREs in gastrointestinal cancer at Johns Hopkins University and the University of Nebraska Medical Center focus heavily on pancreatic cancer.

The Mouse Models of Human Cancer Consortium is designed to derive or refine accurate cancer-prone mouse models of human malignancies; provide a comprehensive analysis of their phenotype and genotype; validate them for use by cancer researchers for a variety of investigations, including testing therapeutic, prevention, early detection, or imaging strategies; and assure their availability to the research community. Three funded applications focus in part on pancreatic cancer:

- Mouse Models for Cancer
- Mouse cancer models via TGF-Beta RII loss
- Mouse models of GI cancer

The following initiatives could potentially address pancreatic cancer:

Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer encourage experienced and new investigators to pursue basic and clinical investigations into the molecular genetics of acute and chronic pancreatitis as well as the "preneoplastic" genetic changes that predispose individuals to adenocarcinoma of the pancreas. Basic studies include the generation of transgenic animal models of pancreatitis that show inherited forms of pancreatitis. Investigators are developing organ-specific transgenic mice that exhibit acute or chronic pancreatitis. Six applications are currently funded under this program announcement. Applications funded under this program announcement include:

- The Role of RE1A in Human Adenocarcinoma of the Pancreas
- Genetic Mechanisms in Experimental Pancreatic Cancer
- Discovery of New Secreted Proteins of Pancreatic Cancer
- Interferon Regulatory Factor 2 Functions
- The PanINs of Pancreatitis, Pancreas Cancer and Controls
- Conditional Deletion of DPC4 in Pancreatic Tumorigenesis

Exploratory Studies in Cancer Detection, Prognosis, and Prediction promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. This initiative supports translational studies that identify promising new means for cancer detection and diagnosis and that provide the initial, critical information necessary to decide whether potential clinical utility justifies further investment. None of the funded applications focuses on pancreatic cancer.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials foster collaborations and interactions between basic researchers, private industry, and clinical investigators to perform translational research on promising predictive and prognostic markers. These studies focus on correlations between biologic features of tissue specimens collected from the NCI Clinical Trials Cooperative Groups or other large multi-institutional clinical trials and patient outcomes. The markers will be assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. None of the funded applications focus on pancreatic cancer.

Phased Application Awards in Cancer Prognosis and Prediction evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy. This will provide tools to improve clinical decisionmaking in the care of cancer patients.

The Cancer Genetics Network (CGN) supports collaborative investigations of the genetic basis of cancer susceptibility; explores mechanisms to integrate this new knowledge into medical practice; and identifies means of addressing the associated psychosocial, ethical, legal, and public health issues. The CGN steering committee has approved two pilot studies whose start dates depend on the availability of funds. One focuses on the feasibility of recruitment of pancreatic patients and their families and the role of polymorphisms in enzymes related to tobacco-derived carcinogens, folate, and cyclooxygenase (COX)-2 on pancreatic cancer risk. The other will examine the risk of pancreatic and breast cancers in relatives of patients with pancreatic cancer compared to relatives of controls.

New Activities Initiated Within the Past Year

NCI will fund at least three meritorious, peer-reviewed pancreatic cancer-specific **SPOREs** next year.

- As it did in the early development of the prostate cancer SPOREs, NCI may loosen human endpoint requirements in pancreatic cancer SPORE research projects until the field of translational research in pancreatic cancer matures.
- New pancreatic SPOREs will be encouraged to develop expanded human tissue collections beyond their institutional boundaries. NCI may allow SPOREs to exceed the current budget cap to develop expanded tissue collections, banking activities, and data from high-risk individuals, including family registries.
- Pancreatic SPOREs are expected to use developmental funds to explore new scientific opportunities and encourage new and established investigators to develop their skills in pancreatic cancer research.
- NCI may require all new gastrointestinal SPOREs to include at least one pancreatic cancer project.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Build on the NCI Cohort Consortium, which consists of investigators of 21 ongoing prospective studies of large population groups. Collectively, these cohorts may have at least 1,500 to 2,000 pancreatic cancer patients available for study. Use of the cohort consortium will provide the opportunity to evaluate many important hypotheses concerning the roles of dietary factors, growth factors, genetic susceptibility, gene/environment interactions, and metabolic pathways in the etiology of pancreatic cancer. This approach has the unique advantage of providing information on environmental/host risk factors and biologic specimens collected prior to disease occurrence on a large number of pancreatic cancer patients. [a]

- Support a large, population-based, case-control study of pancreatic cancer through the Cancer Research Network in health maintenance organizations (HMOs) that have "real-time" electronic reporting of pathology, laboratory, radiology, and outpatient physician visit findings, resulting in ultra-rapid identification of pancreatic cancer within 10 working days of diagnosis. This study will develop a better understanding of risk factors for sporadic and familial pancreatic cancer so that this knowledge can be used for earlier detection and prevention. Data collection will include:

  - Patient interviews about prior medical history and personal and family history of cancer, diabetes, other diseases, smoking, alcohol consumption, physical activity, and occupational exposures;
  - Food frequency questionnaire;
  - Blood specimen for storage as whole blood, plasma, and DNA extraction;
  - Review of electronic and paper medical records for laboratory evidence of prior diabetes, glucose intolerance, elevated lactate dehydrogenase, and other medical conditions that may increase the risk of pancreatic cancer;
  - Cost data from electronic records for future studies of the cost-effectiveness of screening strategies.
  - Consent for passive long-term follow-up for future studies of prognostic markers.[c]

- Encourage formation of a consortium of family registry studies, such as combining the efforts of two or three proposals.[d]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

9 Develop, implement, and evaluate approaches to prevent pancreatic cancer in high-risk cohorts. Studies should be performed in humans and in animal models of early neoplasia

Introduction

Pancreatic cancer usually is identified after the tumor has metastasized beyond the pancreas, and treatment is relatively ineffective. When mutations and polymorphisms that predispose to pancreatic cancer are identified and environmental risk factors are determined, prevention of pancreatic cancer in high-risk groups may become possible. Currently, the ability to consider preventive strategies is limited.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The Cancer Genetics Network (see page 29)

Expand the Rapid Access to Preventive Intervention Development (RAPID) Program in response to high demand. RAPID makes available to academic investigators the preclinical and early clinical drug development contract resources of NCI's Division of Cancer Prevention. The goal of RAPID is the rapid movement of novel molecules and concepts from the laboratory to the clinic for clinical trials of efficacy. RAPID will assist investigators who submit successful requests by providing any (or all) of the preclinical and phase 1 clinical developmental requirements for phase 2 clinical efficacy trials. These include, for example, preclinical pharmacology, toxicology, and efficacy studies; bulk supply, good manufacturing practices (GMP), and formulation; regulatory and investigational new drug (IND) support; and phase 1 clinical studies. Suitable agents for RAPID may range from single chemical or biological entities to defined complex mixtures with the potential to prevent, reverse, or delay carcinogenesis.

Proposed Strategies to Address Gaps

- Encourage collaborations between the CGN, Cancer Family Registries, EDRN, SPOREs, and other parties with population resources, as well as with the Mouse Models of Human Cancer Consortium and its animal models.[d]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

10 Identify and develop surveillance and diagnosis methods for early detection of pancreatic cancer and its precursors

Introduction

Several major barriers to surveillance and diagnosis in pancreatic cancer have been identified. For example, no effective screening protocols are available for any high-risk cohort, and markers —both current serum tumor markers and molecular markers ascertained in pancreatic duct aspirates—are insensitive and nonspecific. Further, detection with available imaging modalities is challenging in a disease characterized by metastatic tumor spread even when the primary tumor is very small. Imaging with computed tomography, magnetic resonance, endoscopic retrograde cholangiopancreatography, laproscopy, PET and endoscopic ultrasound is not specific for pancreatic cancer in the presence of other pancreatic pathology (e.g., chronic pancreatitis, mucinous cystadenoma, or intraductal papillary mucinous neoplasm). In addition, long-term funding would facilitate collection of specimens, clinical information, and natural history data to test the value of tumor markers and assess imaging modalities. Finally, a major barrier to pancreatic cancer research has been the lack of a well-structured biospecimen repository containing specimens that have been well annotated (e.g., information on patient demographics, exposure, family history, clinical course) and for which patients have given full informed consent for their present and future use.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

The Early Detection Research Network (see page 27)

Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer (see page 28)

The following initiatives could potentially address pancreatic cancer:

Exploratory/Developmental Grants for Diagnostic Cancer Imaging are meant to stimulate research that articulates highly innovative research concepts in diagnostic cancer imaging. No funded applications have focused on pancreatic cancer.

***In Vivo* Cellular and Molecular Imaging Centers (ICMICs)** foster interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging, NCI has established 3 ICMICs and awarded 10 planning grants for additional centers. These centers narrow the gap between the discovery of new cancer genes and intracellular pathways, and the translation of these discoveries into clinically useful, minimally invasive imaging approaches to gaining a greater understanding of cancer. No funded applications have focused on pancreatic cancer.

Small Animal Imaging Resource Programs (SAIRP) speeds up the development of new imaging methods. Currently, five SAIRP centers are developing and applying a wide variety of

imaging modalities that focus on functional, quantitative imaging. No funded applications have focused on pancreatic cancer.

Development of Novel Imaging Technologies is a program announcement is to stimulate (1) the development of highly innovative image acquisition and enhancement methods, including high-risk/high-gain projects that exploit our expanding knowledge of the molecular basis of cancer and other diseases; and (2) the integration of these emerging technologies with traditional imaging modalities for more effective solutions for cancer and other diseases. In particular, the development of innovative high-resolution imaging methods at the cellular or molecular scales is encouraged, with emphasis on identification and characterization of either the early formation of disease or early molecular changes during intervention or therapy. For many technologies that have potential for molecular imaging, the use of probes or tracers is considered essential for detection of molecular changes *in vivo*. No funded applications focus on pancreatic cancer.

Exploratory Studies in Cancer Detection, Prognosis, and Prediction (see page 28)

Phased Application Awards in Cancer Prognosis and Prediction (see page 28)

Proposed Strategies to Address Gaps

- Expand the NCI Cohort Consortium (see page 29)
- Consider noncompetitive renewals (as is done for Merit Award renewals) for long-term studies.[c]
- Identify markers for early detection of pancreatic cancer through the Early Detection Research Network (EDRN) and the Center for Proteomics. EDRN is encouraging the submission of proposals for associate membership (see http://www3.cancer.gov/prevention/cbrg/edrn/ for more details) from investigators working on pancreatic cancer. EDRN solicits applications three times a year on collaborative studies, ranging in duration from 1 to 3 years.[d]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
c. While these strategies are important, NCI will not be able to implement them in the near term.
d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort

Section 4
Therapy

A number of inherited and acquired tumor-associated gene alterations present in pancreatic cancer have been identified, but significant gaps exist in our understanding of how these alterations occur in pancreatic cancer development, affect the interaction of signaling proteins in the course of the cancer, and influence molecular interactions between the tumor and host. It remains a challenge to better understand and determine how the molecular biology of pancreatic cancer can be harnessed for therapeutic gain. Three research priorities are to:

"Significant gaps exist in our understanding of how gene alterations occur in pancreatic cancer development and influence molecular interactions between tumor and host."

- Facilitate the discovery and development of targeted therapeutics,
- Facilitate the development of techniques to assess targeted therapeutics and develop and validate preclinical models of human pancreatic cancer for identifying and evaluating therapeutic targets, and
- Accelerate research into the supportive care of patients with pancreatic cancer.

11 Facilitate the discovery and drug development of targeted therapeutics

Introduction

It is likely that specific signaling pathways within tumor cells and between tumor cells, stroma (fibroblasts and endothelium), and the immune system are altered in pancreatic adenocarcinoma and that, once identified, these pathways can be targeted for therapeutic benefit. With this information, it should be possible to identify specific protein targets that are critical to pancreatic cancer growth, metastasis, and drug and radiation resistance, and to design pharmacologic strategies to interact with these critical pathways. Growing knowledge of the molecular biology of pancreatic cancer should be used to identify both existing agents that target biologic pathways already known to be critical to pancreatic cancer tumorigenesis, and those that can be identified from new insights into key signaling pathways. It also is likely that substantial benefit can be gained by enhancing standard cytotoxic therapy with new targeted therapeutics.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

Flexible System to Advance Innovative Research for Cancer Drug Discovery By Small Businesses (FLAIR-SBIR) provides a flexible system within NCI's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs to accommodate the special needs of the complex discovery and development process, at least partially, from basic discovery through proof-of-principle demonstration in clinical trials. Two applications focus on pancreatic cancer:

- Survival Signaling Inhibitors as Cancer Drugs
- GFP Imaging for In Vivo High Throughput Drug Screening

The Rapid Access to Intervention Development (RAID) program is designed to efficiently move novel treatment interventions developed in academic settings into the clinic. It makes NCI's drug development resources available to investigators with molecules that hold promise for cancer treatment. By providing the resources needed for preclinical development of drugs and biological agents, this program removes the most common barriers between laboratory discovery and clinical testing. Products developed through RAID are returned directly to the originating laboratory for clinical trial testing. One of the projects supported, "Clinical Development of Allogeneic Pancreatic Tumor Vaccine," focuses on pancreatic cancer. NCI is supporting full-scale production of GMP material that will allow advancement to a clinical trial.

SPOREs support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal).

The following initiatives could potentially address pancreatic cancer:

The Quick Trials for Novel Cancer Therapies program speeds the translation of ideas developed in the laboratory to early-stage clinical trials by simplifying the grant application process and providing a rapid turnaround from application to funding. No applications funded to date focus on pancreatic cancer.

Phased Application Awards in Cancer Prognosis and Prediction evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy. No applications funded to date focus on pancreatic cancer.

Exploratory Studies in Cancer Detection, Prognosis, and Prediction promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. This initiative supports translational studies that identify promising new means for cancer detection and diagnosis and that provide the initial, critical information necessary to decide whether potential clinical utility justifies further investment. None of the funded applications focuses on pancreatic cancer.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials foster collaborations and interactions between basic researchers, private industry, and clinical investigators to perform translational research on promising predictive and prognostic markers. These studies focus on correlations between biologic features of tissue specimens collected from the NCI Clinical Trials Cooperative Groups or other large multi-institutional clinical trials and patient outcomes. The markers will be assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. No projects under this initiative currently focus on pancreatic cancer.

The Molecular Target Drug Discovery For Cancer program solicits cooperative agreement applications to exploit molecular targets for drug discovery. Rather than depending on *in vitro* and *in vivo* screens for antiproliferative activity, investigators can now focus on new molecular targets and pathways essential for the development and maintenance of the cancer phenotype.

The Gastrointestinal (GI) Intergroup consists of cooperative groups working on GI with proposed pancreatic studies

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Offer supplements for tissue acquisition and informatics to GI (and pancreatic cancer) SPOREs, Cancer Therapy Evaluation Program/GI Intergroup, Director's Challenge grantees, and P01 grantees who are willing and able to collect tissue samples and create repositories. Emphasize the institute's special interest in pancreatic specimens and promote this opportunity to the pancreatic cancer research community. It is not clear how many collections of pancreatic tissue exist. This may be another area for collaboration with NIDDK. Expect a maximum of three supplements, since few collections exist.[a]

- Foster partnerships with industry through various funding mechanisms including the National Cooperative Drug Discovery Groups to discover and develop promising drug compounds.[a]

- Expand the Rapid Access to Intervention Development and Rapid Access to NCI Discovery Resources programs in response to high demand.[c]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

12 Facilitate development of preclinical and minimally invasive clinical techniques to assess targeted therapeutics

Introduction

Discovery and development of novel targeted therapeutic strategies with a high probability of success in treating pancreatic cancer will be facilitated by developing relevant preclinical models. These models are needed to validate that a specific therapeutic agent is capable of affecting its target and to assess the impact of intervention on tumor growth and metastasis.

To develop novel targeted therapeutic strategies in the clinic, it will be necessary to obtain and analyze tumor and host tissues for evidence that the target has been affected. This important effort will require (1) minimally invasive surgical and nonsurgical techniques for obtaining tumor tissue serially from patients, and (2) noninvasive imaging techniques that will provide both functional (e.g., antiangiogenesis, immune-mediated mechanisms) and molecular (e.g., apoptosis, inhibition of specific signaling pathways) data sufficient to determine the effect of the targeted therapeutic strategies on the defined signaling pathways. It will be necessary to validate these noninvasive techniques against specific tissue-based assays.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

Diagnostic Imaging Network-American College of Radiology Imaging Network (ACRIN) both funds and provides a complete infrastructure for multi-institutional clinical trials of imaging and related disciplines applied to cancer, with support from NCI. ACRIN facilitates the development and implementation of trials, data acquisition and management, protocol design and biostatistical analysis, monitoring and quality assurance, and financial management and reporting of trial results. ACRIN is not supporting any pancreatic cancer trials at this time but provides an infrastructure for future studies in this area.

Innovative Toxicology Models for Drug Evaluation: Exploratory/Developmental Grants and Phased Innovation Award SBIR/STTR Initiative encourages the development, standardization, and validation of new and innovative assays that determine or predict specific organ toxicities (e.g., cardiotoxicity, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, ototoxicity, bladder toxicity, neurotoxicity, pulmonary toxicity, and endocrine toxicity, including pancreatic beta cell toxicity) of potential cancer therapeutic agents.

Development of Clinical Imaging Drugs and Enhancers is a new program designed to expedite and facilitate both the development of promising imaging enhancers (contrast agents) or molecular probes, and their translation from laboratory synthesis to IND application. Under this program, developers of a promising diagnostic agent or probe can apply to NCI for assistance. NCI will make its preclinical development resources available to competitively selected developers in order to remove the most common barriers between laboratory discoveries and IND status.

The Small Animal Imaging Resource Program (SAIRP) was created to speed the development of new imaging methods. Currently, five SAIRP centers are developing and applying a wide variety of imaging modalities that focus on functional, quantitative imaging.

Establish a loose consortium among modelers supported by NIDDK and NCI to explore difficulties in creating pancreatic models.

New Activities Initiated Within the Past Year

NCI is providing supplements to investigators within the **Mouse Models of Human Cancers Consortium** to further the development of pancreatic cancer mouse models.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Provide supplements to molecular imaging centers for collaborations between drug developers and imaging scientists who propose to tag promising drugs.[c].

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
c. While these strategies are important, NCI will not be able to implement them in the near term.
d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

13 Accelerate research into the supportive care of patients with pancreatic cancer

Introduction

Patients with pancreatic cancer are affected by profound physiologic changes. These changes include severe cachexia, asthenia, and pain, which are experienced by at least 85 percent of patients with pancreatic adenocarcinoma. Emerging data support the hypothesis that many patients with pancreatic cancer die due to the associated wasting. Cachexia is likely to be mediated by specific cytokines and other proteins that are produced by pancreatic cancer cells, stroma, and immune cells. Understanding the biology of cachexia may allow us to develop pharmacologic and other means to reverse wasting, and this should improve quality of life, ability to tolerate anticancer therapies, and survival. The role of nutrition in mitigating this morbidity should be explored.

Additionally, severe visceral pain is often associated with pancreatic cancer. While pancreatic cancer pain syndromes often are treated with potent narcotic analgesics, nerve blocks, or radiation therapy, these approaches have side effects, and nerve blocks often are not available or ineffective. Data also suggest that simply controlling the pain associated with pancreatic cancer translates into improved survival. Therefore, innovative approaches to pain management are critical to optimize the supportive care of pancreatic cancer patients.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

Support research on palliative care and end of life through the **Centers of Excellence in Cancer Communications**.

The Management of Symptoms Secondary to Treatment initiative stimulates research that will lead to improved adherence to treatment regimens and better quality of life. The program supports the development and testing of strategies to decrease the negative impact of physical and psychosocial symptoms that are the secondary result of treatment or prevention regimens. It is cosponsored by NCI, the National Institute of Nursing Research, and the National Institute of Mental Health. The applications funded to date do not focus on pancreatic cancer.

New Activities Initiated Within the Past Year

A State-of-the-Science Meeting on Cancer Symptom Management took place on July 15-17, 2002 and focused on three major symptoms, including fatigue, pain, and depression.

NCI will work with the **HMO Cancer Research Network** to increase palliative care and end-of-life research initiatives throughout this group of community-based investigators.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Develop future proposals in cancer symptom management to advance supportive care research based on the recommendations from the July 2002 state-of-the-science meeting. The funds would support grants on this topic over 3-5 years.[c]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
c. While these strategies are important, NCI will not be able to implement them in the near term.
d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

Section 5
Communications and Health Care Delivery[7]

Communications research is crucial in pancreatic cancer to help ensure that patients, families, and healthcare providers are well informed about all aspects of the disease. NCI's recent enhanced commitment to cancer communication initiatives provides new opportunities for research in communications relative to pancreatic cancer. Advances in tumor biology, diagnosis, and treatment can be expected to promote more hopeful and positive attitudes toward pancreatic cancer. Four key priorities are to:

> *"Communications research is crucial to help ensure that patients, families, and health care providers are well informed about all aspects of the disease."*

- Identify effective forms of healthcare provider communication with pancreatic cancer patients,
- Identify determinants of message effectiveness in aiding decisionmaking by patients,
- Identify workforce requirements and costs of multidisciplinary clinical trials in pancreatic cancer, and
- Determine the efficacy of current practices in pancreatic cancer diagnosis and care and evaluate the impact of improvements in the management of difficult treatment and end-of-life issues.

7 This section is titled "Health Services Research" in the Pancreatic Cancer PRG report.

14 Identify effective forms of healthcare provider communication with pancreatic cancer patients

Introduction

Healthcare providers who treat pancreatic cancer patients must know and communicate the availability and value of clinical trials, treatment options, pre- and postsurgical therapies, and symptom management. They should be able to help facilitate patient decision making after diagnosis and encourage research participation by high-risk families. Healthcare providers also should discuss quality-of-life and end-of-life issues with their patients, and provide current information and/or referrals when necessary. The unique needs of older patients and older caregivers are of special concern.

Previous studies of healthcare provider-patient communication have revealed that when the provider's communication is compassionate and accurate, the patient is more accepting of the messages, thus strengthening the healthcare provider-patient relationship.

Ongoing Activities

The following initiative could potentially address pancreatic cancer:

NCI's Office of Education and Special Initiatives is proposing a partnership with the Education for Physicians on End-of-Life Care project targeted to physicians, nurses, and oncology social workers. The outcome of this partnership would be educational modules for the target population on the end-of-life issues of cancer patients and their families.

New Activities Initiated Within the Past Year

The Pancreas Patterns of Care Study collected detailed treatment information on a population-based sample of cases diagnosed in 1998 and registered at a Surveillance, Epidemiology, and End Results (SEER) registry. African-Americans and Hispanics were oversampled to obtain more stable estimates of treatment. The current analyses will include a description of the therapy provided across geographic regions, age, racial/ethnic groups, and types of treatment facilities.

The Office of Education and Special Initiatives Clinical Trial Education Series disseminates a series of books, brochures, videos, and slides to train advocates, the interested public, and healthcare professionals (including referring physicians and nurse practitioners) about clinical trials. A special section describes resources and communication with the patient.

The Pain Kit is a series of tools for patients and providers to discuss the management of pain throughout the course of treatment and at end of life.

Incorporating Clinical Trials into Your Practice is an online tutorial that will provide referring physicians, nurse practitioners, new research oncologists, and their staff with

information on communicating with patients about prevention and treatment trials. It also provides practical approaches to overcome the common barriers physicians have in implementing clinical trials in their office settings.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Work with advocacy groups and NCI's Office of Liaison Activities to promote education materials and information on the World Wide Web, with increased emphasis on pancreatic cancer.[b].

- Support a large, population-based, case-control study of pancreatic cancer through the Cancer Research Network in health maintenance organizations (HMOs) that have "real-time" electronic reporting of pathology, laboratory, radiology, and outpatient physician visit findings, resulting in ultra-rapid identification of pancreatic cancer within 10 working days of diagnosis. This study will develop a better understanding of risk factors for sporadic and familial pancreatic cancer so that this knowledge can be used for earlier detection and prevention. Data collection will include:

    - Patient interviews about prior medical history and personal and family history of cancer, diabetes, other diseases, smoking, alcohol consumption, physical activity, and occupational exposures;
    - Food frequency questionnaire;
    - Blood specimen for storage as whole blood, plasma, and DNA extraction;
    - Review of electronic and paper medical records for laboratory evidence of prior diabetes, glucose intolerance, elevated lactate dehydrogenase, and other medical conditions that may increase the risk of pancreatic cancer;
    - Cost data from electronic records for future studies of the cost-effectiveness of screening strategies.
    - Consent for passive long-term follow-up for future studies of prognostic markers.[c]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

15 Identify determinants of message effectiveness in aiding decision making by patients

Introduction

Patient decisionmaking is a fundamental step in delivering medical care. Very limited information is available for understanding and predicting how patients make decisions or what environments promote optimal decisionmaking, especially following a pancreatic cancer diagnosis. Patients must be made aware of their options following a pancreatic cancer diagnosis and throughout the entire course of treatment. They also must understand how the medical infrastructure works, including information on different healthcare settings, insurance issues, and how to obtain a second opinion.

The short survival time of pancreatic cancer patients forces them to make rapid decisions under extreme pressure and stress. A number of studies have demonstrated the significant influence of family members and companions on patient decisionmaking. A better understanding is needed of the influence of personal networks on the decisions made by patients with pancreatic cancer.

The Internet now allows many patients to access information quickly and easily, but all of this information is not of equal quality or usefulness. Patients must be helped to understand that these quality differences exist and learn to evaluate Internet (and other) information effectively. This is particularly important for patients with pancreatic cancer; because of the high mortality rate and short survival time associated with the disease, these patients may be particularly vulnerable to claims about the efficacy of unproven therapies promoted through anecdotal reports.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

Research on Ethical Issues in Human Studies encourages empirical studies to fill many gaps in our knowledge and understanding of the complex ethical issues that arise when involving human participants in research. The focus can be on potential, current, or former research participants, investigators, and/or institutional review boards (IRBs). One funded application focuses in part on pancreatic cancer, "Improving Informed Consent in Diverse Populations," and is identifying factors associated with improved comprehension and recall of the information on informed consent forms.

The following initiatives could potentially address pancreatic cancer:

The Management of Symptoms Secondary to Treatment initiative stimulates research that will lead to improved adherence to treatment regimens and better quality of life by the development and testing of strategies to decrease the negative impact of physical and psychosocial symptoms that are the secondary result of treatment or prevention regimens. It is

co-sponsored by the NCI, the National Institute of Nursing Research, and the National Institute of Mental Health. The applications funded to date do not focus on pancreatic cancer.

Informed Consent in Research Involving Human Participants is a joint initiative between nine NIH Institutes (including NCI), the NIH Office of Extramural Research, the U.S. Department of Energy, and the U.S. Department of Veterans Affairs to stimulate investigations into the informed consent process in scientific research. The initiative will develop and test alternative strategies for obtaining informed consent in diverse populations and determine optimal ways to obtain informed consent for research participation. NCI has funded three applications:

- Comparison of Methods to Improve Consent Information
- Therapeutic Research Consent
- Patient Decision Making in Phase I Clinical Trials

New Activities Initiated Within the Past Year

Human Participant Protections for Research Teams is a Web-based course that provides information for the investigator team about the rights and welfare of human participants in research.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Work with advocacy groups and the Office of Liaison Activities to promote education materials and information on the World Wide Web, with increased emphasis on pancreatic cancer.[b]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

16 Identify workforce requirements and costs of multidisciplinary clinical trials in pancreatic cancer. Create a Web-based repository to track, update, and categorize information on pancreatic cancer clinical trial costs

Introduction

Currently, many healthcare providers forgo compensation for the time they spend participating in clinical research, which typically is not reimbursable. This situation can erode the multidisciplinary teamwork necessary to produce robust results from research on pancreatic cancer diagnosis, treatment, and patient outcome. It is important to devise compensation systems that facilitate, rather than hinder, construction of a multidisciplinary infrastructure, not only for pancreatic cancer clinical trials, but also for all types of cancer research. In addition, barriers to patient participation in clinical trials, such as expenses, travel, and time, should be estimated and factored into the infrastructure cost model for pancreatic cancer clinical trials.

A Web-based repository would be useful for health services and clinical researchers to determine normative costs associated with pancreatic cancer research. The data would be especially useful for estimating budget item costs, including personnel.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The NCI Clinical Trials Cooperative Group Program supports organizations that continually generate and conduct new clinical trials consistent with national priorities for cancer treatment research. Emphasis is placed on definitive, randomized phase 3 studies and preliminary developmental efforts. Multicenter trials allow rapid accrual of patients, while reducing the possible bias of studies carried out at a single or a few institutions.

The NCI Evaluation Study of the Cost of Clinical Trials provides national estimates of the patient care costs in NCI-sponsored cancer treatment trials. When completed, results from the study will provide information for clinical researchers, insurers, employers, patient advocates, and policymakers. The study is designed to enroll up to 750 patients in NCI-sponsored phase 1, 2 or 3 treatment studies, using administrative data and chart reviews, and will also include a matched control group of 750 cancer patients treated with standard care. The project has completed site recruitment and will soon complete record abstraction.

The Cancer Centers are 59 research-oriented institutions throughout the Nation that have been designated NCI-supported cancer centers in recognition of their scientific excellence. The Centers are key partners in NCI's efforts to speed the process of discovery and bring the benefits of cancer research directly to the public. Cancer centers provide cutting-edge research, high-quality cancer care, and outreach and education for both healthcare professionals and the public.

17 Determine the effectiveness of current practices in pancreatic cancer care and evaluate new strategies for managing difficult treatment and end-of-life issues

Introduction

Pancreatic cancer is an aggressive disease that swiftly robs patients of quality and quantity of life. The symptoms are particularly onerous and difficult to treat effectively. Additionally, because median life expectancy after diagnosis is 6 months or less, meaningful quality of life with this disease takes on extraordinary significance. Although the high mortality rate leaves few survivors, these survivors can provide valuable information about their experience that could help provide hypotheses for research to improve many aspects of disease management for pancreatic cancer patients. The mortality rate of pancreatic cancer demands research on methods to assist patients, their families, and healthcare professionals in effectively managing the disease in survivors and to assist with the transition to end-of-life care when necessary. Both the struggle for survival and the transition to end-of-life care are often marked by feelings of abandonment on the part of the patient and feelings of inadequacy on the part of families and healthcare providers. A strategic, coordinated research program is needed that addresses methods of improving quality of life in the last months of life. Outcomes research that provides information on these issues is important to all phases of pancreatic (and most other) cancer research.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

Management of Symptoms Secondary to Treatment. (see page 45)

The Cancer Care Quality Measurement Project (CanQUAL) is identifying core process measures for treatment, survivorship, and end-of-life care for the major tumor sites and measures that cut across tumor sites (e.g., for palliative care). NCI is collaborating with Federal agencies and private-sector organizations concerned with quality cancer care to position CanQUAL not only to identify core process measures authoritatively, but also to accelerate their adoption by a broad range of decisionmakers who evaluate or make choices about cancer care.

New Activities Initiated Within the Past Year

A Palliative Care Coordinator has been identified in response to the recommendation from the Institute of Medicine report published in June 2001. Office of Education and Special Initiatives staff coordinate NCI's palliative care, symptom control, and other end-of-life initiatives and research with NCI staff. The palliative care coordinator ensures integration of palliative programs across NCI; chairs the Palliative Care Working Group; and serves as a focus for developing partnerships with other groups (inside and outside the government), including advocacy organizations.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Support a large, population-based, case-control study of pancreatic cancer through the Cancer Research Network in health maintenance organizations (HMOs) that have "real-time" electronic reporting of pathology, laboratory, radiology, and outpatient physician visit findings, resulting in ultra-rapid identification of pancreatic cancer within 10 working days of diagnosis. This study will develop a better understanding of risk factors for sporadic and familial pancreatic cancer so that this knowledge can be used for earlier detection and prevention. Data collection will include:

  - Patient interviews about prior medical history and personal and family history of cancer, diabetes, other diseases, smoking, alcohol consumption, physical activity, and occupational exposures;
  - Food frequency questionnaire;
  - Blood specimen for storage as whole blood, plasma, and DNA extraction;
  - Review of electronic and paper medical records for laboratory evidence of prior diabetes, glucose intolerance, elevated lactate dehydrogenase, and other medical conditions that may increase the risk of pancreatic cancer;
  - Cost data from electronic records for future studies of the cost-effectiveness of screening strategies.
  - Consent for passive long-term follow-up for future studies of prognostic markers.[c]

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b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

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Section 6
Resource Priorities

The lack of key resources and tools poses a major impediment to progress in pancreatic cancer research. The PANC-PRG identified the following resource needs as priorities:

Tumor biology:
- Construct resources to provide access to a range of normal and neoplastic human pancreas samples and all types of biomaterials;
- Construct a relational database of information on the biological profiles of normal and abnormal pancreas cells. Organize knowledge of signaling pathways into interrelated networks and systems;
- Develop biological sampling techniques that permit analyses of minute quantities of biological samples; and
- Develop experimental model systems and establish gene-based model systems *in vivo* and *ex vivo*.

Risk, prevention, screening and diagnosis:
- Develop imaging systems for elucidating, detecting, and monitoring pancreatic cancer;
- Develop a Web-based imaging library;
- Develop new and expanded registries for identification of high-risk patients and kindreds;
- Develop a survivorship registry (related to health services). Create consortia of large, aging cohorts for pooled analysis;
- Develop education for healthcare providers and investigators about pancreatic cancer risk assessment. Create new education and communication tools with education components (related to health services); and
- Establish technology centers for comprehensively assessing gene and protein expression.

Therapy:
- Develop mechanisms to facilitate investigator access to novel targeted therapeutic agents for preclinical studies and clinical trials,
- Develop infrastructure for molecular target assessment, and
- Improve infrastructure for clinical trials and promote patient participation.

Health services research:
- Develop new models that can be applied and validated in community and academic research settings.

18 Construct resources to provide access to a range of normal and neoplastic human pancreas samples and all types of biomaterials

Introduction

Investigators need easy access to high-quality tissue from normal pancreas, precursor lesions, and invasive and metastatic tumors. Also needed are specimen banks for all types of biomaterials (e.g., blood, serum, pancreatic juice, stool, tumors, other body fluids). These specimens must be collected and stored according to standardized procedures. They should be available through an easily accessible repository, with accompanying clinical and epidemiologic data.

Establishing and coordinating these resources and databases will promote efficient and thorough utilization of these precious samples and enable investigators to obtain essential information without the need to build or develop advanced capabilities. Storage may be centralized or dispersed, depending on the exigencies of the specimens, as long as investigators have reasonable access to them. To enable rapid progress, a collaborative, multidisciplinary, multicenter approach is essential.

"Establishing and coordinating resources and databases will promote efficient and thorough utilization of precious samples and enable investigators to obtain essential information."

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The NCI Clinical Trials Cooperative Groups have banked tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. Each cooperative group has a review process for research proposals. If proposals receive favorable reviews, specimens with clinical, treatment, and outcome data can be made available to researchers through collaborative arrangements. These banked specimens are most useful for clinical correlative studies on uniformly treated patient populations. The groups maintain statistical centers with extensive databases and are capable of assisting researchers in correlating their laboratory data with the data from group studies.

The **Cooperative Human Tissue Network** (CHTN) promotes cooperative efforts to collect, preserve, and distribute human tissues for research. Most specimens are collected prospectively to meet investigators' individual protocol requirements. However, some specimens may be immediately available for research. Recently, the CHTN distributed more than 900 pancreatic specimens to researchers in the United States and Canada.

The NCI Tissue Expediter identifies sources of human tissue specimens and helps researchers locate the tissue and related data needed. The expediter can also help researchers identify potential collaborators when necessary.

Shared Resources for Scientists Outside NCI Cancer Centers provide groups of six or more NCI-funded investigators in institutions that do not have NCI-funded cancer centers with additional

shared resource support. Increasing the availability of core resources is expected to improve the ability to conduct research and thereby facilitate scientific progress. This program is establishing cancer-related research resources to provide new sources of technical support and research materials to advance cancer research. No applications funded to date have focused on pancreatic cancer.

NCI Specimen Resource Locator is a database with query tools to locate resources, such as tissue banks and tissue procurement services, and provides access to normal, benign, precancerous, and/or cancerous human tissue covering a wide variety of organ sites.

Continue to fund or enhance the **Tissue Array Research Program** and other tissue microarray efforts. The primary objective of TARP is to develop and disseminate Multi-Tumor Tissue Microarray slides and the related technology to the cancer research investigators.

New Activities Initiated Within the Past Year

Shared Pathology and Informatics Network is a Web-based system that can request and receive data from existing medical databases at multiple institutions. The network is developing and testing the communications protocols needed to access data through Internet queries distributed simultaneously to consortia institutions. The data to be searched include patient demographics, diagnostic information, vital status, clinical history, and, when available, outcome data and information related to recurrence and treatment. The data returned by participating institutions are collated and returned to the requestor as a structured report that preserves patient confidentiality.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Offer supplements for tissue acquisition and informatics to GI (and pancreatic cancer) SPOREs, Cancer Therapy Evaluation Program/GI Intergroup, Director's Challenge grantees, and P01 grantees who are willing and able to collect tissue samples and create repositories. Emphasize the institute's special interest in pancreatic specimens and promote this opportunity to the pancreatic cancer research community. It is not clear how many collections of pancreatic tissue exist. This may be another area for collaboration with NIDDK. Expect a maximum of three supplements, since few collections exist.[b]

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b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

19 Construct a relational database containing information on the biological profiles of normal and abnormal pancreas cells. Organize knowledge of signaling pathways into interrelated networks and systems

Introduction

The PANC-PRG noted a need for a "value-added" pancreas database containing data from allelotyping, DNA sequencing, cDNA expression analysis, tissue arrays, and proteomics studies. Such a database will provide an important tool for interdisciplinary and multi-institutional efforts to understand normal pancreas development, the genesis of preneoplastic lesions, and their progression to invasive and metastatic carcinoma. The PRG stated that data should be gathered from studies exploring the strong intermingling of pancreatic cancer with stromal elements (desmoplastic reaction) and the stromal-epithelial interactions that likely play an important role in the pathogenesis and progression of this disease. A pancreatic cancer research Web page should be developed to make these data freely available to the scientific community, with links to a multitude of relevant bioinformatics tools to permit data access and analysis by all interested parties.

The PRG also noted that in order to assess the ultimate outcome of alterations in the pathways found in pancreatic cancer, knowledge of signaling pathways should be organized into interrelated networks and systems. The perspective of individuals trained in systems analysis in other fields (e.g., mathematics, engineering, bioinformatics) should be applied to these biological networks. This process should start with pathways that currently are understood to contribute to pancreatic cancer, and expand to interconnect pathways affected by genetic alterations and microenvironmental influences.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

The Innovative Technologies for the Molecular Analysis of Cancer program funds research to develop novel technologies that will support the molecular analysis of cancers and their host environment. Technologies solicited include those that are suitable for the detection of alterations and instabilities of genomic DNA; measurement of the expression of genes and gene products; analysis and detection of gene and/or cellular products, including post translational modification, and function of proteins; identification and characterization of exogenous infectious agents in cancer; and assaying the function of major signal transduction networks involved in cancer. One of the applications funded to date, "Gene Expression Profiling of Unknown Primary Cancers," focuses on pancreatic cancer.

The following initiatives could potentially address pancreatic cancer:

Innovations in Biomedical Information Science and Technology stimulates support for fundamental research in biomedical computing science and technology, as well as the development

and application of new biocomputing tools or technologies for a particular area(s) of scientific opportunity in biomedical research. Programs may target one or multiple areas of biomedical computing that will enable progress in biomedical research. Data types that could be considered include genomic sequences, biomedical images, qualitative descriptors for health and social science, remote sensing and geospatial images, and chemical formulae.

Translation of Technologies to Detect Alterations in Human Tumors stimulates the continued development and adaptation of technologies for analysis of the spectrum of molecular alterations in human tumor tissues. The long-term goal of this initiative is the development of integrated molecular analysis systems. These systems will enable the identification of reliable molecular markers or targets for the detection, diagnosis, prognosis, and treatment of cancer. None of the applications funded to date focus on pancreatic cancer.

The Cancer Genome Anatomy Project (CGAP) generates the information and technological tools needed to decipher the molecular anatomy of the cancer cell. CGAP's primary goal is to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. All data and material generated through CGAP are made available to the research community without restrictions.

Director's Challenge: Toward a Molecular Classification of Tumors is a challenge to the research community to revolutionize the classification of human tumors issued by the NCI Director in 1998. The goal of this effort is to develop novel tumor classification schemes based on profiles of molecular alterations present in tumors. None of the applications funded to date focus on pancreatic cancer.

The Cancer Molecular Analysis Project (CMAP) has developed, for each gene, a unique Gene Info page that provides information and links to various National Center for Biotechnology Information and NCI databases. One of the activities related to pancreatic cancer would be to integrate DK gene expression data into CMAP databases.

20 Develop biological sampling techniques that permit analyses of minute quantities of biological samples

Introduction

The scarcity of biological samples of pancreatic intraepithelial neoplasm and invasive pancreatic cancers makes it imperative to develop sampling techniques that will permit analyses of exceedingly small samples.

Ongoing Activities

The following initiative has ongoing projects in pancreatic cancer:

The Innovative Technologies for the Molecular Analysis of Cancer program (see page 53)

The following initiatives could potentially address pancreatic cancer:

The Tissue Array Research Program (TARP) promotes the development and application of tissue microarray technology. TARP has the following goals: (1) Advance tissue microarray technology research and development; (2) produce tissue microarrays for use by the research community; (3) provide help in arraying unique tissue materials, such as those from clinical trial groups or consortiums of rare disease; and (4) disseminate tissue microarray technology by providing training and workshops, and establishing protocols and standards. NCI is in charge of making the tissue microarrays available to the research community, while the National Human Genome Research Institute leads the development of the technology. No funded applications focus on pancreatic cancer.

Translation of Technologies to Detect Alterations in Human Tumors (see page 54)

The NCI Advanced Technology Center (ATC) was established to implement novel technologies to address biological, clinical, and genetic questions pertinent to human cancers. The ATC houses investigators from NCI and the National Human Genome Research Institute whose research focuses on human cancer genetics, molecular epidemiology, and cell biology. This multidisciplinary center serves as the home of the Cancer Genome Anatomy Project, two high-throughput genotyping centers, two sequencing centers, and a microarray facility. The ATC will focus on the development of high-throughput, multiplex techniques for population-based studies; the analysis of expression states using expression array technology; and new gene discovery approaches.

Exploratory Studies in Cancer Detection, Prognosis, and Prediction promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors, or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. New biomarkers and laboratory assays are needed for cancer screening and risk assessment, pathologic characterization of malignant tumors and assessment of disease prognosis, and prediction and measurement of response to treatments, particularly with novel therapeutic or chemopreventive agents. Investigators are encouraged to pursue new clinical insights and to

consider the full array of potentially informative biological characteristics of tumor cells and tissues. This supports translational studies that identify promising new means for cancer detection and diagnosis and provide the initial, critical information necessary to decide whether potential clinical utility justifies further investment.

Improving DNA, RNA, and Protein Availability in Fixed Tissue is designed to develop novel, improved methodologies for tissue preservation and develop methods to reverse the effects of formalin fixation on RNA and proteins to allow the effective use of existing tissue archives in molecular studies. Improved access to adequately preserved tissue is critical to facilitating studies to translate promising comprehensive molecular technologies into medical practice. None of the applications funded to date focus on pancreatic cancer.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Include development of sampling techniques in the annual SBIR/STTR solicitation. The nanotechnology approach to sampling/collection offers a possible means to provide direct readout of genomic and proteomic information, both at the single cell and single molecule levels. One advantage of nanotechnology is that nano-sized tools are small relative to the size of a cell and hold great promise for developing effective techniques to work within cells or even at a subcellular level. The present obstacle to early detection of cancer lies in the inability of existing tools to detect these molecular-level changes directly during early phases in the genesis of a cancer.[d]

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b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

21 Develop experimental model systems and establish gene-based model systems in vivo and ex vivo that faithfully recapitulate the complex biology of human pancreatic adenocarcinoma

Introduction

Models are needed to study signal transduction pathways and gene expression, to test early detection and diagnostic methods, and to develop novel diagnostic and therapeutic strategies. In addition, models are needed that will enable investigators to evaluate the role of key genetic alterations in the development of precursor lesions, tumorigenesis, maintenance, invasion, and metastasis. Also needed are animal models for the study of environmental factors, gene-environment interactions, chemoprevention, chemotherapy, radiation therapy, vaccines, and imaging. Culture systems for identifying and propagating normal human pancreas stem cells, as well as ductal epithelial, acinar, and islet cells, are needed to study and define the biological phenotype of normal pancreas cells, define the changes that occur as pancreas epithelial cells progress from a preinvasive to a fully malignant state, and characterize the cells from which pancreatic adenocarcinoma arises.

It will be essential to apply the compendium of gene expression patterns and genome-wide genotypes of pancreatic adenocarcinoma to the study of these new mouse models and, in turn, to use the models to expand the base of knowledge concerning relevant genotypes and gene expression patterns in pancreatic cancer.

"It will be essential to use models to expand the base of knowledge concerning relevant genotypes and gene expression patterns in pancreatic cancer."

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

The Mouse Models of Human Cancers Consortium (MMHCC) assembles from U01 grants and NIH intramural projects a crossdisciplinary, multi-institutional consortium whose component teams of investigators will derive or refine accurate cancer-prone models of human malignancies; provide a comprehensive analysis of their phenotype and genotype; validate them for use by the cancer research community for a variety of investigations, including for testing therapeutic, prevention, early detection, or imaging strategies; and assure their availability to the research community. Three funded applications focus in part on pancreatic cancer:

- Mouse Models for Cancer
- Mouse Cancer Models Via TGF-Beta RII Loss
- Mouse Models of GI Cancer

Innovative Technologies for the Molecular Analysis of Cancer (see page 53)

The following initiatives could potentially address pancreatic cancer:

The Zebrafish as an Animal Model for Development and Disease Research promotes the zebrafish as an animal model for the study of development and disease, and encourages new and innovative research and approaches using the zebrafish to identify the genes and elucidate the molecular and genetic mechanisms responsible for normal and defective development and disease. No applications have been funded by NCI to date.

Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer stimulates basic and clinical investigations into the molecular genetics of acute and chronic pancreatitis, as well as the "preneoplastic" genetic changes that predispose individuals to adenocarcinoma of the pancreas. Basic studies include the generation of transgenic animal models of pancreatitis that show inherited forms of pancreatitis, as well as studies that identify the numerous genetic alterations that are involved in this form of carcinogenesis. Clinical studies are also sought through this program announcement that increase our knowledge of the early detection and diagnosis, prognostication, prevention, and treatment of pancreatitis and pancreatic cancer.

The Small Animal Imaging Resource Programs (SAIRP) speed the development of new imaging methods. Currently, five SAIRP centers are developing and applying a wide variety of imaging modalities that focus on functional, quantitative imaging.

Establish loose consortium among modelers supported by NIDDK and NCI to explore difficulties in creating pancreatic models.

New Activities Initiated Within the Past Year

NCI is providing supplements to investigators within the Mouse Models of Human Cancers Consortium to further the development of pancreatic cancer mouse models.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Reissue program announcement related to the microenvironment extraordinary opportunity for competing supplements to develop organotypic models of cancer to develop and apply multicellular models that are more representative of the interactions among the various cell types in a tissue or organ than are cultures of single cell types. Encourage pancreatic cancer applications and promote higher payline for them.[c]

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c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

22 Develop imaging systems for elucidating pancreatic cancer biology and for detecting and monitoring this disease. Develop a Web-based imaging library.

Introduction

New imaging technologies should be developed (or existing technologies refined) to more fully analyze the form and function of the pancreas. Ideally, such functional and molecular imaging systems should distinguish benign from malignant pancreatic disease, and identify early pre-invasive lesions and very small primary tumors as well as the extent of invasion and metastasis. In addition, these minimally invasive techniques may be helpful in determining pancreatic tumor response to conventional and novel therapies. They also should be designed for use in animal model studies aimed at developing and evaluating novel diagnostic and therapeutic agents. A Web-based imaging library should be developed to serve as an educational tool, research tool, reference standard for imaging studies, and source of images for the application of new technologies, such as artificial intelligence and other post-imaging processing.

Ongoing Activities

The following initiative has ongoing projects in pancreatic cancer:

Innovative Technologies for the Molecular Analysis of Cancer (see page 53)

The following initiatives could potentially address pancreatic cancer:

***In Vivo* Cellular and Molecular Imaging Centers** foster interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging. NCI has established three of these centers and awarded 10 planning grants for additional centers. These centers narrow the gap between the discovery of new cancer genes and intracellular pathways, and the translation of these discoveries into clinically useful, minimally invasive imaging approaches to gaining a greater understanding of cancer.

The Development and Application of Imaging in Therapeutic Studies integrates and exploits, in clinical and preclinical settings, imaging techniques in the assessment of therapeutic agent development. Projects may address, among other things, development and application of labeled therapeutic agents as compounds for imaging studies, or development and application of imaging
agents as metabolic markers of response to newly developed therapeutic agents. None of the applications funded to date focus on pancreatic cancer.

Exploratory/Developmental Grants for Diagnostic Cancer Imaging stimulates research that articulates highly innovative research concepts in diagnostic cancer imaging. None of the applications funded to date focus on pancreatic cancer.

The Diagnostic Imaging Network-American College of Radiology Imaging Network is an NCI-funded cooperative group that manages clinical trials of imaging technologies as they relate to cancer. The network both funds and provides a complete infrastructure for multi-institutional clinical trials of imaging and related disciplines applied to cancer and facilitates the development and implementation of trials, data acquisition and management, protocol design and biostatistical analysis, monitoring and quality assurance, financial management, and reporting of trials results.

Data banks of standardized digital image data associated with known clinical outcomes are proposed in NCI's 2002 budget and strategic plan

Development of Novel Imaging Technologies is a program announcement is to stimulate (1) the development of highly innovative image acquisition and enhancement methods, including high-risk/high-gain projects that exploit our expanding knowledge of the molecular basis of cancer and other diseases; and (2) the integration of these emerging technologies with traditional imaging modalities for more effective solutions for cancer and other diseases. In particular, the development of innovative high-resolution imaging methods at the cellular or molecular scales is encouraged, with emphasis on identification and characterization of either the early formation of disease or early molecular changes during intervention or therapy. For many technologies that have potential for molecular imaging, the use of probes or tracers is considered essential for detection of molecular changes *in vivo*. No funded applications focus on pancreatic cancer.

Small Animal Imaging Resource Programs (SAIRP) speeds up the development of new imaging methods. Currently, five SAIRP centers are developing and applying a wide variety of imaging modalities that focus on functional, quantitative imaging. No funded applications have focused on pancreatic cancer.

Innovations in Biomedical Information Science and Technology (see page 53)

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Support a database resource for imaging research—supplement databases for imaging agents that have been developed (chemical structure, mouse experiments).[c]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
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Section 6

23 Develop new and expanded registries for identification of high-risk patients and kindreds. Develop a survivorship registry. Create consortia of large, aging cohorts for pooled analyses to elucidate causal factors.

Introduction

Registries are needed to identify high-risk patients and kindreds (familial pancreatic cancer, hereditary pancreatitis, and others) for linkage analysis, as tissue and specimen resources, for the identification of screening and surveillance cohorts, and for epidemiologic assessment of gene-environment interactions. Also needed is a survivorship registry to enable the study of relationships among survival, biological (e.g., genes, markers), and self-report data, beginning at diagnosis and continuing though follow-up care. In many existing cohort studies, participants are too young to provide an adequate number of pancreatic patients for assessing risk factors and the efficacy of screening modalities.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The Cancer Genetics Network (CGN) supports collaborative investigations of the genetic basis of cancer susceptibility; explores mechanisms to integrate this new knowledge into medical practice; and identifies means of addressing the associated psychosocial, ethical, legal, and public health issues. The CGN steering committee has approved two pilot studies whose start dates depend on the availability of funds. One focuses on the feasibility of recruitment of pancreatic patients and their families and the role of polymorphisms in enzymes related to tobacco-derived carcinogens, folate, and cyclooxygenase (COX)-2 on pancreatic cancer risk. The other will examine the risk of pancreatic and breast cancers in relatives of patients with pancreatic cancer compared to relatives of controls.

Shared Resources for Scientists Outside NCI Cancer Centers (see page 51)

The NCI Cohort Consortium consists of investigators of 21 ongoing prospective studies of large population groups. Investigators are pooling their existing resources of high-quality exposure data and biological specimens suitable for genetic analysis, with a combined total of 700,000 study participants.

Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials foster collaborations and interactions between basic researchers, private industry, and clinical investigators to perform translational research on promising

predictive and prognostic markers. These studies focus on correlations between biologic features of tissue specimens collected from the NCI Clinical Trials Cooperative Groups or other large multi-institutional clinical trials and patient outcomes. The markers will be assessed for their ability to predict clinical outcomes in the context of therapy or response to particular therapies. No projects under this initiative currently focus on pancreatic cancer.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Build on the NCI Cohort Consortium, which consists of investigators of 21 ongoing prospective studies of large population groups. Collectively, these cohorts may have at least 1,500 to 2,000 pancreatic cancer patients available for study. Use of the cohort consortium will provide the opportunity to evaluate many important hypotheses concerning the roles of dietary factors, growth factors, genetic susceptibility, gene/environment interactions, and metabolic pathways in the etiology of pancreatic cancer. This approach has the unique advantage of providing information on environmental/host risk factors and biologic specimens collected prior to disease occurrence on a large number of pancreatic cancer patients.[a]
- Support a large, population-based, case-control study of pancreatic cancer through the Cancer Research Network in health maintenance organizations (HMOs) that have "real-time" electronic reporting of pathology, laboratory, radiology, and outpatient physician visit findings, resulting in ultra-rapid identification of pancreatic cancer within 10 working days of diagnosis. This study will develop a better understanding of risk factors for sporadic and familial pancreatic cancer so that this knowledge can be used for earlier detection and prevention. Data collection will include:

    - Patient interviews about prior medical history and personal and family history of cancer, diabetes, other diseases, smoking, alcohol consumption, physical activity, and occupational exposures;
    - Food frequency questionnaire;
    - Blood specimen for storage as whole blood, plasma, and DNA extraction;
    - Review of electronic and paper medical records for laboratory evidence of prior diabetes, glucose intolerance, elevated lactate dehydrogenase, and other medical conditions that may increase the risk of pancreatic cancer;
    - Cost data from electronic records for future studies of the cost-effectiveness of screening strategies.
    - Consent for passive long-term follow-up for future studies of prognostic markers.[c]

- Create Lymphoma/Leukemia Molecular Profiling Project (LLMPP)-like initiative for pancreatic cancer. This international collaborative project involves seven clinical groups that are sending patient samples and clinical data to one laboratory, accruing hundreds of samples. This should lead to a molecular definition of all types of

lymphoid malignancies and identify which genes affect clinical treatment response and outcome. The large sample size provided by the LLMPP will lead to the development of statistically robust diagnostic methods that will provide a new molecular definition of these malignancies that is useful clinically.[c]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort

24 Develop education materials for healthcare providers and investigators about pancreatic cancer risk assessment, evaluation protocols, and sample collection. Create new education, training, and communication tools for providers with education components and collateral materials.

Introduction

The current lack of knowledge and understanding about these central issues greatly limits the likelihood of making significant progress in pancreatic cancer research. Education, training and communication tools would include: (1) Communication toolkits for healthcare providers with education components and collateral materials to enable professionals to better assist and support patient decisionmaking; (2) patient decisionmaking toolkits that are culturally and linguistically appropriate and take into account various literacy levels and familiarity with communication technologies; and (3) mechanisms to facilitate increased interaction among healthcare providers, advocates, and professional and funding organizations.

"Better education, training and communication tools are needed for health care providers and investigators working in the pancreatic cancer field."

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The Office of Education and Special Initiatives Clinical Trial Education Series disseminates a series of books, brochures, videos, and slides to train advocates, the interested public, and healthcare professionals (including referring physicians and nurse practitioners) about clinical trials. A special section describes resources and communication with the patient.

Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens, spearheaded by the NIH Office of Behavioral and Social Sciences Research and involving 12 NIH institute, including NCI, stimulates research on promoting adherence to therapeutic regimens effective in the management of disease. No applications have been funded by NCI to date.

Cancer Education Grant Program (CEGP) is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will have an impact on reducing cancer incidence, mortality, and morbidity, as well as on improving the quality of life of cancer patients. The CEGP will accept

investigator-initiated grant applications that pursue a wide spectrum of objectives. Education grants can focus on education activities before, during, and after the completion of a doctoral-level degree, as long as they address a need that is not fulfilled adequately by any other grant mechanism available at NIH and are dedicated to areas of particular concern to the National Cancer Program. None of the nine applications funded to date focus on pancreatic cancer.

Pancreatic Cancer Section of Cancer.Gov Web site

New Activities Initiated Within the Past Year

An online tutorial, "Incorporating Clinical Trials into Your Practice," provides referring physicians, nurse practitioners, new research oncologists, and staff with information on communicating with patients about prevention and treatment trials. It also provides practical approaches to overcome the common barriers physicians have in implementing clinical trials in their office settings.

NCI established a partnership the Education for Physicians on End-of-Life Care project targeted to physicians, nurses, and oncology social workers. This partnership will produce educational modules for the target population on end-of-life issues related to cancer patients and their families.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Work with advocacy groups to promote education materials and information on the World Wide Web, with increased emphasis on pancreatic cancer.[b]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

c. While these strategies are important, NCI will not be able to implement them in the near term.

d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

25 Create technology centers for comprehensively assessing gene and protein expression for use in identifying biologic indicators of the presence and behavior of pancreatic cancer and its precursors

Introduction

The PANC-PRG recommended delineating and validating effective molecular biomarkers of preinvasive and invasive disease using a variety of banked specimens (blood, serum, pancreatic juice, stool, tissue, other body fluids) in combination with clinical and natural history data.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The NCI Advanced Technology Center (ATC) was established to implement novel technologies to address biological, clinical, and genetic questions pertinent to human cancers. The ATC houses investigators from NCI and the National Human Genome Research Institute whose research focuses on human cancer genetics, molecular epidemiology, and cell biology. This multidisciplinary center serves as the home of the Cancer Genome Anatomy Project, two high-throughput genotyping centers, two sequencing centers, and a microarray facility. The ATC will focus on the development of high-throughput, multiplex techniques for population-based studies; the analysis of expression states using expression array technology; and new gene discovery approaches.

The Tissue Array Research Program (TARP) (see page 55)

The Director's Challenge: Toward a Molecular Classification of Tumors (see page 54)

26 Develop mechanisms to facilitate investigator access to novel targeted therapeutic agents for preclinical studies and clinical trials

Introduction

Both industry and academia are developing a substantial number of new therapeutic agents; however, the broader scientific community often does not have access to these agents for preclinical and clinical studies. In addition, many of these agents are not evaluated for the treatment of pancreatic cancer, as this disease is less common than others. These and other proprietary concerns also limit the use of these agents in combination, especially when multiple pharmaceutical companies are involved. The development process could be facilitated enormously by broad master agreements with the pharmaceutical industry and academia that assure access to these investigational agents by the research community and protect the interests of all parties.

In addition, greater clarification/simplification of U.S. Food and Drug Administration and Office of Human Research Protection regulations is needed. Currently, regulatory discussions affecting new drug development are conducted only on a case-by-case basis. A lack of uniform requirements can create confusion and disincentives for development of new agents targeting pancreatic cancer, particularly with respect to trial design and endpoints specific to this disease. Guidelines addressing development of therapeutics for pancreatic cancer would be useful.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The NCI Research Resources Web Site provides a centralized listing of resources developed by NCI that are available to the research community and accessible without extensive negotiations or intellectual property issues, at a minimal cost. Listed resources include animal resources; specimens; registries; and drugs, chemicals, and biologicals.

The Developmental Therapeutics Program (DTP) Web Site provides information on access to new agents, research samples, and services that are available to researchers (a simple letter agreement for the transfer of materials is needed). Examples include synthetics, natural products, radiolabeled materials, biological reference standards, and reagents.

New Activities Initiated within the Past Year

The Rapid Access to Preventive Intervention Development (RAPID) Program is currently funding three preclinical studies for pancreatic cancer phase 1 and 2 clinical trials of

cancer chemopreventive agents with geraniol, farnesyl transferase inhibitors, and marine extracts from green mussels.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Explore mechanisms to foster testing of promising new agents. If a pilot effort to make drugs available for pediatric clinical trials is successful, issue a request for applications (RFA). Promote new drugs available for study through the DTP Web site. Acquire combinatorial library sets to supply peer-reviewed, funded researchers.[c]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
c. While these strategies are important, NCI will not be able to implement them in the near term.
d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

27 Develop infrastructure for molecular target assessment

Introduction

As we develop and test new targeted therapeutics, appropriate technology must be in place for safe serial tissue acquisition, including standardized protocols for handling the specimens. In addition, noninvasive functional and molecular imaging technology must be available for preclinical and clinical studies.

Ongoing Activities

The following initiatives have ongoing projects in pancreatic cancer:

Flexible System to Advance Innovative Research for Cancer Drug Discovery By Small Businesses (FLAIR-SBIR) provides a flexible system within NCI's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs to accommodate the special needs of the complex discovery and development process, at least partially, from basic discovery through proof-of-principle demonstration in clinical trials. Two applications focus on pancreatic cancer:

- Survival Signaling Inhibitors as Cancer Drugs
- GFP Imaging for In Vivo High Throughput Drug Screening

The Rapid Access to Intervention Development (RAID) program is designed to efficiently move novel treatment interventions developed in academic settings into the clinic. It makes NCI's drug development resources available to investigators with molecules that hold promise for cancer treatment. By providing the resources needed for preclinical development of drugs and biological agents, this program removes the most common barriers between laboratory discovery and clinical testing. Products developed through RAID are returned directly to the originating laboratory for clinical trial testing. One of the projects supported, "Clinical Development of Allogeneic Pancreatic Tumor Vaccine," focuses on pancreatic cancer. NCI is supporting full-scale production of GMP material that will allow advancement to a clinical trial.

The following initiatives could potentially address pancreatic cancer:

The Molecular Targets Laboratories (MTL) initiative is developing a resource of biological assays and chemical probes for biological studies of cancer. The MTLs emphasize the need for collaboration between chemists and biologists to produce libraries of potential anticancer compounds for public distribution, develop screening assays suitable for high-throughput screening of chemical libraries of potential agents, and confirm a drug's initial ability to alter the drug target in cancer cells.

The Innovative Toxicology Models for Drug Evaluation: Exploratory/developmental Grants and Phased Innovation Award SBIR/STTR Initiative encourages the development, standardization, and validation of new and innovative assays that determine or predict specific organ toxicities (e.g., cardiotoxicity, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, ototoxicity, bladder toxicity, neurotoxicity, pulmonary toxicity, and endocrine toxicity, including pancreatic beta cell toxicity) of potential cancer therapeutic agents.

Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation stimulates the initiation and/or continued development of high-risk/high-impact technologies that target the sensitive quantitation of the wide spectrum of proteins in human tissues. Investigators are developing technologies for both comprehensive identification and sensitive quantitation of proteins translated and modified in human tumor specimens. Investigators are also developing sensitive, efficient, and reproducible technologies that reliably measure altered concentrations of individual proteins. These projects are addressing the current needs of identifying and quantitating proteins that are difficult to analyze, including low-abundance proteins and membrane-bound or hydrophobic proteins.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategy:

- Expand the Rapid Access to Intervention Development and Rapid Access to NCI Discovery Resources programs in response to high demand.[c]

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a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.

b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.

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d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

28 Improve infrastructure for clinical trials and promote patient participation

Introduction

The PANC-PRG suggested improvements in the infrastructure for clinical trials. They recommended that NCI:

- Increase multidisciplinary clinical trials and expand the clinical trials network,
- Provide adequate support for performance of clinical trials,
- Optimize clinical trial design specific to pancreatic cancer, and
- Develop a dedicated Web site and/or other mechanisms for disseminating information on pancreatic cancer and clinical trials.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

The NCI Clinical Trials Cooperative Group Program supports organizations that continually generate and conduct new clinical trials consistent with national priorities for cancer treatment research. Emphasis is placed on definitive, randomized phase 3 studies and preliminary developmental efforts. One of the primary objectives underlying the formation of the groups is the conduct of large multicenter trials for the investigational agents sponsored by the Cancer Therapy Evaluation Program. This allows the rapid accrual of patients, while reducing the possible bias of studies carried out at a single or a few institutions.

The Cancer Trials Portal of Cancer.Gov (http://cancertrials.nci.nih.gov) provides information and news about cancer research studies. The site is designed to answer basic questions about clinical trials; provide resources for people considering participation in clinical trials; help people learn which clinical trials are available; and publish current, accurate information about clinical trial results and advances in cancer care.

Diagnostic Imaging Network -American College of Radiology Imaging Network (ACRIN) (see page 60)

The Quick Trials for Novel Cancer Therapies program speeds the translation of ideas developed in the laboratory to early-stage clinical trials by simplifying the grant application process and providing a rapid turnaround from application to funding. No applications funded to date focus on pancreatic cancer.

The Specialized Program of Research Excellence in Human Cancer (SPOREs) support interdisciplinary teams of investigators who are dedicated to translational research focused on an organ-specific human cancer (e.g., breast cancer) or a highly related group of human cancer types (e.g., gastrointestinal). SPOREs differ from program project grants (P01s) in that SPORE grants focus on human disease and support translational research, have a flexible approach to starting and stopping research projects, and have a required tissue bank core as well as required programs for career development and developmental projects.

The Community Clinical Oncology Program is a network of 49 central offices in 31 states that provides the infrastructure to link more than 2,500 community cancer specialists and primary care physicians with clinical cooperative groups and cancer centers. In addition, the program supports scientific development and the implementation of ongoing cancer treatment, prevention, and control clinical trials among community cooperative group members and cancer centers.

The Cancer Information Service (CIS) is NCI's link to the public, interpreting and explaining research findings in a clear and understandable manner. Through a network of 14 regional offices located throughout the country, the CIS serves the entire United States, Puerto Rico, and the U.S. Virgin Islands. Information specialists answer questions in English and Spanish, and TTY is available for deaf and hearing-impaired callers. The toll-free number is 1-800-4CANCER (1-800-422-6237).

The Cancer Trials Support Unit (CTSU) supports a national network of physicians and patients to participate in NCI-sponsored phase 3 cancer treatment trials. The CTSU reduces the regulatory/ administrative burden on cancer cooperative groups, increases physician and patient access to NCI-sponsored clinical trials, and streamlines and standardizes information collection and reporting. The pilot project focuses on phase 3 trials in the adult population for five disease sites: genitourinary, lung, breast, and gastrointestinal cancers, and leukemia. The CTSU also builds communication links to existing educational and training resources (CancerNet and CancerTrials) and provide an additional access portal to the entire menu of NCI-sponsored protocols for both clinicians and patients.

New Activities Initiated within the Past Year

The Office of Education and Special Initiatives Clinical Trial Education Series disseminates a series of books, brochures, videos, and slides to train advocates, the interested public, and healthcare professionals (including referring physicians and nurse practitioners) about clinical trials. A special section describes resources and communication with the patient.

Proposed Strategies to Address Gaps

To address this priority, NCI is considering the following strategies:

- Work with advocacy groups and the Office of Liaison Activities to promote education materials and information on the World Wide Web, with increased emphasis on pancreatic cancer.[b]

- Support the ongoing initiative to develop a Barrett's esophagus GI network. If the network is successful, suggest development of a more inclusive network for all digestive tract diseases to include pancreatic cancer.[c]

a. NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
b. NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
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d. NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

29 Develop new models that can be applied and validated in community and academic research settings for analyzing cost to conduct clinical research in pancreatic cancer, assessing communication effectiveness, improving patient decision making, etc.

Introduction

New models are needed for analyzing the cost to conduct clinical research in pancreatic cancer; assessing communication effectiveness, improving patient decisionmaking, describing and summarizing consistent patterns of variables indicative of longer term survival of pancreatic cancer, and characterizing quality of life and end-of-life parameters for pancreatic cancer patients.

Ongoing Activities

The following initiatives could potentially address pancreatic cancer:

Innovations in Biomedical Information Science and Technology (see page 53)

The NCI Evaluation Study of the Cost of Clinical Trials provides national estimates of the patient care costs in NCI-sponsored cancer treatment trials. When completed, results from the study will provide information for clinical researchers, insurers, employers, patient advocates, and policymakers. The study will enroll up to 750 patients in NCI-sponsored phase 1, 2, or 3 treatment studies, using administrative data and chart reviews, and will also include a matched control group of 750 cancer patients treated with standard care. The project has completed site recruitment, and record abstraction is nearing completion.

Appendix A
Pancreatic Cancer Strategic Plan Workgroup

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Appendix B
Pancreatic Cancer Strategic Plan

Recommendation 1 **Develop sustained, expanded training and career development efforts in pancreatic cancer research and care.**	
Ongoing Activities	**Page**
Transition Career Development Award	13
Cancer Education Grant Program	13
Research Training and Career Development Awards	13
NCI Scholars Program	13
National Research Service Award	14
New Activities	
Fund meritorious peer-reviewed pancreatic cancer-specific SPOREs	14
Proposed Strategies	
Expand The Transition Career Development Award (K22)[a]	14
Fund highly meritorious projects with unsuccessful pancreatic Specialized Program of Research Excellence (SPORE) or program project applications[b]	14
Expand the National Research Service Award (NRSA)[b]	15
Recommendation 2 **Establish centers of excellence for pancreatic cancer research and care.**	
Ongoing Activities	**Page**
SPOREs	16
New Activities	
Fund meritorious peer-reviewed pancreatic cancer-specific SPOREs	16
Recommendation 3 **Create an interdisciplinary coordinating mechanism to track pancreatic cancer research applications and monitor funding patterns.**	
Proposed Strategies	**Page**
The pay line for pancreatic cancer-relevant research will be 50 percent higher than the overall pay line for NCI research grants. Only those applications that are 100 percent relevant to pancreatic cancer will be eligible for this higher exception payline level.[a]	17

[a] NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
[b] NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
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[d] NCI is beginning to implement this strategy. Speed of implementation will depend on the availability of NCI staff to devote appropriate resources to the effort.

Recommendation 4 **Achieve a more complete understanding of the normal biology of the pancreas.**	
Ongoing Activities	**Page**
The Cancer Genome Anatomy Project	18
Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation	18
Proposed Strategies	
Partner with NIDDK to issue a PAR to stimulate research on the normal biology of the pancreas and on pathogenesis of Pancreatic Cancer[a]	19
Fund highly meritorious projects within unsuccessful pancreatic SPORE or program project applications[b]	19
Recommendation 5	
Ongoing Activities	**Page**
Innovative Technologies for the Molecular Analysis of Cancer: Phased innovation Award	20
Molecular and Cellular Biology of Metastatic Tumor Cells	20
Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation	21
Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer	21
New Activities	
Supplement investigators in the Mouse Models of Human Cancers Consortium to further the development of pancreatic cancer mouse models	21
Proposed Strategies	
Partner with NIDDK to issue a PAR to stimulate research on the normal biology of the pancreas and on pathogenesis of pancreatic cancer. [a]	21
Fund highly meritorious projects within unsuccessful pancreatic SPORE or program project applications. [b]	21

[a] NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
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Recommendation 6 **Study the natural history of the pancreatic stroma and desmoplasia.**	
Ongoing Activities	**Page**
Molecular and Cellular Biology of Metastatic Tumor Cells	23
Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation	23
New Activities	
The tumor microenvironment has been incorporated into the Bypass Budget as an Extraordinary Opportunity area for NCI.	23
Proposed Strategies	
Partner with NIDDK to issue a PAR to stimulate research on the normal biology of the pancreas and on pathogenesis of pancreatic cancer. [a]	24
Recommendation 7 **Investigate clinically important host-tumor interactions and develop novel therapeutic strategies to address them.**	
Ongoing Activities	**Page**
Phased Application Awards in Cancer Prognosis and Prediction	25
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	25
New Activities	
Enhance promotion of phased application awards and correlative studies to cooperative groups and SPOREs and inform them of extra funding for pancreatic cancer research	25

[a] NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
[b] NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
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Recommendation 8 **Identify genetic and environmental factors and gene-environment interactions that contribute to pancreatic cancer development.**	
Ongoing Activities	**Page**
Early Detection Research Network	27
SPOREs	27
Mouse Models of Human Cancer Consortium	28
Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer	28
Exploratory Studies in Cancer Detection, Prognosis, and Prediction	28
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	28
Phased Application Awards in Cancer Prognosis and Prediction	28
Cancer Genetics Network	28
New Activities	
SPOREs	29
Proposed Strategies	
Expand NCI Cohort Consortium for Pancreatic Cancer[a]	29
Through the Cancer Research Network, support a large, population-based case control study of pancreatic cancer in four health maintenance organizations (HMOs)[c]	29
Encourage formation of consortium of family registry studies[d]	30
Recommendation 9 **Develop, implement, and evaluate approaches to prevent pancreatic cancer in high-risk cohorts. Studies should be performed in humans and in animal models of early neoplasia.**	
Ongoing Activities	**Page**
Cancer Genetics Network	31
Expand the Rapid Access to Preventive Intervention Development (RAPID) Program	31
Proposed Activities	
Encourage collaborations between the Cancer Genetics Network, Cancer Family Registries, Early Detection Research Network, and SPOREs[d]	31

[a] NCI is developing this strategy further as a first step toward implementation. Actual implementation will depend on the availability of funds, the receipt of high-quality applications, and a final determination that the strategy is feasible and scientifically sound.
[b] NCI has determined that it will develop this strategy further in the near term. Further consideration of this strategy will take place over the next several months.
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Recommendation 10 **Identify and develop surveillance and diagnosis methods for early detection of pancreatic cancer and its precursors.**	
Ongoing Activities	**Page**
Early Detection Research Network	32
Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer	32
Exploratory/Developmental Grants for Diagnostic Cancer Imaging	32
In Vivo Cellular and Molecular Imaging Centers	32
Small Animal Imaging Resource Programs	32
Development of Novel Imaging Technologies	33
Exploratory Studies in Cancer Detection, Prognosis, and Prediction	33
Phased Application Awards in Cancer Prognosis and Prediction	33
Proposed Strategies	
Expand the NCI Cohort Consortium to include pancreatic cancer[a]	33
Consider noncompetitive renewals for long-term studies[c]	33
Identify markers for early detection of pancreatic cancer through the Early Detection Research Network and the Center for Proteomics[a]	33

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Recommendation 11 **Facilitate the discovery and drug development of targeted therapeutics.**	
Ongoing Activities	**Page**
Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses	35
Rapid Access to Intervention Development	35
Phased Application Awards in Cancer Prognosis and Prediction	36
Exploratory Studies in Cancer Detection, Prognosis, and Prediction	36
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	36
The Molecular Target Drug Discovery for Cancer Program	36
SPOREs	36
Quick-Trials for Novel Cancer Therapies	36
The Gastrointestinal (GI) Intergroup	36
Proposed Strategies	
Offer supplements for tissue acquisition and informatics to GI (and pancreatic cancer) SPOREs[b]	36
Foster partnerships with industry through various funding mechanisms, including the National Cooperative Drug Discovery Groups, to discover and develop promising drug compounds[b]	37
Expand the Rapid Access to Intervention Development and Rapid Access to NCI Discovery Resources Programs[c]	37

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Recommendation 12 **Facilitate development of preclinical and minimally invasive clinical techniques to assess targeted therapeutics.**	
Ongoing Activities	**Page**
Diagnostic Imaging Network-American College of Radiology Imaging Network	38
Innovative Toxicology Models for Drug Evaluation: Exploratory/Developmental Grants and Phased Innovation Award Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) Initiative	38
Development of Clinical Imaging Drugs and Enhancers	39
Small Animal Imaging Resource Program	39
Establish loose consortium among modelers	39
New Activities	
Mouse Models of Human Cancers Consortium: Supplements to further the development of pancreatic cancer mouse models	39
Proposed Strategies	
Provide supplements to Molecular Imaging Centers for collaborations between drug developers and imaging scientists[c]	39
Recommendation 13 **Accelerate research into the supportive care of patients with pancreatic cancer.**	
Ongoing Activities	**Page**
Support research on palliative care through the Centers of Excellence in Cancer Communications	40
Management of Symptoms Secondary to Treatment	40
New Activities	
State-of-the-Science Meeting on Cancer Symptom Management on July 15-17, 2002	40
Work with the HMO Cancer Research Network to increase palliative care and end-of-life research initiatives	40
Proposed Strategies	
Develop future proposals in cancer symptom management [c]	41

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Recommendation 14 **Identify effective forms of healthcare provider communication with pancreatic cancer patients.**	
Ongoing Activities	**Page**
Partnership with the Education for Physicians on End-of-Life Care Project	43
New Activities	
Office of Education and Special Initiatives Clinical Trial Education Series	43
Pain Kit	43
Incorporating Clinical Trials Into Your Practice	43
Proposed Strategies	
Promote education materials and information on the World Wide Web with emphasis on pancreatic cancer[b]	44
Through the Cancer Research Network, support a large population-based case control study of pancreatic cancer in HMOs[b]	44
Recommendation 15	
Ongoing Activities	**Page**
Management of Symptoms Secondary to Treatment	45
Research on Ethical Issues in Human Studies	45
Informed Consent in Research Involving Human Participants	46
New Activities	
Human Participant Protections for Research Teams	46
Proposed Strategies	
Promote education materials and information on the World Wide Web with emphasis on pancreatic cancer[b]	46

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Recommendation 16 **Identify workforce requirements and costs of multidisciplinary clinical trials in pancreatic cancer. Create a Web-based repository to track, update, and categorize information on pancreatic cancer clinical trial costs.**	
Ongoing Activities	**Page**
NCI Clinical Trials Cooperative Group Program	47
NCI Evaluation Study of the Cost of Clinical Trials	47
Cancer Centers Program	47
Recommendation 17 **Determine the effectiveness of current practices in pancreatic cancer care and evaluate new strategies for managing difficult treatment and end-of-life issues.**	
Ongoing Activities	**Page**
Management of Symptoms Secondary to Treatment	48
Measures of Quality of Care	48
Support research on palliative care and end of life	48
New Activities	
A Palliative Care Coordinator has been identified in response to the recommendation from the Institute of Medicine report published in June 2001	48
Proposed Strategies	
Through the Cancer Research Network, support large, population-based case control pancreatic cancer in four HMOs[d]	49

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Recommendation 18 **Construct resources to provide access to a range of normal and neoplastic human pancreas samples, and all types of biomaterials.**	
Ongoing Activities	**Page**
NCI Clinical Trials Cooperative Groups	51
Cooperative Human Tissue Network	51
NCI Tissue Expediter	51
Shared Resources for Scientists Outside NCI Cancer Centers	51
NCI Specimen Resource Locator	52
Continue to fund or enhance support for Tissue Array Research Program	52
New Activities	
Shared Pathology and Informatics Network	52
Proposed Strategies	
Offer supplements to GI (and pancreatic cancer) SPOREs, Cancer Therapy Evaluation Program/GI Intergroup, Director's Challenge grantees, and P01 grantees who are willing and able to collect tissue samples and create repositories[b]	52
Recommendation 19 **Construct a relational database containing information on the biological profiles of normal and abnormal pancreas cells. Organize knowledge of signaling pathways into interrelated networks and systems.**	
Ongoing Activities	**Page**
Innovations in Biomedical Information Science and Technology	53
Innovative Technologies for the Molecular Analysis of Cancer	53
Translation of Technologies to Detect Alterations in Human Tumors	54
Cancer Genome Anatomy Project	54
Director's Challenge: Toward a Molecular Classification of Tumors	54
Cancer Molecular Analysis Project	54

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Recommendation 20 **Develop biological sampling techniques that permit analyses of minute quantities of biological samples.**	
Ongoing Activities	**Page**
Innovative Technologies for the Molecular Analysis of Cancer	55
Tissue Array Research Program	55
Translation of Technologies to Detect Alterations in Human Tumors	55
The NCI Advanced Technology Center	55
Exploratory Studies in Cancer Detection, Prognosis, and Prediction	55
Improving DNA, RNA, and Protein Availability in Fixed Tissue	56
Proposed Strategies	
Include development of sampling techniques in the annual SBIR/STTR[d]	56
Recommendation 21 **Develop experimental model systems and establish gene-based model systems in vivo and ex vivo that faithfully recapitulate the complex biology of human pancreatic adenocarcinoma.**	
Ongoing Activities	**Page**
Mouse Models of Human Cancers Consortium	57
Innovative Technologies for the Molecular Analysis of Cancer	57
The Zebrafish as an Animal Model for Development and Disease Research	58
Molecular and Genetic Studies in Pancreatitis and Pancreatic Cancer	58
Small Animal Imaging Resource Programs	58
Establish loose consortium among modelers	58
New Activities	
Supplements to investigators within the Mouse Models of Human Cancers Consortium to further the development of pancreatic cancer mouse models	58
Proposed Strategies	
Reissue program announcement for competing supplements to develop organotypic models of cancer[b]	58

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Recommendation 22 **Develop imaging systems for elucidating pancreatic cancer biology and for detecting and monitoring this disease. Develop a Web-based imaging library.**	
Ongoing Activities	**Page**
Innovative Technologies for the Molecular Analysis of Cancer	59
In Vivo Cellular and Molecular Imaging Centers	59
Development and Application of Imaging in Therapeutic Studies	59
Exploratory/Developmental Grants for Diagnostic Cancer Imaging	59
Diagnostic Imaging Network-American College of Radiology Imaging Network	60
Data banks of standardized digital image data associated with known clinical outcomes	60
Development of Novel Imaging Technologies Initiative	60
Small Animal Imaging Resource Programs	60
Innovations in Biomedical Information Science and Technology	60
Proposed Strategies	
Support a database resource for imaging research[b]	60
Recommendation 23 **consortia of large, aging cohorts for pooled analyses to elucidate causal factors.**	
Ongoing Activities	**Page**
Cancer Genetics Network	61
Shared Resources for Scientists Outside NCI Cancer Centers	61
NCI Cohort Consortium	61
Correlative Studies Using Specimens from Multi-Institutional Prevention and Treatment Trials	61
Proposed Strategies	
Expand NCI Cohort Consortium to include pancreatic cancer	62
Create Lymphoma/Leukemia Molecular Profiling Project-like initiative for pancreatic cancer[c]	62
Through the Cancer Research Network, support a large, population-based case control study of pancreatic cancer in four HMOs[b]	62

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Recommendation 24 **Develop education materials for healthcare providers and investigators about pancreatic cancer risk assessment, evaluation protocols, and sample collection. Create new education, training, and communication tools for providers with education components and collateral materials.**	
Ongoing Activities	**Page**
Office of Education and Special Initiatives Clinical Trial Education Series	64
Testing Interventions to Improve Adherence to Pharmacological Treatment Regiments	64
Cancer Education Grant Program	64
Cancer.gov Web site-pancreatic cancer section	65
New Activities	
An online tutorial, Incorporating Clinical Trials Into Your Practice	65
Partnership with the Education for Physicians on End-of-Life Care Project	65
Proposed Strategies	
Patient and Provider Education[b]	65
Recommendation 25 **Create technology centers for comprehensively assessing gene and protein expression for use in identifying biologic indicators of the presence and behavior of pancreatic cancer and its precursors.**	
Ongoing Activities	**Page**
NCI Advanced Technology Center	66
Tissue Array Research Program	66
Director's Challenge: Toward a Molecular Classification of Tumors	66

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Recommendation 26 **Develop mechanisms to facilitate investigator access to novel targeted therapeutic agents for preclinical studies and clinical trials.**	
Ongoing Activities	**Page**
NCI Research Resources Web Site	67
Developmental Therapeutics Program Web Site	67
New Activities	
Phase 1 and 2 Clinical Trials of Cancer Chemopreventive Agents	67
Proposed Strategies	
Explore mechanisms to foster testing of promising new agents[d]	68
Recommendation 27 **Develop infrastructure for molecular target assessment.**	
Ongoing Activities	**Page**
Flexible System to Advance Innovative Research for Cancer-Drug Discovery by Small Businesses (FLAIR-SBIR)	69
Rapid Access to Intervention Development Program	69
Molecular Targets Laboratories	69
Innovative Toxicology Models for Drug Evaluation: Exploratory/Developmental Grants and Phased Innovation Award SBIR/STTR Initiative	70
Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: Phased Innovation	70
Proposed Strategies	
Expand the Rapid Access to Intervention Development and Rapid Access to NCI Discovery Resources Programs[c]	70

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Recommendation 28 **Improve infrastructure for clinical trials and promote patient participation.**	
Ongoing Activities	**Page**
NCI Clinical Trials Cooperative Group Program	71
Cancer Trials Portal of Cancer.Gov	71
Diagnostic Imaging Network-American College of Radiology Imaging Network	71
Quick-Trials for Novel Cancer Therapies	71
SPORES	72
Community Clinical Oncology Program	72
Cancer Information Service	72
Cancer Trials Support Unit	72
New Activities	
Office of Education and Special Initiatives Clinical Trial Education Series to train advocates and public and healthcare providers about clinical trials	72
Proposed Strategies	
Promote education materials and information on the World Wide Web with emphasis on pancreatic cancer[b]	73
Support the ongoing initiative to develop a Barrett's Esophagus GI Network[d]	73
Recommendation 29 **Develop new models that can be applied and validated in community and academic research settings for analyzing cost to conduct clinical research in pancreatic cancer, assessing communication effectiveness, improving patient decision making, etc.**	
Ongoing Activities	**Page**
Innovations in Biomedical Information Science and Technology	74
NCI Evaluation Study of the Cost of Clinical Trials	74

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