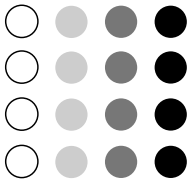

Pancreatic Cancer: An Agenda for Action

Report of the Pancreatic Cancer Progress Review Group

February 2001

NATIONAL® CANCER INSTITUTE

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From the Leadership

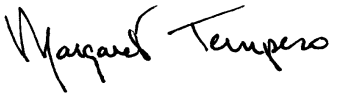
It is a great pleasure to submit this Report of the Pancreatic Cancer Progress Review Group (PRG) to the Director and Advisory Committee to the Director of the National Cancer Institute (NCI). To accelerate progress against pancreatic cancer, the Director, NCI, requested the PRG to identify scientific priorities and needs so that the Institute can forge a national agenda for research on this disease. This report is the outcome of the PRG's 10-month effort to carry out this charge.

Although pancreatic cancer is less common than some other cancers, it is nearly always fatal, so we appreciate the NCI's decision to institute a PRG to address it. The PRG's report demonstrates a need to expand pancreatic cancer research aggressively in almost all areas: biology, etiology, prevention, diagnosis, treatment, control, and perhaps most importantly, training and infrastructure. However, rather than propose a long list of recommendations, the PRG proposes a limited set of them that truly represent the highest priorities in the field. The PRG was able to accomplish this goal by using a structured, formal process at its Roundtable Meeting in which participants integrated the findings from specific breakout groups into the deliberations of more broad ones. The result of this approach, we believe, is a report that is clear and concise in its recommendations.

We believe that the hard work of this PRG has resulted in recommendations that, if pursued, will do much to eradicate morbidity and mortality due to pancreatic cancer. We look forward to assisting the NCI in implementing these recommendations and to following their progress.

Respectfully,

Scott Kern, M.D.
Co-Chair, PRG



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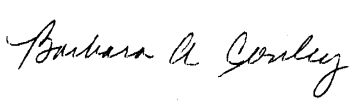

Barbara Conley, M.D.
Executive Director, PRG
National Cancer Institute

We the undersigned members of the Pancreatic Cancer Progress Review Group concur with the enclosed report.

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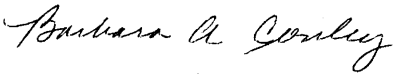
Co-Chair

Margaret Tempero, M.D.
Co-Chair



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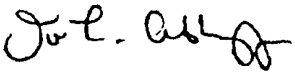

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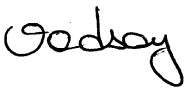

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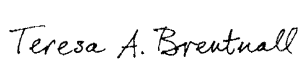

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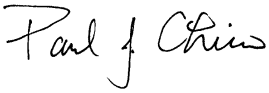

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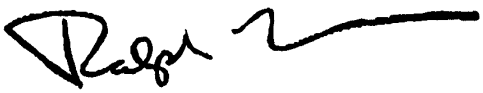

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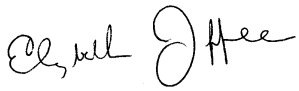

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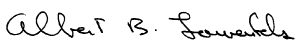

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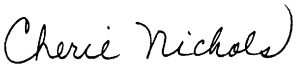

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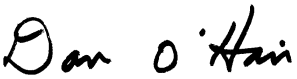

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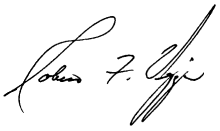

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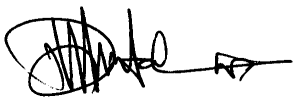

David Whitcomb, M.D., Ph.D.

Acknowledgments

This report is the result of 10 months of intense work, drawing upon the combined skills and efforts of many people. The PRG would like to extend special thanks to the following:

- The researchers, clinicians, and members of the advocacy community who participated in the Pancreatic Cancer Roundtable Meeting. The recommendations of the PRG are the result of their expertise, insight, and effort.

- Lisa Begg, Randall Brand, William Brugge, Carolyn Compton, Ron Depinho, William Lee, Robert Radinsky, Mace Rothenberg, Vito Quarranta, Debra Silverman, Joel Tepper, and Charles Ulrich, who served with us as speakers and co-chairs for breakout sessions at the Roundtable Meeting. We are indebted to them for serving in this capacity so well.

- Kevin Callahan, Annabelle Uy, Kate Nagy, and Terri Hallquist, who, as staff of the NCI's Office of Science Planning and Assessment, provided strong guidance and technical support throughout the life of the PRG.

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- Josette Johnson, Audrey Thomas, Robert Wald, and their colleagues at Palladian Partners, who provided logistical support to the PRG from its first meeting to its last, and provided expertise for the design, formatting, and printing of this report.

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Executive Summary

Executive Summary

Pancreatic cancer is a devastating disease that swiftly robs patients of both quality and quantity of life. It is the fifth leading cause of cancer death in the United States. In 2001, an estimated 29,200 new cases will be diagnosed, and 28,900 people will die from the disease. Most of these tumors will be ductal adenocarcinomas, from which there currently is little chance of long-term survival—median survival is six months or less, and only four percent of patients are alive five years after diagnosis. Given its incidence and almost universal fatality, substantially increased research efforts are clearly warranted to understand, prevent, and control this disease.

Pancreatic cancer has been understudied in both basic research laboratories and the clinic. In terms of total research dollars, total numbers of researchers, and numbers of researchers who are highly focused on this disease, pancreatic cancer lags significantly behind all of the most common tumors, despite their far more favorable survival rates. For example, in 1999, pancreatic cancer research received only $17.3 million in National Cancer Institute (NCI) funding.

Severely limited funding for pancreatic cancer research has likewise limited the size of the research community pursuing progress against any aspect of the disease, and the number of researchers who are able to make pancreatic cancer their principal research focus. In 1999, of the 270 grants recorded by the NCI as relevant to pancreatic cancer, less than three dozen were at least 50 percent relevant to research on the disease. Available data suggest that fewer than ten principal investigators have multiple grants or a primary career focus on pancreatic cancer.

Research over the past decade indicates that pancreatic cancer is sufficiently distinctive in its etiology, pathogenesis, and clinical behavior to justify a major expansion of investigations focused primarily on this disease, and that such research can be accomplished with reasonable efficiency. Greater commitment of resources and scientific expertise are needed to achieve significant improvements in pancreatic cancer diagnosis and management.

To help develop a national agenda for pancreatic cancer research, the Director, NCI, requested that a multidisciplinary Progress Review Group (PRG) on pancreatic cancer analyze the NCI's current research portfolio on the disease and develop and prioritize recommendations for achieving progress. This report details the outcome of that effort.

THE PRG PROCESS AND DEVELOPMENT OF THE PRG REPORT

PRG members included prominent members of the scientific, medical, industry, and advocacy communities, representing the full spectrum of expertise required to make comprehensive recommendations for NCI's pancreatic cancer research agenda. At a Planning Meeting held in May 2000, the Pancreatic Cancer PRG organized a Roundtable to consider progress and identify issues, barriers, and needs across the continuum of pancreatic cancer research. The group was instructed to prioritize suggestions for new research efforts over the next five to ten years. Roundtable participants were identified and topics were selected for breakout sessions, to which the Roundtable participants were assigned. PRG

members served as co-chairs for the breakout sessions.

The Pancreatic Cancer PRG Roundtable of approximately 120 participants met on September 15–17, 2000 in Chantilly, Virginia. Following initial plenary presentations on the state of the art in pancreatic cancer tumor biology, risk/prevention/detection, and therapy, Roundtable participants broke into initial discussion sections addressing Pathology and Tissue Characterization, Signaling, Stromal Interactions, Risk, Diagnostic Technologies, and Host/Tumor Interactions. Overarching resource needs were discussed subsequently in sessions covering the Scientific Toolkit and Clinical Trials Networks. Scientific priorities, related recommendations, and specific resource needs were then established and prioritized in sessions on Tumor Biology, Risk/Prevention/Screening/Diagnosis, Therapy, and Health Services Research. A panel discussion on Career Development and Funding also was held.

The PRG used input from the Roundtable to delineate and prioritize recommendations for research directions, related scientific questions, and resource and infrastructure needs. There was a high degree of agreement on many of the crucial needs of the field. In support of the process, NCI also provided the PRG with an analysis of its current pancreatic cancer research portfolio that assisted the PRG in developing its recommendations.

ORGANIZATION OF THE REPORT

The full report of the Pancreatic Cancer PRG is presented in three sections. Section I, Health of the Field and Overarching Issues, addresses current research and funding levels for pancreatic cancer and critical issues such as manpower development and training needs, and resource deployment and organization.

Section II details Research Priorities in four principal scientific areas of pancreatic cancer research:

- Tumor Biology
- Risk/Prevention/Screening/Diagnosis
- Therapy
- Health Services Research

Section III enumerates key resources, or a Scientific Toolkit, that the PRG believes are urgently needed to accelerate achievement of the research priorities. Requests for components of the Toolkit were often echoed among the recommendations related to the research priorities described in Section II.

A rationale is provided for each priority and resource identified in these sections. Three appendices also are included. Appendix A is a roster of the Pancreatic Cancer PRG members and Roundtable participants. Appendix B describes NCI-supported pancreatic cancer research. A detailed description of the purpose and process of NCI's Progress Review Groups is included as Appendix C.

Sections I, II, and III of the full PRG report are summarized below.

I. Health of the Field and Overarching Issues

Pancreatic cancer research currently suffers from a variety of unmet training, career development, and organizational needs. Very few researchers are dedicated to pancreatic cancer research at any level. In addition to these serious limitations, the pancreatic cancer research field suffers from several challenges, such as low levels of NCI funding, that historically have resulted

in low levels of enthusiasm for pancreatic cancer research among physician-scientists.

Action is needed to significantly augment pancreatic cancer research overall by:

- Developing sustained, expanded training and career development efforts in pancreatic cancer research and care.
- Creating an interdisciplinary coordinating mechanism to monitor funding patterns and identify funding deficits and opportunities in pancreatic cancer research.
- Establishing centers of excellence for pancreatic cancer research and care.

II. Research Priorities

Tumor Biology

Pancreatic cancer is a unique and heterogeneous disease that is difficult to study. Molecular aspects of normal cell differentiation and development of the pancreas are poorly understood. 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. The PRG identified four research priorities:

- Achieve a more complete understanding of the normal biology of the pancreas.
- Elucidate the development of pancreatic adenocarcinoma.
- 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).
- Investigate clinically important host-tumor interactions and develop new therapeutic strategies to address them.

Two resources critical to this research are:

- Specimen banks of normal, proliferative, precancerous, and cancerous human pancreatic tissue.
- Experimental model systems.

Risk/Prevention/Screening/Diagnosis

Pancreatic cancer patients seldom exhibit disease-specific symptoms until the cancer is at advanced stages, 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:

- 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). Studies should be performed in humans and in animal

models of early neoplasia (e.g., PanIN-3).

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

Seven critical resources include:

1. New and expanded registries for:
   — Identification of high-risk patients and kindreds.
   — Linkage analysis.
   — Tissue and specimen resources.
   — Identification of screening and surveillance cohorts.
   — Epidemiologic assessment of gene-environment interactions.

2. Specimen banks for all types of biomaterials (e.g., blood, serum, pancreatic juice, stool, tumors, other body fluids).

3. Consortia of large, aging cohorts for pooled analyses to elucidate causal factors.

4. Education for providers and investigators about pancreatic cancer risk assessment, evaluation protocols, and sample collection.

5. A Web-based imaging library 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.

6. 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.

7. Animal models for the study of environmental factors, gene-environment interactions, chemoprevention, chemotherapy, radiation therapy, vaccines, and imaging.

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 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:

- Facilitate the discovery and development of targeted therapeutics.

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

- Accelerate research into the supportive care of patients with pancreatic cancer.

Three critical resources are needed for this research:

1. Mechanisms to facilitate investigator access to targeted therapeutic agents for preclinical studies and clinical trials.

2. Infrastructure for molecular target assessment.

3. Infrastructure for multidisciplinary clinical trials and promoting patient participation.

Health Services Research

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

- Identify effective forms of health care provider communication with pancreatic cancer patients.

- Identify determinants of message effectiveness in aiding decision making by patients.

- Identify manpower requirements and costs of multidisciplinary clinical trials in pancreatic cancer.

- 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.

The PRG identified four categories of critical resources:

1. 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.

2. A Web-based repository to track, update, and categorize information on the costs of clinical trial research focusing on pancreatic cancer.

3. New models that can be applied and validated in community and academic research settings, including those for:
   — Analyzing cost and level of effort required to conduct clinical research in pancreatic cancer.
   — Assessing communication effectiveness.
   — Improving patient decision making.
   — Describing and summarizing consistent patterns of variables indicative of longer term survival of pancreatic cancer.
   — Characterizing quality of life and end of life parameters for pancreatic cancer patients.

4. Education, training, and communication tools:
   — Communication toolkits for health care providers with education components and collateral materials, particularly to assist/support patient decision making.
   — Patient decision making toolkits for various patient populations.
   — Mechanisms to facilitate increased interaction among health care providers, advocates, and professional and funding organizations.

III. Scientific Toolkit

The lack of six key resources and tools poses a major impediment to progress in pancreatic cancer research:

1. A specimen resource to provide access to a range of normal and neoplastic human pancreas samples.

2. A relational database containing information on the biological profiles of normal and neoplastic pancreas cells.

3. New biological sampling techniques that permit analysis of minute quantities of biological samples.

4. Organization of growing knowledge about signaling pathways into interrelated networks and systems to assess the ultimate outcome of alterations in pathways important in pancreatic cancer.

5. *In vivo* and *ex vivo* gene-based model systems that faithfully parallel the complex biology of human pancreatic adenocarcinoma.

6. Imaging systems for elucidating the biology of pancreatic cancer, detecting disease, and monitoring patients after therapeutic intervention.

CONCLUSION

The Pancreatic Cancer PRG believes that urgently needed progress against pancreatic cancer must be achieved through a concerted and significant effort to build a comprehensive research community focused on this disease. To be effective, this community must have stable support and the scientific depth and diversity to challenge the disease comprehensively, including, but not limited to: the nature of normal pancreas biology, individual risk assessment, surveillance for early disease, diagnosis, prognosis assessment, effective therapy, and beneficial health service design and delivery, including communication mechanisms. The PRG has identified critical opportunities. A greater research emphasis on this cancer, incorporating the suggestions contained in the full report of the Pancreatic Cancer PRG, is essential to take full advantage of these opportunities.

I. Health of the Field and Overarching Issues

Health of the Field and Overarching Issues

Pancreatic cancer is disproportionately underrepresented in both clinical and basic research compared with other cancer sites. Several factors may be contributing to this marginal research base in pancreatic cancer. Scientific investigators with interest and expertise in this area comprise a very small cadre. Pancreatic cancer care is complicated, requiring a multidisciplinary approach, and despite our best efforts, outcomes are nearly always disappointing. To build a robust laboratory, clinical, and population science research program for this disease demands unusual effort that currently is made more difficult by a lack of key resources, such as appropriate preservation of pancreatic tissue and key reagents for translational studies. No specialized scientific infrastructure exists to support training or funding for pancreatic cancer research. Yet novel approaches and unique commitments will be necessary to make progress against pancreatic cancer. Advances in other diseases suggest that increased investment in pancreatic cancer research can be expected to yield dramatic progress.

Steady increases in the National Institutes of Health (NIH) and National Cancer Institute (NCI) budgets have translated into significantly greater funding for research on diseases such as breast, colorectal, and prostate cancer. Pancreatic cancer research funding, however, has not experienced similar growth. In 1999, pancreatic cancer research received only $17.3 million in NCI funding.

Available data do not lend themselves to a precise assessment of the funding deficit in pancreatic cancer research, but figures derived by the PRG from these data outline basic trends. For example, very few investigators focus exclusively on pancreatic cancer. Of slightly more than a dozen principal investigators currently holding multiple grants related to pancreatic cancer, fewer than six have a clear focus on pancreatic adenocarcinoma. Of the nearly two dozen grants with major relevance to pancreatic adenocarcinoma in 1995, just under a dozen of these same investigators still held these grants in 1999. These figures suggest either a striking lack of career commitment to pancreatic cancer research, or other serious barriers such as a lack of funding and/or other resources that makes such commitment difficult.

In 1999, of the 270 funded grants recorded as relevant to pancreatic cancer, fewer than three dozen were at least 50 percent relevant to research on pancreatic adenocarcinoma. Though discouraging, this reflects an improvement over previous years (1990 and 1995). Most grants recorded as relevant to pancreatic cancer had only minor fractions of effort devoted to the disease, with the majority of effort devoted to research on other cancers. Moreover, many of the grants for research on pancreatic adenocarcinoma are relatively small in size and exploratory. These data illustrate the serious underfunding of pancreatic cancer research and the consequent lack of a stable, committed workforce to achieve research goals. As a result, the loss of even a small fraction of these researchers and research projects would seriously undermine an already limited research effort.

The pancreatic cancer research community is encouraged by the comprehensive and effective way that HIV/AIDS has been addressed in America. For this disease, a basic scientific and cultural shift resulted in important progress. New dollars poured in to encourage institutions and investigators to

create an effective infrastructure and launch new research initiatives. As a result, new and outstanding projects were developed, and public and private partnerships were generated to facilitate research, education, and patient access to new drugs. Consequently, transmission and death rates have decreased markedly.

During the Pancreatic Cancer PRG Roundtable, the lack of a critical mass of personnel and resources dedicated to pancreatic cancer research was often cited. A special panel discussion was held on career development and funding issues in pancreatic cancer research and treatment. Overarching issues of resource deployment in funding, career development, and training were discussed. The paragraphs below both summarize the panel discussion and synthesize other discussions of these issues that occurred in many of the breakout sessions.

Three overarching, high-impact strategies were identified to augment pancreatic cancer research levels overall and speed progress against the disease:

- **Specialized training programs in pancreatic cancer research.** 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 the 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 progress in risk factor determination (involving molecular geneticists, physician-scientists, scientists in other disciplines, epidemiologists, statisticians, and data managers), risk reduction (physician-scientists, patient and public educators, epidemiologists, and statisticians), early detection (physician scientists in gastroenterology, abdominal imaging, oncology, biological sciences, physical sciences, engineering, and epidemiology), and treatment (physician-scientists in clinical oncology specialties, gastroenterology, immunology, biology, epidemiology, and pharmacology).

  Funding for such training would build on the commitment of recipient institutions to provide a supportive environment for these activities. Given the troubled health care environment, however, additional incentives may be necessary to encourage institutions to make this commitment. Encouraging established investigators to focus on pancreatic cancer will require new competitive funding opportunities from the NIH to provide some assurance that stable support for this research is possible.

- **NIH-based coordinating mechanism for pancreatic cancer research applications.** NCI resources are needed to produce the paradigm shift that will identify research opportunities and encourage new investigators. Increasing the number of NIH-funded research projects in pancreatic cancer can be addressed in a number of ways, but an important initial step would be for NCI to establish an interdisciplinary coordinating mechanism to foster and track pancreatic cancer research applications and progress. This activity would 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. Establishing pancreatic cancer research as a high priority will inevitably lead to a stronger research base.

- **Centers of excellence for pancreatic cancer care and research.** Currently, only one-third of pancreatic cancer patients are referred to institutions that treat more than 25 patients per year, or that perform more than 25 pancreatic resections per year. Research has shown that institutions that perform more pancreatectomies provide an improved level of care with superior outcomes compared to centers that perform relatively few of these surgeries. Further, to achieve optimal research productivity, scientists need a sufficiently large cohort of patients, excellent access to emerging technology, and effective collaborative and cooperative relationships. 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 integrate with a core of scientific investigators evaluating issues critical to this disease. Established models for organ transplantation and trauma that have improved research and care in those fields by concentrating resources and developing appropriate infrastructures could likewise be used to improve opportunities for focused pancreatic cancer research.

Implementing these strategies will produce a pancreatic cancer research effort that is more robust scientifically, better supported, and more effectively organized. Most importantly, these changes will produce advances that benefit the patients and families who are faced with this extremely difficult disease.

II. Research Priorities

Tumor Biology

STATE OF THE SCIENCE

Recent scientific advances have created an unprecedented opportunity to make significant progress in diagnosing and treating pancreatic cancer. Discoveries made through the Human Genome Project and new array technology for DNA, RNA, proteins, and tissues have enabled us to accomplish multiparametric analyses of gene and protein expression on multiple tissue samples.

Genetic alterations identified to date in invasive pancreatic cancer include activation of the *K-ras2* oncogene, overexpression of specific growth factors and their associated receptors, and inactivation of the *p16, p53, MADH4, BRCA2, MKK4, STK11, TGFBR1,* and *TGFBR2* tumor suppressor genes and certain DNA mismatch-repair genes. These genetic alterations are associated with the activation of specific transcription factors, including relA.

The advances in our understanding of pancreatic cancer biology have a number of important implications. They have shed light on precursor lesions that give rise to infiltrating pancreatic cancer. A number of the genetic alterations characteristic of invasive pancreatic cancer, including activation of the *K-ras2* gene and inactivation of the *p16, p53, DPC4* and *BRCA2* tumor suppressor genes, have been demonstrated in non-invasive epithelial proliferations in the pancreatic ducts and ductules. These epithelial proliferations, called pancreatic intraepithelial neoplasms (PanINs) provide an exciting target of research on chemoprevention and early detection.

Discovery of genetic alterations important in infiltrating pancreatic cancer has advanced our understanding of familial pancreatic cancer. For example, germline mutations in the *p16, BRCA2, PRSS1,* and *STK11* genes have been shown to predispose carriers to pancreatic cancer. These discoveries provide molecular tools for risk assessment and provide insight into signaling pathways altered in these cancers. By characterizing altered signaling pathways, we are discovering novel targets for therapy. Inactivation of the *DPC4 (MADH4, SMAD4)* tumor suppressor gene in the majority of pancreatic cancers disrupts the TGF-β signaling pathway, suggesting that restoring this pathway may be a potential target for therapy.

Infiltrating carcinoma in the pancreas often is accompanied by an intense host-stromal reaction, and recent advances have markedly improved our understanding of host-stromal interactions in these neoplasms. For example, we now know that infiltrating pancreatic carcinoma is characterized by aberrant expression of several growth factors (epidermal growth factor family, fibroblast growth factor, platelet-derived growth factor B, TGF-β, insulin-like growth factor-1 and nerve growth factor), enhanced angiogenesis with increased VEG-F expression, resistance to apoptosis, altered epithelial-mesenchymal interactions, excessive production of proteases including urokinase-like plasminogen activator, and an altered extracellular matrix. Each advance in our understanding of these factors and interactions provides a new target for novel approaches to diagnose and treat pancreatic cancer.

A unique and heterogeneous disease, pancreatic cancer is difficult to study. We

have yet to define all of the molecular processes that cause or accompany the pathogenesis of benign and malignant diseases of the pancreas, and we are hampered by a poor understanding of the molecular aspects of normal cell differentiation and development of the gland itself. The origin and nature of cells that are transformed in pancreatic cancer are not well defined. There is great diversity in the morphology and biological properties of different pancreatic tumors, yet we have little understanding of whether these differences portend differences in prognosis or require distinct treatments. Pancreatic tumors display a high degree of resistance to conventional chemotherapy and radiation therapy. Diagnosis, treatment, and our understanding of the disease are complicated by the intense desmoplastic reaction associated with most pancreatic carcinomas, which has not been studied systematically. Pancreatic tumors display insidious growth properties—they are undetectable at early stages and therefore go undiagnosed for long periods of time. Because clearly evident symptoms of pancreatic cancer are not present until the disease is advanced, patient survival after diagnosis is short.

Nonetheless, many new opportunities exist for research with considerable potential to reduce morbidity and mortality from this difficult disease. The promising early results of tissue-based gene and protein expression analysis in defining tumor biology has created a pressing need for specific resources such as high quality human specimens corresponding to all phases of disease, from incipient neoplasia to invasive and metastatic disease. At the clinical level, uniform reproducible criteria are lacking for classifying tumors and non-invasive epithelial proliferations that may represent precursor lesions. Training and quality control guidelines, and reimbursement for tissue acquisition, handling, and tracking are needed for both pathologists and surgeons. In addition, *in vitro, ex vivo,* and animal models are needed that faithfully recapitulate the complex biology of invasive human pancreatic cancer and its precursors.

RESEARCH PRIORITIES

1. Achieve a more complete understanding of the normal biology of the pancreas.

New information about pancreatic development has led to insights regarding nuclear transcription factors and signaling pathways regulating pancreatic progenitor/precursor cell expansion and differentiation. Many of these transcription factors (e.g., Pax6) are capable of acting as transforming oncogenes when expressed abnormally. While most research in pancreatic development has been directed toward identifying precursor/progenitor cells as a potential source for islet cell transplantation in diabetes, this research also might prove useful in clarifying questions regarding the cell(s) of origin, the nature of precursor lesions, and cell differentiation regulation in pancreatic cancer pathogenesis. In fact, notwithstanding established ductal differentiation features, the true cell of origin for pancreatic ductal adenocarcinoma remains unknown. Ductal adenocarcinomas may arise from fully differentiated ductal epithelium, from other cell lineages (e.g., acinar cells) by means of transdifferentiation/dedifferentiation, or from 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. For example, novel cell labeling techniques have been developed for tracing cell lineage (i.e., mapping precursor-progeny relationships) *in vivo* during embryonic development. Understanding precursor/progenitor cell biology has greatly aided the development of diagnostic and therapeutic tools in leukemias and in cancer immunology. It is reasonable to anticipate that this knowledge will likewise 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.

Recommendations

- Identify the precursor/progenitor cells of the exocrine and endocrine pancreas; determine the plasticity (i.e., vertical or horizontal differentiation) of cells at each step of differentiation, and determine the mechanisms by which one cell type can differentiate into another.

- Discover and validate markers of cell lineage and phenotype; develop normal non-transformed epithelial cell lines for all pancreatic cell types.

- Define the mechanisms of interaction between the principal cell types involved in pancreas development and in the normal adult pancreas (e.g., islet-ductal interactions, stromal-epithelial interactions).

- Characterize patterns of gene expression in cells involved in pancreas development and in the normal adult pancreas, and correlate these patterns with morphology and differentiation; define the molecular control of growth, death, and differentiation during normal pancreatic development and in the normal adult pancreas.

- Define the range of normal variation in anatomy, cell-to-cell interaction, biology, and response to injury in the adult pancreas over time, from person to person, and within the gland. This includes the biology of normal ducts, including flow rates, concentrations (e.g., across ducts, particularly as they apply to screening and imaging), and turnover rates.

- Elucidate the relationship between progenitor/precursor cells and pancreatic neoplasia.

- Develop, contrast, and correlate animal models with human biology in relation to the points above.

2. Elucidate the pathogenesis of pancreatic adenocarcinoma.

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 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 there are specific tumor subtypes. 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 can be expected to 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.

Recommendations

- Identify the precursor lesions to invasive pancreatic carcinoma and define their fundamental genetic alterations, patterns of gene and protein expression, and morphologic phenotypes. This will require new modalities to detect and monitor pancreatic precursor lesions in patients, new sampling methods to perform serial samplings in patients with potential pancreatic precursor lesions, and technologies for genotyping and phenotyping small samples from formalin-fixed, paraffin-embedded tissues.

- Define the fundamental genetic alterations and patterns of gene and protein expression in invasive and metastatic pancreatic carcinoma, and correlate these alterations and patterns with morphologic phenotypes and with clinical outcome.

- Determine the cell-cell and cell-matrix interactions in precursor lesions, invasive, and metastatic cancer, and the relationship of these interactions to the fundamental genetic alterations, gene and protein expression patterns, and morphologic phenotypes.

- Define the biological and clinical parameters that predict the risk of progression from precursor lesions to invasive carcinoma.

- Define the importance of regional variations within the pancreas (field effect) and of individual variation, as well as the aging process, with respect to factors that contribute to pancreatic carcinogenesis.

- Determine the biologic and molecular alterations in the tumor-associated non-neoplastic stroma and their roles in invasion and metastasis.

- Correlate findings from the activities above with diagnosis, response to therapy, outcome, and familial risk.

3. Study the natural history of the pancreatic cancer stroma and desmoplasia.

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 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 development of the stroma, its interaction with pancreatic cancer

cells, and its role in the pathogenesis of pancreatic cancer.

Studies should include evaluations of the role of the stroma in normal pancreatic tissue, chronic pancreatitis, and pancreatic cancer. It is believed that 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 to determine whether cancer growth and spread will be arrested if the stroma is altered. In addition, the potential of stroma to complicate or interfere with diagnostic or surveillance procedures should be investigated.

Recommendations

- Study in detail how tumor-associated stroma arises, and whether and how it contributes to aberrant mitogenic signaling.

- Investigate molecular interactions between stroma and tumor cells, especially concerning the role of the stroma in pancreatic cancer invasion and metastasis, and how the stroma-derived growth advantage of cancer cells can be reduced or eliminated.

- Characterize the cellular and biochemical microenvironment of stroma, including detailed analysis of (1) the cellular components of the stroma, (2) the extracellular matrix, interstitium, and basement membrane (including collagen types and proteoglycan composition), and (3) the various growth factors that mediate stroma growth and its interactions with pancreatic cancer.

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

Understanding host-tumor interactions is critical to understanding basic biologic principles about pancreatic cancer development and progression. These interactions also may offer novel strategies for therapeutic intervention and must be considered when developing and testing new therapeutic interventions for this disease. Studies aimed at understanding the immune system's role in controlling tumor progression, and the role that angiogenesis and apoptosis mechanisms play in pancreatic tumor development, progression, and metastasis are underrepresented in the literature. Even less emphasis has been directed toward 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 treatment and control of pancreatic cancer, and for improved patient performance status and quality of life.

It is well established that tumor proteins can be processed and presented to immune cells, evoking an immune response, and it is reasonable to believe that it is possible to activate the immune system specifically to recognize pancreatic tumor cells. The detection of tumor-specific T cells and antibodies in cancer patients provides additional evidence that the immune system is important in controlling cancer. However, pancreatic tumors may evade immune recognition by altering expression of critical tumor rejection antigens or by employing mechanisms of peripheral immune tolerance or general immune suppression. Despite these factors, early clinical trials testing a

variety of vaccine approaches in pancreatic cancer patients have demonstrated tumor-specific immune response augmentation. Thus, vaccines that target pancreatic tumor antigens may find a role in treating minimal residual disease and/or in primary prevention.

Progress in stimulating immune responses against pancreatic cancer would be accelerated by developing and testing novel vaccine approaches for this disease. This research would be facilitated by appropriate preclinical models that would allow more stringent screening of new vaccine approaches (e.g., transgenic mouse models that express or lose expression of genes known to be important in human pancreatic tumor development and progression, and that develop pancreatic tumors) and vaccine approaches employed early in cancer development to evaluate strategies for primary prevention. Vaccine approaches also would be aided by the identification of new pancreatic tumor-specific immune targets.

Angiogenesis is believed to be necessary for cancer development, growth, invasion, and metastasis, and inhibition of angiogenesis is postulated to be an effective therapeutic strategy. This approach to therapy may be particularly attractive for pancreatic cancers, because the malignant cells have proven refractory to available cytotoxic therapies. However, there exists both a lack of understanding of angiogenesis and concern that antiangiogenic therapy will not be effective against the mature vessels that exist in pancreatic cancer or against metastases to highly vascularized sites such as the liver. Study of the development and function of tumor vasculature in pancreatic cancer specimens and evaluation of the effects of angiogenesis inhibitors in animal tumor models that more closely resemble human pancreatic cancer (e.g., models that reproduce the substantial time course and stromal reaction of human pancreatic tumors) may facilitate evaluation of this approach to therapy.

Ultimately, antiangiogenesis strategies and agents will need to be tested in clinical trials, and informative clinical trials should be considered earlier rather than later in this disease. Research also is needed to define relevant therapeutic endpoints in addition to known clinical endpoints to validate non-invasive monitoring and imaging techniques (e.g., PET, MRI).

In tumors such as pancreatic carcinoma, chemotherapy and radiotherapy resistance are associated with mechanisms that inhibit apoptosis. Genetic alterations identified thus far in pancreatic tumor development and progression (e.g., *K-ras2* mutation, *p53* inactivation, *NF-κB* activation) are known to play a role in inhibiting apoptosis. One research priority should be to define cellular pathways of apoptosis induction and inhibition, and the interaction of these pathways to produce apoptosis resistance in pancreatic cancer. Discovering ways to modulate these pathways or their interaction also is important so that apoptosis of pancreatic cancer cells can be effectively induced by available cytotoxic agents or radiation. Understanding the actions and therapeutic potential of apoptosis-inducing agents would be facilitated by study in appropriate animal models. In addition, non-invasive methods for studying apoptosis *in vivo* are urgently needed. Clinical trials of agents targeting apoptosis should include markers of apoptosis as surrogate endpoints to better understand the mechanisms by which new antitumor agents either succeed or fail.

Pancreatic cancer patients suffer more than most other cancer patients from cancer-related constitutional problems such as cachexia, weight loss, fatigue, and

depression. These symptoms and signs decrease a patient's performance status and both quality and quantity of life, and are thought to adversely affect a patient's ability to respond to therapies. The mechanisms associated with cancer-related sequelae are not well understood, but recent evidence indicates that tumor-derived factors such as zinc alpha2 glycoprotein and a proteolysis-inducing factor may contribute to these symptoms. Clinical trials testing the actions eicosapentaenoic acid (EPA), an inhibitor of this signaling pathway, are underway in Europe. However, this area of pancreatic cancer research is significantly understudied. Therefore, another priority is to identify additional modulators of pancreatic cancer cachexia and the signaling and metabolic pathways by which they produce their effects. These discoveries would provide new targets for modulating pancreatic cancer-associated sequelae, and agents developed for this purpose should be rapidly incorporated into clinical trials testing novel anticancer agents. Improved performance status may extend patients' lifespan and ability to respond to other therapies.

Recommendations

- Investigate clinically important host-tumor interactions, including modulators and pathways that mediate tumor immunity, resistance to chemo- and radiation therapy, cachexia, and other factors that affect quality of life and longevity.

- Investigate and develop novel therapeutic strategies that circumvent resistance to apoptosis and immune attack and modulate secondary effects of tumors on local and distant organs that decrease patient survival.

RESOURCES NEEDED

1. Create specimen banks of normal and neoplastic human pancreatic tissue.

To pursue these research priorities, investigators need easy access to high quality tissue from normal pancreas, precursor lesions, and invasive and metastatic tumors. 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. This resource can be used for DNA analysis, to develop a database of gene and protein expression profiles, comparative genomic hybridization, and analysis of mutations in key genes that contribute to the pathogenesis of the disease. (See also Section III, Scientific Toolkit.)

2. Develop experimental model systems.

Also needed to pursue these priorities are *in vitro, ex vivo,* and animal models that faithfully recapitulate the complex biology of invasive human pancreatic cancer and its precursors. No existing animal model meets this criterion, and the dozens of human pancreatic cell lines that have been isolated remain underutilized for this purpose. Particular emphasis should be given to developing mouse and other models of normal and aberrant development, precursor lesions, signal transduction pathways, gene expression, carcinogenesis, and interactions between the tumor, stroma, and host. (See also Section III, Scientific Toolkit.)

Risk, Prevention, Screening, and Diagnosis

STATE OF THE SCIENCE

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Unfortunately, the vast majority of patients present with non-specific symptoms and do not exhibit specific symptoms until the disease is advanced. Pancreatic cancer also metastasizes rapidly —many primary tumors that are less than 1–2 cm in size have spread beyond the pancreas. Consequently, identifying premalignant lesions and high-risk candidates for prevention are important goals, and determining genetic and environmental risk factors and gene-environment interactions are critical to achieving these goals.

Risk

Pancreatic cancer is a rapidly fatal disease. Median age at diagnosis is 71 years, and incidence varies by race, gender, and geography. The disease occurs more often in African Americans than in whites and in men more than in women; incidence rates around the world vary approximately 30-fold.

In addition to aging, there are four probable risk factors for pancreatic cancer: family history, cigarette smoking, long-standing diabetes, and hereditary and chronic pancreatitis.

Family history—People in affected families have about a three-fold higher risk compared with the general population. At least five percent of patients with pancreatic cancer report a family history of the disease. Hereditary syndromes, such as familial atypical multiple mole melanoma (FAMMM) syndrome, familial breast cancer, Peutz-Jeghers syndrome, inherited mismatch repair deficiencies, and hereditary pancreatitis account for only a small percent of all pancreatic cancer cases. Some genes associated with these syndromes have been identified and include *p16, BRCA2, STK11/LKB1, hMSH2, hMLH1,* and *PRSS1* (cationic trypsinogen).

Cigarette smoking—Smoking is believed to cause about one quarter to one third of pancreatic cancers. People who smoke for twenty years or more have double the risk of those who have never smoked, and recent evidence indicates that this risk may be even higher when certain genetic polymorphisms are present.

Long-standing diabetes—There is a two-fold increased risk of pancreatic cancer among people who were diagnosed with diabetes mellitus at least five years before their diagnosis of pancreatic cancer. This observation suggests that diabetes may be an independent risk factor for pancreatic cancer, as well as a possible consequence of the disease. The mechanism involved, however, is unclear.

Chronic pancreatitis—Pancreatic cancer risk among individuals with hereditary pancreatitis or non-hereditary chronic pancreatitis is about 50 times and 16 to 20 times higher, respectively, than those without chronic pancreatitis.

Studies also have implicated a number of other factors, including diet and nutrition, heavy alcohol consumption, and certain occupational exposures, but these findings have been inconsistent.

Diet and nutrition—Increased pancreatic cancer risk has been associated with high intake of meat, fat, and carbohydrates, and

with elevated body mass index and caloric intake. An NCI study found an interaction between body mass index and caloric intake, suggesting that caloric intake in excess of that required to maintain energy balance may increase risk.

Alcohol—Alcohol consumption at the level typically consumed by the U.S. population does not appear to increase risk; however, approximately ten studies have reported an increased risk associated with heavy alcohol consumption.

Occupational exposures—Organochlorine compounds (DDT, DDE, and PCBs) have been associated with elevated risk in a small number of studies. Dry cleaning workers have an increased risk of pancreatic cancer, possibly due to exposure to chlorinated hydrocarbon solvents.

Prevention

Smoking cessation appears to reduce pancreatic cancer risk. A few recent studies suggest that risk may revert to the level of nonsmokers after long-term cessation.

Fruit and vegetable intake may have a protective effect against pancreatic cancer. The effect appears to be stronger for vegetables, particularly cruciferous vegetables.

Screening and Diagnosis

A number of formidable obstacles limit the ability of health care providers to screen at-risk individuals for early neoplastic changes and to make a very early and specific diagnosis of pancreatic cancer. Although radiologic techniques such as computerized tomographic (CT) scanning, magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) provide high resolution images of small lesions, pancreatic cancers have almost always spread beyond the gland by the time of detection. Known biological markers are less sensitive than imaging techniques, and they lack specificity. Better screening and diagnostic techniques are urgently needed.

RESEARCH PRIORITIES

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

Identifying factors that increase pancreatic cancer risk in humans is critical, not only to understand causes of the disease, but to improve its prevention, detection, and treatment. Until these factors are identified, progress in developing and implementing preventive strategies, screening protocols, early detection technologies, and more effective therapies remains difficult. Intensive research effort has 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.

Because pancreatic cancer is a rapidly fatal disease, many epidemiologic studies have relied principally on data from next of kin. As has been documented in a number of studies, next of kin provide less accurate information than patients, particularly with regard to detailed exposure data. Such misclassification of exposure leads to biased estimates of risk, potentially contributing to the inconsistency of findings across case-control studies conducted to date. However, because of the rapid deterioration in the condition of pancreatic cancer patients, the possibility of recall bias from ill patients is a concern, though its magnitude is not known. Additional complications in epidemiologic studies are the paucity of exposure markers (e.g., organochlorines) and the long latent period of pancreatic cancer, which makes it difficult to identify the timing of exposures to carcinogens.

Obtaining appropriate biological specimens continues to be a critical problem for investigations of genetic and environmental factors, and gene-environment interactions. Obstacles include the lack of cooperation between investigators and various health care providers, and questions about optimal specimens for studying risk (e.g., biopsy, surgical tissue, pancreatic juice, blood, serum, stool) and how to obtain them. The absence of samples readily available for high volume/high throughput analyses in epidemiologic studies has limited the potential impact of such laboratory correlative 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.

Finally, current animal models for pancreatic cancer research are inadequate, and animal models for hereditary pancreatitis are lacking.

Recommendations

- Facilitate the development of interdisciplinary case-control studies that will provide adequate sample size for accurately defining pancreatic cancer risk factors. These should be large, multicenter studies that include ultra-rapid case ascertainment, in-person patient interviews, and comprehensive biospecimen collection.

- Further delineate the genetic basis of familial pancreatic cancer and hereditary pancreatitis. Because of the limited size of most familial pancreatic cancer kindreds, wide geographic dispersion of family members, and heterogeneity of phenotypes, cooperative studies and consortia are recommended.

- Evaluate environmental risk factors and gene-environment interactions in appropriate animal models. Clinical and laboratory studies are needed, and appropriate animal models must be developed to accomplish the latter.

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

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.

Recommendations

- Develop and test risk reduction strategies in high-risk populations (e.g., smoking cessation, reduced alcohol consumption, dietary changes).

- Develop chemoprevention trials using agents that have proven effective in other malignancies or that target pathways critical to neoplastic transformation and progression.

- Develop vaccines focused on immune responses targeted to pre-invasive neoplastic epithelium (PanIN-3).

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

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 CT, MR, ECRP, and EUS is not specific for pancreatic cancer in the presence of other pancreatic pathology (e.g., chronic pancreatitis, mucinous cystadenoma, and intraductal papillary mucinous neoplasm). The rapid fatality of the disease also makes it difficult to follow cohort study participants long enough to determine the efficacy of screening modalities, making cooperative efforts and consortia essential to progress. In addition, the five-year timeframe for NCI grants is inadequate to complete many types of studies. Longer-term arrangements are needed for sufficient collection of specimens, clinical information, and natural history data to test the value of tumor markers and to 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.

Recommendations

- Delineate and validate effective molecular biomarkers of pre-invasive 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.

- Develop tumor-specific imaging such as molecular-targeted imaging; refine state-of-the-art imaging (including CT, MR, ERCP, and EUS) with emphasis on detecting small invasive and pre-invasive lesions in both normal pancreas and abnormal pancreas (e.g., chronic pancreatitis, mucinous cystadenoma, and intraductal papillary mucinous neoplasm). This will require collaborative research and training that provides an interface between molecular biology, pathology, and imaging technology. New technology such as *in vivo* MR microscopy should be evaluated in animal models or explanted specimens of invasive and pre-invasive neoplasia.

- Develop and test screening and surveillance protocols in patients from familial pancreatic cancer kindreds, patients with hereditary pancreatitis, and patients with intraductal papillary mucinous neoplasm or cystadenoma. This will require specimen collection and surveillance by state-of-the-art imaging conducted at regular intervals. Analyses of specimens for biological and molecular markers should be correlated with imaging and patient outcome.

RESOURCES NEEDED

1. **Create new registries and expand existing registries to identify high-risk patients and kindreds (familial pancreatic cancer, hereditary pancreatitis, and others) for linkage analysis, as a tissue and specimen resource, to identify screening and surveillance cohorts, and for epidemiologic assessment of gene-environment interactions.**

2. **Develop specimen banks for all types of biomaterials—blood, serum, pancreatic juice, stool, tumors, other body fluids—to redress the paucity of specimens available for analysis.** (See Scientific Toolkit.)

3. **Establish consortia of large, aging cohorts for pooled analyses to elucidate causal factors for pancreatic cancer.** In many existing cohort studies, participants generally are too young to provide an adequate number of pancreatic patients for assessing risk factors and the efficacy of screening modalities.

4. **Develop education and training resources for investigators and health care providers about pancreatic cancer risk assessment, evaluation protocols, and sample collection.** The current lack of knowledge and understanding about these central issues greatly limits the likelihood of making significant progress in pancreatic cancer research.

5. **Develop a high quality, high resolution, Web-based imaging library to be used as an educational tool for health care providers, a research tool for the scientific community, a reference standard for imaging studies, and a source of images for application of artificial intelligence and other post-imaging processing.** Epidemiological data can be attached to the images for additional research utility.

6. **Establish technology centers for comprehensively assessing gene and protein expression to facilitate identification and evaluation of biomarkers for pancreatic cancer and its precursors, especially carcinoma *in situ*.**

7. **Develop animal models for pancreatic cancer, pre-invasive neoplastic lesions, and hereditary pancreatitis to be used for studies of environmental risk factors, gene-environment interactions, chemoprevention, chemotherapy, radiation therapy, vaccines, and imaging.** (See Scientific Toolkit.)

Therapy

STATE OF THE SCIENCE

While survival has improved for patients with most other gastrointestinal cancers, the five-year survival of patients with pancreatic adenocarcinoma remains less than five percent. Nominal therapeutic advances have been made in recent years. The small percentage of patients who are candidates for resection can undergo surgery with the expectation that post-operative mortality and morbidity can be minimized, especially at experienced centers. A new drug, gemcitabine, has improved the quality of life and modestly affected the survival of patients with locally advanced or metastatic pancreatic cancer. Despite these approaches, however, the overall impact of therapy for pancreatic cancer is quite limited.

Basic research efforts over the past few years have shown that pancreatic adenocarcinomas, like other major human neoplasms, result from accumulating genetic lesions that lead to tumor development and promote progression. Though a number of these germline and somatic tumor-associated alterations have been identified, significant gaps exist in our understanding of how these alterations initiate the process of pancreatic carcinogenesis, how the proteins they encode (or fail to encode) interact in complex signaling cascades, and how the altered intracellular responses mediated by abnormal cellular biochemistry interact with normal host stromal cells and the immune system. In particular, it remains a challenge to better understand and determine how the genetics and molecular biology of pancreatic cancer can be harnessed for therapeutic gain. Given the highly aggressive clinical characteristics and lack of effective therapies for pancreatic cancer, advancing our knowledge in these areas is of special urgency.

RESEARCH PRIORITIES

1. Facilitate the discovery and development of targeted therapeutics.

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, drug and radiation resistance and 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.

Recommendations

- Identify strategies that target specific pathways currently understood to be important in pancreatic tumorigenesis and maintenance, including host-tumor interactions such as tumor immunity, angiogenesis, and growth factor receptors or interactions.

- Identify strategies that target specific biochemical signaling pathways identified from new insights into signal transduction pathways.

- Identify strategies that target specific biochemical signaling pathways and consequently enhance conventional cytotoxic chemotherapy and radiation therapy.

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

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 that 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 non-surgical techniques for obtaining tumor tissue serially from patients, and (2) non-invasive 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 non-invasive techniques against specific tissue-based assays.

Recommendations

- Develop and validate animal models that recapitulate the molecular pathogenesis of pancreatic cancer for use in testing targeted preventive and therapeutic strategies (See also Scientific Toolkit).

- Develop and validate methods (tissue-based and non-invasive) to assess the effects of targeted therapeutics in patients.

3. Accelerate research into the supportive care of patients with pancreatic cancer.

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, the ability of patients to tolerate anti-cancer 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.

Recommendations

- Develop interventions to reverse patient cachexia and asthenia.

- Develop improved interventions to manage pain associated with pancreatic cancer.

RESOURCES NEEDED

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

NCI should develop or facilitate mechanisms to speed development of new agents. 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. As a result of these issues, it has been difficult to develop and test new agents for treating pancreatic cancer. 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 Food and Drug Administration (FDA) and Office of Human Research Protection (OHRP) 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.

2. Develop infrastructure for molecular target assessment.

As we develop and test new targeted therapeutics, appropriate technology will need to be in place for safe serial tissue acquisition, including standardized protocols for handling the specimens. In addition, non-invasive functional and molecular imaging technology must be available for preclinical and clinical studies (See also Scientific Toolkit).

3. Improve infrastructure for clinical trials and promote patient participation.

- Increase multidisciplinary clinical trials and expand the clinical trials network. The existing oncology clinical trials cooperative group system, including the GI Intergroup, develops and conducts therapeutically-oriented clinical trials. However, professionals of several types are not well integrated into the clinical trial structure; these include gastroenterologists, general surgeons, primary care physicians, basic scientists, epidemiologists, and others. Optimal translation of biological insights to clinical use, and of clinical observations to laboratory investigation, requires a

network that will integrate the relevant researchers in real time. Ideally, subsequent integration of successful strategies developed by these researchers with the clinical research trialists currently supported by NCI (e.g., Phase I, Phase II, cooperative groups, Community Clinical Oncology Programs) is desired.

An expanded clinical trials network should facilitate pancreatic cancer-specific investigations of high-risk cohorts, early diagnosis and treatment; coordinate storage of serum, tissue, or tumor samples; and develop standardized methods for tissue handling, processing, storage, and sharing. Theoretically, this could be accomplished by cooperation between two or several centers of excellence for pancreatic cancer research.

- Provide adequate support for performance of clinical trials. Funding has been inadequate to cover the costs of performing therapeutic clinical trials. Additional support is needed for professionals involved in clinical research, including physicians, research nurses, statisticians, and clinical trial coordinators. Moreover, little support exists for the efforts of pathologists, radiologists, and other professionals collaborating within the current structure. Without substantial support for this part of the infrastructure, it will be impossible to collect samples and perform the crucial basic science and correlative studies critical for progress; these activities entail additional procedures and related costs that must be supported by the research budget.

- Optimize clinical trial design specific to pancreatic cancer.
  - — Explore alternative trial designs to address (1) the difficulty of assessing response or benefit in patients with locally advanced and metastatic pancreatic cancer, and (2) the activity of new therapeutic strategies that may not kill tumor cells, but stop their growth.
  - — Validate novel surrogate endpoints, including disease stabilization, biochemical markers, and results of functional imaging studies.
  - — Develop simple, reliable, and valid instruments for assessing clinical benefit in pancreatic cancer patients.

- Develop a dedicated Web site and/or other mechanisms for disseminating information on pancreatic cancer and clinical trials. Research shows that patient outcome is improved for patients who participate in clinical trials. Therefore, all patients with pancreatic cancer should be made aware of clinical trials as a treatment option.

Health Services Research

STATE OF THE SCIENCE

Traditionally, health services research methods have focused on economic profiles, social and behavioral studies, and outcome assessments. Health services research that specifically addresses pancreatic cancer has yet to be fully explored as a field of study; in fact, very little health services research has focused on this disease. For example, NCI has an extensive general health services research program, but supports little research that is specific to pancreatic cancer.

In contrast to other cancers, such as colorectal or breast cancer, the state of pancreatic cancer diagnosis and treatment is such that messages about the need for early diagnosis are not yet useful, since cost-effective tools for population-based screening do not yet exist. Instead, resources are needed for health services research that focuses on post-diagnosis communication.

Health services research is crucial in pancreatic cancer to help ensure that patients, families, and health care providers are well informed about all aspects of the disease. NCI's recent enhanced commitment to cancer communication initiatives provides new opportunities for health services research relative to pancreatic cancer. Advances in tumor biology, diagnosis, and treatment can be expected to promote more positive attitudes toward pancreatic cancer and assist in fulfilling the priorities stated in this section.

RESEARCH PRIORITIES

1. Identify effective forms of health care provider communication with pancreatic cancer patients.

Health care providers treating pancreatic cancer patients must know and communicate to their patients the availability and value of clinical trials, treatment options, pre- and post-surgical therapies, and symptom management. They should be able to help facilitate patient decision making after diagnosis, and encourage research participation by high-risk families. Health care 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 health care 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 health care provider-patient relationship.

Recommendations

- Conduct studies of health care provider-patient communication practices, patterns, and outcomes in academic and community health care systems.

- Conduct studies to determine which health care providers (e.g., physicians, nurses, information liaisons, clinical research assistants, physician assistants) can perform key information dissemination tasks in the most efficient and effective manner. This initiative

should include studies to identify the most effective forms of provider communication.

2. Identify determinants of message effectiveness in aiding decision making by patients.

Patient decision making 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 decision making, especially following a pancreatic cancer diagnosis. Patients must be made aware of their options—whether by a physician, nurse, or other health care professional—following a pancreatic cancer diagnosis and through the entire course of treatment. They also must understand how the medical infrastructure works, including information on different health care settings (e.g., academic medical center, clinical center, community hospital), insurance issues, and how to get a second opinion.

The short survival time of pancreatic cancer patients forces them to make rapid decisions under incredible pressure and stress. A number of studies have demonstrated the significant influence of family members and companions on patient decision making. A better understanding is needed of the influence of personal networks on the decisions made by patients with pancreatic cancer. In addition, studies of patient comprehension and understanding of messages have revealed that both linguistic and paralinguistic variables are involved in information retention and utilization. However, it is not known how these variables influence decision making when time frames are short.

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 they learn of through anecdotal reports. It also must be recognized that although Internet use continues to expand, a large percentage of the pancreatic cancer patient population, particularly the medically underserved, do not have access to this resource.

Recommendations

- Conduct studies of pancreatic cancer patients/caregivers to determine how information acquisition, retention, and comprehension relate to decision making. These studies should address the types and sources of information used (Internet and non-Internet based).

- Develop communication toolkits for patients that focus on specific pancreatic cancer issues to discuss with caregivers.

- Conduct follow-up studies to assess patient satisfaction with information sources, tools, and decisions made, and on the impact of communication toolkits on patient choices, patient care, and patient satisfaction.

3. Identify manpower requirements and costs of multidisciplinary clinical trials in pancreatic cancer.

Currently, many health care providers forgo compensation for the time they spend participating in clinical research, which typically is non-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 facilitate the efficient and economic construction of a multidisciplinary infrastructure, not only for pancreatic cancer clinical trials, but 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 in to the infrastructure cost model for pancreatic cancer clinical trials.

Recommendations

- Identify personnel, time, cost, and material requirements for multidisciplinary trials in pancreatic cancer.

- Conduct studies of patient and physician reimbursement in clinical trials in both fee-for-service and managed care settings. Studies of this nature will provide normative data for determining appropriate remuneration for participation from members of various health care plans.

4. Determine the efficacy of current practices in pancreatic cancer diagnosis and care and evaluate new strategies for managing difficult treatment and end of life issues.

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 six 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 to 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 health care professionals in effectively managing the disease when one does survive and to assist with the transition to end of life care when this is 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 health care providers. A strategic, coordinated research program is needed into 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.

Recommendations

- Conduct empirical investigations targeting pancreatic cancer survivors:
  - — Identify biological and behavioral variables common among pancreatic cancer survivors.
  - — Determine whether there are markers or genetic changes associated with survival and/or recurrence.
  - — Identify problems that may arise in long-term survivors.
  - — Coordinate these studies with rapid autopsy programs, providing a tissue source and an opportunity for patients to contribute to the research effort.

- Identify variables influencing quality of life, including:
  - — Symptom management, including effects of complementary therapies.
  - — Effects of support groups, educational interventions, or other support systems on quality of life.

  - — Effects of patient quality of life on caregivers.
  - — Special problems of the older patient.

- Conduct quantitative and qualitative research studies that improve our understanding of end of life issues, including:
  - — Hospice care/palliative care.
  - — Caregiver knowledge and support.
  - — Informed patient decision making.

RESOURCES NEEDED

1. **Develop a survivorship registry to enable the study of relationships among survival, biological (e.g., genes, markers), and self-report data on patients beginning at diagnosis.**

2. **Create a Web-based repository to track, update, and categorize information on pancreatic cancer clinical trial costs.** This repository would be used by health services researchers and clinical researchers to determine normative costs associated with pancreatic cancer research. These data would be especially useful for estimating budget item costs, including manpower.

3. **Develop new models that can be applied and validated in community and academic research settings, including models for:**

- Analyzing cost and level of effort required to conduct clinical research in pancreatic cancer.

- Assessing communication effectiveness.

- Improving patient decision making.

- Describing and summarizing consistent patterns of variables indicative of longer term survival of pancreatic cancer.

- Characterizing quality of life (e.g., symptom management, family involvement) and end of life (e.g., hospice care, counseling) parameters for pancreatic cancer patients.

4. **Create new education, training, and communication tools, including:**

- Communication toolkits for health care providers with education components and collateral materials to enable professionals to better assist and support patient decision making.

- Patient decision making toolkits that are culturally and linguistically appropriate and take into account various literacy levels and familiarity with communication technologies.

- Mechanisms to facilitate increased interaction among health care providers, advocates, and professional and funding organizations.

III. Scientific Toolkit

Scientific Toolkit

STATE OF THE SCIENCE

The genetic alterations discovered thus far in human pancreatic adenocarcinoma provide a key starting point for understanding the biology of the disease, but we must complete our understanding of these lesions, of the predisposition-modifier genes, and the signaling pathways that play key roles in primary pancreatic tumor development. Moreover, although certain gene mutations have been linked to tumorigenesis, there exists no formal proof that these acquired mutations remain relevant to tumor maintenance. If they are relevant, their specific functions in tumor maintenance also are unclear.

The pancreatic cancer research community has been hampered in its efforts to answer these and other crucial research questions by a dearth of essential tools and technologies needed to conduct the broad range of studies that will lead to progress against the disease. Specifically, a "scientific toolkit" is needed:

- High quality human pancreatic tumor specimens and sampling techniques that permit analysis of minute quantities of biological samples.

- Genetically tractable model systems to investigate the origins and progression of pancreatic neoplasia.

- Minimally invasive imaging techniques to monitor disease progression and response to therapy.

- Specific inhibitors of signaling pathways to define and dissect the role of individual pathways in the genesis and maintenance of pancreatic cancer and to validate targets for intervention.

- Complete compendium of the genetic lesions important in pancreatic cancer.

- Quantitative catalogs of the full spectra of gene expression patterns in normal and neoplastic pancreas.

The following priority initiatives are proposed to address these deficiencies and support multiple avenues of the pancreatic cancer research effort:

RESOURCE PRIORITIES

1. Construct resources to provide access to a range of normal and neoplastic human pancreas samples.

Organized and coordinated pancreatic adenocarcinoma registries, including family histories and extensive clinicopathological information, are urgently needed. These registries should be linked to coordinated resources for storing and distributing biological samples, including pre-invasive, invasive, and metastatic specimens that are equally well characterized. Such samples should include somatic non-cancerous tissues from affected individuals and their family members. In addition, the derivation of representative pancreatic cancer and mesenchymal cell lines is strongly encouraged to augment the current panel of cell lines available for xenograft tumorigenesis studies in nude mice and to allow modeling of stromal-epithelial cell interactions *in vitro*. To be of optimum use, these resources also should maintain one or more frequently updated databases of genome-wide studies, including expression profiling, DNA sequencing, *in situ* hybridization of tissue arrays, high density genotyping, and mutation analysis.

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. Samples must be collected using a standard procedure with appropriate long-term storage techniques and quality control to maximize the usefulness of biological materials. Adequate compensation must be made for time, effort, and supplies to surgeons, research aides, pathologists, and others who provide appropriate oversight and procedural audits.

2. Using this resource, construct a relational database containing information on the biological profiles of normal and abnormal pancreas cells.

The resource described above should be used as the foundation for a "value-added" pancreas database containing data from allelotyping, DNA sequencing, cDNA expression analysis, tissue arrays, and proteomics studies. In addition, 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. The database also should include, when available, information on cancer cell karyotype, comparative genome hybridization, and signal pathway activation. These data will be collected for normal pancreatic ductal epithelial, acinar, and islet cells, primary and metastatic cancer cells, stromal cells, and where feasible, pre-invasive lesions (PanIN). 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.

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. This experimental database also should be constructed to allow rational queries to similar databases that are being constructed for other cancers. Issues of genomics analysis standardization (e.g., reference samples, antibody reagents) must be addressed.

3. Develop biological sampling techniques that permit analyses of minute quantities of biological samples.

The scarcity of biological samples of PanINs and invasive pancreatic cancers, and the infiltrating nature of their growth make it imperative to develop sampling techniques that will permit analyses of exceedingly small samples.

4. Organize knowledge of signaling pathways into interrelated networks and systems to assess the ultimate outcome of alterations in the pathways found in pancreatic cancer.

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, expanding to interconnect pathways affected by genetic alterations and microenvironmental influences.

5. Establish gene-based model systems *in vivo* and *ex vivo* that faithfully recapitulate the complex biology of human pancreatic adenocarcinoma.

These 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. Such studies should include the construction of mouse model systems of pancreatic cancer in conjunction with the pre-existing NCI Mouse Models of Human Cancer Consortium and the study of normal and neoplastic human pancreatic ductal epithelial cells. 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 pre-invasive to a fully malignant state, and characterize the cells from which pancreatic adenocarcinoma arises. (Other developmental systems, such as zebrafish and xenopus, were discussed but no consensus was reached on their use).

It will be essential to apply the compendium of gene expression patterns and genome-wide genotypes of pancreatic adenocarcinoma described above 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. Although the Cancer Genome Anatomy Project (CGAP) is making significant progress with regard to human tumors, the genomics infrastructure to analyze the mouse lags far behind and a pancreatic ductal epithelial cell-specific promoter(s) has not been identified. These problems hamper efforts to rapidly isolate genes based on interspecies sequence homologies and generate mouse models for pancreatic cancer that require pancreas ductal epithelial cell-specific promoters for various tissue-specific strategies. Identifying such promoters quickly through functional genomics efforts in mice and humans is critical to facilitate model systems development.

6. Develop imaging systems for elucidating pancreatic cancer biology and for detecting and monitoring this disease.

Consistent with NCI's Extraordinary Opportunity for Investment in Cancer Imaging, 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.

Appendices

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Appendix B: NCI-Supported Pancreatic Cancer Research

Estimated NCI Support of Pancreatic Cancer Research, 1999

Scientific Area	Estimated Level of Support*
Cancer-Related Biology	$ 5,115,000
Etiology	$ 2,173,000
Prevention	$ 1,310,000
Early Detection, Diagnosis, and Prognosis	$ 1,938,000
Treatment	$ 6,172,000
Cancer Control, Survivorship, and Outcomes Research	$ 134,000
Scientific Model Systems	$ 467,000
Total	**$ 17,309,000**

* Source: NCI

Appendix C: About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge that, while providing a wealth of new scientific opportunities that can further advance our knowledge and progress against these diseases, also requires that limited resources be used to their optimal advantage.

To help ensure the wise use of resources with maximum benefit, NCI has established Progress Review Groups (PRGs) to assist in assessing the state of knowledge, reviewing the Institute's research portfolio, and identifying scientific opportunities and needs within its large, site-specific research programs.

CHARGE TO THE PRGS

Each PRG is charged to:

1. Identify and prioritize scientific research opportunities and needs to advance medical progress against the cancer(s) under review.

2. Define the scientific resources needed to address these opportunities and needs.

3. Compare and contrast these priorities with the current NCI research portfolio.

4. Prepare a written report that describes findings and recommendations.

5. Discuss a plan of action with NCI leaders to ensure that the priority areas are well addressed.

The following section details the process used to execute these charges

THE PRG PROCESS

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The leadership of each PRG finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Topics are identified for Roundtable breakout sessions to which participants will be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable brings together in an open forum approximately 100 to 180 leading members of the relevant cancer research, medical, industry, and advocacy communities to formulate key scientific questions and priorities for the next five to ten years of research on specific cancers. As part of the process, the NCI provides the PRG Roundtable an analysis of its portfolio of cancer research in the relevant organ site. This analysis is intended to enable the Roundtable to compare and contrast identified scientific priorities with the research currently being done under the Institute's auspices. Input from the

Roundtable is used by the PRG in delineating and prioritizing recommendations for research, related scientific questions, and resource and infrastructure needs. At its discretion, the PRG may solicit additional input from the research and advocacy communities through workshops, *ad hoc* groups, or by other means. The PRG also may consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

THE PRG REPORT

After the Roundtable, the PRG's recommendations are documented in a draft report, multiple iterations of which are reviewed by the PRG leadership and PRG members. The final draft report is then submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. Finally, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is then widely disseminated and integrated into the Institute's planning activities.

PRG reports on breast cancer, prostate cancer, colorectal cancer, and brain tumors, and this report on pancreatic cancer, are available online at osp.nci.nih.gov/Prg_assess. Other PRG reports currently in development or being planned include reports on leukemia, lymphoma, and myeloma; gynecologic cancers; and kidney and bladder cancer.

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