A White Paper: The Product of a Pancreas Cancer Think Tank

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Introduction

Contrasting with improved survival for most other gastrointestinal cancers, the 5-year survival of patients with ductal adenocarcinoma of the pancreas remains low at a dismal 4%. In 2000, an estimated 28,300 patients were diagnosed with pancreatic cancer in the United States. These patients can expect to benefit from some progress in management. Minimally invasive procedures such as helical computed tomography and endoscopic ultrasound can be used for accurate initial staging. The application of fine-needle aspiration biopsy and the availability of biliary stents to relieve bile duct compression have resulted in fewer laparotomies. Those patients who are candidates for resection can be reassured that this surgery has become safer, especially at experienced centers. Supportive care, especially in pain management, has improved. Finally, the introduction of a new drug, gemcitabine, for use in pancreas cancer brings hope that the chemoresistance previously observed in this disease can be broken.

Nonetheless, much remains to be learned. In an effort to focus on the issues and the research opportunities in pancreas cancer, a Think Tank was convened on September 16, 1999, in Park City, Utah. This international event was attended by 64 invited extramural scientists with established dedication to and experience in pancreas cancer research, 6 National Cancer Institute scientists, and 12 representatives from industry. The participants were divided into six working groups in the following areas: (a) genetics/risk/prevention; (b) pancreas cancer histology; (c) pancreas cancer biology; (d) early detection; (e) biology of pancreatic cancer associated with cachexia and other constitutional symptoms; and (f) pancreas cancer therapy. These groups met both separately and together for various sessions.

The Think Tank was sponsored by the NCI, the Lustgarten Foundation for Pancreas Cancer Research, and numerous industrial sponsors. Pancreas cancer advocacy was represented through the Pancreas Cancer Action Network (PanCan). The following report summarizes this meeting and represents a first step at identifying the key research opportunities and required infrastructure needed to advance our knowledge about this difficult malignancy.

Biology of Pancreas Cancer

Two general topics of research were selected for discussion related to the biology of pancreatic cancer: transformation and metastasis. Discussions were focused on several specific topics: (a) the nature of cells that become transformed in the pancreas; (b) the process of transformation; (c) the process of invasion and metastasis; (d) strategies to identify molecules involved in transformation and metastasis; and (e) preclinical models for studying transformation and metastasis.

There has been a substantial and longstanding debate about the nature (type and origin) of cells that are transformed and which result in the production of pancreatic adenocarcinoma (1–6). Most malignant and metastatic adenocarcinomas of the pancreas resemble ductal epithelial cells morphologically (7). This has led many to postulate that the transformed cell type is in the ductal epithelial cell lineage. In contrast, other evidence has been published and presented supporting the hypothesis that there is a contribution by islet cells to the transformation process (8, 9). There was speculation at the meeting that the cell type that is transformed in human pancreas is a stem cell; however, no definitive markers for stem cells in the pancreas have been defined to date (10–12). The recent analysis of premalignant lesions in the pancreas (see “Histology,” this report) and the classification based on morphological criteria into the PanIN series of lesions raises the possibility that early events (genetic and biological) can be identified. However, a complete understanding of the relationship of these lesions to each other and to pancreatic adenocarcinoma requires additional study. The known genetic and biological processes that lead to the PanIN lesions and to adenocarcinoma were discussed and are summarized below.

It is well documented (13) that a majority of pancreatic adenocarcinomas (>70% in most studies) contain mutations in K-ras. A significant number (though <50% in most studies) contain mutations in p53 and DPC4. A number of other genetic lesions have been identified in pancreatic tumors, but at very low incidences (<5%). K-ras mutations are also found in a high percentage of normal pancreas samples and in the PanIN lesions described in the section of this report that deals with pathology. However, there has been not been a common pattern of accumulation of genetic defects identified for pancreatic cancer. Thus, no combination of mutations has been found to explain the development of pancreatic adenocarcinoma. Moreover, other biological phenomena contribute to pancreatic carcinogenesis. For example, growth factors and their receptors play a significant role in the transformation of tumor cells. Thus we concluded that much remains to be discovered about the fundamental molecular events during the genesis of pancreatic cancer. Current models of carcinogenesis posit the accumulation of defects in a linear manner. These hypotheses need to be refined to include the impact of multiple factors of variable incidence over time. In the short term, there is a need for the discovery of the remaining uncharacterized genetic defects in human pancreatic tumors, additional hypotheses that explain the acquisition of these defects, and models to test these hypotheses.

The processes of invasion and metastasis are more poorly understood than the process of transformation. Previous experimental evidence (14) has implicated a role for cell surface adhesion molecules,
proteases, signal transduction pathways, and growth factors in the metastatic activity of pancreas cancer cells.

One area of research that should receive increased emphasis in the near future is the study of interactions between tumor cells and the surrounding cells and stromal elements. The desmoplastic response that occurs in many primary pancreatic tumors has been widely noted; however, the cause and influence of this response on tumor growth and invasion requires additional study. In addition, the neovascularization of tumors is an important and currently popular area of research. The role of interactions between tumor cells and surrounding normal cells and elements in producing angiogenic factors should be more carefully studied. The role of the lymphatic endothelium in tumor development and invasion has also received little attention and should be explored.

It is clear that the full process of malignant transformation of pancreatic cells occurs over time. Most current hypotheses posit that a number of molecular alterations (mutations) occur over time and result in transformation when an appropriate set of alterations accumulate in a cell or in a population of cells. Molecular alterations can be considered spatial events, and their accumulation over time can be considered temporal events. The accumulation of multiple molecular defects in a cell that becomes transformed is both spatial and temporal. In addition, pancreatic cells exist in the physical environment of the pancreas, which can be considered an additional spatial parameter. One of the major problems in studying the development, progression, and metastasis of pancreatic cancer is the difficulty of studying both temporal and spatial events using current model systems.

Three primary model systems for studying pancreatic adenocarcinoma were discussed. The first was the use of cell lines (normal and transformed); the second was animal models (transgenic or carcinogenesis); and the third was the study of pathological specimens. Each of these model systems has inherent advantages and disadvantages. Tumor cell lines carry the accumulation of defects that resulted in transformation and perhaps metastasis; however, it is not possible to determine the temporal order and spatial configuration of these cells at the time the defects occurred. Tumor cell lines are useful for evaluating responses of tumors to treatment strategies in a preclinical setting. Analyses of pathological specimens provide snapshots of the condition and the spatial arrangement of tumors or premalignant lesions at a given temporal point; however, the order and timing of events that precede and follow the time point at which the specimen was taken cannot be determined unequivocally. Animal models (particularly syngeneic models) offer the possibility of studying both temporal and spatial events; however, the biological properties of pancreatic tumors that are induced in many animal model systems are distinct from humans, and interpretation of these findings and extrapolation to the clinical setting. Thus, there is a need to use all of these systems to maximize our ability to study both temporal and spatial events in the genesis and progression of pancreatic cancer.

There should be more resources made available for exploratory research that will allow investigators to discover unknown genes or genes previously not known to contribute to the biology of pancreas cancer. This type of research (discovery) often does not include highly structured hypotheses, because it comprises the observation component of the scientific method and, consequently, often is not well received by conventional study sections at NIH. This fact discourages many potential investigations because of concern that they will not be perceived as fundable by conventional mechanisms. Studies of pathological specimens by molecular techniques should be expanded to include the use of DNA arrays, technology, SAGE analysis, and other advances. Investigators should continue to study pancreatic tumor cell lines to gain insight into the biological processes that accompany transformation, invasion, and metastasis. There should be renewed effort to identify pancreatic stem cells and other populations that are transformed and to develop “normal” cell lines for comparative studies. Animal models should be developed further and investigated to provide insight into the process of pancreatic cancer genesis and progression. There is also a need for model systems that will facilitate the development of diagnostic and therapeutic reagents.

Finally, pancreatic cancer researchers continue to face the particularly daunting problem of obtaining sufficient high quality material of human origin to allow for the types of studies that need to be undertaken. The main reason for this is the fact that the disease is seldom treated by surgical resection and is otherwise highly inaccessible for obtaining biopsies. For example, it is practically impossible to obtain primary tumor and multiple examples of metastatic lesions from the same individual. One proposal to address this problem was to develop a system whereby patients who die of pancreatic cancer can donate selected organs for research. Organs of sufficient quality for study would need to be harvested and treated in the same manner as those that are harvested for transplantation, and then directed to multidisciplinary teams that were prepared to preserve and use the organs immediately for the multiple types of studies that are now possible.

Pancreas Cancer Histology

Although there are a number of important issues and controversies related to the histology of pancreatic cancer, the histology working group felt that incipient ductal pancreatic neoplasia was the single most pressing issue that needed to be addressed. Incipient pancreatic cancer was felt to be important because an understanding of incipient neoplasia is essential to the development of screening tests for the early detection of pancreatic ductal cancer. For example, if a genetic alteration can be identified that is highly associated with an incipient neoplasm at risk for progression to invasive cancer, then that genetic alteration could form the basis of a gene-based screening test, and the incipient neoplasm might even serve as a target for chemoprevention.

Despite their importance, the study of precursor lesions and the early stages of ductal adenocarcinoma of the pancreas has been hampered by the relative inaccessibility of the pancreas to biopsy and by the absence of a standard nomenclature and diagnostic criteria for the histological classification of many of these lesions. For example, some investigators have suggested that the epithelial lesions which occur in the small and medium sized ducts and ductules of the pancreas are the precursors to infiltrating adenocarcinoma, and yet these duct lesions have been designated variously in the literature as “metaplasia,” “hyperplasia,” “hypertrophy,” and “neoplasia” (see Table 1). These differences in terminology have made it difficult, and at times impossible, to compare studies from different investigators. As a result, the incidence of incipient neoplasia is unknown, and the risk for progression posed by other pancreatic conditions, either inflammatory or neoplastic, remains undefined. The members of the histology working group therefore felt that an important first step in the study of incipient pancreatic cancer would be to standardize the nomenclature and diagnostic criteria used to classify these duct lesions.

The group unanimously agreed to adopt the designation Pancreatic Intraepithelial Neoplasia, or PanIN, as originally proposed by Klimestone and Longnecker (21), for these lesions. This terminology was adopted because the group felt that it reflected the growing body of evidence supporting the neoplastic nature of many of these duct lesions. It was hoped that the term “neoplasia” in the definition would foster the additional study of these lesions.

PanIN was subclassified by the histology working group into Pan...
nIN-1A, PanIN-1B, PanIN-2, and PanIN-3 based on the degree of cytological and architectural atypia present (Fig. 1). In a global sense, PanIN-1A and PanIN-1B are those lesions that show slight or no atypia; PanIN-2 designates lesions with moderate atypia; and PanIN-3 designates those lesions with severe atypia.

PanIN-1A designates flat (nonpapillary) epithelial lesions composed of tall columnar mucin-containing cells that show slight or no atypia. It was recognized that the neoplastic nature and the precursor potential of many of PanINs-1A has not been established, and some investigators may therefore choose to add the modifier [L] (for lesion) to PanINs-1A (i.e., PanIN-1A [L]: Refs. 30 and 31). PanIN-1B designates epithelial lesions that have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A.

PanIN-2 are epithelial lesions that may be nonpapillary or papillary with no more than moderate cytological atypia, including loss of polarity, nuclear crowding, nuclear enlargement, pseudo-stratification, and nuclear hyperchromatism.

PanIN-3 epithelial lesions are usually papillary or micropapillary, but they are rarely flat. Cribriform growth and the budding-off of small clusters of epithelial cells into the lumen support the diagnosis of PanIN-3. Severe atypia is manifested cytologically as the loss of polarity, the loss of differentiated cytoplasmic features, cellular and nuclear pleomorphism, and the presence of mitoses—especially if atypical suprabasal or luminal in location.

Details of this new nomenclature as well as representative examples of each lesion can be found on the World Wide Web. The working group felt that the establishment of this Web page was an important mechanism for promulgating this new nomenclature.

Although the establishment of a new standard nomenclature for incipient pancreatic cancer is an important first step, the participants in the histology working group agreed that additional studies are needed to validate the reproducibility of this classification system and, very importantly, to define the genetic alterations associated with each grade of PanIN as well as the risk of each lesion progressing to cancer. It is hoped that such studies will form a foundation for the development of new screening tests for the early detection, and possibly the prevention, of pancreatic cancer.

A second pathway for the development of invasive carcinomas in the pancreas was the subject of limited discussion. IPMNs of the pancreas may progress from adenomas to borderline tumors to intra-ductal carcinomas and then to invasive carcinomas. The infiltrating carcinomas associated with IPMNs may show solid desmoplastic, mucinocystic, or adenosquamous growth patterns. The histology working group noted that IPMNs may serve as a useful model system for the study of genetic progression in the pancreas.

### Genetics, Risk, and Prevention

The genetics, risk, and prevention working group represented a broad range of interests, including those of somatic genetics, inherited susceptibility, and environmental influences and epidemiology. Among the members there was also considerable interest in the subjects represented by the other working groups, especially in the application of screening techniques, early disease progression, and the histological classification of tumors.

The members felt that their work was highly translational, having a practical importance for the ultimate benefit of pancreatic cancer patients. Their goals included the better recognition of disease variants and an improved classification of patients into distinct and relevant subgroups. These subgroups would aid efforts to screen for the disease by a better targeting of clinical resources and the provision of new markers for screening efforts (34, 35). Genetic markers are currently aiding the development of a tumor-progression model and a nomenclature system for the precursor lesions. There exists considerable hope that therapeutic advances also will benefit from these classifications, and that rational new therapies might be suggested by the genetic and other etiological insights that clarify the biological foundations of this disease.

The long-term goals proposed by the group included: (a) to decrease the mortality of the disease; (b) to evaluate promising preventative measures; and (c) to gain insight into new biological models through which to understand the disease. No borders were seen for these goals, in that there remains hope that general models will emerge to aid the understanding of multiple tumor types as well as that considerable cross-pollination between various tumor types and scientific disciplines would continue to enrich the overall problem of controlling cancer. This is evidenced by the remarkable ties between dissimilar cancers, such as the susceptibility to melanoma and pancreatic cancer seen in families that harbor a p16 gene mutation (36) and the increased rates of breast, pancreatic, and other cancers in those with a BRCA2 gene mutation (37, 38). An enhanced outreach to the nonneoplastic diseases was envisioned as well, especially a need to better understand the relationships between exocrine and endocrine diseases (especially diabetes) of the pancreas.

A number of problems were seen as hindering research in this area. The attainment of adequate family histories is complicated by the late onset of pancreatic cancer, the high variety of other cancer types to be seen in susceptible families, and the low penetrance for the disease among persons with inherited susceptibility. Financial, legal, and ethical considerations provide barriers to the collection of the tissues, blood, and other archival resources necessary to better understand this disease. There is a need for increased input from outside fields and
diseases. Facilitation of interactions between basic scientists and clinicians to the point of significant and productive collaborative efforts will be essential, but this remains inadequate in many of the current research settings. The current size of the scientific community in pancreatic cancer remains far inadequate to attain the necessary pace of discovery—a work force 20–100 times larger was thought to be more comparable with the tasks at hand and also more comparable with the efforts now devoted to other major cancer types.

These considerations produced recognition of the need for additional funding, added visibility of the field itself, and the welcoming of the emerging advocacy movements in pancreatic cancer. These emerging and fluid issues can be seen as vital to research progress as is the performance of current research efforts. There is a need for seed money to establish banks of resources modeled after the successful sharing of CEPH family DNA samples and pedigree information. There is a need to attract young investigators and the money to provide stability in their early career development.

The greatest excitement among this working group concerned the opportunities to improve the study of inherited risks. A definition of FEPC was undertaken. There was recognition of the need for an open definition to emphasize that classification and reclassification is an ongoing process as we gain new knowledge of the patterns of inherited disease. Two major divisions of FEPC were obvious: one syndromic and one idiopathic. Syndromic FEPC includes persons with inherited mutations of tumor suppressor genes (the p16 gene (familial atypical moles and melanoma syndrome), the BRCA2 gene, the p53 gene (Li-Fraumeni cancer syndrome), and the LKB1/STK11 gene (Peutz-Jeghers syndrome)), genes of the mismatch repair system (hereditary nonpolyposis colorectal cancer), the cationic trypsinogen (PRSS1) gene (hereditary pancreatitis), and an association with familial diabetes (39–42). Clinicians are most often responsible for the recognition of affected families, and need to be familiar with inheritance patterns that predispose to pancreatic cancer. In contrast, idiopathic FEPC is a category of exclusion, comprising families that cannot be classified as syndromic. This category has a moving, operational definition that is flexibly redefined as needed for particular clinical or research needs, and it is broadly recognized as any clustering of pancreatic cancer within a family, with or without associations with other cancer types.

A number of caveats were seen as important when referring to FEPC. “Familial” does not necessarily mean “hereditary.” Because of low penetrance of disease among carriers, only one or possibly no members with pancreatic cancer may be found within a particular family; i.e., syndromic does not refer to the bedside clinical recognition of an individual patient, but can require also a genetic laboratory component to the diagnosis and a constellation of risks rather than a constellation of clinical signs and symptoms. An individual with FEPC may come to clinical attention because of multiple neoplasms rather than because of a classic family pedigree. Depending on the particular aims of a research study, the designation as FEPC may be based on two first-degree relatives with pancreatic cancer or on two second-degree relatives connected by a blood relative having any form of cancer. The designation as FEPC may require a systematic review of all cases of cancer in the family, including a full histological reevaluation of archival specimens and a review of clinical records.

Major goals related to the study of FEPC include the establishment of a large collaborative research effort and database made possible by new resources but preceded by the coordination of current databases based in a core center. One immediate suggestion was to analyze (by linkage, sibpair analysis, or mutational study of candidate genes) the families that have three affected first-degree relatives. There is a need to define and disentangle the etiological [i.e., the genetic and environmental (43) heterogeneity of FEPC (43)]. Consideration should be given to eventually developing a resource of families for screening and for intervention.

**Early Detection**

The aim of this working group was to explore many of the vital issues involved in the early detection of adenocarcinoma of the pancreas. By the time of diagnosis, an adenocarcinoma of the pancreas likely will have spread because of local infiltration and/or...
metastases. Some of the challenges presented by pancreatic adenos- 
carcinoma include the retroperitoneal location of the pancreas, diffi- 
culties in differentiating between focal pancreatitis and carcinoma, 
and the identification of high-risk groups. One approach to improve 
the dismal prognosis for an individual affected with pancreatic ade- 
ocarcinoma consists of diagnosing the disease at an earlier, and 
hopefully more curable, stage. Members of this working group came 
from diverse backgrounds, including gastroenterology, oncology, ep- 
idiology, surgery, radiology, and molecular biology.

The first issue addressed by the working group was whether screen- 
ing/surveillance for pancreatic adenocarcinoma is a viable policy at 
the present time. It is essential to resolve this issue, because the 
assumption of any surveillance or screening program is that it will be 
of benefit to the patient. For example, in colon cancer, it is well 
recognized that there is improved survival when the disease is found 
at an early stage. Only limited data are available to address this issue 
in pancreatic cancer. A recent paper from Ariyama et al. (44) reported 
a postoperative 5-year cumulative survival rate of 100% for patients 
with tumors <1 cm. There was no difference statistically in the 
 survival rate of patients with tumors >1.1 cm.

One member of the working group, A. Lowenfels (41), performed 
a general analysis of surveillance for patients at high risk for pancre- 
atic cancer. His example used the imaging technique of EUS in a 
cohort of high-risk patients with a 10% incidence of cancer at ~65 
years of age. The following assumptions were used in the analysis: (a) 
cohort size of 1000 suspected high-risk patients; (b) EUS has a 
history of 90% and a specificity of 74%; (c) operative mortality 
from pancreatectomy, 5%; (d) survival of 40–50% for pancreatic 
cancer patients with an early diagnosis; (e) nonscreened patients who 
develop pancreatic cancer will die from their disease at that age of 
~65; and (f) the the expectancy of the cohort members who do not 
develop pancreatic cancer is about 80 years. Lowenfels’ analysis 
found that screening this high-risk cohort extended the life span 
an average of 3 to 4 months.

An additional analysis by Lowenfels to determine the years of life 
gained in screening high-risk patients at 50 years of age for adenoc- 
carcinoma of the pancreas is shown below and emphasizes the im- 
portance of the sensitivity and specificity of the screening method.

<table>
<thead>
<tr>
<th>Risk of cancer</th>
<th>Specificity/Sensitivity</th>
<th>Years gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>0.80</td>
<td>0.11</td>
</tr>
<tr>
<td>10%</td>
<td>0.80</td>
<td>0.49</td>
</tr>
<tr>
<td>20%</td>
<td>0.80</td>
<td>1.24</td>
</tr>
<tr>
<td>30%</td>
<td>0.80</td>
<td>1.98</td>
</tr>
<tr>
<td>5%</td>
<td>0.90</td>
<td>0.28</td>
</tr>
<tr>
<td>10%</td>
<td>0.90</td>
<td>0.69</td>
</tr>
<tr>
<td>20%</td>
<td>0.90</td>
<td>1.52</td>
</tr>
<tr>
<td>30%</td>
<td>0.90</td>
<td>2.34</td>
</tr>
</tbody>
</table>

There was general consensus among the working group that the 
ideal histological stage that warrants aggressive intervention, such 
as a total pancreatectomy, and offers the best chance of cure would be 
an advanced precursor lesion (PanIN-3 or carcinoma-in situ). However, 
the working group felt that the current imaging studies were inade- 
quate for the identification of lesions at the severe dysplastic stage 
(PanIN-3). There was a great deal of discussion about the recently 
published University of Washington experience that evaluated various 
imaging studies including EUS, computed tomography, and ERCP in 
pancreatic cancer-prone families (45). They felt that pancreatic ductal 
abnormalities detected on ERCP represented dysplasia. More impor- 
tantly, every patient with an abnormal ERCP had an abnormal EUS 
that demonstrated echogenic foci, hypoechoic nodules, or an echo- 
genic main duct. The group discussed that these findings on EUS and 
ERCP were nonspecific and seen in chronic pancreatitis. The majority 
of the working group would not recommend a pancreatectomy based 
on these findings alone, but preferred confirmation by another method 
such as a biological marker. Some participants felt that using biologi- 
cal markers to decide upon pancreatectomy would have to await 
long-term studies addressing the predictive value of such markers.

Most of the group felt that EUS was an appropriate first choice for 
an imaging technique in screening high-risk individuals, and all mem- 
bers of the working group believed it should only be done in a 
research setting. It was also recognized that imaging studies might 
have limited, if any, value in certain high-risk groups with underlying 
pancreatic changes, e.g., hereditary pancreatitis patients. Magnetic 
resonance imaging and positron emission tomography were two 
promising imaging modalities that were discussed, and which group 
members particularly believed warranted additional investigation.

There was a general consensus regarding the importance of biolog- 
cal markers for the early detection of pancreatic cancer. Potential 
specimen sources include serum or plasma; pancreatic juice obtained 
via ERCP or secretin stimulation; or pancreatic cells obtained by 
fine-needle aspiration, cytological brushings, or large-bore-needle bi-
opsy. Recently evaluated markers such as CA 19–9 or amylin in the 
serum or k-ras in the pancreatic juice were felt not to be clinically 
useful because of poor specificity and/or sensitivity. It was recognized 
that there were no tumor-specific markers available for pancreatic 
cancer. Members of the group felt that the best means of improving 
specificity and sensitivity was to use a panel of markers. Suggested 
markers to be evaluated for this “ideal” panel included telomerase, 
TAG-72, k-ras, p53 and p16. It was concluded that K-ras will not 
suffice as a marker alone, because of poor specificity, and it probably 
will not be that useful, even as part of a panel, for the same reason. 
Limitations of some of these markers, such as p53, are the need for 
neoplastic cells, which are few in numbers with current collection 
techniques such as secretin stimulation.

It was the group’s belief that because of the above-mentioned 
issues, candidates for pancreatic cancer screening should only be 
from high-risk groups, e.g., individuals from pancreatic cancer-prone 
or hereditary pancreatitis families. No consensus could be reached on 
when surveillance should begin for pancreatic cancer-prone families. 
Suggestions included the initiation of surveillance at either 5 or 10 
years before the earliest age of onset of pancreatic cancer in the 
family.

Treatment options for high-risk individuals were discussed briefly. 
No participant supported the approach of prophylactic pancreatec- 
tomy. Some participants stated that they would follow the natural 
course of these patients while collecting specimens prospectively and 
banking them. Other participants favored the approach from the 
University of Washington, with the performance of a pancreatectomy 
in patients believed to have dysplasia by ERCP. However, there were 
concerns expressed with the latter approach related to the fact that 
these findings may not be applicable to all pancreatic cancer-prone 
families because of the heterogeneous make-up of these families.

In summary, several important points should be emphasized from 
this working group. First, all participants felt that surveillance of 
high-risk individuals should only be performed in a research setting. 
Second, the goal of surveillance should be the detection of an ad- 
vanced precursor stage, such as carcinoma-in situ (PanIN-3). It was 
perceived that this could best be achieved by the use of a panel of 
biological markers in association with imaging studies, again stressing 
that this should be done in the context of a research protocol. Third, 
the importance of studying these high-risk patients cannot be over-
stated. It was believed that focusing our limited resources on high-risk 
individuals was a more effective and efficient means to evaluate 
different detection techniques; and furthermore, that any new ad-
vances could eventually be applied to sporadic pancreatic carcinoma cases. Lastly, members of the working group identified several areas of research that merit immediate attention. These areas include: (a) continued advancement in the knowledge of the molecular biology of pancreatic cancer to assist in the diagnosis of advanced precursor lesions; (b) improvement in imaging studies to allow for the identification of smaller tumors or, more ideally, advanced precursor lesions; and (c) the application of animal models to study the early detection of pancreatic cancer.

Cachexia and Insulin-Resistance in Pancreatic Cancer Patients

The cachexia and metabolic disturbance working group represented rather diverse, but overlapping, interests in the mechanisms of weight loss and wasting in pancreatic cancer. There was some contention about which factors are of greatest importance in mediating cachexia, and much of the discussion centered around cataloguing possible factors of importance. However, the group was in total agreement that cachexia represents a major clinical problem in these patients and is an area where therapeutic improvements are likely to have a great impact.

Cancer cachexia is a complex syndrome that is directly responsible for the death of a large number of cancer patients and contributes to morbidity and mortality in many other cases. In addition to anorexia, cachexia is characterized by muscle wasting, weakness, and weight loss that progress until the time of death. The metabolic abnormalities associated with cachexia include negative nitrogen balance attributable to an increased muscle proteolysis, alterations in carbohydrate metabolism, and accelerated adipose tissue dissolution. In pancreatic cancer patients, the onset of cachexia usually takes place long before the tumor is diagnosed. Erosion of skeletal muscle is a major contributory factor in the poor survival of these patients, leading to death by respiratory failure and hypostatic pneumonia. The major metabolic event activated during muscle wasting is the ATP- and ubiquitin-dependent proteolytic system. Activation of this pathway promotes amino acid release from skeletal muscle in to the circulation. The amino acids released are taken by the tumor mass and the liver to sustain growth and acute phase protein synthesis as well as to provide substrate for the increased gluconeogenesis associated with cachexia. Table 2 lists various factors or cytokines involved in these processes and appropriate references. PIF, lipid-mobilizing factor, and cytokines such as IFN-α play a major role in cancer cachexia.

Of particular interest is recent progress with the polyunsaturated fatty acid EPA, a fish-derived n-3 fatty acid. A clinical trial in the United Kingdom suggested EPA was effective in attenuating the development of weight loss in pancreatic cancer patients and when combined with nutritional supplementation resulted in significant weight gain (57). This weight gain is attributable to the accumulation of lean body mass with no change in adipose tissue or body water. Weight gain (57). This weight gain is attributable to the accumulation of lean body mass with no change in adipose tissue or body water. EPA appears to inhibit the up-regulation of the ATP-ubiquitin-dependent proteolytic pathway in skeletal muscle induced by PIF. The effect appears to be attributable to the inhibition of downstream signaling events. EPA also inhibits proteolysis, including factor production by the tumor, which may be evidence of a direct effect on tumor cell proliferation. A full knowledge of the mechanism of the beneficial effect of EPA on cancer cachexia will provide vital information for the development of new agents.

The profound cachexia associated with pancreatic cancer also includes characteristic abnormalities in carbohydrate metabolism and marked peripheral insulin resistance. Most likely, this results from the release of islet-associated pancreatic polypeptide. The abnormal metabolism of proteins, carbohydrates, and lipids in pancreatic cancer patients apparently arises from a complex interplay between cancer-derived factors and probably also involves inflammatory cytokines and circulating metabolic hormones. Understanding these relationships will advance our understanding of pancreas cancer biology. In addition, PIF, lipid-mobilizing factor, selected inflammatory cytokines, and other cachexia- or wasting-inducing polypeptides could serve as novel new targets for cancer therapy.

Pancreas Cancer Therapy

Progress in the development of more effective treatments for pancreatic adenocarcinoma has been slow, a problem that is reflected in the fact that there has not been much change in mortality rates over many decades. Therefore, the overall goals of the working group on therapy were: (a) to identify specific areas of pancreatic cancer therapeutics that require progress; and (b) to generate a plan of attack to facilitate rapid progress in sorting through selected new treatment approaches.

Participants in this group brought a wide range of expertise to the table, including surgery, medical oncology, radiation therapy, immunotherapy, and cancer biology. The participants were asked to identify areas of pancreatic cancer therapy that required immediate focus. As a result, four main areas were identified that require significant progress. These included the immediate need for: (a) new therapies; (b) novel clinical trial approaches designed to facilitate therapy development more rapidly; (c) improved measurements of treatment efficacy; (d) improved access to clinical trials; and (e) the availability of pancreatic cancer tissue banks with a corresponding outcomes database.

Regarding therapeutic agents, a number of participants felt that priority should be given to the immediate testing of currently available agents or modalities that are active in other diseases (and not yet tested in patients with pancreatic adenocarcinoma) or of existing agents that target biological pathways and which have already been identified as critical to pancreatic cancer tumorigenesis but have not yet been optimized or tested in combinations. A list of currently available or developing agents that require additional testing either alone or in combination was generated (Table 3).

### Table 3 Available therapeutic agents for pancreatic adenocarcinoma: Do they warrant more study?

<table>
<thead>
<tr>
<th>Agent type/class</th>
<th>Suggested examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional chemotherapeutics: test in new ways</td>
<td>Carboplatin, 5-FU/mitomycin-C, Liposome-encapsulated Adriamycin, CPT-11 (tritnomecan)</td>
</tr>
<tr>
<td>Topoisomerase I inhibitors: test alone or in combination in pancreatic cancer</td>
<td>Herceptin antibody+/− Taxol</td>
</tr>
<tr>
<td>Inhibitors of signaling pathways: test alone or with other agents</td>
<td>Herceptin antibody+/− Taxol, Thalidomide, Flutamide</td>
</tr>
<tr>
<td>Antiangiogenesis agents</td>
<td></td>
</tr>
<tr>
<td>Antiandrogens</td>
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### Table 2 Metabolic factors in pancreatic cancer

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<tr>
<td>Proteolysis-inducing factor (PIF)</td>
<td>Refs. 46, 47</td>
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<td>Lipid-mobilizing factor (LMF)</td>
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<td>Tumor necrosis factor α (TNFα)</td>
<td>Refs. 49 and 50</td>
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<td>IGF-1</td>
<td>Refs. 51–55</td>
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<td>Cancer cell-derived polypeptide affecting glucose metabolism</td>
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Another approach would entail primary focus on new discoveries in pancreatic cancer biology leading to new targets, which might include proteins involved in tumor growth and signaling pathways (58–61) or new or altered proteins that are the products of the genetic alterations occurring during the process of tumorigenesis (62, 63). Another category of potential targets are the proteins recognized by activated immune cells (64). Additionally, targets within the tumor’s microenvironment, including endothelial cells and stromal cells, should be considered (65, 66). A list of novel potential targets that were discussed during the working group are presented in Table 4.

Controversy ensued when the question was asked, How do we proceed with the clinical development of existing agents and new agents directed at potential new targets? It was agreed that some empiricism in testing combinations of existing agents is warranted because pancreatic cancer patients are in immediate need of new therapies (67, 68), but that decisions concerning these agents and combinations should be based on our current knowledge of the mechanisms of the drug action. An example would be to combine agents that target signaling pathways such as K-ras and HER-2/neu with agents that induce tumor killing through a non-cross-resistant pathway. However, at the same time, preclinical studies must proceed in parallel to test and optimize various combinations and to identify new targets for intervention. This two-step approach toward the development of new therapies takes into consideration the needs of patients who are currently in need of new therapeutic options and who cannot wait for the results of preclinical studies.

New targets for pancreatic cancer therapy are likely to arise from a better understanding of pancreas cancer biology. Two requirements to facilitate this process were identified. First, there needs to be a focused effort at developing relevant preclinical models for pancreatic cancer (69). Examples of animal models were suggested based on the panel of known tumor suppressor genes and oncogenes involved in the tumorigenesis of pancreatic adenocarcinomas that have already been identified. Specifically, it should now be possible to develop transgenic animal models that incorporate serial gene expression of these tumor suppressor genes and oncogenes to simulate the gene alterations that occur in pancreatic adenocarcinomas. The development of gene knockout mice deficient in these tumor suppressor genes and oncogenes found to be implicated in both pancreatic adenocarcinoma development and progression are also needed (70). Both the transgenic and knockout mice should rapidly clarify which genes and gene products are critical to tumorigenic pathways in pancreatic adenocarcinoma. This knowledge should then lead to the rapid identification of important therapeutic targets. Transgenic animal models that express one or more of the critical oncogenes under a pancreatic tissue-specific promoter to result in naturally arising tumors would accelerate the preclinical evaluation of agents that act directly on the tumor or on cells in the tumor’s microenvironment, provide critical information about drug delivery, angiogenesis, and other strand interactions and immune surveillance.

Second, there needs to be a focused effort to collect and store pancreatic adenocarcinoma tissue. Pancreatic cancer is less common than other malignancies and is difficult to treat. Many patients are not referred to experienced centers, limiting access of patients to clinical trials. Even within centers with access to a larger number of patients, it is difficult to obtain tumor tissue because a minority of patients are candidates for resection. Also, the development of new therapies may require repeated tumor sampling pre- and posttreatment to assess intermediate end points. Therefore, the development of less invasive methods for tissue sampling will be important. It is also critical that a plan be formulated to educate professionals in cancer care and regulatory agencies about the importance of tissue procurement, especially at the time of autopsy. The recent emergence of pancreatic cancer advocacy groups can help with this process.

The participants all agreed that there is an urgent need to test new treatment approaches more rapidly. However, many questions were raised about how to effectively accomplish this task. One set of questions concerned implementing trials. How can we do it faster? How can we learn more with less testing? Who should sponsor these studies? The answers to the first two questions were clear: clinical trials need to be redesigned with novel end points (71) and with strategies that allow more rapid testing of new therapies. In addition, multicenter studies will permit wider access to patients. It is also important to identify improved methods for recruiting patients into the trials. A minority of pancreatic cancer patients currently enroll in studies. Patient education programs can heighten awareness about opportunities in clinical investigation. The answer to the third question is more difficult. All of the participants agreed that industry should play a significant role in the development of new therapies. One issue that often arises is that pancreatic is not a common cancer (although it is a deadly one), and it is often viewed by industry as a low priority. However, experience with gemcitabine has shown that a drug active in pancreatic cancer is likely to translate into a treatment with wide application for more common cancers. Therefore, industry, the National Cancer Institute, and extramural investigators need to partner closely and invest more in the development of new agents for pancreatic cancer.

A second set of questions was raised that focused on improving clinical trial design so that more can be learned about a new treatment in less time. The questions raised included: Who should be treated? And, How do we sequence new therapy into existing therapies? All participants agreed that we need to target both minimal residual disease and advanced disease. In the case of minimal residual disease, we need to introduce new agents in sequence with existing treatments in the adjuvant setting. The recent trend toward preoperative adjuvant therapy offers an excellent opportunity to test developing new single agents later in the postoperative setting. In the case of advanced disease, we need to develop predictors of response and surrogate markers of efficacy to select and sequence agents more efficiently (72).

Currently, overall survival, time-to-tumor progression, and objective response are still the most common end points used in clinical trial design. However, measurements of time-to-tumor progression can be difficult because this parameter requires frequent evaluations, involves some subjectivity, and is difficult to use in comparative or Phase II settings. Objective response is difficult to measure in this disease; technical factors can lead to inaccurate measurements of the primary site; and both primary and secondary tumors can be composed largely of reactive tissue (desmoplasia), which overestimates disease bulk. Quality of life and symptom relief are also considered end points; however, these studies are more labor intensive. A wish list for the development of new methods for measuring pancreatic adenocarcinoma response to therapy was created. This list included: (a) the development of molecular markers to predict outcome; (b) the development of noninvasive techniques to evaluate the mechanisms of
action (such as apoptosis) of new agents; and (c) the identification of surrogate markers of objective response or improved survival, such as circulating biomarkers or new imaging techniques.

In summary, a plan of attack for improving therapy for pancreas cancer was formulated by the working group. We need to accelerate testing treatments against known targets in new ways. In parallel, we need to aggressively support and encourage the development of new, rationally derived therapies that target molecules that are identified as a result of studies aimed at dissecting pancreatic cancer genetics and biology. The development of clinically relevant animal models and improved access to patient tumor tissue will greatly facilitate progress in the identification of new biologically relevant targets for therapeutic manipulation. Better predictors of outcome will also facilitate these efforts. The development of non- or minimally invasive methods for assessing mechanisms of action or predicting response to new agents are essential. Programs aimed at patient awareness and education need to be initiated to increase participation in clinical trials. The success of this plan will be dependent on the availability of additional resources dedicated to the fight against pancreatic cancer. It is hoped that this working group will lead to additional fora for future discussions of these important issues.

**Summary**

The groups’ recommendations are summarized in Table 5. Many of the research questions and required resources surfaced in multiple working groups. Of the many research opportunities identified, the highest priority went to the development of relevant animal models, understanding premalignant events, and selection of appropriate new biological or biochemical targets for therapy. Of the resources required, the most pressing was a need for comprehensive tissue banks.

### Appendix A: Pancreas Cancer Think Tank Working Groups

**Pancreas Cancer Biology**
Workshop Chair: Michael Hollingsworth—University of Nebraska Medical Center, Omaha, NE
Surinder Batra—University of Nebraska Medical Center, Omaha, NE
Robert Jensen—National Cancer Institute, Bethesda, MD
Young S Kim—UCSF VA Medical Center—San Francisco, CA
Murray Korc—UC Irvine Medical Center, Irvine, CA
Nicolas Lemoine—ICSM at Hammersmith, London, UK
Parviz Pour—University of Nebraska Medical Center, Omaha, NE

**Pancreas Cancer Histology**
Workshop Chair: Ralph Hruban—Johns Hopkins Medical Institutions, Baltimore, MD
Volkan Adsad—Wayne State University, Detroit, MI
Carolyn Compton—Massachusetts General Hospital, Harvard University, Boston, MA
Donald Henson—National Cancer Institute, Bethesda, MD

**Pancreas Cancer Think Tank Working Groups**
Meeting Co-Chairs: Scott Kern and Margaret Tempero

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