EMERGING SCIENCE AND RELEVANT RESEARCH DIRECTIONS

ADVANCING THE STATE OF SCIENCE IN PANCREATIC CANCER

The Summit on Pancreatic Cancer

August 2007 - La Jolla, CA

PANCREATIC CANCER ACTION NETWORK
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

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The Problem - Pancreatic Cancer Remains a Leading Cause of Death

The American Cancer Society recently released a report on cancer statistics showing that pancreatic cancer is one of the few cancers for which the survival rate has not improved substantially over the last 25 years. Of those diagnosed with pancreatic cancer, 75% of them die within the first year of their diagnosis, and the five year survival rate is less than 5%. More daunting facts:

- Pancreatic cancer is the fourth leading cause of cancer death in the United States (lung, breast, and colon cancer are first, second, and third, and prostate cancer is fifth).
- In 2008, an estimated 37,680 Americans will be diagnosed with pancreatic cancer and 34,290 will die from the disease.

- The number of people diagnosed with pancreatic cancer and number of deaths caused by pancreatic cancer are going UP, not down. These numbers are up 3,800 and 1,070 respectively in the last year alone.

From a scientific research perspective, the status of pancreatic cancer is where breast cancer was in the 1930s. By the 1930s, rudimentary surgical methods to remove early breast and pancreatic cancer tumors had been developed. However, while mammography was developed by the 1950s, and many effective breast cancer treatments followed, similar tools for pancreatic cancer still do not exist. **Advancing pancreatic cancer research into the 21st century is dependent upon the increase of basic science research.**

There are NO early detection methods. Many patients finally receive the diagnosis of pancreatic cancer when they seek medical attention for jaundice (yellowing of the skin and eyes). Jaundice typically occurs as a result of the pancreatic tumor growing large enough to block the bile duct. At this point, the disease is often too advanced to treat successfully.

Curative treatments are almost non-existent. Surgery offers the only potential for a cure. At most, only 15% of pancreatic cancer cases are caught early enough for surgery, and most patients will have a recurrence within two years. Treatments are generally decided based on the stage of the cancer:

- Only 7% of pancreatic cancer patients are diagnosed with early stage pancreatic cancer when the tumor is small in size and contained within the pancreas. The most commonly used surgical procedure to remove tumors in this stage is called the Whipple procedure, after the doctor who developed the technique in 1935. Surgery may be followed by chemotherapy or chemotherapy with radiation. **While patients diagnosed at this early stage have a slightly increased chance of surviving, statistics show that only 19.6% of these early diagnosed patients will survive more than 5 years.**

- Once the tumor has spread into surrounding tissue or organs and cannot be removed by surgery (not resectable), treatment becomes focused on control of the disease and optimal symptom relief with a **chance** for increased survival. **Approximately 26% of pancreatic cancer patients are diagnosed at this stage, and only 8% of them will survive more than 5 years**.

- **An estimated 52% of pancreatic cancer patients are diagnosed with late stage pancreatic cancer that has spread to distant organs or sites**. Chemotherapy alone, without surgery or radiation, is the recommended treatment for patients at this stage. The goal of treatment in this case is palliative care – optimal relief of symptoms and improvement in quality of life. A mere **2%** of pancreatic cancer patients who are diagnosed at this stage **will survive for more than 5 years**.

Research funding for pancreatic cancer by the National Cancer Institute (NCI) poses a challenge for the research community. Despite approximately $1.5 billion spent each year in the United States on the treatment of cancer, there has been few research dollars or researchers dedicated to discovering the causes and potential cures for pancreatic cancer. NCI funding for pancreatic cancer has increased from $17.5 million in 1999to $74.2 million in 2007. However, it still remains a challenge to determine how pancreatic cancer research can be leveraged for therapeutic gain, in particular what the best therapy is to decrease mortality incidence for this devastating disease.

Many questions remain

- Which approaches to studying the disease show the most promise? Which are dead ends?
- Where are the gaps in understanding this disease and how can we address them?
- And how can scientists at different institutions better coordinate their efforts to produce discoveries that have the greatest potential to benefit patients?

These questions must be answered if pancreatic cancer researchers are to achieve the kind of progress that has led to significant decreases in the morbidity and mortality rates of other forms of cancer. It is especially important during this time of heightened advances in genetics, biotechnology, bioinformatics and other fields which have transformed scientific understanding of cancer and laid the groundwork for more effective detection methods and treatments.

The Solution - Create the Change Needed to Advance Research in Pancreatic Cancer

With these challenges in mind, the Pancreatic Cancer Action Network hosted a major scientific summit in August 2007 bringing together the world's leading pancreatic cancer investigators as well as other luminaries of the biological sciences.

Objectives of the Summit

- A succinct review of current information and concepts relating to the biology of pancreatic cancer
- A discussion as to how this information can be translated into new ways to prevent, diagnose and treat the disease
- A compilation of recommendations for implementation

Format of the Summit

- A small group of experts (40-50) from relevant basic and clinical science disciplines, including selected investigators who have made advances in other cancers, assembled to undertake an interactive discussion of opportunities and challenges facing pancreatic cancer research during the next five year period.

- The intent was not to duplicate the format of other conferences where presentations simply provide summaries of current research and reviews. The agenda dedicated a substantial amount of time for extensive interactive discussions for purposes of providing recommendations as to which available findings from basic research merit implementation and validation in clinical settings.

Outcomes of the Summit

White Paper

The discussions and conclusions of the conference resulted in the attached lay level White Paper, intended to inform the community about the challenges and opportunities our research community faces. It provides an overview of the major themes in the presentations from the Summit:

- Cancer Stem Cells
- Mechanism Based Therapeutics
- Novel Therapeutics and Early Detection
- Early Detection
- Molecular Profiling of Tumors
- Familial Pancreatic Cancer

RAISE THE CURE

Based upon the analysis of the challenges/opportunities presented in the Summit, the Pancreatic Cancer Action Network created a multi-level action plan - the *National Plan to Advance Pancreatic Cancer* to advocate for increased federal funding, and the Visionary Circle to increase private donations. We invite you to join us in whatever capacity, financial or direct advocacy, to push these critical initiatives forward.

In keeping with our mission to share information and expand ideas, the Summit is available via webcast at www.pancan.org. We were honored to work with The Science Network to capture, webcast and archive the meeting.

Executive Summary

Cancer stem cells and cell of origin

Where does pancreas cancer start? What is the **stem cell** or **cell of origin** of pancreas cancer? This particular scientific endeavor highlights two things: the understanding of the pathogenesis of the disease will be incomplete without a definitive identification of the initiating cell type(s), and that the development of curative therapies may depend upon identifying this population. The Pancreatic Cancer Action Network provided an in depth newsletter article on this complex subject and continues to monitor scientific progress and challenges in this area.

Mechanism based therapeutics

Mechanism based therapeutics have provided "magic bullets" for other cancers, however, to date, pancreas biology holds particular challenges for identifying useful **targeted therapies**. Based upon this presentation and the resulting discussion, the Pancreatic Cancer Action Network will hold a small Think Tank in May 2008 to talk about strategies to support the scientific challenges in this area. Of particular interest are the accurate usage of mouse models to better validate KRAS as a target and identifying and validating other genetic targets for drug discovery.

Novel therapeutics and early detection

Scientific progress in **novel therapeutics and early detection** is critical for pancreatic cancer. Significant advances have been made in mouse models for other cancers and now that there are three working mouse models for pancreatic cancer, researchers are directing efforts toward the following key areas: validating new anticancer drugs, assessing the therapeutic index, identifying surrogate markers of tumor progression, and defining epigenetic and environmental influences on tumorigenesis.

Early detection

Early detection remains one of the most critical and elusive areas of study in pancreatic cancer. Screening of high risk families is underway (CAPS4) and markers, such as DNA methylation alterations and gene mutations that are prevalent are part of this study. Additionally, scientists are reviewing patient studies on adults with new onset diabetes over age 50 (1/125 of these patients will develop pancreatic cancer). Much basic research is still needed to profile the genetic, epigenetic and proteomic profiles of pancreatic cancer and advanced PanIN in order to identify an optimal panel of circulating markers of early-stage pancreatic cancer. The Pancreatic Cancer Action Network continues to support and challenge this work by active participation in the Early Detection Research Network and by funding pilot grants focused in this area.

Molecular profiling of tumors

One of the most exciting advances utilizing technology is work being conducted in **molecular profiling of tumors**. The backbone of this work is the study of tissue, analyzing the "driver" molecular pathways, rather than a single gene, and identifying the patients whose tumors depend upon these pathways for growth (and then matching that pathway with a specific, targeted therapy). In order for this endeavor to be truly successful, quantities of tissue, reflecting the wide differences of pancreatic cancer must be held in a robust pancreatic cancer biorepository. The Pancreatic Cancer Action Network is hosting a Think Tank on this important community resource in 2008/2009 and will be moving forward on the development of a business plan to support the recommendations of the Think Tank members.

Familial pancreatic cancer

Familial pancreatic cancer remains a key area of scientific study. Advances in technology give scientists the opportunities to discover familial susceptibility genes and to use this knowledge to best identify individuals at risk of developing pancreatic cancer; identifying those high risk individuals and enrolling them in screening studies will allow us to better understand the natural history and then, progression of cancer, before it becomes invasive. The Pancreatic Cancer Action Network continues to support this area of study by educating patients and families on the importance of participating in registries and by providing pilot grants for these innovative studies.

Cancer Stem Cells and Cell of Origin

Presenter: Dr. Diane Simeone
Moderators: Dr. Geoff Wahl, Dr. Susan Bonner-Weir

Summary of Presentation
Evidence for the existence of cancer stem cells continues to build. Support for the cancer stem cell theory is based on the identification of a small subpopulation of cancer cells which have the ability to recreate the heterogeneic tumor and all of the sub-populations of cells found within them. In some models, stem cells are the only sub-population capable of conferring sustained or transplantable tumor growth and/or metastasis. Recently, a subgroup of cells meeting these characteristics has been described for pancreas adenocarcinoma.(ref) These cells are described by CD44+/CD24+/ESA+ and constitute <1% of cells within a primary pancreatic tumor.

Key Concept: The full characterization of pancreas cancer stem cells and their relationship to other tumor cell populations are the subject of ongoing investigation. The existence of pancreas cancer stem cells may help explain some of the frustration met in the clinical treatment of pancreas cancer patients.

Research Questions:

1. The existence of cancer stem cells also presents several challenges to clinicians and investigators. It is important to shed light on how this population responds to standard therapy and experimental therapies as cancer stem cells may be more resistant to these therapies. For example they may be capable of dormancy making them refractory to metabolic stress. There is some evidence that stem cells become a larger percentage of the tumor in the face of some therapies. Is this by increased proliferation or by preferential survival?
2. Some investigators have postulated that stem cells may have the ability to evade immunosurveillance or may be refractory to apoptotic signals. What is the definition of pancreatic cancer stem cells.
3. We require better methods to select for stem cells and we would like to understand the relationship these cells play with other tumor cells and other cells of the micro-environment, including fibroblasts, immune cells and stellate cells. Can other tumor cells regress into a cancer stem cell, and if so, under what conditions? Conversely can we force a cancer stem cell to terminally mature or become dormant?

Cell-of-Origin of Pancreas Cancer

Presenter: Dr. Steven Leach
Moderator: Dr. Sunil Hingorani

Summary of Presentation
An understanding of the pathogenesis of pancreatic cancer would otherwise be incomplete without a definitive identification of the initiating cell type(s), and that the development of ultimately curative therapies may very well depend on identifying and characterizing this population.

Important differences between mice and humans notwithstanding (Rangarajan and Weinberg, 2004), advances in genetic engineering in mammalian systems have given rise to a new generation of animal models that hold enormous potential for revealing molecular mechanisms of disease pathogenesis, while also providing improved platforms for the identification and evaluation of therapeutic targets. These systems have also been employed in experiments to elucidate the cell-of-origin and include models based on conditional expression of oncogenic and tumor suppressor gene mutations (Hingorani et al., 2003; Aguirre et al., 2003), inducible expression of the same genetic events (Guerra et al., 2007), and viral-mediated somatic targeting of genetic mutations (Lewis et al., 2003). Combining inducible expression systems with lineage tracing techniques affords the possibility of more definitively identifying the cell(s) in which specific types of lesions and precursors originate. More recent studies (see for example Izeradjene et al., 2007) also underscore the intriguing possibility of distinct types of progenitor cells along the length of the organ (i.e. head, body and tail) which may differ in their susceptibilities to distinct genetic perturbations and in the particular phenotypic responses such insults elicit (reviewed in Hingorani, 2007). The same types of genetic approaches can also be extended to other vertebrate animals such as zebrafish, further expanding the experimental possibilities for unraveling the molecular and cellular origins of the disease. Finally, the ability to grow isolated cells in three-dimensional culture systems with defined matrix components provides a methodology to interrogate the functional capabilities of distinct sub-populations of pancreatic cells complementing the *in vivo* approaches.

Key Concept: Defining cellular compartments in the pancreas that are competent to initiate pancreas cancer is not necessarily the same as establishing which compartment does in fact support disease formation in humans. In other words, the possible does not establish the actual.

Nevertheless, it is interesting to note that neoplasms of the acinar compartment are relatively rare, comprising approximately 5% of epithelial cancers of the pancreas, despite representing 90% or so of the bulk mass of the organ. Islet tumors are similarly rare. Conversely, carcinomas with ductal differentiation constitute 80-90% of pancreatic tumors, although ductal cells constitute 3-5% of the organ mass. In this regard, that endogenous expression of oncogenic *Kras* in murine pancreatic tissue progenitor cells results almost exclusively in ductal cancers appears to confirm a propensity of cancers to evolve along ductal pathways and/or a resistance of the acinar and islet differentiation programs to transformation by oncogenic *Kras*.

Key Concept: Ductal differentiation may either be a consequence of the genetic insult or instead reflect the cell-of-origin. In either case, further study of the mechanisms by which acinar and islet cells largely resist the transforming effects of oncogenic *Kras* may reveal new approaches to the treatment of PDA.

A remarkable plasticity has been described of acinar cells to undergo so-called transdifferentiation *in vitro* toward a more ductal or islet cell phenotype, processes potentially involving intermediate states with progenitor cell properties (reviewed in Konieczny and Leach, 2007). Recent studies have corroborated this inherent plasticity of mature acinar cells *in vivo* as manifested in their ability to

contribute to the repair of organ injury and to support the formation of early grade PanINs (Strobel et al., 2007). This work has further refined our understanding of metaplastic changes in the pancreas in response to caerulein-induced inflammatory injury in defining three distinct types of lesions (two types of “tubular complex” lesion and mucinous metaplastic lesions) each with distinct cellular origins.

Key Concept: The role of inflammatory injury in the initiation and/or progression of disease has long been suspected and is substantiated by the increased risk of PDA in patients with chronic pancreatitis (Lowenfels et al., 1993). How chronic injury may cooperate with additional events to support PDA and whether acute injury also plays a role are at present unknown.

A recent study involving inducible expression of activated *Kras* in adult pancreatic acinar or centroacinar cells suggested an absolute requirement for concomitant inflammatory injury by caerulein to support disease initiation (Guerra et al., 2007). If so, is this also true if *Kras* is activated in other cellular compartments? Do other mechanisms of injury (e.g. acute ductal obstruction, partial pancreatectomy, genetic models of chronic pancreatitis, alcohol etc.) cooperate similarly with the genetic events described above to promote transformation? The more nuanced description of discrete types of metaplastic lesions, together with the recent demonstrations of the potential applications of caerulein-based studies, should further inform attempts to more narrowly define the cell of origin for PDA.

Research Questions:

1. What is cell-of-origin in spontaneous human disease? Can/does more than one cell type give rise to human PDA?
2. How do mature acinar and islet cells resist the transforming effects of oncogenic *Kras*?
3. Is concomitant inflammatory injury required for pancreas cancer formation or does it merely potentiate it?
4. Can each of the discrete types of metaplastic lesion progress to PDA? If so, is there a *ras*-independent route to PDA?

Mechanism Based Therapeutics

Presenter: Dr. Neal Rosen
Moderators: Dr. Channing Der and Dr. Murray Korc

Summary of Presentation: There is considerable evidence that mechanism-based targeted anti-cancer therapies can work. The success of Gleevec, Tarceva and other targeted drugs support this belief. However, pancreas cancer biology holds particular challenges for identifying useful targeted therapies. There is currently uncertainty as to whether the present lack of dramatic responses to any available therapy is a reflection of unique features and characteristics of this particular cancer, and whether lessons learned in other cancers can be applied successfully in pancreatic cancer. It is clear that the KRAS oncogene is an important target, but it has been difficult to develop inhibitors of this target. Are there better ways to develop effective anti-KRAS therapies? Other targets have been identified – should we put more focus on these? Alternatively, are the best targets still to be identified? If so, how do we identify them? Aside from target identification and inhibitor development, a key barrier to success has been how to accurately identify what targets and drugs will work in the patient. There is great optimism that new mouse models of pancreatic cancer will solve this problem, but will they live up to that promise? A rigorous evaluation of mouse models remains to be done. Will a focus on cancer stem cells be critical? There is also much room for improvement in how we evaluate novel therapies in clinical trials. The standard approaches used for development of conventional anti-cancer drugs cannot be used for targeted therapies. Finally, mechanisms are needed to improve the communication and cooperation between academic and clinical researchers, as well as with the government and with the pharmaceutical industry.

Key Concepts: While it is generally agreed that molecularly-targeted therapies hold the greatest potential for effective therapies for pancreatic cancer, what the best targets are, how to develop inhibitors of these targets, how to best identify the patients who will respond to that drug, and finally, how to best apply these drugs, are all concepts that remain unresolved.

Research Needs:

1. Better validation of KRAS as a target, using accurate mouse models of human disease.
2. Identification and validation of other genetic targets for drug discovery.
3. Characterization and validation of pancreatic cancer stem cells; are these the tumor cells that we should be targeting?
4. Improved mouse models for more predictive preclinical evaluation of targeted therapies: validation of existing mouse models, development of better models that more closely mimic the complexity of pancreas cancer biology.
5. Better choice, design and interpretation of preclinical studies and clinical trials, to generate more effective approaches to define clinically useful combination therapies.
6. Establishment of molecular markers to identify patients who can be treated successfully with a specific target-based drug, and of reliable biomarkers to monitor drug activity.
7. Better communication and cooperation with the different institutions involved in drug discovery and evaluation.

Research Questions:

1. **Is KRAS still the best target?** Common misconceptions to the contrary are based partly on the fact that mutational activation of K-Ras is an early event in pancreatic cancer development – therefore, is it a useful target when we detect cancers only at advanced stages? Also, the poor clinical results with farnesyltransferase inhibitors and sorafenib, which are wrongly

thought of as inhibitors of Ras and of the Ras target, Raf, respectively, have given the misimpression that KRAS is NOT a good target. We must continue to assess if KRAS is indeed a useful target and then consider more creative ways to develop true anti-KRAS drugs.

2. **If not KRAS, are there better targets?** Other candidate targets include the TGFbeta-SMAD4, Notch, Hedgehog, and NF-kappaB signaling pathways. Some of these are controversial. Each pathway needs better validation in appropriate models, and better strategies for inhibitor development. If these are not good targets, then how should we identify, select and validate new ones? Is genome-wide sequencing the way to go? Will application of genome-wide microarray gene expression, proteomics, plasma-secreted proteins, RNA interference, and microRNA technologies be a good use of time and money?

3. **What are the best cell culture models to validate targeted therapies?** Our current pancreatic tumor cell lines have been in culture for decades; do they accurately reflect the biology of the tumors from which they were derived? Cell culture models that have properties of tumor stem cells need to be considered. More complex cell culture models that better mimic the 3-dimensional nature of tumors and that recapitulate tumor-stromal interactions may provide better predictors of drug activity in the patient. Such cell culture models may also better facilitate the identification of effective drug combination approaches.

4. **What are the best mouse models to validate targeted therapies?** While the classical, widely used mouse xenograft tumor models using established tumor cell lines remain the gold standard of the FDA and the pharmaceutical industry, it is clear that these models are highly ineffective in predicting what drugs will work in the patient. Recently developed genetically-engineered mouse models of pancreatic cancer hold great promise of providing more predictive models, but this promise will remain purely speculative until rigorously tested. It has also been suggested that individualized, patient-derived tumor xenograft models may be superior; but again, validation is still needed.

5. **Are there molecular determinants that can be identified and validated to predict patient response to specific targeted therapies?** The key factor for successful targeted therapy is identification of a molecular determinant that predicts patients who will respond to that therapy (e.g., the BCR-ABL translocation chromosome for Gleevec response). Concurrent with the development of promising targeted therapies, it will be important to identify and validate such determinants of their response. Additionally, we need to identify and utilize reliable biomarkers to monitor drug activity. If we can't conclude that a particular treatment is successfully blocking the target, then no reliable and accurate interpretation of the preclinical or clinical results of that treatment can be made. Will gene signatures to predict drug sensitivity be realistic possibilities?

6. **What is different about pancreatic cancer that prevents the dramatic albeit unsustainable responses to targeted therapies seen in other diseases?** Are there issues unique to pancreatic cancer that we need to understand that makes this cancer so refractory to treatment? Does its propensity to spread to the celiac plexus mean that we need to model it in the presence of nerve interactions? Does its propensity to become extremely fibrotic mean that we need to model it in the presence of stromal elements that recapitulate this desmoplastic reaction? Can we port over from other diseases anything useful for pancreatic cancer? Is drug delivery a more significant problem in the context of these highly fibrotic/desmoplastic tumors with poorly accessible vasculature? It is critical to test therapies in the context of a model that has the same issues as pancreatic cancer; otherwise, we will be misled by results from improper preclinical cell culture and mouse models.

Animal Models: Development of Novel Therapeutics and Early Detection Strategies

Presenters: Dr. David Tuvenson and Dr. Dafna Bar-Sagi

Key Concept: Many of the genetic theories, early detection strategies, and novel therapies scientists thought would work in humans have failed. Much of this early work was based on cell culture studies and in pancreatic cancer; however we have learned this research doesn't necessarily translate to accurate human responses. To counter that, sophisticated animal models and cellular models of pancreatic cancer have been developed and show great promise in elucidating the key features of tumorigenesis. Today, there are three working mouse models.

Research Initiatives: Autochthonous mouse models of ductal pancreatic cancer have demonstrated the relevance of previously described common genetic mutations in the development of pancreatic intraepithelial neoplasms and mucinous cystic neoplasms, and advanced invasive and metastatic pancreatic ductal carcinoma. Such models are now being used to unravel the critical cellular and biochemical facets of early and advanced pancreatic cancer using in vivo and ex-vivo approaches. Indeed, the capacity to culture primary pancreatic cells of different origins (ductal, acinar, islet) in three dimensional structures provides a readily accessible approach to investigate both cell autonomous and non-cell autonomous elements of the tumorigenic process. Specific examples pertaining to ductal cells include modeling of the interplay between genetically altered cells and normal cells, evaluation of the impact of extracellular matrix interaction and assessment of region-specific molecular attributes.

Current milestones and challenges include the utilization of these models for preclinical applications including tumor diagnostics and therapeutic evaluation. The identification of serum biomarkers for early pancreatic cancer has proven elusive using human samples, and autochthonous mouse models should be exploited for the evaluation of new technological approaches. The therapeutic utility of the autochthonous animal models and cell culture models will be most apparent if they are more predictive of tumor responsiveness in patients than the currently employed tumor xenografts and two-dimensional cell culture systems.

Research Needs: All of these studies require special resources and mechanisms to foster such investigations

Research Directions:

1. **Validating new anticancer drugs**
2. **Assessing the therapeutic index**
3. **Identifying surrogate markers of tumor progression**
4. **Defining epigenetic and environmental influences on tumorigenesis**

Break Out Session - New Information on Early Detection

Presenter: Dr. Michael Goggins

Key Concept:
The meeting highlighted recent advances in the early detection of pancreatic neoplasia, particularly the success of the screening high risk individuals such as Cancer of the Pancreas Screening Trials (CAPS) and the description of recently identified pancreatic cancer markers.

Research Initiatives:

1. The CAPS studies are enrolling first degree relatives of individuals with familial pancreatic cancer and carriers of germline mutations (such as BRCA2) with a family history of pancreatic cancer. The current CAPS3 study is a multicenter study evaluating the role of different pancreatic imaging tests (endoscopic ultrasound (EUS), pancreatic CT and MRI/MRCP).

2. A 4th study (CAPS4) has been funded and is just beginning at UCLA.

3. Once pancreatic lesions have been identified by EUS, new management strategies must be employed. Today, patients are often taken to surgery when a small intraductal papillary mucinous neoplasms (IPMN) is identified, but typically at resection such patients also have extensive pancreatic intraepithelial neoplasia (PanIN) that are not directly visible by imaging.

4. The need to identify which patients carry advanced and extensive but microscopic PanIN highlights the need for molecular markers of PanIN that could be detected in pancreatic secretions to facilitate screening efforts. Markers such as DNA methylation alterations and gene mutations that are prevalent in pancreatic neoplasms are undergoing evaluation as part of the CAPS studies.

5. Although EUS can detect subtle abnormalities in the pancreas that may indicate PanIN, the findings are non-specific. Markers of PanIN that could be detected with novel imaging strategies would represent an important advance.

6. The meeting also highlighted recent efforts to identify new protein markers of pancreatic cancer. One approach by Bardeesy et al profiled serum proteins in mice with pancreatic neoplasia and validating candidate markers in human tissues.

7. Apart from family history, there are few strong risk factors for developing pancreatic cancer. There is increasing recognition that the frequent detection of small asymptomatic pancreatic cysts in patients undergoing imaging is an opportunity to detect and treat early pancreatic neoplasms before the development of invasive cancer.

8. Recent studies suggest that 1/125 patients with new onset diabetes over age 50 have pancreatic cancer. Since diabetes or impaired glucose tolerance is present in more than ½ of all patients with pancreatic cancer, research is needed to distinguish new onset diabetics with pancreatic cancer from usual adult onset diabetes.

Research Directions: Many patients with pancreatic cancer undergo delays in diagnosis that contribute to their poor outcome.

1. There is need for epidemiological research to better understand the reasons for the late diagnosis for patients with pancreatic cancer and whether better recognition of the often subtle warning symptoms of pancreatic cancer improve early diagnosis.
2. As the success of clinical trials of pancreatic cancer screening are realized, the main challenges and opportunities in the early detection of pancreatic neoplasia is the need to fund studies that enroll as many high risk individuals as possible.
3. As evidence accumulates that pancreatic cancer screening is worthwhile, expert societies will need to train specialists skilled in performing EUS and advocating that pancreatic cancer screening for high-risk individuals is covered by insurance.
4. Meanwhile, there are important unanswered questions about screening high risk individuals, including whether patients with lesions should undergo a partial pancreatic resection or a total pancreatectomy, the role of pancreatic juice collection, the future role of gene testing to identify at risk individuals.
5. Basic research is also needed to continue to profile the genetic, epigenetic and proteomic profiles of pancreatic cancer and advanced PanIN in order to identify an optimal panel of circulating markers of early-stage pancreatic cancer.

Exploiting Molecular Tools to Personalize Pancreatic Cancer Therapeutics

Presenter: Dr. Timothy Yeatman
Moderators: Dr. Mace Rothenberg

Key Concept: Pancreatic cancer is likely a molecularly heterogeneous disease, explaining why some patients do see responses to therapy and others do not. As new agents are developed that precisely target "driver" molecular pathways rather than single genes, identifying the patients whose tumors depend on these pathways for growth will be critical. One means of accomplishing this is to simply profile each tumor for thousands of genes, resulting in a digital signature representative of each individual's tumor. This technology is currently available today.

Research Initiatives:

1. The future holds promise for researchers to actually match the right patients to the right drugs, first in clinical trials and then in practice. The "Total Cancer Care" initiative in personalized cancer care, led by the Moffitt Cancer Center, Tampa, FL, seeks to develop a database of thousands of patients, each with a personal tumor gene profile that might be later used to perform "trial matching" through a larger nationwide consortium of hospitals. The hope would be that trials could be completed faster and that response rates would be higher in these trials, simply because the right patients were accrued to these specialized trials.

2. Work is also being conducted on personalized medicine through the Partnership for Personalized Medicine, a combined effort joining talents and resources from TGEN, the Biodesign Institute at Arizona State University, and the Fred Hutchinson Cancer Research Center.
3. This team focuses on the use of proteomics to develop personalized diagnostic tests. Proteomics is a promising and cutting-edge field that studies proteins and their functions in the body. The Partnership for Personalized Medicine will focus on discovering new proteins for the development of diagnostic tests for patients with cancer or other illnesses. These tests could ultimately lead to earlier disease detection and more precise disease management.
4. Even though the necessary technologies to develop personalized diagnostic tests are available, barriers such as the expense of clinical trials and difficulty obtaining clinical samples (tissue) have significantly slowed the development process. The Partnership will focus on the development, testing and validation of new molecular diagnostic tools and the approval and distribution of these tools for widespread clinical use. This will be accomplished through a series of collaborative demonstration projects that integrate key health organizations.

Research Needs: Biospecimens (Tissue) The success of these research projects would depend heavily on the capacity to obtain fresh biopsies of the tumor, usually done with a small needle by interventional radiologists, so that gene analysis can be performed. While these sorts of population based matching trials are not yet available today, they could be within a matter of a few years.

Research Challenges:

1. **Genome analysis for all individuals**: Rapid, automated methods must be developed to efficiently identify SNPs in the three-billion-base-pair genome that influence susceptibility to disease and individual drug response.
2. **Studying the biology of genes involved in disease and drug reactions**: It can take decades to study a gene's product, function and association to drug response.
3. **New techniques need to prove their worth**: SNP analysis and expression profiling are in their infancy, and few success stories exist.

4. **Complex diseases really are complex:** In reality, disease and drug response can involve hundreds of genes. Environmental factors such as age, nutrition and lifestyle can influence disease and drug response as well.

Identifying Familial Pancreatic Cancer Genes

Presenter: Dr. Ralph Hruban
Moderator: Dr. David Tuveson

Key Concept: Despite considerable progress in characterizing somatic genetic alterations in pancreatic cancer, the genetic basis for most forms of familial pancreatic cancer is not yet known.

Research Initiatives:

1. The inherited mutations that contribute to pancreatic cancer susceptibility (BRCA2, p16, STK11, FANCC and cationic trypsinogen*)* explain susceptibility in only ~10% of families. Ongoing studies of linkage by the Pancreatic Cancer Genetic Epidemiology consortium (PACGENE), studies of genome wide association such as the Pancreatic Cancer Cohort Consortium (PanSCAN), analysis of germline copy number variants and cancer genome sequencing projects are expected to accelerate the identification of familial pancreatic cancer susceptibility genes.

2. Knowledge of the genetic basis of pancreatic cancer susceptibility is important for genetic counseling and is being used to identify individuals who should undergo pancreatic cancer screening through the CAPS studies and it is expected that gene testing will be an increasingly important selection criterion for undergoing pancreatic cancer screening in the future. The identification of more and more patients with precancerous lesions undergoing screening has led to detailed descriptions of the pancreatic phenotype of familial pancreatic neoplasia which is characterized by extensive PanIN and associated lobulocentric atrophy.

3. Understanding the genetic basis for pancreatic cancers may help select targeted therapies. For example, patients with cancers with deficient BRCA2/Fanconi pathways are more sensitive to DNA crosslinking agents such as mitomycin C.

Research Directions:

Advances in the technology to rapidly interrogate the human genome are providing a tremendous opportunity to:

- discover familial susceptibility genes and to use this knowledge to best identify individuals at risk of developing pancreatic cancer so that patients can undergo genetic counseling and pancreatic cancer screening to prevent them developing the disease
- identify individuals at risk of developing pancreatic cancer and enrolling them in screening studies will allow us to better understand the natural history of pancreatic neoplasia before the development of invasive cancer

Profiles Based on Order of Presentations

Diane M. Simeone, MD, University of Michigan, Ann Arbor, MI
Dr. Simeone is the principal director of a research laboratory that is funded by the National Institutes of Health. Her basic science laboratory investigates mechanisms of pancreatic growth regulation and molecular events important in the development and progression of pancreatic adenocarcinoma. She is also an associate member of the Early Detection Research Network (EDRN), an NCI-funded initiative to identify and validate early detection biomarkers for the diagnosis of pancreatic cancer.

Geoffrey M. Wahl, PhD, Salk Institute, La Jolla, CA
Dr. Wahl is a professor in the Gene Expression Laboratory studying the genetic basis of the origin and progression of cancer and why tumors become resistant to drugs.
The underlying mechanisms of the genetic instability of cancer cells, and of their ability to develop resistance to anti-cancer drugs have remained a mystery to cancer biologists for the better part of a century. Wahl has found evidence that the instability derives from mutations in key genes that determine when it is safe for the cell to begin the important process of duplication of the genetic material. Such mutations also prevent cancer cells from responding to treatments commonly used in therapy that produce DNA damage, such as ionizing radiation. This increases the chances that a mutant cell will be produced every time it tries to reproduce itself. While this gives cancer cells many advantages for growth under stressful conditions, it also provides novel routes for the development of new anti-cancer therapies. The lab is now investigating how p53 is regulated, as 50% of human cancers express wild type p53 that is functionally compromised. Their efforts center on the use of in vitro systems and genetically modified mice to understand the contributions of two related proteins, Mdm2 and Mdm4 (Mdmx) to p53 regulation. Previous studies have shown that these proteins are essential for controlling p53 activity, and that they are frequently over-expressed in cancer cells as a way to mitigate p53 function in tumors containing wild type p53 genes. A goal of these studies is to develop drugs that antagonize Mdm2 and Mdmx to treat patients when tumors over-express these proteins. Another area of investigation concerns the identification and isolation of stem cells that are required to form each of the different types of cells in organs such as the mammary gland. This is important as the special properties of such cells, including their abilities to self-renew and to divide infrequently may enable them to contribute to cancer formation and to drug resistance.

Susan Bonner-Weir, PhD, Joslin Diabetes Center, Harvard Medical School, Boston, MA
Dr. Bonner-Weir and her colleagues believe that a better understanding of the regulation of pancreatic growth and differentiation may lead to new therapies, including generation of new beta cells and amplification of beta cells from the pancreas (either human or animal) to be used for transplantation. Her research has focused on the endocrine pancreas (the islets of Langerhans) in three areas: 1) the architecture of the islet and its implications for function; 2) the in vivo regulation of beta-cell mass; and 3) the factors involved in islet growth and differentiation.

With a series of rodent models they have provided compelling evidence that adult pancreatic beta-cell mass increases in response to a metabolic need and have been examining the mechanisms of this postnatal pancreatic growth. In the adult rat after partial pancreatectomy, massive regeneration occurs with both enhanced replication of preexisting beta cells and ductal expansion and subsequent differentiation into endocrine, exocrine or mature duct cells. They are defining the cells that are involved and the factors that are carefully orchestrated in vivo to stimulate the growth and differentiation of the beta cells. Another project is to define markers of newly formed beta cells. Additionally they have been successful in vitro cultivation of human islets from pancreatic ductal cells and are characterizing the cells that give rise to the new islets. Their overall hypothesis has been that in the adult pancreas duct cells act as pancreatic progenitors, such that with replication the mature duct cell regresses to a less differentiated cell (perhaps equivalent to a embryonic pancreatic duct cell) and regains its potential to differentiate into islet, acinar or mature duct cell, and that this

phenotypic differentiation is directed by external signals or morphogens. Using the Cre-lox system for lineage tracing they are showing that in growth after birth and injury that mature duct cells serve as the progenitor for new islets and new acini.

Steven Leach, MD, Johns Hopkins University, Baltimore, MD
Dr. Leach studies epithelial differentiation in exocrine pancreas, using both mouse and zebrafish model systems. This work is guided by the principle that pancreatic cancer may be initiated by changes in epithelial differentiation involving reprogramming of pancreatic progenitor cells. Our recent work has demonstrated that exocrine progenitor cells in adult and embryonic pancreas are regulated by specific interactions between the Notch and EGF signaling pathways, and that these interactions may be involved in the initiation of human pancreatic cancer. Current areas of emphasis include: 1) Evaluation of musashi RNA binding proteins in the regulation of pancreatic progenitor cells; 2) Identification of novel transcription factors regulating pancreatic epithelial differentiation; 3) Generating a zebrafish pancreatic cancer model amenable to high-throughput small molecule screens; 4) Application of transposon technology for large-scale mutagenesis of the zebrafish genome.

Sunil Hingorani, MD, PhD, Fred Hutchinson Cancer Institute, Seattle, WA
Dr. Hingorani focuses his laboratory on the use of genetically engineered mouse models to answer fundamental questions about the biology of pancreas cancer. By directing the expression of key mutations in specific oncogenes and tumor suppressor genes to the mouse pancreas, we have developed models that faithfully mimic the spectrum of human pancreatic ductal adenocarcinoma (PDA) from its earliest preinvasive lesions to locally invasive and widely metastatic disease. Our goals are to use these models to reveal basic mechanisms of disease pathogenesis, as well as to serve as platforms for the design and testing of strategies for early detection and for treatment and chemoprevention.

Three broad areas of inquiry are currently being pursued: 1) continuing investigations into the molecular requirements for disease progression and their respective impact on the resultant clinical and biological phenotype; 2) investigations into the cell-of-origin for preinvasive and invasive ductal carcinoma and the possibility that it may represent a mutated tissue progenitor cell; 3) efforts to identify biomarkers of early disease and markers associated with disease response and resistance to therapy.

Neal Rosen, MD, PhD, Memorial Sloan Kettering, New York, NY
Dr. Rosen focuses his laboratory on the identification and characterization of signal transduction pathways that cause the dysregulation of growth and inhibition of apoptosis that characterize advanced human cancer. Our laboratory is dedicated to understanding the consequences of activation of these pathways and to using this information to develop mechanism-based therapeutic strategies. A major focus is the evaluation of Hsp90 as a therapeutic target in cancer patients. Hsp90 is a cellular chaperone that is required for maintaining the proper conformation of several important signaling proteins, including transmembrane tyrosine kinases and steroid receptors. The laboratory is studying the role of Hsp90 family members in maintaining the transformed phenotype of cancer cells. The knowledge gained is being used to develop strategies for using Hsp90 inhibitors in patients. A lead compound, the ansamycin 17-AAG, is currently in clinical trial at MSKCC. The laboratory has developed, and is currently evaluating, second generation ansamycins and small-molecule inhibitors with potentially greater selectivity and more favorable pharmacologic properties. (See ansamycin and small-molecule inhibitor projects.)

In addition, the laboratory is studying kinase inhibitors that target *EGFR, HER2, MEK, src, mTOR, Met,* and small molecules that inhibit androgen receptor and estrogen receptor. These compounds are being used as re-agents to define the role of these pathways in tumor cells with the goal of developing strategies for using these agents in patients.

Channing J. Der, PhD, University of North Carolina, Chapel Hill, NC
Dr. Der's research focuses on understanding the molecular basis of human carcinogenesis**.** Specifically, their research studies have dealt with three distinct aspects of Ras family oncogene proteins and on the discovery of novel oncogenes involved in specific human cancers. First, we are interested in complex nature of signal transduction pathways that mediate the oncogenic actions of Ras. Ras is mutationally activated in 30% of all human cancers, with high frequencies seen in lung, colon, and pancreatic cancers. It has become apparent that Ras regulates a multitude of signaling pathways via its interaction with a surprisingly diverse spectrum of downstream effector targets, which include the Raf serine/threonine kinase and the Tiam1 activator of Rac. To date, at least a dozen distinct Ras effector targets have been identified and we are interested in how each contributes to oncogenic Ras deregulation of gene expression and promotion of tumor cell invasion and metastasis.

Second, we now know that the three Ras proteins represent only a mere subset of a large superfamily of Ras-related proteins. Mammalian members of this family number more than 100, with more likely to be discovered. Since Ras-related proteins share strong sequence and biochemical similarities with Ras proteins, a logical question is whether the aberrant function of any other members of this superfamily are also oncogene proteins involved in cancer development. Much of our current interest has centered on members of the Rho family of Ras-related proteins, which function as regulators of a wide spectrum of cellular processes that include actin cytoskeletal organization, gene expression and cell cycle progression. How Rho proteins contribute to Ras transformation, and what signaling pathways connect Ras with Rho, are questions that we are pursuing in our studies. Another class of Ras superfamily proteins appears to function as tumor suppressors, rather than oncogenes. Understanding why these proteins share significant biochemical properties with Ras, yet inhibit tumor progression, is a goal of our studies.

Third, we are involved in drug discovery efforts to target Ras for cancer treatment. For example, our studies involve evaluating the ability of inhibitors of Ras signaling (e.g., Raf and MEK kinase inhibitors) to block the growth of Ras mutation positive human cancers. Finally, we have developed biological screens to search for novel oncogenes that are activated in a variety of human cancers, including carcinomas of the breast, colon, prostate and pancreas. In summary, our studies span the broad range from gene discovery to drug discovery, with the long range goal of identifying better diagnostic and therapeutic approaches for cancer treatment.

Murray Korc, PhD, Norris Cotton Cancer Center, Dartmouth, NH
Dr. Korc is interested in the molecular biology of pancreatic cancer; mechanisms of action of peptide hormones and growth factors; abnormal gain of function through negative pathways; resistance of cancer cells to apoptosis; tumor angiogenesis. Most of the work in Dr. Korc's laboratory explores aberrant signaling pathways in cancer cells. Studies include signaling by the epidermal growth factor (EGF) receptor, fibroblast growth factor (FGF) receptors, transforming growth factor beta (TGF-b) receptors and vascular endothelial cell growth factor (VEGF) receptors. The potential role of co-receptors such as glypican-1 and neuropilins are also being actively investigated. The model system that is most often studied is pancreatic cancer. The overall hypothesis guiding the studies of pancreatic cancer is that superimposed on alterations in oncogene and tumor suppressor gene functions, there is evidence for excessive mitogenic signaling, loss of negative growth constraints, and abnormal gain of function through negative signaling pathways, through suppression of differentiation, through excessive resistance to apoptosis, and through aberrant angiogenesis. Knowledge gained from these studies is being used to devise novel therapeutic strategies for this deadly disease.

David Tuveson, MD, PhD, Cambridge Research Institute, Cambridge, England
Dr. Tuveson is interested in Tumour Modeling & Experimental Medicine (Pancreatic Cancer). His research interests involve pancreatic cancer and melanoma---deadly malignancies when detected at late stages. His laboratory investigates both of these cancers by producing models in *Mus musculus* that mimic the human diseases closely, and participating in clinical trials with experimental

therapeutics. The goals of the laboratory are to identify the essential components of malignant transformation of pancreatic cells and melanocytes *in vivo*, and to translate this knowledge into effective tumour detection and treatment strategies.

Dafna Bar-Sagi, PhD, New York University, New York, NY
Dr. Bar-Sagi directs research to understand the processes of life at the biochemical level. Her research includes studies on the molecular mechanisms and regulation of RNA and DNA synthesis, recombination, oxygen sensing and signaling, mechanisms of nitric oxide action, mechanisms of chaperone-assisted protein folding, protein structure, stress signaling and response, mechanisms of G-protein function, HIV prophylaxis, neuron receptor localization and signaling mechanisms that determine the spatial directions of neuron motility

Michael Goggins, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Dr. Goggins' research interests include the molecular genetics of pancreas cancer, particularly the role of germline BRCA2 mutations in pancreas cancer and characterizing the molecular genetic progression model for pancreas cancer.

Timothy Yeatman, MD, Moffitt Cancer Center, Tampa, FL
Dr. Yeatman has focused his research on the management of gastrointestinal malignancies with a special research emphasis on using genome scale microarrays to identify the molecular signatures of cancer that provide diagnosis, prognosis and response to therapy. Dr. Yeatman recently compared microarray data of 540 human tumors of 21 different tumor types with the diagnoses obtained from tumor biopsies. He found that microarray was 88 percent accurate in predicting all tumor types. The results of his investigation, the first such work to be reported in this depth, appeared in the January 2004 issue of the *American Journal of Pathology*. In addition, he and his colleagues have detected 340 new tumor markers and more than 100 tumor progression markers whose expression correlated with progressing tumor stage. Some of these markers may be useful in the clinical management of colon cancer patients because of their capacity to detect and predict the stage of cancer.

Mace Rothenberg, MD, Vanderbilt University, Nashville, TN
Dr. Rothenberg is a medical oncologist who specializes in Phase I drug development and clinical trial design with an emphasis in gastrointestinal cancers (particularly colorectal and pancreatic). His research focuses on evaluating new drugs in humans from a clinical, pharmacological, biological and genetic perspective. He studies novel cancer therapeutic agents to determine their safety and clinical application, and his most significant contributions have been in the development and FDA approval of drug treatments for colorectal and pancreatic cancer.
Dr. Rothenberg is recognized nationally and internationally as an expert on clinical trial design and evaluating new treatments. Vanderbilt is one of only 16 institutions designated and funded by the National Cancer Institute (NCI) as a Phase I Center. Several of Dr. Rothenberg's studies focus on investigational drugs for patients with advanced cancers for which there is no known effective or curative therapy. He is recognized nationally and internationally for his work, serves on a number of advisory committees, and is an editorial board member for numerous publications including *Clinical Cancer Research, Clinical Colorectal Cancer and Investigational New Drugs*, and *The Journal of New Anticancer Agents.*

Ralph Hruban, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Dr. Hruban received his Doctor of Medicine from The Johns Hopkins University. He continued at Johns Hopkins for his residency training, spent one year as a Fellow at Memorial Sloan-Kettering Cancer Center in New York and then returned to Johns Hopkins to join the Faculty in 1990. He established the National Familial Tumor Registry January 1, 1994.

Dr. Hruban is currently Director of The Sol Goldman Pancreatic Cancer Research Center and Director of the Division of Gastrointestinal/Liver Pathology. Dr. Hruban has written over 400 scientific papers,

80 book chapters and reviews, and three books. He is recognized by the Institute for Scientific Information as a Highly Cited Researcher and by Essential Science Indicators as the most highly cited pancreatic cancer scientist - designations given to the most highly influential scientists. In addition to his research efforts, he helped create the Johns Hopkins Pancreatic Cancer Web Page, http://pathology.jhu.edu/pancreas. Dr. Hruban has received a number of awards including the Arthur Purdy Stout Prize for significant career achievements in surgical pathology, the Young Investigator Award from the United States and Canadian Academy of Pathology, the Pancreatic Cancer Action Network Medical Visionary Award, and five teaching awards from Johns Hopkins School of Medicine. Dr. Hruban is a member of the Scientific Advisory Board of the Pancreatic Cancer Action Network, The Joseph C. Monastra Foundation and The Michael Rolfe Pancreatic Cancer Foundation, and the Director of Science for The Lustgarten Foundation.