The unifying hypothesis that forms the basis for our research is that pancreatic cancer is fundamentally a disease of inherited and acquired mutations in cancer-associated genes. Our efforts began in earnest in 1991 when a surgeon (Charles Yeo) teamed with a pathologist (Ralph Hruban) and a cancer geneticist (Scott Kern). We obtained one of the first SPORE grants in 1993, and since then many talented physician-scientists have joined the group, fostering new careers and productive collaborative pancreatic cancer research. The team now includes 34 investigators from eight Departments in two Schools (Medicine and Nursing).

I. Clinical Care

The team has its origins in patient care. In the 1970s there was no hope for patients with pancreatic cancer. Ninety percent of patients presented with metastatic disease. The only option for patients with localized disease was surgery, and surgery had a 20-25% operative mortality rate. John Cameron, then Chairman of Surgery, dedicated his career to improving pancreatic cancer surgery. In his hands the operative mortality rate fell to <2%, and large numbers of patients began to come to Hopkins for treatment. The impact of this regionalization of care was dramatic. Statewide in-hospital mortality rate for pancreatic cancer surgery dropped from 17% to 4.9%, and an estimated 61% of this decline was attributable to the increase in share of surgeries performed at Hopkins1. For the first time there was a glimmer of hope.

The large numbers of patients treated at Hopkins provided a unique opportunity to study new therapies and to correlate tumor parameters with patient outcome (see John Cameron’s CV). For example, in a prospective clinical trial of the standard vs. radical Whipple resection the team showed that the two surgeries can be performed with similar mortality.

Building on our surgical successes the team created a multi-disciplinary clinic (http://pathology.jhu.edu/pancreas/mdc/). This clinic provides patients a comprehensive single day evaluation that incorporates all the resources available for patient education, diagnosis, treatment and research of pancreatic cancer. Faculty from the departments of Oncology, Radiation Oncology, Surgery, Gastroenterology, Pathology, and Radiology participate in the clinic. Patients also meet with clinical trials coordinators. The impact of this team approach to patient care has been dramatic. More than 80% of the patients who have attended the clinic have enrolled in a research study.

While these improvements in clinical care provide hope, they clearly are not enough.

II. Genetic Profile of Pancreatic Cancer

The pancreatic cancers surgically resected at Hopkins provided a unique opportunity to study the genetics of the disease. Other than KRAS2, little was known when we first started studying pancreatic cancer back in 1991. Even worse, the desmoplastic stroma that characterizes pancreatic cancer made it almost impossible to obtain the neoplastic cellularity necessary for molecular genetic studies.
Members of the team overcame this hurdle by xenografting resected pancreatic cancers into nude mice. The neoplastic cellularity achieved opened the flood gates for genetic discoveries. Using a homozygous deletion screen, the team discovered the SMAD4/DPC4 gene and demonstrated that it is mutated in 55% of pancreatic cancers\(^2\). This discovery launched the field of TGF signaling in cancer. Using representational difference analysis the team went on to discover a homozygous deletion on chromosome 13q in a pancreatic cancer that greatly facilitated the discovery of the BRCA2 gene\(^3\), and team members were among the first to demonstrate most of the known genetic alterations in pancreatic cancer, including alterations in the p16/CDKN2A, TP53, BRAF, FANCC, FANCG, FBXW7, ACVR2, FHIT, STK11, and M KK4 genes (see Scott Kern’s CV). These discoveries represent the fruits of a team approach - surgeons resecting the cancers, pathologists harvesting the cancers, oncologists xenografting the tumors, molecular biologists analyzing the xenografts using cutting edge technologies, and statisticians validating the results. The impact of this work can be appreciated by the citations it has received. Essential Science Indicators (ESI) reported that the SMAD4/DPC4 paper is the most highly cited paper in all of pancreatic cancer research (http://www.esi-topics.com/pancan/papers/a1.html).

As exciting as these discoveries are, they are not enough. The next challenge became to translate them to improved patient care.

### III. Familial Pancreatic Cancer

Based on Knudson’s Hypothesis, a natural area to apply genetic discoveries to patient care is the familial aggregation of cancer. Again, the team at Johns Hopkins had to overcome significant hurdles. Pancreatic cancer is so rapidly lethal that it is unusual to identify a family with multiple living affected family members. The team rose to the challenge, founding the National Familial Pancreas Tumor Registry (NF PTR) in 1994. To date, close to 2,200 kindreds with pancreatic cancer have enrolled in this registry, including 811 families in which at least a pair of first-degree relatives has been diagnosed with pancreatic cancer. This national resource is shared with investigators outside of Hopkins, and it has formed the basis for a number of key genetic and epidemiologic discoveries. These include the demonstration that inherited mutations in the BRCA2, STK11, p16/CDKN2A, and hMLH1 genes can cause familial pancreatic cancer\(^4\), segregation analyses that support a major autosomal dominant gene as the cause of familial pancreatic cancer, and prospective analyses that quantify the risk of pancreatic cancer in families\(^5\). The team has shown that individuals with three or more first-degree relatives with pancreatic cancer have a remarkable 32-fold increased risk of developing pancreatic cancer.

These results have immediate translational implications. First, based on their family history and genetic status, individuals can be identified who may benefit from screening for early pancreatic neoplasia (see Progression Model and Screening below). Second, the team has shown that pancreatic cancers with BRCA2 or FANC gene mutations are exquisitely sensitive to DNA cross-linking agents (mitomycin C), and we are now conducting a clinical trial in which patients with pancreatic cancer are genotyped for BRCA2 gene mutations. Those found to carry a mutation are treated with specific DNA cross-linking agents.
IV. Progression Model

The first step in screening for any cancer is to define the non-invasive precursor lesions that give rise to that cancer. Integrating careful pathologic examination with molecular analyses, the team at Hopkins has characterized the precursors to invasive pancreatic cancer and defined the relative order in which genetic alterations occur in the development of pancreatic neoplasia (see Ralph Hruban’s CV). These lesions are called Pancreatic Intraepithelial Neoplasia (PanIN), and the team has shown that PanINs harbor many of the same genetic alterations as are found in infiltrating pancreatic cancer. Activating point mutations in the \( \textit{KRAS2} \) gene occur in early lesions (PanIN-1), while \( \textit{p16/CDKN2A} \) is inactivated in PanIN-2 lesions. Inactivating mutations in \( \textit{SMAD4} \), \( \textit{TP53} \) and \( \textit{BRCA2} \) occur in PanIN-3 lesions. The team also discovered that telomere shortening occurs early, contributing to the accumulation of chromosomal abnormalities in PanINs. The Hopkins team has also defined the patterns of expression of selected proteins in PanINs.

The characterization of well-defined precursor lesions by the Hopkins team forms the basis for the chemoprevention and the early detection of pancreatic cancer. It was also essential in generating the first transgenic mouse models that recapitulate the multi-step progression of pancreatic cancer. Extramural investigators actively sought, and received, the collaboration of our team in the histologic and molecular characterization of these early mouse models.

V. Early Detection

Using gene expression platforms including SAGE, and cDNA and oligonucleotide microarrays, the Hopkins team has identified a large number of genes highly overexpressed in pancreatic cancer. The expression of these genes has been validated at the protein level, and several of the new markers discovered by the team are now being brought to patient care as diagnostic markers, as prognostic markers, and as therapeutic targets. For example, the technology serial analysis of gene expression was developed here at Hopkins and was used to discover that mesothelin is overexpressed in pancreatic cancer. Mesothelin is now used as an aid to the interpretation of difficult cytology samples, as a blood marker, and as a therapeutic target in clinical trials (see Michael Goggins’ CV).

The team is also exploring methylation and DNA-based screening technologies that can be used to detect rare DNA alteration. For example, "LigAmp" was developed by the team and can be used to detect rare mutant \( \textit{KRAS2} \) genes in pancreatic juice samples.

We recognize that the currently available blood markers lack the sensitivity and specificity to be used in screening the general population. The team is therefore spearheading efforts to screen asymptomatic at-risk individuals using existing technologies such as endoscopic ultrasound (EUS). In a collaborative effort involving gastroenterologists, the NFPTR, pathologists and radiologists, the team has shown that screening using EUS and computerized tomography (CT) can detect clinically significant asymptomatic pancreatic and extrapancreatic neoplasms in high-risk individuals.
findings form the basis for a national screening study called "CAPS 3" in which risk is quantified based on family history, and high-risk individuals are screened for pancreatic neoplasia using EUS and CT.

VI. Immune Therapies

Overexpressed proteins are also useful in designing immunotherapies. For example, Dr. Elizabeth Jaffee and colleagues developed a whole cell vaccine treatment for pancreatic cancer, and in a recently completed Phase II clinical trial in which patients were treated following Whipple resection, this vaccine produced an anti-tumor immune response and 76% survival at two-years (compared to 45% in non-vaccinated patients). In studies designed to form the basis for the next generation vaccine, the team found that mesothelin, the same protein found to be upregulated in pancreatic cancer in our screening studies, appears to be responsible for the anti-tumor effect seen with the vaccine. This finding provides insight into the immune mechanisms underlying anti-tumor responses, and will form the basis for new peptide based vaccines.

VII. Targeted Therapies/Pathways

The identification of the genes mutated or overexpressed in pancreatic cancer has also helped the team identify cellular pathways disregulated in pancreatic cancer. These pathways are potential therapeutic targets. For example, the team has demonstrated that the Hedgehog pathway is activated in pancreatic cancer and that cyclopamine, a specific inhibitor of the Hedgehog pathway, dramatically reduces pancreatic cancer growth. Anirban Maitra was awarded the Benjamin Castleman Award for the best pathology paper published in the English language in 2004 for this work.

The team has also helped overcome another roadblock in the testing of new therapies - the lack of a good animal model. Steve Leach has developed a zebra fish model of pancreatic cancer, and, as described in a recent JNCI editorial, Antonio Jimeno has developed a parallel xenograft model in which multiple different agents can be tested against a single well-characterized xenografted human cancer. These studies demonstrate how knowledge of underlying molecular abnormalities in tumors can lead to new therapies.

VIII. Classification of Pancreatic Neoplasms:

By integrating molecular analyses with tumor morphology the team has also identified a new type of cancer of the pancreas, the medullary cancer. It has also helped define the genetic alterations in acinar cell carcinomas, in solid-pseudopapillary neoplasms, and in pancreatoblastomas (see Ralph Hruban’s CV). These findings define specific molecular genetic alterations associated with each tumor type. These alterations, in turn, are now used to aid diagnosis. For example, the team showed that solid-pseudopapillary neoplasms of the pancreas have mutations in the beta-catenin gene. These mutations produce an abnormal immunolabeling pattern for the beta-catenin protein which is currently used in surgical pathology clinical practice. In recognition of the impact the
Hopkins team has had on classifying pancreatic neoplasia, Dr. Hruban was selected to be the primary author of the 4th edition Fascicle on tumors of the pancreas.

IX. Recent Recognition/Awards:

Four members of the Johns Hopkins Pancreatic Cancer Team were recently recognized by ESI as being in the Top 10 most highly cited Pancreatic Cancer scientists. Dr. Hruban was recognized as the most highly cited of all of pancreatic cancer investigators. The paper reporting the discovery of the DPC4/SMAD4 gene is the most highly cited paper in all of pancreatic cancer research. Ralph Hruban was awarded the 2006 Medical Visionary Award from PanCAN, the national pancreatic cancer patient advocacy group. Dr. Jaffee was awarded the Outstanding SPORE Investigator in 2006, Anirban Maitra, the Maryland 2006 Outstanding Young Scientist Award, and Scott Kern the Louis Cochet Award for Outstanding Pancreatic Cancer Research.

Reference List


