I am pleased to announce that each of the following members of the nationally recognized faculty of the Division of Gastroenterology at Penn Medicine has been promoted:

MEENAKSHI BEWTRA, MD, MPH — Assistant Professor of Medicine (GI) and Epidemiology, Senior Scholar, Center for Clinical Epidemiology and Biostatistics (CCEB). A graduate of the University of Pennsylvania School of Medicine and an MPH from Harvard, Dr. Bewtra did her medicine residency and GI fellowship at Penn. Dr. Bewtra’s research and clinical interests are in inflammatory bowel diseases (IBD). She sees patients at the Perelman Center for Advanced Medicine.

ANNA BUCHNER, MD, PHD — Assistant Professor of Medicine (GI). A graduate of Wroclaw Medical University in Wroclaw, Poland, and an advanced endoscopy fellowship at Penn. Her clinical and research interests are in colorectal cancers, Barrett’s esophagus, and IBD. She sees patients at the Perelman Center for Advanced Medicine.

KIMBERLY FORDE, MD, MHS — Assistant Professor of Medicine (GI) and Epidemiology, Senior Scholar, Center for Clinical Epidemiology and Biostatistics (CCEB). A graduate of the Columbia College of Physicians and Surgeons, Dr. Forde did her medicine residency at Columbia, her MHS at Johns Hopkins and GI fellowship at Penn. Her research and clinical interests are in liver diseases. She sees patients at the Perelman Center for Advanced Medicine.

MÁAROUF HOTTEIT, MD — Assistant Professor of Clinical Medicine (GI). A graduate of the American University of Beirut, Lebanon, Dr. Hotteit completed his medicine residency and GI fellowship at Emory University followed by a transplant hepatology fellowship at Mayo Clinic (Rochester). His clinical and research interests are in all liver diseases, liver cancer and liver transplantation. He sees patients at the Perelman Center for Advanced Medicine.

"A facility of the Hospital of the University of Pennsylvania.

Pancreatic Cancer Research

Pancreatic cancer is the second most common gastrointestinal malignancy and the fourth leading cause of cancer-related deaths in the United States. Because the majority of patients are diagnosed late in the course of the disease, the prognosis for pancreatic cancer is dismal. More than 95 percent of patients die within five years of diagnosis. There is thus a great need to discover early methods of detection for the disease.

The molecular pathogenesis of pancreatic cancer is being elaborated at Penn and elsewhere, and is known to include mutations of the K-ras oncogene (seen in 90 percent of pancreatic adenocarcinomas), the Hedgehog signaling pathway and the inactivation of the tumor suppressor genes p53 and p16/ink4a, among others.

At Penn’s Division of Gastroenterology, researchers Andrew Rhim, MD, and Ben Stanger, MD, have been investigating oncogenic mutations to identify biomarkers with the potential to aid in the early diagnosis of pancreatic cancer. Their study is representative of recent research in pancreatic cancer at Penn Medicine.

Epithelial-to-Mesenchymal Transition and Hematogenous Dissemination Precedes Histologic Diagnosis of Pancreatic Cancer

Primary Investigators: Andrew Rhim, MD; Ben Stanger, MD.

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Background: Metastatic disease is the predominant mode by which cancer and, particularly pancreatic cancer, kills patients. Indeed, the vast majority of those who are diagnosed with pancreatic cancer also have metastatic disease upon presentation. Of those with limited or small tumors and no radiographic evidence of metastases, many will undergo surgical resection; however, up to 90 percent of all of these patients will eventually succumb to metastatic disease. These clinical observations thus suggest that the seeds of metastatic disease may be established long before pancreatic tumors are detected, or perhaps, form. The current study tests the hypothesis that pancreatic cell dissemination into the blood stream and colonization of distant organs occur prior to tumor formation.

Objectives: To determine when cancer progression epithelial-to-mesenchymal transition (EMT), a
molecular reprogramming event thought to be required for the first steps of metastasis; hematogenous dissemination; and distant organ colonization occurs.

Methods: Two unique lineage-labeled mouse models of spontaneous pancreatic ductal adenocarcinoma (PDAC) were created to study the fate of pancreatic epithelial cells during various stages of tumor progression. Both models relied on the Pdx1-Cre transgenic strain to generate pancreas-specific mutations in Kras and either p53 or Ptenkn4a/Arf, genes that are mutated with high frequency in human pancreatic cancer. The Rosas2YFP allele was introduced in both groups to track the fate of pancreatic epithelial cells, resulting in highly specific and efficient fluorescent labeling (>95% of all pancreatic epithelial cells). Pancreas and blood specimens were analyzed from 1) “PanIN” mice with only the precancerous pancreatic intraepithelial neoplasia (PanIN) lesion and no histologic evidence of cancer by hematoxylin and eosin (H&E) staining [aged 2.2-2.5 mo] and 2) “PDAC” mice harboring pancreatic tumors [aged 3.5-4.5 mo]. Expression of the markers Zeb1 and Epl (independent predictors of mortality in pancreatic cancer) and the absence of epithelial markers E-cad and CK19 were used to detect EMT in YFP+ pancreatic epithelial derived cells as mesenchymal markers. Fluorescent pancreatic cells in the blood stream and the liver were detected using flow cytometry (FACS) analysis and immunofluorescent staining of liver sections. 

Results: Multicolor immunofluorescent (IF) staining for the YFP epithelial lineage label and the mesenchymal markers Zeb1 and Epl revealed double positive (EMT+) cells residing in 2.2% and 17.4% of all PanIN2 and PanIN3 (low- and high-grade dysplasia) lesions, respectively. Further, individual spindle-shaped YFP+ cells were observed invading into the pancreatic stroma of PanIN mice, despite the absence of a pathologic diagnosis of cancer based on H&E staining. Using FACS, YFP+ pancreatic cells were found in the blood of both tumor-bearing PDAC mice and PanIN mice (94.5 ± 35.4, 42.9 ± 20.5 cells/ml blood; p<0.001; n=30) but not in control Pdx-Cre; RosasYFP mice. These circulating YFP+ cells were devoid of CD45 and Ter-119 (markers of white and red blood cells), expressed YFP, E-cadherin and Pdx-1 transcripts, and formed pancreatostromes in attachment-free cultures, a surrogate test for cancer stem cells. Finally, while rare individual YFP+ cells were found in small hepatic veins of PanIN mice, no metastatic lesions were appreciated, such as those seen in PDAC mice.

Conclusions: Using sensitive genetic tools, this study offers evidence that EMT, invasion, and hematogenous dissemination precede conventional histologic diagnosis of PDAC. These data argue against the classical linear progression model of cancer, whereby dissemination occurs after tumors form. Further, it suggests that current tools that are being used to diagnose carcinoma on biopsy specimens may not be sensitive enough to detect the earliest stages of cancer. However, it is still unclear if circulating PanIN cells are the source of metastatic lesions. Nevertheless, based on this data, circulating pancreatic cells may be specific biomarkers for advanced PanIN disease and early pancreatic carcinoma. Clinical trials are planned to translate these results to humans.

The National Cancer Institute recommends that patients with pancreatic cancer be treated at sites it has designated Comprehensive Cancer Centers. Penn’s Abramson Cancer Center is one of only 39 NCI-designated Comprehensive Cancer Centers in the nation.

Invasion, Hematogenous Dissemination and Seeding Precede Pancreatic Tumor Formation

Acute & Chronic Pancreatitis

Chronic pancreatitis (CP) accounts for 80,000 hospital admissions annually in the United States at an estimated annual cost of $2.1 billion. Many patients with chronic pancreatitis are disabled from pain and their disease, leading to far greater indirect costs. Alcohol, smoking and very high triglyceride levels are strong predictors for the development of CP, but the cause of this disease remains unknown in 25 percent of patients even after careful investigation. Among other objectives, clinical research at Penn Gastroenterology is focusing on the race-dependent risk factors for pancreatitis and the identification of biomarkers that will determine the malignant potential of pancreatic cystic neoplasms.

North American Pancreatitis Study 2 (NAPS2): Race- Dependent Genotype-phenotype Associations for the Development of Chronic Pancreatitis and Its Subtypes

Primary Investigators: J. Golub MD, Z. Kercher MD, Primary Contact: Karima S. Wypchuscar, MPH iaron.wypchuscar@uphs.upenn.edu.

Background: In the United States, the rate of chronic and acute pancreatitis among African Americans is about twice that of the white population. Only 63 of 1403 patients with CP enrolled in the NAPS1 study were African American, however, resulting in a sample size insufficient for robust analyses. This study will enroll a cohort of African American patients with CP of sufficient size to permit comparisons with the NAPS1 dataset.

Objectives: To identify genotype, phenotype, epidemiologic, social, medical, surgical, environmental and novel risk factors that lead to the development of nonalcoholic CP, especially in African-Americans. To study whether these risk factors (e.g., obesity, diabetes, race) interact to determine genotype-phenotype associations in CP patients. To quantify pain and quality of life patterns in these CP subtypes in African Americans and try to correlate these to genotype.

Methods: This is a multicenter prospective cohort study performed as an ancillary to the North American Pancreatitis Study 2 (NAPS2) using that trial’s pancreatic cancer markers, including lifestyle, environmental, clinical and imaging data, to subclassify CP in African-Americans. A linked biorepository (serum and DNA) will also be established. These sporadic patients will be tested for known variants in major susceptibility genes for chronic pancreatitis, as well as for associations with genes hitherto unknown to be related to CP (genome wide association studies). These initial genotyping efforts will support analysis of gene-environment interactions to identify specific risk factors and optimal treatment options in African-Americans and permit comparisons with the NAPS2 dataset.

Pancreatic Cysts

Researchers with the Division of Gastroenterology at Penn Medicine are working with the Department of Pathology to investigate ways to better diagnose and differentiate pancreatic cysts and their progression.

Mesothelin: A Potential Biomarker for the Diagnosis of Mucinous Cystic Lesions of the Pancreas

Principal Investigators: Nuzhat Ahmad, MD; Nirag Jhala, MD; Primary Contact: Pari Shah, MD (pari.shah@uphs.upenn.edu).

Background: Optimal management of pancreatic cystic neoplasms depends upon accurate diagnosis. Because it can be difficult to differentiate cystic lesions without malignant potential, (i.e., pancreatic pseudocysts) from cysts with high malignant potential, such as mucinous cystadenoma, cystadenocarcinoma and intraductal papillary mucinous tumors (IPMTs) with and without ductal neoplasms, the diagnosis can be challenging.

Objective: The purpose of this study is to determine if mesothelin expression can be used to differentiate mucinous cystic lesions with low malignant potential from those with high malignant potential, as well as predict the malignant potential of mucinous lesions of the pancreas.

Methods: This study will involve developing a database to perform a retrospective review of all patients who underwent resection for cystic lesions of the pancreas between 2001 and 2009 at the Hospital of the University of Pennsylvania. From this cohort, 20 patients will be randomly selected with MCNs, IPMNs, mucin secreting adenocarcinoma, serous cystadenoma and pseudocysts. Patients may also have prior cytology samples from cyst aspirates. This selection will be stratified according to the trial’s parameters, including lifestyle, environmental, clinical and imaging data, to subclassify CP in African-Americans. A linked biorepository (serum and DNA) will also be established. These sporadic patients will be tested for known variations in major susceptibility genes for chronic pancreatitis, as well as for associations with genes hitherto unknown to be related to CP (genome wide association studies). These initial genotyping efforts will support analysis of gene-environment interactions to identify specific risk factors and optimal treatment options in African-Americans and permit comparisons with the NAPS2 dataset.


PANCREATITIS RESEARCH AT PENN

Inflammation, Hematogenous Dissemination and Seeding Precede Pancreatic Tumor Formation

Immunofluorescence microscopy of pancreas cell seeding of the liver in a mouse model of pancreatic cancer progression. Note: pancreas cells are labeled green. A) Macrometastasis in a liver from a tumor-bearing mouse (PDAC Liver). BPC Individual circulating pancreatic cells seeding the liver at the precancerous PanIN stage (PanIN Liver). Vascular lumens are outlined. A) PDAC Liver B) PanIN Liver C) PanIN Liver