Academic Purpose in Gastroenterology

This issue of Digest provides a glance at how patient care, research, and education at the University of Pittsburgh and UPMC are integrated. Collectively, we are a unique national resource which brings major advances to the care of patients with complex inflammatory diseases of the digestive system.

The Division is structured as a Matrix Academic Division (MAD) which allows for immediate, direct, and comprehensive communication. More than 50 physicians and scientists collaborate with the common purpose of understanding complex digestive diseases. Recently, details of this collaboration were published in Academic Medicine (2011, 26;86.(11):1353-9, PMID 21952059).

We are able to reduce the time for completion of bed-to-bench-to-bed translational research projects from more than 17 years to less than one year.

In this issue, we share two aspects of our translational research program. Dhiraj Yadav, MD, MPH, describes fellow-directed research education through translational projects. This effort utilizes the solid educational background of clinical fellows, and guides them to make advances in the understanding of common digestive diseases. Brian M. Davis, PhD, describes our partnership with UPMC to deliver science-based solutions to personalize medicine and speed research translation to clinics. This program provides an infrastructure for guiding success in high-value projects through clinical questions and available scientific expertise. Information systems and other components of the research program were described in the Spring 2011 edition of Digest. (archived issues may be viewed at UPMCPhysicianResources.com/GI).

Three clinical cases are highlighted by gastroenterology fellows, Matthew Coates, MD, PhD, Jana Al Hashash, MD, and John Scherer, MD. Such select, edited cases have become a highlight of Digest by providing clear illustrations of the presentation and management of unique problems seen by practicing gastroenterologists and hepatologists.

We hope you enjoy this issue. Our physicians are eager to help with tough cases and to provide the best of tomorrow’s medicine, today.
Research Experience during Gastroenterology Fellowship

INTRODUCTION

Dhiraj Yadav, MD, MPH
Associate Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition

Education and research are central to the core mission of the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh and UPMC. The GI division provides an outstanding environment for clinical and research training and enjoys a full training complement of 18 gastroenterology fellows.

In addition to its advanced clinical and procedural training, the Gastroenterology Fellowship provides unique opportunities for clinical and translational research. Early in training, fellowship program leaders meet with each fellow to structure individualized research training to complement long-term career goals.

Depending on unique interests, fellows complete one or more research projects under the supervision and mentorship of clinical and/or research faculty, many of whom are internationally recognized leaders in their field. Typically, protected research time is provided during the second year of fellowship training. Fellows participating in the NIH T32 training and those dedicated to a research career are eligible for up to 18 months of research training.

During the required biweekly journal club, our fellows receive a “mini course” in evidence based medicine and learn how to interpret and critique scientific literature, design a study and write a scientific manuscript.

Opportunities exist for interested fellows to enroll in a formal training program offered through the University of Pittsburgh’s Institute of Clinical Research Education (ICRE) to receive a certificate or masters degree.

At a minimum, each fellow is expected to participate in at least one research project from “start to finish” and publish their findings in a peer-reviewed journal or make an oral/poster presentation at a national or international subspecialty meeting. Most fellows exceed this requirement, and this success is demonstrated by significant productivity in presentations and publications. During the past five years, for example, our fellows have published 39 peer-reviewed papers and have made four oral and ten poster presentations at national annual meetings. Fifteen fellows have received career development awards. During the same time period, 50 percent have accepted academic positions to continue their research endeavors and train the next generation of gastroenterologists. All of the program’s current Year III fellows expect to join academic practices upon graduation.

This issue of Digest highlights the research of four of the six graduating clinical fellows this year, Drs. Venkata Muddana, John Nasr, Amit Raina and Matthew Rockacy.

Dr. Yadav is an associate professor of Medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He works closely with the Division’s 18 gastroenterology fellows and mentors the fellows’ Journal Club.
Amit Raina, MD

My research focuses on pancreatic disorders and nutritional therapy in pancreatitis, with special interests in autoimmune pancreatitis and pancreatic necrosis. As a resident in Dr. David Whitcomb’s laboratory, I studied serum IgG4 levels in patients with pancreatic cancer using single Immunodiffusion Assays. At that time, serum IgG4 was known to be a very specific marker for autoimmune pancreatitis (AIP), and we were able to show elevated levels in about seven percent of cancer patients. Working with Dhiraj Yadav, MD, MPH, I then reviewed our experiences with AIP patients over a ten-year period. Our data confirmed that serum IgG4 was not a very sensitive marker for AIP (44 percent in our cohort). We also learned that AIP is often associated with significant vascular complications. During these chart reviews, we found a high prevalence of inflammatory bowel disease (IBD) in patients with AIP as well, a finding complemented by a 2009 paper by Chari et al. which concluded that AIP increases the risk of IBD seven fold. In this paper, researchers stained colonic biopsies of AIP and IBD patients and found high prevalence of IgG4 cells in colonic biopsies. The Charistudy lacked controls and did not consider or stratify for disease activity. To bridge this gap, I wrote a protocol in collaboration with pathology colleagues. Our group studied the IgG4-laden plasma cells in colonic biopsies in the following groups: patients without IBD undergoing colonoscopy; primary sclerosing cholangitis; primary sclerosing cholangitis patients with IBD; IBD in remission; and IBD during a flare up. This study is currently in progress.

I also am doing a retrospective, chart review of patients with pancreatic necrosis. We are studying about 250 patients seen at UPMC over the past ten years. Data collection includes demographics, laboratory abnormalities, organ failure, SIRS, severity scores, infective complications including development of clostridium difficile infection, antibiotic usage for prophylaxis or treatment, nutritional interventions and their complications, and long term outcomes such as the development of diabetes or chronic pancreatitis. We have already begun to see the change in practice such as use of jejunal feeding using deep jejunal feeding tubes instead of TPN, the latter used in patients prior to 2003/04. It will be interesting to see if this change of practice translates into improved outcomes in these patients.

I am also interested in nutritional therapies for pancreatitis and short-bowel patients and was involved in two retrospective studies which investigated our experiences with feeding tubes in patients with pancreatitis and gastric outlet obstruction. This work was presented as an oral presentation at Digestive Disease Week (DDW) and has been published in peer-reviewed journals as well.

I am honored to collaborate with Jaideep Behari, MD, PhD who is the principle investigator for a study entitled “Biomarkers in Alcoholic and Nonalcoholic Fatty Liver Diseases.” We are prospectively collecting blood samples for patients with alcoholic hepatitis and discriminate factors of more than 32. We hope to conduct a wide array of genomic, proteomic testing on these samples in an endeavor to better understanding the role genes play in predisposing patients to alcohol related hepatitis or to a more virulent course. We plan to investigate whether any serum markers can predict clinical course in these patients.

Venkata Muddana, MD

My research focuses on acute and chronic pancreatitis. I collaborate with Dr. David Whitcomb’s laboratory team to understand the role of complex gene-environment interactions in acute and chronic pancreatitis, including several projects from the North American Pancreatitis Study (NAPS2).

Major NAPS2 reviews study the role of calcium sensing receptor genes and platelet derived growth factors in chronic pancreatitis. Previous studies from Germany and India have shown an association between various CASR genotypes and SPINK1 N34S high-risk haplotypes in subjects with chronic pancreatitis. We screened the CASR exons previously demonstrated to harbor hypercalcemia-associated mutations (i.e., 2–5 and 7) in NAPS2 subjects and found that CASR exon 7 R990G was significantly associated with chronic pancreatitis (p = 0.015, OR 2.01, 95% CI 1.12–3.59). Additionally, the association between CASR R990G and chronic pancreatitis was stronger in subjects who reported moderate or heavy alcohol consumption (p = 0.018, OR 3.12, 95% CI 1.14–9.13).

I was honored to collaborate with project leader Dr. Georgios Papachristou on the Severe Acute Pancreatitis Study (SAPS). We identified and recruited patients with acute pancreatitis, collected clinical data and examined polymorphisms in the inflammatory markers linked with disease severity. Currently, we are investigating genetic polymorphisms of several cytokines and adipokines that are likely to alter the immunological response to pancreatic injury and increase the risk of severity.

Pancreatic necrosis (PNec) has long been recognized as a major complication of acute pancreatitis, which results in significant morbidity and mortality and is included in the Atlanta criteria of severity. Therefore, early identification of patients at risk of PNec is of great importance.

Hemoconcentration on admission (hematocrit > 44%) has been identified as an accurate marker for the development of PNec with a high negative-predictive value of 89 percent, although admission hematocrit positive-predictive value is moderate to low. We demonstrated that peak creatinine levels greater than 1.8mg/dl within 48h of admission were also strongly associated with PNec, with a very high positive-predictive value of 93 percent. Visceral vein thrombosis is one of the complications seen with acute pancreatitis. Morbidity involved with this complication is unknown at this time, and using anticoagulation in this setting is controversial. Currently, I am reviewing our SAPS database to determine the prevalence of thrombosis and the outcomes with this complication.

Endoscopic retrograde cholangiopancreatography (ERCP) has a five to seven percent risk of acute pancreatitis. I am involved in a new study of ERCP patients that collects complications, demographic and clinical data, and blood samples before and after procedures to conduct genomic and proteomic testing. We believe that measuring the cytokines before and after the insult is an ideal setting to study pathophysiology and the process of inflammatory cascades in complex diseases like acute pancreatitis. We are ready to start this interesting project this winter, and our goal is to enroll 100 subjects.

In addition, I also worked with Dr. Dhiraj Yadav on a chronic pancreatitis population-based study using the Pennsylvania Health Care Cost Containment Council (PHC4) dataset. We found that the rates of hospitalization for chronic pancreatitis patients in Allegheny County, Pa., from 1996 to 2005 were 7.75 per 100,000 of the population and did not fluctuate during the study period. Hospitalization rates were significantly higher (2.4-fold) in African Americans compared to Caucasians, particularly for those with an alcoholism diagnosis. This manuscript is in press and will be published in Pancreatology.
Matthew Rockacy, MD

Pancreatic cysts represent a range of clinical entities including congenital, inflammatory and neoplastic, with the latter group including mucinous neoplasms with malignant potential. Once thought to be a rare occurrence, widespread use and improvements in abdominal imaging have led to an increase in the identification of pancreatic cystic lesions, many of which are neoplastic, and for which the natural history is not understood completely.

My research, done under the mentorship of Dr. Asif Khalid, focuses on endoscopic ultrasound (EUS) with fine needle aspiration (FNA) and cyst fluid analysis for the evaluation of pancreatic cysts. The aims of my research are to provide long term follow up of patients with pancreatic cysts and to determine which, if any, features at the time of the index EUS-FNA evaluation are predictive of the development of pancreatic cancer, mucinous pathology, and cyst progression, stability or resolution. These features include patient demographics and clinical presentation, cyst size and morphology, and cyst fluid analysis. For the first time, our analysis includes long term follow up of patients with cyst fluid DNA analysis obtained at the time of the index EUS.

A total of 134 patients who underwent EUS-FNA with cyst fluid DNA analysis were included in this study, and the mean follow up period was approximately four years. Our results to date may be summarized as:

1) The presence of symptoms and a solid component on EUS are considered the most important predictors of outcome,
2) In the absence of these findings, a KRAS mutation and an elevated cyst fluid CEA level are associated with mucinous pathology, and
3) A KRAS mutation and cyst size over 3cm are associated with pancreatic surgery, pancreatic cancer and pancreatic cancer related death.

John Nasr, MD

Advancements in endoscopy have allowed improved therapeutic and diagnostic yields, facilitating treatment for patients with a multitude of pancreatic and biliary diseases.

With mentorship from Drs. Adam Slivka and Georgios Papachristou, my current studies focus on endoscopic research. I am interested in advancing endoscopic therapies, especially improved biliary drainage through biliary stenting and other therapies for biliary disease.

Recently, our group published the first report of biliary cutaneous fistula healing using the Rendezvous technique. Rendezvous procedures are combined endoscopic and percutaneous techniques which facilitate the establishment of intra- and extra-hepatic biliary access. These procedures have been used to restore anatomic drainage in cases where retrograde and/or trans-hepatic access has failed.

Our research team is conducting a prospective randomized trial which compares plastic to metal stents for treatment of malignant biliary obstruction. This study assigns patients with malignant biliary obstructions to receive either a metal stent or two plastic stents. This study will facilitate assessment of stent efficacy in these patients and will issue a cost analysis comparison.

Two recent book chapters have been published by our group as well. “Colonic Stents as a Bridge to Surgery in Patients with Colonic Obstruction” may be found in Self-Expanding Stents in Gastrointestinal Endoscopy, by Dr. Douglas Adler. Our chapter was written under the mentorship of Dr. Andres Gelrud and discusses the multiple aspects of colonic stent usage prior to colonic surgery, particularly in the setting of colonic obstruction. Additionally, the AGA Educational Review Manual in Gastroenterology included our chapter, “Biliary Stents” in it most recent edition. Dr. Adam Slivka provided mentorship for this chapter, which describes all aspects of biliary disorders and is considered a major reference for review of the biliary system.

Through this current research, we hope to provide additional insights into biliary diseases and improved therapy for patients.
A 66-year-old Caucasian male presented with acute-onset, stabbing epigastric pain, which developed two days prior to presentation and one hour after eating. The patient never had similar pain; it was constant, stabbing and radiated to his back. He had one episode of nausea and vomiting. Past medical history was notable for a remote history of gallstone pancreatitis, ITP diagnosed two years ago, coronary artery disease complicated by myocardial infarction, hypertension, type 2 diabetes, and GERD. Previous surgeries included laproscopic cholecystectomy and CABG. Current medications included furosemide, cyclobenzaprine, oxycodone, pregabalin, esomeprazole, carvedilol, ramipril, atorvastatin, and insulin. Medications were not changed during the past year and family history was unremarkable. He is married with three children and denied alcohol, tobacco, or illicit drug use.

The patient’s vital signs included temperature 38.3°C, heart rate 105 beats/min, blood pressure 138/72, respiratory rate 22/minute, and pulse oximetry 94% on 3L NC. Physical exam revealed a mildly tachypneic, diaphoretic gentleman with icteric sclerae and jaundice. Bilasial rales were present. Moderate epigastric abdominal pain was elicited with palpation. No rebound, hepatosplenomegaly, peripheral edema, spider angioma, caput medusa, or asterixis were detected.

Labs were notable for WBC 9.6, hemoglobin 15.1, platelet 20, BUN 12, creatinine 0.9, alkaline phosphatase 159, GGT 237, total bilirubin 6.9, direct bilirubin 4.5, AST 274, ALT 330, Lipase 5862 (ULN=393), amylase 434 (ULN=115), INR 1.2. A CT scan of abdomen and pelvis with IV contrast was notable for mild diffuse pancreatic edema with mild peripancreatic inflammatory stranding consistent with mild acute pancreatitis in addition to right-sided intrahepatic biliary dilatation. No pancreatic necrosis was evident. Following platelet transfusion, an ERCP was performed, since clinical history, laboratory data, and imaging were all consistent with acute pancreatitis due to biliary obstruction. ERCP revealed oozing of heme from the papilla prior to instrumentation. A cholangiogram revealed a large filling defect in the distal common bile duct (CBD) with proximal CBD dilation (Figure 1). Due to thrombocytopenia, neither endoscopic sphincterotomy nor papillary balloon dilation were performed. A plastic 10 French by 7cm stent was placed for biliary decompression, followed by immediate brisk flow of dark red blood consistent with hemobilia (Figure 2).

While the patient was observed in ICU, his hemoglobin dropped from 15.1 to 8.0. A STAT CT angiogram showed no active bleeding, but detected an infiltrative hepatic lesion with bile duct invasion. Cirrhotic-appearing liver morphology raised suspicion for hepatocellular carcinoma (HCC).

Bleeding ceased spontaneously without intervention. Further tests were notable for AFP 2, CA 19-9 524, CEA 1.6, and a negative chronic liver disease workup. MRI with Eovist detected a hypervascular 3.9 x 3.5cm segment 8 lesion (Figure 3). Targeted liver biopsy confirmed a diagnosis of HCC with background cirrhosis.

This is a case of HCC presenting as acute pancreatitis due to tumor invasion of the biliary tree with resultant hemobilia. Few similar cases have been reported in the literature. HCC invasion of the biliary tree occurs in approximately 2% to 9% of cases based on autopsy series. HCC biliary involvement can be classified by direct biliary invasion with associated hemobilia, bile duct tumor thrombus with resultant biliary obstruction, or extrinsic biliary compression. Biliary tumor invasion is most commonly associated with infiltrative HCC and a worse prognosis due to higher rates of portal vascular invasion and intrahepatic metastasis. Some case reports describe successful treatment of intractable hemobilia with hepatic artery embolization or radiofrequency ablation, although hepatectomy is the only definitive therapy.

After CBD stent placement, the patient’s liver function tests normalized. He recovered from acute pancreatitis quickly, and his hemoglobin remained stable. Considering his multiple metabolic syndrome risk factors, NASH seemed to be the likely etiology of underlying cirrhosis, and the diagnosis of ITP likely represented an early manifestation of portal hypertension rather than actual ITP. Currently, the patient is considering sorafenib or transarterial chemoembolization (TACE), since he is not a liver transplant candidate.

References:
A Young Woman with Upper Gastrointestinal Tract Bleeding

Jana Al Hashash, MD
Gastroenterology Fellow
Division of Gastroenterology, Hepatology, and Nutrition

A 19-year-old female presented to the emergency department with abdominal pain and gastrointestinal bleeding. She reported diffuse abdominal pain starting four days prior to admission with nausea and vomiting on the day of admission. Emesis was initially bilious but subsequently became bloody. She experienced two episodes of melena on the day of admission as well. The patient had a history of a hypercoagulable state resulting from a JAK-2 mutation and was known to have portal vein thrombosis along with splenic vein and superior mesenteric venous thromboses and esophageal varices, yet she had no prior history of gastrointestinal bleeding. Warfarin had been prescribed to promote anticoagulation, but she was noncompliant until four days prior to admission at the onset of abdominal pain.

The patient was awake and alert at presentation but appeared anxious. Blood pressure was 90/55 mm Hg, and an abdominal examination was unremarkable. Laboratory studies revealed hemoglobin of 7.6 g/dL and INR of 2.1. After fluid resuscitation, blood transfusion, and correction of coagulopathy, an emergent upper endoscopy was performed. Moderate-sized varices were found in the distal esophagus, and small nonbleeding gastric varices were revealed. A suspicious lesion was visualized in the duodenal bulb (Figure A).

A contrast-enhanced CT scan of the abdomen was performed which showed extensive thrombosis of the portal venous system with portal cavernoma formation (Figure B). Endoscopic ultrasound confirmed the presence of periduodenal varices (Figure C), and a subsequent visceral angiogram revealed extensive portal venous system thrombosis and presence of large intraabdominal collaterals that precluded placement of a transjugular intrahepatic portosystemic shunt (TIPS). Diagnosis was determined as upper gastrointestinal bleeding from an ectopic varix in the duodenal bulb. The patient elected to undergo surgery with creation of a venocaval shunt to decompress the portal hypertension.

This patient had been stable on warfarin therapy but stopped anticoagulation and nonselective beta-blocker therapy one month prior to her presentation. Most likely, she developed additional thromboses of the portal venous system resulting in abdominal pain and further increases in non-cirrhotic portal hypertension, all leading to duodenal varix bleeding. An upper endoscopy performed four months prior to the patient’s presentation showed no duodenal varices. Venous porto-systemic collaterals present in locations other than in the most commonly encountered locations (i.e., esophagus and proximal stomach) are called ectopic varices. The duodenum is a common site of bleeding ectopic varices, including massive upper gastrointestinal bleeds. Treatment options for bleeding ectopic varices include standard intensive care and fluid resuscitation, use of vasoactive drugs such as octreotide, and early endoscopy to identify the bleeding source. Limited data exists about endoscopic management of ectopic varices, but TIPS, when feasible, and surgical shunts, are viable long-term treatment options.

References:

Figure A: Source of the upper GI bleed (duodenal ectopic varix).
Figure B: CT scan of the abdomen revealing the portal cavernoma.
Figure C: Endoscopic ultrasound appearance of the duodenal varix.
Pittsburgh Gut Club 2012

The Pittsburgh Gut Club is a gastroenterology education and networking series designed to bring novel and relevant subspecialty advancements to the Pittsburgh region. All gastroenterologists, interested physicians, and allied health professionals are encouraged to attend.

“I am pleased to announce the Pittsburgh Gut Club 2012 lineup,” reports Robert Schoen, MD, MPH, professor of Medicine and Epidemiology at the University of Pittsburgh’s Division of Gastroenterology, Hepatology and Nutrition, and course director, Pittsburgh Gut Club. “We have another terrific panel of speakers, and I hope you will take advantage of this opportunity to expand your GI knowledge and socialize with your hometown, professional colleagues.”

The Gut Club’s 2012 season will welcome the following nationally recognized speakers:

Thursday, March 8 at University Club
Preventing Neoplastic Progression in IBD: The Link Between Inflammation and Dysplasia
Thomas A. Ullman, MD
Associate Professor of Medicine
Director, Center for IBD
Division of Gastroenterology
The Mount Sinai Medical Center
New York, NY

Thursday, April 5 at Pittsburgh Athletic Association (PAA)
Food Allergy: Update on Novel Therapies and Eosinophilic Esophagitis
Robert A. Wood, MD
Professor of Pediatrics
Director, Division of Allergy and Immunology, The Johns Hopkins School of Medicine
Professor of International Health
The Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Thursday, May 10 at University Club
Hepatitis C Virus in the Era of Direct-Acting Antivirals
Paul J. Pockros, MD
Head, Division of Gastroenterology and Hepatology
Director, Center for Liver Diseases
Director, Scripps Clinic Liver Research Consortium
Scripps Clinic
La Jolla, CA

All Gut Club presentations will include a networking reception and dinner. Pittsburgh Gut Club membership at the $150 level is requested from physicians. Membership will enable participants to attend all three 2012 lectures. Per-presentation admission is available for $50 per lecture. Trainees may attend for free but must register.

The University Club is located in the Oakland section of Pittsburgh at 123 University Place. The Pittsburgh Athletic Association also is in Oakland at 4215 Fifth Avenue.

For more information, visit Educational & Training Programs at www.dom.pitt.edu/gi.
PancreasFest 2012

**PANCREATIC CANCER: RISK, EARLY DETECTION, DIAGNOSIS AND TREATMENT**

JULY 26 – 27, 2012

THE UNIVERSITY CLUB
123 University Place
Pittsburgh, PA 15213

SAVE THE DATE!

The Division of Gastroenterology, Hepatology, and Nutrition, in conjunction with the University of Pittsburgh School of Medicine, is pleased to sponsor the annual PancreasFest conference on July 26 – 27, 2012. This year’s conference will discuss the risks, importance of early detection, diagnosis, and treatment of pancreatic cancer, including both acute and chronic pancreatitis.

PancreasFest 2012 is open to all gastroenterologists, surgeons, researchers, and related health care professionals interested in pancreatic disease research and clinical care. Education programs will be interspersed with investigative research meetings to further the multidisciplinary understanding and treatment of pancreas diseases.

To learn more information about PancreasFest2012, visit www.pancreasfest.org. To register, please contact Joy Jenko Merusi in the Division of Gastroenterology and Nutrition by calling 412-578-9518, or e-mail joj2@pitt.edu.

Online CME Opportunities

**Sepsis: Systemic inflammation gone wrong**
Derek C. Angus, MD, MPH, discusses the strengths and weaknesses of current pathophysiological models in the management and treatment of systematic sepsis in the hospital setting.

**Risk factors and Markers for Severe Acute Pancreatitis**
Georgios Papachristou, MD, reviews important markers for the diagnosis of severe acute pancreatitis, including the risk factors.

Visit UPMCPhysicianResources.com/GI to view these courses.

Discovery Channel Physician Podcasts

**Personalized Care: A New Approach to Diagnosing & Treating Pancreatic Disease**
David Whitcomb, MD, PhD, Giant Eagle Foundation professor of Cancer Genetics and division chief, and Adam Silvka, MD, PhD, professor of Medicine and associate chief for Clinical Services, discuss their team’s approach to clinical treatment and research advances.

**Crohn’s Disease: A New Paradigm for Patient care**
Miguel Regueiro, MD, discusses medical advancements which can, in some patients, lessen IBD surgery.

Visit UPMCPhysicianResources.com/Discovery to view these videos.
UPMC Support for Translational GI Research

By Brian M. Davis, PhD

We are living in a time of great promise for biomedical research. It will soon be cost-effective to sequence the entire genome of individual patients. Vaccines and antibody therapies are being developed that target tumor cells with specific mutations on a patient-by-patient basis. Basic science techniques make it possible to produce animal models of human disease that express specific pathologic changes and symptoms found in patients.

These advances result from well-integrated translational research collaborations between clinicians and basic science investigators. Unfortunately, funding for this type of research, from both private and government, has been declining and will likely continue to do so.

To address this crisis, our academic gastrointestinal (GI) group has partnered with UPMC to support new research projects that will contribute to the direct improvement of patient outcomes. Our division asked me to serve as associate chief of research to coordinate this new approach. I will help faculty to develop strong collaborative projects and prepare grant applications for translational research to rapidly advance patient care.

My laboratory studies development and plasticity within the sensory nervous system. Since arriving in Pittsburgh in 2001, I have focused on how disease and injury of visceral organs lead to persistent pain, the number one reason for doctor visits in the United States.

Our biggest current project supports a multi-investigator research program, directed by fellow faculty member Eva Szigethy, MD, PhD, (Psychiatry/GI), which combines clinical and laboratory studies of the role that inflammation plays in the development of depression in Crohn’s patients. Patients often present with a combination of inflammatory bowel disease, depression, and pain. We will learn if depression treatment also controls the inflammation and pain, and whether treating the inflammation and pain (using different drugs) can reduce depression. The clinical trial will be paired with animal studies led by faculty member Anthony Bauer, PhD that combine the seminal features of the disease: inflammation, psychological stress, and bowel resection. Data from the human studies will allow us to validate the animal models, which will in turn be used to identify underlying disease mechanisms and develop novel therapies.

For this project, my lab is focusing on the interactions between inflammation, psychosocial stress, and pain. We are particularly interested in the pain neurons that innervate the gut and in gene expression changes that occur in response to various insults. Previous studies from my lab have shown that inflammation of the viscera leads to an increase in receptors (TRPV1) that are responsible for the sensations of heat and spiciness associated with eating chili peppers. These receptors appear to be required for the development of inflammatory hyperalgesia in several tissues, and drugs that block these receptors can prevent both inflammation and pain.

We are also working with current GI fellow and future faculty member, David Levinthal, MD, who is exploring the potential of transcranial magnetic stimulation (TMS) to treat functional GI disorders. Dr. Levinthal has mapped portions of the cerebral cortex that control visceral function, and he is exploring the use of TMS to regulate neural activity in specific brain circuits. If successful, his technique will offer patients a non-pharmacologic method to control organ function, such as gastric emptying.

Additionally, we are using new research approaches to learn when and how pancreatic cancer cells first occur, so we can identify blood tests or other diagnostic measures of early disease. We are using a unique transgenic mouse line engineered by Ronald DePinho, MD, from the M.D. Anderson Cancer Center that expresses the same mutations found in the majority of patients with pancreatic ductal adenocarcinoma and develops cancers that are
remarkable similar to those seen in humans (see photo). We are breeding these mice with a second line that adds a fluorescent tag to the tumor cells. We will use this new line of mice to determine when metastatic cells first arise, to identify biomarkers that correlate with the appearance of these cells, and, hopefully, to gain clues to prevent these cells from invading other organs.

Figure 1. In situ appearance of normal (A) and cancerous (B) pancreas at 18.3 wks of age. These mice express the same genetic mutation in the Kras gene seen in ~90% of patients with pancreatic ductal adenocarcinoma and are missing one copy of the P53 tumor suppressor gene, which also occurs in the majority of patients. In the Kras/p53 mice, the glandular morphology of the pancreas has been replaced by rigid, segmented compartments. By 30 to 40 weeks, these cancers form large masses that invade the mesentery, and white islands of metastases can be seen in the liver.

The new UPMC research funding will allow us to use these and other powerful tools and collaborations among physicians and scientists to explore the mechanisms responsible for disease. Our task as academic researchers is to take advantage of the discoveries that, with a little help, can be brought into the clinic and improve patient care.


Dr. Davis is a Professor of Medicine and is the Associate Chief for Research with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition.


**Faculty Updates**

**Miguel Regueiro, MD**, professor of medicine and co-director and clinical head of the Division’s IBD Center, will serve as the 2011-2012 National Chair for Professional Education on the Crohn’s & Colitis Foundation of America’s National CCFA Medical & Science Advisory Board.

Two division faculty members were recognized at the 2011 Curriculum Colloquium by the University of Pittsburgh School of Medicine (UP SOM) Curriculum Colloquium for outstanding service:

**Patricia Eagon, PhD**, associate professor of medicine was honored for her exceptional master educator contributions to the training of medical students. Dr. Eagon received the Kenneth E. Schuit Award, which honors basic science and clinical faculty for education-related contributions to the UPSOM curriculum.

**Shahid Malik, MD**, clinical assistant professor of medicine in the division’s Center for Liver Diseases, was recognized as a 2011 Clinical Educator of the Year at this UPSOM Colloquium for providing outstanding clinical education for third or fourth year UPSOM medical students.

WHAT IS THIS?
A 17-year-old female with no known past medical history presented with a two-year history of dysphagia. She described a sensation of material “getting caught” behind her sternum once daily. Typically, symptoms occurred only with smaller quantities of solid foods and “rapid gulping.” Ingestion of larger food boluses or increased fluid intake often improved symptoms. Physical examination and labs (CMP, CBC) were unrevealing. The patient underwent an upper GI series and Magnetic Resonance (MR) angiogram of the chest.