The gastroenterology team at the Perelman School of Medicine at the University of Pennsylvania School of Medicine and the University of Pennsylvania Health System is nationally recognized for clinical research and supravital care of its patients. I am pleased to announce the following honors and accomplishments of its faculty:

JONATHAN KATZ, MD, has been elected to the American Society of Clinical Investigation, a national society and honor for physician-scientists.

BEN STANGER, MD, and ANDREW RHIM, MD, published a landmark paper on circulating pancreatic cells from pre-cancerous lesions:


Columbia University and the UNIVERSITY OF PENNSYLVANIA have collaborated on the first animal model of Barrett’s esophagus:


RESEARCH IN GASTROINTESTINAL MEDICINE AT PENN

Penn Gastroenterology researchers are advancing the understanding of the intricate pathophysiology of gastrointestinal disease. Gastrointestinal research has historically been an important focus at Penn Medicine. Thus, this issue of the Division of Gastroenterology newsletter focuses on the Division’s substantial contribution to the field of basic research and the rapid translation of that research into improved care at the Hospital of the University of Pennsylvania and other Penn facilities. The Division of Gastroenterology has realized dramatic growth in the past 15 years. With a cadre of new and established faculty recruited from among the nation’s finest research institutions, and the many developed within Penn, a consequent increase in the number, complexity and diversity of research has occurred throughout the institution.

Funding for the division’s research programs has seen significant increases, as well. National Institutes of Health (NIH) grants make up nearly 95 percent of the research portfolio at Penn. Total research is over $14 million/year. The GI division is currently home to one of only 16 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) P30 GI/Liver Centers in the United States, several U01/U54 multiconsortia grants (imaging and translational medicine in GI cancers, intestinal stem cells, Barrett’s esophagus, drug-induced liver injury, viral hepatitis B, liver transplantation) and a program project in esophageal cancer.

The division also receives a variety of training and lectureship grants to support the education of clinical investigators and physician scientists. The numerous educational initiatives under way at the division include a highly esteemed NIH undergraduate student scholar program; a “sabbatical” program that permits Penn medical students to devote a year of their education to research supported by the NIH; a GI pathophysiology module for medical students; and the division’s renowned GI fellowship program. Supported by two NIH training grants, the GI fellowship program at Penn attracts the best medical residents in the country.

I hope you find this report, which highlights two of the many important research efforts within the Division of Gastroenterology at Penn, both informative and useful.
Biliary atresia (BA) is the leading indication for liver transplantation in children. The condition is characterized by a progressive fibroinflammatory process that leads to the obliteration of all or part of the extrahepatic biliary tree, and manifests in the neonatal period. Surgery (i.e., Kasai portoenterostomy) in infancy is required in virtually all cases to permit bile drainage. Approximately two-thirds of children with the disease ultimately require a liver transplant due to overwhelming fibrosis (deposition of scar tissue). Biliary atresia is uncommon (~1/15,000 live births) and has no known cause. Most researchers suspect it occurs in genetically susceptible patients who receive an environmental exposure (potentially a virus or toxin) late in gestation; however, no specific exposure has ever been identified, and the nature of the bile duct damage that leads to biliary atresia is not known.

This may soon change as a result of the combined efforts of Rebecca Wells, MD, and Michael Pack, MD, at the Perelman School of Medicine and their collaborator John Porter at the University of Pennsylvania. Dr. Wells’ laboratory studies mechanisms of liver fibrosis, while Dr. Pack’s laboratory uses zebrafish models to study the development of the biliary system. Dr. Wells’ interest in biliary atresia began in 2004 when Elizabeth Rand, MD, medical director of the liver transplant program at Children’s Hospital of Philadelphia (CHOP), urged her to investigate the mechanism of fibrosis in this disease. Several years later, while gathering background material on the disease, Dr. Wells discovered that there had previously been developed assays to identify biliary damage in zebrafish.

To identify the molecular structure of the plant toxin, Dr. Wells and Dr. Pack contacted John Porter, PhD, an experienced natural products biologist at the University of the Sciences in Philadelphia. Dr. Porter agreed to fractionate the plant in an attempt to isolate a toxic fraction. The team was able to import the plant samples in 2008. For the next 16 months, Dr. Porter fractionated the plant and Dr. Pack tested the fractions to determine whether they caused biliary damage in zebrafish. Throughout this process, they received support from the Biesecker Center and the University of Pennsylvania NIDDK Center for Molecular Studies in Digestive and Liver Diseases.

In July 2009, Dr. Pack found that exposure to a highly purified fraction of the plant caused damage to the gallbladders and extrahepatic bile ducts of zebrafish, mimicking biliary atresia—a new animal model of the disease. In February 2012, Dr. Porter’s team identified the structure of one of the toxins, a compound never before described. These data were used to optimize protocols to collect, process and sequence bacterial 16S rDNA from fecal samples in subsequent studies. Fecal Storage Methods (FSM)

This initial study was designed to systematically evaluate methods for surveying bacterial communities in human feces using 454/Roche pyrosequencing of 16S rDNA sequences, generating a total of 797,276 tags. Fecal samples from 10 individuals were analyzed and compared made of methods for fecal storage, DNA purification and sequence acquisition and assembly. These data were used to develop potential therapies for biliary atresia. The collaborators have recently been awarded four years of funding from the NIH to further this line of research.

Zebrarh assay for biliary abnormalities. A) normal fish with arrowhead on right showing location of the gallbladder and asterisks showing the intestine. B) normal fish showing uptake of fluorescent lipids into the gallbladder (white arrowhead). C) toxin-treated fish showing lack of uptake of lipids into the gallbladder (location of gallbladder shown by white arrowhead). Photo courtesy of Michael Pack, MD.

Diet, Genetic Factors, and the Gut Microbiome in Crohn’s Disease

With Frederic Bushman, PhD, of the Department of Microbiology at the Perelman School of Medicine, Gary Wu, MD, and James Lewis, MD, MSCE, of Penn Gastroenterology have initiated a series of studies to investigate the relationship between alterations in the human gut microbiome and the pathogenesis of Crohn’s disease and colitis. The large intestine is home to one of the most densely populated microbial communities on earth, with the number of bacteria exceeding host cells by more than ten-fold. The aggregate of all human gut bacteria, or microbiome, holds 100 fold more genes than those of its host. These microbiota provide a metabolic diversity that, among other benefits, aids in the digestion of foods and the development of the immune system. Alterations in the gut microbiome are associated with numerous diseases, however, including opportunistic infections such as C. difficile colitis and inflammatory conditions such as Crohn’s disease.

Dr. Wu, Bushman and Lewis of Penn have previously examined the role of diet in modulating the gut microbiota composition. More recently, they have initiated a series of studies, as part of the NIH Human Microbiome Project, to investigate the hypothesis that dietary therapy leads to consistent changes in the gut microbiota that are associated with clinical response in Crohn’s disease. The investigators are using deep sequencing to characterize the composition of the gut microbiome. Described below are two completed studies, FSM and COMBO, and a third study (known as PLEASE) that is ongoing.

Fecal Storage Methods (FSM)

Currently under way, this study examines the effects of an elemental diet treatment on pediatric patients diagnosed with inflammatory bowel disease (IBD), particularly Crohn’s disease. Elemental diet therapy is often effective in treating pediatric Crohn’s disease. This study permits investigators to examine the microbiome changes associated with successful therapy, failed therapy and relapse. Longitudinal studies allow the investigators to specify microbial changes associated with successful or failed elemental diet therapy.