UPMC Inflammatory Bowel Disease Center

by Miguel D. Regueiro, MD

Idiopathic inflammatory bowel diseases (IBDs), Crohn’s disease and ulcerative colitis, are characterized by chronic, intermittent inflammation of the gastrointestinal tract. Incidence appears to be increasing at a dramatic rate, and etiology remains unknown but likely involves genetic predisposition, environmental influences and a dysregulated immune response. The past ten years have heralded an explosion of IBD research and the advent of novel therapies. Today, IBD management requires integration of gastroenterology and surgical care and an understanding of the risks and benefits of novel biologic therapies. Future progress relies on genetic and immunologic discoveries made in the laboratory and translated to clinical care. The UPMC Inflammatory Bowel Disease Center is uniquely equipped to meet the new and progressive treatment challenges of these diseases.

Located in the Oakland section of Pittsburgh, the UPMC IBD Center is an innovative, internationally recognized program that has enjoyed tremendous growth over the past five years.

As a structural and functional entity designed to attract and care for IBD patients, the IBD Center has successfully incorporated gastroenterologists, surgeons and nutritionists. In addition to comprehensive primary care for patients, specific IBD Center attention is directed to cancer surveillance, women’s health, intestinal rehabilitation and transplantation medicine, and the transition of care from the pediatric to adult gastroenterologist. As such, the IBD clinical care is offered at the UPMC Presbyterian campus by David Binion, MD, Leonard Baidoo, MD and myself, while Janet Harrison, MD sees patients at the Magee-Womens Hospital of UPMC.

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Inflammatory Bowel Disease Center physicians (L to R): seated Dr. Andrew R. Watson (surgery), Dr. Richard H. Duerr, Dr. David G. Binion; standing Dr. Leonard Baidoo, Dr. Miguel D. Regueiro, Dr. Janet R. Harrison, Dr. Wolfgang Schraut (surgery). For more information about UPMC’s IBD Center, visit http://www.dom.pitt.edu/gi/ibd.html.
The University of Pittsburgh Medical Center has made a major investment to strengthen its inflammatory bowel disease (IBD) program into a major center of excellence. This issue of Digest highlights the translational research that is a priority for this Center. Related to our programs, “translation” is discovering basic mechanisms of disease in human subjects and translating this knowledge into “personalized medicine.” Personalized medicine, in turn, is the process of integrating all relevant variables which lead to a disease in an individual patient and designing a patient-specific treatment plan to manage that disease and its complications. With revolutionary advances in IBD genetics, innate and mucosal immunology, vascular biology, regenerative medicine, epidemiology, detailed patient phenotyping and the use of advanced medical-record information systems, we believe that we are very close to reaching this goal.

The UPMC IBD Center, one of the fastest growing programs of its type in the country, manages over 1,000 patients and continues to expand as additional physicians are recruited and integrated into the program. These benchmarks and Center goals are described by Miguel Regueiro, MD in the cover story. This clinical foundation is critical to the evaluation and assessment of new treatment strategies.

We also highlight specific projects that our faculty and fellows have accomplished or are developing. The IBD genetics team, led by Richard Duerr, MD with Dr. Regueiro and M. Michael Barmada, PhD has made major contributions to the discovery of more than 30 Crohn’s disease and ulcerative colitis genes. The next translative step, as outlined by Arthur “Tripp” Barrie, MD, PhD, a senior fellow focusing on immunology, is to understand how these genetic variants lead to disease. The pathology of IBD encompasses the complex nature of intestinal mucosa and is the research focus of Ian McGowan, MD, PhD. David Binion, MD, our newest faculty member and translational researcher in IBD, describes his innovative and exciting research focused on vascular biology and regenerative medicine.

This basic research, plus clinical projects on IBD in women, racial variations and variable responses to medical or surgical therapy are being brought together with the goal of bringing personalized medicine to patients with IBD.

In good health,

David C. Whitcomb, MD, PhD
Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition

Faculty Member’s Cookbook Promotes Healthy Eating

Division faculty member Julia B. Greer, MD, MPH, has published The Anti-Cancer Cookbook, a novel review of the relationship between the foods we eat and cancer.

Dr. Greer is an assistant professor of medicine with the University of Pittsburgh Division of Gastroenterology and Nutrition, where she works as an epidemiologist, focusing on pancreatic, ovarian and breast cancers.

With The Anti-Cancer Cookbook, Dr. Greer has written an excellent cookbook to promote better food choices and to explain how these choices can reduce cancer risk. The recipes are informative and easy-to-read and include foods that are bulky, satisfying and low in calories.

The Anti-Cancer Cookbook is available at Barnes & Noble stores and at amazon.com.
The connection of immunology investigation and inflammatory bowel disease (IBD) research is a promising field, and such clinical applications have begun to change the course of IBD treatment over the past decade. My research lab focuses on the mucosal pathogenesis and prevention of HIV infection. Interestingly, the similarities and differences between HIV infection and IBD hold great promise in understanding both of these diseases.

Approximately one million Americans have HIV infection, and more than 50,000 new infections occur each year. With the advent of potent combination antiretroviral therapy (ART), patient prognosis has improved dramatically. It is unusual to see patients present with opportunistic enteric infections such as microsporidiosis, unless they present late in the course of their infection or have treatment failure associated with the development of ART resistance. However, it has become clear that HIV has a unique relationship with gut associated lymphoid tissue (GALT), and the mucosal immunology of HIV infection has become a critical new frontier in research on the treatment and prevention of HIV infection.

The most striking immunological deficit associated with HIV infection is the progressive CD4+ T cell lymphopenia that occurs in the peripheral blood following HIV infection. GALT CD4 lymphopenia has been documented using immunohistochemical and flow cytometric techniques. Recently, a number of investigators have characterized the mucosal pathogenesis of simian immunodeficiency virus (SIV) or recombinant SIV/HIV (SHIV) in non-human primates and of early HIV infection in humans. These findings have been dramatic. It appears that approximately 50 percent of GALT CD4 lymphocytes are lost within weeks of acute HIV/SIV infection, and this observation was seen in both human and primates studies. Mattapallil, et. al. were able to demonstrate that 60 percent of GALT CD4+ T cells are infected in the primate acute infection model. This observation suggests that the acute loss of CD4+ T cells may, indeed, be directly related to viral infection. Further studies have documented that the use of ART is associated with recovery of the GALT CD4 lymphopenia (Figure 1), although the timing and magnitude of recovery remain controversial.

Mucosal cytokine expression is increased in HIV infection, and the degree of abnormality appears to be related to the level of mucosal viral replication. Using immunohistochemical techniques, Olsson et. al. were able to show increased expression of the proinflammatory cytokines RANTES, MIP-1a, and MIP-1b equivalent to the changes seen in active IBD. Recently, Brenchley et al. have suggested that a key step in the mucosal pathogenesis of HIV infection is a disruption of the epithelial barrier, which allows passage of luminal bacteria into the lamina propria resulting in low-grade infection that stimulates mucosal inflammation. A similar effect has been described in HIV-positive patients with hepatitis C infection. Researchers debate whether an HIV-associated idiopathic proctitis/colitis can occur in the absence of enteric infection that is distinct from Crohn’s disease or ulcerative colitis but which responds to treatment with thalidomide. We presume that the nonspecific histological changes seen in HIV-associated proctitis/colitis occur secondary to the mucosal inflammation induced by HIV infection.

Mucosal T cell dysfunction plays a critical role in IBD pathogenesis, and it is logical to hypothesize that the T cell changes associated with HIV infection may alter the pathogenesis of IBD in patients diagnosed with both conditions. It has been suggested that CD4 lymphopenia may reduce Crohn’s disease severity, whereas the increase in TH2 cytokine responses seen in HIV might exacerbate ulcerative colitis. The anecdotal HIV/IBD case literature does not provide comprehensive support for these hypotheses currently, and future developments may be further confused by the degree of immune reconstitution associated with ART.

References upon request.

Dr. McGowan is a professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. His clinical practice and research laboratory are located at Magee-Womens Hospital of UPMC.
Inflammatory Bowel Disease (IBD) is characterized by an aberrant immune response against normal gut flora in genetically predisposed individuals. The first IBD susceptibility gene was discovered in 2001, when University of Pittsburgh Medical Center researchers, as part of a multistitutional effort, reported that mutations in the NOD2 gene are associated with Crohn’s disease. UPMC researchers Richard Duerr, MD and M. Michael Barmada, PhD, working in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium and its European counterparts, have shared in the identification of more than 30 distinct susceptibility loci for Crohn’s disease.

The accelerated rate of gene discovery during this decade has been fostered by Human Genome Project knowledge in combination with more sophisticated molecular techniques and bioinformatics. In contrast to pioneering genetic studies that began by testing single nucleotide polymorphisms (SNPs) individually, geneticists now perform genome wide association studies on microchips via the analysis of 300,000 to over a million SNPs at a time. Essential to the recent success of IBD genetic studies is the rigorous recruitment and phenotyping of IBD patients, facilitated by Miguel Regueiro, MD, research coordinator Joann Fultz, Leonard Baidoo, MD, David Binion, MD and Janet R. Harrison, MD. As one of the largest IBD centers in the United States, UPMC has contributed more study subjects for IBD genetics studies than any of the other NIDDK IBD Genetics Consortium participating institutions.

Genetic studies have elucidated cellular functions and signaling pathways previously unknown and/or unassociated with IBD. For example, the discovery of the NOD2 gene enhanced our understanding of intracellular bacterial sensors within innate immune cells and the intestinal epithelium implicating the innate immune response in IBD pathogenesis. Additionally, the NOD2/IBD association further strengthened the hypothesis that IBD is mediated by an abnormal immune response against bacteria. Subsequent genetic studies highlighted the significance of another intracellular process, autophagy, through the identification of the auto-phagocytic gene ATG16L1. Autophagy protects mammalian cells against bacterial pathogens and toxins via the intracellular compartmentalization and elimination of bacteria. Consequently, ATG16L1 mutants increase the risk for Crohn’s disease, possibly by predisposing intestinal epithelial cells to apoptosis.

Identification of multiple susceptibility loci in the interleukin-23 (IL-23) signaling pathway was a major breakthrough in IBD genetics. The IL-23 signaling pathway augments IL-17 expressing T helper (Th17) cells which regulate the immune response against various extracellular pathogens, and, in certain situations, promote chronic inflammation. Dr. Duerr and colleagues discovered that various genetic alterations in the IL23R gene markedly alter a person’s risk for IBD. This finding makes more relevant mouse models of IBD where disease can be prevented or improved by blocking IL-23 and helps to explain why IL-23/IL-12 specific antibodies induce clinical responses in Crohn’s disease patients. Thus, the IL-23 pathway is seminal to IBD pathogenesis and will likely become an important therapeutic target.

Clinical relevance of the IBD susceptibility loci remains limited, as we do not yet understand how the gene variants alter immune cell function and IBD pathogenesis in patients. Dr. Duerr and I, in collaboration with Anuradha Ray, PhD, professor of medicine and immunology, are investigating this question with a novel translational study. We are isolating immune cells from the blood and intestines of healthy controls and IBD patients and analyzing immune cell development and differentiation, receptor signaling, and gene and protein expression. Observations will be correlated with the subjects’ genotypes. This approach is critical to the development of personalized medicine for IBD patients to ensure that the right person receives the right medicine at the right dose at the right time. Importantly, this work has broader implications, as our findings in IBD relate to and enhance our understanding of other genetically related, immune-mediated diseases.
Emergent Plan “B”

by Shahid Malik, MD  
Gastroenterology Fellow

Case Presentation

A 49-year-old Caucasian female with no significant past medical history was in good health, until she presented to an outside hospital with a five-day history of nausea, fatigue and general malaise. One day prior to admission she developed abdominal discomfort and “coke colored urine.” Married for 25 years, she lived with her husband and 15-year-old son and worked full time as a bank teller until the day of admission. There was no recent travel or contacts with other illness. She denied any history of tobacco, alcohol or illicit drug use and was taking no prescription or over-the-counter medications.

Initial physical exam was notable for a temperature of 100.5°F and a heart rate of 100 beats per minute. She appeared ill but was awake with good mentation. She was jaundiced with scleral icterus, and her abdomen was soft with no hepatosplenomegaly, but she had tenderness in the right upper quadrant.

Labs were notable for a WBC count of 6,000/L with normal differential, normal electrolytes and renal function but significant hypophosphatemia (1 mg/dL). Liver function tests revealed a total bilirubin of 4.6 mg/dL, AST 3700 IU/L, ALT 6500 IU/L, AP 240 IU/L and an INR of 1.5. A CT scan of the abdomen revealed an ‘edematous’ gallbladder with thickened wall, but normal caliber common bile duct (CBD). The initial concern at the outside hospital was a CBD stone. GI was consulted to consider ERCP. Two days after presentation, she was transferred to UPMC Presbyterian.

Upon arrival, the patient’s INR had risen to 11.5 (PT > 100 seconds). Within 12 hours of transfer the patient’s mental status rapidly declined with increasing somnolence and the development of asterixis. AST and ALT declined precipitously to 700 IU/L and 2500 IU/L respectively.

Serologies revealed HBsAg +, HBcIgM + and HBV DNA 135,000 IU/mL. The patient was diagnosed with Acute Liver Failure (ALF) secondary to hepatitis B viral (HBV) infection. She was listed ‘status 1’ and underwent orthotopic liver transplantation within 48 hours of arrival at UPMC Presbyterian. The patient did well after surgery and was discharged two weeks after transplant.

The patient’s husband had been diagnosed with HBV infection three years earlier, and he was being treated with antivirals. Because of finances, however, he stopped taking his medications six months prior to his wife’s admission.

ALF is a rare condition with only approximately 2,000 cases per year in the U.S. In ALF, rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals. The most common cause of ALF in the U.S. is acetaminophen toxicity.

ALF secondary to HBV develops in less than one percent of patients infected with the virus. Without liver transplantation, fatality rate is 93 percent. There are approximately 50 cases of ALF due to HBV in the U.S. each year. If detected in time, transplantation can be life-saving, with a one year survival of approximately 85 percent.

Transmission of HBV among adults is through sexual contact predominantly. HBV is a preventable disease and all adults with potential exposure risk should be offered vaccination.
Bridging the Gap from Scientific Discovery to Improved Patient Treatment

by David G. Binion, MD

The ability to understand human disease mechanistically at a molecular level is the core of translational research, a growing area of biomedical investigation. Translational investigators bring scientific expertise to the clinic and hospital bedside to deepen our understanding of disease processes and improve care for the sickest patients, where cures have remained elusive. Successful translational researchers require a strong scientific foundation in such disciplines as molecular biology, immunology and related disciplines as well as highly developed clinical skills obtained during subspecialty training. A commitment to years of additional training can be daunting for young physicians, and the numbers of translational investigators have dwindled over the past decade, to the point that the NIH has made the training of these highly valuable individuals a priority.

In this context, it was with great excitement that I joined the Division of Gastroenterology, Hepatology and Nutrition this past summer to lead its efforts in translational IBD research. It has been my honor to care for more than 1,700 IBD patients during my tenure with the Medical College of Wisconsin, and I look forward to additional clinical involvement here at UPMC.

My clinical research interests explore the natural history of severe IBD phenotypes, better treatment algorithms, and improved strategies for patients’ medical and surgical options. I am particularly interested in patient groups with severe and refractory Crohn’s disease and ulcerative colitis. Defining and characterizing individuals who have suffered from the most severe complications of IBD represents a fundamental step in stratifying patients based on their unique natural histories and enables physicians to conduct appropriate risk-benefit therapeutic assessments and understand the beneficial effects of drug therapy on natural history. My philosophy has been that every clinical encounter is data. When we are dealing with an incurable, lifelong illness, it is essential that all opportunities to understand patient phenotypes, natural histories, responses to therapy and important complications of both disease and treatment be defined.

With basic science interests focusing on the microvascular biology of human chronic intestinal inflammation, I am interested in the development of protocols for the isolation and long-term culture of microvascular endothelial cells isolated from chronically inflamed IBD intestine as well as normal margins of surgically resected bowel. My research group has demonstrated fundamental alterations in the nitric oxide biology of gut vascular cells exposed to chronic inflammatory stress. Mechanistically, this underlies microvascular endothelial dysfunction in the IBD intestinal microcirculation, where blood vessels demonstrate an impaired ability to vasodilate, or to regulate inflammatory activation. This investigation is significant, as none of our current therapeutic strategies for IBD target microvascular dysfunction, suggesting new avenues for the treatment of refractory patients.

Pitt has become a top ten institution for biomedical investigation in the U.S., and its premier record in IBD genetics and clinical care are testimony to the efforts of Drs. Richard Duerr and Miguel Regueiro, who have lead the IBD Center over the past several years. I look forward to complementing their talents through mechanistic insight into these diseases.

Dr. Binion is a visiting professor of medicine, and he directs the University of Pittsburgh’s program in Translational IBD Research and co-directs the Division of Gastroenterology, Hepatology and Nutrition’s IBD Center. Dr. Binion has received the Premier Physician Award from the Crohn’s & Colitis Foundation of America, and he has been named to the Top Doctors list in Milwaukee Magazine as well as Best Doctors in America from 2001 to the present. Dr. Binion sees patients at UPMC Presbyterian and at a UPMC McKeesport IBD satellite clinic.
Barrett’s Esophagus Specialist’s Treatment (BEST) Clinic: Major Focus of the Digestive Disease Center

Barrett’s Esophagus (BE) describes the presence of an abnormal type of cell in the esophagus lining, which is thought to be a complication of gastroesophageal reflux disease (GERD). Many Barrett’s patients are concerned about increased cancer risk, and “best” treatment approaches continue to be debated.

Division of Gastroenterology, Hepatology and Nutrition faculty members, Kevin McGrath, MD and Kenneth Fasanella, MD, specialize in BE non-surgical diagnosis and treatment. Drs. McGrath and Fasanella analyze and compare current treatment options based on disease severity and unique features of the patient. Based on UPMC’s large patient volume, a growing demand for expert evaluation and our gastroenterologists’ utilization of effective new therapies, additional resources and dedicated clinical space have been allocated to expand the Barrett’s Esophagus Specialist’s Treatment (BEST) Clinic in a multidisciplinary approach.

UPMC’s BEST Clinic will promote meaningful advances concerning Barrett’s Esophagus through innovative research and focused teaching, complemented by outstanding clinical care. The Best Clinic will match the recognized success of the Division’s IBD Center (focus of this issue), Pancreaticobiliary Center, Center for Liver Diseases and other UPMC digestive disease programs. For more information on the BEST Clinic or to refer patients for evaluation please contact Ms. Emily O’Connor at 412-648-9325.

UPMC IBD Center
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IBD Center has integrated care of Crohn’s disease and ulcerative colitis patients at the University of Pittsburgh Medical Center with the Pittsburgh Cancer Institute, Magee-Womens Hospital of UPMC, the Thomas E. Starzl Transplantation Institute and Children’s Hospital of Pittsburgh. Such service collaboration across specialties provides IBD patients with “one stop shopping” for expert consultations and superior diagnostic techniques. The IBD Center continues to attract increasingly large numbers of patients from the tri-state area and beyond.

IBD Center goals coordinate success in the following complementary areas:

- Immediate patient access to IBD specialists at multiple locations within the UPMC system;
- High quality patient outcomes related to medical management, social/emotional support, surgical success, and delivery of innovative therapies; and
- Integration of patients into clinical, epidemiological, genetic and basic science research programs.

The IBD Center has capitalized on its clinical strengths due to exciting advancements from internationally recognized IBD bench researchers. The Center includes well established physician scientists and clinical researchers including Richard H. Duerr, MD in IBD genetics, David Binion, MD in the novel field of IBD regenerative medicine, and senior GI fellow Arthur “Tripp” Barrie, MD, PhD in IBD immunology.

Research highlights featuring the work of Drs. Binion and Barrie are discussed in this issue of Digest. Such research advances improve patient care daily and may one day yield a cure for IBD.

Dr. Regueiro is an associate professor of medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He serves as the associate chief for education, the program director for the Division’s Gastroenterology Fellowship Program and the co-director and clinical head of the UPMC IBD Center.
What Is This?

Presentation: A 46-year-old Caucasian male with schizophrenia was admitted with six months of progressive weakness, ataxia, altered mental status and suspected normal pressure hydrocephalus. During hospitalization, he was found to have persistent fevers, bilateral deep venous thrombosis and pulmonary emboli, and HIV testing was positive with a CD4 count of 388. A colonoscopy was performed for anemia, weight loss and need for chronic anticoagulation. At ten centimeters from the dentate line, this small ulcerated lesion was seen and biopsied (see figure below).

Compare your answer to Dr. Collinson’s answer on page 6.

Welcome to New Fellows

The Division of Gastroenterology, Hepatology and Nutrition is pleased to welcome the following Year I Gastroenterology Fellows:

David Broki, MD – (M) University of Virginia School of Medicine, (R) University of Pittsburgh Medical Center

Su Min Cho, MD – (M) Royal Free & University College Medical School / UK, (R) University of Pittsburgh Medical Center

Kofi Clarke, MD – (M) University of Ghana, (R) Temple University / Western PA Hospital Campus

Julie Holinga, MD – (M) The Ohio State University College of Medicine, (R) Washington University

Priya Roy, MD – (M) The Ohio State University College of Medicine, (R) Beth Israel Deaconess Medical Center

Ari J. Wiesen, MD – (M) Albert Einstein College of Medicine, (R) Long Island Jewish Medical Center

Bahar Madani, MD – (M) Tehran University of Medical Sciences, (R) Rochester General Hospital

(M) = Medical School
(R) = Residency

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