Cincinnati Children's

2015 Research Annual Report

Gastroenterology, Hepatology, and Nutrition

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	**37**
Joint Appointment Faculty	**2**
Research Fellows	**9**
Research Students	**9**
Support Personnel	**45**
Direct Annual Grant Support	**$6,054,898**
Direct Annual Industry Support	**$558,000**
Peer Reviewed Publications	**120**

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	**71**
Staff Physicians	**3**

Clinical Fellows	**13**
Other Students	**2**
Inpatient Encounters	**9,501**
Outpatient Encounters	**19,827**

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Research Highlights

Diarrhea and Malnutrition

The mission is to improve the prevention and treatment of childhood diarrhea and undernutrition by implementing best practices and creating new knowledge through bench-to-bedside research collaborations between Cincinnati Children's Hospital Medical Center and global partners. C. Cole, MD, MPH, MSc; S. Huppert, PhD; S. Moore, MD, MS; and S. Saeed, MD, FAAP, AGAF, have established individual partnerships with investigators in Brazil, Ghana, Nigeria and Pakistan focused on micronutrient deficiencies (zinc and iron), undernutrition, diarrheal diseases, and environmental enteropathy. Dr. Cole and colleagues at the Federal University of Bahia, Brazil recently completed and published the results of a clinical trial using micronutrient sprinkles in at-risk children enrolled in a daycare.

Dr. Aldo Lima at Federal University of Ceará and Dr. Moore's research groups have recently completed IMAGINE (Interventions and Mechanisms of Alanyl for Inflammation, Nutrition, and Enteropathy), a clinical dose-response trial of alanyl-glutamine supplementation in 140 children with environmental enteropathy in the Brazilian semi-arid, and are now leveraging biospecimens from IMAGINE for biomarker discovery. Drs. S. Hogan, PhD (Division of Allergy and Immunology), Huppert, and Moore continue to collaborate on novel mouse models of environmental enteropathy. Last, Dr. Moore is engaged in NIAID-supported collaborations with the University of Cincinnati (Christian Hong, PhD; Alison Weiss, PhD; and Yana Zavros, PhD) and Cincinnati Children's Michael Helmrath, MD, MS (Division of Pediatric General and Thoracic Surgery) and James Wells, PhD (Division of Developmental Biology) to model *Helicobacter pylori*, Shiga toxin-producing *E. coli*, and *Clostridium difficile* in human gastrointestinal stem cell culture models.

Digestive Health Center: A catalyst for research on digestive disease

The Digestive Health Center (DHC) directed by Jorge Bezerra, MD, and managed by Cynthia Wetzel, PhD, is one of only 17 Silvio O. Conte Digestive Diseases Research Core Centers in the U.S., and the only one dedicated to pediatric diseases. The center seeks to improve diagnosis, treatments and outcomes for chronic liver disease, inflammatory and diarrheal diseases and obesity. It does so by enabling investigators to have timely access to state-of-the-art technologies at four cores: Integrative Morphology, Gene and Protein Expression, Bioinformatics, and Pluripotent Stem Cell and Organoid Cores. With 94 investigators, the DHC contributes to the research goals of faculty from 22 divisions in the Department of Pediatrics and eight other departments of the University of Cincinnati, College of Medicine. This year, the DHC welcomed seven new center investigators; collectively, DHC investigators have $30.6 million in extramural research funds. The DHC's successful Pilot and Feasibility Program has distributed $1.45 million among 35 junior investigators since 2007. These investigators have since attracted $27.9 million in extramural grant funding. In addition to an outstanding record of publications with 135 peer-reviewed articles during the past 12 months, the following center investigators received national and international recognition for their clinical, research, and educational accomplishments:

- Theresa Alenghat, VMD, PhD, became a PEW Scholar.
- Jorge Bezerra, MD, was elected to the Association of American Physicians.

- Patricia Fulkerson, MD, PhD, received the 2015 Young Physician-Scientist Award from The American Society for Clinical Investigation.
- Michael Rosen, MD, MSCI, and Pranavkumar Shivakumar, PhD, were elected to the Society for Pediatric Research.

Cincinnati Center for Eosinophilic Disorders (CCED)

The Cincinnati Center for Eosinophilic Disorders (CCED) is an established multidisciplinary referral center for evaluation and treatment of eosinophilic gastrointestinal disorders in children. Physicians representing the Divisions of Gastroenterology, Hepatology and Nutrition; Allergy and Immunology; and Pathology provide comprehensive clinical services supported by experienced nurses, dieticians, psychologist and social workers. More than 100 new patients are evaluated per year, many of whom are referred from outside the local catchment area.

Most of the patients seen agree to participate in clinical, and basic science, research studies. Clinical research has included important studies of both dietary and pharmacologic management of eosinophilic esophagitis (EoE). Prospective and retrospective studies were completed in collaboration with P. Backeljauw, MD, and M. Golekoh, MD, from the Division of Endocrinology to evaluate the effects of swallowed glucocorticoids (employed to treat eosinophilic esophagitis) on growth and adrenal function, revealing a small but important subset of patients who develop adrenal suppression while taking these medications.

Dr. Marc Rothenberg's (Allergy and Immunology) laboratory, and collaborators, have continued to investigate the genetic and immunologic factors responsible for eosinophilic inflammation in the gut. In the past year, genetic studies have included a study of twins who have eosinophilic esophagitis, revealing that both genetic and environmental factors are necessary for development of the disease. A genome wide association study (GWAS) further clarified the genes responsible for making the esophagus a target for eosinophilic inflammation; in particular, this effort has led to the identification of calpain-14 as a causative pathway in directing eosinophils to the esophagus and raised the possibility of enzymatic blockade of this pathway as a possible therapeutic strategy. Recent efforts have highlighted the role of IL-13 in eosinophilic esophagitis pathogenesis, and the preliminary positive effects of antibodies against IL-13 in human patients with EoE. This has led to a number of therapeutic trials in which the CCED is an active participant. The CCED was also the site for identification and development of a novel molecular diagnostic test for EoE, which has now been commercialized and made available clinically. A novel study has started the process of expanding our understanding of eosinophilic gastritis, using techniques employed previously for studying the esophagus, including elucidation of the transcriptome.

Physicians within the CCED participate in the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGiR), which is funded by the National Institutes of Health (NIH) as part of the Rare Diseases Clinical Research Network. Dr. Rothenberg is the principal investigator of this project, which has four primary pieces, including: Clinical Research Projects, a Pilot/Demonstration Clinical Research Program, and the Training (Career Development) Program. There is also an administrative component centered at Cincinnati Children's that directs and coordinates the activities of these programs. In addition, the CCED (with Dr. Rothenberg as principal investigator) is also the central site for a new Patient Centered Outcomes Research Institute contract for a multicenter trial examining the efficacy of minimally restrictive empiric diets in the management of pediatric eosinophilic esophagitis.

Interdisciplinary Feeding Team

Under the GI leadership of Scott Pentiuk, MD, and Vince Mukkada, MD, the Interdisciplinary Feeding Team (IFT) provides comprehensive evaluation for children with swallowing/feeding disorders. This multidisciplinary team includes experts from the Divisions of Gastroenterology, Hepatology and Nutrition; Otolaryngology; Human Genetics; Speech-Language Pathology, Occupational Therapy and Physical Therapy, Social Services, and Nutrition Therapy. The IFT evaluated over 1,200 patient visits in FY15. In addition to comprehensive consultation and care, the IFT offers unique treatment sessions and parent-child interaction training for families. Ongoing research projects by IFT investigators include the use and

development of a pureed by G-tube diet, methods to evaluate children with swallowing dysfunction, and a quality improvement project to decrease patient wait time during clinic visits.

Intestinal Rehabilitation and Intestinal Transplantation Program

The expanding clinical profiles of the Intestinal Rehabilitation Program (IRP) and the Intestinal Transplantation Program continue to fuel the translational and clinical research conducted by both programs. A circumspect, thoughtful approach to intestinal rehabilitation has obviated the need for intestinal transplantation for many of the patients referred for transplantation. The mission is to provide the best possible care for children with intestinal failure through innovation. Outcomes for both intestinal rehabilitation and intestinal transplantation are excellent. Indeed, since 2008, there is a one year survival of 100% for intestinal transplantation, and central line associated blood stream infection rate of <2/1000 catheter days is among the best in North America. As the lead center in a recently completed multicenter pediatric clinical trial funded by NPS Pharmaceuticals for Teduglutide (Gattex®) staff are actively involved in the analysis of the data and publication of the results. Additional studies include the use of fish-oil derived lipid (Omegaven®) to prevent chronic liver disease associated with the use of parenteral nutrition, the efficacy of ethanol lock therapy for bloodstream infection prevention in patients with central venous catheters, and analysis of the value of selective decontamination of the small bowel in intestinal transplant recipients. Among the pre-clinical studies is the effect of oral galacto-oligosaccharide supplementation upon growth and weight gain in weanling rats (Ethan Mezoff, MD) and cutting edge research on the differentiation of stem cells into intestinal organoids (Michael Helmrath, MD, MS). Jaimie Nathan, MD, was honored by receiving a highly competitive grant from the American Society of Transplant Surgeons to study microbiome changes in stool and intestinal tissue, and to correlate them with diminution of the Treg population in tissue and blood during intestinal allograft rejection.

Liver Care Center

The Pediatric Liver Care Center provides comprehensive care for children with liver diseases. Staffed by eight pediatric hepatologists; four hepatobiliary surgeons; and three specialty nurses, the program serves a national and international referral population via a comprehensive evaluation of all medical and surgical aspects of liver disease. The evaluation includes a full spectrum of metabolic analysis, inflammatory processes, and gene sequencing techniques to diagnose mutations that cause clinical phenotypes. The multidisciplinary nature of the comprehensive care makes the center a “one-stop-shop” in which the timely consultation with surgeons, pathologists, radiologists, and nutritionists with expertise in pediatric liver disease optimizes patient care. It also catalyzes patient-based research, which is critical to improved outcomes.

Physicians, surgeons and scientists in the center are performing exciting research with the goal to discover the causes and pathogenesis of pediatric liver disease, and to design new therapies to block progression of liver injury. Focusing on advances in the past year, the work by J. Bezerra, MD; A. Miethke, MD; and P. Shivakumar, PhD, have focused on understanding the mechanisms of biliary injury, and biomarkers and new treatments for biliary atresia. One key finding was the discovery of a molecular signature in livers of children with the disease (published in *Hepatology*). Dr. Miethke also studies sclerosing cholangitis, and recently found that molecular blockade of the intestinal bile acid receptor improves experimental cholestasis and chronic cholangitis (published in *Hepatology*). Dr. Goldschmidt found that the coexistence of heterozygous mutations in two or more genes is more frequent in children with chronic liver disease. To further advance knowledge of how mutations result in liver disease, these investigators are collaborating with C. Yin, PhD, to study how genetic mutations in children with cholestasis cause liver injury and impaired biliary secretion using novel approaches that combine human tissue, exome sequencing and zebrafish models. S. Huppert, PhD, is using unique mouse models to uncover cellular and molecular pathways that promote recovery of the biliary system in children with chronic cholestasis.

Several lines of important clinical investigation are opening new diagnostic and treatment options for children with liver disease. M. Leonis, PhD, leads the study of acute liver failure in children; and W. Balistreri, MD, and J. Bezerra are

conducting new clinical trials to determine: 1) the efficacy of Tenofovir in children with chronic hepatitis B infection: and 2) the efficacy of direct acting antivirals to completely eradicate hepatitis C virus during childhood. Dr. Miethke leads studies to determine whether molecular inhibition of the intestinal receptor for bile acids improves cholestasis in children with Alagille syndrome and other inherited syndromes of intrahepatic cholestasis.

Liver Transplantaion

The mission of the Pediatric Liver Transplant Program is to advance the care of liver transplant recipients by improving the health care delivery system; providing unparalleled clinical care; addressing gaps in knowledge through patient-based and basic laboratory research; and serving as advocates for organ donation and allocation in our community and country. As one of the largest pediatric liver transplant programs in the country, more than 560 liver transplants have been performed since the program began in 1986. Patient and graft survival rates are at, or above, the national average at one month, one year and three years post-transplant. In addition to providing care for the most common pediatric liver disorders leading to transplantation, staff are able to leverage institutional strengths to provide care and the best outcomes available to a number of patients with rare diseases and extremely complex needs. This includes children with advanced liver tumors. Since 2007, the Cincinnati Children's Liver Transplant Team has performed more pediatric liver transplants for hepatic tumors than any other program in the United States (a total of 29, 15% of all transplants). Survival for this high-risk group is excellent, with one, three, and five-year survival rates of 90%, 88% and 81% respectively (compared to 85%, 81% and 80% for all pediatric transplant recipients nationwide).

In addition to providing outstanding patient care, the Liver Transplant Program is a leader in national quality improvement efforts and multicenter clinical and translational research studies. These include: Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients (iWITH), the Studies in Pediatric Liver Transplantation (SPLIT) quality improvement community and clinical registry, the Clinical Trials in Organ Transplantation in Children (CTOT-C) research initiative, and multiple local projects and initiatives.

Neurogastroenterology and Motility

Under the leadership of Ajay Kaul, MD, the Neurogastroenterology and Motility Disorders Program has seen unprecedented growth (46% increase) over the past year, with 624 outpatient encounters seen by three providers. Last year, we received about 20 new referrals per month, primarily from patients outside of our primary service area. Patients came from 30 states, as well as 32 from outside the country. In addition, the Neurogastroenterology team, in collaboration with the Alberto Peña, MD, Colorectal Center, started an interdisciplinary clinic in July 2014 to evaluate and treat children with complex colorectal and motility disorders such as Hirschprung’s disease and severe idiopathic chronic constipation with a goal to improve patient outcomes through standardization of practice and clinical research. In the first year, the team saw about 60 medically complex patients for second opinions from all over the country and overseas. This rapid growth resulted in a significant increase in the number of diagnostic and therapeutic procedures performed over the past year. As an example, there was a 30% increase in the performance of manometry procedures compared to last year. The plan is to expand our services to the Cincinnati Children's Liberty Campus this winter with the addition of a third neurogastroenterologist, Dr. Khalil El Chammas this fall. Exploring new research opportunities, the program was selected as a trial site to investigate the efficacy of Linaclotide in children with functional constipation.

Pancreas Care Center (PCC)

The team mission is to provide comprehensive multidisciplinary management of pancreatic disorders that strives to improve patient outcomes through focused expertise, standardization of care and clinical research. The program is led by Joseph Palermo, MD, PhD; Tom Lin, MD; and Maisam Abu-El-Haija, MD, in collaboration with Jaimie Nathan, MD, (Surgery) and Deborah Elder, MD, (Endocrinology) currently follows 100 patients with various pancreatic disorders including pancreatitis, pancreatic insufficiency, congenital anomalies of the pancreas, and pancreatic tumors. With its inception in 2013, the program has already completed a survey of Cincinnati Children’s providers to better understand the

variation in management of acute pancreatitis; assembled a multidisciplinary care team to evaluate and treat complex pancreatic disorders; established a REDCap database for patient registry; and instituted an evidence based order set for the management of acute pancreatitis. In 2015, the team successfully completed the first two total pancreatectomy and islet autotransplantation surgeries (TPIAT) for treatment of unremitting pain and prevention of brittle diabetes in chronic pancreatitis.

Research highlights for this past year include three projects: 1) demonstration that standardization of care for acute pancreatitis improves outcomes; 2) development of a prognostic tool to stratify pediatric patients at risk for severe acute pancreatitis; and 3) identification of the optimal timing of cholecystectomy in patients with gallstone pancreatitis. The team is now investigating the role of genetic factors in differentiating chronic pancreatitis from other forms of pancreas inflammation. Staff are also on the forefront of genetic testing in recurrent and chronic pancreatitis with the development of a gene chip that will screen the 12 known genes associated with increased risk of recurrent pancreatitis which will soon be commercially available. In addition, the Pectus Program of Cincinnati (PPC) participates in the INSPPIRE consortium for pediatric chronic pancreatitis and, in association with the National Pancreas Foundation, has organized the first annual Pancreatitis Education Day for families and providers at Cincinnati Children's.

Schubert-Martin Inflammatory Bowel Disease (IBD) Center

More than 700 patients with inflammatory bowel disease (IBD) are seen in the Division of Gastroenterology, Hepatology and Nutrition and the IBD Center. Close to 100 new patients are diagnosed annually, and close to 90 second-opinion patients are seen by the physicians of the Schubert-Martin Pediatric IBD Center from more than 25 states, and abroad. These numbers reflect a 33% increase in total patient volume, and a 347% increase in second opinions over the last five years.

The center is an integral and leading participant in collaborative consortia like the ImproveCareNow Quality Improvement Network, and the Crohn's and Colitis Foundation's PRO-KIDS Clinical Research Network. This role is reflected in superior outcomes for patients with more than 80% of IBD patients within the center being in remission, 58% in sustained remission, and 84% having a good quality of life. These outcome measures are shared transparently on the center's website. Our Annual IBD Family Education Day, co-hosted by the local chapter of Crohn's and Colitis Foundation continues to be one of the largest educational events of its kind in the country. A rejuvenated and energized Parent Advisory Board has been established to partner with center providers and identify priority areas for improvement, education, increased awareness and community involvement with an active Facebook page.

Physicians within the center continue to develop and lead basic, translational and clinical research in identifying key etiopathogenic mechanisms for inflammatory bowel diseases, minimally invasive biomarkers for predicting disease flares and remission, development of mobile phone apps for patient engagement and self management, transition of patients to adult providers, and pilot testing of eVisits. Results were reported in the *Journal of Clinical Investigation* of a comprehensive analysis of the ileal global pattern of gene expression and microbial community in several hundred newly diagnosed pediatric Crohn's disease patients. In this paper we identified novel host anti-inflammatory pathways and beneficial microbes which will now serve as new therapeutic targets. Findings reported in the *Inflammatory Bowel Diseases* journal about the development of a novel biomarker for intestinal inflammation, CD64, showed that patients with low levels of CD64 experience much higher rates of sustained remission. This biomarker has now entered clinical practice at Cincinnati Children's, and will next be tested as part of a multi-center clinical trial. Collaborations within the institution and the James M. Anderson Center for Health System Excellence, the Division of Behavioral Medicine and Clinical Psychology, the Center for Adherence and Self-Management, the Division of Pediatric General and Thoracic Surgery, the Division of Allergy and Immunology, the Division of Adolescent and Transition Medicine, and the Department of Radiology continue to make significant contributions to finding a cure as well as improving outcomes and self-management skills for children suffering from IBD.

Steatohepatitis Center

Ongoing research to understand and treat Nonalcoholic Fatty Liver Disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is led by S. Xanthakos, MD, MS, and R. Kohli, MBBS, MS. They lead the Cincinnati Children's Steatohepatitis Center (CCSC) is a multidisciplinary program that provides care to a growing population of children and adolescents with NAFLD and NASH, the most common causes of liver disease in the United States, and an increasing cause of liver transplantation. NAFLD may begin in childhood and progress to severe fibrosis in early adolescence. Thus, early identification and intervention is critical to prevent progression to end-stage liver disease.

With data from over 300 children and adolescents with NAFLD/NASH, center investigators collaborate with the Center for Better Health and Nutrition, The Sleep Center, Hypertension and Lipid, the Diabetes Center and the Surgical Weight Loss Program for Teens.

Seminal research highlights include the high prevalence, phenotype and gene expression signatures of NAFLD in adolescents undergoing bariatric surgery, and the high prevalence of hepatitis B non-immunity in pediatric NAFLD patients. Team investigators maintain a robust bio-specimen repository to facilitate translational work and work as a leading pediatric site in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded NASH Clinical Research Network (NASH-CRN), a multi-center study investigating the natural history and determinants of NASH in adults and children. The NASH-CRN completed a clinical trial investigating cysteamine versus placebo for the treatment of pediatric NASH (CyNCH) has now completed the follow-up phase with data analysis ongoing. The CCSC began a clinical trial comparing the effectiveness of comprehensive lifestyle intervention to bariatric surgery in treating NASH in severely obese adolescents. Funding sources include the National Institutes of Health (NIH) and the North American Society for Pediatric Gastroenterology and Hepatology Foundation (NASPGHAN). The work by the CCSC investigators has been published in *Gastroenterology*, *Obesity*, *JAMA Pediatrics*, *Nature Reviews Gastro Hepatology* and others.

Significant Publications

Gandhi CR, Chaillet JR, Nalesnik MA, Kumar S, Dangi A, Demetris AJ, Ferrell R, Wu T, Divanovic S, Stankeiwicz T, Shaffer B, Stolz DB, Harvey SA, Wang J, Starzl TE. Liver-specific deletion of augmenter of liver regeneration accelerates development of steatohepatitis and hepatocellular carcinoma in mice. *Gastroenterology.* 2015 Feb;148(2):379-391.e4.

Dr. Gandhi and colleagues generated mice with liver-specific deletion of augmenter of liver regeneration (ALR) and found that it impaired mitochondrial function and lipid homeostasis in the liver. These hepatic loss of ALR resulted in heavy steatosis within two weeks after birth, followed by steatohepatitis, fibrosis and hepatocellular carcinoma by one year. This unique mouse model will prove useful to uncover the molecular underpinnings of the relationship between steatohepatitis and hepatocellular carcinoma.

Gilbert S, Nivarthi H, Mayhew CN, Lo YH, Noah TK, Vallance J, Rulicke T, Muller M, Jegga AG, Tang W, Zhang D, Helmrath M, Shroyer N, Moriggl R, **Han X.** Activated STAT5 confers resistance to intestinal injury by increasing intestinal stem cell proliferation and regeneration. *Stem Cell Reports.* 2015 Feb 10;4(2):209-25.

Intestinal epithelial stem cells (IESCs) maintain intestinal homeostasis and regeneration in response to injury. Dr. Han and his collaborators demonstrated that depletion of intestinal STAT5 impairs intestinal crypt regeneration and is associated with deregulation of IESC markers. Conversely, the activation of STAT5 promoted IESC proliferation, accelerated crypt regeneration, and conferred resistance to intestinal injury. These results suggest that activating STAT5 could serve as a therapeutic treatment to induce the regeneration of the intestinal epithelium in response to gut injury.

Heubi JE, Setchell KD, Jha P, Buckley D, Zhang W, Rosenthal P, Potter C, Horslen S, Suskind D. Treatment of bile acid

amidation defects with glycocholic acid. *Hepatology.* 2015 Jan;61(1):268-74.

Dr. Heubi and coworkers studied the effect of glycocholic acid (GCA) on patients with defective bile acid amidation due to a genetically confirmed deficiency in bile acid CoA:amino acid N-acyl transferase (BAAT). The treated patients demonstrated efficient intestinal absorption, hepatic extraction, and biliary secretion of GCA. Oral glycocholic acid therapy was safe and effective in improving growth and fat-soluble vitamin absorption. Clinicians should be observant to potential patients who present with neonatal cholestasis, growth failure, or fat-soluble vitamin deficiencies since treatment with GCA offers clear therapeutic benefit without adverse effects.

Li J, Razumilava N, Gores GJ, Walters S, Mizuochi T, Mourya R, Bessho K, Wang YH, Glaser SS, Shivakumar P, **Bezerra JA**. Biliary Repair and Carcinogenesis are Mediated by IL-33-Dependent Cholangiocyte Proliferation. *J Clin Invest.* 2014 July;124:3241-3251

Development of a type 1 immune response has been linked to the pathogenesis of biliary injury. Studying biliary atresia, Dr. Bezerra and colleagues found that the Th2-activating cytokine IL-33 is elevated in children with biliary atresia and in the experimental mouse model of disease. Exploring the biological roles of IL-33, they found it to induce a potent proliferative response in the epithelium of extrahepatic bile ducts via activation of type 2 innate lymphoid cells and the release of IL-13. In normal mice, they found the molecular circuit promoted epithelial repair, while experimental cancer models; however, induction of this circuit in mice with constitutive activation of AKT and YAP in bile ducts induced cholangiocarcinoma with liver metastases. These results demonstrate that IL-33 mediates epithelial proliferation and suggest that activation of IL-33/type 2 innate lymphoid cells/IL-13 may improve biliary repair and disruption of the circuit may block progression of carcinogenesis.

Moore SR, Guedes MM, Costa TB, Vallance J, Maier EA, Betz KJ, Aihara E, Mahe MM, Lima AA, Oria RB, Shroyer NF. Glutamine and alanyl-glutamine promote crypt expansion and mTOR signaling in murine enteroids. *Am J Physiol Gastrointest Liver Physiol.* 2015 May 15;308(10):G831-9.

L-glutamine (Gln) is a key metabolic fuel for intestinal epithelial cell proliferation and survival and may be conditionally essential for gut homeostasis during catabolic states. Dr. Sean Moore and colleagues showed that L-alanyl-L-glutamine (Ala-Gln), a stable Gln dipeptide, protects mice against jejunal crypt depletion in the setting of dietary protein and fat deficiency. Additionally, the group demonstrated that murine crypt cultures (enteroids) derived from the jejunum require Gln or Ala-Gln for maximal expansion. Together, these findings provide new insights into nutritional regulation of intestinal epithelial homeostasis.

Division Publications

1. Abdel-Kader Hassan HH, Balistreri WF. **Cholestasis**. In: RM Kliegman, BF Stanton, JW St Geme, NF Schor, eds. *Nelson Textbook of Pediatrics*. Philadelphia, PA: Elsevier; 2015:1928-1936.

2. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H, Eby MD, Grotjan TM, Greenler AJ, Dellon ES, Demain JG, Furuta GT, Gurian LE, Harley JB, Hopp RJ, Kagalwalla A, Kaul A, Nadeau KC, Noel RJ, Putnam PE, von Tiehl KF, Rothenberg ME. **Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis**. *J Allergy Clin Immunol*. 2014; 134:1084-1092 e1.

3. Arasada RR, Amann JM, Rahman MA, Huppert SS, Carbone DP. **EGFR blockade enriches for lung cancer stem-like cells through Notch3-dependent signaling**. *Cancer Res.* 2014; 74:5572-84.

4. August KJ, Chiang KY, Qayed M, Dulson A, Worthington-White D, Cole CR, Horan JT. **Relative defects in mucosal**

immunity predict acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2014; 20:1056-9.

5. Balistreri WF. (2015) **Eschewing the Fat – What's on the horizon for the treatment of NASH?**. Medscape. .
6. Balistreri WF. (2015) **HBV: React Before the Virus Does - "Reactivation of HBV**. Medscape. .
7. Balistreri WF. (2015) **Prevention of Perinatal Transmission of HBV**. Medscape. .
8. Balistreri WF. (2015) **What's Hot – "Non-invasive Assessment of Liver Disease**. Medscape. .
9. Balistreri WF. (2015) **What's Hot - Part II – Hepatitis B Highlights from The Liver Meeting – AASLD 2014**. Medscape. .
10. Balistreri WF. (2015) **What's Hot - Part III – Top Highlights from The Liver Meeting – AASLD 2014**. Medscape. .
11. Balistreri WF. **Early diagnosis of biliary atresia**. *J Pediatr*. 2015; 166:783-787.
12. Balistreri WF. (2014) **A Future Without Hepatitis C?" Highlights from The Liver Meeting – AASLD 2014**. Mredscape. .
13. Balistreri WF. (2014) **What's Hot - Part I - NAFLD/NASH – Highlights from The Liver Meeting – AASLD 2014**. Medscape. .
14. Balistreri WF. **The natural course of HBV infection**. *J Pediatr*. 2014; 165:647-649.
15. Balistreri WF, Xanthakos S, Nobili V. (2015) **Guidelines for the Application of Bariatric Surgery for Chilren and Adolescents with NASH? Is Surgery the Answer to Fatty Liver Disease in Children?**. Medscape. .
16. Begg DP, Steinbrecher KA, Mul JD, Chambers AP, Kohli R, Haller A, Cohen MB, Woods SC, Seeley RJ. **Effect of guanylate cyclase-C activity on energy and glucose homeostasis**. *Diabetes*. 2014; 63:3798-804.
17. Bell KN, Shroyer NF. **Krupple-like factor 5 is required for proper maintenance of adult intestinal crypt cellular proliferation**. *Dig Dis Sci*. 2015; 60:86-100.
18. Bessho K, Mourya R, Shivakumar P, Walters S, Magee JC, Rao M, Jegga AG, Bezerra JA. **Gene expression signature for biliary atresia and a role for interleukin-8 in pathogenesis of experimental disease**. *Hepatology*. 2014; 60:211-23.
19. Bezerra JA. (2015) **Extrahepatic Biliary Atresia**. National Organization of Rare Disorders: A guide to rare disorders, National Organization of Rare Disorders (NORD). .
20. Burrow TA, Sun Y, Prada CE, Bailey L, Zhang W, Brewer A, Wu SW, Setchell KD, Witte D, Cohen MB, Grabowski GA. **CNS, lung, and lymph node involvement in Gaucher disease type 3 after 11 years of therapy: clinical, histopathologic, and biochemical findings**. *Mol Genet Metab*. 2015; 114:233-41.
21. Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, Kramer RE, Collins MH, Stucke E, Mangeot C, Jackson WD, O'Gorman M, Abonia JP, Pentiuk S, Putnam PE, Rothenberg ME. **Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis**. *Gastroenterology*. 2014; 147:324-33 e5.
22. Caldwell JM, Collins MH, Stucke EM, Putnam PE, Franciosi JP, Kushner JP, Abonia JP, Rothenberg ME. **Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome**. *J Allergy Clin Immunol*. 2014; 134:1114-24.
23. Canet MJ, Merrell MD, Hardwick RN, Bataille AM, Campion SN, Ferreira DW, Xanthakos SA, Manautou JE, Hesham AKH, Erickson RP, Cherrington NJ. **Altered regulation of hepatic efflux transporters disrupts acetaminophen**

disposition in pediatric nonalcoholic steatohepatitis. *Drug Metab Dispos*. 2015; 43:829-35.

24. Cast AE, Walter TJ, Huppert SS. **Vascular patterning sets the stage for macro and micro hepatic architecture**. *Dev Dyn*. 2015; 244:497-506.

25. Chen WH, Garza J, Choquette M, Hawkins J, Hoeper A, Bernstein DI, Cohen MB. **Safety and immunogenicity of escalating dosages of a single oral administration of peru-15 pCTB, a candidate live, attenuated vaccine against enterotoxigenic Escherichia coli and Vibrio cholerae**. *Clin Vaccine Immunol*. 2015; 22:129-35.

26. Clarridge KE, Conway EE, Bucuvalas J. **Hypothyroidism and iodine deficiency in an infant requiring total parenteral nutrition**. *JPEN J Parenter Enteral Nutr*. 2014; 38:901-4.

27. Corey KE, Vuppalanchi R, Vos M, Kohli R, Molleston JP, Wilson L, Unalp-Arida A, Cummings OW, Lavine JE, Chalasani N, Nonalcoholic Steatohepatitis Clinical Research N. **Improvement in liver histology is associated with reduction in dyslipidemia in children with nonalcoholic fatty liver disease**. *J Pediatr Gastroenterol Nutr*. 2015; 60:360-7.

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Research Interests Pediatric liver transplantation; post-transplant renal dysfunction; long-term outcomes after pediatric liver transplantation.

Mitchell B Cohen, MD, Adjunct

Research Interests Diarrheal diseases.

Conrad R Cole, MD, MPH, MSc, Associate Professor

Leadership Clinical Director, Gastroenterology, Hepatology and Nutrition; Medical Director, Intestinal Rehabilitation Program/Intestinal Care Center

Research Interests Intestinal failure; micronutrient malnutrition.

Lee A Denson, MD, Professor

Leadership M. Susan Moyer Chair in Pediatric IBD; Director, Schubert-Martin Pediatric IBD Center; Director of Research, Gastroenterology, Hepatology and Nutrition

Research Interests Inflammatory bowel diseases.

Dana "Chelly" Dykes, MD, Assistant Professor

Research Interests Inflammatory bowel disease; clinical and quality improvement research.

Michael K Farrell, MD, Professor

Leadership Director of Gastroenterology Center of Excellence

Research Interests General gastroenterology; functional abdominal pain; constipation; consultation.

Shekhar Gandhi, PhD, Professor

Research Interests Liver transplantation immunology; liver regeneration; hepatic stellate cells.

Yael Haberman-Ziv, MD, PhD, Adjunct

Research Interests Inflammatory bowel disease.

Xiaonan Han, PhD, Assistant Professor

Research Interests Inflammatory bowel diseases.

James E Heubi, MD, Professor

Leadership Associate Dean for Clinical and Translational Research; Director, Center of Clinical and Translational Science & Training

Research Interests Chronic liver disease.

Stacey Huppert, PhD, Associate Professor

Research Interests Hepatic development and regeneration; alagille syndrome and cholangiopathies.

Heidi J Kalkwarf, PhD, RD, Professor

Leadership Scientific Director, Bionutrition and Body Composition Core Laboratory, Clinical Translational Research Center

Research Interests Bone density; body composition; growth; physical activity; dietary intake; fracture.

Ajay Kaul, MD, Professor

Leadership Director, Neurogastroenterology and Motility Disorders Program

Research Interests Intestinal motility disorders.

Samuel A Kocoshis, MD, Professor

Leadership Medical Director, Intestinal Care Center; Medical Director, Intestinal Transplantation

Research Interests Intestinal failure and intestinal transplantation.

Rohit Kohli, MD, Associate Professor

Leadership Medical Director, Complex Surgery and Transplant Inpatient Unit; Co-Director, Steatohepatitis Center; Associate Medical Director, Pediatric Liver Care Center; Director of Clinical Research Program, Digestive Health Center (DHC)

Research Interests Non-alcoholic steatohepatitis.

Mike A Leonis, MD, PhD, Associate Professor

Leadership Director of Training and Education Gastroenterology, Hepatology, and Nutrition; Director of Gastroenterology Fellowship Program

Research Interests Liver failure and liver transplantation; liver tumors.

Tom K Lin, MD, Assistant Professor

Leadership Director of Endoscopy, Pancreas Care Center

Research Interests Pancreatitis and other pancreas disorders; pancreaticobiliary disorders; therapeutic endoscopy.

Daniel Mallon, MD, Assistant Professor

Leadership Associate Program Director, Student and Resident Education

Research Interests Medical education; primary-specialty care integration; celiac disease.

Alexander Miethke, MD, Assistant Professor

Leadership Director, Transplant Hepatology Fellowship Program; Associate Medical Director, Pediatric Liver Care Center

Research Interests Biliary atresia and primary sclerosing cholangitis.

Phillip Minar, MD, Assistant Professor

Research Interests Inflammatory bowel disease; biomarker development.

Sean Moore, MD, MS, Assistant Professor

Research Interests Diarrheal disease; undernutrition and global health.

Vincent Mukkada, MD, Assistant Professor

Research Interests Eosinophilic gastrointestinal disorders and pediatric feeding disorders.

Joseph Palermo, MD, PhD, Assistant Professor

Leadership Co-Director, Pancreas Care Center

Research Interests Pancreatic disorders; hereditary polyposis and cystic fibrosis liver disease.

Scott Pentiuk, MD, Assistant Professor

Leadership Associate Clinical Director, Gastroenterology, Hepatology and Nutrition; Associate Director, Fellowship Program

Research Interests Feeding disorders; eosinophilic esophagitis; failure to thrive; gastroesophageal reflux; medical education and nutrition.

Philip E Putnam, MD, Professor

Leadership Director, Endoscopy Services; Medical Director, Cincinnati Center for Eosinophilic Disorders

Research Interests Eosinophilic gastrointestinal disorders.

Michael J Rosen, MD, MSCI, Assistant Professor

Research Interests Inflammatory bowel disease; mucosal immunology.

Shehzad A Saeed, MD, Professor

Leadership Clinical Director, Schubert-Martin IBD Center; Medical Director, GI/ColorectalInpatient Unit; Director, GI Operations at Liberty Campus

Research Interests Inflammatory bowel disease.

Pranav Shivakumar, PhD, Assistant Professor

Research Interests Biliary atresia.

Noah Shroyer, PhD, Adjunct

Research Interests Intestinal development.

Kris Steinbrecher, PhD, Assistant Professor

Research Interests Diarrheal diseases; inflammatory bowel diseases.

Cynthia C Wetzel, PhD, Assistant Professor

Leadership Program Manager, Digestive Health Center; Director, Research and Faculty Affairs for Gastroenterology, Hepatollogy and Nutrition

Research Interests Research administration.

Stavra A Xanthakos, MD, MS, Associate Professor

Leadership Medical Director, Surgical Weight Loss Program for Teens; Co-Director, Steatohepatitis Center; Physician Leader for the Clinical Research Coordinators; Associate Director, Fellowship Program

Research Interests Obesity; non-alcoholic steatohepatitis.

Chunyue Yin, PhD, Assistant Professor

Research Interests Liver biology.

Joint Appointment Faculty Members

Lin Fei, PhD, Associate Professor (Biostatistics and Epidemiology)

Anjaparavanda Naren, PhD, Professor (Pulmonary)

Clinical Staff Members

- **Kristin Bramlage, MD**
- **Monique Goldschmidt, MD**
- **Sandra Wright, MD**

Trainees

- **Antonio Vinicios Alves da Silva, MS**, PL-3, Ceara Federal University, Brazil
- **Surya Prakash Amarachintha, PhD**, PL-4, Bowling Green State University
- **Catalina Arce Clachar, MD**, PL-4, Cleveland Clinic
- **Ashish Dhawan, MD**, PL-5, B.J. Medical College, University of Pune
- **David Galloway, MD**, PL-6, Phoenix Children's Hospital Maricopa Medical Center
- **Einar Hafberg, MD**, PL-5, University of Iceland
- **Karla Hicks, MD**, PL-6, Cincinnati Children's Hospital Medical Center
- **M. "Raphaelle" Jean, MD**, PL-4, University of Medicine and Dentistry of New Jersey
- **Junbae Jee, MS, PhD**, PL-6, The Ohio State University
- **Chatmanee Lertudomphonwanit, MD**, PL-11, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
- **Yang Li, MD**, PL-2, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
- **Ethan Mezoff, MD**, PL-6, Children's National Medical Center
- **Tatsuki Mizuochi, PhD**, PL-15, Nagasaki University School of Medicine, Japan
- **Andriy Myronovych, MD, PhD**, PL-4, University of Tsukuba, Tsukuba, Ibaraki, Japan
- **Stephanie Oliveira, MD**, PL-5, Universidade Federal Do Ceará Faculdade
- **Anna Peters, MD**, PL-4, Cincinnati Children's Hospital Medical Center
- **James Squires, MD**, PL-7, Cincinnati Children's Hospital Medical Center
- **Flora Szabo, MD**, PL-6, University of Kentucky
- **Amy Taylor, MD**, PL-5, Northwestern University, Feinberg School of Medicine
- **Amanda Waddell, PhD**, PL-3, Pennsylvania State University
- **Justin Wheeler, MD**, PL-4, Phoenix Children's Hospital
- **Changwen Zhang, PhD**, PL-2, Fudan University, China

Grants, Contracts, and Industry Agreements

Grant and Contract Awards **Annual Direct**

Abu-El-Haija, M.

PancreasCHIP - A Diagnostic Tool for Inheritable Pancreatic Disease

National Institutes of Health(Phase 2 Discovery, Inc)

R43 DK105640	3/01/2015-2/29/2016	$30,913

Bezerra, J

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Diseases

National Institutes of Health

P30 DK078392	6/1/2012-5/31/2017	$718,626

Bezerra, J	Admininstrative Core	$390,869
Potter, S	Gene Expression Core	$33,048
Mayhew, C	Stem Cell Core	$25,907
Keddache, M	Sequencing Core	$42,618
Witte, D	Integrative Morphology Core	$80,966
Aronow, B	Bioinformatics Core	$94,377
Bezerra, J	Flow Cytometry/Luminex Core	$37,674
Matte, M	Pilot & Feasibility	$46,750
Nakamura, T	Pilot & Feasibility	$46,750
Wen, T	Pilot & Feasibility	$46,750
Yin, C	Pilot & Feasibility	$6,750

Immunologic Dysfunction in Biliary Atresia

National Institutes of Health

R01 DK064008	2/1/2013-1/31/2017	$266,617

Biological Basis of Phenotypes and Clinical Outcomes in Biliary Atresia

National Institutes of Health

R01 DK083781	9/24/2014-8/31/2019	$289,655

Colorado Center for Childhood Liver Disease Research and Education

National Institutes of Health(University of Colorado)

U01 DK062453	6/1/2013-5/31/2019	$5,408

The LiverChip - A Diagnostic Tool for Genetic Liver Diseases

National Institutes of Health (Phase 2 Discovery, Inc)

R44 DK093214	4/1/2014-2/28/2016	$85,493

Clinical Center for Cholestatic Liver Disease in Children

National Institutes of Health

U01 DK062497	8/10/2014-5/31/2019	$383,450
Bezerra, J	Administrative Core	$262,543
Heubi, J	Bile Acid Core	$23,386
Bove, K	Central Pathology Core	$37,354
Bezerra, J	RNA Purification Core	$60,167
Miethke, A	Disovery Study #2 Mitochondrial Hepatopathies	$11,512

Bucuvalas, J

Biomarkers for Post-Transplant Lymphoproliferative Disorders in Children

National Institutes of Health(Stanford University)

U01 AI104342	2/1/2014-1/31/2018	$31,904

Medication Adherence in Children Who Had Liver Transplant

National Institutes of Health(Mount Sinai Medical Center)

R01 DK080740	12/22/2009-6/30/2015	$29,412

Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients

National Institutes of Health(The Regents of the Univ of California)

U01 AI100807	7/27/2012-6/30/2017	$99,108

Denson, L

Pediatric Gastroenterology and Nutrition Training Grant

National Institutes of Health

T32 DK007727	7/1/2010-6/30/2020	$436,778

Risk Stratification and Identification of Immunogenetic and MicrobialMarkers of Rapid Disease Progression in Children with Crohn's Disease

Crohn's & Colitis Foundation of America(Emory University)

CCFA Ref# 3189	7/1/2013-6/30/2017	$274,215
Denson, L	RISK Research Component	$131,364

Kim, M	Aim 1 Supplement	$132,851
Aronow, B	Aim 2 Supplement	$10,000

Risk Stratification and Identification of Immunogenetic and MicrobialMarkers of Rapid Disease Progression in Children with Crohn's Disease

Crohn's & Colitis Foundation of America(Emory University)

CCFA Ref# 3189	7/1/2013-6/30/2017	$4,091

Ulcerative Colitis Genetics Initiative

Crohn's & Colitis Foundation of America(Washington University)

CCFA Ref# 326556	4/15/2014-4/14/2017	$231,138

A Multidisciplinary Human Study on the Genetic, Environmental and Microbial Interactions that Cause IBD

Crohn's & Colitis Foundation of Canada(Mount Sinai Medical Center)

	1/1/2012-6/30/2017	$44,007

Causes and Consequences of Neutrophil Dysfunction in Early Onset Crohn's Disease

National Institutes of Health(Emory University)

R01 DK098231	9/17/2013-7/31/2018	$103,236

CCFA Partners-Pediatrics

Crohn's & Colitis Foundation of America(Emory University)

CCFA Ref# 288053	4/15/2013-4/14/2015	$750

Predicting Response to Standardized Pediatric Colitis Therapy: The PROTECT Study

National Institutes of Health(Connecticut Children's Medical Center)

U01 DK095745	5/1/2012-4/30/2017	$188,798

Predicting Response to Standardized Pediatric Colitis Therapy: The PROTECT Study - Per Patient

National Institutes of Health(Connecticut Children's Medical Center)

U01 DK095745	5/1/2012-4/30/2017	$6,476

Han, X

Development of Somatic Cell Therapy for Infection-induced Gut Barrier Dysfunction: Role of Intestinal Stem Cell in Barrier Regeneration

Department of Defense

W81XWH-13-1-0437	9/30/2013-9/29/2015	$45,924

Heubi, J

Sterol and Isoprenoid Diseases Rare Diseases Consortium

National Institutes of Health(University of Nebraska Medical Center)

U54 HD061939	9/4/2014-8/31/2019	$23,027

Kohli, R

Role of Bile acid-FGF19 Signaling in NASH Improvement after Bariatric Surgery

NASPGHAN Foundation

	11/15/2013-11/14/2015	$75,000

NAFLD Improvement after Bariatric Surgery: The Role of Bile Acid-FXR Signaling

National Institutes of Health

R01 DK100314	4/1/2015-3/31/2020	$289,113

Leonis, M

A Multi-Center Group to Study Acute Liver Failure in Children

National Institutes of Health(University of Pittsburgh)

U01 DK072146	9/01/2010-6/30/2015	$29,412

A Multi-Center Group to Study Acute Liver Failure in Children

National Institutes of Health(University of Pittsburgh)

U01 DK072146	9/01/2010-6/30/2015	$1,000

Miethke, A

The Role of Regulatory T Cells in Biliary Atresia

National Institutes of Health

R01 DK095001	8/15/2012-6/30/2017	$218,186

Regulation of Hepatic Lymphocyte Responses in Sclerosing Cholangitis

PSC Partners Seeking a Cure

	11/13/2013-11/12/2015	$30,000

Minar, P

Redefining Deep Remission in Pediatric Crohn's Disease

NASPGHAN Foundation

	11/15/2014-11/14/2016	$75,000

Therapeutic Monitoring and Targeting of Neutrophil Activation in Pediatric IBD

National Institutes of Health

K23 DK105229	4/6/2015-3/31/2019	$165,689

Moore, S

Global and Liver-Specific Knockout of Pigr to Generate Environmental Enteropathy in Mice

Bill & Melinda Gates Foundation

OPP 1092957	9/27/2013-8/31/2015	$75,000

Epigenetic Modeling of Environmental Enteropathy in Mice

Bill & Melinda Gates Foundation

OPP1109785	7/11/2014-6/30/2016	$456,606

Uncovering General Principles of Network Dynamic of Circadian Rhythms, Cell Cycle, DNA Damage Response and Metabolism in Interconnected Modules

Department of Defense(University of Cincinnati)

D12 AP00005	1/1/2012-12/31/2015	$68,536

Cellular and Molecular Mechanisms of Alanyl-Glutamine Oral Rehydration and Nutrition Therapy

National Institutes of Health

K02 TW008767	9/16/2011-7/31/2016	$116,070

Glycosyn Health Initiatives Pilot Grant

Glycosyn Health Initiatives

	3/1/2015-2/29/2016	$4,545

Palermo, J

Longitudinal Study of Cystic Fibrosis Liver Disease

Cystic Fibrosis Foundation Therapeutics, Inc(Children's Hospital of Denver)

NARKEW07A0	1/1/2011-12/31/2015	$40,339

Longitudinal Study of Cystic Fibrosis Liver Disease_Patient

Cystic Fibrosis Foundation Therapeutics, Inc(Children's Hospital of Denver)

NARKEW07A0	1/1/2011-12/31/2014	$10,951

Rosen, M

Th2 Cytokines and Signaling in Pediatric Inflammatory Bowel Disease

National Institutes of Health

K23 DK094832	12/1/2013-3/31/2018	$166,100

Squires, J

2014-2015 AASLD Advanced/Transplant Hepatology Fellowship Program

American Association for the Study of Liver Disease

	7/1/2014-6/30/2015	$60,000

Steinbrecher, K

cGMP Metabolism in Resistance to Bacterial Infection

National Institutes of Health

R21 AI107274	8/8/2013-7/31/2015	$125,000

Xanthakos, S

Outcome of NASH in Adolescents after Bariatric Surgery vs. Lifestyle Intervention

National Institutes of Health

R01 DK100429	8/25/2014-6/30/2019	$393,032

Clinical Research Network in NASH

National Institutes of Health(Cleveland Clinic Lerner College of Medicine)

U01 DK061732	8/1/2014-6/30/2019	$205,160

Yin, C

Regulation of Hepatic Stellate Cells in Development and Alcoholic Liver Injury

National Institutes of Health

R00 AA020514	3/1/2014-2/28/2017	$151,133

	Current Year Direct	**$6,054,898**

Industry Contracts

Balistreri, W

Gilead Sciences, Inc.	$22,405

Bezerra, J

Gilead Sciences, Inc.	$26,050

Cohen, M

PaxVax, Inc.	$269,373

Heubi, J

Asklepion Pharmaceuticals, LLC	$51,603
Nordmark Arzneimittel GmbH & Co.	$1,540

Kocoshis, S

NPS Pharmaceuticals, Inc.	$123,997

Leonis, M

Novartis Pharmaceuticals Corporation	$1,078

Miethke, A

Lumena Pharmaceuticals Inc.	$34,635

Mukkada, V

Meritage Pharma, Inc.	$27,319
Current Year Direct Receipts	**$558,000**

Service Collaborations

Kohli, R

PPD Global Central	$21,830

Steinbrecher, K

Ironwood Pharma	$129,159
Current Year Direct	**$150,989**
Total	**$6,763,887**

Novel Genetic, Bacterial Signature for IBD Suggests a Target for Developing New Therapies

Lee Denson, MD

RESEARCH AND TRAINING DETAILS

Faculty	37
Joint Appointment Faculty	2
Research Fellows	9
Research Students	9
Support Personnel	45
Direct Annual Grant Support	$6M
Direct Annual Industry Support	$558,000
Peer Reviewed Publications	120

Haberman Y, Tickle TL, Dexheimer PJ, Kim MO, Tang D, Karns R, Baldassano RN, Noe JD, Rosh J, Markowitz J, Heyman MB, Griffiths AM, Crandall WV, Mack DR, Baker SS, Huttenhower C, Keljo DJ, Hyams JS, Kugathasan S, Walters TD, Aronow B, Xavier RJ, Gevers D, Denson LA. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest.* 2014;124(8):3617-3633.

PUBLISHED ONLINE JULY 8, 2014
Journal of Clinical Investigation

Gastroenterologists have known that several genes and types of bacteria are associated with inflammatory bowel disease (IBD) in children, including Crohn's disease and ulcerative colitis. And while more than 160 areas of the genome have been identified as containing risk factors for IBD, no definite cause has been found.

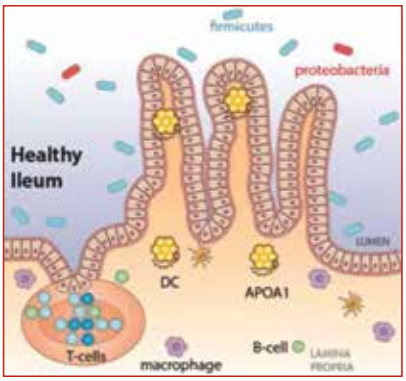
Lee Denson, MD, Director of the Inflammatory Bowel Disease Center, and his team have narrowed the focus to the ileum as the primary inductive site for IBD, and they have identified specific bacteria activated by ileal cells, depending on the IBD diagnosis. Their findings appeared July 8, 2014, in the *Journal of Clinical Investigation*.

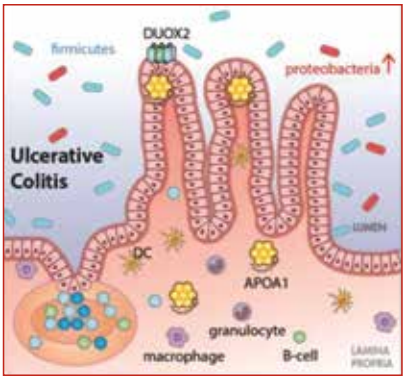
By comparing ileal tissues from children with IBD and healthy tissues, they found that Crohn's disease and ulcerative colitis patients had higher levels of Proteobacteria and an increase in the activity of the DUOX2 gene. Some patients with Crohn's disease also had lower levels of Firmicutes bacteria and lower activity of the APOA1 gene.

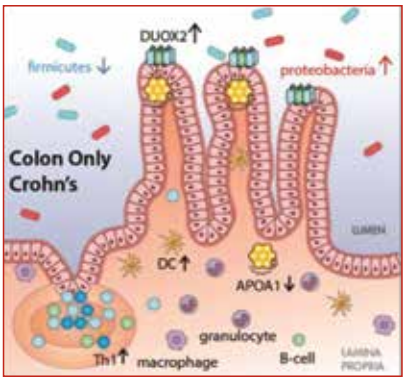
More than 80,000 children in the U.S. have been diagnosed with IBD, and the number is climbing. By identifying a microbial and gene expression "signature" for the disease, researchers are now better positioned to understand IBD, diagnose it more accurately and develop targeted therapies, Denson says.

Of special interest, he notes, is new knowledge about the role of the APOA1 gene, which is linked to changes in about 500 other genes. Patients with the APOA1 profile, regardless of the type of therapy or length of treatment, tend to have less successful outcomes.

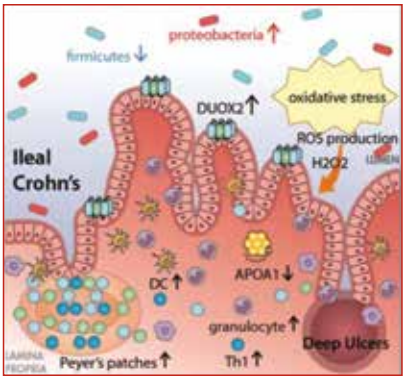
"By characterizing this profile, we have potentially identified a new pathway to target to benefit kids who have not done well with other types of treatments," Denson says.







These illustrations show the progressive induction of an ileal DUOX2 host gene coexpression signature in association with expansion of Proteobacteria taxa across multiple forms of inflammatory bowel disease. The greatest change was detected in those with ileal Crohn's disease with deep ulcers (bottom). These findings emphasize the central role of the ileum in the pathogenesis of Crohn's disease. Maximal alteration of microbial shifts was associated with the most severe tissue injury.



More than 80,000 children in the U.S. have been diagnosed with IBD, and the number is climbing.