Gastroenterology, Hepatology, and Nutrition

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**38**
Joint Appointment Faculty	**2**
Research Fellows and Post Docs	**10**
Research Graduate Students	**13**
Total Annual Grant Award Dollars	**$9,185,873**
Total Annual Industry Award Dollars	**$100,997**
Total Publications	**142**

CLINICAL ACTIVITIES AND TRAINING	
Staff Physicians	**2**
Clinical Fellows	**13**
Inpatient Encounters	**9,528**
Outpatient Encounters	**21,923**

Row 1: P Shivakumar, C Wetzel, V Mukkada, W Balistreri, S Xanthakos, J Bezerra, S Huppert, C Yin

Row 2: C Cole, D Mallon, J Palermo, A Kaul, M Abu-El-Haija, X Han, H Kalkwarf

Row 3: T Lin, A Miethke, M Rosen, D Dykes, M Leonis, P Minar, C Gandhi

Research Highlights

Digestive Health Center: A catalyst for research on digestive disease

The Digestive Health Center (DHC), directed by Dr. Jorge Bezerra, MD, and managed by Dr. 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. Drs. Lee Denson, MD; Heidi Kalkwarf, PhD; and Aaron Zorn, PhD, serve as DHC associate directors. 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 three cores: Integrative Morphology, Gene Analysis, and Pluripotent Stem Cell and Organoid Cores. With 83 investigators, the DHC contributes to the research goals of faculty from 19 divisions in the Department of Pediatrics and eight other departments of the University of Cincinnati, College of Medicine. This year, the DHC welcomed four new center investigators; collectively, DHC investigators have $31.9 million in extramural research funds. The DHC's successful Pilot and Feasibility Program has distributed $1.64 million among 39 junior investigators since 2007. These investigators have since attracted $39.7 million in extramural grant funding. In addition to an outstanding record of publications with 155 peer-reviewed articles during the past 12 months, the following center investigators received national and international recognition for their clinical, research, and educational accomplishments:

- Artem Barski, PhD, received the National Institutes of Health Director's New Innovator Award
- Jorge Bezerra, MD, elected as councilor and member of the Governing Board of the American Association for the Study of Liver Disease

- James Heubi, MD, president elect for the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
- Sing Sing Way, MD, received the 2016 E. Mead Johnson Award for Pediatric Research

Advanced Nutrition

Our 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. Drs. Conrad Cole, MD, MPH, MSc; Stacey Huppert, PhD; and Moore 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. Drs. Simon Hogan, PhD (Division of Allergy and Immunology), Huppert, and Moore continue to collaborate on novel mouse models of environmental enteropathy.

Drs. Heidi Kalkwarf, PhD, RD, and Strava Xanthakos, MD, MS, are collaborating with Dr. Thomas Inge, MD, PhD, FACS, FAAP (Division of Pediatric General and Thoracic Surgery), to investigate deficiencies of iron, vitamin B-12 and calcium in adolescents who have undergone bariatric surgery. Drs. Kalkwarf and James Heubi, MD, are investigating trajectories of bone mineral accrual in young children and the influences of dietary intake, growth, body composition and motor skill development. The data obtained from bone density measurements in children obtained in Cincinnati has contributed to understanding the normal pediatric range for bone density based on age.

Cincinnati Center for Eosinophilic Disorders

The Cincinnati Center for Eosinophilic Disorders (CCED) is an established multidisciplinary referral center for evaluation and treatment of eosinophilic gastrointestinal disorders in children and adults. Physicians representing the Divisions of Gastroenterology, Hepatology and Nutrition; Allergy and Immunology; and Pathology provide comprehensive clinical services supported by experienced nurses, dieticians, a psychologist and social worker. Over 70% of our patients agree to participate in clinical and basic science research studies. Our clinical research has included important studies of both dietary and pharmacologic management of eosinophilic disorders. Dr. Philip Putnam, MD, and Dr. Vincent Mukkada, MD, collaborate with CCED leading investigators in studies of genetic and immunologic factors responsible for eosinophilic inflammation in the gut, and in evaluating the effectiveness of anti-interleukin 5 (IL-5), biological agents and topical glucocorticoids in the management of eosinophilic disease. The CCED team was the first to investigate eosinophil progenitor (EoP) levels in patients with eosinophilic esophagitis (EoE), leading to the identification of a potential new noninvasive biomarker, which is an essential step toward better treatment options with the potential of reduced discomfort, costs and side effects for patients with EoE.

Recent research includes the transcriptomic study of proton pump inhibitor (PPI)–responsive esophageal eosinophilia (PPI-REE), providing convincing evidence that PPI-REE is an EoE sub-entity with significant molecular overlap with EoE but that PPI therapy reverses nearly the entire allergic inflammatory transcriptome in PPI-REE. In a collaborative effort led by Dr. Margaret Collins, MD, from the Division of Pathology, we recently published our experience developing a novel histologic scoring system using multiple microscopic changes seen in EoE patients which outperforms the current histologic gold standard. In addition, the CCED (with Dr. Marc Rothenberg, MD, PhD, as principal investigator) continued work as the central site for a Patient Centered Outcomes Research Institute (PCORI) contract for a multicenter trial examining the efficacy of minimally restrictive empiric diets in the management of pediatric eosinophilic esophagitis. 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. A novel study continues the process of expanding our understanding of eosinophilic gastritis, using techniques employed previously for studying the esophagus, including elucidation of the transcriptome.

With the support of a five-year, $6.25-million grant from the National Institutes of Health (NIH) to Dr. Rothenberg, Division of Allergy and Immunology, the CCED leads a consortium of organizations with a common goal to conduct clinical research into eosinophilic disorders and to train investigators in how to conduct clinical research. This Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is a collaboration of clinician investigators, translational scientists, physicians, patients, families and patient advocacy groups and is part of the Rare Disease Clinical Research Network (RDCRN).

IBD-The Schubert-Martin Inflammatory Bowel Disease Center

The Division of Gastroenterology, Hepatology and Nutrition, and the Schubert-Martin Inflammatory Bowel Disease (IBD) Center, sees more than 700 patients with IBD. The physicians of the Center diagnose close to 100 new patients annually, and also see almost 90 second-opinion patients, from more than 20 states and abroad. These numbers reflect a significant increase in both total patient volume, and 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 reflects in superior outcomes for our patients with more than 83% of IBD patients within the center being in remission, 62% in sustained remission, and 84% having a good quality of life. The Center's website shares these outcome measures transparently. 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. The establishment of a rejuvenated and energized parent advisory board will 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. Our partners in colorectal surgery reported our experience with surgery for ulcerative colitis in the *Journal of Pediatric Surgery*, demonstrating that both very young and older patients experienced significant improvements in bowel function and quality of life. We reported in the *Inflammatory Bowel Diseases Journal,* and the *Journal of Pediatric Gastroenterology and Nutrition* ,development of a novel biomarker for intestinal inflammation, CD64, and the relationship between CD64, infliximab drug levels, and sustained remission. This biomarker has now entered clinical practice here at Cincinnati Children's, and will next be tested as part of a multi-center infliximab clinical trial. Collaborations within Cincinnati Children's with the James M. Anderson Center for Health System Excellence, and the Divisions of Behavioral Medicine and Clinical Psychology, Pediatric General and Thoracic Surgery, Allergy and Immunology, Adolescent and Transition Medicine, the Center for Adherence and Self-Management, 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.

Interdisciplinary Feeding Team

Under the GI leadership of Drs. Scott Pentiuk, MD, MEd, 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 Dvisions of Gastroenterology, Hepatology and Nutrition; Pediatric Otolaryngology - Head and Neck Surgery; Speech-Language Pathology Therapy; Occupational Therapy, Phyiscal Therapy and Therapeutic Recreation; and Social Services. The IFT evaluated over 1,300 patient visits in FY16. In addition to comprehensive consultation and care, the IFT offers unique multidisciplinary treatment sessions and Parent-Child Interaction Training for families. Ongoing research projects by IFT investigators include the use and development of the pureed by G-tube diet, methods to evaluate children with swallowing dysfunction, and quality improvement projects to decrease patient wait time within clinic visits.

Intestinal Rehabilitation and Intestinal Transplantation Programs

The expanding clinical profiles of the Intestinal Rehabilitation Program (IRP) and the Intestinal Transplant Program continue to fuel the translational and clinical research conducted by both programs. Our circumspect, thoughtful approach to intestinal rehabilitation has obviated the need for intestinal transplantation for many of the patients referred for transplantation. Our 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. Our central line associated blood stream infection rate of <1.8/1000 catheter days is among the best in North America. We were the lead center in a recently completed multicenter pediatric clinical trial funded by Shire Pharmaceuticals for Teduglutide (Gattex®), and 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. In collaboration with our colleagues in the Division of Infectious Diseases (Dr. David Haslam, MD), we are evaluating the interaction of diet and antimicrobials on intestinal microbiome and how this impacts adaptation. Among the pre-clinical studies is the effect of oral galacto-oligosaccharide supplementation upon growth and weight

gain in weanling rats, as well as cutting edge research on the differentiation of stem cells into intestinal organoids (Dr. Michael Helmrath, MD, MS). Our small bowel transplant surgical research team, led by Dr. Jaimie Nathan, MD, is studying microbiome changes in stool and intestinal tissue, to correlate them with diminution of the Treg population in tissue and blood during intestinal allograft rejection.

Liver Diseases

The Pediatric Liver Care Center provides comprehensive care for children with liver diseases. Staffed by eight pediatric hepatologists, four hepatobiliary surgeons and two specialty nurses. The center 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 Drs. Jorge Bezerra, MD; Alexander Miethke, MD; and Pranavkumar Shivakumar, PhD, have focused on understanding the mechanisms of biliary injury and biomarkers, and new treatments for biliary atresia and sclerosing cholangitis. One key advance was Dr. Miethke’s discovery that molecular blockade of the intestinal bile acid receptor improves experimental cholestasis and chronic cholangitis (published in *Hepatology*). Ongoing disease-based research focuses on minimally invasive biomarkers of cholangiopathies, the function of novel liver-specific immune cells, the crosstalk between the intestinal microbiome and liver immune cells.

Several lines of important clinical investigation are opening new diagnostic and treatment options for children with liver disease. Dr. Mike Leonis, MD, PhD, leads the study of acute liver failure in children. Drs. William Balistreri, MD, and 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.

Exciting laboratory work includes studies by Drs. Stacey Huppert, PhD, and Chunyue Yin, PhD, focused on the development of the biliary system. Drs. Yin and Miethke using the zebrafish model to study how human mutations can cause liver disease. Notable is the work by Dr. Takanori Takebe, MD, and his research team in using pluripotent stem cells to engineer small liver organs (also known as liver organoids) and exploring the use of organoids to restore metabolic liver disease. Using liver organoids and hepatocytes produced from stem cells, our new faculty Dr. Akihiro Asai, MD, PhD, is modeling cholestatic liver diseases to discover pathogenic mechanisms of disease and identify new strategies.

Neurogastroenterology and Motility

Under the leadership of Dr. Ajay Kaul, MD, the Neurogastroenterology and Motility Disorders Program has seen continued to experience growth, with 733 outpatient encounters seen by three providers. Last year we received about 30 new referrals per month, primarily from patients outside of our primary service area. Patients came from 35 states and 15 from outside the country. In addition, the Neurogastroenterology team, in collaboration with the Colorectal Center, started an interdisciplinary clinic in July 2014 to evaluate and treat children with complex colorectal and motility disorders, such as Hirschsprungs disease and severe idiopathic chronic constipation, with a goal to improve patient outcomes through standardization of practice and clinical research. In the first two years the team saw about 147 medically complex patient visits for second opinion from all over the country and overseas. As an example, there was an 18% increase in the performance of just manometry procedures compared to last year. The plan is to expand our services to the Liberty campus next year with the addition of a third neurogastroenterologist. Exploring new research opportunities, the program has initiated trials to investigate the efficacy of Linaclotide in children with functional constipation and irritable bowel syndrome with constipation.

Pancreas Care Center

Our mission is to continue to be leaders in delivering world class healthcare to children with pancreatic disease through a comprehensive multidisciplinary management that puts patient outcomes at the forefront of the desired center goals. We implement

chronic care algorithms that enhance the care coordination and apply state of the art research methodology to lead innovative research in pancreatic disorders.

The Pancreas Care Center (PCC) which is led by Drs. Maisam Abu-El-Haija, MD (Medical Director); Joseph Palermo, MD, PhD (associate director and total pancreatectomy with islet autotransplantation (TPIAT) leader); Tom Lin, MD (associate director and Endoscopy director); Jaimie Nathan, MD (surgical director); and Deborah Elder, MD (Endocrinology director), in collaboration with the Pain Management Services team and the Division of Behavior Medicine and Clinical Psychology, currently follows more than 200 patients with various pancreatic disorders including pancreatitis, exocrine 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 that led to decreased length of hospital stay and intensive care admissions related to pancreatitis. By end of FY 2016, we have successfully completed eight total pancreatectomy, and one distal pancreatectomy with islet autotransplantation surgeries for treatment of unremitting pain and prevention of brittle diabetes in chronic pancreatitis.

Our research highlights for this past year include studies in acute severe pancreatitis, validation of a prognostic tool to stratify pediatric patients on admission along with studying the outcomes from different management elements. We are also investigating the role of genetic factors in differentiating chronic pancreatitis from other forms of pancreas inflammation. We are also on the forefront of genetic testing in recurrent and chronic pancreatitis with the development of a pancreas gene panel that will screen for 10 known genes using NGS technology and will soon be commercially available for clinical use. PCC has successfully acquired extramural funding during FY 16:

1. National Institutes of Health (NIH) U01 Conwell (PI)/Palermo (Site PI) – The Ohio State University Pancreatic Disorders Network (OSU-PDN)
2. NIH U01 Uc (PI)/Abu-El-Haija (Site PI) – CSCPDPC INSPPIRE International Study Group to Study Pediatric Acute Recurrent and Chronic Pancreatitis: In Search for a Cure.
3. NIH R01 Bellin (PI)/Nathan (Site PI) – Advancing Treatment for Pancreatitis: A Prospective Observational Study of TPIAT
4. National Pancreas Foundation (NPF). PI (Abu-El-Haija/ Trout) The use of MRCP to stage chronic pancreatitis in the pediatric population.

In addition, the PCC participates in community related activities to increase awareness of pancreatic disorders, and collaborates with the National Pancreas Foundation (NPF) in a gala to increase awareness and help support patients and families with the disease through fund raising and research. The PCC at Cincinnati Children's is one of only a few pediatric centers that is an NPF approved center of excellence for pancreatic care in the nation.

Pediatric Liver Transplantation

The mission of the Pediatric Liver Transplant Program is to advance the care of liver transplant recipients by providing unparalleled clinical care, addressing gaps in knowledge through patient-based and basic laboratory research, improving the health care delivery system through continuous quality improvement, 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, we have performed more than 630 liver transplants since the program began in 1986. Our 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, we 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 Childrens's liver transplant team has performed more pediatric liver transplants for hepatic tumors than any other program in the United States. In addition to providing outstanding patient care, the Liver Transplant Center is a leader in multicenter clinical and translational research studies and national quality improvement efforts. These include: Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients (iWITH), the Studies in Pediatric Liver

Transplantation (SPLIT) quality improvement community and clinical registry, Clinical Trials in Organ Transplantation in Children (CTOT-C) research initiative, the Medication Adherence in Liver Transplant (MALT) study group, and multiple local projects and initiatives.

Steatohepatitis Center

Understanding and treating Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH): the Cincinnati 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 and young adulthood. Thus, early identification and intervention is critical to prevent progression to end-stage liver disease.

With data from over 400 children and adolescents with NAFLD/NASH, center investigators, including Drs. Xanthakos, MD, MS, and Bramlage, MD, collaborate with the Center for Better Health and Nutrition, the Sleep Center, the Hypertension Clinic, the Lipid Clinic, the Diabetes Center, and the Surgical Weight Loss Program for Teens.

Team investigators maintain a robust bio-specimen repository to facilitate translational work and also 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. Seminal research highlights in 2016 included investigating novel non-invasive magnetic resonance and ultrasound imaging modalities in children with NAFLD with collaborating investigators in radiology. Within the NASH CRN, team investigators described the high prevalence of prediabetes and diabetes among children with NASH. The NASH CRN also recently published the results of a clinical trial investigating cysteamine versus placebo for the treatment of pediatric NASH (CyNCH). The CCSC has an active clinical trial comparing the effectiveness of comprehensive lifestyle intervention to bariatric surgery in treating NASH in severely obese adolescents. Researchers are studying outcomes of NAFLD among participants in the Teen-Longitudinal Assessment of Bariatric Surgery cohort. Funding sources include the NIH and the North American Society for Pediatric Gastroenterology and Hepatology and Nutrition Foundation (NASPGHAN). The work by the CCSC investigators is published in *Gastroenterology*, *Obesity*, *New England Journal of Medicine*, *Nature*, *JAMA Pediatrics*, *Nature Reviews Gastro Hepatology* and others.

Significant Publications

Abu-El-Haija M, Wilhelm R, **Heinzman C**, Siqueira BN, Zou Y, Fei L, **Cole CR**. **Early enteral nutrition in children with acute pancreatitis**. *J Pediatr Gastroenterol Nutr.* 2016 Mar;62(3):453-6.

Nutrition is an essential part in the management of acute pancreatitis and is not well studied in the pediatric population. Dr. Abu-El-Haija, MD, and coworkers performed a retrospective chart review of the prospectively collected nutrition database on acute pancreatitis admissions to Cincinnati Children's. They found that there is no difference in the level of pain between the groups allowed to feed and those who were not allowed any food by mouth. This study shows that starting oral feeding upon admission of acute pancreatitis without increasing the pain severity and length of hospital stay.

Mezoff EA, Hawkins JA, Ollberding NJ, **Karns R**, Morrow AL, Helmrath MA. **The human milk oligosaccharide 2'-fucosyllactose augments the adaptive response to extensive intestinal**. *Am J Physiol Gastrointest Liver Physiol*. 2016 Mar 15;310(6):G427-38.

Short bowel syndrome caused by intestinal resection leads to a significant increase in morbidity, mortality, and cost of care. When infants with short bowel syndrome are fed human milk in lieu of formula, they have an increase in intestinal adaptation. Using a mouse model of intestinal adaptation, Dr. Mezoff and colleagues discovered that 2'-Fucosyllactose, which is the most abundant oligosaccharide found in human milk and is not a component of infant formulas, improved weight gain and intestinal crypt depth. This study suggests that 2'-Fucosyllactose supplementation after intestinal resection improves intestinal adaptation.

Miethke AG, Zhang W, **Simmons J**, **Taylor AE**, **Shi T**, Shanmukhappa SK, **Karns R**, White S, Jegga AG, **Lages CS**, Nkinin S, Keller BT, Setchell KD. **Pharmacological inhibition of apical sodium-dependent bile acid transporter changes bile composition and blocks progression of sclerosing cholangitis in multidrug resistance 2 knockout mice**. *Hepatology.* 2016 Feb;63(2):512-23.

Chronic fibrosing cholangiopathies, such as progressive familial intrahepatic cholestasis type 3, biliary atresia, or primary sclerosing cholangitis, carry high morbidity and mortality due to complications from progressive cholestasis and fibrosis. Dr. Miethke, MD, and his colleagues used a mouse model for chronic cholestatic disorders to show that inhibiting the apical sodium-dependent bile acid transporter resulted in an increase in bile acid excretion. Additionally, they discovered a significant reduction of liver and serum concentrations of bile acids as well as biomarkers of hepatocellular and cholestatic injury. This preclinical study demonstrates the possibility of pharmacologically blocking the apical sodium-dependent bile acid transporter to inhibit the progression of fibrosing cholangiopathies during the early phase of the disease process.

Waddell A, **Vallance JE**, Moore PD, **Hummel AT**, Wu D, Shanmukhappa SK, Fei L, Washington MK, **Minar P**, Coburn LA, Nakae S, Wilson KT, **Denson LA**, Hogan SP, Rosen MJ. **ILI-33 signaling protects from murine oxazolone colitis by supporting intestinal epithelial function**. *Inflamm Bowel Dis*. 2015 Dec;21(12):2737-46.

Inflammatory bowel disease is often described as chronic inflammation of the intestine resulting from the dysregulation of the mucosal immune response and epithelial barrier dysfunction. Dr. Rosen, MD, MSCI, and his collaborators used the oxazolone murine model to produce a type-2 cytokine mediated model of colitis with pathologic and immunologic features similar to ulcerative colitis to determine the role of interleukin 33 (IL-33). They were able to show that IL-33 deficient mice displayed an increased severity of oxazolone colitis. These results suggest that understanding the mechanisms of the protective effect of IL-33 will lead to the identification of therapeutic approaches to maintain epithelial barrier function and control inflammation in ulcerative colitis.

Xanthakos SA, Jenkins TM, Kleiner DE, Boyce TW, **Mourya R**, **Karns R**, Brandt ML, Harmon CM, Helmrath MA, Michalsky MP, Courcoulas AP, Zeller MH, Inge TH, Teen-LABS Consortium. **High prevalence of nonalcoholic fatty liver disease in adolescents undergoing bariatric surgery**. *Gastroenterology*. 2015 Sep;149(3):623-34.e8.

We know little regarding the prevalence or the factors causing the development of nonalcoholic fatty liver disease (NAFLD) in the severely obese adolescent population. Dr. Xanthakos, MD, MS, and colleagues discovered that despite high prevalence of NAFLD, severe nonalcoholic steatohepatitis (NASH) was uncommon in a multicenter cohort of adolescents who underwent bariatric surgery. Gene expression studies identified altered expression of genes that regulate macrophage chemotaxis, cholesterol absorption, and fatty acid binding among those with severe NASH. This study suggests there maybe protective factors among the severely obese that lowers the risk of developing NASH.

Division Publications

1. Abu-El-Haija M, Palermo JJ, Fei L, Lin TK. **Variability in Pancreatitis Care in Pediatrics: A Single Institution's Survey Report.** *Pancreas*. 2016; 45:40-5.
2. Abu-El-Haija M, Wilhelm R, Heinzman C, Siqueira BN, Zou Y, Fei L, Cole CR. **Early Enteral Nutrition in Children with Acute Pancreatitis.** *J Pediatr Gastroenterol Nutr*. 2016; 62:453-6.
3. Arora K, Sinha C, Zhang WQ, Moon CS, Ren AX, Yarlagadda S, Dostmann WR, Adebiyi A, Haberman Y, Denson LA, Wang XS, Naren AP. **Altered Cgmp Dynamics at the Plasma Membrane Contribute to Diarrhea in Ulcerative Colitis.** *Am J Pathol*. 2015; 185:2790-804.
4. Asai A, Kohli R. **Familial Homozygous Hypercholesterolemia: When to Turn to Transplant?** *Pediatr Transplant*. 2015; 19:577-79.
5. Ayalon I, Alder MN, Langner TR, Hafberg ET, Miethke AG, Kaplan JM. **A Case of Salicylate Intoxication Complicated by Coagulopathy, Pulmonary Edema, and Pancreatitis.** *Am J Ther*. 2016.
6. Balistreri W. **Welcoming Another New Associate Editor to the Journal.** *J Pediatr*. 2016; 170:1-4.
7. Balistreri W. **New Data May Soon Reshape Transplantation Decisions in End-Stage Liver Disease**. New York: Medscape; 2016 [updated April 12, 2016].
8. Balistreri W. **A Focus on Hepatitis C: Novel Therapeutic Regimens**. New York: Medscape; 2016 [updated March 22, 2016].

9. Balistreri W. **A Focus on Hepatitis C: Outcomes**. New York: Medscape; 2016 [updated March 28, 2016].
10. Balistreri W. **Progress Noted in Treatment of Several Common Liver Diseases**. New York: Medscape; 2016 [updated April 08, 2016].
11. Balistreri W. **Should We All Go Gluten-Free?** Medscape; 2016 [updated ebruary 04, 2016].
12. Balistreri W. **Unsafe at Any Lunch?** New York: Medscape; 2016 [updated ebruary 08, 2016].
13. Balistreri W. **A Focus on Hepatitis C: Cascade of Care**. New York: Medscape; 2016 [updated March 17, 2016].
14. Balistreri W. **Hepatitis B Takes Center Stage**. New York: Medscape; 2016 [updated March 30, 2016].
15. Balistreri W. **Welcoming a New Associate Editor to the Journal.** *J Pediatr*. 2015; 167:1179-82.
16. Balistreri W. **The Increasing Pace of Progress in Hepatology**. New York: Medscape; 2015 [updated November 05, 2015].
17. Balistreri W. **Advances in Diagnoses and Treatment Options for Celiac Disease, Ibs, Ibd, and Eoe**. New York: Medscape; 2015 [updated November 06, 2015].
18. Balistreri W. **Hepatitis C: The Pill, $1000; the Cure, Priceless**. New York: Medscape; 2015 [updated September 10, 2015].
19. Balistreri W. **Liver Diseases in Children: Challenges and Opportunities**. New York: Medscape; 2015 [updated September 28, 2015].
20. Bezerra JA. **Mdr3 Mutation Analysis: A Step Closer to Precision Medicine.** *Hepatology*. 2016; 63:1421-3.
21. Bolton S, Campbell K, Kukreja M, Kohli R. **Neurologic Outcome of Urea Cycle Disorder Liver Transplant Recipients May Be Predicted by Pretransplant Neurological Imaging.** *Pediatr Transplant*. 2015; 19:527-30.
22. Broadus MR, Chen TW, Neitzel LR, Ng VH, Jodoin JN, Lee LA, Salic A, Robbins DJ, Capobianco AJ, Patton JG, Huppert SS, Lee E. **Identification of a Paralog-Specific Notch1 Intracellular Domain Degron.** *Cell Rep*. 2016; 15:1920-9.
23. Chen J, Ryzhova L, Sewell-Loftin M, Brown C, Huppert S, Baldwin H, Merryman W. **Notch1 Mutation Leads to Valvular Calcification through Enhanced Myofibroblast Mechanotransduction.** *Arterioscl Throm Vas*. 2015; 35:1597-605.
24. Chesi A, Mitchell JA, Kalkwarf HJ, Bradfield JP, Lappe JM, McCormack SE, Gilsanz V, Oberfield SE, Hakonarson H, Shepherd JA, Kelly A, Zemel BS, Grant SFA. **A Trans-Ethnic Genome-Wide Association Study Identifies Gender-Specific Loci Influencing Pediatric Abmd and Bmc at the Distal Radius.** *Hum Mol Genet*. 2015; 24:5053-59.
25. Cleynen I, Boucher G, Jostins L, Schumm LP, Zeissig S, Ahmad T, Andersen V, Andrews JM, Annese V, Brand S, Brant SR, Cho JH, Daly MJ, Dubinsky M, Duerr RH, Ferguson LR, Franke A, Gearry RB, Goyette P, Hakonarson H, et al. **Inherited Determinants of Crohn's Disease and Ulcerative Colitis Phenotypes: A Genetic Association Study.** *Lancet*. 2016; 387:156-67.
26. Coburn-Miller C, Casey S, Luong Q, Cameron N, Hocevar-Trnka J, Leung DH, Gelfond D, Heubi JE, Ramsey B, Borowitz D. **Standardization of Research-Quality Anthropometric Measurement of Infants and Implementation in a Multicenter Study.** *Clin Transl Sci*. 2015; 8:330-3.
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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Maisam Abu-El-Haija, MD	PancreasCHIP? A Diagnostic Tool for Inheritable Pancreatic Disease	National Institutes of Health (Phase 2 Discovery, Inc)	R43 DK105640	3/1/2015 - 2/29/2016	$34,004
Akihiro Asai, MD-PHD	Advanced/Transplant Hepatology Fellowship	Amer Assoc for the Study of Liver Dis	AASLD_Asai	7/1/2015 - 6/30/2016	$60,000
Jorge A Bezerra, MD	Immunologic Dysfunction in Biliary Atresia	National Institutes of Health	R01 DK064008	2/1/2016 - 1/31/2017	$407,924
Jorge A Bezerra, MD	Biological Basis of Phenotypes and Clinical Outcomes in Biliary Atresia	National Institutes of Health	R01 DK083781	9/24/2014 - 8/31/2019	$459,726
Jorge A Bezerra, MD	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	$106,866

Jorge A Bezerra, MD	Clinical Center for Cholestatic Liver Disease in Children	National Institutes of Health	U01 DK062497	8/10/2014 - 5/31/2019	$548,896
John C Bucuvalas, MD	Medication Adherence in Children Who Had Liver Transplant	National Institutes of Health (Icahn School of Medicine at Mount Sinai)	R01 DK080740	12/22/2009 - 6/30/2016	$5,000
John C Bucuvalas, MD	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	$149,847
Lee A Denson, MD	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	$585,545
Lee A Denson, MD	Risk Stratification and Identification of Immunogenetic and Microbial Markers of Complicated Disease Course in Pediatric Crohn's Disease	Crohn's & Colitis Foundation of America (Emory University)	CCFA 292052	7/1/2013 - 6/30/2017	$157,315
Lee A Denson, MD	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	$308,385
Lee A Denson, MD	Pediatric Gastroenterology and Nutrition Training Grant	National Institutes of Health	T32 DK007727	7/1/2015 - 6/30/2020	$446,001
Lee A Denson, MD	Characterizing the Gut Microbial Ecosystem for Diagnosis and Therapy in IBD	National Institutes of Health (Broad Medical Research Program)	U54 DK102557	9/1/2014 - 8/31/2016	$84,197
Chandrashekhar Gandhi	Mechanisms of Nonalcoholic Steatohepatitis	Department of Defense Army	W81XWH-15-1-0370	9/30/2015 - 9/29/2018	$445,489
James E Heubi, MD	Sterol and Isoprenoid Diseases Rare Diseases Consortium	National Institutes of Health (University of Nebraska Medical Center)	34-5321-2003-606 (pr	9/4/2014 - 8/31/2019	$2,842
Heidi J Kalkwarf, PHD	Exposure and Development of Poor Bone Health among African American Women	National Institutes of Health (University of Cincinnati)	R01 ES024074	6/9/2014 - 3/31/2018	$123,895
Heidi J Kalkwarf, PHD	Bone Mineral Accretion in Young Children	National Institutes of Health	R01 HD076321	9/30/2013 - 7/31/2016	$1,030,524
Rohit Kohli, MD	NAFLD Improvement after Bariatric Surgery: The Role of Bile Acid-FXR Signaling	National Institutes of Health	R01 DK100314	4/1/2015 - 3/31/2020	$451,720
Alexander Miethke, MD	The Role of Regulatory T Cells in Biliary Atresia	National Institutes of Health	R01 DK095001	8/15/2012 - 6/30/2016	$333,825
Alexander Miethke, MD	The Evaluation of the Intestinal Bile Acid Transport (IBAT) Inhibitor LUM001 in the	National Institutes of Health (University of Michigan)	U01 DK062456	8/1/2014 - 5/31/2019	$136,840

	Management of Pruritus in Alagille Syndrome and Familial Intrahepatic Cholestasis 1 (FIC1/BYLER) Disease: ITCH Study				
Phillip P. Minar, MD	Therapeutic Monitoring and Targeting of Neutrophil Activation in Pediatric IBD	National Institutes of Health	K23 DK105229	4/6/2015 - 3/31/2019	$175,500
Phillip P. Minar, MD	Redefining Deep Remission in Pediatric Crohn?s Disease	NASPGHAN Foundation	NASPGHAN Foundation	11/15/2014 - 11/14/2016	$75,000
Sean R Moore, MD-MS	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)	D12AP00005	1/1/2012 - 12/31/2016	$153,216
Sean R Moore, MD-MS	Epigenetic Modeling of Environmental Enteropathy in Mice	Bill & Melinda Gates Foundation	ID OPP1109785	7/11/2014 - 6/30/2016	$497,732
Sean R Moore, MD-MS	Cellular and Molecular Mechanisms of Alanyl-Glutamine Oral Rehydration and Nutrition Therapy	National Institutes of Health	K02 TW008767	9/16/2011 - 7/31/2016	$125,356
Sean R Moore, MD-MS	Study of Environmental Enteropathy and Malnutrition in Pakistan (SEEM Pakistan)	Bill & Melinda Gates Foundation	OPP1144149	11/19/2015 - 12/31/2019	$698,106
Joseph Palermo, MD-PHD	Longitudinal Study of Cystic Fibrosis Liver Disease	Cystic Fibrosis Fdn Therapeutics, Inc (The Children's Hospital of Denver)	NARKEW07AO	1/1/2011 - 12/31/2016	$57,856
Michael Rosen, MD-MS	Anti-TNF Therapy for Refractory Colitis in Hospitalized Children (ARCH Study)	Broad Medical Research Program	367711	11/1/2015 - 3/31/2017	$132,000
Michael Rosen, MD-MS	Th2 Cytokines and Signaling in Pediatric Inflammatory Bowel Disease	National Institutes of Health	K23 DK094832	12/1/2013 - 3/31/2018	$179,388
Noah F Shroyer;James Wells, PHD Michael Anthony Helmrath, MD	Investigation of Regional Identity in Human Intestinal Stem Cells	National Institutes of Health	U01 DK103117	9/1/2014 - 8/31/2019	$122,567
Takanori Takebe, MD	Precursory Research for	Japan Science and	JST_Takebe	12/1/2015 -	$45,074

	Embryonic Science and Technology	Technology Corporation		3/31/2019	
Amanda Waddell, PHD	Role of Epithelial IL-33 Signaling in Chronic Colitis	Crohn's & Colitis Foundation of America	370202	1/1/2016 - 12/31/2018	$58,250
Stavra A Xanthakos, MD	Clinical Research Network in NASH	National Institutes of Health (Cleveland Clin Lerner Col of Med of CWRU)	U01 DK061732	8/1/2014 - 6/30/2019	$202,264
Stavra A Xanthakos, MD	Outcome of NASH in Adolescents after Bariatric Surgery vs. Lifestyle Intervention	National Institutes of Health	R01 DK100429	8/25/2014 - 6/30/2019	$547,628
Chunyue Yin, PHD	Regulation of Hepatic Stellate Cells in Development and Alcoholic Liver Injury	National Institutes of Health	R00 AA020514	3/1/2014 - 2/28/2017	$237,095
Total Annual Grant Award Dollars					**$9,185,873**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
William F Balistreri, MD	Gilead Sciences, Inc.	$100,997
Total Annual Industry Award Dollars		**$100,997**