

Gastroenterology, Hepatology and Nutrition

Division Photo



First Row: N. Shroyer, J. Bezerra, W. Balistreri, M. Cohen, J. Heubi, C. Wetzel, S. Pentiuik; Second Row: L. Denson, A. Mezoff, A. Kaul, S. Moore, A. Miethke, P. Shivakumar, R. Kohli, X. Han.

Division Data Summary

Research and Training Details

Number of Faculty	26
Number of Research Fellows	3
Number of Research Students	1
Number of Support Personnel	57
Direct Annual Grant Support	\$4,584,429
Direct Annual Industry Support	\$30,773
Peer Reviewed Publications	40

Clinical Activities and Training

Number of Clinical Staff	34
Number of Clinical Fellows	13
Inpatient Encounters	10,612
Outpatient Encounters	12,589

Significant Publications

Shanmukhappa K, Matte U, Degen JL, Bezerra JA. Plasmin-mediated proteolysis is required for hepatocyte growth factor activation during liver repair. J Biol Chem 2009; 284:12917-23.

Plasminogen (Plg) plays a key role in liver regeneration and repair. To determine whether Plg-mediated activation of growth factors is critical to the reparative response after an injury, we investigated whether the defective liver repair in mice lacking Plg is due to impaired activation of Hgf. Loss of Plg in vivo suppressed Hgf activation and signaling through its Met tyrosine kinase receptor. Without Plg, hepatocytes were unresponsive to Hgf-induced proliferation and migration. Most notably, circumventing the defect in proteolytic activation of Hgf by the downstream expression of an activated Met receptor corrected the functional deficits and improved liver repair. These findings support a fibrinolysis-unrelated role for Plg in modulating cell proliferation and migration by activation of Hgf.

Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, Cucchiara S, Kim CE, Frackelton EC, Annaiah K, Glessner JT, Santa E, Willson T, Eckert AW, Bonkowski E, Shaner JL, Smith RM, Otieno FG, Peterson N, Abrams DJ, Chiavacci RM, Grundmeier R, Mamula P, Tomer G, Piccoli DA, Monos DS, Annese V, Denson LA, Grant SF, Hakonarson H. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet.* 2008; 40: 1211-5.

Inflammatory bowel disease (IBD) is a common inflammatory disorder with complex etiology that involves both genetic and environmental triggers, including but not limited to defects in bacterial clearance, defective mucosal barrier and persistent dysregulation of the immune response to commensal intestinal bacteria. IBD is characterized by two distinct phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). Previously reported genome wide associate (GWA) studies have identified genetic variation accounting for a small portion of the overall genetic susceptibility to CD and an even smaller contribution to UC pathogenesis. Stratification of IBD by age of onset was thought to identify additional genes associated with IBD. To that end, the authors carried out a GWA analysis in a cohort of 1,011 individuals with pediatric-onset IBD and 4,250 matched controls. They identified and replicated significantly associated, previously unreported loci on chromosomes 20q13 (rs2315008[T] and rs4809330[A]; $P = 6.30 \times 10^{-8}$ and 6.95×10^{-8}), respectively; odds ratio (OR) = 0.74 for both) and 21q22 (rs2836878[A]; $P = 6.01 \times 10^{-8}$; OR = 0.73), located close to the TNFRSF6B and PSMG1 genes, respectively.

Division Highlights

Jorge Bezerra, MD, Mitchell B. Cohen, MD, Lee (Ted) Denson, MD

Digestive Health Center (DHC)

The DHC is one of only 16 Silvio O. Conte Digestive Diseases Research Core Centers in the nation supported by the National Institutes of Diabetes & Digestive & Kidney Diseases. The DHC, located within the Division of Gastroenterology, Hepatology, and Nutrition at Cincinnati Children's Hospital Medical Center is the only center dedicated to pediatric digestive diseases research. The DHC administrative body is comprised of Dr. Jorge Bezerra serving as the Director, Drs. Mitchell Cohen, Lee Denson, and Aaron Zorn serving as Associate Directors, and Dr. Cynthia Wetzel serving as the Program Manager. The DHC includes 49 investigators and 28 associate members from 16 different divisions within the Department of Pediatrics and a total of 8 departments within within the University of Cincinnati, College of Medicine. The DHC serves as a resource that has attracted new investigators to foster digestive disease research and make significant discoveries relating to pediatric digestive diseases. The overall goal of the DHC, is to promote research that will yield insights into the fundamental processes and pathogenic mechanisms of digestive disease in children and generate innovative treatment to restore digestive health. Specifically, the long term goals are to improve child health through better diagnosis, treatments and outcomes for our 4 key targeted focus areas and diseases including: 1) Chronic Liver Disease (biliary atresia and chronic cholestasis); 2) Digestive Organ Failure and Transplantation (liver and intestinal failure, short gut syndrome and liver and intestinal transplantation) 3) Inflammatory and Diarrheal Diseases (inflammatory bowel disease, eosinophilic gastrointestinal disorders, infectious diarrhea) 4) Obesity (including liver related complications of obesity). The focus areas are linked by four highly innovative Biomedical Research Cores: Gene Expression and Sequencing, Bioinformatics, Integrative Morphology, and a Biostatistical Service (a collaborative effort with the Center for Clinical and Translational Science and Training Program). In addition, the DHC provides 3-6 pilot and feasibility awards each year to investigators starting research projects with the potential for extramural funding.

Scott Pentiuik, MD**Interdisciplinary Feeding Team (IFT)**

This is a multi-disciplinary team which provides comprehensive evaluation of children with swallowing/feeding disorders. It consists of members from gastroenterology, otolaryngology, human genetics, speech therapy, occupational therapy, social work, and nutrition. Over the past academic year Dr. Scott Pentiuik MD, replaced Dr Ajay Kaul as the pediatric gastroenterologist on the team. The team continues to grow with 1100 patient visits with 289 new patients seen over the last year. The team has also expanded its outpatient treatment programs with the development of co-treatment sessions and Parent-Child Interaction Training for families. Current IFT research projects include the use and development of a pureed by G-tube diet, methods to evaluate children with swallowing dysfunction, and the creation of a prospective database in order to track the effectiveness of therapies and patient outcomes.

Lee (Ted) Denson, MD, Gitit Tomer, MD**Schubert Martin Inflammatory Bowel Disease (IBD) Center**

The number of patients receiving medical and surgical care for IBD both from the region and nationally has continued to grow. State-of-the art services including newer diagnostic imaging modalities and psychology interventions for non-adherence have been added. With support from the Crohn's and Colitis Foundation of America, and the Pediatric Research Organization for Kids with Intestinal Inflammatory Disorders (PRO-KIIDS), the center has been a leader in establishing multi-center clinical trials in children with IBD. IBD center investigators have completed the first randomized, controlled trial of human growth hormone in children with Crohn's Disease, and have contributed to the first genome-wide association study to identify susceptibility genes specifically for pediatric-onset IBD. The IBD center has also played a leading role in ImproveCareNow (ICN), the national pediatric IBD quality improvement network. Over the past year, the ICN network has achieved a 20% improvement in patient remission rates with implementation of consensus patient care guidelines and practices.

**John Bucuvalas, MD; Jorge Bezerra, MD, Kathleen Campbell, MD; Mike Leonis, MD Ph.D.
Liver Failure and Transplant Program**

Members of the Pediatric Liver Transplant Program continue to advance science via insightful leadership of multi-center clinical and translational studies, including the NIH-sponsored Studies in Pediatric Liver Transplantation (SPLIT) and the Pediatric Acute Liver Failure Study Group (PALF). Under the leadership of John Bucuvalas, MD, SPLIT successfully competed for an NIH planning grant (U34) to design a clinical and translational study focused on withdrawal of immunosuppression and the biological mechanisms underlying tolerance. The PALF group has continued its' collaboration with Alexandra Filipovich, MD, in preliminary studies investigating the role of Natural Killer (NK) cell dysfunction in acute liver failure. An increase in the number of referrals for hepatoblastoma resection and/or transplantation, combined with ongoing collaboration with James Geller, MD in Pediatric Oncology, has provided the infrastructure and patient population necessary for CCHMC to take a lead in patient-based research in this field.

Two endowed chairs were established in the Liver Care Center – Jorge Bezerra, MD received the William and Rebecca A. Balistreri Chair in Pediatric Hepatology, while John Bucuvalas MD was appointed the first Chair of Pediatric Transplant Hepatology. Finally, Kathleen Campbell, MD was appointed Medical Director of the Liver Transplant Program.

Samuel Kocoshis, MD; Adam Mezzoff MD, Jeffrey Rudolph, MD

The Nutrition and Intestinal Care Center/Small Intestinal Transplantation Program

This program has been focused on process improvement for the past year. The intestinal rehabilitation program has initiated a quarterly meeting with stakeholders to provide a forum whereby caregivers involved in the treatment of patients with short-gut syndrome (non-transplant) could identify quality improvement opportunities that exist or could be improved, through collaboration, communication, and research across departmental lines. The small intestinal transplant program convened a retreat to identify current opportunities for improvement, and to incorporate the expertise of other clinical care divisions such as infectious disease and bone marrow transplant. Furthermore, the program has utilized DSIOP resources to further process improvement. A scorecard has been developed, and the program has worked to improve outpatient efficiency by initiating preclinic planning with the assistance of DSIOP staff. Research continued to focus on identifying biomarkers for prediction of blood stream infections, and in identifying biomarkers for prediction of progression of parenteral nutrition associated cholestasis to end stage liver disease. Utilizing the internal registry, team has noted that the conjugated bilirubin to GGT ratio has better predictive power than conjugated bilirubin alone. Work with the Pediatric Intestinal Failure Consortium (PIFCON) funded by the NIH (R21DK081059) continues as well. The site principal investigator is Samuel Kocoshis, and the project is designed to initially establish a multicenter intestinal failure registry and then embark upon prospective clinical and translational studies of pediatric intestinal failure. Fifteen major programs throughout North America participate in the project.

Ajay Kaul, MD

Motility and Functional Bowel Disorders Program

The goal of this unique program at Cincinnati children's hospital is to evaluate and improve outcomes of children with complex neurogastrointestinal and functional bowel disorders. The program operates a motility laboratory with cutting edge manometry and combined pH-impedance technology. A subspecialty clinic dedicated to this population was successfully established this year and we saw an unprecedented increase in regional and national referrals with doubling of the manometry procedures performed. The members of the program presented award-winning abstracts at international and national meetings. Invited talks on related topics were delivered at the annual Arab Health Conference and the team provided expertise towards program development in the middle-east as part of the

institutional global health initiative. Current clinical research topics include GERD, gastroparesis, achalasia, Hirschsprung's disease and constipation.

Stavra Xanthakos, MD; Rohit Kohli, MD
Cincinnati Steatohepatitis Center

The Cincinnati Steatohepatitis Center (CCSC) is a multidisciplinary clinic initiated in November 2008 to care for the unique needs of pediatric patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NAFLD, the hepatic consequence of obesity and metabolic syndrome, affects about 10% of children and ranges from fatty liver alone (NAFLD) to fatty liver with varying degrees of liver inflammation and fibrosis (NASH). NASH is estimated to progress to cirrhosis and liver failure in an estimated 25% of adult individuals; we have recently shown that fibrosis can progress even in childhood. The CCSC evaluates patients for alternate causes of elevated liver enzymes and screens for closely related comorbidities including insulin resistance, hypertension, dyslipidemia, type 2 diabetes mellitus, polycystic ovarian syndrome and obstructive sleep apnea. For therapy, enrollment into intensive weight management programs such as Healthworks is encouraged, but the clinic also provides individualized dietary consultation and recommendations for families who cannot participate in more intensive programs and follows progress in meeting nutritional and activity goals. The CCSC faculty include Stavra Xanthakos MD (medical director), Rohit Kohli MBBS and William Balistreri, MD. Research programs in the CCSC have significantly expanded since its inception and aim to improve our understanding and treatment options for this disease. Researchers in the CCSC are currently studying the outcome of NASH after bariatric surgery in adolescents (K23DK080888, PI: Xanthakos) and animal models of bariatric surgery and NASH (K08 DK084310, PI: Kohli). The CCSC has also recently joined the NIH-funded NASH Clinical Research Network (U01 DK08505, Center PI: Xanthakos), a multi-center study investigating the natural history and determinants of NASH in adults and children and will be offering clinical therapeutic trials in the near future.

Jorge Bezerra, MD
Chronic liver disease program

The goal of the Chronic Liver Disease Program is to improve the long-term outcome of children with liver disease by delivering timely and innovative care and by advancing knowledge through research and education. The Program, a key component of the Pediatric Liver Care Center (PLCC), is staffed by 9 hepatologists, 3 surgeons, and 4 clinical care coordinators. It serves a national and international referral population via a comprehensive evaluation of all medical/surgical aspects of liver disease and the initiation of conventional and innovative treatment. The Program is integrated with the Liver Failure and Liver Transplant Program and provides multi-disciplinary pre-transplant care for patients with end-stage liver disease. Recognizing that improved care requires research, PLCC investigators play key roles in five multi-center consortia sponsored by the National Institutes of Health to advance knowledge on mechanisms of pediatric liver disease and to develop new diagnostic and treatment modalities. Recent innovations include: 1) the development by PLCC investigators of a high-throughput gene chip to diagnose mutations in children with genetic liver diseases – now made available for clinical use by the medical community at large, 2) an ongoing trial to determine the efficacy of corticosteroids in children with biliary atresia, 3) a trial to evaluate whether an antioxidant improves recovery of patients with acute liver failure, 4) study to examine the role of immune dysregulation in the etiology of acute liver failure, and 5) studies to discover the molecular basis of fatty liver disease and biliary atresia. To foster education, the PLCC successfully implemented an Advanced Hepatology Fellowship to train future leaders in the field.

Phil Putnam, MD; James Franciosi, MD
The Cincinnati Center for Eosinophilic Disorders

The Cincinnati Center for Eosinophilic Disorders is a multidisciplinary program, including physicians, nurses, and specialists from: gastroenterology, allergy, otorhinolaryngology, pathology, nutrition, social work, psychology, speech pathology. The Center offers comprehensive diagnostic evaluation and treatment for children with eosinophilic gastrointestinal disorders, and is a nationally-known program that sees over 100 new patients per year from around the country. In addition to receiving clinical care, patients and their families are recruited to participate in clinical research, and to support the efforts in Dr Rothenberg's laboratory by providing tissue for basic science research. These studies are intended to establish an understanding of the pathogenesis of eosinophilic gastrointestinal disorders and thereby to offer both more effective treatment options and simpler disease monitoring. The physicians (Putnam, Rothenberg, and Collins) are part of an international committee (the International Gastrointestinal Eosinophil Researchers) that seeks to organize multicenter studies on eosinophilic disorders.

Division Collaboration

Collaboration with Allergy & Immunology

Collaborating Faculty: Simon P. Hogan, PhD

Regulation of Intestinal Barrier Function by Signal Transducers and Activators of Transcription 5b - Xiaonan Han, PhD

Collaboration with Allergy & Immunology

Collaborating Faculty: Simon P. Hogan, PhD

Paired Immunoglobulin Receptor B Regulation of Innate Intestinal Immunity - Kris Steinbrecher, PhD

Collaboration with Allergy & Immunology

Collaborating Faculty: Marc E. Rothenberg, MD, PhD

Digestive Health Center: A double blinded, randomized trial of swallowed 1760 mcg Fluticasone propionate versus placebo in the treatment of Eosinophilic Esophagitis - Scott Pentiuik, MD

Collaboration with Biomedical Informatics; Pathology; Developmental Biology

Collaborating Faculty: Bruce Aronow, PhD; Anil Jegga, DVM, MRes; David P. Witte, MD; Keith F. Stringer, MD; S. Steven Potter, MD

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Mitchell Cohen, MD and Jorge Bezerra, MD

Collaboration with Biomedical Informatics

Collaborating Faculty: Anil Jegga, DVM, MRes

The Jaundice Chip: diagnostic tool for cholestatic liver disease - Jorge Bezerra, MD

Molecular phenotyping in children with biliary atresia - Jorge Bezerra, MD

Collaboration with Biostatistics and Epidemiology; Mass Spectrometry Laboratory

Collaborating Faculty: Jane Houry, PhD; Kenneth D. Setchell, PhD

Intraluminal Effects of Cholesterol Absorption/Synthesis - James Heubi, MD

Collaboration with Biostatics and Epidemiology

Collaborating Faculty: Mi-Ok Kim, PhD

GM-CSF Bioactivity and IBD Phenotype - Lee Denson, MD

Biomarkers in Pediatric Intestinal Failure - Emily Kevan, MD, Samuel Kocoshis, MD, Jeffrey Rudolph, MD

Collaboration with Hematology/Oncology

Collaborating Faculty: Alexandra H. Filipovich, MD

Pediatric Acute Liver Failure U01 - Immunology and GI: Assessment of NK cell function - John Bucuvalas, MD

Collaboration with Hematology/Oncology

Collaborating Faculty: Joseph Palumbo, MD

Hemostatic Factors in Colitis and Colitis-Associated Colon Cancer - Kris Steinbrecher, PhD

Collaboration with Molecular Immunology

Collaborating Faculty: Claire A. Chougnet, PhD; Kasper Hoebe, PhD

Immunologic Dysfunction in Biliary Atresia - Jorge Bezerra, MD

Mutagenesis-induced hepatic steatosis - Jorge Bezerra, MD

Collaboration with Molecular Immunology

Collaborating Faculty: Kasper Hoebe, PhD

Role of Gimap5 in Immune Tolerance - Kris Steinbrecher, PhD

Collaboration with Neonatology & Pulmonary Biology

Collaborating Faculty: Bruce C. Trapnell, MD, MS

GM-CSF Bioactivity and IBD Phenotype - Lee Denson, MD

Collaboration with Pathology

Collaborating Faculty: Kevin E. Bove, MD

Molecular Determinants of Phenotypes in Biliary Atresia - Jorge Bezerra, MD

Morphology in Cholestatic Liver Consortium - James Heubi, MD

Faculty Members

Mitchell B Cohen, MD, Professor ; *Gastroenterology Endowed Chair; Vice-Chair of Pediatrics for Clinical Affairs; Director, Division of Gastroenterology, Hepatology and Nutrition; Associate Director, Digestive Health Center*

Research Interests: Diarrheal diseases

William F Balistreri, MD, Professor ; *Dorothy M.M. Kersten Endowed Chair; Director Emeritus, Pediatric Liver Care Center; Medical Director Emeritus, Liver Transplantation; Program Director, Advanced Hepatology Fellowship; Editor, Journal of Pediatrics*

Research Interests: Chronic liver disease

Jorge A Bezerra, MD, Professor ; *William and Rebecca Balistreri Chair in Pediatric Hepatology; Director of Research, Division of Gastroenterology, Hepatology and Nutrition; Director, Biliary Atresia Center; Director, Digestive Health Center*

Research Interests: Biliary atresia and chronic liver disease

John C Bucuvalas, MD, Professor ; *Endowed Chair in Pediatric Transplant Hepatology; Associate Medical Director, Pediatric Liver Care Center; Director, Disease Specific Innovations and Outcomes Program*

Research Interests: Liver failure and liver transplantation

Kathleen M Campbell, MD, Assistant Professor ; *Medical Director, Pediatric Liver Transplant*

Research Interests: Liver failure and liver transplantation

Lee A Denson, MD, Associate Professor ; *M. Susan Moyer Chair in Pediatric IBD; Director, Schubert-Martin Pediatric IBD Center; Director, Fellowship Training Program in Pediatric Gastroenterology, Hepatology and Nutrition; Associate Director, Digestive Health Center*

Research Interests: Inflammatory Bowel Diseases

Michael K Farrell, MD, Professor ; *Chief of Staff*

Research Interests: Nutrition

James Franciosi, MD, Assistant Professor

Research Interests: Eosinophilic Gastrointestinal Disorders

Monica Garin-Laflam, MD, Instructor

Research Interests: Diarrheal diseases

Xiaonan Han, PhD, Instructor

Research Interests: Inflammatory Bowel Diseases

James E Heubi, MD, Professor ; *Associate Chair for Clinical Investigation of Pediatrics; Associate Dean for Clinical and Translational Research; Co-Director, Center of Clinical and Translational Science & Training*

Research Interests: Chronic liver disease

Ajay Kaul, MD, Associate Professor ; *Director, Impedance/Motility Disorders Program; Medical Director, Liberty Campus for GI*

Research Interests: Intestinal motility disorders

Samuel A Kocoshis, MD, Professor ; *Medical Director, Pediatric Nutritional and Intestinal Care Center; Medical Director, Small Bowel Transplantation Program*

Research Interests: Intestinal Failure and Intestinal Transplantation

Rohit Kohli, MD, Assistant Professor

Research Interests: Non-alcoholic steatohepatitis

Mike A Leonis, MD, PhD, Assistant Professor ; *Associate Fellowship Director, Training Program in Pediatric Gastroenterology, Hepatology and Nutrition*

Research Interests: Liver failure and liver transplantation; liver tumors

Adam G Mezzoff, MD, Professor ; *Associate Director, Intestinal Failure and Transplant Program*

Research Interests: Intestinal failure and intestinal transplantation

Scott Pentiuik, MD, Assistant Professor ; *Medical Director, Interdisciplinary Feeding Team*

Research Interests: Feeding disorders; medical education

Philip E Putnam, MD, Associate Professor ; *Director, Endoscopy Services; Medical Director, Cincinnati Center for Eosinophilic Disorders*

Research Interests: Eosinophilic Gastrointestinal Disorders

Jeffrey A Rudolph, MD, Assistant Professor

Research Interests: Intestinal Failure and Intestinal Transplantation

Pranav Shivakumar, PhD, Instructor

Research Interests: Biliary Atresia

Noah Shroyer, PhD, Assistant Professor

Research Interests: Intestinal development

Kris Steinbrecher, PhD, Assistant Professor

Research Interests: Diarrheal diseases; Inflammatory Bowel Diseases

Gitit Tomer, MD, Assistant Professor

Research Interests: Inflammatory Bowel Diseases

Cynthia C Wetzel, PhD, Assistant Professor ; *Program Manager, Digestive Health Center*

Research Interests: Research Administration

Stavra Xanthakos, MD, Assistant Professor ; *Medical Director, Surgical Weight Loss Program for Teens*

Research Interests: Obesity; Non-alcoholic steatohepatitis

Nada Yazigi, MD, Assistant Professor ; *CSI Inpatient Co-Director A4N*

Research Interests: Liver failure and liver transplantation

Trainees

- **Alexander Miethke, MD,** PL-7, Cincinnati Children's Hospital Medical Center
- **Katie Moyer, MD,** PL-6, Oregon Health and Sciences University
- **Melanie Rhue, MD,** PL-6, Carolinas Medical Center
- **Charles Samson, MD,** PL-6, University of North Carolina at Chapel Hill
- **Bella Zeisler, MD,** PL-6, New York University
- **Sharon D'Mello, MD,** PL-5, St. Christopher's Hospital for Children
- **Jose Garza, MD,** PL-5, Cincinnati Children's Hospital Medical Center
- **Emily Kevan, MD,** PL-5, University of Colorado
- **Cade Nylund, MD,** PL-5, San Antonio Military Pediatric Center
- **Stephanie Appleman, MD,** PL-4, INOVA Fairfax Hospital for Children
- **Benjamin Kuhn, DO,** PL-4, Penn State Children's Hospital
- **Anna Trauernicht, MD,** PL-4, Indiana University
- **Amy Tsai, MD,** PL-4, New York Medical College
- **Jason Hasenstein, PhD,** Iowa State University
- **Li Jun, MD, PhD,** Beijing Medical University and Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China
- **Ingrid Jurickova, MD,** Second Medical Faculty, Charles University, Prague, Czech Republic
- **Avedis Kazanjian, PhD,** University of Louisville
- **Elizabeth Mann, PhD,** State University of New York at Buffalo
- **Ethan Mezzoff, MD,** Wright State University
- **Taeko Noah, PhD,** University of Nevada, Reno
- **Vijay Saxena, PhD,** Kanpur University, India

- **Kumar Shanmukhappa, PhD**, Kansas University, Missouri
- **Tara Willson, BS**, University of Kentucky, Lexington

Significant Accomplishments

Schubert Martin Inflammatory Bowel Disease (IBD) Center

The number of patients receiving medical and surgical care for IBD both from the region and nationally has continued to grow. State-of-the-art services including newer diagnostic imaging modalities and psychology interventions for non-adherence have been added. With support from the Crohn's and Colitis Foundation of America, and the Pediatric Research Organization for Kids with Intestinal Inflammatory Disorders (PRO-KIIDS), the center has been a leader in establishing multi-center clinical trials in children with IBD. IBD center investigators have completed the first randomized, controlled trial of human growth hormone in children with Crohn's Disease, and have contributed to the first genome-wide association study to identify susceptibility genes specifically for pediatric-onset IBD. The IBD center has also played a leading role in ImproveCareNow (ICN), the national pediatric IBD quality improvement network. Over the past year, the ICN network has achieved a 20% improvement in patient remission rates with implementation of consensus patient care guidelines and practices.

Liver Failure and Transplant Program

Members of the Pediatric Liver Transplant Program continue to advance science via insightful leadership of multi-center clinical and translational studies, including the NIH-sponsored Studies in Pediatric Liver Transplantation (SPLIT) and the Pediatric Acute Liver Failure Study Group (PALF). Under the leadership of John Bucuvalas, MD, SPLIT successfully competed for an NIH planning grant (U34) to design a clinical and translational study focused on withdrawal of immunosuppression and the biological mechanisms underlying tolerance. The PALF group has continued its' collaboration with Alexandra Filipovich, MD, in preliminary studies investigating the role of Natural Killer (NK) cell dysfunction in acute liver failure. An increase in the number of referrals for hepatoblastoma resection and/or transplantation, combined with ongoing collaboration with James Geller, MD in Pediatric Oncology, has provided the infrastructure and patient population necessary for CCHMC to take a lead in patient-based research in this field.

Division Publications

1. Cohen MB. ["Gastroenterology." Blueprints pediatrics](#). Philadelphia: Lippincott Williams & Wilkins; 2009: 88-105.
2. Cohen MB. [Clostridium difficile infections: emerging epidemiology and new treatments](#) . *J Pediatr Gastroenterol Nutr*. 2009; 48 Suppl 2: S63-5.
3. Franciosi JP, Tam V, Liacouras CA, Spergel JM. [A case-control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis](#) . *Clin Gastroenterol Hepatol*. 2009; 7: 415-9.
4. Garin-Laflam MP, Steinbrecher KA, Rudolph JA, Mao J, Cohen MB. [Activation of guanylate cyclase C signaling pathway protects intestinal epithelial cells from acute radiation-induced apoptosis](#) . *Am J Physiol Gastrointest Liver Physiol*. 2009; 296: G740-9.
5. Han X, Uchida K, Jurickova I, Koch D, Willson T, Samson C, Bonkowski E, Trauernicht A, Kim MO, Tomer G, Dubinsky M, Plevy S, Kugathasan S, Trapnell BC, Denson LA. [Granulocyte-macrophage colony-stimulating factor autoantibodies in murine ileitis and progressive ileal Crohn's disease](#) . *Gastroenterology*. 2009; 136: 1261-71, e1-3.
6. Putnam PE. [Stop the PPI express: they don't keep babies quiet!](#) . *J Pediatr*. 2009; 154: 475-6.
7. Yi MS, Britto MT, Sherman SN, Moyer MS, Cotton S, Kotagal UR, Canfield D, Putnam FW, Carlton-Ford S, Tsevat J. [Health values in adolescents with or without inflammatory bowel disease](#) . *J Pediatr*. 2009; 154: 527-34.
8. Franciosi JP, Liacouras CA. [Eosinophilic esophagitis](#) . *Immunol Allergy Clin North Am*. 2009; 29: 19-27, viii.
9. Franciosi JP, Mascarenhas M, Semeao E, Flick J, Kelly J, Mamula P. [Randomised controlled trial of paediatric magnetic positioning device assisted colonoscopy: a pilot and feasibility study](#) . *Dig Liver Dis*. 2009; 41: 123-6.
10. Olver IN, Whitford HS, Denson LA, Peterson MJ, Olver SI. [Improving informed consent to chemotherapy: a randomized controlled trial of written information versus an interactive multimedia CD-ROM](#) . *Patient Educ Couns*. 2009; 74: 197-204.
11. Pentiuk S, Putnam PE, Collins MH, Rothenberg ME. [Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis](#) . *J Pediatr Gastroenterol Nutr*. 2009; 48: 152-60.
12. Putnam PE. [Evaluation of the child who has eosinophilic esophagitis](#) . *Immunol Allergy Clin North Am*. 2009; 29: 1-10, vii.
13. Steinberg SJ, Snowden A, Braverman NE, Chen L, Watkins PA, Clayton PT, Setchell KD, Heubi JE, Raymond GV, Moser AB, Moser HW. [A PEX10 defect in a patient with no detectable defect in peroxisome assembly or](#)

- [metabolism in cultured fibroblasts](#). *J Inherit Metab Dis*. 2009; 32: 109-19.
14. Bossuyt W, Kazanjian A, De Geest N, Van Kelst S, De Hertogh G, Geboes K, Boivin GP, Luciani J, Fuks F, Chuah M, VandenDriessche T, Marynen P, Cools J, Shroyer NF, Hassan BA. [Atonal homolog 1 is a tumor suppressor gene](#). *PLoS Biol*. 2009; 7: e39.
 15. Han X, Ren X, Jurickova I, Groschwitz K, Pasternak BA, Xu H, Wilson TA, Hogan SP, Denson LA. [Regulation of intestinal barrier function by signal transducer and activator of transcription 5b](#). *Gut*. 2009; 58: 49-58.
 16. Perman MJ, Lucky AW, Heubi JE, Azizkhan RG. [Severe symptomatic hypocalcemia in a patient with RDEB treated with intravenous zoledronic acid](#). *Arch Dermatol*. 2009; 145: 95-6.
 17. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, Liacouras CA. [14 years of eosinophilic esophagitis: clinical features and prognosis](#). *J Pediatr Gastroenterol Nutr*. 2009; 48: 30-6.
 18. Putnam PE, Rothenberg ME. [Eosinophilic esophagitis: concepts, controversies, and evidence](#). *Curr Gastroenterol Rep*. 2009; 11: 220-5.
 19. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP, Murray KF, Narkewicz MR, Rosenthal P, Smith LJ, Schwarz KB, Robuck P, Barton B, Gonzalez-Peralta RP. [Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes](#). *J Pediatr Gastroenterol Nutr*. 2009; 48: 341-7.
 20. Rudnick DA, Dietzen DJ, Turmelle YP, Shepherd R, Zhang S, Belle SH, Squires R. [Serum alpha-NH-butyric acid may predict spontaneous survival in pediatric acute liver failure](#). *Pediatr Transplant*. 2009; 13: 223-30.
 21. Wang K, Zhang H, Kugathasan S, Annese V, Bradfield JP, Russell RK, Sleiman PM, Imielinski M, Glessner J, Hou C, Wilson DC, Walters T, Kim C, Frackelton EC, Lionetti P, Barabino A, Van Limbergen J, Guthery S, Denson L, Piccoli D, Li M, Dubinsky M, Silverberg M, Griffiths A, Grant SF, Satsangi J, Baldassano R, Hakonarson H. [Diverse genome-wide association studies associate the IL12/IL23 pathway with Crohn Disease](#). *Am J Hum Genet*. 2009; 84: 399-405.
 22. Uchida K, Nakata K, Suzuki T, Luisetti M, Watanabe M, Koch DE, Stevens CA, Beck DC, Denson LA, Carey BC, Keicho N, Krischer JP, Yamada Y, Trapnell BC. [Granulocyte/macrophage-colony-stimulating factor autoantibodies and myeloid cell immune functions in healthy subjects](#). *Blood*. 2009; 113: 2547-56.
 23. Moyer K, Balistreri W. [Hepatobiliary disease in patients with cystic fibrosis](#). *Curr Opin Gastroenterol*. 2009; 25: 272-8.
 24. Tomer G, Wetzler G, Keddache M, Denson LA. [Polymorphisms in the IBD5 locus are associated with Crohn disease in pediatric Ashkenazi Jewish patients](#). *J Pediatr Gastroenterol Nutr*. 2009; 48: 531-7.
 25. Shanmukhappa K, Matte U, Degen JL, Bezerra JA. [Plasmin-mediated proteolysis is required for hepatocyte growth factor activation during liver repair](#). *J Biol Chem*. 2009; 284: 12917-23.
 26. Carvalho RS, Michail S, Ashai-Khan F, Mezoff AG. [An update on pediatric gastroenterology and nutrition: a review of some recent advances](#). *Curr Probl Pediatr Adolesc Health Care*. 2008; 38: 204-28.
 27. Furuta GT, Forbes D, Boey C, Dupont C, Putnam P, Roy S, Sabra A, Salvatierra A, Yamashiro Y, Husby S. [Eosinophilic gastrointestinal diseases \(EGIDs\)](#). *J Pediatr Gastroenterol Nutr*. 2008; 47: 234-8.
 28. Xanthakos SA. [Bariatric surgery for extreme adolescent obesity: Indications, outcomes, and physiologic effects on the gut-brain axis](#). *Pathophysiology*. 2008; 15: 135-46.
 29. Bucuvalas JC, Alonso E, Magee JC, Talwalkar J, Hanto D, Doo E. [Improving long-term outcomes after liver transplantation in children](#). *Am J Transplant*. 2008; 8: 2506-13.
 30. Carrasco R, Lovell DJ, Giannini EH, Henderson CJ, Huang B, Kramer S, Ranz J, Heubi J, Glass D. [Biochemical markers of bone turnover associated with calcium supplementation in children with juvenile rheumatoid arthritis: results of a double-blind, placebo-controlled intervention trial](#). *Arthritis Rheum*. 2008; 58: 3932-40.
 31. Denson LA. [Growth hormone therapy in children and adolescents: pharmacokinetic/pharmacodynamic considerations and emerging indications](#). *Expert Opin Drug Metab Toxicol*. 2008; 4: 1569-80.
 32. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, McDiarmid S, Cohen G, Anand R. [Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a north american multicenter registry](#). *Pediatrics*. 2008; 122: e1128-35.
 33. Stadler LP, Mezoff AG, Staat MA. [Hepatitis B virus screening for internationally adopted children](#). *Pediatrics*. 2008; 122: 1223-8.
 34. Blanchard C, Mingler MK, McBride M, Putnam PE, Collins MH, Chang G, Stringer K, Abonia JP, Molkentin JD, Rothenberg ME. [Periostin facilitates eosinophil tissue infiltration in allergic lung and esophageal responses](#). *Mucosal Immunol*. 2008; 1: 289-96.
 35. Hommel KA, Mackner LM, Denson LA, Crandall WV. [Treatment regimen adherence in pediatric gastroenterology](#). *J Pediatr Gastroenterol Nutr*. 2008; 47: 526-43.

36. Ahrens R, Waddell A, Seidu L, Blanchard C, Carey R, Forbes E, Lampinen M, Wilson T, Cohen E, Stringer K, Ballard E, Munitz A, Xu H, Lee N, Lee JJ, Rothenberg ME, Denson L, Hogan SP. [Intestinal macrophage/epithelial cell-derived CCL11/eotaxin-1 mediates eosinophil recruitment and function in pediatric ulcerative colitis](#). *J Immunol*. 2008; 181: 7390-9.
37. Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, Cucchiara S, Kim CE, Frackelton EC, Annaiah K, Glessner JT, Santa E, Willson T, Eckert AW, Bonkowski E, Shaner JL, Smith RM, Otieno FG, Peterson N, Abrams DJ, Chiavacci RM, Grundmeier R, Mamula P, Tomer G, Piccoli DA, Monos DS, Annese V, Denson LA, Grant SF, Hakonarson H. [Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease](#). *Nat Genet*. 2008; 40: 1211-5.
38. Britto MT, Byczkowski TL, Anneken AM, Hausfeld J, Schoettker PJ, Farrell MK, Kotagal UR. [Improving access to pediatric subspecialty care: initial failures and lessons learned](#). *Qual Manag Health Care*. 2008; 17: 320-9.
39. Calvo-Garcia MA, Campbell KM, O'Hara SM, Khoury P, Mitsnefes MM, Strife CF. [Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction](#). *Pediatr Transplant*. 2008; 12: 666-71.
40. Peterson N, Guthery S, Denson L, Lee J, Saeed S, Prahalad S, Biank V, Ehlert R, Tomer G, Grand R, Rudolph C, Kugathasan S. [Genetic variants in the autophagy pathway contribute to paediatric Crohn's disease](#). *Gut*. 2008; 57: 1336-7; author reply 1337.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

BALISTRERI, W

Pegylated Interferon +/- Ribavirin for Children With HCV

National Institutes of Health (Johns Hopkins University)

U01 DK 067767

09/30/03 - 08/31/09

\$16,506 / \$110,120

BEZERRA, J

The Plasminogen System and Liver Repair

National Institutes of Health

R01 DK 055710

02/15/07 - 11/30/10

\$200,900 / \$820,000

Jaundice Chip: A Diagnostic Tool for Cholestatic Liver Disease

National Institutes of Health (P2D, Inc.)

R42 DK 075162

07/01/07 - 06/30/09

\$92,425 / \$176,059

Immunologic Dysfunction In Biliary Atresia

National Institutes of Health

R01 DK 064008

02/25/08 - 01/31/13

\$212,500 / \$1,062,500

Clinical Center for Biliary Atresia: Etiopathogenesis and Clinical Outcome

National Institutes of Health

U01 DK 062497

09/15/02 - 12/31/09

\$159,329 / \$1,101,428

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

National Institutes of Health

P30 DK 078392

08/01/07 - 05/31/12

\$727,500 / \$3,637,500

Bezerra, J

Administrative Core

325,499

Potter, S

Gene Expression Core

53,741

Aronow, B

Bioinformatics Core

106,171

Witte, D

Integrative Morphology Core

113,119

Grabowski, G

Sequencing Core

21,332

Hommel, K

P&F Study

30,000

Miethke, A

P&F Study

30,000

Hoebe, K

P&F Study

30,000

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

National Institutes of Health

P30 DK 078392 (supplement)	07/25/09 - 05/31/11	\$215,033 / \$215,033
Bezerra, J	Administrative	155,033
Hoebe, K	P&F Study	20,000
Hommel, K	P&F Study	20,000
Miethke, A	P&F Study	20,000

BUCUVALAS, J**Functional Outcomes in Pediatric Liver Transplantation**

National Institutes of Health (Children's Memorial Hospital)

R01 HD 045694	04/01/05 - 03/31/10	\$12,595 / \$119,188
---------------	---------------------	----------------------

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

National Institutes of Health (Children's Hospital of Pittsburgh)

U01 DK 072146	09/01/05 - 08/31/10	\$39,167 / \$197,941
---------------	---------------------	----------------------

Studies of Pediatric Liver Transplantation

National Institutes of Health (Emmes Corporation)

U01 DK 61693	05/15/04 - 03/31/10	\$21,670 / \$138,600
--------------	---------------------	----------------------

COHEN, M**Expression and Function of the Guanylin Ligand Family**

National Institutes of Health

R01 DK 047318	02/01/05 - 11/30/09	\$204,428 / \$1,100,000
---------------	---------------------	-------------------------

Pediatric Gastroenterology and Nutrition Training Grant

National Institutes of Health

T32 DK 007727	07/01/05 - 06/30/10	\$315,213 / \$1,771,477
---------------	---------------------	-------------------------

A Randomized, Double-Blind, Placebo Controlled Dose Escalation Inpatient Phase I Study to Determine the Safety of ETEC

National Institutes of Health (University of Maryland)

N01 AI 040014	12/01/08 - 11/30/09	\$307,045 / \$460,468
---------------	---------------------	-----------------------

DENSON, L**Cytokine Regulation of Growth Hormone Signaling**

National Institutes of Health

R01 DK 068164	04/01/06 - 12/31/10	\$190,316 / \$1,000,000
---------------	---------------------	-------------------------

Prospective Study of Immuno-genetic Determinants of Growth in Pediatric IBD

Crohn's and Colitis Foundation of America

	07/01/07 - 06/30/09	\$130,000 / \$260,000
--	---------------------	-----------------------

GM-CSF Bioactivity and IBD Phenotype

Broad Medical Research Program

IBD-0211	10/01/07 - 09/30/09	\$61,956 / \$195,089
----------	---------------------	----------------------

Biomarkers for Inflammatory Bowel Disease Behavior and Treatment Response

National Institutes of Health

R01 DK 078683	04/01/09 - 03/31/13	\$401,274 / \$1,581,829
---------------	---------------------	-------------------------

Risk Stratification and Identification of Immunogenetic and Microbial Markers of Complicated Disease

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

6-38778-G1	07/01/08 - 06/30/09	\$10,000 / \$10,000
------------	---------------------	---------------------

FRANCIOSI, J**Outcome Measures in Eosinophilic Esophagitis: Beyond Eosinophil Counting**

Children's Digestive Health and Nutrition Foundation

	12/15/08 - 12/14/10	\$75,000 / \$150,000
--	---------------------	----------------------

GARIN-LAFLAM, M

Guanylin Cyclase C Activation in Intestinal Epithelial Survival and Migration

National Institutes of Health

F32 DK 080588

07/01/08 - 06/30/09

\$56,702 / \$56,702

HEUBI, J**Intraluminal Effects of Cholesterol Absorption/ Synthesis**

National Institutes of Health

R01 DK 068463

05/01/05 - 01/31/10

\$375,217 / \$1,653,077

Rare Liver Disease Network- CLIC6001

National Institutes of Health (The Children's Hospital of Denver)

U54 DK 078377

08/01/07 - 07/31/09

\$6,249 / \$6,249

BARC Central Lab CRC

National Institutes of Health (University of Michigan)

U01 DK 062456

09/01/05 - 05/31/10

\$11,863 / \$11,863

KOCOSHIS, S**Intestinal Failure in Children: A Contemporary Retrospective Review by the Pediatric Intestinal Failure Consortium**

National Institutes of Health (Children's Hospital of Pittsburgh)

R21 DK 081059

06/15/08 - 05/31/10

\$3,643 / \$9,107

KOHLI, R**Effect of Ileal Transposition on Nutritional Associated Hepatic Steatosis**

Children's Digestive Health and Nutrition Foundation

11/15/07 - 11/14/09

\$50,000 / \$100,000

Pediatric Center for Gene Expression and Development

National Institutes of Health

K12 HD 028827

10/01/07 - 08/31/09

\$98,331 / \$193,272

LEONIS, M**The RON Receptor Tyrosine Kinase in Hepatic Tumorigenesis**

National Institutes of Health

K08 CA 111819

08/01/06 - 07/31/11

\$123,000 / \$615,000

MIETHKE, A**AASLD Advanced Transplant Hepatology Fellowship**

American Association for the Study of Liver Diseases

07/01/08 - 06/30/09

\$60,000 / \$60,000

SHROYER, N**Intestinal Secretory Lineage Development and Function**

National Institutes of Health

K01 DK 071686

09/01/06 - 07/31/09

\$124,417 / \$371,138

STEINBRECHER, K**Role Of Epithelial GSk-3 β in Initiation and Resolution of Intestinal Inflammation**

AGA Foundation for Digestive Health and Nutrition

07/01/07 - 06/30/10

\$18,750 / \$56,250

Role of p65/GSK-3 β -mediated Gene Expression in Initiation of IBD

Crohn's and Colitis Foundation of America

01/01/08 - 12/31/10

\$90,000 / \$270,000

XANTHAKOS, S**Biological Determinants of Steatohepatitis after Adolescent Bariatric Surgery**

National Institutes of Health

K23 DK 080888

07/01/08 - 06/30/13

\$173,400 / \$820,600

Current Year Direct**\$4,584,429**

Industry Contracts

Balistreri, W

Digestive Care, Inc.

\$ 1,121

Gilead Sciences, Inc.

\$ 2,796

Denson, L

Abbott Laboratories

\$ 24,293

Yazigi, N

IWK Health Care

\$ 2,563

Current Year Direct Receipts

\$30,773

Total

**\$
4,615,202**
