

Gastroenterology, Hepatology and Nutrition

Division Photo



Front Row: X. Han, S. Saeed, S. Kocoshis, M. Cohen, R. Kohli, N. Yazigi, J. Heubi, C. Wetzel Back Row: P. Shivakumar, K. Steinbrecher, A. Mezoff, C. Cole, M. Farrell, A. Miethke, M. Leonis

Division Data Summary

Research and Training Details

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Number of Faculty	26		
Number of Research Fellows	5		
Number of Research Students	1		
Number of Support Personnel	56		
Direct Annual Grant Support	\$5,013,394		
Direct Annual Industry Support	\$38,949		
Peer Reviewed Publications	56		
Clinical Activities and Training			
Number of Clinical Staff	40		
Number of Clinical Fellows	12		
Inpatient Encounters	9,336		
Outpatient Encounters	12,537		

Significant Publications

Imielinski, M., R. Baldassano, A. Griffiths, R. Russell, V. Annese, M. Dubinsky, S. Kugathasan, J. Bradfield, T. Walters, P. Sleiman, C. Kim, A. Muise, K. Wang, J. Glessner, S. Saeed, H. Zhang, E. Frackelton, C. Hou, J. Flory, G. Otieno, R. Chiavacci, R. Grundmeier, M. Castro, A. Latiano, B. Dallapiccola, J. Stempak, D. Abrams, K.Taylor, D. McGovern, Western Regional Research Alliance for Pediatric IBD, International IBD Genetics Consortium, M. Heyman, G. Ferry, B. Kirschner, J. Lee, J. Essers, R. Grand, M. Stephens, A. Levine, D. Piccoli, J. Limbergen, S. Cucchiara, D. Monos, S. Guthery, L. Denson, D. Wilson, S. Grant, M. Daly, M. Silverberg, J. Satsangi, H. Hakonarson. Common variants at five new loci associated with early-onset inflammatory bowel disease. Nature Genetics. 2009 Dec;41(12):1335-40.

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. Stratification of IBD by age of onset may identify additional genes associated with IBD. Here we reported the results of a genome-wide association study in early-onset IBD involving 3,426 affected individuals and 11,963 genetically matched controls recruited through international collaborations in Europe and North America, thereby extending the results from a previous study of 1,011 individuals with early-onset IBD. We identified five new regions associated with early-onset IBD susceptibility, including 16p11 near the cytokine gene IL27 (rs8049439, P = 2.41 x 10(-9)), 22q12 (rs2412973, P = $1.55 \times 10(-9)$), 10q22 (rs1250550, P = $5.63 \times 10(-9)$), 2q37 (rs4676410, P = $3.64 \times 10(-8)$) and 19q13.11 (rs10500264, P = $4.26 \times 10(-10)$). Our scan also detected associations at 23 of 32 loci previously implicated in adult-onset IBD.

Miethke, A.G., Saxena, V., Shivakumar, P., Sabla, G.E., Simmons, J., Chougnet, C. A. Post-natal paucity of regulatory T cells and control of NK cell activation in experimental biliary atresia. J Hepatol, 2010. 52(5): p. 718-26.

Biliary atresia is a fibroinflammatory obstruction of the extrahepatic biliary tree and the most common cause of pediatric liver transplantation worldwide. Although recent studies have identified important roles for T and NK cells in the pathogenesis of biliary atresia (BA), the mechanisms by which susceptibility to bile duct injury is restricted to the early neonatal period are unknown. Using the well-established murine model of rotavirus (RRV)-induced experimental biliary atresia, we found no increase in hepatic Tregs (Foxp3+ CD4+ CD25+) within 3 days following infection on day 1 of life. In contrast, late RRV inoculation on day 7 of life, which renders neonatal mice not susceptible to BA, increased hepatic Tregs by 10-fold within the same time period. In vitro, Tregs effectively suppressed NK cell activation by hepatic dendritic cells and decreased the production of pro-inflammatory cytokines, including TNFalpha and IL-15, following RRV infection. In vivo, adoptive transfer of CD4+ cells prior to RRV inoculation led to increased survival, improved weight gain, decreased population of hepatic NK cells, and persistence of donor Tregs in the liver. Thus, the post-natal absence of Tregs may be a key factor that allows hepatic DCs to act unopposed in NK cell activation during the initiation of neonatal bile duct injury.

Division Highlights

Jorge Bezerra, MD, Mitchell B. Cohen, MD, Cynthia Wetzel, Ph.D.

Digestive Health Center (DHC)

The DHC is one of only 17 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 research on pediatric digestive diseases. The DHC administrative body is comprised of Dr. Jorge Bezerra serving as the Director, Drs. Mitchell Cohen, Aaron Zorn, and Chip Montrose as Associate Directors, and Dr. Cynthia Wetzel as Program Manager. The DHC includes 52 investigators and 33 associate members from 18 different divisions within the Department of Pediatrics and a total of 8 departments within within the University of Cincinnati, College of Medicine. The DHC Cores provide services to increase the tempo of scientific discoveries in digestive disease research and to attract new investigators in the field. 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 focus areas and diseases: 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), and 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). 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 Pentiuk, MD

Interdisciplinary Feeding Team (IFT)

This multi-disciplinary team provides comprehensive evaluation of children with swallowing/feeding disorders. It includes members from gastroenterology, otolaryngology, human genetics, speech therapy, occupational therapy, social work, and nutrition. Dr. Scott Pentiuk MD is the pediatric gastroenterologist on the team. The IFT continues to grow at nearly 10% per year with approximately 1200 patient visits 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, quality of life assessment of feeding therapies, 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, Chip Samson, MD Schubert Martin Inflammatory Bowel Disease (IBD) Center

The number of patients receiving multi-disciplinary care for IBD has continued to grow, with children from more than 20 states seen over the past year. State-of-the art services including diagnostic imaging modalities which do not require radiation exposure, and targeted psychology interventions for non-adherence, have been implemented. We have continued to contribute to ongoing international genome-wide association studies to identify susceptibility genes specifically for pediatric-onset disease. A collaboration with Dr. Bruce Trapnell in Pulmonary Biology has defined the role of Granulocyte-Macrophage Colony Stimulating Factor Auto-Antibodies in more aggressive Crohn's Disease. This has now been tested in patients from throughout North America and Australia. A study in collaboration with Dr. Christopher Karp in the Division of Molecular Immunology linked endotoxin exposure to activation of systemic inflammation and growth failure in patients with IBD. A study in collaboration with Dr. Simon Hogan in Allergy/Immunology identifed a novel anti-inflammatory pathway in the affected intestine of patients. With support from the Crohn's and Colitis Foundation of America, the center has been a leader in successfully launching the first large inception cohort study of 1100 newly diagnosed patients. This study will examine the interplay between the genetic, immune, and microbial influences which drive outcomes for children with Crohn's Disease (CD). A study performed together with Dr. Meena Thayu at the Children's Hospital of Philadelphia for the first time defined the relationship between therapeutic control of inflammation, and improvements in growth, in affected children. In collaboration with Dr. David Klein in Endocrinology, center investigators published the first randomized controlled trial of human growth hormone in children with CD, demonstrating beneficial effects upon both symptoms and growth. Studies performed in collaboration with Dr. Kevin Hommel in the Center for Adherence identified barriers to medication adherence in children with IBD. The IBD center has continued to play a leading role in ImproveCareNow (ICN), the national pediatric IBD quality improvement network. The ICN network has achieved a 20% improvement in patient remission rates with implementation of consensus patient care guidelines and practices. This network was the basis for a National Institutes of Health award to Dr. Peter Margolis in the Center for Health Care Quality to now develop an innovative web-based social networking model to improve outcomes for children with IBD.

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

In May 2010, the Pediatric Liver Transplant Program celebrated performing its 500th pediatric liver transplant since the program was founded in 1986. The program remains one of the largest pediatric liver transplant programs in the country, with excellent outcomes as marked by 1-year and 3-year survival rates at or above the national average. In addition to clinical excellence provided by an interdisciplinary team and enterprise-wide attention to health care delivery, members of the Pediatric Liver Transplant Program continue to advance science and focus patient based research on defined gaps in knowledge via insightful leadership of multi-center clinical and translational studies. These studies include: the sponsored Pediatric Acute Liver Failure Study Group (PALF); Medication adherence in children who had a liver transplant (MALT); Functional outcomes in liver transplant recipients (FOG) Immunosuppression withdrawal for sable pediatric liver transplant recipients (iWITH) studies; the multi-center collaborative Studies in Pediatric Liver Transplantation (SPLIT) and a collaborative effort with investigators from Children's Hospital of Philadelphia focused on Calcineurin Inhibitor Minimization and Foxp3+ T-regs post-transplant, a project funded through the American Recovery and Reinvestment Act of 2009. Through these and other projects, the Liver Transplant Program remains a leader in clinical and bench-to-bedside research designed to improve the outcomes for pediatric liver transplant patients.

Samuel Kocoshis, MD; Adam Mezoff MD, Nada Yazigi, MD, Noah Shroyer, PhD The Nutrition and Intestinal Care Center/Small Intestinal Transplantation Program

This program has experienced considerable growth during the past year in order to position itself to take a national leadership role in conducting basic scientific, translational, and clinical research. Dr. Mezoff has taken ever increasing responsibility for daily programmatic operations of the intestinal rehabilitation program, and he has led the multidisciplinary DSIO initiative to standardize and protocolize care among the three disciplines (surgery, gastroenterology, and neonatology) providing care to infants and children with intestinal failure. A major clinical initiative has included the development of a specific emergency department protocol for standardized evaluation and treatment fevers among children with central venous catheters. In addition , we have protocolized management of central venous catheters with suspected bacterial biofilms by initiating ethanol lock therapy. Dr. Conrad Cole, a

nationally recognized translational researcher in intestinal rehabilitation was successfully recruited to spearhead new research initiatives.

Dr. Yazigi has accepted the position of associate director of small intestinal transplantation, emphasizing new initiatives in patient safety and programmatic growth. The transplant program has expanded it's bimonthly multidisciplinary rounds, and routine attendees have included Dr. Rebecca Brady who adds expertise in infectious disease, Elizabeth Williams who adds expertise in clinical protocol development and oversight, and two new transplant coordinators who increase the meticulousness of monitoring and intensity of support for our patients. Having identified psychosocial dysfunction as a major risk factor in poor transplant outcomes, we have recruited psychologists from the patient adherence program to follow our patients routinely. We have also initiated a process by which a structured psychosocial evaluation is added during initial transplant evaluation and periodically afterward by a number of evaluators who are charged to identify high-risk situations which require preemptive intervention. In addition, a detailed account (entitited a Medical Passport) of the patient's progress, management strategies, medications and special considerations has become a routine aspect of recordkeeping, facilitating safe handoffs. Following initiation of this innovation we have observed no serious safety events. We have also seen an improvement in overall survival of 78% among our most recent 13 transplant recipients as well as a 100% survival among our most recent 7 recipients.

We have advanced knowledge in intestinal failure by studying the relative value of biomarkers of infection (sTREMs [triggering receptors of myeloid cells] and LBP [lipoprotein binding protein]) for identifying acute blood stream infections (BSI) and for predicting need for liver/bowel transplant and death among our population on TPN. Concommitantly we have used our clinical registry to do retrospective analyses of the value of enteral nutrition in reversing TPN associated cholestasis and to evaluate the bilirubin to ggt ratio as a predictor of irreversible TPN associated cholestasis. Dr. Mezoff is currently in the process of validating bomb calorimetry as a measure of enteral energy balance among intestinal failure patients. We continue participation in the 15-center Pediatric Intestinal Failure Consortium (NIHR21DK081059) and are in the process of analyzing data collected to date describing factors impacting upon outcomes in pediatric intestinal failure. A retrospective, detailed analysis of the characteristics of epithelial apoptosis in mild acute cellular rejecton of intestinal allografts has been published, and a description of our improved outcomes following the inception of a Medical Passport has been accepted for presentation at the annual meeting of the Transplantation Society.

Ajay Kaul, MD

Neurogastroenterology and Motility Program

This is a unique program, one of only a few in the country, that offers comprehensive evaluation for children with motility disorders of the gastrointestinal tract which are often associated with other complex medical conditions. These include GERD, gastroparesis, intestinal pseudo-obstruction, Hirschsprungs disease and constipation. It collaborates with other multidisciplinary programs at CCHMC including small bowel transplant and aerodigestive and sleep centers in their evaluation process. It has a state-of-the-art motility laboratory with cutting edge manometry and combined pH-impedance technology. Since the inception of a dedicated motility clinic the volume of patients referred, especially from outside the tristate region, has increased significantly and in 2009 we performed 136 manometry and 379 pH-impedance studies. With the addition of another faculty (Jose M Garza, MD) we have been able to improve access and the program now offers an accredited fellowship in pediatric motility disorders as well. The physicians (Kaul and Garza) have presented at national and international meetings and published on related topics in medical journals.

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

The Cincinnati Steatohepatitis Center (CCSC) is a multidisciplinary clinic initiated in November 2007 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, MS (medical director), Rohit Kohli MBBS, MS 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 is also a participating site in 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. The CCSC has published clinical and pre-clinical papers in the area of steatohepatitis research over the last year in the following journals: Hepatology; Journal of Pediatric Gastroenterology and Nutrition. The CCSC continues to give talks to local community pediatric care providers and practices. The CCSC shall also be presenting its outcomes data at the annual meeting of the North American Society for Pediatric Gastroenterology at its annual meeting later this year.

Jorge Bezerra, MD, Alex Miethke, 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, 4 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. Children are evaluated in the outpatient clinic in a timely fashion, and are treated by state-of-the-art and innovative care protocols. 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. One example is the development of a high-throughput gene chip to diagnose mutations in children with genetic liver diseases - now available for clinical use by the medical community at large. Current studies are addressing: 1) the efficacy of corticosteroids in children with biliary atresia, 2) bile acid replacement in children with genetic and autoimmune liver disease, 3) genetics of liver disease, 4) the use of antioxidants to improve recovery of patients with acute liver failure, and 5) the role of immune dysregulation in the etiology of acute liver failure. To foster education, the PLCC successfully developed an Advanced Hepatology Fellowship to train future leaders in the field.

Phil Putnam, MD; James Franciosi, MD

The Cincinnati Center for Eosinophilic Disorders

The CCED is a high volume, multidisciplinary care center specializing in Eosinophilic Gastrointestinal Disorders (EGID) in both the pediatric and adult population. The core clinical group is made up of members from the Divisions of Gastroenterology, Nutrition and Hepatology, Allergy and Immunology, Social Work and Nutrition. The CCED extensively utilizes a number of ancillary services within the hospital during the process of treating these patients. Families are seen for a week long baseline visit and then subsequent, one day follow visits on a regular basis (at least once yearly). Patients are offered enrollment in diverse research studies including descriptive research databanks, specimen databanks (collections of endoscopy tissue, blood, and DNA), translational studies, and clinical trials.

In 2009 the CCED cared for 104 new patient cases from 38 states (including Ohio) and one country (Peru). Our combined patient volume for 2009 including new cases and the subsequent follow-up patients was over 320 patients.

Research through the CCED involves basic, clinical and translational studies. Patients are offered enrollment in diverse research studies including descriptive research databanks, specimen databanks (collections of endoscopy tissue, blood, and DNA), and clinical trials.

In October of 2009 the CCED was awarded a \$1.5 million stimulus research grant from the NIH to develop and operate the first National Eosinophilic Gastrointestinal Disorders registry. Our center is currently in the development phase of this registry and has begun negotiations with other centers around the country to take part in this first multi-center research registry.

Division Collaboration

Collaboration with Otolaryngology; Human Genetics; Speech Therapy; Occupational Therapy; Social Services; Nutrition

Collaborating Faculty:

This is a multi-disciplinary team which provides comprehensive evaluation of children with swallowing/feeding disorders - Scott Pentiuk, MD, Interdisciplinary Feeding Team (IFT)

Collaboration with Hematology/Oncology Collaborating Faculty: Joseph Palumbo, MD Hemostatic Factors in Colitis and Colitis-Associated Colon Cancer - Kris Steinbrecher, 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 Molecular Immunology Collaborating Faculty: Kasper Hoebe, PhD Role of Gimap5 in Immune Tolerance - Kris Steinbrecher, PhD Collaboration with Pathology and Lab Medicine; Biomedical Informatics Collaborating Faculty: Kenneth D. Setchell, PhD; Michael Miles, PhD; Peter Tang, PhD; Lili Miles, MD; Bruce Aronow, PhD High-Fructose-Diet Induces Hepatic Fibrosis and Elevates Plasma Oxidized Coenzyme Q9 in a Novel Murine Model of Obesity and NASH - Rohit Kohli, MD, Stavra Xanthakos, MD, William F. Balistreri, MD Collaboration with Biostatistics 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, Mitchell Cohen, MD Collaboration with Allergy & Immunology; Developmental Biology; Neonatology & Pulmonary Biology Collaborating Faculty: Simon Hogan, PhD; Jeffrey Whitsett, MD; James Wells, PhD iPSC-derived intestinal tissue from CF patients - Noah F. Shroyer, PhD Collaboration with Developmental Biology **Collaborating Faculty: James Wells. PhD** In vitro growth and differentiation of gastrointestinal tissue from human pluripotent stem cells - Noah F. Shroyer, PhD Collaboration with Immunobiology Collaborating Faculty: De'Broski Herbert, PhD T helper 2 and alternatively activated macrophages in colitis associated cancer - Noah F. Shrover, PhD **Collaboration with Neonatology & Pulmonary Biology Collaborating Faculty: Jeffrey Whitsett, MD** Transcriptional control of intestinal differentiation and neoplasia by SPDEF - Noah F. Shroyer, PhD KLF5 control of gastrointestinal morphogenesis and stem cell homeostasis - Noah F. Shroyer, PhD Collaboration with Pediatric Ophthalmology **Collaborating Faculty: Richard Lang, PhD** Macrophage supplied WNT suports regeneration and repair - Noah F. Shroyer, PhD **Collaboration with Pediatric Surgery** Collaborating Faculty: Michael Helmrath, MD, MS Transplantation of intestinal stem cells and organoids - Noah F. Shrover, PhD **Collaboration with Nephrology and Hypertension Collaborating Faculty: Jens Goebel, MD**

Calcineurin Inhibitor Minimization and Foxp3+ Tregs Post-Transplant - John Bucuvalas, MD Collaboration with Adherence Psychology

Collaborating Faculty: Dennis Drotar, PhD Clinical Center for Medical Adherence in Liver Transplant Recipients: Etiopathogenesis and clinical outcome - John Bucuvalas, MD

Collaboration with Bone Marrow Transplantation

Collaborating Faculty: Lisa Filipovich, MD

Acute Liver Failure in Children: Role of immune dysregulation - John Bucuvalas, MD Collaboration with Center for Health Care Quality

Collaborating Faculty: Peter Margolis, MD, PhD; Michael Seid, PhD

"Transforming Chronic Illness Care" - The specific aim is to design, prototype, optimize, and evaluate a patient-provider C3N to improve clinical practice, patient self-management, and disease outcomes of pediatric inflammatory bowel disease (IBD) - John Bucuvalas, MD Collaboration with Biomedical Informatics

Collaboration with Biomedical Informatics

Collaborating Faculty: Bruce Aronow, PhD; Anil Jegga, DVM, MRes

Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Jorge A. Bezerra, MD

Studies of the molecular basis of clinical phenotypes of biliary atresia - Jorge A. Bezerra, MD

Collaboration with Developmental Biology; Pathology

Collaborating Faculty: S. Steven Potter, MD; Aaron Zorn, PhD; David P. Witte, MD; Keith F. Stringer, MD Collaboration through the Digestive Health Center: Bench to Bedside Research in Pediatric Disgestive Disease - Jorge A. Bezerra, MD

Collaboration with Developmental Biology

Collaborating Faculty: James Wells, PhD

Studies on development and function of biliary glands - Jorge A. Bezerra, MD

Collaboration with Molecular Immunology Collaborating Faculty: Claire Chougnet, PhD

Studies of the role of the immune system in pathogenesis of biliary atresia - Jorge A. Bezerra, MD Collaboration with Molecular Immunology; Pathology

Collaborating Faculty: Kasper Hoebe, PhD; Kevin Bove, MD Studies of the role of Lampe1 in liver cell injury and hepatic tumorigenesis - Jorge A. Bezerra, MD Collaboration with Pediatric Surgery Division and Liver Care Center

Collaborating Faculty: Greg Tiao, MD

Studies of the virologic basis of biliary atresia - Jorge A. Bezerra, MD Collaboration with Pathology

Collaborating Faculty: Kevin Bove, MD Molecular staging of liver injury in biliary atresia - Jorge A. Bezerra, 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 Mezoff, MD, Professor ; Associate Director, Intestinal Failure and Transplant Program Research Interests: Intestinal failure and intestinal transplantation
Scott Pentiuk, MD, Assistant Professor; Medical Director, Interdisciplinary Feeding Team Research Interests: Feeding disorders; medical education
Philip E Putnam, MD, Associate Professor ; <i>Director, Endoscopy Services; Medical Director, Cincinnati Center for Eosinophilic Disorders</i> Research Interests: Eosinophilic Gastrointestinal Disorders
Jeffrey A Rudolph, MD, Assistant Professor Research Interests: Instestinal 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 ; <i>Medical Director, Surgical Weight Loss Program for Teens</i> 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 Mezoff, 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

Cincinnati Steatohepatitis Center

The Cincinnati Steatohepatitis Center (CCSC), a multidisciplinary clinic for patients with nonalcoholic fatty liver disease, publishes clinical and pre-clinical papers in peer-reviewed journals, gives talks to local community pediatric care providers, and will present outcomes data at the annual meeting of the North American Society for Pediatric Gastroenterology later this year.

The CCSC is a participating site in the NIH-funded non-alcoholic steatohepatitis (NASH) Clinical Research Network, which is conducting a multi-center study investigating the natural history and determinants of NASH in adults and children. This network plans to offer clinical therapeutic trials in the near future.

A study led by Rohit Kohli, MD, MS, published online in June 2010 in *Hepatology*, reports that mice became obese when fed high-calorie diets containing either trans-fats alone or a combination of trans-fat and high fructose. Only the group fed the combination diet went on to develop advanced fatty liver disease including fibrosis. These findings highlight the liver-specific injury that can be caused by high levels of dietary fructose. This study also included preliminary data on a simple blood test that differentiated the stages of liver disease in this model.

Cincinnati Center for Eosinophilic Disorders

James Franciosi, MD, MS, helped launch the national Registry for Eosinophilic Gastrointestinal Disorders (www.regid.org), which seeks to gather clinical, pathologic, and translational outcome measures for collaborative, multisite investigations. This project is supported by a NIDDK grant through the American Recovery and Reinvestment Act.

An additional grant from the Children's Digestive Health Foundation allowed Franciosi to develop validated patient and parent-proxy outcome measures for Eosinophilic Esophagitis (EoE). The Pediatric EoE Health Related Quality of Life (PEEHRQOL v1.0) and the Pediatric EoE Symptom Severity Score (PEESS v2.0) instruments will seek to become the key patient reported outcome measures for patients and their families with EoE.

Intestinal Rehabilitation

In the laboratory, Noah Shroyer, PhD, identified new factors in intestinal growth and development, including a network of genes that control cell fate and proliferation of intestinal stem cells. In collaboration with researchers in Developmental Biology, we are investigating the potential for growing and manipulating intestinal tissue from human pluripotent stem cells. We are also working with researchers in Surgery to develop methods for transplantation of intestinal tissues grown in the laboratory.

Together, these advances may help us repair or replace damaged tissue in patients with intestinal failure and allow them to continue without parenteral nutrition.

Meanwhile, assembled a group of 40 care providers, researchers, administrative personnel, and business partners from Gastroenterology, Neonatology, and Surgery to transform our system of care for intestinal failure patients.

We have established working groups to address these key goals for the Intestinal Rehabilitation Program: improving the data management system, seamlessly integrating care amongst Gastroenterology, Neonatology, and Surgery and establishing research priorities and procedures.

Our goal is to become fully functional and integrated within 18 months.

Division Publications

1. :

Grants, Contracts, and Industry Agreements Grant and Contract Awards Annual Direct / Project Period Direct Bezerra, J The Plasminogen System and Liver Repair National Institutes of Health R01 DK 055710 02/15/07 - 11/30/10 \$198,891 / \$805,691 Immunologic Dysfunction in Biliary Atresia National Institutes of Health R01 DK 064008 02/25/08 - 01/31/13 \$210,375 / \$1,060,375 Biological Basis of Phenotypes and Clinical Outcomes in Biliary Atresia National Institutes of Health

09/01/09 - 08/31/13	\$240,000 / \$915,000
tic Liver Disease in Children	
09/10/09 - 05/31/14	\$458,835 / \$2,075,237
Administrative Core	394,826
Histopathology Core	34,201
Bile Acid Core	29,808
tic Liver Disease in Children	
02/05/10 - 01/31/11	\$76,534 / \$76,534
nch to Bedside Research in Pediatric Digestive Disease	
08/01/07 - 05/31/12	\$767,638 / \$3,717,776
Administrative Core	365,374
Integrative Morphology Core	114,168
Bioinformatics Core	111,234
Gene Expression Core	54,582
Sequencing Core	21,421
Flow Cytometry Service	34,180
Luminex Service	32,000
P&F Study	50,000
nch to Bedside Research in Pediatric Digestive Disease	
07/25/09 - 05/31/11	\$100,000 / \$214,200
P&F Study	50,000
S. P&F Study	50,000
Idy Acute Liver Failure in Children	
09/01/05 - 08/31/10	\$64,684 / \$288,460
awal for Stable Pediatric Liver Transplant Recipients	
an Francisco (National Institutes of Health) 09/30/09 - 08/31/11	\$27.237 / \$54.640
ization and FOXP3+ Tregs Post Transplant	· · · · · · · · · · · · · · · · · · ·
phia (National Institutes of Health) 09/30/09 - 07/31/11	\$83,128 / \$166,256
and Nutrition Training Grant	
07/01/05 - 06/30/10	\$410,523 / \$1,788,778
lera Vaccine	
	09/01/09 - 08/31/13 tic Liver Disease in Children 09/10/09 - 05/31/14 Administrative Core Histopathology Core Bile Acid Core tic Liver Disease in Children 02/05/10 - 01/31/11 nch to Bedside Research in Pediatric Digestive Disease 08/01/07 - 05/31/12 Administrative Core Integrative Morphology Core Bioinformatics Core Gene Expression Core Sequencing Core Flow Cytometry Service Luminex Service P&F Study nch to Bedside Research in Pediatric Digestive Disease 07/25/09 - 05/31/11 P&F Study s. P&F Study the found

Cytokine Regulation of Growth Hormone Signaling

National Institutes of Health	04/01/06 - 12/31/10	\$188 413 / \$063 245
Immuno-genetic Determinants of I	Linear Growth in Pediatric IBD	\$100,410 <i>7</i> \$903,243
Crohn's & Colitis Foundation of Ame	rica	
	07/01/07 - 12/31/10	\$117,000 / \$377,000
National Institutes of Health	el Disease Benavior and Treatment Respo	Inse
R01 DK 078683	04/01/09 - 03/31/13	\$405,332 / \$1,570,022
Risk Stratification and Identification	on of Immunogenetic and Microbial Marke	rs of Complicated Disease Course
in Pediatric Crohn's Disease	Foundation of Amorica)	-
S305815	07/01/09 - 06/30/13	\$135,592 / \$331,705
Frencisci I		+····,···
Franciosi, J Related Quality of Life and Sympt	om Sovority Outcomo Mossuros in Eosing	philic Econhagitic: Boyond
Eosinophil Counting		prinic Esophagnis. Beyond
Children's Digestive Health and Nutri	12/15/08 - 12/14/10	\$75,000 / \$150,000
	12/15/08 - 12/14/10	\$75,0007 \$150,000
Han, X		
Methyl Protodioscin (MPD) Preclin	ical Studies on Inflammatory Bowel Disea	ISE
KL2 RR 026315	04/03/09 - 03/31/11	\$93.463 / \$167.580
llauht l		
Heubi, J	Absorption/Synthesis	
National Institutes of Health	TADSolption/Synthesis	
R01 DK 068463	09/01/09 - 08/31/10	\$66,666 / \$66,666
Kaaaahia C		
Intestinal Failure in Children: A Co Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059	tional Institutes of Health) 06/15/08 - 05/31/11	Pediatric Intestinal Failure \$3,643 / \$9,107
Intestinal Failure in Children: A Co Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059	tional Institutes of Health) 06/15/08 - 05/31/11	Pediatric Intestinal Failure \$3,643 / \$9,107
Intestinal Failure in Children: A Co Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11	Pediatric Intestinal Failure \$3,643 / \$9,107
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310	tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200
Intestinal Failure in Children: A Co Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 7 Related Comorbidities 09/01/09 - 08/31/13	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati)	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of	Antemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develope Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000
 Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute K08 CA 111819 	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis 08/01/06 - 07/31/11	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000 \$123,000 / \$615,000
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develope Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute K08 CA 111819	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis 08/01/06 - 07/31/11	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000 \$123,000 / \$615,000
Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute K08 CA 111819 Miethke, A Regulatory T Cells and the Pathog American Liver Foundation	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis 08/01/06 - 07/31/11 genesis of Biliary Atresia	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000 \$123,000 / \$615,000
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 Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute K08 CA 111819 Miethke, A Regulatory T Cells and the Pathog American Liver Foundation Moore, S Pediatric Center for Gene Express 	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis 08/01/06 - 07/31/11 genesis of Biliary Atresia 07/01/09 - 06/30/12 ion and Development	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000 \$123,000 / \$615,000 \$75,000 / \$225,000
 Intestinal Failure in Children: A Consortium Children's Hospital of Pittsburgh (Nat R21 DK 081059 Kohli, R Role of Ileum in Reducing Obesity National Institutes of Health K08 DK 084310 Ethicon Enhanced Assay Develop Ethicon Endo-Surgery (University of Leonis, M The Ron Receptor Tyrosine Kinas National Cancer Institute K08 CA 111819 Miethke, A Regulatory T Cells and the Pathog American Liver Foundation Moore, S Pediatric Center for Gene Express National Institutes of Health K12 HD 028827 	ontemporary Retrospective Review by the tional Institutes of Health) 06/15/08 - 05/31/11 Related Comorbidities 09/01/09 - 08/31/13 ment Cincinnati) 06/11/09 - 01/22/11 e In Hepatic Tumorigenesis 08/01/06 - 07/31/11 genesis of Biliary Atresia 07/01/09 - 06/30/12 ion and Development 07/01/09 - 11/30/10	Pediatric Intestinal Failure \$3,643 / \$9,107 \$139,300 / \$557,200 \$21,021 / \$71,000 \$123,000 / \$615,000 \$75,000 / \$225,000

Granulocyte-Macrophage Colony Stimulating Factor and Homeostatic Responses to Gut I	njury
AGA Foundation for Digestive Health & Nutrition	

	07/01/09 - 06/30/11	\$40,000 / \$80,000
Shroyer, N SPDEF in Intestinal Differentiation		
National Institutes of Health	07/15/00 06/20/11	
		\$20,0007 \$99,500
National Cancer Institute	essor in Colorectal Cancer	
R01 CA 142826	02/23/10 - 01/31/15	\$207,500 / \$1,037,500
Steinbrecher, K		
Role of Epithelial GSK-3B in Initiation AGA Foundation for Digestive Health &N	and Resolution of Intestinal Inflammation utrition	
	07/01/07 - 06/30/10	\$18,750 / \$56,250
Role of p65/GSK-3-Mediated Gene Exp Crohn's & Colitis Foundation of America	ression in Initiation of Inflammatory Bowel Disea	ISE
	01/01/08 - 12/31/10	\$90,000 / \$270,000
Xanthakos, S		
Biological Determinants of Steatohepa National Institutes of Health	titis after Adolescent Bariatric Surgery	
K23 DK 080888	07/01/08 - 06/30/13	\$164,300 / \$821,600
Clinical Research Network in Non-Alco Case Western University (National Institu	bholic Steatohepatitis tes of Health)	
U01 DK 061732	08/30/09 - 04/30/14	\$106,426 / \$551,190
	Current Year Direct	\$5,013,394
ndustry Contracts		
Balistreri, W		
Digestive Care, inc.		\$ 1,183
Denson, L		• • • • • • • •
Genetech, Inc.		\$ 16,326
Abbott Laboratories		\$ 4,577
Franciosi, J		
UCB Pharma, Inc.		\$ 8,470
Kaul, A		
Pfizer, Inc.		\$ 7,007
Samson, C		
Connecticut Children's Medical Center		\$ 1,386
	Current Year Direct Receipts	\$38,949