Gastroenterology, Hepatology and Nutrition

Division Photo

First Row: *K. Campbell, M. Cohen, W. Balistreri, G. Tomer, J. Bezerra, S. Pentiuk;* ***Second Row:*** *N. Yazigi, A. Kaul, M. Leonis, M. Farrell, L. Denson, R. Kohli, J. Heubi*

Division Data Summary

Research and Training Details

Number of Faculty	22
Number of Research Fellows	5
Number of Research Students	1
Number of Support Personnel	73
Direct Annual Grant Support	$4,892,192
Direct Annual Industry Support	$125,036
Peer Reviewed Publications	45

Clinical Activities and Training

Number of Clinical Fellows	13
Inpatient Encounters	8,305
Outpatient Encounters	11,978

Faculty Members

Mitchell B Cohen, MD, Professor ; *Pediatric Gastroenterology Endowed Chair; Director, Division of Gastroenterology, Hepatology and Nutrition; Director, Digestive Health Center*

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

Michael D Bates, MD, PhD, Assistant Professor

Jorge A Bezerra, MD, Professor ; *Director of Research, Division of Gastroenterology, Hepatology and Nutrition; Director, Biliary Atresia Center; Associate Director, Digestive Health Center*

John C Bucuvalas, MD, Professor ; *Associate Medical Director, Pediatric Liver Care Center; Director of Clinical Operations, Division of Gastroenterology, Hepatology and Nutrition*

Kathleen M Campbell, MD, Assistant Professor

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*

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

Xiaonan Han, PhD, Instructor

James E Heubi, MD, Professor ; *Director, General Clinical Research Center; Associate Dean for Clinical Research, University of Cincinnati College of Medicine; Associate Chair for Clinical Research, Department of Pediatrics*

Ajay Kaul, MD, Associate Professor ; *Director, Impedance/Motility Disorders Program*

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

Rohit Kohli, MD, Assistant Professor

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

M Susan Moyer, MD, Professor ; *Director, Schubert-Martin Inflammatory Bowel Disease Center*

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

Jeffrey A Rudolph, MD, Assistant Professor

Noah Shroyer, PhD, Assistant Professor

Kris Steinbrecher, PhD, Assistant Professor

Gitit Tomer, MD, Assistant Professor

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

Nada Yazigi, MD, Assistant Professor

Trainees

- **Monica Garin-Laflam, MD,** PL-7, Jackson Memorial Hospital
- **Jill Dorsey, MD,** PL-6, Medical University of South Carolina
- **Alexander Miethke, MD,** PL-6, Cincinnati Children's Hospital Medical Center
- **Brad Pasternak, MD,** PL-6, SUNY Downstate Medical Center
- **Scott Pentiuk, MD,** PL-6, Cincinnati Children's Hospital Medical Center
- **Katie Moyer, MD,** PL-5, Oregon Health and Sciences University
- **Melanie Rhue, MD,** PL-5, Carolinas Medical Center
- **Charles Samson, MD,** PL-5, University of North Carolina at Chapel Hill
- **Bella Zeisler, MD,** PL-5, New York University
- **Sharon D'Mello, MD,** PL-4, St. Christopher's Hospital for Children
- **Jose Garza, MD,** PL-4, Cincinnati Children's Hospital Medical Center
- **Emily Kevan, MD,** PL-4, University of Colorado
- **Cade Nylund, MD,** PL-4, San Antonio Military Pediatric Center
- **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
- **Jitesh Kawedia, PhD,** University of Cincinnati
- **Avedis Kazanjian, PhD,** University of Louisville
- **Elizabeth Mann, PhD,** University of New York at Buffalo
- **Taeko Noah, PhD,** University of Nevada, Reno

- **Vijay Saxena, PhD,** Kanpur University, India
- **Kumar Shanmukhappa, PhD,** Kansas University, Missouri
- **Pranav Shivakumar, PhD,** New Delhi University, India
- **Cynthia Wetzel, PhD,** Wright State University
- **Tara Willson, BS,** University of Kentucky, Lexington

Significant Accomplishments in FY08

Liver Failure and Liver Transplant Program

Our long term goal is to improve outcome for pediatric liver transplant recipients by acquisition and application of new discoveries and/or ensuring that the health care delivery system provides them the best possible care. Advances in immunosuppression and surgical care have improved short term patient and graft survival for liver transplant recipients but left us with a different challenge: maintaining allograft function while minimizing the long-term immune and non-immune complications related to immunosuppressive medications. Thus, when short term outcomes do not reach or exceed benchmarks, they may be addressed by efforts to improve the delivery system. In contrast, efforts to minimize long term complications likely reflect gaps in knowledge and require research efforts. The challenges are perhaps most important for children who have a longer life span and consequently a greater potential to develop significant allograft and other end organ damage. When we found that 30 day survival rates for liver transplant recipients at CCHMC were below the median for pediatric liver transplant centers across the country, we defined the driving factors for short term outcome and initiated improvement efforts to improve our evaluation process and pre-transplant care. For the former we changed our decision making structure to focus on five predictive questions to be explicitly addressed at evaluation for each transplant candidate. To address pre-transplant care, we initiated pre-visit planning for children on the waiting list and developed standards of care, two components of the chronic care model. As a result of these efforts, our 30 day patient survival increased from 88% to 100%. To improve long term outcomes, we need additional knowledge and the focus areas aligned below are aligned with the NIDDK strategic plan for hepatology. The pediatric liver transplant team is involved in or leading proposed and ongoing studies funded by NIDDK to: 1) Identify biomarkers that predict immunosuppression efficacy and toxicity and expand our understanding of mechanisms of tolerance would lessen the risk for these complications, 2) Identify patients who can be successfully withdrawn from immunosuppression, 3) Assess clinical outcomes and risk factors in longitudinal, 4) Measure wellness and define predictors of outcome for pediatric LT recipients, and 5) Define and address the complex issue of non-adherence that may play a central role in late allograft loss.

Chronic Liver Disease

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. 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.

Schubert-Martin Pediatric Inflammatory Bowel Disease Center

We continue to strive to improve the care and quality of life for children with the Inflammatory Bowel Diseases, e.g., Crohn's Disease (CD) and Ulcerative Colitis (UC). Over the past five years, our research enterprise has grown considerably, and now includes several CCHMC faculty performing extramurally-funded laboratory research designed to uncover fundamental mechanisms of disease. For each of these basic research programs, we have included translational studies designed to test mechanisms in patients, and so more rapidly advance knowledge. Our multi-center collaborative studies over the past few years have now led to the discovery of the first IBD susceptibility gene identified in affected

children, and the development of new biomarkers which will improve our ability to provide personalized care. These will now move forward nationally as we participate in a North American Pediatric IBD Research Collaborative sponsored by the Crohn's and Colitis Foundation of America whose Aims will be to identify high risk patients, and thereby offer more effective therapy earlier in their course. We have now translated our laboratory findings into a randomized controlled clinical trial of human growth hormone (hGH) which we have recently completed at CCHMC; findings suggest that this will provide a useful adjunct in the care of children with CD. In order to optimize our use of existing therapies, we have developed evidenced-based guidelines for the medical management of IBD in children, and have implemented these within our CCHMC group, and made them available through our website to outside practitioners. Remission rates and quality of life indices for our CCHMC patient population now exceed those observed in our National Collaborative Registry. We are actively participating in the Trailblazers national collaborative whose Aims are to improve the quality of care for children with IBD in the U.S. Locally, we have sought to improve patient support through the development of an annual Family Education Day, and support for the Camp Oasis summer program. Over the next five years, we will continue to purse this integrated, multi-dimensional approach to improve outcomes for children with IBD, both here in Cincinnati, and at the national level through our ongoing collaborative efforts.

Significant Publications in FY08

Steinbrecher KA, Harmel-Laws E, Sitcheran R, and Baldwin AS. Loss of Epithelial RelA Results in Deregulated Intestinal Proliferative/Apoptotic Homeostasis and Susceptibility to Inflammation. J Immunol. 180(4):2588-99, 2008.

Toll-like receptor and cytokine signaling pathways are required for proper epithelial cell monolayer homeostasis and resistance to spontaneous, or induced, inflammation. This manuscript addresses the function of RelA, the predominant Nuclear Factor-κB subunit in intestinal epithelial cells, in mediating the important protective capacity of these signaling cascades. Our work demonstrates that RelA is necessary for both suppression of spontaneous intestinal disease as well as resistance to chemically-induced colitis and establishes this NF-κB subunit as a central mediator of epithelial monolayer maintenance.

Shivakumar P, Sabla G, Mohanty S, McNeal M, Ward R, Stringer K, Caldwell C, Chougnet C, Bezerra JA. Effector role of neonatal hepatic CD8+ lymphocytes in epithelial injury and autoimmunity in experimental biliary atresia. Gastroenterology. 2007; 133: 268-77.

Livers of infants with biliary atresia are populated by inflammatory cells. In this paper, we used a unique mouse model of the disease to examine the role of lymphocytes in the pathogenesis of disease. We found that activated neonatal CD8+ lymphocytes are cytotoxic to the biliary epithelium and regulate the prominent inflammatory obstruction of the duct lumen. Thus, CD8+ lymphocytes play a key role in the phenotypic expression of experimental biliary atresia and constitute a potential therapeutic target to halt disease progression.

Kohli R, Pan X, Malladi P, Wainwright MS, Whitington PF. Mitochondrial reactive oxygen species signal hepatocyte steatosis by regulating the phosphatidylinositol 3-kinase cell survival pathway. J Biol Chem. 2007; 282: 21327-36.

Abnormal dietary intake of macronutrients is implicated in the development of obesity and fatty liver disease – current national epidemics. Our study examined the mitochondrial reactive oxygen species (ROS)-dependent regulation of the phosphoinositol (PI) 3-kinase pathway in steatosis induced by exposure of mouse hepatocytes to exogenous nutritional stress such as an increased free fatty acid growth milieu. Pharmacologically inhibiting electron transport chain complex III production of ROS prevented activation of PI 3-kinase during macronutrient perturbation, whereas pharmacologically promoting electron transport chain complex III ROS production activated PI 3-kinase independent of nutrient input. The data suggest that H2O2 is the ROS species involved in signal transduction; promoting the rapid conversion of superoxide to H2O2 does not inhibit PI 3-kinase pathway activation during nutrient perturbation, and exogenous H2O2 activates it independent of nutrient input. Our findings suggest a common path for response to altered nutrition involving mitochondrial ROS-dependent PI 3-kinase pathway regulation, leading to steatosis and fatty liver disease.

Division Highlights

The Cincinnati Center for Eosinophilic Disorders (CCED)

This is a combined program with Allergy/Immunology welcomed six new staff, including James Franciosi, MD, a

pediatric gastroenterologist with expertise in eosinophilic disorders. Dr. Franciosi joins Dr. Philip Putnam who leads the medical component of this program for Gastroenterology, Hepatology and Nutrition . Reflecting the growth of the center's reputation, 80 percent of the 380 patients seen this year came from outside our region, many from outside the country. The CCED continues to pioneer new treatments for eosinophilic gastrointestinal disorders and CCED members were major contributors to the recently published consensus guidelines: Eosinophilic Esophagitis In Children And Adults: A Systematic Review And Consensus Recommendations For Diagnosis And Treatment.

The Nutrition and Intestinal Care Center/Small Intestinal Transplantation Program

This program has enjoyed great progress in research over the past academic year. Team members have embarked upon a prospective translational study exploring whether they can identify biomarkers for bloodstream infections among our intestinal rehabilitation patients. Having received IRB approval, this project, entitled "Identification of Biomarkers to Predict Bloodstream Infections in the Pediatric Intestinal Failure Population," is now underway. The principal investigator is Jeffrey Rudolph with Emily Kevan and Samuel Kocoshis as coinvestigators. This group has also entered a multicenter consortium entitled the "Pediatric Intestinal Failure Consortium (PIFCON) funded by the NIH (R21DK081059). 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.

The Digestive Health Center (DHC): Bench-to-Bench Research in Pediatric Digestive Diseases

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 administrative body of the DHC is led by Dr. Mitchell Cohen and Dr. Jorge Bezerra. Dr. Cynthia Wetzel serves as the Program Manager. The DHC includes 40 investigators and 27 associate members from 14 different divisions within the Department of Pediatrics and a total of 7 departments 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 (liver and intestinal) 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. In addition, the DHC provides 4-6 pilot and feasibility awards each year to investigators starting research projects with the potential for extramural funding.

Division Collaboration

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 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: 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 Pentiuk, MD

Collaboration with Biomedical Informatics

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

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

Collaboration with Biomedical Informatics

Collaborating Faculty: Anil Jegga, DVM, MRes

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

Collaboration with Biostatistics and Epidemiology

Collaborating Faculty: Jane Khoury, PhD

Intralumenal Effects of Cholesterol Absorption/Synthesis - James Heubi, 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, Jeffrey Rudolph, MD

Collaboration with Developmental Biology

Collaborating Faculty: S. Steven Potter, PhD

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

Collaboration with Mass Spectrometry Laboratory

Collaborating Faculty: Kenneth D. Setchell, PhD

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

Collaboration with Neonatology & Pulmonary Biology

Collaborating Faculty: Bruce C. Trapnell, MD, MS

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

Collaboration with Molecular Immunology

Collaborating Faculty: Claire A. Chougnet, PhD

Immunologic Dysfunction In Biliary Atresia - Jorge Bezerra, 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

Collaboration with Pathology

Collaborating Faculty: David P. Witte, MD; Keith F. Stringer, MD

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

Mentions in Consumer Media

- **Best Children's Hospitals** U.S. News and World Report , Magazine

Division Publications

1. Balistreri WF. **Landmark, landmine, or landfill? The role of peer review in assessing manuscripts**. *J Pediatr.* 2007; 151: 107-8.
2. Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, Jonas MM, Mohan P, Molleston JP, Murray KF, Narkewicz MR, Rosenthal P, Smith LJ, Robuck PR, Schwarz KB. **Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial**. *Hepatology.* 2008; 47: 836-43.
3. DeRusso PA, Ye W, Shepherd R, Haber BA, Shneider BL, Whitington PF, Schwarz KB, Bezerra JA, Rosenthal P, Karpen S, Squires RH, Magee JC, Robuck PR, Sokol RJ. **Growth failure and outcomes in infants with biliary atresia: a report from the Biliary Atresia Research Consortium**. *Hepatology.* 2007; 46: 1632-8.
4. Erickson N, Mohanty SK, Shivakumar P, Sabla G, Chakraborty R, Bezerra JA. **Temporal-spatial activation of apoptosis and epithelial injury in murine experimental biliary atresia**. *Hepatology.* 2008; 47: 1567-77.
5. Shivakumar P, Sabla G, Mohanty S, McNeal M, Ward R, Stringer K, Caldwell C, Chougnet C, Bezerra JA. **Effector role of neonatal hepatic CD8+ lymphocytes in epithelial injury and autoimmunity in experimental biliary atresia**. *Gastroenterology.* 2007; 133: 268-77.
6. Sokol RJ, Shepherd RW, Superina R, Bezerra JA, Robuck P, Hoofnagle JH. **Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop**. *Hepatology.* 2007; 46: 566-81.

7. Alonso EM, Neighbors K, Barton FB, McDiarmid SV, Dunn SP, Mazariegos GV, Landgraf JM, Bucuvalas JC. Health-related quality of life and family function following pediatric liver transplantation. *Liver Transpl.* 2008; 14: 460-8.
8. Bucuvalas JC, Alonso E. Long-term outcomes after liver transplantation in children. *Curr Opin Organ Transplant.* 2008; 13: 247-51.
9. Ryckman FC, Bucuvalas JC, Nathan J, Alonso M, Tiao G, Balistreri WF. Outcomes following liver transplantation. *Semin Pediatr Surg.* 2008; 17: 123-30.
10. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. *Pediatr Transplant.* 2008; 12: 67-72.
11. Cohen M, Barnard J. **"The National Institutes of Health Consensus Conference Report."** In: A Fasano, R Troncone, D Branski, eds. *Frontiers in celiac disease (Pediatric and adolescent medicine; v.12).* New York: Karger; 2008: 133-138.
12. Cohen MB, Gunter JB. How safe is intravenous sedation with midazolam and fentanyl for pediatric gastrointestinal endoscopy? *Nat Clin Pract Gastroenterol Hepatol.* 2007; 4: 538-9.
13. jRothenberg ME, Cohen MB. An eosinophil hypothesis for functional dyspepsia. *Clin Gastroenterol Hepatol.* 2007; 5: 1147-8.
14. Pasternak B, Grom A, Yazigi N, Cohen MB. Suppurative peripheral arthritis in inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2007; 45: 117-20.
15. Sellers ZM, Mann E, Smith A, Ko KH, Giannella R, Cohen MB, Barrett KE, Dong H. Heat-stable enterotoxin of Escherichia coli (STa) can stimulate duodenal HCO3(-) secretion via a novel GC-C- and CFTR-independent pathway. *Faseb J.* 2008; 22: 1306-16.
16. Dejkhamron P, Thimmarayappa J, Kotlyarevska K, Sun J, Lu C, Bonkowski EL, Denson LA, Menon RK. Lipopolysaccharide (LPS) directly suppresses growth hormone receptor (GHR) expression through MyD88-dependent and -independent Toll-like receptor-4/MD2 complex signaling pathways. *Mol Cell Endocrinol.* 2007; 274: 35-42.
17. Wang X, Jiang J, Warram J, Baumann G, Gan Y, Menon RK, Denson LA, Zinn KR, Frank SJ. Endotoxin-induced proteolytic reduction in hepatic growth hormone (GH) receptor: a novel mechanism for GH insensitivity. *Mol Endocrinol.* 2008; 22: 1427-37.
18. Stehr W, Farrell MK, Lucky AW, Johnson ND, Racadio JM, Azizkhan RG. Non-endoscopic percutaneous gastrostomy placement in children with recessive dystrophic epidermolysis bullosa. *Pediatr Surg Int.* 2008; 24: 349-54.
19. Carey R, Jurickova I, Ballard E, Bonkowski E, Han X, Xu H, Denson LA. Activation of an IL-6:STAT3-dependent transcriptome in pediatric-onset inflammatory bowel disease. *Inflamm Bowel Dis.* 2008; 14: 446-57.
20. Cohran VC, Griffiths M, Heubi JE. Bone mineral density in children exposed to chronic glucocorticoid therapy. *Clin Pediatr (Phila).* 2008; 47: 469-75.
21. Heubi JE, Setchell KD, Bove KE. Inborn errors of bile acid metabolism. *Semin Liver Dis.* 2007; 27: 282-94.
22. Jafri M, Alonso M, Kaul A, Dierig J, Racadio J, Inge T, Brown R, Ryckman F, Tiao G. Intraoperative manometry during laparoscopic Heller myotomy improves outcome in pediatric achalasia. *J Pediatr Surg.* 2008; 43: 66-70; discussion 70.
23. Kohli R, Pan X, Malladi P, Wainwright MS, Whitington PF. Mitochondrial reactive oxygen species signal hepatocyte steatosis by regulating the phosphatidylinositol 3-kinase cell survival pathway. *J Biol Chem.* 2007; 282: 21327-36.
24. Caldwell CC, Martignoni A, Leonis MA, Ondiveeran HK, Fox-Robichaud AE, Waltz SE. Ron receptor tyrosine kinase-dependent hepatic neutrophil recruitment and survival benefit in a murine model of bacterial peritonitis. *Crit Care Med.* 2008; 36: 1585-93.
25. Leonis MA, Balistreri WF. Evaluation and management of end-stage liver disease in children. *Gastroenterology.* 2008; 134: 1741-51.
26. Leonis MA, Balistreri WF. Is there a "NAC" to treating acute liver failure in children? *Liver Transpl.* 2008; 14: 7-8.
27. Leonis MA, Thobe MN, Waltz SE. Ron-receptor tyrosine kinase in tumorigenesis and metastasis. *Future Oncol.* 2007; 3: 441-8.
28. Kugathasan S, Nebel J, Skelton JA, Markowitz J, Keljo D, Rosh J, LeLeiko N, Mack D, Griffiths A, Bousvaros A, Evans J, Mezoff A, Moyer S, Oliva-Hemker M, Otley A, Pfefferkorn M, Crandall W, Wyllie R, Hyams J. Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. *J Pediatr.* 2007; 151: 523-7.
29. Zeisler B, Moyer SM, Farrell M, Collins MH, Tomer G. Electronic clinical challenges and images in GI. Meckel's diverticulum. *Gastroenterology.* 2008; 134: e3-4.

30. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, Collins MH, Putnam PE, Wells SI, Rothenberg ME. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol.* 2007; 120: 1292-300.
31. Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH, Putnam PE, Collins MH, Risma KA, Akers RM, Kirby CL, Buckmeier BK, Assa'ad AH, Hogan SP, Rothenberg ME. Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2007; 45: 22-31.
32. Collins MH, Blanchard C, Abonia JP, Kirby C, Akers R, Wang N, Putnam PE, Jameson SC, Assa'ad AH, Konikoff MR, Stringer KF, Rothenberg ME. Clinical, pathologic, and molecular characterization of familial eosinophilic esophagitis compared with sporadic cases. *Clin Gastroenterol Hepatol.* 2008; 6: 621-9.
33. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology.* 2007; 133: 1342-63.
34. Liacouras CA, Bonis P, Putnam PE, Straumann A, Ruchelli E, Gupta SK, Lee JJ, Hogan SP, Wershil BK, Rothenberg ME, Ackerman SJ, Gomes I, Murch S, Mishra A, Furuta GT. Summary of the First International Gastrointestinal Eosinophil Research Symposium. *J Pediatr Gastroenterol Nutr.* 2007; 45: 370-91.
35. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, Blanchard C, Putnam PE, Rothenberg ME. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology.* 2008; 134: 204-14.
36. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. *Gastroenterol Clin North Am.* 2008; 37: 369-81, vi.
37. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. *Gastrointest Endosc Clin N Am.* 2008; 18: 11-23; vii.
38. Kiesslich R, Goetz M, Angus EM, Hu Q, Guan Y, Potten C, Allen T, Neurath MF, Shroyer NF, Montrose MH, Watson AJ. Identification of epithelial gaps in human small and large intestine by confocal endomicroscopy. *Gastroenterology.* 2007; 133: 1769-78.
39. Shroyer NF, Wong MH. BMP signaling in the intestine: cross-talk is key. *Gastroenterology.* 2007; 133: 1035-8.
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41. Steinbrecher KA, Harmel-Laws E, Sitcheran R, Baldwin AS. Loss of epithelial RelA results in deregulated intestinal proliferative/apoptotic homeostasis and susceptibility to inflammation. *J Immunol.* 2008; 180: 2588-99.
42. Inge TH, Zeller M, Harmon C, Helmrath M, Bean J, Modi A, Horlick M, Kalra M, Xanthakos S, Miller R, Akers R, Courcoulas A. Teen-Longitudinal Assessment of Bariatric Surgery: methodological features of the first prospective multicenter study of adolescent bariatric surgery. *J Pediatr Surg.* 2007; 42: 1969-71.
43. Miller RJ, Xanthakos SA, Hillard PJ, Inge TH. Bariatric surgery and adolescent gynecology. *Curr Opin Obstet Gynecol.* 2007; 19: 427-33.
44. Roehrig HR, Xanthakos SA, Sweeney J, Zeller MH, Inge TH. Pregnancy after gastric bypass surgery in adolescents. *Obes Surg.* 2007; 17: 873-7.
45. Wong LJ, Brunetti-Pierri N, Zhang Q, Yazigi N, Bove KE, Dahms BB, Puchowicz MA, Gonzalez-Gomez I, Schmitt ES, Truong CK, Hoppel CL, Chou PC, Wang J, Baldwin EE, Adams D, Leslie N, Boles RG, Kerr DS, Craigen WJ. Mutations in the MPV17 gene are responsible for rapidly progressive liver failure in infancy. *Hepatology.* 2007; 46: 1218-27.

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 - 08/31/08 — $9,982 / $93,614

Bezerra, J

Molecular Determinants of Phenotypes in Biliary Atresia
National Institutes of Health
R56 DK 070820 — 07/01/06 - 06/30/08 — $180,607 / $372,000

Pre-Clinical Trial to Block Progression of Duct Obstruction in Biliary Atresia
American Liver Foundation

07/01/06 - 06/30/08 $90,909 / $181,818

Clinical Center for Biliary Atresia: Etiopathogenesis and Clinical Outcome
National Institutes of Health
U01 DK 062497 09/15/02 - 05/31/09 $159,329 / $1,101,428

Jaundice Chip: A Diagnostic Tool for Cholestatic Liver Disease
National Institutes of Health (P2D, Inc)
R42 DK 075162 07/01/07 - 06/30/09 $83,646 / $176,059

The Plasminogen System and Liver Repair
National Institutes of Health
R01 DK 055710 02/15/07 - 11/30/10 $200,900 / $820,000

Immunologic Dysfunction In Biliary Atresia
National Institutes of Health
R01 DK 064008 02/25/08 - 01/31/13 $212,500 / $1,062,500

Bucuvalas, J

Studies of Pediatric Liver Transplantation
National Institutes of Health (The EMMES Corporation)
U01 DK 061693 05/15/04 - 03/31/09 $34,646 / $116,930

Functional Outcomes in Pediatric Liver Transplantation
National Institutes of Health (Children's Memorial Hospital)
R01 HD 045694 04/01/05 - 03/31/10 $25,289 / $106,593

A Multi-Center Group to Study Acute Liver Failure in Children
National Institutes of Health (Children's Hospital of Pittsburgh)
U01 DK 072146 09/01/05 - 08/31/09 $39,167 / $158,774

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 $357,017 / $1,731,384

A Randomized, Double-Blind, Placebo Controlled Dose Escalation Inpatient Phase I Study to Determine the Safety of ETEC-Cholera Vaccine
National Institutes of Health (University of Maryland)
N01 AI 040014 05/01/08 - 11/30/10 $825,003 / $1,718,133

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

Cohen, M	Administrative Core	334,248
Potter, S	Gene Expression Core	68,476
Aronow, B	Bioinformatics Core	105,395
Witte, D	Integrative Morphology Core	111,861
Keddache, M	Sequencing Core	21,243
Mattner, J	P&F #5	25,000
Karp, C	P&F #6	25,000
Blanchard, C	P&F #7	25,000

Denson, L

Immunogenetic Determinants of Linear Growth Determinants 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 $133,133 / $258,064

Cytokine Regulation of Growth Hormone Signaling
National Institutes of Health
R01 DK 068164 04/01/06 - 12/31/10 $190,316 / $1,000,000

Garin-Laflam, M

Training Program in Environmental Toxicology
National Institutes of Health (University of Cincinnati)
T32 ES 010957 07/01/07 - 06/30/08 $51,636 / $51,636

Han, X

Characterization of STAT5b in Crohn's Disease
Crohn's and Colitis Foundation of America
01/01/06 - 12/31/08 $79,537 / $229,737

Heubi, J

Rare Liver Disease Network
National Institutes of Health (The Children's Hospital Association)
U54 DK 078377 08/01/07 - 07/31/08 $9,250 / $9,250

Rare Liver Disease Network- CLIC6001
National Institutes of Health (The Children's Hospital Association)
U54 DK 078377 08/01/07 - 07/31/08 $4,807 / $4,807

Intraluminal Effects of Cholesterol Absorption/Synthesis
National Institutes of Health
R01 DK 068463 05/01/05 - 01/31/10 $366,229 / $1,653,077

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 $5,464 / $5,464

Kohli, R

Effect of Ileal Transposition on Nutrition Associated Hepatic Steatosis
Children's Digestive Health and Nutrition Foundation
11/15/07 - 11/14/09 $50,000 / $100,000

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

Genetic Basis of Cholestatic Liver Disease
National Institutes of Health (The Children's Hospital Association)
U54 DK 078377 07/01/06 - 07/31/08 $50,000 / $100,000

Pasternak, B

Pediatric Physician Scientist Program Award
National Institutes of Health (Yale University School of Medicine)
K12 HD 000850 07/01/06 - 06/30/08 $100,500 / $195,250

Rudolph, J

Cyclic-AMP Induced Crypt Cell Survival in the Intestine

National Institutes of Health
K08 DK 066297 02/01/04 - 12/31/08 $115,751 / $578,750

Shroyer, N

Intestinal Secretory Lineage Differentiation and Function
AGA Foundation for Digestive Health and Nutrition
07/01/06 - 06/30/08 $16,250 / $32,500

Math 1 as a Tumor Suppressor in Colorectal Cancer
American Cancer Society - Ohio
09/01/07 - 08/31/08 $25,000 / $25,000

Intestinal Secretory Lineage Development and Function
National Institutes of Health
K01 DK 071686 09/01/06 - 07/31/09 $123,706 / $371,138

Steinbrecher, K

A Protective Role for GSK-3β During Initiation of Inflammatory Bowel Disease
Children's Digestive Health and Nutrition Foundation
11/15/06 - 11/14/08 $50,000 / $100,000

Role of Epithelial GSK-3β 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-3β-mediated Gene Expression in Initiation of IBD
Crohn's and Colitis Foundation of America
01/01/08 - 12/31/10 $90,000 / $270,000

Yazigi, N

Development & Validation of a Health-Related Quality of Life Questionnaire for Children after Liver Transplantation
IWK Health Centre
09/01/07 - 08/31/08 $7,940 / $7,940

Current Year Direct **$4,892,192**

Industry Contracts

Balistreri, W

Digestive Care, Inc.	$ 2,562
Gilead Sciences, Inc.	$ 2,097
The EMMES Corporation	$ 1,925

Denson, L

Abbott Laboratories	$ 10,289
Genentech, Inc.	$ 32,323

Heubi, J

GlaxoSmithKline	$ 44,770
Mead Johnson & Company	$ 31,070

Current Year Direct Receipts **$125,036**

Total $5,017,228