2014 Research Annual Report

Pediatric General and Thoracic Surgery

Division Summary

RESEARCH AND TRAINING DETAILS

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CLINICAL ACTIVITIES AND TRAINING

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Significant Accomplishments

**Intestinal Models Pave the Way for Intestinal Rehabilitation**

Michael Helmrath, MD, Surgical Director of the Intestinal Rehabilitation Center, and his team focus on strategies to improve the outcomes of children with intestinal failure. Understanding the biology of intestinal stem cells is a key to unravel the mechanism involved during the disease process. To that end, the Helmrath team developed *in vitro* culture techniques to maintain and expand individual human intestinal stem cells derived from human tissue samples.

Utilizing those techniques, the Helmrath lab is able to culture intestinal stem cells derived from a variety of diseased tissues. In association with colleagues in Pulmonary Medicine, we are using stem cells derived from patients with cystic fibrosis as a tool for evaluating promising drug compounds. In collaboration with investigators at the University of Cincinnati and in Gastroenterology, we also use intestinal stem cells to study intestinal infectious diseases.

The Helmrath lab, in collaboration with James Wells, PhD, Developmental Biology, and Noah Shroyer, PhD, Gastroenterology, also has developed a murine model of a vascularized and functional human intestine to study human intestinal physiology. These intestinal models will pave the way for understanding gastrointestinal related diseases and lead to the personalized treatment of patients.

**Discovering Strategies for Treating Fetal Myelomeningocele**
A team led by Jose Peiro, MD, Director of Endoscopic Fetal Surgery at the Cincinnati Fetal Center, is investigating the basic mechanisms of pediatric and fetal surgical congenital malformations, focusing especially upon fetal myelomeningocele (MMC), fetal congenital diaphragmatic hernia (CDH) and gastroschisis.

In MMC, we are improving the fetoscopic approach for intrauterine repair by evaluating different patches and sealants in animal models then translating these techniques for use in the human fetus. A new clinical trial will compare fetoscopic MMC repair in humans against the standardized open fetal surgery approach.

We are using a mouse model of neural tube defects to investigate how maternal immune status can influence incidence of congenital malformations. We also are studying ways to use neural progenitor cells collected from the amniotic fluid of MMC patients as a potential form of neural regeneration (cell therapy).

**Evaluating Fetal Surgery to Support Lung Development**

In CDH, studies in animal models indicate that early fetal tracheal occlusion may induce faster and better fetal lung growth. A new animal model of CHAOS ligation of the fetal trachea early in gestation perfectly resembles the human histology of this condition. To continue this work, our team has begun studies to evaluate the metabolomics and proteomics of these tissues and fluids.

We expect to start very soon with fetoscopic tracheal occlusion in human fetuses with severe CDH by detachable balloon insertion. This work will contribute to the ongoing multicenter TOTAL trial.

**Can Elective Preterm Delivery Prevent Gastroschisis?**

In gastroschisis, we are leading/participating in an innovative international multicenter study designed to analyze elective preterm deliveries at 34 weeks’ gestation instead of spontaneous delivery as an approach to avoid intestinal inflammation and obtain better neonatal outcomes.

**Research Highlights**

Professor of Pediatric Surgery Nikolai A. Timchenko, PhD

Dr. Timchenko and his lab apply comprehensive basic science approaches to investigate the molecular mechanisms of liver cancer. Three major discoveries have been made in his lab during last year. First: normal liver expresses several tumor suppressor proteins which protect the liver from development of cancer. Dr. Timchenko found that a small subunit of proteasome, gankyrin, is a key molecule which is activated during development of liver cancer and eliminates five tumor suppressor proteins including p53, Rb, C/EBPa, HNF4a and p16 (Jiang et al. Hepatology 2013). Second: the main characteristic of liver cancer is a failure of hepatocytes to stop proliferation leading to liver tumors. Using unique animal models, Dr. Timchenko found that a complex communication of several signaling pathways is required for termination of liver proliferation. His recent work shows that disruption of this network leads to failure of liver to stop proliferation. This finding has been recently published in Hepatology (Jin et al 2014). In the same issue of Hepatology, Dr. G. Michalopoulos has written a review emphasizing the significance of this work for the field of liver cancer. Third: it is known that fatty liver might cause the development of hepatocellular carcinoma. Dr. Timchenko has elucidated mechanisms of development of fatty liver diseases (Jin et al 2013 Cell Reports). These mechanisms include epigenetic elevation of enzymes of triglyceride synthesis and following accumulation of fat droplets.

Dr. Timchenko’s studies are supported by two NIH R01 grants.
Dr. Tiao is the surgical director of Liver Transplantation. He is now developing research in liver disease with the focus on hepatoblastoma. In addition, he continues to develop his research in Biliary Atresia through an ongoing R01 project funded by the National Institute of Health.

Richard Falcone, MD
Trauma research continues to focus on the triage of pediatric trauma patients within the trauma system and at the level of the pediatric trauma hospital. The trauma group is currently working on a project in collaboration with researchers from Children’s Hospital of LA and the Medical College of Wisconsin on work to better understand how pediatric trauma teams are activated to minimize under-triage to improve care. We are also working on a project to understand the statewide triage of pediatric trauma patients. In addition, work has continued on expanding our trauma simulation program to educate rural emergency department providers and studying the impact of this training on quality of care for pediatric trauma. Finally, our group continues to expand our work on reducing unintentional injuries to children under five in Hamilton County with support from Kohl’s Cares for Kids and Messer Construction funding.

Center for Bariatric Research and Innovation – Thomas Inge, MD, PhD
Dr. Inge and Dr. Jenkins together direct the Center for Bariatric Research and Innovation (CBRI). In addition to participation in a long and growing list of collaborative studies, this Center partners with four other adolescent bariatric centers and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to lead the national effort to prospectively gather data and publish evidence-based recommendations for use of weight loss surgery in adolescents. The Teen LABS study is in the second cycle, eighth year of funding by the NIDDK. Additionally, Dr. Inge received an award from Ethicon EndoSurgery to conduct a long-term follow-up study (FABS5+) to assess health and weight maintenance of patients who had surgery five through 12 years ago. The CBRI is currently partnering with Dr. Aaron Kelly (Univ. of Minn.) and Dr. Elaine Urbina (Cincinnati Children’s- Heart Institute) on an NIH-funded study to assess cardiovascular changes in patients after bariatric surgery.

Daniel von Allmen, MD
Dr. von Allmen continues work on surgical innovation focused on image guided surgery. His work seeks to combine advances in imaging technology with the accuracy and reliability of robotics to improve patient care. His work is supported through joint funding between the Cincinnati Children’s Hospital Medical Center and the Ben Gurion University in Israel.

Chronic Liver Disease – Jaimie Nathan, MD
Dr. Nathan continues to focus on elucidating the role of gut microbiota in the modulation of liver injury and cholangiopathies. His studies involve a novel mouse model of small bowel bacterial overgrowth, in which a small bowel self-filling blind loop is surgically created. With this model, he is studying the gut-liver axis as it relates to the pathogenesis of a number of cholangiopathies which can progress to end-stage liver disease. Dr. Nathan is surgical director of the Intestinal Transplant Program.

Biology of Vascular Malformations – Belinda Dickie, MD, PhD, and Peter Dickie, PhD
Dr. Dickies’ research lab is continuing their work in exploring the underlying genetic and cellular defects associated with the pathogenesis of lymphatic and venous malformations. Several unique endothelial cell lines have been established and potential novel genetic mutations have been identified.

Dr. Belinda Dickie is also a part of the Colorectal Center and is looking at the long term outcomes of patients with congenital colorectal anomalies (Hirschsprung’s disease and anorectal malformations).

Mounira Habli, MD
The mission of the Habli Laboratory of Fetal growth and Developmental Origins of Adult Disease is to deliver healthier babies, free of adult diseases. This mission drives everything we do.

Our lab has taken on an extremely challenging project examining the cellular and molecular mechanisms of fetal programming in IUGR and tries to develop targeted therapy. We developed and validated a unique surgical IUGR mouse model that recapitulates human placental insufficiency. We are examining a novel placental therapy leading to fetal reprogramming and alleviating the risk of adult onset of disease such as metabolic syndrome. We further identified potential pathways for development of adult onset disease in growth-restricted newborn. Our intention to apply in 2015 for external funding.

Laboratory for Regenerative Wound Healing – Sundeep Keswani, MD, FACS, FAAP

Dr. Keswani is focusing on the molecular mechanisms underlying the fetal regenerative wound healing phenotype. If the goals of the project are realized, his work may yield a wide range of therapeutics for diseases characterized by excessive fibroplasia. To that end, this year, he has developed and patented a novel hydrogel that results in regenerative tissue repair in the skin. His collaborators at Stanford University have also demonstrated that this hydrogel has beneficial effects in a model of lung fibrosis. His basic science interests in fetal wound healing are closely paired with his clinical practice in fetal surgery. His research is funded by a K08 award and he has also recently been awarded a five-year $1.6 million R01 from the National Institute Health.

Significant Publications


The purpose of this publication was to show the testing of the hypothesis that adolescent obesity would be associated with greater risks of adverse health in severely obese adults. It was concluded that severe obesity at age 18 was independently associated with increased risk of several comorbid conditions in adults undergoing bariatric surgery.


Past body weight may be a more informative factor than current weight for risk of chronic disease development. Often, investigators must rely on subject recall to gauge past body weights. The Cincinnati Weight History Questionnaire (CWHQ) was developed to aid in the retrospective identification of adults who were obese during adolescence. The CWHQ proved to be a moderately sensitive, but highly specific instrument for detecting adolescent obesity in a cohort of young adult females. Epidemiologic research seeking to discriminate between adults with adult-onset vs. adolescent-onset obesity may find the CWHQ useful.


Biliary atresia (BA) is a neonatal disease that results in obliteration of the biliary tree. The murine model of BA, which mirrors the human disease, is based upon infection of newborn mice with rhesus rotavirus (RRV), leading to an obstructive cholangiopathy. The purpose of this study was to characterize the temporal relationship between viral infection and the induction of this model. The findings of this research confirm a temporal dependence of RRV infection in murine BA and begin to define a pathophysiologic role of the maturing cholangiocyte.

Previous work in our laboratory demonstrated that over-expression of human insulin-like growth factor -1 (hIGF-1) in the placenta corrects fetal weight deficits in mouse, rat, and rabbit models of intrauterine growth restriction without changes in placental weight. The underlying mechanisms of this effect have not been elucidated. To investigate the effect of intra-placental IGF-1 over-expression on placental function we examined glucose transporter expression and localization in both a mouse model of IUGR and a model of human trophoblast, the BeWo Choriocarcinoma cell line. It was found that enhanced GLUT isoform transporter expression and relocalization to the membrane may be an important mechanism in Ad-hIGF-1-mediated correction of placental insufficiency.


This study aimed to assess the feasibility of single-access fetal endoscopy (SAFE) for the management of myelomeningocele (MMC) using intrauterine carbon dioxide as a distension medium in a sheep model. It confirmed the validity of the animal MMC model. None of the control animals was able to stand or walk, and all had a significant defect in the lumbar area with continuous leakage of cerebrospinal fluid, ventriculomegaly, and a Chiari-II malformation. All the treated animals, independently of the number of ports used in the repair, were able to walk and had a closed defect with resolution of the Chiari malformation. Therefore, the SAFE patch and glue coverage of surgically created fetal MMC is feasible and effective in restoring gross neurologic function in the fetal lamb model.

### Division Publications

9. Bischoff A, Levitt MA, Breech L, Pena A. *Covered cloacal extrophy—a poorly recognized condition:


26. Gerrein BT, Williams CE, Von Allmen D. Establishing a portfolio of quality-improvement projects in...


Faculty, Staff, and Trainees

Faculty Members

Daniel von Allmen, MD, Professor

Leadership Division Director

Richard Azizkhan, MD, Professor

Leadership Surgeon-in-Chief

Maria H. Alonso, MD, Associate Professor

Leadership Surgical Director, Kidney Transplant Program; Co-Surgical Director, Intestinal Transplant Surgery

Andrea Bischoff, MD, Assistant Professor

Leadership Assistant Professor, Pediatric Surgery; Pediatric Surgeon, Colorectal Center

Rebeccah L. Brown, MD, Associate Professor

Leadership Associate Director, Trauma Services

A. Roshni Dasgupta, MD, MPh, Assistant Professor

Peter Dickie, MD, Assistant Professor
Richard A. Falcone, MD, MPh, Associate Professor  
Leadership Director, Trauma Services

Jason S. Frischer, MD, Associate Professor  
Leadership Director, Colorectal Center; Director, Extracorporeal Membrane Oxygenation Program

Victor F. Garcia, MD, Professor  
Leadership Founding Director, Trauma Services

Mounira Habli, MD, Assistant Professor  
Leadership Maternal Fetal Medicine Specialist, Fetal Care Center; Co-Director of Fetal Fellowships

Michael A. Helmrath, MD, MS, Professor  
Leadership Director of Surgical Research; Surgical Director, Intestinal Rehabilitation Center

Belinda Hsi Dickie, PhD, MD, Assistant Professor  
Leadership Colorectal Center

Jose Peiro Ibanez, Associate Professor

Thomas H. Inge, MD, PhD, FACS, FAAP, Professor  
Leadership Surgical Director, Surgical Weight Loss Program for Teens; Director, Center for Bariatric Research and Innovation

Todd M. Jenkins, PhD, MPh, Assistant Professor  
Leadership Director, Data Coordinating Center

Helen Jones, PhD, Assistant Professor  
Leadership Fetal Care Center

Sundeep G. Keswani, MD, Associate Professor  
Leadership Director, Pediatric Advanced Wound Care and Skin Service

Foong-Yen Lim, MD, Associate Professor  
Leadership Surgical Director, Fetal Care Center of Cincinnati

Sujit Mohanty, PhD, Instructor

Jaimie D. Nathan, MD, Assistant Professor  
Leadership Surgical Director, Intestinal Transplant Program; Surgical Director, Pancreas Center

Alberto Pena, MD, Professor  
Leadership Founding Director, Colorectal Center

Frederick C. Ryckman, MD, Professor  
Leadership Senior Vice President, Medical Operations; Professor of Surgery/Transplantation

Aimen Shaaban, MD, Professor  
Leadership Director, Center for Fetal Cellular and Molecular Therapy

Gregory M. Tiao, MD, Associate Professor  
Leadership Surgical Director, Liver Transplantation; Director, Small Bowel Program; Associate Director, Pediatric Surgery Training Program

Nikolai Timchenko, PhD, Professor

Trainees
Division Collaboration

Characterization of intestinal stem cells during intestinal adaptation and development of intestinal regenerative strategies. (Michael Helmrath, MD, MS)

Developmental Biology  » James Wells, PhD

Single Cell RNAseq iPS cell (Michael Helmrath, MD, MS)

Developmental Biology  » S. Steven Potter, PhD

Personalized Cystic Fibrosis Therapy and Research Center. (Michael Helmrath, MD, MS)

Pulmonary Medicine  » John P. Clancy, MD and Anjaparavanda P. (AP) Naren, PhD

Section of Neonatology, Perinatal and Pulmonary Biology  » Jeffrey A. Whitsett, MD

Intestinal Organoids as a model system for studying enteric diseases. Oversee human specimen enteroids core. (Michael Helmrath, MD, MS)

Oncology  » Brian D. Weiss, MD, Susanne Wells, PhD, , and

Section of Neonatology, Perinatal and Pulmonary Biology  » Ardythe Morrow, PhD and

University of Cincinnati, Department of Molecular and Cellular Physiology  » Yana Zavros, PhD

Gastroenterology  » Sean Moore

University of Cincinnati, Department of Molecular and Cellular Physiology  » Marshall Montrose, PhD

Role of FANCD2/BRCA2 in ISCs during irradiation induced injury. (Michael Helmrath, MD, MS)

Experimental Hematology  » Qishen Pang, PhD

Training on murine and human enteroids techniques. (Michael Helmrath, MD, MS)

Allergy and Immunology  » Simon P. Hogan, PhD

Collection of biological specimens from obese patients and lean comparison patients seeking surgical care at Cincinnati Children’s Hospital Medical Center. Provide a long-term repository of such biological specimens and collect sufficient demographic information, anthropometric information, past medical history, surgical information, and clinical test results to permit selection of specimens to be used in hypothesis-driven research studies. These specimens are available to qualified researchers at Cincinnati Children’s, or other institutions with IRB approved studies aimed at better understanding the biology of pediatric obesity and related disorders. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH; Stavra A. Xanthakos, MD, MS)

Pathology and Laboratory Medicine | BioBank »

Collaborative effort to design and maintain the website, and web registry site, for the International Registry for Hypothalamic Obesity Disorders. (Thomas H. Inge, MD, PhD, FACS, FAAP)

Division of Biomedical Informatics »

Collaborative effort to design and maintain the secure web portal used for the adjudication process of the Teen-LABS study. (Thomas H. Inge, MD, PhD, FACS, FAAP)

Division of Biomedical Informatics »
We have been funded by NIH to conduct a controlled study of weight loss surgery for pediatric nonalcoholic steatohepatitis (NASH) (ROI, PI = Xanthakos)
(Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Gastroenterology, Hepatology and Nutrition** » Stavra A. Xanthakos, MD, MS

Explore the role of IL-17 in NAFLD development and progression in obese adolescents to devise novel preventive and therapeutic strategies for NAFLD. (Thomas H. Inge, MD, PhD, FACS)

**Gastroenterology, Hepatology and Nutrition** » Senad Divanovic, PhD

Pilot study to correlate bile acid levels in serum to the reduction in weight in post-bariatric surgery in adolescents. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Gastroenterology, Hepatology and Nutrition** » Rohit Kohli, MBBS, MS

Locating non-operative cohort of patients who have been out of the Surgical Weight Loss Program for Teens, as well as Healthworks for five or more years to recruit for a follow-up study to obtain height, weight, and blood samples for analysis. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Heart Institute | Healthworks**

Teen View, Teen-View2, TeenView 3 looking at risk behaviors in the Teen-LABS cohort. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Behavioral Medicine and Clinical Psychology** » Meg H. Zeller, PhD

The objective of the present study is to describe the prevalence of kidney abnormalities in severely obese children, and to evaluate risk factors for kidney abnormalities in severely obese children using the Teen-LABS baseline status. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Nephrology and Hypertension** » Nianzhou Xiau

Assessment of appetite regulatory peptides following gastric bypass surgery in adolescents. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Endocrinology** » Janet Chuang, MD

Assessment of body composition via dual-energy X-ray absorptiometry (DEXA) in adolescents undergoing bariatric surgery. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**General & Community Pediatrics** » Heidi J. Kalkwarf, PhD, RD

Data collection and management collaboration for the Teen-LABS, FABS, and FABS 5+ studies. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Biostatistics & Epidemiology** » Rachel Akers, MPH, CCDM

Effect of obesity duration on obstructive sleep apnea syndrome (OSAS) severity and sleep quality in morbidly obese patients with OSAS. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)

**Pulmonary Medicine** » Stacey L. Ishman, MD, MPH

Clinical research coordinator support for the FABS 5+ study. (Thomas H. Inge, MD, PhD, FACS, FAAP; Todd M. Jenkins, PhD, MPH)
Clinical and Translational Research Center » Allison Greenberg

Studying the role of the gut microbiome in the modulation of liver injury and cholangiopathies, which can progress to end-stage liver disease. (Jaimie D. Nathan, MD)

Gastroenterology, Hepatology and Nutrition » Jorge A. Bezerra, MD

Sequencing of somatic mutations in lymphatic malformations. (Peter Dickie, PhD; Belinda Hsi Dickie, MD, PhD)

Human Genetics » Derek E. Neilson, MD

Histopathology of lymphatic malformations. (Peter Dickie, PhD; Belinda Hsi Dickie, MD, PhD)

Pathology and Laboratory Medicine » Anita Gupta, MD

Zebra fish models of vascular malformation. (Peter Dickie, PhD; Belinda Hsi Dickie, MD, PhD)

Developmental Biology » Saulius Sumanas, PhD

Medical management of vascular diseases. (Peter Dickie, PhD; Belinda Hsi Dickie, MD, PhD)

Cancer and Blood Diseases Institute » Denise M. Adams, MD

Placental pathologies in Hypoplastic Left Heart Syndrome. (Helen N. Jones, PhD)

The Heart Institute » Robert B. Hinton, MD and James F. Cnota, MD

CFCMT Placental effects of Fetal NK cells. (Helen N. Jones, PhD)

Center for Fetal Cellular and Molecular Therapy » Aimen F. Shaaban, MD

Maternal Regulatory T cells in Fetal Tolerance. (Aimen F. Shaaban, MD)

Infectious Diseases » Sing Sing Way, MD, PhD

Developmental Brain Disorders in Fetal Myelomeningocele: Can they be Reverted by Fetal Prenatal intervention? (Jose L. Peiro, MD)

Developmental Biology » Kenneth J. Campbell, PhD

Pediatric Neuroimaging Research Consortium » Weihong Yuan, PhD

Amniotic fluid neural progenitor cells for fetal myelomeningocele regeneration. (Jose L. Peiro, MD)

Developmental Biology » Masato Nakafuku MD, PhD

Cell therapy with amniotic fluid progenitor cells and growth factors added to the fetal tracheal occlusion to treat pulmonary hypoplasia of CDH in the fetal lamb. (Jose L. Peiro, MD)

Section of Neonatology, Perinatal and Pulmonary Biology » Jeffrey A. Whitsett, MD

Development of colon-rectal muscles and anal sphincter in myelomeningocele patients. (Jose L. Peiro, MD)

Peña Colorectal Center » Alberto Peña, MD and Andrea Bischoff, MD

Gastroschisis Ultimate Trial (GUT). An international multicentric randomized study. (Jose L. Peiro, MD)

Intestinal Rehabilitation Program » Michael A. Helmrath, MD, MS
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**Current Year Direct** $2,157,854

**Current Year Direct Receipts** $77,085

**Total** $2,234,939