Pediatric General and Thoracic Surgery

RESEARCH AND TRAINING DETAILS

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CLINICAL ACTIVITIES AND TRAINING

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Research Highlights

Richard Falcone Jr., MD, MPH

Pediatric 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. This work is funded, for two consecutive years, by the Ohio Department of Public Safety. At the system level, this work has allowed an improved understanding of state wide under-triage of injured children, and is now focusing on a better understanding of the triage of pediatric traumatic brain injuries patients throughout the state trauma system. Extensive work by our group has also explored the appropriate triage of injured children on arrival to the pediatric trauma center based on pre-hospital information. As an expansion of this work, Cincinnati Children’s is part of an important R24 funding proposal to further understand EMS triage of children, and how this interacts with trauma center triage. In addition to this important work, the group has published groundbreaking research on how adult trauma centers can significantly improve their care of injured children by partnering with a pediatric trauma center. Finally, our injury prevention work continues to explore the impact of our home safety program and our national Buckle Up for Life program on reducing pediatric injuries. This important work receives funding from Kohl’s Cares for Kids, Messer Construction Company and Toyota.

Michael Helmrat, MD

Dr. Helmrat is the surgical director of the Intestinal RehabilitationCenter. His laboratory’s basic and clinical studies focus on evaluating the adaptive response of the bowel to injury and loss. Specifically, the laboratory focuses on the role of intestinal stem cells in small intestinal physiology. His work has been continuously funded by multiple NIH awards. His U01 award aims to lead to a deeper understanding of regional influence within intestinal stem cell populations that may contribute to physiological and disease specific difference commonly seen between the proximal and distal intestine. As part of the Intestinal Stem Cell Consortium (ISCC, NIH), he is
actively involved in the intestinal stem cell field. His long-term research goal is to establish translational therapies for the management of patients with short bowel syndrome.

Thomas Inge, MD, PhD
Dr. Thomas Inge is a full-time attending physician in the Division of Pediatric General and Thoracic Surgery, the director of the Surgical Weight Loss Program for Teens, and is also the co-director of the Center for Bariatric Research and Innovation (CBRI). He has extensive clinical expertise in medical and surgical management of patients with severe obesity. The main focus of his research is the outcomes of bariatric surgery, for which he has funding from the National Health Institutes (NIH) continuously since 2005. He is the principal investigator of the multicenter Teen-LABS study which was recently awarded five additional years of funding (2017-2022) by the National Institute of Diabetes and Digestive and Kidney Diseases. The CBRI is currently partnering with Cincinnati Children's divisions and other institutions to study the changes in patients after bariatric surgery. Dr. Inge collaborated with other leading Cincinnati Children's physicians and investigators to create the Pediatric Diabetes and Obesity Center (PDOC) with an Academic and Research Committee award from the Children's Cancer Research Fund (CCRF). A PDOC research study is currently recruiting and enrolling participants to address the role of the immune system in the development and progression of obesity and obesity-associated sequelae.

Helen Jones, PhD
Helen Jones, PhD, and her lab members investigate the maternal-fetal interface in a broad range of pathologies, and are developing targeted gene therapy protocols to use during pregnancy to improve placental function and fetal growth. With collaborators from the University of Cincinnati, they have developed, and demonstrated, successful, cell-specific gene expression both in primary human trophoblast cultures and a mouse model of placental insufficiency, along with maintenance of normal fetal growth in the mouse model upon treatment. Current studies are underway into the inclusion of targeting peptides onto the nanoparticles for systemic delivery and incorporation of MiRNA seed sequences to address off-target effects.

In collaboration with James Cnota, MD, and the Heart Institute, the Jones lab has demonstrated significant alteration of placental vascular and villous development in cases of congenital heart defects, including hypoplastic left heart syndrome (HLHS), and transposition of the great arteries in humans. They have demonstrated a new mouse model of HLHS recapitulates the human placental phenotype, and will use this to investigate the heart-placenta axis throughout gestation.

Dr. Jones and her team have also established new collaborations with Dr. Kasper Hoebe, PhD, the Division of Immunobiology, to study the role of maternal immune modulation of placental invasion; and Dr. Gruschen Veldtman, FRCP, MBChB, director of Adult Congenital Heart Disease, to investigate placentation in mothers with heart diseases. Dr. Jones has maintained collaborations with Dr. Laura Woollett, UC Pathology, to study the effects of cholesterol on placental development and function, as well as collaborations with Drs. Louis Muglia, MD, PhD, and Michaela Pavlicev, PhD, Center for Prevention of Preterm Birth, to investigate placental involvement in preterm birth.

Maxime M. Mahe, PhD
Dr. Maxime Mahe is an instructor in the Division of Pediatric General and Thoracic Surgery. His research goals are to study human enteric nervous system regulation of intestinal growth and its impact on gastrointestinal dysfunctions. Dr. Maxime Mahe studies the molecular and cellular mechanisms underlying the effects of the enteric nervous system on intestinal epithelial functions using integrated human gut models derived from pluripotent stem cells. The overall goal of his research is to provide insight into the gastrointestinal pathophysiology relevant to congenital dysmotilities, gastrointestinal infections, irritable bowel syndrome (IBS), and Hirschsprung disease. Additionally, Dr. Mahe received the Athena Troxnel Blackburn Research Scholar Award from the American Gastroenterology Association.

Jaimie Nathan, MD
Jaimie Nathan, MD, surgical director of the Intestinal Transplant Program, and his team are investigating the role of intestinal microbiota in intestinal transplantation and in progression of chronic liver diseases. With grant funding from the American Society of Transplant Surgeons, the team is studying the role of intestinal microbiota in acute rejection after intestinal transplantation with the goal of identifying novel non-invasive biomarkers to predict the development of rejection. Investigating the role that changes in intestinal microbiota play in
Jose L. Peiro, MD, PhD
A research team led by Jose L. Peiro, MD, PhD, director of Endoscopic Fetal Surgery at the Cincinnati Fetal Center, is continuing investigating the basic mechanisms of pediatric and fetal surgical congenital malformations, focusing especially upon fetal myelomeningocele (MMC), congenital diaphragmatic hernia (CDH), and gastrochisis.

New Trends in Spina Bifida and Neural Tube Defects
Improving the fetoscopic approach for intrauterine repair by evaluating different patches and sealants in animal models (in collaboration with biomedical engineers at the University of Cincinnati, Professor Chia-Ying Lin’s Laboratory, and then translating these techniques for use in the human fetus is the focus in MMC. A new clinical trial will compare fetoscopic MMC repair in humans against the standardized open fetal surgery approach. They are determining the mechanistic processes and pathways activated in the neuro-inflammation and neurodegeneration that appear in open neural tube defects in rodent models. The team is also studying ways to use neural progenitor cells collected from the amniotic fluid of MMC patients as a potential form of neural regeneration (cell therapy). In collaboration with Dr. Shaaban’s lab, they are using a mouse model of neural tube defects to investigate how maternal immune status can influence incidence of congenital malformations.

Evaluating Fetal Surgery to Support Lung Development
In CDH, they will continue studies in animal models that 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. They described comparison of a novel CDH surgically induced model in rats with gene-expression to the teratogen nitrofen-induced CDH model in a collaborative study with Dr. Jeffrey Whitsett's research group. Also, an excessive reversal of epidermal growth factor receptor and ephrin signaling has discovered the following tracheal occlusion in a rabbit model of congenital diaphragmatic hernia. They started this year with fetoscopic tracheal occlusion in human fetuses with severe CDH by detachable balloon insertion. This work will contribute to the ongoing multicenter TOTAL trial.

Neuroenteric and Lymphatic Disorders Related to Gastroschisis
In gastroschisis, they are analyzing the neurodegenerative and lymphatic anomalies that associates with fetal gastrochisis and their relation with intestinal hypo-motility and malabsorption in the fetal rabbit model. They are also studying the origin and presence of intrauterine growth restriction in these fetuses with gastrochisis, in collaboration with Dr. Habli and Dr. Helen Jones’ Lab.

Aimen Shaaban, MD
Immunologic Tolerance to In Utero Hematopoietic
Cell transplantation Aimen F Shaaban, MD, is the director for the Center for Fetal Cellular and Molecular Therapy. Research focuses on in utero hematopoietic cell transplantation (IUHCT) for the treatment of congenital diseases such as sickle cell disease and thalassemia with the goal of understanding the steps necessary for successful engraftment and long-term tolerance induction. In a small-animal model, the team is defining the manner in which the fetal immune system first learns to differentiate self from foreign cells. Over the past year, these studies have resulted in publications in the Journal of Immunology and Scientific Reports, as well as research presentations at the American Society of Hematology. Our research program is funded by support from the National Institutes of Health (NIH), and the Children’s Hospital Research Foundation.

Additionally, maintained productive collaborations with: 1) Dr. Sing Sing Way from the Division of Infectious Diseases in probing how fetal exposure to mother’s cells affects future reproductive fitness; 2) Dr. Helen Jones in exploring how the cross-talk between the maternal and fetal immune system affects placental development; 3) Drs. Foong-Yen Lim from the Cincinnati Fetal Center; Jose Luis Peiro from the Division of Pediatric General and Thoracic Surgery; and Beth Kline-Fath from the Department of Radiology in the study of how the human fetal lung grows in cases of congenital diaphragmatic hernia; 4) Dr. Kasper Hoebe from the Division of Immunobiology in exploring the mechanisms underlying fetal NK cell development; and 5) Dr. Damien Reynaud from the Division of Experimental Hematology and Cancer Biology in exploring the mechanisms controlling cell-fate decisions in the hematopoietic system. These collaborative works were published in Chimerism, Prenatal Diagnosis, and the Journal of Pediatric Surgery.
Soona Shin, PhD

Soona Shin, PhD, is a member of the Liver Tumor Program. Her research aims to decipher the molecular and cellular mechanism of childhood liver cancer, with a focus on adult hepatic progenitor cells, fetal hepatoblasts and hepatocytes. Facultative adult hepatic progenitor cells and fetal hepatoblasts are tissue-specific stem cells that can differentiate into hepatocytes and cholangiocytes, the two major epithelial cell populations in the liver. The research team investigates the hypothesis that while adult hepatic progenitor cells promote pathological angiogenesis, dysregulated differentiation of both fetal hepatoblasts and hepatocytes initiates tumorigenesis. The Shin lab employs molecular genetic approaches to test this hypothesis and collaborates with Drs. Nikolai Timchenko, PhD, and Anita Gupta, MD, to discover novel strategies for prevention and treatment of liver cancer.

Gregory Tiao, MD

Dr. Greg Tiao is the director for the Division of Pediatric General and Thoracic Surgery and surgical director of liver transplantation. Dr. Tiao is also a member of the Liver Tumor Program and a member of the Children’s Oncology Group Rare Tumor Liver Subcommittee. Dr. Tiao’s lab continues to work on the pathogenesis of Biliary Atresia through an ongoing R01 project funded by the National Institutes of Health (NIH) with the assistance of his research team including Dr. Sujit Mohanty and research assistants Bryan Donnelly and Sarah Mowery. Recently published data from his lab illustrated the role of rotavirus VP6 protein phosphorylating the mitogen activated protein kinase, ERK allowing virus replication. ERK phosphorylation leads to calcium influx in biliary epithelial cells (cholangiocytes). Pre-treatment with an ERK inhibitor or a calcium channel blocker Verapamil, resulted in lower viral yields in vitro. ERK inhibition in BALB/c pups resulted in reduced viral yield within their bile ducts and decreased symptoms of biliary atresia. In an additional study, his lab has identified a novel cell binding site on rotavirus’s VP4 protein. The amino acid sequence “srl” (445-447) within VP4 binds to the heat shock cognate protein 70 (Hsc70) expressed on cholangiocytes membrane. Utilizing an innovative reverse genetics system his lab generated a mutant virus where amino acid arginine (R) in the “srl” sequence changing it to glycine (G). Mice injected with this mutant strain of RRV no longer develop murine biliary atresia.

Nikolai Timchenko, PhD

Nikolai Timchenko, PhD, is a professor within the UC Department of Surgery, and a leader of the Liver Tumor Program. His lab investigates mechanisms of hepatoblastoma (HBL), hepatocellular carcinoma (HCC), and mechanisms of non-alcoholic fatty liver disease (NAFLD). Liver Cancer: The main hypothesis of cancer related studies is that the cause of HBL is a failure of hepatic stem cells to differentiate into mature hepatocytes; while development of HCC is associated with de-differentiation of hepatocytes into cancer stem cells. Dr. Timchenko’s lab has generated five unique animal models with accelerated or inhibited liver cancer after treatments with certain carcinogens. Investigations of molecular pathways in these animal models revealed that the key event in the development of HCC is the proteosome-mediated elimination of tumor suppressor proteins and proteins that support differentiation status of hepatocytes. In collaborations with Dr. Gregory Tiao, MD, and Dr. James Geller, MD, from the Division of Oncology, along with other members of Liver Tumor Program, Dr. Timchenko has analyzed a large cohort of liver samples from patients with HBL and found the elimination of tumor suppressor proteins in the majority of HBL samples. Surprisingly, a significant portion of aggressive HBL samples have elevated levels of tumor suppressor proteins which underwent modifications and lost their tumor suppressor activities. Using animal models of HBL, Dr. Timchenko identified a unique type of hepatocytes which display properties of tumor initiating cells. Current studies are examining if these hepatocytes give rise to liver cancer. These studies translate the knowledge of the molecular mechanisms of liver cancer, generated in animal models, to clinical application in human patients. NAFLD. Investigations of NAFLD by Dr. Timchenko’s lab resulted in the discovery of a triggering event that causes NAFLD. This event is the elevation of cdk4 and subsequent stimulation of a cascade of pathways that lead to NAFLD. Dr. Timchenko also found that the inhibition of cdk4 prevents/reverses early steps of NAFLD. Since the FDA approved the use of cdk4 inhibitors, and are in clinical trials for liver cancer, it is possible to initiate clinical trials for NAFLD with these drugs. These studies have been recently published in Cell Reports and received extensive media coverage.

Significant Publications

There is little known about the prevalence of nonalcoholic fatty liver disease (NAFLD) among severely obese adolescents or factors that determine its development. We investigated the prevalence of NAFLD in a multicenter cohort of adolescents undergoing bariatric surgery, and the factors associated with it.


The epidermal growth factor/epidermal growth factor receptor (EGF-EGFR) signaling regulates the inflammatory microenvironment, and associates with development of hepatocellular carcinoma (HCC). In this editorial, Dr. Timchenko has analyzed recently published observations showing that EGFR has opposite functions in different cell types of the liver. EGFR promotes HCC in Kupffer cells of the liver, while it inhibits HCC in hepatocytes. These observations demonstrated that the therapeutic approaches designed should be for a specific inhibition of EGFR only in macrophages, and should not affect EGFR in parenchymal cells given that the latter scenario might promote tumorigenesis.


Liver regeneration after surgical resections is a complex process which includes multiple alterations in gene expression. Despite significant progress in the studies of liver regeneration, there is little known about triggering events. In this article, Valanejad and Timchenko have analyzed findings by Pauta and colleagues that revealed a critical role of serine-threonine kinase Akt/PKB-Foxo1 pathway in liver regeneration. This axis controls at least four highly significant signaling activation of this axis required for liver regeneration.


In this study, we review the burden of type 2 diabetes in youth including its associated complications. We discuss the outcomes and complications of bariatric surgery in adolescents with diabetes. The conclusion includes recommendations for future research and options for refinement of the use of bariatric surgery in this patient population.


Neurogenin3 (NEUROG3) is a basic helix-loop-helix transcription factor required for development of the endocrine pancreas in mice. In contrast, humans with NEUROG3 mutations are born with endocrine pancreas function, calling into question the requirement of NEUROG3 for human endocrine pancreas development. To test this directly, we generated human embryonic stem cell (hESC) lines and disrupted both alleles of NEUROG3 using CRISPR/Cas9-mediated gene targeting. NEUROG3(−/−) hESC lines efficiently formed pancreatic progenitors but lacked detectible NEUROG3 protein and did not form endocrine cells in vitro. Moreover, NEUROG3(−/−) hESC lines were unable to form mature pancreatic endocrine cells after engraftment of PDX1(+)/NKX6.1(+) pancreatic progenitors into mice. In contrast, a 75-90% knockdown of NEUROG3 caused a reduction, but not a loss, of pancreatic endocrine cell development. We conclude that NEUROG3 is essential for endocrine pancreas development in humans and that as little as 10% NEUROG3 is sufficient for formation of pancreatic endocrine cells.

**Division Publications**


### Grants, Contracts, and Industry Agreements

#### Annual Grant Award Dollars

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<td>Timing of Inguinal Hernia Repair in Premature Infants: A Randomized Trial</td>
<td>National Institutes of Health (Vanderbilt University)</td>
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Annual Industry Award Dollars

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Industry Sponsor: Navidea Biopharmaceuticals
Amount: $157,307