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UPMC Children's Hospital of Pittsburgh is affiliated with the University of Pittsburgh School of Medicine and nationally ranked in nine clinical specialties by *U.S. News & World Report*.

Research Update: NFkB, Autophagy, and Asparaginase-Associated Pancreatitis



Amitava Mukherjee, PhD, is a research instructor in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition. A cell and molecular biologist, Dr. Mukherjee specializes in the study of the molecular drivers of protein turnover, cellular homeostasis, and proteotoxicity. For the past two years he also has been interested in various cellular autophagic processes related to the development of asparaginase-associated pancreatitis (AAP) in the treatment of acute lymphoblastic leukemia (ALL). Dr. Mukherjee, in collaboration with former chair of the Department of Pediatrics, David H. Perlmutter, MD, has spent many years investigating the roles of the protein α 1-antitrypsin in proteinopathy that drive fibrosis and cancer in the liver.

Dr. Mukherjee and colleagues recently published findings in the journal *Cell Death & Differentiation* identifying the role of the NFkB signaling pathway with respect to dysregulation and misfolding of the α 1-antitrypsin protein.

"The primary function of α 1-antitrypsin is in the lungs where it neutralizes neutrophil hydrolysis. Dysregulation and misfolding of the protein cause it to essentially become stuck in the endoplasmic reticulum (ER) of the liver cell. This leads to a two-fold problem. The lungs need this protein to help protect them against emphysema. In the liver, hepatocytes end up with an overload of misfolded α 1-antitrypsin. Accumulation of this misfolded protein leads to fibrosis and liver damage, and ultimately it can be responsible for the development of some liver cancers," explains Dr. Mukherjee.

The recently published paper showed that the nuclear transcription factor NFkB, which is involved in many cellular processes, has a

protective effect in the liver through two mechanisms. It protects the liver hepatocytes from fibrosis, and it also induces an autophagic response to target and clear the misfolded α 1-antitrypsin proteins.

"We were able to show that NFkB signaling leads to autophagy, and autophagy leads to fewer accumulated misfolded proteins inside the ER of the liver cells. NFkB also is responsible for activating a process that degrades fibrotic protein collagen accumulation in the extra-cellular matrix of the liver. Now we are excited to begin to explore how exactly NFkB induces autophagy. That will be our next target of investigation," says Dr. Mukherjee.

New Award to Study Asparaginase-Associated Pancreatitis

In June, Dr. Mukherjee was awarded a UPMC Children's Rangos Advisory Committee (RAC) start-up award to support his research into the pathogenesis of asparaginase-associated

Advanced Practice Provider GI Fellowship Program

A broad initiative is underway at UPMC and UPMC Children's Hospital of Pittsburgh to create subspecialty programs for advanced practice providers (APP). The goal of the fellowship program is to increase access to care for patients and families by conducting highly targeted and specific education for physician assistants and certified registered nurse practitioners who will specialize in treating patients in a specific subspecialty.



"With respect to our goals for the fellowship program in the Division of Gastroenterology, Hepatology, and Nutrition, we hope to have a set of advanced practice providers working in the community — either

autonomously or semi-autonomously — handling some of the more common types of cases, allowing families and patients to be seen by a specialist sooner, and at the same time giving the physicians in the Division the ability to see more of our higher acuity patients with Crohn's disease, ulcerative colitis, pancreatitis, and other complex cases," says **Whitney Sunseri, MD**, assistant professor of pediatrics in the Division, and director of the Pediatric Gastroenterology, Hepatology, and Nutrition Advanced Practice Provider Education Program.

Fellowship Training Details

Enrollment into the fellowship program will occur on a rolling basis. One of the first three months of training will consist of a pediatric boot camp where APPs will have pediatric didactics five days a week. "The remaining nine months of training will be subspecialty specific with curriculums designed by each division. We will start our GI trainees with shadowing and seeing patients with a proctor. Based on certain benchmarks and feedback related to each individual's progress, they will be able to slowly, over time, start to see patients on their own. Eventually we want them to function autonomously, knowing they will always have a clinician from the Division available to speak to on the phone or consult with in person in the office if they need assistance with a specific case," says Dr. Sunseri.

Built into the GI curriculum are shadow rotations with the Medical Coping Clinic, the Feeding and Swallowing Center, IBD Center, radiology, allergy and immunology, and others. The program will allow for a broad base of understanding in GI conditions, but at the same time individuals may be able to specialize in one or several kinds of conditions based on their training, goals, and aptitude.

A Part of the Future of Medicine

"This is an exciting program," says Dr. Sunseri. "It will be of great benefit to our patients because they will have increased access to care from subspecialty providers who are well-trained in their discipline. I think this type of approach to care can become an integral part of the future of medicine."

Research Update *(Continued from Page 1)*

pancreatitis. The RAC award is a two-year grant that is designed to support junior faculty in their progress toward becoming independent investigators.

Asparaginase is a first-line, crucial therapeutic agent for the treatment of acute lymphoblastic leukemia (ALL). In some patients, however, treatment with asparaginase can lead to acute pancreatitis with high rates of morbidity and mortality. Dr. Mukherjee's research, in collaboration with Sohail Husain, MD, seeks to understand why only a small percentage of asparaginase-treated patients develop the condition, and what mechanisms are driving its induction.

"We think some patients could be lacking in production of asparagine synthetase in the pancreas, which is a protein that helps counteract the reduction in the amino acid asparagine that is selectively targeted by asparaginase in the treatment of ALL. The other theory is that there is dysregulation of autophagic processes in the pancreas of these patients that leads to amino acid imbalances at the cellular level, eventually leading to injury of the pancreas and pancreatitis," says Dr. Mukherjee.

Dr. Mukherjee's investigations will attempt to determine whether asparagine synthetase does in fact play a protective role in pancreas cells, as well as whether dysregulation of the normal autophagy process is a contributing

factor. If this is the case, the research could point to potential therapeutic targets and further drug discovery avenues to develop a means to either treat cases of AAP after they arise or even potentially derive a combinative therapy delivered at the time of asparaginase therapy as a matter of prophylaxis.

Further Reading

Mukherjee A, Hidvegi T, Araya P, Ewing M, Stolz DB, Perlmutter DH. NFκB Mitigates the Pathological Effects of Misfolded α1-Antitrypsin by Activating Autophagy and an Integrated Program of Proteostasis Mechanisms. *Cell Death Differ*. 2018 May 23. Epub ahead of print.

GI Nutrition Retreat: Training for Fellows and Advanced Practice Providers

In 2018, **Wednesday Sevilla, MD, MPH, CNSC**, assistant professor of pediatrics in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition, received a grant from the Office of Faculty Affairs at the University of Pittsburgh School of Medicine for an educational innovation project.



Dr. Sevilla and colleagues' program is an immersive and intensive nutrition education course designed to meet the nutrition knowledge objectives for pediatric gastroenterology fellows. "We also have

included our advanced practice providers in our curriculum planning," says Dr. Sevilla. The new educational course, dubbed the Nutrition Retreat, is the first time the Division is holding an intensive training course specifically for fellows and advanced practice providers.

"The curriculum development and implementation team is composed of pediatric gastroenterologists, dietitians, nurse practitioners, and specialty care nurses. This broad, multidisciplinary group of educators will ensure that participants in the program receive nutrition education from the perspectives of the different professionals they will be working with, which will allow development of a perspective that is cognizant of how nutrition concepts and skills are utilized in the clinical spectrum," says Dr. Sevilla.



The overarching goal of the Nutrition Retreat is to improve nutrition care provision in the busy ambulatory setting. To accomplish this, the Nutrition Retreat is designed to teach

fellows and practitioners the basics of providing individualized nutrition care to a complex patient population, as well as to build a tool kit to access specialized nutrition care for patients.

Division Names New Clinical Director



Jeffrey Rudolph, MD, associate professor of pediatrics and director of the Intestinal Care and Rehabilitation Center (ICARE) at UPMC Children's, was recently appointed as the clinical

director of the Division of Pediatric Gastroenterology, Hepatology, and Nutrition.

Dr. Rudolph also is the primary investigator of the ICARE Research Registry database, which serves as a means to identify the clinical characteristics of patients with intestinal failure. In addition to the ICARE Research Registry study, Dr. Rudolph is primary investigator of a number of studies involving the provision of novel lipid therapies to patients on TPN. He has practiced as a board-certified gastroenterologist since 2001 and has been named to *Pittsburgh Magazine's* "City's Best Doctors" from 2012-2018.

Dr. Rudolph completed his medical degree at the University of Pittsburgh School of Medicine, followed by residency and fellowship training at the Washington University Medical Center in St. Louis, and the University of Cincinnati College of Medicine, respectively.

Dr. Rudolph joined UPMC Children's in 2009. His clinical specialties include intestinal failure and transplant, and the full spectrum of intestinal disorders.

Feeding and Swallowing Center Program Advancements

Good nutrition for the growing infant and toddler is one of the most critical aspects of ensuring proper physical and emotional development, and overall health. Feeding and swallowing issues in the young child can lead to immediate nutritional deficits and longer-term complications if not adequately addressed in a timely manner.

The Feeding and Swallowing Center (FASC) in the Division of Pediatric Gastroenterology, Hepatology, and Nutrition, and the Division of Pediatric Rehabilitation Medicine at UPMC Children's was initiated more than 10 years ago to provide comprehensive, interdisciplinary care with a family-centric approach for infants and children. The FASC has seen changes and advancements in recent years, beginning with a higher level of collaboration between clinicians in gastroenterology and pediatric rehabilitation medicine, along with elements from dietetics, nursing, occupational therapy, behavioral therapy, and speech-language pathology.

The FASC sees patients for a number of disorders, and also those individuals who have difficulties with limited or poor food intake, food refusal or selectivity, inadequate or slow weight gain, suspected or identified problems with airway protection and swallowing, choking, picky eating, and other difficulties that may not be immediately attributable to an underlying disorder or pathology.

Why an individual, for example, may be a picky eater could involve issues related to food textures and tastes, undiagnosed anatomical anomalies that make chewing or swallowing difficult or painful, conditions such as gastroesophageal reflux disorder, and many more potentialities.

Discovering the cause or causes for feeding and swallowing issues and providing comprehensive, patient- and family-centric plans of care are at the heart of what the FASC does in more than 800 cases every year.

Clinical Configuration

Currently the FASC sees patients in the clinic two days per week. Patients and families are typically triaged into a specific clinic day during the initial appointment request based

on whether the probability the child's issue stems from a GI-related issue or not. During the initial calls, parents are walked through a detailed questionnaire to provide as much information as possible about the symptoms and difficulties their child is having, and also what the parents' goals are for treatment.

The initial clinic evaluations are thoroughly multidisciplinary, typically take 90 minutes to two hours, and include both the parent(s) and child. FASC team members begin with interviews and questioning to find out more about the problem at hand. They also observe the child as they eat, looking for signs of physical or behavioral issues. Parents are encouraged to bring finger foods or other items the child likes to eat to be used during the evaluation process. The evaluation culminates in a recommendation plan which is given to the parents, and includes any necessary follow-up care suggestions with other specialties as warranted by the team's evaluation and careful consideration of the patient's presentation.

Changes in Patient Care and Follow-up

Recent changes to the FASC have begun to allow for more, continued follow-up care of patients and families. In its early years and incarnation, its function was more of an evaluation clinic. Leadership at the clinic is now working to build out the necessary infrastructure to allow the clinic to expand into longer-term follow-up care by leveraging advanced practice providers to help manage the additional patient volume, while at the same time setting up the FASC to be able to better track long-term patient outcomes.

On the Horizon at FASC

Discussions and plans are underway to create a dedicated gastrostomy tube clinic to handle neonatal patients as they get older and can

begin to take in food orally. This effort will bring together elements of neonatology, pediatric surgery, clinical nutrition, and gastroenterology in the FASC to better manage these patients after their discharge from the NICU.

FASC Team

Gastroenterologists

Wednesday Sevilla, MD, MPH, CNSC

Neonatology

Arcangela Lattari Balest, MD

Pediatric Rehabilitation Medicine

Jason Edinger, DO

Dina B. Patterson, MD

Behavioral Health

Jenny Halper, MSW, LCSW

Nurse Coordinator

Nancy Weichler, RN, MSN, CNS

Occupational Therapists

Kelly Fill, MOT, OTR/L

Kim Kubistek, OTD, OTR/L

Reena McCormick, MOT, OTR/L

Nicole Orlando, MOT, OTR/L

Amy Zuraski, MOT, OTR/L

Registered Dietitians

Barbara Horne, RD, LDN

Ann Meyers, MS, RD, LDN

Sharon Strohm, MS, RD, LDN

Stacey Zettle, MS, RD, LDN

Speech Language Pathologists

Lynn Golightly, MA, CCC-SLP

Patricia Kovacs, MA, CCC-SLP

Maxine Orringer, MA, CCC-SLP

Dayna Revetti, MA, CCC-SLP

Support Staff

Michele Hahner

Insurance Case Manager

Dee Pinney

Patient Information Coordinator

Intestinal Failure and Rehabilitation Symposium

The 10th International Pediatric Intestinal Failure and Rehabilitation Symposium was held September 20-22 in Pittsburgh. Sponsored by UPMC Children's, the annual event brings together pediatric gastroenterologists, surgeons, hepatologists, scientists, and allied health professionals who have dedicated themselves to the care of children with intestinal failure.

The theme of the 2018 event was "Bridges in Pediatric Intestinal Failure and Transplant: Creating New Paradigms." The three-day gathering attracted more than 250 attendees from 23 countries and included more than three dozen speakers from around the world who presented on a variety of topics that included enteral autonomy, implications of the microbiome, vaccine research, liver disease in intestinal failure, and many more.

Keynote speakers at this year's event included David Hackam, MD, PhD, FACS, from Johns Hopkins Children's Center, and Sue Beath, MD, with Birmingham Children's Hospital in England.

This year's course directors included:

Kimberly Ackerman, CRNP — UPMC Children's

Geoffrey Bond, MD, FRACS — UPMC Children's

George Mazariegos, MD, FACS — UPMC Children's

Beverly Kosmach-Park, DNP, RN, FAAN — UPMC Children's

Anita Nucci, PhD, RD, LD — Georgia State University

Jeffrey Rudolph, MD — UPMC Children's

Jane Anne Yaworski, MSN, RN — UPMC Children's



Scenes from the
2018 Intestinal Failure
and Rehabilitation
Symposium



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CME Courses in Pediatric Gastroenterology, Hepatology, and Nutrition



Blood, Sweat, and Cheers! Scientific Discovery and Cystic Fibrosis Research

*Presented by Andrew Feranchak, MD
Chief, Division of Pediatric Gastroenterology, Hepatology, and Nutrition*

Dr. Feranchak gives a presentation on the history of cystic fibrosis and important research discoveries impacting the disorder.

Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians, covering a variety of medical and surgical disciplines.



Pediatric Metabolic Liver Disease

*Presented by Patrick McKiernan, MD
Director, Pediatric Hepatology Program*



Treatment of Acute Liver Failure

Presented by Robert Squires, MD



Treating Pediatric Inflammatory Bowel Disease

*Presented by David Keljo, MD, PhD
Director, Inflammatory Bowel Disease Center*



About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 13th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2017).