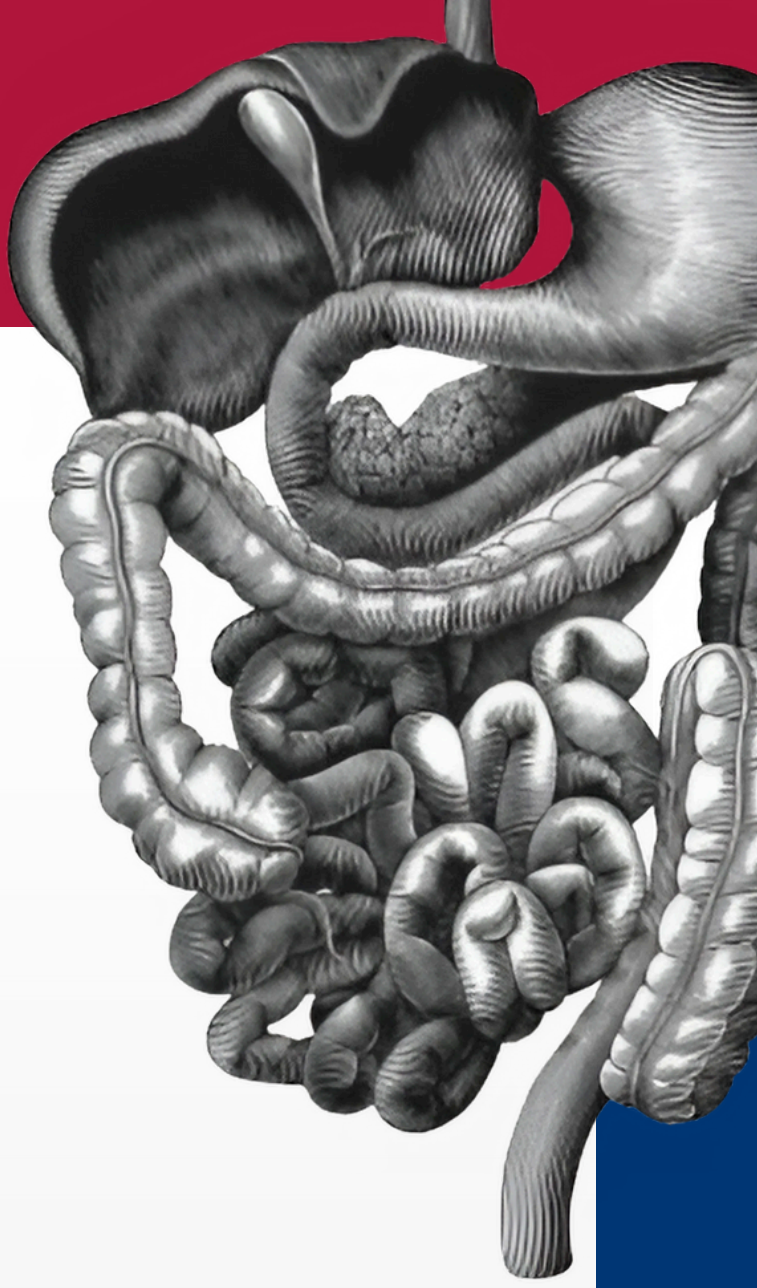
FRONTIERS IN DIGESTIVE DISEASES

SYMPOSIUM

SIXTEENTH ANNUAL



DDC
Texas Medical Center Digestive Diseases Center

"Immune Dysregulation and Digestive Diseases"

Saturday, 2/22/2025

8:00 am - 3:00 pm

Baylor St. Luke's Medical Center
7200 Cambridge
Houston Tx, 77030

Baylor College of Medicine

Provided by Baylor College of Medicine

ACCREDITATION/CREDIT DESIGNATION STATEMENTS

Baylor College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Baylor College of Medicine designates this live activity for a maximum of *4.50 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Opportunity for Physician and Physician Assistant QI Poster Authors and Co-Authors to earn Maintenance of Certification (MOC) Part 4 Credits.

DDC
Texas Medical Center Digestive Diseases Center

About the Texas Medical Center Digestive Disease Center (DDC)

The Texas Medical Center Digestive Diseases Center facilitates cutting-edge digestive diseases research, promotes translational collaborative research between basic and clinical areas, develops new projects, nurtures new investigators, and provides GI educational activities.

The DDC is a federally funded center (NIH P30DK056338) designed to serve basic and clinical scientists at institutions within the Texas Medical Center, including Baylor College of Medicine, The University of Texas Health Science Center at Houston, and the MD Anderson Cancer Center.

The DDC supports three basic science cores: Tissue Analysis and Molecular Imaging, Functional Genomics and Microbiome, Gastrointestinal Experimental Module Systems; and one clinical core: Study Design and Clinical Research.

Current DDC membership includes 121 members, with 80 full members and 41 associate members. DDC members have approximately $42.6 million in digestive diseases-related research funding as of 2024. The overall theme of the DDC is “Molecular mechanisms and outcomes of injury, infection, or metabolic dysfunction of the digestive system.”

Visit the DDC website to learn more about upcoming enrichment activities, funding opportunities, and other valuable resources.

Visit the DDC online!

https://www.bcm.edu/research/research-centers/texas-medical-center-digestive-

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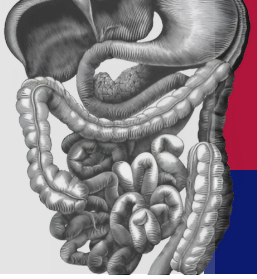

FRONTIERS IN DIGESTIVE DISEASES
SYMPOSIUM
SIXTEENTH ANNUAL

AGENDA

	7:30 AM – 8:10 AM	**Check-In / Breakfast**
	8:10 AM – 8:25 AM	**Welcome Remarks** Jason C. Mills, M.D., Ph.D., DDC Co-Director
	8:25 AM – 8:30 AM	**Patient Advocacy & Community Outreach** Lisa Brunet, APFED (American Partnership for Eosinophilic Disorders)
SESSION ONE	8:30 AM – 9:10 AM	**"Dysregulated immunity driving tissue remodeling in eosinophilic esophagitis"** Seema Aceves, M.D., Ph.D. Professor, Pediatrics and Medicine University of California San Diego, San Diego, CA
	9:10 AM – 9:50 AM	**"Spatial and temporal resolution of eosinophil specialization in allergic microenvironments"** Julia Dunn, Ph.D. Assistant Professor, Pediatrics-Gastroenterology, Hepatology and Nutrition University of Colorado, Denver, CO
	9:50 AM – 10:10 AM	**"Stomach microenvironment aids in ascaris pathogenicity"** Jill Weatherhead, M.D., Ph.D. *(2021 Pilot Feasibility Awardee)* Associate Professor, Tropical Medicine & Infectious Disease Baylor College of Medicine, Houston, TX
	10:10 AM – 10:50 AM	**"Deciphering the immunopathogenesis of celiac disease"** Valerie Abadie, Ph.D. Research Associate Professor, Medicine University of Chicago Pritzker School of Medicine, Chicago, IL
	10:50 AM – 11:05 AM	**Coffee Break**
SESSION TWO	11:05 AM – 11:45 AM	**"Crosstalk between eosinophils and macrophages controls liver regeneration after ischaemia and reperfusion injury"** Cynthia Ju, Ph.D. Professor, Joseph C. Gabel, M.D. Endowed Chair in Anesthesiology University of Texas McGovern Medical School, Houston, TX
	11:45 AM – 12:05 PM	**"Do gut microbes trigger fibrosis in neonatal obstructive cholestasis?"** Greg Guthrie, Ph.D. *(2020 Pilot Feasibility Awardee)* Assistant Professor of Pediatrics, Children's Nutrition Research Center Baylor College of Medicine, Houston, TX
	12:05 PM – 12:45 PM	**"Beyond the gut and liver: bile acids shape peripheral immunity"** Krupa Mysore, M.D., M.S. *(2023 Pilot Feasibility Awardee)* Assistant Professor of Pediatrics, Gastroenterology, Hepatology and Nutrition Baylor College of Medicine, Houston, TX
	12:45 PM – 2:15 PM	Poster Session *(boxed lunches provided)*
	2:15 PM – 2:45 PM	**Breakout Sessions** *(with select speakers)*
	2:45 PM – 3:00 PM	**Post Awards / Closing Remarks** Geoffrey A. Preidis, M.D., Ph.D., Enrichment Program Director

Provided by Baylor College of Medicine

Texas Medical Center Digestive Diseases Center
16th Annual Frontiers in Digestive Diseases Symposium
"Immune Dysregulation and Digestive Diseases"

Saturday, February 22, 2025 | 8 am – 3 pm | Baylor St. Luke's Medical Center | 7200 Cambridge

This symposium aims to bridge the gap in understanding the role of immune dysregulation in digestive health and its impact as a precursor to digestive diseases by providing a balanced blend of research insights and clinical applications related to immune dysregulation in digestive diseases. Through presentations by leading experts in the field, participants will gain valuable knowledge of emerging research and current clinical best practices, ultimately enhancing their ability to apply these advancements in their work.

TARGET AUDIENCE: Gastroenterologists, Hepatologists, Digestive Diseases Researchers, Scientists Medical Students and Trainees, and other healthcare professionals with an interest in digestive diseases research.

LEARNING OBJECTIVES: At the conclusion of the conference, participants should be able to:

- Define immune dysregulation within digestive diseases, its historical and future applications in treatment and prevention.
- Interpret current research developments regarding immune dysregulation and its role in digestive diseases.
- Identify opportunities to apply knowledge of immune dysregulation to the detection and treatment of digestive diseases.
- Apply best practices concerning immune dysregulation within the GI tract to better prevent and treat digestive diseases.

EDUCATIONAL METHODS: Lecture, Small Group Breakout Session, and Poster Session

ACTIVITY EVALUATION: Evaluation by questionnaire will address program content, presentation, and possible bias.

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Harvard Medical School

Gary D. Wu, M.D.
University of Pennsylvania

Symposium Speakers

Seema Aceves, M.D., Ph.D.
University of California San Diego

Seema Aceves, M.D., Ph.D., is a Professor of Pediatrics and Medicine at the University of California, San Diego (UCSD). She is also the Director of the Eosinophilic Gastrointestinal Disorders Clinic at Rady Children's Hospital in San Diego. Dr. Aceves earned her M.D. and Ph.D. through the NIH-funded Medical Scientist Training Program at UCSD.

She specializes in the diagnosis and treatment of eosinophilic esophagitis (EoE), a chronic immune-mediated disease. Her research focuses on understanding the mechanisms behind EoE and improving treatment strategies. Dr. Aceves has received NIH funding for her studies, leading to key insights into tissue remodeling and the esophageal microenvironment.

In 2020, she was named the inaugural MRD Endowed Chair in Pediatrics at UCSD. Dr. Aceves has published over 130 scientific papers and is a co-inventor of oral viscous budesonide, a widely used therapy for EoE. Her work has earned her membership in the American Society for Clinical Investigation. Dr. Aceves is highly regarded for her translational research and its impact on pediatric gastrointestinal medicine.

Julia Dunn, Ph.D.
University of Colorado

Julia Dunn, Ph.D., is an Assistant Professor in the Department of Pediatrics, specializing in Gastroenterology, Hepatology, and Nutrition, at the University of Colorado Anschutz Medical Campus. She earned her Ph.D. in Biomedical Engineering from the University of North Carolina at Chapel Hill in 2016.

Dr. Dunn's research focuses on innate immunity, particularly the role of eosinophils in allergic diseases. Her lab investigates how eosinophils specialize in different environments and their interactions with other cells in the mucosal environment.

She has published several significant papers, including studies on eosinophil specialization and their role in allergic inflammation.

Dr. Dunn is committed to advancing the understanding of allergic diseases and developing innovative treatments. Her work aims to revolutionize the treatment of allergic conditions by exploring unexpected aspects of innate immunity.

Jill Weatherhead, M.D., Ph.D.
Baylor College of Medicine

Jill Weatherhead, M.D., Ph.D., is an Assistant Professor at Baylor College of Medicine, specializing in Tropical Medicine and Infectious Diseases. She holds board certifications in Internal Medicine, Pediatrics, and Infectious Diseases. Dr. Weatherhead earned her M.D. from Michigan State University and completed her residency at BCM.

Her research focuses on immune responses to parasitic infections, particularly Ascaris, and their role in allergic diseases. Dr. Weatherhead is also the Director of Medical Education at BCM's National School of Tropical Medicine, where she teaches courses on global health and tropical diseases.

Dr. Weatherhead has received multiple awards, including the 2022 Women of Excellence Award from BCM and was a 2021 recipient of a DDC Pilot Feasibility Award. She also provides clinical care at Texas Children's Hospital, with a focus on parasitic and tropical diseases.

Valerie Abadie, Ph.D.
University of Chicago

Valerie Abadie, Ph.D., is a Research Associate Professor of Medicine at the University of Chicago, specializing in immunology and gastroenterology. She earned her Ph.D. in Microbiology-Virology from the University of Paris VII Denis Diderot in 2005. Her research focuses on understanding how mucosal immune responses are dysregulated in intestinal inflammatory disorders, particularly celiac disease. She investigates the roles of B lymphocytes beyond antibody production and their contribution to autoimmune diseases.

In 2023, she received a grant from the GI Research Foundation to study the loss of tolerance to commensal microbiota in celiac disease, aiming to understand its role in disease development and progression. Dr. Abadie has published extensively on celiac disease and mucosal immunity, contributing to the understanding of its immunopathogenesis. Dr. Abadie's work has been recognized with the Celiac Disease Foundation's Young Investigator Prize in Basic Science.

Cynthia Ju, Ph.D.
UTHealth

Changqing (Cynthia) Ju, Ph.D., is a Professor and Vice Chair for Research in the Department of Anesthesiology at the University of Texas Health Science Center at Houston (UTHealth). She holds the Joseph C. Gabel, M.D. Endowed Chair in Anesthesiology. Dr. Ju earned her Ph.D. in Microbiology-Virology from the University of Paris VII Denis Diderot in 2005.

Her research focuses on understanding the inflammatory mechanisms of acute and chronic liver diseases, including acetaminophen-induced liver injury, liver ischemia/reperfusion injury, and alcohol-induced chronic liver disease. Dr. Ju has published extensively on liver diseases and immunology, contributing to the understanding of liver injury and repair mechanisms.

In 2019, she received two NIH grants totaling $3.6 million to study molecules linked to life-threatening liver injuries. Dr. Ju is also an Associate Editor for JHEP Reports, focusing on basic and translational research.

Greg Guthrie, Ph.D.
Baylor College of Medicine

Gregory Guthrie, Ph.D., is an Assistant Professor at Baylor College of Medicine in Houston, Texas, specializing in pediatric nutrition and liver diseases. He earned his bachelor's degree in Dietetics from Louisiana State University, followed by a master's degree in human resources (Nutrition) from the University of Louisiana at Lafayette. Dr. Guthrie completed his doctorate in Nutritional Sciences at the University of Florida, focusing on nutritional genomics under Dr. Robert Cousins.

His research centers on understanding the mechanisms driving parenteral nutrition-associated liver disease in neonates on long-term parenteral nutrition. Dr. Guthrie investigates the role of lipid emulsion constituents in disease progression, utilizing a neonatal piglet model to assess physiological and molecular alterations similar to those observed in neonates. He has published several significant papers, including studies on the impact of parenteral lipid emulsion components on cholestatic liver disease in neonates and the association between phytosterol depletion and serum markers of cholestasis in preterm parenteral nutrition-fed pigs.

Dr. Guthrie leads the DDC GI Focus Group which organizes semi-monthly meetings for early career investigators and is a 2020 DDC Pilot Feasibility Awardee. He also serves on the DDC PIE Committee.

Krupa Mysore, M.D., M.S.
Baylor College of Medicine

Krupa R. Mysore, M.D., M.S., is an Assistant Professor in the Department of Pediatrics at Baylor College of Medicine, specializing in pediatric gastroenterology and hepatology. She earned her medical degree from Bangalore Medical College and Research Institute in 2008. Dr. Mysore completed her pediatric residency at the University of Iowa Hospitals and Clinics in 2013, followed by fellowships in pediatric gastroenterology and pediatric transplant hepatology at Baylor College of Medicine.

Her research focuses on transplant immunology, gastrointestinal diseases, and hepatology, with a particular interest in biliary atresia and liver transplantation. Dr. Mysore has published numerous articles on these topics, contributing to the understanding of pediatric liver diseases.

In 2023, she received the Biliary Atresia Fund for the Cure Pilot Research Award from the American Liver Foundation to study the molecular mechanisms of immune dysfunction in biliary atresia. She is also a 2023 recipient of a DDC Pilot Feasibility Award.

Patient Advocacy & Community Outreach Spotlight

The American Partnership for Eosinophilic Disorders (APFED) is a nonprofit organization dedicated to supporting individuals affected by eosinophilic diseases, which are a group of rare, chronic conditions caused by elevated levels of eosinophils (a type of white blood cell) in the body. These disorders, such as eosinophilic esophagitis (EoE) and eosinophilic gastritis, can cause a range of symptoms including severe gastrointestinal issues, and can be challenging to diagnose and manage.

Apfed
American Partnership for Eosinophilic Disorders

Founded in 2001, APFED works to raise awareness, provide educational resources, advocate for better medical research, and offer support to patients and their families. The organization is committed to funding scientific research to advance the understanding of these conditions, improving treatment options, and fostering a sense of community among those affected.

APFED's efforts include hosting patient education conferences, providing support groups, and collaborating with medical professionals and researchers to promote better care and more effective treatments. Through its advocacy work, APFED also helps to shape policies that benefit patients living with eosinophilic disorders. The organization continues to be a vital resource for those impacted by these rare diseases, working to ensure that they receive the support and care they need.

For more information, please visit apfed.org.

Poster Session

"Development of an Induced Differentiation Culture System for Mouse Gastric Cells"

Sumimasa Arimura
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Poster #1
See abstract on page 14

"Microbiome changes associated with nitazoxanide in a randomized, double-blind study for the treatment of chronic norovirus infections in solid organ transplant recipients"

Sohini Banerjee
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Poster #2
See abstract on page 15

"Differential effects of early-life malnutrition and stress on gastric emptying and gastrointestinal pathophysiology in neonatal mice"

Donovan Berens
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Poster #3
See abstract on page 16

"Gremlin1 promotes an immunogenic tumor microenvironment in pancreatic ductal adenocarcinoma"

Yanna Cao
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Poster #4
See abstract on page 17

"Missed opportunities for surveillance of preneoplasia in patients with incident gastroesophageal junction adenocarcinoma in a U.S. safety-net hospital"

Nia Choi
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Poster #5
See abstract on page 18

"Putative functions of the lipogenic enzyme aspartoacylase in the intestine"

Evelyn de Groot
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Poster #6
See abstract on page 19

"Novel SIRT1-ERRγ co-regulation promotes the differentiation of gastric parietal cells and presents therapeutic potential to reverse intestinal metaplasia in the stomach"

Margarita Divenko
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Poster #7
See abstract on page 20

"Enteral agonism of farnesoid X receptor-fibroblast growth factor 19 prevents cholestasis in TPN-fed neonatal pigs"

Sarah Elefson
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Poster #8
See abstract on page 21

"Limosilactobacillus reuteri-educated T cells ameliorate liver inflammation in immunocompromised mice"

Ana Fadhel-Alvarez
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Poster #9
See abstract on page 22

Poster Session

"Poglut1 reduction in hepatocytes by using GalNAc conjugated ASO does not rescue the liver phenotypes of Alagille Syndrome, in contrast to unconjugated ASO"

Yaniv Faingelernt
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Poster #10
See abstract on page 23

"Family-based screening for Helicobacter pylori infection and comparison of antibiotic susceptibility in high-risk Hispanic families in the U.S."

Franciska Gudenkauf
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See abstract on page 24

"New ex vivo approaches to quantify colon migrating motor complexes in mice: route of drug delivery matters"

Carine Halaby
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Poster #12
See abstract on page 25

"Microbiome profiles of children with Autism Spectrum Disorder (ASD) with and without GI symptoms"

Vaishali Harne
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Poster #13
See abstract on page 26

"Bridging the brain-gut axis: the role of psychiatric interventions in managing co-existing digestive and psychiatric illnesses"

Madeline Hawkins
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Poster #14
See abstract on page 27

"The Role of Kynurenine-AHR Signaling in Mitochondrial Homeostasis and Liver Pathology"

Mi Jeong Heo
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See abstract on page 28

"Quantitative Analysis of the Enteric Nervous System in Pediatric Human Small Intestine and Tissue-Engineered Human Small Intestine"

Madushani Herath
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Poster #16
See abstract on page 29

"A YAP1-DDIT4-NME1 axis in paligenosis"

Raymond Ho
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See abstract on page 30

"The commensal bacterium Limosilactobacillus reuteri generates novel microbial-conjugated bile acids"

Thomas Horvath
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Poster #18
See abstract on page 31

Poster Session

"Epigenetic alteration for cellular identity switching during metaplasia and tissue injury"

Yang-Zhe Huang
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Poster #19
See abstract on page 32

"Efficacy and safety of transoral incisionless fundoplication in nonobese and obese adults: A population-based cohort study from the United States"

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"Glucagon-like peptide-1 (GLP-1) receptor agonists are associated with reduced risk of gastrointestinal cancers: Insights from a nationwide real-world analysis."

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Poster #21
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"TIRZEPATIDE Shows Lower Risk of Gastrointestinal Side Effects Compared to Single-Agent GLP-1 Receptor Agonists: A Real-World Analysis of Over 1 Million Patients"

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See abstract on page 35

"Overcoming host restriction to enable continuous passaging of human noroviruses in human intestinal enteroids"

Gurpreet Kaur
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Poster #23
See abstract on page 36

"Comparison of risk factors and cancer outcomes between young-onset (<50 years) and average-onset gastric cancer patients at two U.S. medical centers: a case-case study"

Min Kim
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See abstract on page 37

"Associations of demographic and food scarcity factors with Helicobacter pylori seroprevalence in an urban U.S. population

Min Kim
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Poster #25
See abstract on page 38

"Impact of 'gut immune axis' shift on progressive liver disease"

Shwetha Kumar
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Poster #26
See abstract on page 39

"Detection of macrophage phagocytosis in human norovirus infection using ex vivo human intestinal enteroids-immune cell coculture system"

Ngan Fung Li
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See abstract on page 40

Poster Session

"Adipose tissue response to vitamin E status in the regulation of whole-body homeostasis"

Elizabeth Lieu
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See abstract on page 41

"Microbially Derived Branched-Chain Fatty Acids Regulate Colonic Permeability in Protein Malnutrition"

Lauren Lynch
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See abstract on page 42

"Colonization of the nasopharynx by Klebsiella pneumoniae is associated with establishment of gastrointestinal carriage in mice"

Rina Matsuda
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Poster #30
See abstract on page 43

"Gut pathobiont enrichment observed in a population predisposed to dementia, type 2 diabetics of Mexican descent living in South Texas

Lisa Matz
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Poster #31
See abstract on page 44

"Investigating the effects of diet and the gut microbiome on the pathogenesis of necrotizing enterocolitis (nec)"

Valeria Melendez
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See abstract on page 45

"Preclinical models for functional studies of the infant gut microbiome"

Firas Midani
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See abstract on page 46

"Intestinal insufficiency increases risk of death and prolonged hospitalization: a large single-center cohort study of pediatric liver transplant recipients."

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See abstract on page 47

"The role of IL4:microbiome interaction in acute colitis"

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Poster #35
See abstract on page 48

"Probiotic administration in Treg deficient mice decreases lung inflammation and modulates gut and lung microbiota"

Melissa Munroe
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See abstract on page 49

"Altered phospholipid biosynthesis drives hepatic steatosis in malnutrition

Larissa Neves
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See abstract on page 50

Poster Session

"Evaluating mechanisms of human norovirus gastroenteritis using human intestinal enteroids"

Hephzibah Nwanosike
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Poster #38
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"Prevalence of sucrase-isomaltase gene variants in people with and without IBS using the NIH/HGRI All-of-Us mega-database"

Antone R Opekun
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Poster #39
See abstract on page 52

"Microbial therapeutics to prevent ExPEC colonization and disease"

Jason Pizzini
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Poster #40
See abstract on page 53

"Evaluating human intestinal organoids as a model of very early onset inflammatory bowel disease"

Faith Sawyer
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Poster #41
See abstract on page 54

"Phenotype-informed clustering of genetic variants highlights germline heterogeneity in Crohn's disease"

Vikram Shaw
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Poster #42
See abstract on page 55

"Revealing an anti-inflammatory role of pancreatic fibroblasts in acute pancreatitis in mice

Kevin Shi
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Poster #43
See abstract on page 56

"Urinary ammonium: a potential novel biomarker for diarrhea severity"

Jared Sninsky
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"Malnutrition Impairs Krebs Cycle Function and Bile Acid Biosynthesis"

Krishnakant Soni
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See abstract on page 58

"Unraveling the progenitors of the neosquamous epithelium following radiofrequency ablation in Barrett's Esophagus patients using spatial transcriptomics"

Sarah To
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See abstract on page 59

"Characterizing enteric neuronal subtypes in pediatric human intestine using a novel 3D imaging technique"

Lindsey Vongthavaravat
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Poster #47
See abstract on page 60

Poster Session

"Decoding Human Norovirus Tropism via Single-Cell RNA Analysis"

Luqiong Wang
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Poster #48
See abstract on page 61

"Examining the interplay between the gut microbiome and intestinal epithelium after radiation

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Poster #49
See abstract on page 62

"Yap1 is essential for paligenosis stage 1 and stage 2 transition"

Yongji Zeng
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Poster #50
See abstract on page 63

"Sex dimorphic protection by neutrophil-derived COX-2 against hepatic ischemic-reperfusion injury"

Jie Zhao
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Development of an Induced Differentiation Culture System for Mouse Gastric Cells

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The differentiation of tissue-specific stem cells is a fundamental biological process. In mouse gastric research, elucidating the mechanisms of gastric stem cell differentiation has often relied on studying the recovery processes following gastric cell injury in mice. This approach has limitations because it is not feasible to continuously monitor the differentiation of individual stem cells. Observing stem cell differentiation at the cell culture level could be a viable way to address this limitation, however, existing culture systems do not effectively maintain stem cells with high purity while inducing their differentiation with high efficiency.

In this study, we aimed to overcome these challenges by establishing novel stem cell maintenance and differentiation media specifically customized for mouse corpus organoids. Here, we adopted a two-dimensional (2D) culture system, which facilitates easier induction of differentiation. We screened over 100 different media formulations and conducted detailed investigations on approximately 50 of them to identify optimal conditions for culturing corpus stem cells in 2D organoids. From this extensive screening, we found that Matrigel was a superior coating substrate for 2D organoid cultures compared to other coatings tested. Notably, our medium formulation No. 21 emerged as the most effective for maintaining corpus stem cells in an undifferentiated state. Conversely, differentiation studies using TaqMan quantitative PCR revealed that our media formulations No. 3, 1, 36, and 50 effectively induced the differentiation of corpus stem cells into pit, mucous neck, parietal, and chief cells, respectively. Immunofluorescence analyses confirmed that approximately 80-90% of the cultured cells were positive for their respective cell markers, indicating a high efficiency of differentiation under optimized conditions.

Our findings establish a robust 2D differentiation system that can be widely applied in various experimental settings to advance the understanding of gastric biology. This system is expected to enable continuous monitoring of the differentiation of individual gastric stem cells, providing a valuable tool for future research in stem cell biology and regenerative medicine.

Microbiome changes associated with nitazoxanide in a randomized, double-blind study for the treatment of chronic norovirus infections in solid organ transplant recipients

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Human norovirus (HuNoV) infections in immunosuppressed transplant recipients can become persistent, debilitating, and sometimes life-threatening. There are currently no licensed therapeutics for treatment of HuNoV-associated gastroenteritis. Treatment for chronic HuNoV infection in immunosuppressed patients includes the off-label use of nitazoxanide (NTZ), a broad-spectrum antimicrobial licensed for treatment of parasite-induced gastroenteritis; however, the data on clinical effectiveness of NTZ is unclear. Recently, a randomized, double-blind study of NTZ for the treatment of HuNoV in adult solid organ transplant recipients was conducted. HuNoV positive patients with active gastrointestinal symptoms were assigned 1:1 to NTZ 500 mg twice daily or placebo for 28 days and were followed-up for 6 months. While NTZ did not shorten time to clinical resolution or viral shedding duration, the collected stool samples provided an opportunity to assess the effect of NTZ on the intestinal microbiome.

We performed metagenomic whole genome shotgun sequencing, including analysis of taxonomy (MetaPhlAn4) and enriched pathways (HUMAnN3.8) in stool samples from 29 participants. A single sample collected at enrollment and up to 4 samples each collected during treatment and post treatment phase, for each patient were tested. Correction for biases arising due to longitudinal repeat samplings was performed using MaAsLin2.

There were no significant differences in either alpha or beta diversity at enrollment, suggesting that the baseline microbiome of the NTZ and placebo arms were comparable. However, treatment with NTZ was associated with significant differences in the microbiome composition and diversity, and changes appeared to resolve when treatment was concluded. On-going analyses focus on identifying specific taxa and pathways associated with NTZ treatment. NTZ is used off-label for the treatment of many infections although the mechanisms of action are unknown. Together these data demonstrate that NTZ alters the gut microbiome composition and may provide new insights into its modes of action.

Funding: This research was supported by a National Institutes of Health Genomic Centers for Infectious Diseases Grant U19 AI144297 and National Institute of Allergy and Infectious Diseases(HHSN272201600016C).

Differential effects of early-life malnutrition and stress on gastric emptying and gastrointestinal pathophysiology in neonatal mice

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Background: Pediatric gastroparesis (GP) causes significant morbidity with rising hospitalization rates and healthcare costs. Etiologies of pediatric GP are poorly understood, and treatment options are limited. GP is prevalent in children with severe acute malnutrition, adolescents with anorexia nervosa, and neonates born small-for-gestational age, implicating malnutrition as a potential cause of GP. We recently described a neonatal mouse model of GP induced by 12 hours/day of timed maternal separation ($TmSep_{12}$). $TmSep_{12}$ pups, which exhibit GP, are exposed to stress from maternal separation and to malnutrition from reduced nursing time. To distinguish the effects of stress vs malnutrition, we explored how various degrees of maternal separation and litter crowding-induced malnutrition – alone and in combination – affect gastric emptying.

Methods: C57BL/6 pups were randomized on day of life (DOL) 5 to one of 5 groups: control, $TmSep_{12}$, $TmSep_3$ (maternal separation for just 3 hours/day, no malnutrition), crowded (no maternal separation, crowding-induced malnutrition), and crowded-$TmSep_3$ (maternal separation for 3 hours/day, crowding-induced malnutrition). On DOL 15 we assessed gastric emptying by quantifying the amount of fluorescein isothiocyanate (FITC)-dextran in the small bowel 15 minutes after gastric gavage. We assessed body weight, bowel length, and brain corticosterone levels with ELISA.

Results: Malnourished pups ($TmSep_{12}$, crowded, and crowded-$TmSep_3$) had lower mean body weight and bowel length compared to controls. However, body weight and bowel length were similar between pups in the control and $TmSep_3$ groups, confirming that 3 hours of maternal separation alone does not cause malnutrition. Corticosterone levels were similar in the control, $TmSep_3$, and $TmSep_{12}$ groups, but were significantly increased in both crowded groups. Only $TmSep_{12}$ pups had reduced gastric emptying of FITC-dextran compared to controls (44.5% vs 67.8%, $p<0.0001$).

Conclusions: Malnutrition induced by litter crowding (with or without 3 hours/day of maternal separation) decreases body weight and bowel length, increases brain corticosterone, but does not cause GP. Exposure to 3 hours/day of maternal separation alone does not increase corticosterone and is insufficient to cause GP. Only malnutrition induced by 12 hours/day of maternal separation causes growth faltering, shortened bowel length, and prominent GP. Unexpectedly, brain corticosterone was not elevated in malnourished pups separated for 12 hours/day. These data suggest that delayed gastric emptying can be caused by the combination of malnutrition and prolonged maternal separation and is not primarily mediated by stress.

Gremlin1 promotes an immunogenic tumor microenvironment in pancreatic ductal adenocarcinoma

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Background: We have previously demonstrated that Gremlin1 (Grem1) is upregulated in pancreatic ductal adenocarcinoma (PDAC) and plays a profibrogenic role. Whether Grem1 regulates the infiltrating macrophages is not defined. In this study, we performed *in vitro* studies for the effect of Grem1 on macrophage activation and examined correlation of Grem1 with infiltrating macrophages in PDAC.

Methods: Macrophages were isolated from bone marrows of C57BL/6 mice and treated with recombinant Grem1 protein *in vitro* (500 ng/ml) for 2 days followed by flow cytometry assay. The Cancer Genome Atlas (TCGA) RNA-sequencing data of human PDAC was stratified as $Grem1^{High}$ (n=50) and $Grem1^{Low}$ (n=90). The distribution of immune cells was extracted from The Cancer Immunome Database and immune scores were calculated. Pancreatic tumor microarray (duplicate cores of 19 PDAC cases and one acinar cell carcinoma) was obtained for immunohistochemistry (IHC) with a custom Grem1 antibody and CD68 antibody and correlation was performed across 34 cores (excluding 6 deficient cores).

Results: The *in vitro* study demonstrated that Grem1 treatment increased expression of CD80 ($p<0.01$), iNOS ($p<0.05$), and CD206 ($p<0.05$), the respective markers to total, classically activated M1, and alternatively activated M2 macrophages. The TCGA RNA-sequencing data analysis demonstrated that M1 and M2 macrophage fractions were higher in $Grem1^{High}$ compared to $Grem1^{Low}$ ($p<0.001$). The IHC staining in the pancreatic tumor microarray showed that Grem1 was detected in tumor epithelial cells (Grem1-E) and stromal cells (Grem1-S) and CD68-positive macrophages were detected in the stroma. With a total of 34 PDAC cores, 19 cores stained Grem1-E-positive were all Grem1-S-positive and CD68-positive (100%, $p<0.001$); whereas 15 Grem1-E-negative cores were corresponding to 11 Grem1-S-negative (73%) and 9 CD68-negative (60%, $p<0.001$) cores. Similarly, 23 cores stained Grem1-S-positive were all CD68-positive (100%) and 11 Grem1-S-negative cores were corresponding to 9 CD68-negative cores (82%, $p<0.001$).

Conclusions: Upregulated Grem1 in PDAC may activate macrophages, contributing to a fibrogenic and immunogenic tumor microenvironment in PDAC.

Missed opportunities for surveillance of preneoplasia in patients with incident gastroesophageal junction adenocarcinoma in a U.S. safety-net hospital

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Background: Gastroesophageal junction (GEJ) adenocarcinoma incidence rates are rising in the U.S. While some studies showed Barrett's esophagus as a risk factor for GEJ adenocarcinoma, other studies suggest alternative mechanisms of carcinogenesis (e.g., *H pylori*). We aimed to identify risk factors, preneoplastic conditions, and cancer outcomes among patients with newly diagnosed GEJ adenocarcinoma in a predominantly immigrant, racially diverse U.S. safety-net population.

Methods: We performed a retrospective study of patients newly diagnosed with GEJ adenocarcinoma in Harris Health, a county hospital system in Houston, Texas providing care for uninsured and underinsured patients. Using the Harris Health Cancer Registry, we identified patients with GEJ adenocarcinoma diagnosed between 1/2014-12/2023. On review of the electronic medical record, we confirmed the cancer diagnosis and extracted potential risk factors (demographic, *Helicobacter pylori* infection, GERD). We evaluated missed opportunities for surveillance of preneoplastic conditions diagnosed prior to cancer diagnosis (Barrett's esophagus, gastric intestinal metaplasia, esophageal or gastric dysplasia). We also examined cancer-related outcomes (stage, treatment, survival).

Results: Among 37 patients with GEJ adenocarcinoma, 25 (67.6%) were men. The mean age at diagnosis was 55.2 years (standard deviation [SD] 13.2 years), and 9 (24.3%) were non-Hispanic white, 5 (13.5%) non-Hispanic black, and 19 (51.4%) Hispanic. Most had at least one risk factor: 8 patients (21.6%) were smokers, 6 (16.2%) were alcohol users, 8 (21.6%) had a positive test for *Helicobacter pylori*. However, only 5 patients (13.5%) had an endoscopy performed prior to GEJ adenocarcinoma diagnoses, and 2 of these patients (5.4%) had a prior diagnosis of a high-risk gastric lesion (gastric intestinal metaplasia, dysplasia) of whom only 1 patient received appropriate surveillance endoscopy. While 13 patients (35.1%) had concurrent Barrett's esophagus, only 1 patient had been diagnosed with Barrett's esophagus prior to the cancer diagnosis and did not receive appropriate surveillance endoscopy. Most patients were diagnosed at a late stage (59.5% stage 4,13.5% stage 3), and 10 patients (27.0%) received surgery and 25 (67.6%) received chemotherapy. The mean survival was 11.1 months (SD 12.4 months) among 21 patients (56.8%) who had died.

Conclusion: Most patients with GEJ cancer had known established risk factors or preneoplastic lesions. For example, both Barrett's esophagus (35%) and *H. pylori* infection (22%) were common in these patients with GEJ adenocarcinoma. However, most patients never underwent endoscopy prior to cancer diagnosis, and the few with known prior preneoplastic condition did not have appropriate surveillance. These patients with GEJ have poor outcomes.

Putative functions of the lipogenic enzyme aspartoacylase in the intestine

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The intestine requires constant replenishment of energy-carrying intermediates to support the metabolic demands of rapid intestinal cell turnover, nutrient absorption, and hormone secretion in the villus epithelium. However, the metabolites fueling energy pools for intestinal absorption and endocrine functions remain poorly characterized. Acetate, along with glucose and fatty acids, is an essential metabolic intermediate that provides carbon for acetyl-CoA to serve essential energy metabolism pathways and histone acetylation. Acetate can also be generated from N-acetylaspartate (NAA), an abundant and critical brain metabolite for myelin lipids. The only enzyme capable of cleaving NAA is aspartoacylase (ASPA), which generates acetate and aspartate. Although the role of NAA breakdown by ASPA is well-established in the brain, its function in other tissues is unknown. We found that *Aspa* is highly expressed in the mid-villus absorptive enterocytes in the small intestine. Contrary to other tissues, the enzyme responsible for generating NAA, *NAT8L*, is not expressed along the digestive tract. To nominate functions of ASPA, we generated tamoxifen-inducible whole-body *Aspa* knockouts ($Aspa^{cKO}$), obviating developmental phenotypes observed in germline knockouts. We then performed untargeted metabolomics to broadly assess metabolite changes among knockouts and controls. As such, we found reduced aspartic acid in the ileum, suggesting that *Aspa* deletion lowers the availability of NAA hydrolysis products. Oral glucose tolerance tests showed $Aspa^{cKO}$ exhibit greater glucose disposal and higher plasma levels of glucose-dependent insulinotropic polypeptide (GIP) and insulin. As *Aspa* is not expressed in any endocrine cells of the pancreas, this suggests that intestinal ASPA expression supports gut hormone responses to carbohydrates and lipids. Our preliminary analysis of ASPA expression in vivo and in vitro reveals an unknown and important role for NAA in metabolic influence of the incretin axis and cellular acetate and aspartate supply. This research addresses intestine-specific roles for ASPA and NAA that have never been previously defined. Further research will nominate novel NAA-ASPA pathways and aid in understanding how metabolic and digestive diseases alter gut epithelial homeostasis and nutrient absorption in ways that can influence physiology.

Novel SIRT1-ERRγ co-regulation promotes the differentiation of gastric parietal cells and presents therapeutic potential to reverse intestinal metaplasia in the stomach

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Background: Gastric intestinal metaplasia (GIM) is a precancerous condition that can advance to gastric adenocarcinoma, characterized by the loss of acid-secreting parietal cells (PCs). Key knowledge gaps include the transcriptional regulators of GIM, the origin of new intestinal cells, and the potential reversibility of intestinal metaplasia, as well as the development of new therapeutics. Our previous studies identified the nuclear receptor estrogen-related receptor gamma (*Esrrg*, ERRγ) as vital for PCs differentiation from progenitors. This work shows *Esrrg* knockout in PC progenitors in aged mice leads to significant spontaneous intestinal metaplasia. ERRγ, an orphan nuclear factor, is primarily influenced by cofactors. Here, we present a novel positive co-regulation of ERRγ by Sirtuin 1 (*Sirt1*, SIRT1). We hypothesize that targeting ERRγ-SIRT1 is important for: 1) normal PCs differentiation but 2) can also halt and reverse GIM phenotype.

Methods: We assessed ERRγ and SIRT1's roles using patient-derived GIM organoids and a gastric cancer cell line with inducible *ESRRG* overexpression. We developed an aged mouse model (≥ 40 weeks) with *Esrrg* conditional deletion in PCs (*Atp4b-Cre*$^{+}$ *Esrrg* $^{fl/fl}$ *mTmG*$^{+}$). To demonstrate ERRγ-SIRT1 co-regulation, we conducted co-immunoprecipitation (Co-IP) and ERRγ-driven luciferase reporter assay. Bulk RNA sequencing (RNA-seq), Western blotting (WB), quantitative PCR (qRT-PCR), were employed to evaluate GIM reversal. Alcian blue staining, immunohistochemistry (IHC), hematoxylin and eosin staining (H&E) and immunofluorescence (IF) were used to phenotype the mouse GIM model. SLU-PP-915 and resveratrol were used to target ERRγ and SIRT1, respectively. To dissect the role of SIRT1 for PC differentiation, we employed *in vivo* and *in vitro* models, including PCs ablation and stomach injury models (a high-dose tamoxifen, *Atp4b-Cre*$^{+}$*, iDTR*$^{+}$ mice), gastric organoid culture, and lineage-traceable *Sirt1* conditional knockout mice (*Fgf20-Cre*$^{+}$*, Sirt1* $^{fl/+}$*, mTmG*$^{+}$*; Esrrg-CreERT2*$^{+}$*, Sirt1*$^{fl/fl}$*, mTmG*$^{+}$*; Apt4b-Cre*$^{+}$*, Sirt1*$^{fl/+}$*; Apt4b-iDTR*$^{+}$*, mTmG*$^{+}$*).*

Results: *Esrrg* knockout in PC progenitors induced GIM with aging characterized by an enhanced intestinal signature. Lineage tracing indicated *Atp4b+ ERRγ-* clones originating new intestinal cells. Interaction between ERRγ and SIRT1 enhanced ERRγ transactivation both *in vitro* and *in vivo*, with co-localization in PCs at homeostasis. Pharmacological activation of ERRγ or SIRT1 decreased intestinal markers and restored some gastric gene expression *in vitro*. Resveratrol treatment elevated PC numbers in organoids, increased *in vivo* PC numbers, and upregulated ERRγ target genes via facilitated SIRT1 nuclear localization, promoting interaction with ERRγ. Conditional *Sirt1* knockout demonstrated reduced PC numbers and delayed recovery in PC ablation models.

Conclusion: ERRγ is essential for maintaining gastric cell identity and, together with its co-regulator SIRT1, shows potential in reversing the GIM phenotype, thus presenting a novel therapeutic avenue. Our findings indicate FDA-approved agents like resveratrol could facilitate therapeutic strategies to prevent gastric cancer through promoting PC differentiation, warranting further exploration of the clinical potential of the SIRT1-ERRγ interaction. Furthermore, the ERRγ-SIRT1 co-activation could have broader implications beyond stomach pathophysiology for studying diseases where both targets are co-expressed.

Enteral agonism of farnesoid X receptor-fibroblast growth factor 19 prevents cholestasis in TPN-fed neonatal pigs

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Background: Administration of total parenteral nutrition (TPN) ensures the delivery of nutrients to infants who cannot tolerate enteral feeding. However, long-term use of TPN can result in cholestasis. Currently, the enteral administration of the secondary bile acid, ursodeoxycholic acid (UDCA), is used clinically to treat cholestasis by promoting enterohepatic bile flow but this has had mixed results. We hypothesize that modulation of the nuclear receptor farnesoid X receptor (FXR) signaling is important to restore normal bile flow. FXR is part of a negative feedback loop through the production of the gut hormone fibroblast growth factor 19 (FGF19) to regulate bile acid synthesis. Tropifexor (TPX) is a new, non-bile acid therapeutic agent with potent FXR agonist activity that we hypothesize can be used to mitigate cholestasis.

Methods: TPN was administered to piglets for three weeks. During this time, piglets were treated enterally with either UDCA (25 mg/kg*day) or TPX (7.5 µg/kg*day) in minimal milk-based formula (12 mL/kg*day), or with daily intravenous FGF19 (0.25 mg/d) injection. Control and FGF19 pigs also received minimal milk-based formula (12 mL/kg*day).

Results: Serum markers for cholestasis direct bilirubin, gamma glutamyl transferase, and plasma bile acids were lower for TPX pigs compared to the control. Quantitation of colonic bile acids demonstrated TPX promoted increased bile flow into the intestines. TPX also significantly increased the liver bile acid efflux transporters organic solute transporter alpha (OSTα) and bile salt export pump (BSEP). Furthermore, pigs that received TPX tended to have an increased relative concentration of chenodeoxycholic acid, making the bile acid profile more FXR agonistic compared to other treatments. Delving further into tissue-specific responses, ileal explants from newborn pigs and three-week-old pigs were treated with UDCA, TPX, and obeticholic acid. An increased amount of FGF19 was released into the media from explants treated with TPX. This indicated activation of the FXR-FGF19 axis in the ileum. We also tested liver-specific responses using hepatocyte spheroids and showed that TPX treatment decreased cholesterol 7α-hydroxylase, but induced a robust increase in the expression of OSTα.

Conclusion: Overall, FGF19 and UDCA treatments had minimal effects, while TPX activated the FXR-FGF19 axis and prevented cholestasis in TPN-fed piglets via increased hepatobiliary transport of bile acids.

Limosilactobacillus reuteri-educated T cells ameliorate liver inflammation in immunocompromised mice

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Background: *Limosilactobacillus reuteri* DSM 17938 significantly reduces multi-organ injury, as exemplified by reduced liver inflammation in Foxp3$^+$Treg deficient mice with the autoimmune scurfy (SF) phenotype, a model of human IPEX syndrome. DSM 17938-educated regulatory T cells (Tregs) have more effective anti-inflammatory properties than naïve Tregs in stressed newborn mice. Currently, it is unclear how DSM 17938-modulated T cells interact with other immune cells. RAG1KO mice have no T or B cells, providing a tool to investigate their interactions with liver macrophages and their metabolism. In this study, CD4$^+$T cells from SF mice were isolated and adoptively transferred (AT) into RAG1KO mice to analyze the effects on this T-cell mediated hepatitis.

Objective: To evaluate if orogastric administration of DSM 1938 to SF mice would modulate pro-inflammatory T-cell activity in RAG1KO mice.

Methods: SF mice were fed DSM 17938 (10^7 CFU/day in 100 µL) or fresh MRS media by gavage, daily from d8 to d20. At d21, CD4$^+$T cells (1×10^6 cells/mouse) isolated from the spleen were AT to RAG1KO mice via intraperitoneal injection. After 4 weeks, liver samples from RAG1KO mice were evaluated histologically for hepatitis using the Batts-Ludwing grading system, with severity ranging from Grade 0 (normal) to Grade 4. Liver macrophages were analyzed by IHC staining and transcriptomic analysis were performed by using bulk RNAseq.

Results: T cells from SF mice fed with control media were AT into RAG1KO mice (RAG1KOATSFC, n=10). We identified an increased incidence and severity of liver inflammation in these mice, compared to RAG1KO mice without AT (RAG1KOnoAT, n=4) (p=0.011). Liver Inflammation was ameliorated in RAG1KO mice receiving T cells from SF mice fed with DSM 17938 (RAG1KOATSFL, n=10) (p=0.025). In RAG1KOATSFC, 5 mice exhibited Grade 1 and 5 mice exhibited Grade 2 histological severity. However, in RAG1KOATSFL, only 2 mice had Grade 2 inflammation, while 4 had Grade 1 and 4 were normal. The numbers of F4/80$^+$ macrophages/hpf were significantly increased in the liver of RAG1KOATSFC mice compared to either RAG1KOATSFL (p=0.03) or RAG1KO (p=0.002). RNAseq indicated significant alterations with 1238 down-regulated genes and 731 up-regulated genes after only AT of SF T cells compared to RAG1KOnoAT. Many genes participate in protein translation and elongation in liver mitochondria. Nine genes associated with defense response to other pathogens and mitochondrial electron transport were significantly affected by probiotic-educated T cells.

Conclusions: DSM 17938 demonstrated inflammatory T cell modulating capacity. Probiotic-trained CD4$^+$T cells had anti-inflammatory properties in the liver and their interactions with other immune cells (e.g. macrophages) and mitochondrial-associated genes warrant further exploration for potential benefit in autoimmune hepatitis.

Poglut1 reduction in hepatocytes by using GalNAc conjugated ASO does not rescue the liver phenotypes of Alagille Syndrome, in contrast to unconjugated ASO

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Haploinsufficiency of *JAG1* causes Alagille syndrome (ALGS), a multisystem disorder characterized by bile duct paucity that often necessitates liver transplantation. The current therapeutic approaches for ALGS liver disease do not address the root cause of the disease, which is paucity of the bile ducts. Our previous work demonstrated that *Jag1* heterozygous (*Jag1+/–*) mice on a C57BL/6 background recapitulate ALGS liver phenotypes. Moreover, we have reported that reducing the expression of the glycosyltransferase gene *Poglut1*, either genetically or by subcutaneous injection of an unconjugated anti-*Poglut1* antisense oligonucleotide (ASO), significantly improves the bile duct paucity and the associated liver damage in *Jag1+/–* animals. However, the cell type(s) that respond to ASO-mediated *Poglut1* knockdown in this model are not known, which is an important question for advancing this strategy toward clinical trials. To address this issue and develop a more specific therapeutic approach, we evaluated a GalNAc conjugated anti-*Poglut1* ASO (GalNAc-ASO) to deliver the ASO to hepatocytes. We administered the GalNAc-ASO or PBS subcutaneously to *Jag1+/–* and control animals at postnatal day 1 (P1), P7, P14, and P21, and analyzed their liver structure and function at P30. Despite significant *Poglut1* knockdown (~50%) in GalNAc-ASO-treated animals compared to controls, no rescue of liver phenotypes was observed. ASO staining confirmed localization in hepatocytes, although ASO uptake was also observed in some non-hepatocyte liver cells. These findings suggest that hepatocyte-enriched *Poglut1* knockdown is not sufficient to rescue ALGS liver phenotypes. Given the critical role of vascular smooth muscle cells (VSMCs) in bile duct development and our previous report on the role of POGLUT1 in regulation of JAG1 protein levels, future efforts will focus on approaches targeting *Poglut1* in VSMCs.

Family-based screening for *Helicobacter pylori* infection and comparison of antibiotic susceptibility in high-risk Hispanic families in the U.S.

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Background: The prevalence of *Helicobacter pylori* infection is higher in certain racial/ethnic groups in the U.S. (e.g., Hispanics). Intrafamilial spread is likely the main mode of transmission. We compared *H. pylori* infection status and antibiotic susceptibility profiles among family members in a predominantly immigrant Hispanic U.S. population.

Methods: In this prospective cross-sectional study, asymptomatic patients aged 30-65 from primary care clinics in Harris Health (Houston, Texas) from April 2021-October 2024 were screened for *H. pylori* infection using IgG serology. Index patients positive for *H. pylori* and their eligible household members were offered *H. pylori* stool testing with polymerase chain reaction (PCR) and next generation sequencing (NGS) for antibiotic susceptibility. We analyzed concordance in *H. pylori* positivity and antibiotic susceptibility within families. Subgroup analysis was performed for vertical relationships (parent-offspring pairs) and horizontal relationships (spouse, roommate, or sibling pairs).

Results: A total of 77 individuals (91% Hispanic) were recruited across 36 families. Of 36 index patients with *H. pylori* infection, 41 family members submitted stool for testing, and 53.6% (22/41) were *H. pylori* positive. We collected antibiotic susceptibility data for ≥2 family members in 31 families; 5 families lacked NGS data for the index patient. In 55 individuals from these 31 families, 21.8% (12/55) were resistant to clarithromycin, 21.8% (12/55) to fluoroquinolone, 14.5% (8/55) to metronidazole, 3.6% (2/55) to amoxicillin, and 1.8% (1/55) to rifabutin; there was no tetracycline resistance. *H. pylori* infection status was concordant in 55.5% of families, meaning all family members were infected. Concordance in antibiotic susceptibility within 16 families with ≥2 infected family members was 62.5% (10/16) for clarithromycin and fluoroquinolone; 68.8% (11/16) for metronidazole; 87.5% (14/16) for amoxicillin; 100% (16/16) for tetracycline; and 93.8% (15/16) for rifabutin. *H. pylori* infection status was concordant in 50.0% (5/10) of vertical relationships and 54.8% (17/31) of horizontal relationships. Antibiotic susceptibility concordance was mostly higher or equal for vertical than horizontal relationships (clarithromycin 100% vs. 53.8%, fluoroquinolone 66.7% vs. 61.5%, amoxicillin 100% vs. 84.6%, tetracycline 100% vs. 100%) except for metronidazole (66.7% vs. 69.2%) and rifabutin (66.7% vs. 100%).

Conclusion: Family-based screening of *H. pylori* positive index patients showed 53.6% infection rate among family members. All family members were infected in 55.5% of families. Concordance in antibiotic susceptibility within families was high for all antibiotics, but higher in vertical relationships than horizontal relationships. This study lends further support for family-based testing in U.S. populations.

New *ex vivo* approaches to quantify colon migrating motor complexes in mice: route of drug delivery matters

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Background: Gastrointestinal (GI) motility disorders including gastroparesis, functional dyspepsia, and subsets of irritable bowel syndrome are highly prevalent and impact quality of life for millions of children. Therapeutic options are limited, in part because our basic understanding of the mechanisms that regulate GI motility is incomplete. In standard ex vivo tissue bath assays, whole segments of mouse intestine are suspended in organ baths via sutures that tie off and exclude the mucosal surface from the surrounding buffer. These assays can capture responses to drugs applied to the serosal surface, but not the mucosal surface. We sought to test the hypothesis that mucosal versus serosal drug delivery will have different effects on colon migrating motor complexes (CMMCs) using an adapted tissue bath technique featuring cannulated segments of large bowel.

Methods: Colon segments from young adult C57BL/6 mice were gently flushed with Krebs buffer to remove fecal pellets then cannulated to cecal (inflow) and anal (outflow) ends and suspended in a custom-built heated, oxygenated organ bath. CMMCs were recorded via overhead video in 15-minute intervals. The cholinergic prokinetic drug carbachol (10 µmol/L) or vehicle control was administered intraluminally through the inflow tube or extraluminally into the surrounding bath. The frequency of CMMCs was recorded per unit time.

Results: Carbachol increased the mean number of CMMCs throughout the 15-minute interval approximately 2-fold ($p < 0.05$), irrespective of delivery route (Figure 1). However, within the first 2 minutes of drug exposure, carbachol-induced CMMCs were dramatically reduced when drug was delivered extraluminally versus intraluminally (Figure 2, 0.5 vs 1.7, $p < 0.05$).

Conclusions: Cannulated ex vivo preparations of mouse colon can be used to quantify CMMC responses to pharmacotherapy. Delivering a cholinergic agent to the mucosal versus the serosal surface differentially affects CMMC responses in the first 2 minutes of exposure. These findings establish an ex vivo model for future studies of neurogastrointestinal physiology and underscores the necessity of considering enteral versus systemic drug administration in developing therapies for GI motility disorders.

Figure 1

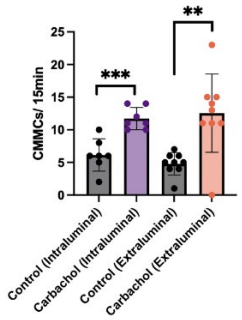
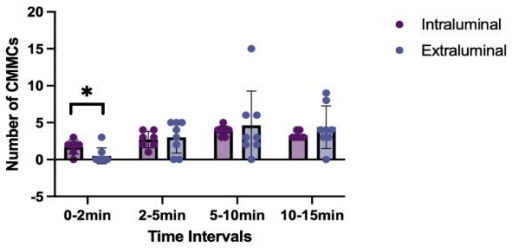


Figure 2



Microbiome profiles of children with Autism Spectrum Disorder (ASD) with and without GI symptoms

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Background: Autism spectrum disorder (ASD) affects 1 in 36 children. Gastrointestinal (GI) symptoms including selective eating, constipation, diarrhea, and bloating are present in 23-70% of children with ASD. Our group previously demonstrated that children on the autism spectrum with severe ASD, especially nonverbal males, have worse GI symptoms. We did not find evidence of significantly increased gastrointestinal inflammation, neuroinflammation, or intestinal permeability in children with ASD. Studies have suggested a possible role of intestinal dysbiosis in GI symptoms in children with ASD. We have now assessed the role of dysbiosis in children with ASD compared to their siblings and typically developing (TD) children.

Objective: To explore the relationship between microbiome and GI symptoms in children with ASD.

Methods: Patients who met DSM-5 criteria for ASD were recruited and underwent testing to determine the severity of GI symptoms using the GI severity index (GSI), with a level ≥7 (out of 17) considered positive for GI symptoms. Children with ASD without GI symptoms, siblings of children with ASD, and typically developing children were recruited from another site in the same city. Microbiome analysis was performed using 16S rRNA sequencing to determine the differences in microbial diversity and community composition in ASD patients with and without GI symptoms compared to siblings of children with ASD and typically developing children.

Results: Children with ASD and GI symptoms (n = 45) had the lowest fecal alpha diversity, followed by those with ASD without GI symptoms (n = 43, p = NS), followed by siblings of children with ASD (n = 20, p = 0.01) and typically developing children (TD) (n = 27, p = 0.06). Beta diversity showed distinct clustering of samples of children with ASD compared to a more random distribution of siblings and TD groups. Children with ASD had a higher abundance of *Fusicatenibacter*, *Blautia*, and *Sarcina* compared to the TD group ($p < 0.01$). Children with ASD and GI symptoms had a higher abundance of *Bacteroides* and *Ruminococcus* compared to children with ASD without GI symptoms ($p < 0.05$).

Conclusions: Children on the autism spectrum with GI symptoms have a distinct microbiome profile compared to those without GI symptoms. Children with ASD have a lower fecal alpha diversity compared to their siblings and typically developing children. Dysbiosis can contribute to GI symptoms in children with ASD, and probiotics may help manage GI symptoms.

Bridging the brain-gut axis: the role of psychiatric interventions in managing co-existing digestive and psychiatric illnesses

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Background: Psychiatric and digestive diseases are closely related through the brain-gut axis, a bidirectional communication system linking the central nervous system and the gastrointestinal tract. This relationship plays a critical role in the overlap of psychiatric and digestive disorders, as symptoms in one system can influence the other. Psychiatric comorbidities such as anxiety and depression are often observed in patients with digestive illness, and vice versa. Recognizing this connection has led to a growing interest in the integration of psychiatric and GI care to better address the needs of patients. However, the specific mechanisms underlying this relationship are not well understood.

Case description: This study includes three pediatric cases evaluated by the consult-liaison psychiatry team at Texas Children's Hospital. Each patient presented with complex medical histories involving both digestive and psychiatric illnesses, including but not limited to cyclic vomiting syndrome, anxiety, depression, and malnutrition. Management involved an interdisciplinary approach, utilizing both psychiatric and GI-specific interventions.

Discussion: A review of six key studies supports the evidence base for psychogastroenterology. These studies demonstrate the bidirectional influence of psychiatric and GI conditions, particularly in functional GI disorders and inflammatory bowel disease (IBD). Integrated psychiatric and medical care has been shown to significantly improve GI symptoms, psychiatric comorbidities, and quality of life. Furthermore, the role of the microbiota-gut-brain connectome and mechanisms like vagal nerve signaling and serotonin pathways are pivotal in understanding this relationship.

Conclusions: This study highlights the importance of addressing both psychiatric and digestive conditions concurrently in patients with co-existing illnesses. Although the relationship between psychiatric illness and IBD is well-established and improvement in GI symptoms was observed following integrated treatment, the causal role of psychiatric interventions remains an area for further research. The bidirectional nature of the brain-gut axis underscores the value of early psychiatric evaluation in GI conditions, and more studies are needed to elucidate the mechanisms and refine treatment strategies. Providers should be encouraged to adopt a multimodal, integrated approach to care, considering psychiatric comorbidities as a routine component of GI disease management.

The Role of Kynurenine-AHR Signaling in Mitochondrial Homeostasis and Liver Pathology

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Mitochondria are essential metabolic hubs that regulate hepatocyte homeostasis, and their dysfunction is closely associated with liver disease. Aryl hydrocarbon receptor (AHR) plays a crucial role in supporting normal liver functions. Kynurenine (Kyn), a tryptophan-derived metabolite and endogenous AHR ligand, exhibits diverse roles across various metabolic disorders and cancers. However, its impact on mitochondrial function in specific liver disease contexts remains poorly understood. In the current study, we identified a novel role of AHR in liver physiology and pathology through its regulation of mitochondrial function. Transcriptomic analysis indicated that mitochondria-related gene sets were dysregulated in the AHR KO livers. AHR inhibition in primary mouse hepatocytes and AML12 hepatocyte cell lines significantly suppressed mitochondrial respiration rate and substrate utilization. In addition, the fasting response of several key autophagy genes and the mitophagy process were impaired in AHR KO mice, a defect that was reversed by Kyn treatment in AML12 cells, suggesting that AHR signaling is crucial for mitophagy regulation. We also identified BCL2 interacting protein 3 (BNIP3), a mitophagy receptor that senses nutrient stress, as an AHR target gene through chromatin immunoprecipitation assay. Mechanistically, overexpression of *Bnip3* in AHR knockdown cells mitigated the production of mitochondrial reactive oxygen species (ROS) and restored functional mitophagy. Furthermore, we observed that Kyn-AHR signaling is significantly suppressed in cholestatic liver injury models, accompanied by mitochondrial dysfunction. In conclusion, AHR regulates the mitophagy receptor BNIP3 to coordinate hepatic mitochondrial function, which is suppressed by cholestatic liver injury. These findings underscore the potential importance of Kyn-AHR signaling in cholestasis, offering a new molecular basis for bile acid-induced liver injury and suggesting new strategies or therapeutic targets for cholestasis treatment.

Quantitative Analysis of the Enteric Nervous System in Pediatric Human Small Intestine and Tissue-Engineered Human Small Intestine.

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Background: Objectively quantifying the enteric nervous system (ENS) in human intestine is challenging. Specifically, the traditional 2D sectioning method is not a reliable approach to analyze ENS cell types. Two recent publications by the Heuckeroth lab demonstrated that adult and pediatric human colonic neurons and glia can be reliably quantified using a novel 3D imaging method. This method has not yet been applied to human small intestine. Tissue-engineered human small intestine derived from human intestinal organoids (HIOs) is a promising treatment for intestinal failure. Incorporation of the ENS into HIOs improves anatomy and function. The presence of neurons and glia in HIO+ENS has been detected in traditional 2D sections; however, quantification has not been reported.

Methods: Pediatric human small intestine samples were obtained from our IRB approved biobank. HIOs and enteric neural crest cells (ENCCs) were generated from human embryonic stem cells and co-cultured in vitro for 28-40 days. HIO+ENCCs were transplanted (tHIO+ENCCs) into adult immunodeficient mice and harvested after 2, 4, 6 weeks *in vivo*. Tissues were pinned flat, fixed and neurons and glia were immunostained using HuCD and S100β antibodies respectively. Tissues were cleared, mounted and imaged with confocal microscopy at 20x and 1µm Z increment. Neurons and glia were counted using Image J. The volume of the ganglionated area and ganglia within the myenteric plexus were determined using Imaris software. Cell counts were used to calculate the neurons, glia, and neuron/glia ratio per ganglionated area, and the neurons, glia, and neuron/glia ratio per ganglion.

Results: Ganglia within pediatric jejunum contained 2,809,098±483,172 neurons/mm^3 and 8,271,046±1,173,641 glia/mm^3, with a neuron/glia ratio of 0.31±0.03. In pediatric ileum, ganglia contained 4,174,534±86,967 neurons/mm^3 and 9,453,455±759,670 glia/mm^3, with a neuron/glia ratio of 0.45±0.04. The number of neurons per ganglion was higher in ileum than jejunum (p=0.04) whereas glia per ganglion were similar and the neuron/glia ratio was not statistically different. Ganglion-like structures were present in tHIO+ENS at all timepoints, with often higher but more variable neuron counts. Quantification of the ENS in tHIO+ENS demonstrated 6,555,208±848,738 neurons/mm^3, 4,913,815±1,222,144 glia/mm^3, and neuron/glia ratio of 1.36±0.66 at 2 weeks; 11,187,728±2,904,559 neurons/mm^3, 14,531,236±4,364,898 glia/mm^3, and neuron/glia ratio of 0.97±0.1 at 4 weeks; and 5,522,524±1,205,196 neurons/mm^3, 10,675, 945 glia/mm^3, and neuron/glia ratio of 1.0±0.03 at 6 weeks.

Conclusion: This study demonstrates successful application of a novel 3D imaging method for reliable quantification of the ENS in pediatric human small intestine and tissue-engineered human small intestine. Future studies will utilize this technique to further evaluate neurochemistry, including neuronal subtypes such as excitatory and inhibitory neurons, and to optimize ENS development in tissue-engineered small intestine for human therapy.

A YAP1-DDIT4-NME1 axis in paligenosis

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Paligenosis is an evolutionarily conserved process that cells undergo in response to injury or stress, which can result in diseases like cancer when dysregulated. We have established an *in vivo* model using high-dose tamoxifen (HDT) intraperitoneal injections to induce this process in mouse gastric chief cells. Interrogation of this model led us to uncover distinct paligenosis stages: In stage 1, the chief cells undergo autodegradation downscaling with decreased mTORC1 activity; in stage 2, reprogramming of cells into a more progenitor-like state occurs with expression of embryonic and metaplastic genes; in stage 3, reentry into the cell cycle occurs in which mTORC1 activity returns. We have identified several key proteins that play critical roles in regulating this process, including DDIT4 which increases in stage 1 and functions as the initial suppressor of mTORC1. As paligenosis progresses and DDIT4 decreases, p53 maintains mTORC1 suppression throughout stage 2 until IFRD1 licenses cell cycle reentry via p53 suppression in the transition to stage 3. However, the underlying mechanism behind the reduction of DDIT4 in the later stages of paligenosis remains unclear. Our preliminary data indicate that the Hippo pathway effector YAP1 is activated during stage 1 and facilitates the transition from stage 1 to stage 2. Previous research has identified YAP1 as a transcriptional repressor of DDIT4, thus we hypothesize that YAP1 activation may also function to suppress DDIT4 in the context of paligenosis. Using a Cre-recombinase-inducible, constitutively active YAP1 mutant (LSL-*Yap*^{S112A}) driven by a chief cell-specific Cre, we observed the loss of DDIT4 in chief cells by immunohistochemistry (IHC). Moreover, we found that DDIT4 levels can instead be rescued when YAP1 and its paralog TAZ are floxed out using the same Cre driver in a paligenosis-induced setting. Enrichment analysis, single-cell and bulk RNA sequencing experiments identified a list of E2F target genes as downstream targets of YAP1 activation in chief cells during paligenosis. We conducted phosphoproteomic analyses using HDT-treated C57BL/6J mice and *Ddit4*$^{-/-}$ mice and mapped the E2F target gene list identified by transcriptomics onto our proteomic dataset. Importantly, we identified *Nme1*, a well-known tumor suppressor gene that activates and stabilizes p53, to be downregulated during stage 1 of paligenosis but returned to basal levels by stage 3 in C57BL/6J mice, whereas such recovery was not observed in *Ddit4*$^{-/-}$ mice. Finally, we validated our multi-omic observations through western blotting and IHC. Our findings uncover a potentially novel YAP1-DDIT4-NME1 axis that suppresses p53 activity in paligenosis stage 2, which helps release p53 suppression of mTORC1 activity, together with the already described IFRD1-p53 regulation of the stage 2 to 3 transition. Elucidation of these and other molecular mechanisms that govern paligenosis will ultimately facilitate the development of novel therapies that can target tumorigenesis.

The commensal bacterium *Limosilactobacillus reuter* generates novel microbial-conjugated bile acids

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Background: Bile acids are potent digestive surfactants that promote the absorption of lipids in the intestine. Bile acids are known to be conjugated with Gly or taurine in the liver and then further modified (deconjugated, dehydroxylated, dehydrogenated and epimerized) by bacteria in the intestine. Recently, there have been a handful of reports describing the ability of the gut microbiota as a community to perform novel conjugation reactions of metabolites, such as amino acids (Phe, Tyr, Leu, Gln, Glu, Asp, Asn, Met, His, Lys, Ser, Try, Val, Ala, and Arg) or neurotransmitters (GABA and tyramine) to bile acids in the gut. These novel microbial-conjugated bile acids (MCBAs) are considered a new class of bacterial-derived metabolites and have greatly expanded our view on how bacteria can communicate with the host. Existing studies have used non-targeted approaches to identify these MCBAs, and to date, *no targeted bioanalytical platform exists*. Our aim was to create a targeted approach to examine for the production of MCBAs by the commensal bacterium *Limosilactobacillus reuteri* using a SCIEX QTRAP 7500 MS system.

Methods & Results: First, we examined the ability of *L. reuteri*; ATCC 6475 to grow with cholic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), or ursodeoxycholic acid (UDCA) in the lactic acid bacteria defined medium (LDM4) under anaerobic culture conditions at 37°C in a Cerillo Plate reader. *L. reuteri* tolerated LDM4 supplemented with up to 1.25 mM of CA and UDCA, and 0.625 mM of CDCA and DCA. To assess the ability of *L. reuteri* to synthesize MCBAs, we grew our primary *L. reuteri* cultures in Man, Rogosa, and Sharpe (MRS) medium under anaerobic conditions overnight at 37°C. We then subcultured *L. reuteri* at an OD_{600nm} of 0.1 in LDM4 (5 mL final volumes) supplemented with additional bacterial metabolites and the targeted bile acid or the vehicle control ethanol. The following day, the cultures were centrifuged and the cell-free supernatant was examined by LC-MS/MS. MCBA standard mixtures produced by BileOmix were used to optimize the selected-reaction monitoring (SRM) parameters for each of ~150 MCBA compounds included in the six mixtures and were used as retention time and analytical response standards for this analysis. Using the CDCA-based LDM4 cultures as an example dataset, *L. reuteri* produced high levels (>2x the standard signal) of Gln-CDCA (5.5x), His-CDCA (11.3x), Lys-CDCA (6.0x), Thr-CDCA (7.2x), and Asp-CDCA (3.8x); intermediate levels (1.99x < b > 0.40x the standard signal) of Asn-CDCA (0.68x), Isoleu-CDCA and Leu-CDCA (0.70x; co-eluting peaks), and Tyr-CDCA (1.0x); low levels (0.399x < b > 0.001x the standard signal) of Gly-CDCA (0.06x), Ala-CDCA (0.05x), Tauro-CDCA (0.03x), Met-CDCA (0.33x), Phe-CDCA (0.32x), Ser-CDCA (0.09x), and Val-CDCA (0.25x). *L. reuteri* ATCC 6475 was unable to produce Arg-CDCA, Glu-CDCA, Pro-CDCA, Trp-CDCA, GABA-CDCA, or Tryptamine-CDCA. Low levels of Gly-CDCA and Tauro-CDCA were the only CDCA-based MCBAs detected in the neat LDM4 (+/- CDCA) medium controls examined as part of this study. Similar screening assessments have been performed on *L. reuteri* based LDM4 cultures that that were supplemented with 0.5 mM CA, DCA, and UDCA.

Conclusions: These data indicate that *L. reuteri* alone can extensively modify primary and secondary bile acids and generate multiple novel compounds. These modifications could alter the biochemical properties of bile acids, potentially influencing their signaling capacity through receptors such as TGR5 and FXR. This study lays the groundwork for future exploration of MCBAs as potential modulators of health and disease.

Epigenetic alteration for cellular identity switching during metaplasia and tissue injury

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Cellular plasticity normally decreases as development progresses, especially when cells reach their fully differentiated status. However, certain conditions can promote cells to regain their plasticity such as induced reprogramming, tissue injury, or carcinogenesis. Regardless of the conditions, cellular plasticity involves alteration of cellular identity, which is known to be regulated largely by epigenetics. To identify the specific epigenetic alterations where cellular identity switching or metaplasia occurs, our investigation targets an evolutionarily conserved injury-induced process for tissue regeneration that is known as paligenosis. This process has 3 discrete stages, and their sequence aligns with early stages of gastric adenocarcinoma carcinogenesis, such as loss of parietal cells and emergence of metaplastic cells. These metaplastic cells or mucinous Spasmolytic Polypeptide Expressing Metaplasia (SPEM) cells originate from the initially fully differentiated chief cells located at the base of the stomach glands and could be the possible source of carcinogenic cells. However, little is known about the epigenetic regulation during the transition from chief to SPEM cell. Here, using transmission electron microscopy, single-cell transcriptomics, and proteomics, we directly and indirectly showed that the chromatin of chief cells loosens during paligenosis. Complementing sc-RNA-seq with proteomic analysis by mass spectrometry, we further identified DNA methyltransferase (DNMT1) as a key epigenetic factor upregulated during paligenosis where its main roles in proliferation align with what is known in the field. Although DNMT1 is not associated with identity switching during metaplasia or paligenosis, we found that inhibition of DNMT1 after SPEM cells proliferate suppresses the return of chief cell identity after regeneration. This indicates a possible role for DNMT1 in regulating cellular identity reversion after regeneration that could potentially link with DNMT1's function of closing up accessible chromatin by methylating DNA and by the crosstalk with histone-modifying enzymes. Taken together, paligenosis and metaplasia are associated with loosening of the chromatin, and reversion of these processes involves the closing of chromatin where DNMT1 is required for both processes.

Efficacy and safety of transoral incisionless fundoplication in nonobese and obese adults: A population-based cohort study from the United States

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Introduction: The ideal approach for patients with class I obesity (BMI 30-34.9 kg/m2) and refractory GERD remains elusive. Literature on outcomes of surgical fundoplication in patients with class I obesity has been inconsistent. We aimed to assess the efficacy and safety of transoral incisionless fundoplication (TIF) in adults with class I obesity. **Methods:** We conducted a retrospective cohort study using TriNetX US Research Network database, a multi-institutional database that integrates data from 69 healthcare organizations from inception until 12/2024. Patients aged ≥18 years with GERD who underwent TIF were identified using validated ICD-10 and CPT codes. Cohorts were stratified into 2 groups based on BMI at the time of TIF (nonobese and class I obesity). Exclusion criteria included patients with a BMI >35 kg/m², major disorder of esophageal motility or concomitant TIF, and hiatal hernia repair (cTIF). To minimize confounding, one-to-one propensity score matching was performed. Cohorts were balanced for age, sex, race, ethnicity, diaphragmatic hernia, and proton pump inhibitor (PPI) use. The primary endpoints were postoperative PPI prescription (defined as any PPI prescription in 12 months post-TIF excluding the first 3 months to account for routine post-procedure PPI use), post-TIF esophagitis, and the need for any subsequent foregut surgery (fundoplication or bariatric surgery). Secondary outcomes included post-TIF side effects (dysphagia and gas-bloat) up to 1 year and 30-day complications. Risks were expressed as adjusted odds ratios (aOR) or risk difference (RD) with 95% confidence intervals (CIs). **Results :** Ninety-six patients with a BMI <30 kg/m² and 226 patients with a BMI of 30–35 kg/m² underwent TIF. After propensity score matching, cohorts were well-balanced in sociodemographic and baseline clinical characteristics (Table 1). The mean follow-up time was 33 months (±25.89) and 32.51 months (±26.01) in nonobese and class I obesity groups, respectively. PPI prescription rates post-TIF were similar between the two groups (aOR: 0.955, 95% CI: 0.526-1.732). Similarly, post-operative esophagitis (aOR: 0.698, 95% CI: 0.302-1.612) and the need for subsequent surgical fundoplication (aOR: 1; 95% CI: 0. 0.396-2.528) were comparable between the two groups. However, the need for subsequent gastric bypass surgery was significantly higher in patients with a BMI of 30–35 kg/m² (RD: 11.364, 95% CI: 4.733-17.995). Side effects of dysphagia and gas bloating were comparable between both cohorts (Table 2). The risk of aspiration pneumonia and perforation was lower in patients with BMI of 30-35 kg/m² (RD: -0.110, (-0.174-0.046). **Conclusions:** This study provides real-world evidence that TIF is safe and effective for GERD in class I obesity. Higher rates of bypass surgery in patients with class I obesity undergoing TIF warrant further investigation.

	Before Matching			After Matching		
Cohort	**BMI <30**	**BMI 30–35**	**P-Value**	**BMI <30**	**BMI 30–35**	**P-Value**
Number of Patients	226	96	--	91	91	
Age at TIF (Mean ± SD)	55.1 ± 15.8	54.2 ± 13.1	0.602	52.7 +/- 15.3	54.2 +/- 13.1	0.473
Sex (%)						
Female	104 (46.0%)	53 (55.2%)	0.131	43 (47.3%)	48 (52.7%)	0.459
Male	103 (45.6%)	36 (37.5%)	0.181	40 (44.0%)	36 (39.6%)	0.548
Non-binary	19 (8.4%)	7 (7.3%)	-	8 (8.8%)	7 (8.7%)	
Race (%) *						
Black or African American	10 (4.4%)	10 (10.4%)	0.042	10 (11.0%)	10 (11.0%)	1
White	153 (67.7%)	68 (70.8%)	0.579	68 (74.7%)	65 (71.4%)	0.616
Asian	17 (7.5%)	10 (10.4%)	0.391	10 (11.0%)	10 (11.0%)	0.001
Native Hawaiian or Other Pacific Islander	10 (4.4%)	10 (10.4%)	0.042	0 (11.0%)	10 (11.0%)	0.001
American Indian or Alaska Native	0 (0%)	0 (0%)	--	0 (0%)	0 (0%)	--
Other Race	13 (5.8%)	10 (10.4%)	0.137	10 (11.0%)	10 (11.0%)	0.001
Unknown Race	33 (14.6%)	13 (13.5%)	0.804	13 (14.3%)	13 (14.3%)	1
Ethnicity (%) *						
Not Hispanic or Latino	180 (79.6%)	74 (77.1%)	0.606	73 (80.2%)	70 (76.9%)	0.588
Hispanic or Latino	15 (6.6%)	10 (10.4%)	0.246	10 (11.0%)	10 (11.0%)	1
Unknown Ethnicity	31 (13.7%)	15 (15.6%)	0.654	13 (14.3%)	15 (16.5%)	0.681
History of Esophagitis (%)	43 (18.6%)	19 (18.6%)	0.998	18 (19.8%)	16 (17.6%)	0.704
Diaphragmatic Hernia (%)	99 (42.9%)	49 (48.0%)	0.380	47 (51.6%)	46 (50.5%)	0.882
Number of PPI prescription pre-TIF**	182	94	-	91	91	-

* Some patients declared ≥ 1 race or ethnicity category
** Defined as any PPI prescription t-minus 6 months preceding TIF procedure

Table 1: Baseline characteristics of the included cohorts before and after matching

Outcome Variable	Adjusted Odds Ratio (aOR) / Risk Difference (RD)	95% Confidence Interval (CI)
***Efficacy outcomes**		
- PPI prescription post TIF*	aOR: 0.955	(0.526-1.732)
- Post-operative esophagitis (any)	aOR: 0.698	(0.302-1.612)
- Need for subsequent surgical fundoplication (any)	aOR: 1	(0.396-2.528)
- Need for subsequent bariatric surgery (any)	RD: 11.364	(4.733-17.995)
***Side effects**		
-Dysphagia (6 months)	aOR: 1	(0.467-2.140)
- Dysphagia (1 year)	aOR: 1.164	(0.542-2.500)
- Bloating (6 months)	aOR: 0.898	(0.362-2.228)
Bloating (1 year)	aOR: 0.579	(0.247-1.354)
***30-day complications**		
- Aspiration Pneumonia	RD: -0.110	(-0.174-0.046)
- Perforation	RD: -0.110	(-0.174-0.046)
- ER Visit	aOR: 1	(0.395-2.532)
- GI bleeding	aOR: 1	(0.395-2.532)
- hospitalization	aOR: 1.220	(0.657-2.267)
- Infection	aOR: 1	(0.396-2.528)

* Defined as any PPI prescription t+ 3-12 months post TIF procedure

Table 2: Outcomes of interests (OR and RD are adjusted for age, sex, race, ethnicity, diaphragmatic hernia and proton pump inhibitor use)

Glucagon-like peptide-1 (GLP-1) receptor agonists are associated with reduced risk of gastrointestinal cancers: Insights from a nationwide real-world analysis.

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used for type 2 diabetes (T2D) management and weight loss. While their benefits in metabolic control are well-documented, the association between GLP-1RA use and the risk of developing gastrointestinal-related cancers remains uncertain. This study evaluates the risk of GI-related cancers among patients with T2D or obesity treated with GLP-1RAs compared to those receiving insulin or metformin. **Methods:** This retrospective cohort study analyzed electronic health records (EHRs) from a nationwide database covering 113 million US patients. Adults with T2D or obesity, with no prior diagnosis of GI-related cancers, were included if they were prescribed GLP-1RAs, insulin, or metformin. The primary outcomes were the first-time diagnosis of GI-related cancers, including colorectal, esophageal, gastric, small intestine, liver, gallbladder, cholangiocarcinoma, and pancreatic cancers, during a 15-year follow-up. Propensity score matching was used to balance baseline characteristics across treatment groups. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated for outcome analysis. **Results:** A total of 691,454 patients received GLP-1 receptor agonists without insulin, while 3,408,360 received insulin without GLP-1 receptor agonists. Similarly, 502,964 received GLP-1 receptor agonists without metformin, and 2,555,902 received metformin without GLP-1 receptor agonists. GLP-1 receptor agonists, compared to insulin, were associated with a reduced risk of esophageal cancer (aOR: 0.35, 95% CI: 0.263–0.465), colorectal cancer (aOR: 0.336, 95% CI: 0.300–0.376), gallbladder cancer (aOR: 0.159, 95% CI: 0.084–0.301), stomach cancer (aOR: 0.298, 95% CI: 0.225–0.393), small intestine cancer (aOR: 0.148, 95% CI: 0.093–0.237), pancreatic cancer (aOR: 0.235, 95% CI: 0.196–0.281), liver cancer (aOR: 0.227, 95% CI: 0.187–0.276), and cholangiocarcinoma (aOR: 0.077, 95% CI: 0.058–0.104). Compared to metformin, GLP-1 receptor agonists were associated with a reduced risk of esophageal cancer (aOR: 0.443, 95% CI: 0.346–0.568), colorectal cancer (aOR: 0.479, 95% CI: 0.434–0.529), gallbladder cancer (aOR: 0.273, 95% CI: 0.154–0.483), stomach cancer (aOR: 0.412, 95% CI: 0.330–0.514), pancreatic cancer (aOR: 0.419, 95% CI: 0.372–0.471), liver cancer (aOR: 0.528, 95% CI: 0.455–0.613), small intestine cancer (aOR: 0.411, 95% CI: 0.297–0.570), and cholangiocarcinoma (aOR: 0.424, 95% CI: 0.345–0.521). **Conclusion:** This study provides real-world evidence that GLP-1RAs are linked to a lower risk of gastrointestinal cancers compared to insulin or metformin. These findings suggest a dual benefit of GLP-1RAs in diabetes management and cancer risk reduction, warranting further research to confirm and explore their preventive potential.

Cancer Type	GLP-1 vs Insulin (aOR, 95% CI)	GLP-1 vs Metformin (aOR, 95% CI)
Esophageal Cancer	0.35 (0.263–0.465)	0.443 (0.346–0.568)
Colorectal Cancer	0.336 (0.300–0.376)	0.479 (0.434–0.529)
Gallbladder Cancer	0.159 (0.084–0.301)	0.273 (0.154–0.483)
Stomach Cancer	0.298 (0.225–0.393)	0.412 (0.330–0.514)
Small Intestine Cancer	0.148 (0.093–0.237)	0.411 (0.297–0.570)
Pancreatic Cancer	0.235 (0.196–0.281)	0.419 (0.372–0.471)
Liver Cancer	0.227 (0.187–0.276)	0.528 (0.455–0.613)
Cholangiocarcinoma	0.077 (0.058–0.104)	0.424 (0.345–0.521)

Table 1:Adjusted Odds Ratios (aOR) for Cancer Risk: Comparison of GLP-1 Receptor Agonists vs Insulin and Metformin

TIRZEPATIDE Shows Lower Risk of Gastrointestinal Side Effects Compared to Single-Agent GLP-1 Receptor Agonists: A Real-World Analysis of Over 1 Million Patients

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Introduction: Tirzepatide, a dual GLP-1 and GIP receptor agonist, has demonstrated superior efficacy in glycemic control and weight loss compared to GLP-1 receptor agonists (GLP-1 RAs). However, its potency and dual agonist action may theoretically increase the risk of gastrointestinal (GI) side effects, such as constipation, nausea/vomiting, gastroparesis, irritable bowel syndrome (IBS), and GERD, though data on these outcomes remain limited. This study utilizes the TriNetX database to compare the risk of GI side effects and overall safety profile between tirzepatide and GLP-1 RAs in patients with type 2 diabetes mellitus, providing insights into their tolerability in real-world settings. **Methods:** We performed a retrospective cohort study utilizing the TriNetX US Collaborative Network, a multi-institutional database that aggregates data from 69 healthcare institutions. Patients aged ≥18 years who were prescribed either tirzepatide or a single-agent GLP-1 receptor agonist for type 2 diabetes or obesity were identified using validated ICD-10 and CPT codes. Exclusion criteria included patients with pregnancy, liver cirrhosis, inflammatory bowel disease (IBD), heart failure, chronic pancreatitis or active malignancy. Primary endpoints included gastroparesis, reflux, Barrett's esophagus, and GERD at 6 months, 1 year and 2 year follow up. Secondary outcomes included constipation, dyspepsia, nausea/vomiting, biliary disease (cholecystitis, choledocholithiasis, need for cholecystectomy), acute pancreatitis, and bowel obstruction. One-to-one propensity score matching was conducted, and the cohorts were balanced for age, sex, race, ethnicity, diabetes, gastroparesis, nicotine use, alcohol dependence, opioid use, and both acute and chronic pancreatitis. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were used to analyze the outcomes. **Results:** A total of 81,738 patients received Tirzepatide, while 851,379 patients were treated with single-agent GLP-1 receptor agonists. After propensity score matching, the cohorts were well-balanced in terms of demographic and clinical characteristics (Table 1). At 6 months, Tirzepatide was associated with a significantly lower risk of gastroparesis (aOR: 0.280, 95% CI: 0.239, 0.328), GERD (aOR: 0.473, 95% CI: 0.459, 0.487), and Barrett's esophagus (aOR: 0.431, 95% CI: 0.370, 0.502). Additionally, the risk of acute pancreatitis (aOR: 0.314, 95% CI: 0.293, 0.336), IBS (aOR: 0.414, 95% CI: 0.379, 0.453), and bowel obstruction (aOR: 0.353, 95% CI: 0.280, 0.445) were also significantly lower in the Tirzepatide cohort. The risk of nausea and vomiting was significantly lower in the Tirzepatide group (aOR: 0.291, 95% CI: 0.258, 0.328), as was the risk of constipation (aOR: 0.380, 95% CI: 0.370, 0.391) and dyspepsia (aOR: 0.421, 95% CI: 0.385, 0.461). The results were consistent at 1 year and 2 year follow up. Similarity, Tirzepatide was associated with lower risks of biliary diseases, including cholecystitis, cholelithiasis, choledocholithiasis, and cholecystectomy at 6 months, (Table 2), but not at 1 year or 2 year follow-up. **Conclusion:** Our study provides real-world evidence that tirzepatide has a significantly lower risk of gastrointestinal side effects compared to single GLP-1 receptor agonists, including conditions such as gastroparesis, GERD, and dyspepsia. These results suggest that tirzepatide may offer a better gastrointestinal safety profile for patients with obesity or type 2 diabetes. However, additional long-term studies are needed to fully evaluate the safety and efficacy of tirzepatide in diverse patient populations.

	Before Matching			After Matching		
Baseline Variable	**Cohort 1 (N = 81,738)**	**Cohort 2 (N = 851,379)**	**P-Value**	**Cohort 1 (N = 81,623)**	**Cohort 2 (N = 81,623)**	**P-Value**
Age at Index	51.5 ± 13.4	53.7 ± 14.3	<0.001	51.5 ± 13.4	51.5 ± 13.4	0.999
White	56,590 (69.3%)	513,804 (61.3%)	<0.001	56,590 (69.3%)	56,625 (69.4%)	0.851
American Indian or Alaska Native	307 (0.4%)	4,468 (0.5%)	<0.001	307 (0.4%)	289 (0.4%)	0.460
Female	51,790 (63.5%)	498,442 (59.5%)	<0.001	51,790 (63.5%)	51,771 (63.4%)	0.922
Native Hawaiian or Other Pacific Islander	118 (0.1%)	1,367 (0.2%)	0.209	118 (0.1%)	101 (0.1%)	0.250
Unknown Gender	4,111 (5.0%)	33,674 (4.0%)	<0.001	4,111 (5.0%)	4,097 (5.0%)	0.874
Not Hispanic or Latino	56,548 (69.3%)	521,334 (62.2%)	<0.001	56,548 (69.3%)	56,576 (69.3%)	0.881
Hispanic or Latino	5,370 (6.6%)	78,893 (9.2%)	<0.001	5,370 (6.6%)	5,365 (6.6%)	0.960
Black or African American	11,974 (14.7%)	155,213 (18.5%)	<0.001	11,974 (14.7%)	11,991 (14.7%)	0.905
Male	25,722 (31.5%)	306,210 (36.5%)	<0.001	25,722 (31.5%)	25,755 (31.6%)	0.860
Other Race	2,166 (2.7%)	36,410 (4.3%)	<0.001	2,166 (2.7%)	2,146 (2.6%)	0.758
Asian	1,394 (1.7%)	20,330 (2.4%)	<0.001	1,394 (1.7%)	1,404 (1.7%)	0.849
Type 2 Diabetes Mellitus	27,874 (34.1%)	438,184 (52.3%)	<0.001	27,874 (34.1%)	27,871 (34.1%)	0.988
Gastroparesis	422 (0.5%)	5,663 (0.7%)	<0.001	422 (0.5%)	402 (0.5%)	0.485
Alcohol Use	498 (0.6%)	4,283 (0.5%)	<0.001	498 (0.6%)	459 (0.6%)	0.206
Acute Pancreatitis	453 (0.6%)	5,162 (0.6%)	0.033	453 (0.6%)	342 (0.4%)	<0.001
Nicotine Dependence	7,436 (9.1%)	85,219 (10.2%)	<0.001	7,436 (9.1%)	7,399 (9.1%)	0.750
Opioids and Opiate Analogs	113 (0.1%)	1,211 (0.1%)	0.665	113 (0.1%)	95 (0.1%)	0.212

Table 1: Baseline characteristics of the included cohorts before and after matching

Outcome	**aOR**	**95% CI**
Gastroparesis	0.280	(0.239, 0.328)
GERD	0.473	(0.459, 0.487)
Barrett's Esophagus	0.431	(0.370, 0.502)
Constipation	0.380	(0.370, 0.391)
Acute Pancreatitis	0.314	(0.293, 0.336)
IBS	0.414	(0.379, 0.453)
Bowel Obstruction	0.353	(0.280, 0.445)
Cholecystitis	0.425	(0.357, 0.505)
Cholecystectomy	0.667	(0.299, 1.484)
Cholelithiasis	0.421	(0.385, 0.461)
Choledocholithiasis	0.480	(0.392, 0.588)
Dyspepsia	0.421	(0.385, 0.461)
Nausea and Vomiting	0.291	(0.258, 0.328)

Table 2: Outcomes of interests at 6 months.

Overcoming host restriction to enable continuous passaging of human noroviruses in human intestinal enteroids

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Human noroviruses (HuNoVs) are the leading cause of virus-induced gastroenteritis. We established human intestinal enteroids (HIEs) as a robust model system that supports infection and replication of multiple HuNoVs (Ettayebi et al., Science 2016; Ettayebi et al., mBio 2024), which overcame a 50-year barrier to cultivation of HuNoVs. Currently, a significant bottleneck in HuNoV research is our inability to indefinitely passage any HuNoV in HIEs to generate virus stocks. This creates a dependency on stool samples from infected patients as viral inocula. Therefore, it is crucial to understand the barrier that limits continuous passaging of HuNoVs. We used comparative transcriptomics (RNA-seq) to define HuNoV responses in HIEs and to identify host restriction factors that could block viral passaging.

The top upregulated pathway identified by RNA-seq was the host innate immune response, primarily driven by interferons and CXC based chemokines. Notably, CXCL10, CXCL11, and CCL5 emerged as the top up-regulated interferon-stimulated genes (ISGs) in response to GII.3 HuNoV infection indicating their potential role as host restriction factors in HIEs. To overcome this response, we used TAK-779, a selective nonpeptide antagonist for chemokine receptors CCR5 and CXCR3. Treatment with TAK-779 enhanced GII.3 HuNoV replication (1.5 log10 genome equivalents) and viral spread in a dose- and time-dependent manner. For the first time, we have passaged GII.3 HuNoV in the presence of TAK-779 for over 10 passages in two different HIE lines. The ability to passage virus is a major achievement that will allow the generation of virus in sufficient quantities for structural and biochemical studies as well as assessment of targeted therapeutics to combat these major disease-causing viruses. Interestingly, there was no impact on replication of a pandemic GII.4 HuNoV strain, suggesting GII.4 induces a different host response from GII.3 or has developed a mechanism to antagonize these immune responses. Currently, we are dissecting the mechanism of TAK-779 action through transcriptomics and secretome analysis. We are also investing the strategies employed by the pandemic GII.4 HuNoVs in evading the cellular innate immune response.

Comparison of risk factors and cancer outcomes between young-onset (<50 years) and average-onset gastric cancer patients at two U.S. medical centers: a case-case study

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Background: The incidence of gastric cancer is increasing in adults <50 years old in the U.S., particularly in Hispanic and non-Hispanic (NH) white individuals. Our aim was to gain insight into the reasons underlying these trends by comparing risk factors among young-onset (<50 years) and average-onset (≥50 years) patients diagnosed with gastric adenocarcinoma in two U.S. populations. **Methods:** In this retrospective case-case study, we included adults newly diagnosed with gastric adenocarcinoma from two hospitals in Houston, Texas: Harris Health (safety-net hospital) and the Michael E. DeBakey VA Medical Center (MEDVAMC). Harris Health patients diagnosed from 1/2014-12/2023 were identified through the cancer registry, and MEDVAMC patients diagnosed from 11/2007-6/2023 were identified through the histopathology database. Demographic, lifestyle, and laboratory characteristics of young- (<50 years) and average-onset (≥50 years) gastric cancer (GC) patients were compared using a case-case study design. We estimated adjusted odds ratios (AOR) and 95% confidence intervals (CI) using logistic regression models. **Results:** We included 523 gastric adenocarcinoma patients with mean age 67.3 years (standard deviation 11.9 years), of which 62.7% were male, 10.1% NH white, 24.7% NH black, and 61.2% Hispanic. We included 156 (29.8%) young- and 367 (70.2%) average-onset patients (Table 1). Hispanic ethnicity (vs. NH white; AOR 5.68, 95% CI 1.64-19.75) and normal vitamin B12 levels (vs. <200pg/mL; AOR 2.50, 95% CI 1.16-5.38) were associated with young-onset GC. MEDVAMC site was inversely associated with young-onset GC (vs. Harris Health; AOR 0.24, 95% CI 0.10-0.62) (Table 2). *H pylori* was tested in 83.3% of young-onset patients, and of those 55.4% were positive. Autoimmune gastritis (AIG) antibodies (anti-parietal, anti-intrinsic factor) were tested in 3 (1.9%) young-onset patients and of those, 1 patient was positive. Therefore, 83.3% of young-onset GC were tested for the two main risk factors (*H. pylori* and AIG), and of these, only 56.2% were positive. *H. pylori* infection, AIG antibodies, and gastrin level were not associated with increased risk of young-onset GC. There was a higher proportion of stage 4 cancers (66.7% vs. 49.9%, p<0.01) and less surgical treatments (19.9% vs. 28.6%, p=0.02) among young-onset GC patients compared to average-onset GC patients. **Conclusion:** Our data indicate that the strength of association of Hispanic ethnicity was stronger for young-onset compared to average-onset GC. Presence of *H. pylori* or AIG antibodies accounted for only 56% of young-onset GC and was not different from average-onset GC, although low vitamin B12 level was associated with average-onset GC. Distinct epidemiologic characteristics and worse prognosis among patients with young-onset GC emphasize the need for future studies to examine causal factors in these patients.

Associations of demographic and food scarcity factors with *Helicobacter pylori* seroprevalence in an urban U.S. population

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Background: *Helicobacter pylori* is a common, chronic infection with over 25% of the U.S. population estimated to be infected. The burden of infection disproportionately affects Black and Hispanic individuals complicated by socioeconomic factors and food and water sources. Our aim was to examine demographic and food scarcity factors for *H. pylori* seropositivity in the greater Houston area. **Methods:** In this retrospective cross-sectional study, we included adult patients who had received *H. pylori* IgG serologic testing at Harris Health (a safety-net hospital system in Houston, Texas) from December 2023-September 2024. Using the Epic electronic medical record SlicerDicer data mining tool, patients with positive and negative *H. pylori* results were identified along with their demographic and clinical data and addresses. Addresses were cross-referenced with the 2019 U.S. Department of Agriculture (USDA) Food Access Research Atlas to determine residence in a low-income, low-food access census tract. Associations of demographic, clinical and food scarcity factors were examined using logistic regression models, reported as adjusted odds ratios (AOR) and 95% confidence intervals (CI). **Results:** We included 1328 total patients who underwent *H. pylori* IgG serologic testing with mean age 50.2 years (standard deviation 13.6 years). Most patients were Hispanic (69.5%) with 7.2% non-Hispanic White and 18.1% non-Hispanic Black. Of those tested, 636 patients (47.9%) had negative *H. pylori* serology and 692 patients (52.1%) had positive *H. pylori* serology (52.1% seroprevalence of *H. pylori*). Those with *H. pylori* were more likely to be male (43.5% vs. 36.2%) and Hispanic (72.8% vs. 65.9%). There was no difference in residing in low-food access areas between those with and without *H. pylori* infection (18.6% vs. 17.9%) (Table 1). Non-Hispanic Black (vs. non-Hispanic white; AOR 1.86, 95% CI 1.13-3.05), Hispanic (AOR 2.41, 95% CI 1.53-3.80), and Non-Hispanic Asian race/ethnicity (AOR 2.75, 95% CI 1.28-5.93) and body mass index (BMI) above 30 kg/m^2 (vs. < 25 kg/m^2; AOR 1.36, 95% CI 1.02-1.82) were independently associated with positive *H. pylori* serology. Female sex was protected against positive *H. pylori* serology (AOR 0.67, 95% CI 0.53-0.84). Residence in a low-food access census tract was not associated with *H. pylori* seropositivity (Table 2). **Conclusion:** We found increased risk of *H. pylori* seropositivity among non-Hispanic Black, Hispanic, and non-Hispanic Asian patients as well as increased risk in those with BMI over 30 kg/m^2 in the Houston population. Female sex was protective against *H. pylori*. While residence in a low-income, low-food access area was not associated with *H. pylori* seropositivity, further studies are needed on the downstream effects of socioeconomic status and food access on *H. pylori* infection.

	Patients with negative *H. pylori* Serology (N = 636)	Patients with positive *H. pylori* Serology (N = 692)	p-value
Sex			<0.01
Male	230 (36.2)	301 (43.5)	
Female	406 (63.8)	391 (56.5)	
Race/Ethnicity			<0.01
Non-Hispanic White	62 (9.8)	34 (4.9)	
Non-Hispanic Black	121 (19.0)	120 (17.3)	
Hispanic	419 (65.9)	504 (72.8)	
Non-Hispanic Asian	18 (2.8)	22 (3.2)	
Unknown/Other	16 (2.5)	12 (1.7)	
Age (years)			0.82
< 40	152 (23.9)	166 (24.0)	
40 - 60	327 (51.4)	365 (52.8)	
> 60	157 (24.7)	161 (23.3)	
BMI (kg/m^2)			0.24
< 25	161 (25.3)	146 (21.1)	
25 – 30	200 (31.5)	216 (31.2)	
> 30	274 (43.1)	328 (47.4)	
Unknown	1 (0.2)	2 (0.3)	
Low-income Low-Access Residence			0.56
No	509 (80.0)	543 (78.5)	
Yes	114 (17.9)	129 (18.6)	
Unknown	13 (2.0)	20 (2.9)	

Table 1. Characteristics of 636 patients seronegative for *H. pylori* and of 692 patients seropositive for *H. pylori*.

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex		
Male	ref	ref
Female	0.74 (0.59-0.92)	0.67 (0.53-0.84)
Race/Ethnicity		
Non-Hispanic White	ref	ref
Non-Hispanic Black	1.81 (1.11-2.95)	1.86 (1.13-3.05)
Hispanic	2.19 (1.42-3.40)	2.41 (1.53-3.80)
Non-Hispanic Asian	2.23 (1.05-4.72)	2.75 (1.28-5.93)
Unknown/Other	1.37 (0.58-3.22)	1.48 (0.62-3.51)
Age (years)		
< 40	ref	
40 - 60	1.02 (0.78-1.33)	
> 60	0.94 (0.69-1.28)	
BMI (kg/m^2)		
< 25	ref	ref
25 – 30	1.19 (0.89-1.60)	1.17 (0.86-1.58)
> 30	1.32 (1.00-1.74)	1.36 (1.02-1.82)
Unknown	2.21 (0.20-24.58)	2.17 (0.19-24.37)
Residence in Low-Food Access Area		
No	ref	ref
Yes	1.06 (0.80-1.40)	1.06 (0.80-1.41)
Unknown	1.44 (0.71-2.93)	1.87 (0.89-3.93)

Table 2. Associations of demographic factors with patients seronegative and seropositive for *H. pylori*.

Impact of 'gut immune axis' shift on progressive liver disease

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Background Liver cirrhosis, the chronic fibrosis or scarring of liver tissue, affects nearly one in 400 US adults and causes irreversible structural damage, impairing organ function. Underdiagnosis and late-stage disease presentation are major challenges to cirrhosis management. Communication between the gut and liver, known as the 'gut-liver' axis, is severely altered in liver cirrhosis and can trigger dysbiosis of the gut microbiota due to increased gut permeability. We hypothesized that increasingly worse disease, characterized by complications from acute liver failure (i.e., liver decompensation), is associated with ever worse changes to the gut microbiome.

Methods We used shotgun metagenomics to characterize the fecal microbiome of 75 patients with liver cirrhosis. Taxonomic annotation and functional gene content were determined using Biobakery3 tools MetaPhlAn3 and HUMAnN3, respectively. We evaluated the microbiome, including measures of diversity, taxa, and metabolic pathways, across a spectrum of cirrhosis decompensation complications: hepatic encephalopathy, ascites (fluid retention), and varices (enlarged blood vessels). We also profiled the microbiome by disease status, with severe disease characterized by presence of decompensation complications.

Results Approximately 60% of patients with liver cirrhosis had at least one form of decompensated complications of either hepatic encephalopathy (26%), varices (44%), or ascites (30%). Among liver cirrhosis patients with severe disease, bacterial species richness decreased with increasing number of decompensatory changes. Overarching differences in microbial communities were also evident across disease stages. These differences were driven in part by significant depletion of *Ruminococcus*, *Clostridium, Bacteroides, and Roseburia—genera responsible for* regulation and maintenance of the gut mucosal barrier and host immune system. We also observed marked abundance of potential opportunistic pathogens, including *Streptococcus* and *Veillonella spp.* more commonly found in the oral cavity.

Conclusions Patients with liver cirrhosis exhibit altered gut microbiome profiles, with greater dysbiosis found in those with more severe disease. Further studies are needed to determine the directionality of this relationship, though our study highlights the potential of the microbiota as a biomarker of cirrhosis complications and as a target for modulation of the gut-immune axis, thereby preventing liver decompensation.

Detection of macrophage phagocytosis in human norovirus infection using *ex vivo* human intestinal enteroids-immune cell coculture system

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Human norovirus (HuNoV) causes acute gastroenteritis in immunocompetent hosts and chronic infection in immunocompromised individuals. Recent studies of innate immunity in the context of HuNoV infection utilized epithelium-only human intestinal enteroids which lack immune cells. Here, we developed an *ex vivo* immune cell-enteroid coculture model consisting of human intestinal enteroids (HIEs) and human peripheral blood mononuclear cell-derived macrophages to better recapitulate the *in vivo* gut biology and explore the role of macrophages in HuNoV pathogenesis.

Previous histopathological studies using intestinal biopsies derived from chronically infected immunocompromised individuals identified enterocytes and enteroendocrine cells as the primary sites for HuNoV infection and replication. Additionally, HuNoV viral antigens were also found in macrophages, suggesting their role in eliciting a host response. By performing HuNoV infection in HIEs cocultured with human peripheral blood mononuclear cell-derived macrophages, we showed that pro-inflammatory macrophages exhibit the highest potency in phagocytic activity for HuNoV-infected epithelial cells. These findings indicate a specific macrophage phenotype readily recognizes HuNoV-infected cells and may play a protective role in controlling virus spread. The establishment of the macrophage/HIE co-culture model enables future studies to identify host cell molecules unique to epithelial-macrophage crosstalk and to develop preventative or treatment strategies to lessen the severe disease associated with HuNoV infection.

This research was supported in part by National Institutes of Health U19 grants AI116497 and P30AI161943 that supports the Texas Developmental Center for AIDS Research.

Adipose tissue response to vitamin E status in the regulation of whole-body homeostasis

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The essential, fat-soluble nutrient vitamin E performs antioxidant properties by preventing lipid peroxidation in times of elevated free radical generation. Dietary vitamin E is absorbed in the intestine and packaged in lipid-carrying vesicles and undergoes preferential export by the liver in the form of α-tocopherol. Ultimately, 90% of α-tocopherol is stored in the lipid droplets of adipocytes and becomes rapidly mobilized during high oxidative stress conditions such as in traumatic burn or irradiation injuries. However, the regulation of vitamin E levels in chronic disease such as obesity or type 2 diabetes is less clear, and studies on human subjects evaluating the relationship between adiposity and circulating vitamin E levels yield conflicting results. Further, several attempts to improve metabolic outcomes in obesity or type 2 diabetes by vitamin E supplementation fail to achieve meaningful, clinical endpoints. Together, these knowledge gaps highlight how the modulation of vitamin E storage in fat and the mechanism of purposeful vitamin E release from adipose tissue remain poorly defined. Since vitamin E cannot be endogenously synthesized and is mostly stored in adipose tissue, we implemented an α-tocopherol stripped diet to study the impact of vitamin E demand on whole-body metabolism. We placed 6-week-old male mice on vitamin E deficient (VED) or control diet for 8 weeks and characterized whole-body metabolism using the comprehensive lab animal monitoring system (CLAMS) and conducted studies of glucose disposal. Despite observing nominal energy balance changes in the metabolic cages, fasting in VED mice strongly decreased adipose tissue mass, especially in gonadal white adipose tissue, compared to age-matched controls. In line with adipose tissue reduction, VED mice exhibited lower circulating leptin and displayed elevated serum free fatty acid levels which predicts a role for lipolysis in regulating tissue vitamin E stores. Vitamin E status also seemingly affected insulin sensitivity as VED mice had lower serum insulin but improved glucose tolerance. Interestingly, H&E staining and morphometry analysis revealed decreased villus length and crypt depth only in the proximal small intestine of VED mice compared to controls, a finding associated with decreased capacity for nutrient uptake and impaired stem cell turnover. These findings emphasize the importance of adipose tissue in regulating whole-body redox and glucose homeostasis, and future work will determine why and how certain fat depots respond to whole-body vitamin E demands.

Microbially Derived Branched-Chain Fatty Acids Regulate Colonic Permeability in Protein Malnutrition

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Background: Malnutrition contributes to 45% of global child deaths and disrupts the gut microbiome, impairing intestinal functions such as barrier integrity. Increased intestinal permeability facilitates bacterial translocation, leading to sepsis, a major cause of mortality in malnourished children. The intestinal barrier is partially regulated by microbial metabolites, including branched-chain fatty acids (BCFAs), produced during bacterial fermentation of branched-chain amino acids. This study aims to investigate whether changes in gut microbiota function contribute to heightened gut barrier permeability in malnutrition.

Methods: Specific pathogen-free (SPF) and germ-free C57BL/6 mice were weaned to a low-protein, low-fat diet to induce malnutrition or maintained on an isocaloric control diet. SPF mice were administered leucine via oral gavage twice daily for 2.5 days. Stool samples were analyzed via metagenomic sequencing and mass spectrometry to determine BCFA levels. Gut barrier permeability was quantified *ex vivo* in Ussing chambers by measuring fluorescein isothiocyanate-dextran flux across the colonic epithelium. Bacterial translocation was assessed by culturing liver and spleen aerobically and anaerobically on Brain Heart Infusion agar. *Muc2* expression was quantified using qPCR and immunofluorescence. *In vitro* permeability was evaluated by measuring transepithelial electrical resistance (TEER) across human-derived colonoid monolayers after BCFA treatment.

Results: Malnutrition tripled *ex vivo* colonic permeability and increased culturable anaerobic bacteria in spleen and liver of SPF mice more than 40-fold. Germ-free malnourished mice did not exhibit increased permeability. In SPF mice, malnutrition decreased microbial community richness and evenness and decreased levels of BCFAs, including 2-methylbutyrate, isobutyrate, and isovalerate. In the malnourished mouse colon, there was a 40% reduction in transcription of *Muc2*, the predominant secretory mucin, accompanied by decreased immunofluorescence. Abundance of the mucin-degrading bacterium *Akkermansia muciniphila* increased in malnourished mice. Human-derived colonoid monolayers treated with isovaleric acid exhibited dose-dependent increases in TEER. Oral gavage of leucine, a branched-chain amino acid precursor to isovalerate, improved *ex vivo* colonic permeability in malnourished mice, while alanine, a non BCFA forming amino acid, had no effect. Leucine administration reduced the number of culturable colonies, suggesting that microbial formation of BCFAs improves colonic permeability and reduces bacterial translocation.

Conclusion: The gut microbiome contributes to malnutrition-induced gut barrier dysfunction, and the microbial-derived BCFA isovaleric acid improves colonic permeability. These results may facilitate novel precision nutrition microbiome-targeting therapeutic strategies to restore gut barrier integrity and decrease the risk of sepsis in malnourished children.

Colonization of the nasopharynx by *Klebsiella pneumoniae* is associated with establishment of gastrointestinal carriage in mice

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Klebsiella pneumoniae (Kp) is a bacterial pathogen of significant clinical concern due to high rates of multi-drug resistance. Gut colonization by Kp is a key precursor for dissemination to sites including the lung, bloodstream, and urinary tract, as patients often develop infections with their gut colonizing strain. Animal models are critical to increase our understanding of mechanisms underlying gut colonization and systemic dissemination by Kp. While inoculation of mice by oral gavage is a common model, this approach typically requires antibiotic pre-treatment to induce susceptibility to colonization. In contrast, oral pipette feeding of Kp facilitates robust colonization of the intestine without the need for antibiotic pre-treatment, allowing for investigation of Kp colonization within an unperturbed gut environment. However, mechanisms that facilitate establishment of gut colonization by Kp following oral feeding are unknown. Here, we find that Kp colonizes the nasopharynx and esophagus of mice following oral pipette feeding. Bypassing nasal colonization by feeding in a small volume failed to establish gut colonization, suggesting that the nasopharynx is a previously unappreciated niche that promotes establishment of gastrointestinal carriage by Kp. Future work will further characterize the host-pathogen interface in the nasopharynx and investigate if this niche primes Kp for intestinal colonization by upregulating virulence factor expression. Findings from this work will uncover mechanisms of Kp carriage and dissemination, providing key insight into interventions to mitigate Kp gut colonization and prevent subsequent systemic infections.

Gut pathobiont enrichment observed in a population predisposed to dementia, type 2 diabetics of Mexican descent living in South Texas

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Type 2 diabetes (T2D) is a common forerunner of neurodegeneration and accompanying dementia, including Alzheimer's Disease (AD), yet the mechanisms underlying this comorbidity remain unresolved. Individuals of Mexican descent living in South Texas have increased prevalence of comorbid T2D and early onset AD, despite low incidence of the APOE-e4 risk variant among the population and an absence of a similar predisposition among relatives residing in Mexico – suggesting a role for environmental factors in coincident T2D and AD susceptibility. We therefore sought to test if differences in gut community structure could be observed in this population prior to any AD diagnosis. Here, in a small clinical trial (ClinicalTrials.gov Identifier NCT04602650), we report evidence for altered gut microbial ecology among subjects of Mexican descent living in South Texas with T2D (sT2D) compared to healthy controls without T2D (HC), despite no differences in expressed dietary preferences. We performed metataxonomic 16S rRNA gene amplicon sequencing of study participant stool samples. Although no significant decrease in microbial alpha diversity was observed between sT2D gut communities versus those of HC, body mass index was identified as a driver of gut community structure. Intriguingly, we observed a significant negative association of *Faecalibacterium* and *Lachnospiraceae* with T2D and an increase in the abundance of pathobionts *Escherichia-Shigella*, *Enterobacter*, and the erysipelotrichial species *Clostridia innocuum* among sT2D gut microbiota, as well as differentially abundant gene and metabolic pathways. Future large-scale, longitudinal sequencing efforts of the gut microbiome of individuals with T2D who go on to develop AD might identify key actors among "disease state" microbiota that contribute to increased susceptibility to comorbid dementia. Finally, we identified candidate microbiome-targeted approaches for the treatment of T2D.

Investigating the effects of diet and the gut microbiome on the pathogenesis of necrotizing enterocolitis (nec)

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Necrotizing enterocolitis (NEC) is the leading cause of death from gastrointestinal disease in premature infants. Although its pathogenesis is incompletely understood, prematurity, diet, and the gut microbiome have been identified as risk factors for this disease. Breastmilk feeding significantly decreases the incidence of NEC in preterm infants compared to infant formula, however, the mechanisms through which these diets affect the pathogenesis of NEC remain elusive. This project aims to elucidate how the interplay between diet and the gut microbiome affects susceptibility to NEC. Feeding studies using a preterm piglet model of NEC have demonstrated that feeding a commercially available infant formula results in higher incidence of NEC compared to donor human milk (DHM). Formula feeding results in significantly higher relative abundance of the species *Clostridium perfringens* (*C. perfringens*), which also correlates with disease incidence and severity in both the small intestine and the colon. Using *C. perfringens* isolates from both piglets and infants, we've found that this species grows to higher densities in formula compared to DHM. Additionally, C. perfringens produces higher levels of toxin perfringolysin O when cultured in formula compared to DHM. Importantly, we found that both piglet and infant isolates grow to higher densities in maltodextrin, the most abundant carbohydrate in preterm infant formula, compared to lactose, the most abundant carbohydrate in breast milk. However, growth in maltodextrin-supplemented media does not result in higher levels of toxin production, suggesting that the presence of this sugar, at least *in vitro*, does not result in higher virulence of this bacterium. Using a bacterial community derived from small intestinal contents of preterm piglets, we evaluated how supplementation of minimal media with different percentages of DHM and formula shapes the bacterial community. We found that formula supplementation leads to a dramatic increase in the relative abundance of *C. perfringens*, suggesting that formula supports the growth of this bacterium independent of the host and NEC. Currently, we are focused on examining the effects of formula and DHM supplementation on the structure and cytotoxicity of preterm infant-derived bacterial communities with the ultimate goal of better understanding the interplay between diet and the gut microbiome in relation to the pathogenesis of NEC.

Preclinical models for functional studies of the infant gut microbiome

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Background and Aims. The human gut microbiome undergoes rapid development in the first year of life, and its disruption during infancy can have long-lasting health consequences later in life. Yet, it is challenging to understand how dietary changes, gastrointestinal insults, or environmental factors precisely alter infant-microbial interactions because we lack preclinical models that adequately recapitulate the infant gut microbiome. To address this gap, we established preclinical mouse and bioreactor models that reproducibly recover the gut microbiome of infant donors.

Methods. Through a prospective cohort study in Ireland, we acquired stool samples that were collected throughout the first year of life from 35 infants. Using these stool samples, we established 117 humanized-microbiota mouse lines such that each line was humanized with a single unique infant stool sample, and we also cultivated each of the stool samples in continuous-flow bioreactors. We profiled the microbial composition of preclinical models corresponding to 55 unique stool samples using whole-genome shotgun sequencing and metabolic composition of preclinical models corresponding to 33 unique stool samples using untargeted metabolomics.

Results. Our preclinical models recovered more than 75% of the most abundant species in infant stool samples. For fastidious members of the Bifidobacteriaceae and Lactobacillaceae families, we showed that their abundances can be increased by the addition of select sugars and oligosaccharides to the bioreactor growth media. Further, bioreactors contained more than 44% of the metabolites detected in the feces of humanized-microbiota mice and allowed us to delineate the contribution of individual gut bacteria to the metabolic environment in mouse feces. In addition, both mouse and bioreactor models recapitulated the increase in alpha-diversity of the infant microbiome during the first year of life and supported complex communities with up to 49 unique species. Importantly, mice or bioreactors humanized with the same stool sample showed high reproducibility in terms of microbial composition and function.

Conclusions. We established an integrative approach using both humanized-microbiota mouse lines and continuous-flow bioreactors that reproducibly recovered the microbial species composition and function of infant donors. Both of these models are amenable to controlled experiments that can precisely test how various treatments, including dietary changes and gastrointestinal insults, mechanistically impact the infant gut microbiome.

Intestinal insufficiency increases risk of death and prolonged hospitalization: a large single-center cohort study of pediatric liver transplant recipients.

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Aim: This study aims to determine if pre-transplant intestinal insufficiency is associated with mortality following orthotopic liver transplant (OLT) in pediatric patients.

Methods: A large, single-center, retrospective cohort study was performed. The study included 245 pediatric patients (age < 18) who received an OLT between January 1, 2012 and March 11, 2019. Based on individualized nutritional goals defined by clinical dietitians, we defined pretransplant intestinal insufficiency as the inability to tolerate greater than 50% of nutritional goals enterally before a liver transplant. Feeding intolerance was a clinical determination made by the care team based on symptoms including abdominal distension, vomiting, feeding discomfort, or dumping. The primary outcome variable analyzed was death after OLT. Secondary outcome variables included post-transplant hospital length of stay and post-operative complications. Kaplan-Meier survival analysis and multiple variable logistic regression analyses were performed to analyze the primary and secondary outcomes. Independent variables included patient demographics, MELD and PELD scores, stunted growth (based on WHO definition), pre-OLT renal or ventilatory support requirements, cause of liver disease, donor type, and prior hospitalizations. Variables with $p<0.2$ on univariate regression and those considered clinically significant were included in the multiple-variable adjusted analysis.

Results: Patients were determined to be intestinally insufficient (n= 63) or sufficient (n= 182) prior to transplant. Kaplan-Meier analysis revealed a significant increase in 1-year mortality and mortality during follow-up among intestinally insufficient patients ($p<0.001$). Multivariable regression analysis found intestinal insufficiency to be associated with increased odds of death within 1-year after transplant (HR: 6.79 95% CI: 1.75-26.31) and during overall follow-up (HR: 5.38, 95% CI: 1.88-15.51). Patients with intestinal insufficiency had increased odds of postoperative length of stay greater than 60 and 90 days (OR: 3.03, 95% CI: 1.14-8.01, OR: 4.40, 95% CI: 1.32-14.72).

Conclusions: In our cohort of pediatric patients, pre-transplant intestinal insufficiency was independently associated with death and prolonged hospitalization after an orthotopic liver transplant. Pre-transplant intestinal insufficiency and other functional measures of nutritional status deserve consideration as prognostic factors that predict post-transplant outcomes for pediatric patients with end-stage liver disease. Our findings emphasize the importance of pre-transplant nutritional rehabilitation, and of considering feeding intolerance as a potential risk factor for post-transplant mortality. By understanding such risk factors, we can further optimize patient care and surveillance and promote equitable organ allocation for pediatric patients.

The role of IL4:microbiome interaction in acute colitis

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Introduction: Therapies that restore mucosal homeostasis would be major advancements in the treatment of inflammatory bowel disease (IBD). IBD is characterized by relapsing and remitting inflammation which are often exacerbated by incomplete mucosal healing and dysbiosis. Existing therapies have high failure and non-response rates, failing to control relapse effectively. There is a critical need to explore mechanisms that restore homeostasis after IBD. **This project aims to characterize the interactions of Interleukin-4 (IL4) with immune cells and the microbiome and their contribution to colon homeostasis after colitis.**

Methods: IL-4$^{-/-}$ mice and controls were treated with 3% dextran sulfate sodium (DSS) for 5 days to induce colon injury. Mice were observed until day 21, recording daily weight changes and colitis symptoms. Colon length was measured on day 21, and IHC analysis of Ki67 staining was performed. Whole genome shotgun sequencing was performed and pre-processing, filtering, and quality control was performed. Metagenomic coverage estimates were generated using Nonpareil. Metagenomic distance estimation was performed using MASH with NMDS clustering. Taxonomic analyses were performed using Kraken2 and Braken referencing the MGnify Genomes mouse catalogue v1.0.

Results and Discussion: After DSS, IL-4$^{-/-}$ mice (n=12) had more severe weight loss and disease activity compared with controls in separate cages (n=12). On day 21, IL-4 deficient mice had shorter colon length and decreased epithelial cell proliferation (Ki67 IHC). However, when co-housed IL-4 deficient and littermate controls (n=10) were treated with DSS, the phenotypic differences were abrogated, suggesting that the microbiome may modulate the role of IL4 in colitis. Thus, we performed whole genome shotgun sequencing on the microbiota of separately housed IL4$^{-/-}$ (n=10) and C57 mice (n=10) and performed metagenomic analysis. Nonpareil analysis revealed increased metagenomic coverage per sequencing effort in IL4$^{-/-}$ mice ($p=0.031$), suggesting decreased metagenomic complexity. MinHash distance estimation and NMDS clustering revealed non-overlapping 95% confidence intervals between groups. IL4$^{-/-}$ mice had decreased inter-group variance (PERMANOVA $p=0.012$), increased inter-group similarity (ANOSIM $p=0.016$), and increased dissimilarity between groups (MRPP $p=0.001$) compared with controls. Taxonomic analysis using LefSe revealed genus and species level differences (LDA >3) between IL4$^{-/-}$ and wild-type metagenomes. This suggests that IL4 deficiency may alter metagenomic structure and function, and that these differences are transferable by microbiome sharing and impact disease severity after DSS. Naïve and DSS-treated IL4$^{-/-}$ mice were found to have colon-specific deficiency of the antimicrobial peptides Reg3b and Reg3g compared with controls by qPCR, western blot, and IHC staining, which may contribute to dysbiosis during DSS treatment.

Future directions: Going forward, I will perform fecal transfer experiments using gnotobiotic mice to define the contribution of IL4 to microbiome structure and the impact of these changes on tissue repair after colitis. I will also investigate the mechanism of colon-specific Reg3b/g deletion in IL4 deficient mice using molecular studies, metabolomics, and cell-specific IL4-receptor deletion mice

Probiotic administration in Treg deficient mice decreases lung inflammation and modulates gut and lung microbiota

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Background: A Foxp3 transcription factor mutation in scurfy (SF) mice leads to regulatory T-cell (Treg) deficiency, which manifests as multiorgan inflammation. In humans, a similar Treg deficiency results in IPEX syndrome (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked inheritance). Dysbiosis has been linked to immunodysregulation, and there is interest in the influence of local microbiota on immunity at distal sites. In prior studies, SF mice treated with *Limosilactobacillus reuteri* DSM 17938 showed changes in gut microbiota, immune response, and liver inflammation which correlated with prolonged survival. To date, the effect of probiotics on lung microbiota and inflammation in SF mice has not been studied.

Objective: To assess the effect of DSM 17938 on T-cell mediated inflammation and microbiota in the lung of SF mice.

Methods: SF mice (B6. Cg-Foxp3sf/Y) were fed DSM 17938 (10^7 CFU/day) (SFL, n=7), daily from d8 of life. The comparison groups, SF (SFC, n=7) and Wild Type (WTC, n=5) were fed control media. Biospecimens were collected at d21. 16S rRNA sequencing was performed to characterize lung microbiota and analyzed by QIIME2 pipeline. IL-1β, IL-12 and KC/GRO levels were measured from lung lysates by ELISA. Lung injury scores (LIS) were calculated by evaluating alveolar septal thickening and proteinaceous debris.

Results: SF mice showed reduced α-diversity of lung microbiota compared to WTC. α-diversity increased with DSM 17938 (SFL vs. SFC): Shannon diversity (p=0.03), PD Whole Tree (p=0.002) and Observed Species (p=0.004). Distinct cluster shifts were noted between SFC and WTC, as assessed by principal coordinates analysis. However, there was no effect of DSM 17938. Firmicutes (69%), Bacteroidetes (24%), Proteobacteria (3%) dominated the lung microbiota of WTC. The relative abundance (RA) of Firmicutes was reduced in the lungs of SFC compared to WTC while RA of Bacteroides and uncategorized bacteria was increased. SF lungs also showed reduced RA of *Lactobacillus (including Lactobacillus reuteri*), *Prevotella*, *Bacteroides S24-7*, and *Ruminococcaceae* (*Ruminococcus bromii*), compared to WTC. We noted a positive correlation between RA of *Parabacteroides* in lung and RA in stool and negative correlation between RA of *Lachnospiracea* in these areas, which highlights the complex interplay between lung and gut microbiomes. Although DSM 17938 had no significant effect on bacterial taxa, it was noteworthy that SFL had lower LIS and IL-1β levels compared to SFC.

Conclusions: T cell-mediated inflammation in the lungs of Treg deficient SF mice is associated with gut and lung dysbiosis. DSM 17938 may reduce lung inflammation by modulating gut microbiota, influencing bacterial-associated metabolites, and ultimately influencing immune pathways. Future studies may focus on modulating microbiota to treat Treg-deficiency-associated pulmonary diseases.

Altered phospholipid biosynthesis drives hepatic steatosis in malnutrition

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Globally, malnutrition is responsible for 45% of deaths of children under the age of five. Malnutrition impairs gastrointestinal and metabolic functions resulting in dyslipidemia, nutrient malabsorption, and slow gut motility. In severely malnourished children, lipid accumulation in the liver results in steatosis. Steatosis is the most prevalent form of liver disease worldwide, with nearly 10% of children affected. Currently, there is no FDA-approved drug to treat steatosis in children or adults, and mechanisms by which malnutrition causes steatosis are poorly understood. Mouse models of steatosis suggest that impaired phospholipid metabolism alters lipid homeostasis and secretion. Rodents fed a choline-deficient or methionine-choline-deficient diet exhibit steatosis and altered quantities and ratios of phosphatidylcholine (PC) and phosphatidylethanolamine (PE). Disrupting PC and PE homeostasis impairs hepatic secretion of triglycerides by very low-density lipoproteins (VLDL). Therefore, I hypothesize that malnutrition causes hepatic lipid accumulation by altering phospholipid biosynthesis and reducing VLDL secretion. Our lab induces malnutrition by feeding weanling male and female C57BL/6 mice a low-protein, low-fat diet that is isocaloric to control diet. We previously reported that malnutrition reduces body weight and body length, with males more severely affected than females. To examine hepatic lipid accumulation, I stained flash-frozen liver sections with oil red O and quantified hepatic triglycerides via thin-layer chromatography. I used western blot to quantify the expression of key phospholipid biosynthesis enzymes, including Phosphatidylethanolamine N-methyltransferase (PEMT), phosphatidylserine decarboxylase (PISD), choline dehydrogenase (CHDH), and betaine-homocysteine S-methyltransferase (BHMT). Hepatic lipid accumulation and liver triglycerides were dramatically increased, and PEMT expression was markedly decreased, in both malnourished male and female mice. In contrast, expression of PISD, CHDH, and BHMT were reduced in malnourished males but not females. These results suggest that malnutrition impairs phospholipid biosynthesis in a sexually dimorphic manner. Preliminary serum lipoprotein profiling with high-performance liquid chromatography revealed that malnourished females have reduced VLDL in serum compared to controls. Together, these results suggest that malnutrition alters phospholipid biosynthesis and impairs VLDL secretion, leading to liver steatosis. Understanding the role that phospholipids play in malnutrition-induced steatosis allows for further exploration of therapeutics that may ameliorate or prevent steatosis in malnourished children.

Evaluating mechanisms of human norovirus gastroenteritis using human intestinal enteroids

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Human noroviruses (HuNoVs) are the leading cause of nonbacterial gastroenteritis worldwide and are associated with 19-21 million cases in the US annually. HuNoVs cause acute, self-limiting illness in immunocompetent individuals and chronic illness in some immunocompromised patients. The mechanisms by which HuNoVs cause diarrhea and/or vomiting are poorly defined.

Our previous work using patient biopsies and human intestinal enteroids (HIEs) showed that HuNoVs primarily infect enterocytes in the small intestine. However, two recent publications using jejunal biopsies from a 9-month-old patient and a rhesus macaque model showed the presence of HuNoV RNA and capsid protein VP1 in enteroendocrine cells (EECs). Upon stimulation, these gut neurohormonal cells signal to the enteric nervous system and activate brain centers involved in nausea and vomiting. We hypothesized that secretion of neuroactive hormones such as serotonin from infected EECs is a mechanism of HuNoV-associated vomiting. Since the number of EECs is low in adult HIEs, we used a genetically modified NGN3 line that can be induced to overexpress EECs to test our hypothesis. We also used two infant HIEs that naturally express higher numbers of EECs than adult HIEs.

GII.4 HuNoV replication as measured using RT-qPCR and immunofluorescence staining for VP1 was significantly lower in the induced NGN3 HIEs compared to the parental and uninduced lines. This could possibly be due to the low numbers of enterocytes in the induced HIE line. Further, we do not see any co-localization of VP1 with EEC markers in adult HIEs. Infection was not associated with increased secretion of serotonin in these HIEs. Increased secretion of serotonin was also not detected following infection of infant HIEs where there were sufficient numbers of enterocytes for robust infection. In on-going studies, we are examining whether other neuroactive hormones are produced following infection. Our work is critical to elucidate mechanisms of HuNoV-induced vomiting.

Prevalence of sucrase-isomaltase gene variants in people with and without IBS using the NIH/HGRI All-of-Us mega-database

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Irritable bowel syndromes (IBS) occur with great frequency in the US population based on Rome IV criteria. The etiology is thought to be multifactorial and has been associated with dysbiosis, GI motility disorders, anxiety, food triggers/intolerance infection, and more. IBS has been associated with intestinal mucosal brush-border disaccharidase deficiency and more than 40 sucrase-isomaltase (SI) mutations (Chr3q26.1) have been identified, but it is unclear which among them are not associated with loss of complete or partial gene product function and which less-common mutations contribute to a compound heterozygous (CMP_HT) condition. Helm et al. (PMID 27872184) reported on a multicenter cohort of only 1887 cases and controls and found that SI mutations were more common in patients than asymptomatic controls (p=0.074; OR=1.84). In the US, the frequency of SI recessive mutations is unknown and any relationship between SI mutations and IBS has been speculative. The ALL OF US (AOU) human genomic database (-DB) includes 45,388 clinical-grade sequences, with 77% of participants from demographic groups that are traditionally underrepresented in clinical research and contains electronic health record data from more than 287,000 individuals. AIM: to determine the frequency of several SI mutations found in the AOU-DB within the IBS cohort. METHODS: Non-affected and affected cohorts were stratified by ICD-9 or ICD-10 codes. Four common SI mutations were selected for study. Data analysis was extracted using Python and Hail, and McNemar's statistical test of proportions was used to compare groups and the genetic variant subgroups. Study of the other 40+ known variants was deferred at this time. RESULTS: This analysis found that the most common genetic variant was found at rs9290264 (p.Val15Phe). Among those affected, 4363/10745 (40.6%) had heterozygous genotypes, whereas 87481/234643 (37.3%) of those controls without IBS had the same genotype (p< .000001; OR: 8.1X). The frequency of CMP_HT for the SI-gene was greater for those reporting the diagnosis of IBS (n= 129/10745, 1.20%) when compared with those without the IBS diagnosis (n= 2023/234643, 0.86%). (P=0.000001; OR: 5.56X) Among the 4 other more common variants (Figure 2), two variants were shown to occur more frequently in those cases with IBS (rs121912615 or rs121912616) versus those without IBS (p=0.00013, 0.02). This was not the finding among those having mutations at rs79717168 or rs200451408 (p=0.31, 0.48). CONCLUSIONS: The association between compound heterozygous SI gene mutations and IBS was affirmed using these data. Most of the CMP_HT combinations have not yet been examined. It is probable that new variants to the SI genes will be identified that could explain the loss of SI function or partial gene product expression. These findings contribute to deeper understanding of the IBS condition.

Microbial therapeutics to prevent ExPEC colonization and disease

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Extraintestinal pathogenic Escherichia coli (ExPEC) are the leading cause of extraintestinal infections globally, predominantly affecting the blood, urinary tract, and brain. Rising morbidity and mortality rates are largely due to multidrug-resistant strains. Currently, no vaccines or non-antibiotic treatments exist, highlighting the urgent need for new therapeutic options. ExPEC behave as commensals while in the gastrointestinal tract (GIT) and only cause disease upon dissemination. To disseminate to non-intestinal sites and cause infection, ExPEC must first outcompete and then coexist with the native microbial community of the GIT. The necessity of establishment in the GIT as a precursor to extraintestinal infections, provides an opportunity to target ExPEC colonization as a preventative measure to disease. We predict that administration of microbial communities that are resistant to ExPEC colonization in the GIT will prevent ExPEC disseminated disease. To test this hypothesis, we are utilizing simplified microbial communities generated through dilution of human fecal samples. Using a continuous flow culturing technology developed in our laboratory, in vitro minibioreactor arrays (MBRAs), we can rapidly screen simplified microbial communities for inhibition of ExPEC colonization. To date, most simplified communities screened exhibit consistent susceptibility to ExPEC invasion. Currently, only two communities have shown resistance below this level of invasion and out of these communities, FS2C, exhibits the most consistent and robust resistance to ExPEC invasion. FS2C shows complete resistance to ExPEC invasion, preventing growth and eliminating ExPEC by day 3 in our MBRAs. To uncover the mechanisms behind this resistance, we have isolated all members of the FS2C community and are investigating their metabolic potential. We are also creating synthetic communities with different combinations of these members to identify the minimal community necessary to reproduce the resistant phenotype. Our ultimate goal is to develop a defined live microbial therapeutic capable of resisting ExPEC colonization in the GIT, thereby reducing the spread and impact of this deadly pathogen.

Evaluating human intestinal organoids as a model of very early onset inflammatory bowel disease

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Background: Very early onset inflammatory bowel disease (VEO-IBD), defined as IBD diagnosed in children under six years of age, is a chronic inflammatory disorder that primarily affects the intestines. Histologically, VEO-IBD epithelium shows pathological changes such as crypt apoptosis and small intestinal villous blunting, suggesting alterations in intestinal stem cell (ISC) function, as these cells reside at the base of intestinal crypts and are responsible for generating new epithelium via proliferation. As VEO-IBD is primarily a disorder of the immune system, it is unknown whether these histopathological findings are a characteristic of the diseased epithelium itself at a cellular and epigenetic level, or if the patient's immune system is responsible for inducing the epithelium to display these abnormalities. The epithelial abnormalities seen in VEO-IBD patients suggest that ISCs might by dysregulated in VEO-IBD, yet whether ISCs play a role in VEO-IBD pathophysiology has not yet been explored. **Aims:** Using human intestinal organoids (HIOs) derived from VEO-IBD patients, we investigated if VEO-IBD is associated with alterations in the biology of ISCs and if VEO-IBD HIOs display phenotypic changes characteristic of the disease. **Methods:** To address this question, we established 48 HIO lines from various small and large intestine biopsy sites from 14 VEO-IBD patients and 25 lines from eight control patients. We investigated aspects of cell proliferation, cell death, organoid growth, and barrier function to observe if pathological changes and changes involving ISC function were present in VEO-IBD HIOs ex vivo. **Results:** We identified increased downstream WNT activity, the major pathway that regulates ISC activity, in rectosigmoid VEO-IBD lines and increased proliferation in terminal ileum VEO-IBD HIOs following differentiation. We also found that VEO-IBD HIOs show reduced barrier function compared to controls as determined by transepithelial resistance experiments. **Conclusions:** Ultimately, our study provided insight that ISC function is indeed pathologically altered in VEO-IBD, providing an important future avenue for the exploration of VEO-IBD pathogenesis. Additionally, we discovered that VEO-IBD HIOs show reduced barrier function, suggesting that VEO-IBD HIOs may serve as an effective screening platform for the development of new therapeutics. These VEO-IBD HIOs will continue to be used to dissect the role of ISCs in VEO-IBD and to understand phenotypic differences in VEO-IBD epithelium.

This work was supported by grant 5T32GM13655403 from the NIH, the Intestinal Stem Cell Consortium grant U01 DK103168 from the NIH and NIDDK, and the Baylor College of Medicine Digestive Diseases Center, grant P30 DK56338 from the NIH and NIDDK.

Phenotype-informed clustering of genetic variants highlights germline heterogeneity in Crohn's disease

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Background: Crohn's disease (CD) is heritable, and genome-wide association studies (GWAS) have implicated many variants and dozens of genes in its pathogenesis. Phenotype-informed clustering of genetic variants has provided insights into germline genetic heterogeneity in other diseases, such as Type II DM[1] and polycystic ovarian syndrome (PCOS)[2]. Identified genetic clusters may help to identify orthogonal disease driving axes and genetic risk groups that contribute to subphenotypes of disease.

Methods: A *jxn* input matrix was created with genome-wide significant disease-associated SNPs (j) and genetically correlated trait Z-scores (n). Unsupervised consensus hierarchical clustering was used to identify SNP clusters. Pathway enrichment analysis of mapped genes for each cluster was used to identify differentially involved pathways. Next, cluster genomic risk scores (CGRSs) were created, similar to polygenic risk scores, in United Kingdom Biobank (UKBB) individual-level data. Each CGRS was calculated by multiplying the number of risk alleles by the log(OR) for a given variant, and then adding up the scores for each of the variants in that cluster. Finally, immune cell expression quantitative trait loci (eQTL) analysis (via the DICE database[3]) of variants in top quartile of alleles with allele frequency differences between 1st and 2nd line treated CD from the FinnGen database was used to highlight associated transcripts.

Results: Unsupervised consensus hierarchical clustering identified five SNP clusters in CD. Cluster 1 enriched for pathways including the defense response, cellular response to cytokine stimulus, and regulation of response to external stimulus, among others. Cluster 3 enriched for pathways involved in lymphocyte and T-cell activation, in addition to T-cell differentiation. Cluster 4 enriched for pathways involved in IL-23 signaling, IL-12 signaling, and the JAK-STAT signaling pathway, in addition to T-cell activation. Next, cluster genomic risk scores (CGRSs) were constructed for CD patients identified in UKBB data, with 33% of participants in the top decile for only one CGRS. Immune eQTL analysis of the alleles with the greatest allele frequency differences between 1st and 2nd line treated CD highlighted several significant associations in cluster 3 in disease-relevant immune cells, such as naïve CD4 and CD8 T-cells. Pathway enrichment analysis of the associated cluster 3 transcripts identified enrichment of pathways including linoleoyl-CoA desaturase activity, acyl-CoA desaturase activity, metabolism of alpha linoleic acid, and unsaturated fatty acid biosynthetic processes.

Conclusions: Phenotype-informed CD SNP clusters may functionally correspond to different parts of the immune system, and some patients may have higher genetic risk from a specific underlying SNP cluster. Finally, immune eQTL and pathway enrichment analysis highlights an association between cluster 3 variants and lipid metabolism dysregulation.

Revealing an anti-inflammatory role of pancreatic fibroblasts in acute pancreatitis in mice

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Background: Persistently activated pancreatic fibroblasts (PFs) produce excessive extracellular matrix, leading to pancreatic fibrosis in chronic pancreatitis and pancreatic cancer. However, their role in acute pancreatitis (AP) is not defined. To explore PFs' role in AP, our lab has recently utilized lineage tracing to characterize collagen-producing fibroblasts in AP mouse model and demonstrated PF activation and proliferation as the disease progresses. We hypothesize that PFs may be a critical player in AP pathogenesis. In this study, we further characterized Col1a2CreER^{tdTom} mice and studied the functional outcomes of PF depletion in AP using Col1a2CreER^{DTA} mice.

Methods: Col1a2CreER^{tdTom} mice were bred and used to characterize fibroblasts in several vital organs. These mice express tamoxifen (TAM)-inducible Cre recombinase with a Col1a2 promoter for fibroblast-specific targeting and a fluorescence reporter, tdTomato (tdTom). The mice received TAM and were euthanized 2 days later for organ collection. Fibroblasts in each organ were quantified via tdTom+ fluorescence. To deplete PFs, Col1a2CreER$^{diphtherial\ toxin\ A\ (DTA)}$ mice were bred and used. The mice received TAM for PF depletion and were then treated with cerulein (50 μg/kg, 7 hourly injections, ip) for AP induction. The mice were euthanized 17h after the last injection. The blood and pancreata were collected for respective serum amylase measurement and AP histopathological evaluation on edema, necrosis, and inflammation (scored 0-4 from no lesions to severe lesions). Total RNA was extracted from the pancreatic tissue and qPCR was conducted to evaluate inflammatory markers Il6 and Cox2.

Results: In Col1a2CreER^{tdTom} mice, the numbers of tdTom+ fibroblasts (% of total cells) in each organ range from high in lung (65.39±2.7%), skin (51.69±6.8%), and colon (32.87±5.4%), to medium in pancreas (11.54±1.4%), and to low in kidney (5.43±0.3%), liver (0.92±0.4%), and heart (4.56±1.9%). In Col1a2CreER^{DTA} mice, histopathological evaluation showed a higher inflammation score than the sibling controls (2.43±0.55 vs. 0.75±0.24, $p<0.05$), and qPCR demonstrated higher Il6 and Cox2 mRNA levels than the controls ($p<0.05$). There were no significant differences in amylase levels, pancreatic edema, and necrosis between Col1a2CreER^{DTA} mice and the controls.

Conclusions: Fibroblasts can be effectively tracked in multiple vital organs in Col1a2CreER^{Tom} mouse model, raising its potential use as a powerful tool to study the role of fibroblasts in these organ diseases. Depletion of PFs exacerbated AP inflammation in Col1a2CreER^{DTA} mice compared to the controls, suggesting that PFs may play an anti-inflammatory role in AP.

Urinary ammonium: a potential novel biomarker for diarrhea severity

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Introduction: Diarrhea is a leading cause of outpatient gastroenterology visits, yet its severity is challenging to quantify due to the subjectivity of self-reported symptoms. Laboratory markers such as hypokalemia, elevated creatinine, and low serum bicarbonate are often altered in severe cases but are less applicable in outpatients with milder disease. Urinary ammonium, a key physiological marker of metabolic acidosis from diarrhea-induced bicarbonate loss, remains underexplored as an objective biomarker of diarrhea severity.

Methods: We investigated spot urinary ammonium as a potential biomarker of diarrhea severity in ulcerative colitis (UC) patients. Urinary ammonium levels were measured in 10 patients with active UC (PRO-2 ≥ 3) and 10 patients in remission (PRO-2 = 0). Exclusion criteria included serum creatinine >1.5 mg/dL, corticosteroid therapy, and acute severe UC. Spot urine samples were analyzed for ammonium concentration, and bowel movement data, basic metabolic panel, and fecal calprotectin levels were recorded. Statistical analyses included Wilcoxon rank-sum tests and Spearman correlation for associations between urinary ammonium and bowel movements.

Results: UC patients with active disease reported had an average of 7.1 bowel movements per day versus 1.9 in remission, with corresponding Bristol stool scores of 5.8 and 4.1, respectively. No significant differences between serum potassium, creatinine, or bicarbonate were noted between study groups. Patients with active UC demonstrated significantly elevated urinary ammonium levels (mean: 32.0 mmol/L, SD: 18.7) compared to those in remission (mean: 16.5 mmol/L, SD: 5.5; p = 0.03). Urinary ammonium correlated significantly with average reported daily bowel movements (r=0.47, p=0.04). These findings persisted independent of dietary acid load, as measured by urine sulfate.

Conclusion: This study provides the first systematic evaluation of urinary ammonium as a biomarker for diarrhea severity. Urinary ammonium offers a physiologically robust objective metric for diarrhea-induced bicarbonate loss. Our findings suggest that urinary ammonium could guide clinical evaluation of chronic diarrhea and its associated severity. Further research is warranted to validate this biomarker and explore its diagnostic utility in broader clinical settings with various diarrhea etiologies.

PRO-2: UC patient reported outcome consisting of stool frequency and rectal bleeding

Malnutrition Impairs Krebs Cycle Function and Bile Acid Biosynthesis

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Background: Bile acids (BAs) are cholesterol derivatives synthesized in hepatocytes. BAs play key roles in child growth by emulsifying dietary fats in the intestinal lumen and by acting as signaling molecules that regulate metabolic pathways throughout the body. The rate-determining enzyme in BA synthesis is CYP7A1. Its essential cofactor is heme, which is synthesized in 8 enzymatic steps starting with the Krebs cycle product succinyl-CoA. BA synthesis is markedly suppressed in malnutrition by unknown mechanisms. We sought to determine whether impaired Krebs cycle function and depletion of hepatocyte heme causes decreased BA biosynthesis in a mouse model of malnutrition.

Methods: Weanling C57BL/6 mice were fed a low-protein, low-fat diet to induce malnutrition or were maintained on isocaloric control chow. At 8 weeks of life, livers were harvested for heme quantification and western blots, and primary mouse hepatocytes were isolated for metabolomic analyses. Total BA quantities were measured by ELISA.

Results: The total BA pool was reduced by 50% in malnourished mice, but their livers contained normal CYP7A1 expression and 2-fold increased levels of cholesterol. These findings suggest impaired CYP7A1 activity, and this was confirmed with a mass spectrometry-based enzyme activity assay. Congruent with decreased CYP7A1 activity, malnutrition reduced hepatocyte heme by 44%. Decreased heme was not due to altered iron storage, based on normal expression of ferritin and iron regulatory proteins. Metabolomic analyses of malnourished livers revealed evidence of Krebs cycle dysfunction including a 2.7-fold buildup of α-ketoglutarate, a Krebs cycle metabolite, and a 35% reduction in its downstream product succinyl-CoA, the starting substrate for heme biosynthesis.

Conclusions: Malnourished hepatocytes exhibit Krebs cycle dysfunction evidenced by reduced conversion of α-ketoglutarate to succinyl-CoA. Krebs cycle dysfunction might be responsible for decreased hepatocyte heme, decreased CYP7A1 activity, and decreased BA biosynthesis.

Unraveling the progenitors of the neosquamous epithelium following radiofrequency ablation in Barrett's Esophagus patients using spatial transcriptomics

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Barrett's Esophagus (BE), a precursor of esophageal adenocarcinoma, develops from chronic epithelial damage caused by gastrointestinal reflux, where normal squamous epithelium is replaced by columnar intestinal metaplasia. The cellular origin of BE remains controversial, with various progenitors proposed, including basal cells of the squamous epithelium, cells within the ducts of esophageal submucosal glands, cells from the proximal stomach, and specialized populations of cells at the squamo-columnar junction (transitional basal cells and residual embryonic cells).

Radiofrequency ablation (RFA) is commonly performed in high-risk patients to reduce the risk of BE progressing to cancer. RFA creates a wound that typically heals with squamous epithelium; however, the mechanisms driving post-RFA repair and the cellular source of the neosquamous epithelium remain poorly understood. Recent studies suggests that re-epithelialization may originate from squamous cells at the proximal wound edge or from squamous islands emerging from ducts of the underlying esophageal submucosal glands. However, the specific progenitors involved in this repair process have not been fully characterized.

To investigate the regeneration process and the origin of the neosquamous epithelium following RFA, we performed spatial transcriptomic analyses on endoscopic biopsies from BE patients collected at baseline (pre-RFA) and at 1, 2, and 4 weeks post-RFA. Our results revealed significant temporal changes in cell populations during the healing process. At baseline, the squamous epithelium is characterized by the expression of *TP63* and *KRT5*. By 1 and 2 weeks post-RFA, we observed the re-emergence of p63+ KRT5+ cells. By 4 weeks, a neosquamous epithelium had formed, exhibiting expression of both *TP63* and *KRT5*, as well as the BE marker, *KRT7*. We also observed an increase in transitional basal cells (p63+ KRT5+ KRT7+) at 4 weeks, suggesting that this population may serve as progenitors for the neosquamous epithelium during the repair process. These findings enhance our understanding of the cellular dynamics involved in epithelial regeneration after RFA in BE patients and could inform strategies to minimize BE recurrence and improve treatment outcomes.

Characterizing enteric neuronal subtypes in pediatric human intestine using a novel 3D imaging technique

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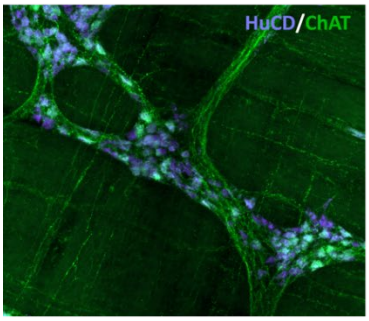
Introduction: Short bowel syndrome (SBS) is the leading cause of pediatric intestinal failure (IF). Human intestinal organoids (HIOs) can generate tissue-engineered intestine that can potentially cure IF. However, HIOs lack an enteric nervous system (ENS), which limits their therapeutic application. Our lab and others have developed protocols to innervate HIOs; yet, ENS spatial development has not been rigorously investigated. Confirmation of proper ENS development is crucial to therapeutic tissue-engineered intestine generation. Traditional 2D imaging analysis is limited; therefore, our lab utilizes a novel 3D imaging technique to visualize and quantify the ENS. We have previously demonstrated feasible and reliable quantification of enteric neurons and glia in pediatric human small intestine (hSI) and HIOs. In this study, we aim to extend the application of this method to quantification of enteric neuronal subtypes, such as inhibitory and excitatory neurons in pediatric hSI. **Methods:** Pediatric hSI tissue was acquired through our IRB-approved biobank. Intestinal tissues were pinned flat, fixed, immuno-stained with pan-neuronal marker, HuC/D, and enteral neuronal subtype markers nitric oxide synthase 1 (NOS1) to label inhibitory neurons and choline acetyltransferase (ChAT) to label excitatory neurons in the myenteric plexus, and then imaged using confocal microscopy at 20x and 1 μM Z increments. Myenteric plexus volumes were determined using Imaris software. Enteric neurons and neuronal subtypes were counted manually using cell counter plugin. The percent NOS1 positive and ChAT positive per total neurons per ganglionated area were calculated using cell counts (mean±SEM). **Results:** In pediatric human ileum, the myenteric plexus ganglionated volume demonstrated 1,892,552 ± 309,121 of 2,307,736 ± 254549 ChAT positive neurons/mm^3 (n=1), representing 62.95 ± 5.87% of the total myenteric plexus neurons per ganglionated volume (Figure 1). In pediatric human ileum, the myenteric plexus ganglionated volume demonstrated 2,212,320 ± 75,289 of 6,268,471 ± 466,859 NOS1 positive neurons/mm^3 (n=3), representing 41.67 ± 2.5% of the total myenteric plexus neurons per ganglionated volume. NOS1 positive neuron percentages significantly differed between pediatric hSI samples 1054 and 1063 (1054; 36.84 ± 2.312, 1059; 45.44 ± 2.492, p value=0.03) (Figure 2). **Conclusion:** This study demonstrates the feasibility of a novel 3D imaging method to quantify enteric neuronal subtypes in the pediatric hSI. Future studies will apply this technique to analyze neuronal subtypes in HIOs at various developmental stages, aiming to optimize ENS development over time by ensuring the presence of appropriate enteric neuronal subtypes, determining their proportional representation, and assessing their morphological and spatial similarity to hSI.



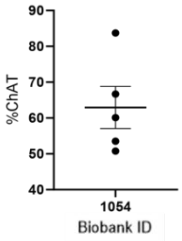
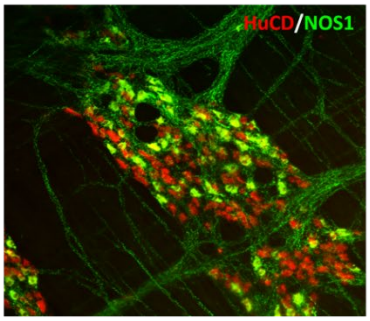


Figure 1



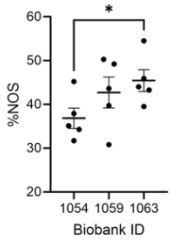


Figure 2

Decoding Human Norovirus Tropism via Single-Cell RNA Analysis

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Human noroviruses (HuNoVs) are the leading viral cause of acute gastroenteritis worldwide in all age groups. The intestinal epithelium is considered the primary target for infection and viral replication. While several previous investigations have demonstrated that enterocytes are the predominant cell type susceptible to HuNoV infection, one recent study showed that enteroendocrine cells are another permissive cell type for HuNoV infection suggesting that HuNoV may have yet unexplored cellular targets. Notably, these studies used biopsies from immunocompromised transplant patients, leaving the question of HuNoV cellular targets in immunocompetent patients unanswered.

Developing tissue stem cell-derived organoids (HIOs) as an ex-vivo model of HuNoV cultivation has provided tremendous insights into HuNoV tropism and pathogenesis. To delineate detailed HuNoV tropism, we infected HIOs with a globally dominant GII.4 HuNoV strain and used single-cell RNA sequencing (scRNA-Seq) technology to comprehensively profile transcriptomics of 69,536 individual cells. scRNA analysis revealed an increase of cells expressing the tuft cell specification transcriptional factor *POU2F3*, and the colocalization of HuNoV transcripts in some $POU2F3^{+}$ cells. Tuft cells are rare chemosensory cells in the intestinal epithelium and are best characterized by their role in activating type 2 immunity against intestinal helminths and protists infection in mice. Murine tuft cells are the target of a persistent murine norovirus strain, but the role of human tuft cells in HuNoV infections remains unknown. IL-32 gene, a pro-inflammatory cytokine, is one of the top differentially expressed genes in $POU2F3^{+}$ cells. IL-32 has been shown to inhibit the replication of multiple viruses and modulate anti-viral responses by stimulating the production of type III interferon. Overall, our scRNA results indicate that tuft cells play a potential anti-viral role during GII.4 infection, possibly through IL-32. Future in-vitro studies will be using the POU2F3-inducible HIOs to explore the role of tuft cells during GII.4 infection.

Acknowledgments: This research was supported by BCRC funding (U19 AI116497) and PPG funding (P01 AI57788).

Examining the interplay between the gut microbiome and intestinal epithelium after radiation

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Exposure to radiation, whether from radiotherapy used in cancer treatment or cosmic radiation astronauts experience in space, causes significant health problems. One of the most radiation-sensitive organs in the body is the intestinal tract, primarily due to the high turnover rate of gut epithelium. Radiation damages the DNA of intestinal stem cells that are essential for intestinal renewal and alters the gut microbiome, which is intimately linked to many aspects of human health. Recent evidence has demonstrated that the presence of a healthy gut microbiome increases tolerance to radiation and mitigates radiation-induced side effects of cancer patients, suggesting that there is a protective effect of the microbiome on the gastrointestinal tract. This research aims to understand the underlying biological response of the intestinal epithelium and its microbiome to radiation to create new therapeutics that mitigate the detrimental impacts on host health. To accomplish this goal, we used continuous flow minibioreactor arrays (MBRAs) to stabilize two independent human fecal microbiomes and define daily fluctuations in community members in response to differing doses of proton radiation. We are characterizing the changes this resulting gut microbiome has on survival and proliferation of human intestinal organoids. Together, this work will help us understand the underlying mechanisms by which the microbiome maintains health of the human intestinal epithelium and will aid in development of radioprotectants for cancer patients and astronauts alike.

Yap1 is essential for paligenosis stage 1 and stage 2 transition

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We are investigating the initiation and progression of precursor metaplasias in the stomach to elucidate the mechanisms underlying the origins of gastric cancer. Chief cells in the stomach transform into proliferative spasmolytic polypeptide-expressing metaplasia (SPEM) cells through a recently described three-stage process known as paligenosis, which involves dynamic mTORC1 regulation. In stage 1, chief cells upregulate autophagic activity while mTORC1 activity decreases. In stage 2, SPEM genes are expressed. In stage 3, mTORC1 activity increases, prompting previously quiescent cells to re-enter the cell cycle. Dysregulated paligenosis allows mature, nondividing cells to re-enter the cell cycle despite genomic abnormalities, making paligenosis a potential initiator of gastrointestinal cancers, such as gastric cancer and pancreatic cancer. Although the Hippo pathway is well known for its role in regulating cell proliferation, differentiation, and autophagy through its main effectors YAP1/TAZ, its involvement in metaplasia and paligenosis remains unclear. We hypothesize that the upregulation of YAP1 activity is sufficient and necessary for the paligenosis stage 1 and 2 transitions.

Our study showed the accumulation of nuclear YAP1 during paligenosis stages 1 and 2, resulting in the upregulated expression of canonical transcriptional targets. Despite this, there was no significant change in total YAP1 protein levels detected by proteomics or western blot. Single-cell RNA sequencing identified alterations in *Yap1* downstream target gene mRNAs in acute SPEM cells, indicating the activation of YAP1 in paligenosis potentially via dephosphorylation. Our previous research highlighted the necessity of autophagy for the initiation of paligenosis. Interestingly, no YAP1 activation was detected in the early stage of paligenosis in $Atf3^{-/-}$ autophagy-deficient mice. Our multi-omic data, corroborated by western blot and immunohistochemistry results, suggested a non-canonical Hippo pathway kinase-dependent modulation of YAP1 localization in an autophagy-dependent manner. Paligenosis was impeded upon $Mist1^{CreERT2/+}; ROSA26^{LSL\text{-}Ai9/+}; Yap1^{flox/flox}$; or $Mist1^{CreERT2/+}; ROSA26^{LSL\text{-}Ai9/+}; Taz^{flox/flox}$; or $Mist1^{CreERT2/+}; ROSA26^{LSL\text{-}Ai9/+}; Yap1^{flox/flox}$; $Taz^{flox/flox}$ mice models, leading to the failure of chief cells to undergo paligenosis, similar to what was observed in $Atf3^{-/-}$ autophagy-deficient mice. In contrast, the activation of endogenous YAP1 levels in chief cells by NF2 deletion in $Mist1^{CreERT2/+}; ROSA26^{LSL\text{-}Ai9/+}; Nf2^{flox/flox}$ mice was sufficient to induce SPEM. Induction of mitosis in chief cells was observed upon overexpression of YAP1-S127A, a constitutively active mutant form of YAP1, via low-dose tamoxifen treatment in $Mist1^{CreERT2/+}; ROSA26^{LSL\text{-}rtTA.IRES.EGFP/+}; tetO^{Yap1S127A}$ mice induced by doxycycline. Our multi-omic data indicated that this intricate regulation involves autophagy in stage 1 and implicates SMAD2/3, key effectors of TGF-β signaling, as plausible downstream targets. Additionally, we found that YAP1 activation could be associated with the upregulation of genes related to allograft rejection, apoptosis, and E2F targets.

Our findings emphasize the vital role of YAP1 activity in paligenosis. YAP1 is a key factor activated in an autophagy-dependent manner, promoting the switch between paligenosis stages 1 and 2. We provide a comprehensive description of upstream kinase regulation and downstream targets associated with YAP1 regulation during the paligenosis process. These insights contribute to a deeper understanding of gastric cancer initiation and offer potential avenues for targeted therapeutic interventions.

Sex dimorphic protection by neutrophil-derived COX-2 against hepatic ischemic-reperfusion injury

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Hepatic ischemia-reperfusion (IR) injury is a major complication of liver transplantation and surgery, contributing to graft dysfunction and poor outcomes. Single-cell RNA sequencing revealed that Ptgs2, which encodes cyclooxygenase (COX)-2, was elevated and predominantly expressed by neutrophils in the liver after IR injury. Interestingly, deletion of Ptgs2 specifically in neutrophils exacerbated hepatic IR injury, a phenomenon observed only in female but not male mice. Ovariectomy and estrogen supplementation experiments further validated an estrogen-dependent protective function of Ptgs+ neutrophils. Mechanistic studies demonstrated that neutrophils from female mice expressed higher levels of COX-2 and produce higher amount of prostacyclin (PGI_2) than neutrophils from male mice. Experiments of administrating a PGI_2 analogs or a PGI_2 receptor inhibitor revealed the protective role of PGI_2, through upregulating hemooxygenase (HO)-1 in liver IR injury. In sum, we uncovered a previously unrecognized sex-dimorphic hepato-protective function of neutrophils, through the COX-2/PGI_2/HO-1 axis. These findings provide a more nuanced mechanistic insight into hepatic IR injury and potentially offer novel therapeutic strategies.

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