DDC
Texas Medical Center Digestive Diseases Center

12TH ANNUAL
Frontiers in Digestive Diseases Symposium

THE TMC DIGESTIVE DISEASES CENTER PRESENTS

Phages, Viruses & Digestive Diseases

VIRTUAL SYMPOSIUM

SATURDAY, MARCH 6, 2021

PROVIDED BY TEXAS CHILDREN'S HOSPITAL

Target Audience: physicians, fellows, residents, researchers and other health care providers who are interested in digestive diseases

Educational Objectives: At the conclusion of this live activity, participants should be better able to identify phages and viruses related to GI infection and injury, apply best practices and treatments for these infections, identify opportunities to apply this knowledge to the detection of these infections, and interpret the current research concerning phages, viruses, and digestive diseases.

Accreditation / Credit Designation: Texas Children's Hospital (TCH) is accredited by the Texas Medical Association to provide continuing medical education for physicians. Texas Children's Hospital designates this live educational activity for a maximum of *4.5 AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with their participation.

Texas Children's Hospital®

About the Texas Medical Center Digestive Diseases Center (DDC)

The Texas Medical Center Digestive Diseases Center (DDC), promotes cutting-edge, translational collaborative research in digestive diseases between basic science and clinical areas, develops new projects, nurtures new investigators, and provides educational and consultation activities.

The DDC is a federally funded Digestive Diseases Research Core Center (NIH P30DK056338) and serves basic and clinical scientists at institutions within the Texas Medical Center. Membership in the DDC is open to clinicians and researchers at Baylor College of Medicine, The University of Texas Health Science Center, MD Anderson Cancer Center, and their affiliated institutions who have an interest in GI Research. Membership in the DDC has many benefits, including subsidized services, funding opportunities, and a network of over 150 clinicians and researchers in the field of digestive diseases.

The DDC supports three basic science cores: Cellular and Molecular Morphology, Functional Genomics and Microbiome, Gastrointestinal Experimental Module Systems; and one clinical core: Study Design and Clinical Research. The DDC has strengths in the areas of gastrointestinal development, infection, and injury.

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

Contents

General Information

Symposium Program

DDC Frontiers in Digestive Diseases Virtual Symposium Program

"Phages, Viruses, and Digestive Diseases"

March 6, 2021 ◆ 8:00 am CST – 2:00 pm CST

SESSION 1 **8:00 am – 8:10 am**

Welcome Remarks

Hashem B. El-Serag, M.D., M.P.H.
Director
TMC Digestive Diseases Center

8:10 am – 8:50 am

"Emerging Human Coronaviruses: One Health Perspectives from Animal Coronaviruses"

Linda J. Saif, Ph.D.
Distinguished University Professor
Veterinary Preventative Medicine
Ohio State University
Columbus, Ohio

8:50 am – 9:30 am

"Gastrointestinal tract in the pathogenesis of COVID-19 infection"

Saurabh Mehandru, M.D.
Associate Professor
Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
New York, NY

9:30 am – 10:00 am

"A Conserved, Cellular Program for Regeneration and Tumorigenesis Goes Viral"

Jason Mills, M.D., Ph.D.
Professor
Department of Medicine
Baylor College of Medicine
Houston, Texas

10:00 am – 10:40 am

"Chronic Norovirus Infection in Immunocompromised Patients"

Kim Y. Green, Ph.D.
Senior Investigator
NIAD / DIR
National Institute of Health
Bethesda, Maryland

SESSION 2 **10:45 am – 11:15 am**

"DGAT1 Degradation: A New Mechanism of Rotavirus Diarrhea"

Sue Crawford, Ph.D.
Assistant Professor (2015 DDC Pilot Awardee)
Virology & Microbiology
Baylor College of Medicine
Houston, Texas

11:15 am – 11:45 am

"Viruses as Medicines"

Anthony Maresso, Ph.D.
Associate Professor (2012 DDC Pilot Awardee)
Virology & Microbiology
Baylor College of Medicine
Houston, Texas

11:45 am – 12:25 pm

"The gut virome and its role in microbiome structure and function"

Colin Hill, Ph.D.
Professor of Microbial Food Safety
School of Microbiology
University College Cork
Ireland

12:25 pm – 12:55 pm

"SARS-CoV-2 Vaccines: Successes and Challenges"

Hana M. El Sahly, M.D.
Associate Professor
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, Texas

12:55 pm – 1:05 pm

Poster Award and Concluding Remarks

Doug Burrin, Ph.D.
Pilot / Feasibility Program Director
TMC Digestive Diseases Center

1:10 pm – 1:55 pm

Virtual Breakout Sessions

Linda Saif, Ph.D.……Session 1
Jason Mills, M.D.,Ph.D……..Session 2
Saurabh Mehandru, M.D……..Session 3
Colin Hill, Ph.D……Session 4
Kim Green, Ph.D…….Session 5

2:00 pm – 3:00 pm

Virtual Poster Session

The Virtual Poster Session will remain open throughout the entire symposium. We have asked submitters to remain available between 2 pm – 3 pm for live chats; however, you can request meetings, leave feedback, and send messages at any time during and after the event.

Texas Children's Hospital

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Directly provided by Texas Children's Hospital
Hosted by the Texas Medical Center Digestive Diseases Center
Saturday, March 6, 2021 | 8:00 am – 2:00pm | Virtual Symposium

"Emerging Human Coronaviruses: One Health Perspectives from Animal Coronaviruses"
Linda J. Saif, Ph.D., Distinguished Professor, Veterinary Preventative Medicine, Ohio State University

"Gastrointestinal tract in the pathogenesis of COVID-19 infection"
Saurabh Mehandru, M.D., Associate Professor, Gastroenterology, Icahn School of Medicine at Mount Sinai

"A Conserved, Cellular Program for Regeneration and Tumorigenesis Goes Viral"
Jason Mills, M.D., Ph.D., Professor, Department of Medicine, Baylor College of Medicine

"Chronic Norovirus Infection in Immunocompromised Patients"
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"DGAT1 Degradation: A New Mechanism of Rotavirus Diarrhea"
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EDUCATIONAL OBJECTIVES

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- Identify phages and viruses related to GI infection and injury.
- Apply best practices and treatments for these infections.
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- Interpret the current research concerning phages, viruses, and digestive diseases.

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DISCLOSURE

Saurabh Mehandru, M.D., provides research support to Takeda Pharmaceutical and consulting services for Takeda Pharmaceutical, Morphic and GSR. Mary K. Estes, Ph.D., provides research support and consulting services to Takeda Pharmaceutical and holds intellectual property for patents relating to human norovirus. Other speakers listed above have reported no relationships with proprietary entities related to the content of this activity. Persons involved in the planning of this activity have reported no relevant financial relationships with any commercial interest.

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Speakers

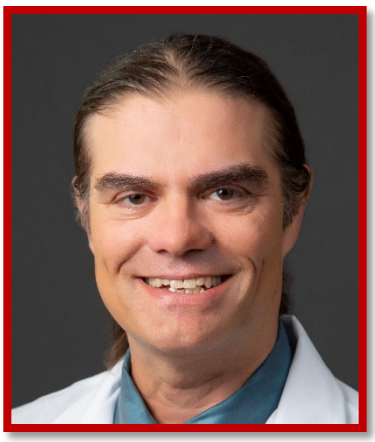
Dr. Linda J. Saif is a Distinguished University Professor at The Ohio State University (OSU) in the Food Animal Health Research Program (CFAES, OARDC) and the Veterinary Preventive Medicine Department (CVM, OSU). She is a virologist and immunologist, whose research focuses on comparative aspects of enteric and respiratory viral infections (coronaviruses, rotaviruses and caliciviruses) of food animals and humans. Her lab studies mucosal immunity and vaccine development and is currently focusing on the impact of malnutrition and micronutrient deficiencies (vitamin A) on vaccines and interactions of probiotics and the gut microbiota with the neonatal immune system, vaccines and viral pathogenesis. Dr. Saif's coronavirus research spans 4 decades and includes her MS and PhD research on swine coronaviruses, immunity and vaccines.

Dr. Saif is known nationally and internationally for her work on enteric and respiratory viruses (rotaviruses, caliciviruses and coronaviruses) that affect food producing animals, wildlife, and humans [Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS)] and their zoonotic potential and mechanisms of interspecies transmission. Dr. Saif was an advisor to the WHO and CDC during the 2003 SARS outbreak and her laboratory is a WHO International Reference Lab for Animal coronaviruses in the SARS network. She was an advisor to the Ministry of Agriculture in Saudi Arabia on MERS in camels and control strategies. She is a member of the US National Academy of Sciences since 2003. During the COVID-19 pandemic, she is providing One Health expertise about the SARS-CoV-2, including diagnostics, interspecies transmission, vaccines and control strategies. Dr. Saif holds 5 US/foreign patents and has authored or coauthored over 400 referred journal publications and 78 book chapters pertaining to her research.

Dr. Saurabh Mehandru is a physician-scientist who straddles clinical gastroenterology and laboratory-based investigation. He completed his residency training in Internal Medicine at the New York University School of Medicine where he also served as Chief Resident. He received subspecialty training in Gastroenterology at The Icahn School of Medicine at Mount Sinai. For his laboratory training, Dr. Mehandru did two post-doctoral fellowships at the Rockefeller University, first working in the Laboratory of Dr. David Ho (with Dr. Martin Markowitz) and then in the Laboratory of Dr. Ralph Steinman, Nobel Laureate in Physiology or Medicine, 2011.

Dr. Mehandru serves as an Associate Professor of Gastroenterology And Associate Chief of Gastroenterology Research at the Icahn School of Medicine at Mount Sinai, where he also leads an NIH-funded laboratory of Mucosal Immunology. Dr. Mehandru's research interests include mucosal trafficking and the host-microbial interface during health and disease.

Dr. Jason Mills is currently a Professor of Medicine at the University of Washington School of Medicine in St. Louis. Dr. Mills be joining the faculty at Baylor College of Medicine in April 2021. He was trained as a human pathologist and cell and developmental biologist.



His research has focused on how stem cells give rise to mature, functional cells in homeostasis and how these processes are reversed during regeneration and tumorigenesis, especially as induced by pathogens. Dr. Mills recieved his M.D., Ph.D. in Cell Biology from the University of Pennsylvania. He has led several translational efforts, including clinical trials, to use his ongoing research of the study of paligenosis to better prevent or treat tumors.

Dr. Kim Y. Green specializes in the study of viral diarrheal diseases. After recruitment to the Laboratory of Infectious Disease (LID) rotavirus vaccine program led by Dr. Albert Kapikian in NIAID as a postdoctoral fellow, Dr. Green was asked to investigate the role of other potentially important viruses in human gastrointestinal illness. Her early work helped establish the major role of the noroviruses in acute gastroenteritis and their molecular epidemiology.

Since then, Dr. Green and her team in the Caliciviruses Section of LID have used a multidisciplinary approach to investigate basic features of norovirus molecular biology, pathogenesis, and immunity relating to the development of vaccines and therapeutics. In tandem with basic research, collaborative efforts are underway to translate these findings to the clinic in order to lessen the norovirus disease burden in patients with severe disease. Dr. Green was trained as a virologist and received her Ph.D. in Microbiology and Immunology from the University of Tennessee Center for Health Sciences in Memphis, Tennessee in 1986.

Dr. Sue Crawford is an Assistant Professor at Baylor. Her research goals are to gain mechanistic insight into how infectious diseases pose significant risks for human health. A better understanding of the mechanisms of how pathogens exploit cellular pathways for invasion and replication as well as the mechanisms that host cells mount to fend off infections, are key to diagnosis, treatment and prevention of infection and disease spread. She uses multi-omics approaches to study host-pathogen interactions and to identify biological pathways that represent anti- and pro-pathogenic responses. In her current research, she is interrogating rotavirus interactions with stem cell-derived intestinal organoids to study mechanisms of rotavirus-mediated pathophysiology.

Rotavirus co-opts and manipulates many cellular pathways including calcium homeostasis, intracellular membranes, cellular trafficking, autophagy and lipid metabolism. Rotavirus induces the formation of cellular lipid droplets that colocalize with sites of rotavirus replication and

immature particle assembly in the cytoplasm. Despite years of study, the site of origin, the mechanisms, and the machinery involved in lipid droplet formation remain poorly understood. Thus, rotavirus is an excellent model to dissect the cellular process of lipid droplet formation and determine how rotavirus induces and usurps lipid droplet biogenesis to form cytoplasmic platforms for virus replication. In addition to rotavirus, other pathogens such as enteroviruses and HIV exploit normal cellular pathways or processes such as autophagy or lipid metabolism. Defining common cellular pathways pathogens exploit and require for replication is expected to aid in the development of interventions that target cellular pathways to combat pathogens.

Dr. Anthony William Maresso is Associate Professor of Molecular Virology and Microbiology at Baylor College of Medicine. His research program spans the range of vaccine development, the molecular basis of bacterial virulence, biomimetics for infectious disease models, mechanisms of mutagenesis, and evolvable antibacterials. He is the recipient of numerous R01, U19, and R21 NIAID grants, has published greater than 50 original peer reviewed articles, and is the author of the textbook "Bacterial Virulence: A Conceptual Primer". He also founded TAILOR LABS, a BCM initiative engaged in developing phage for use in antibiotic-resistant infections.

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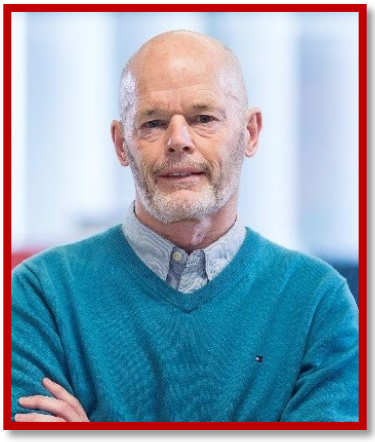

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Dr. El Sahly received her medical degree from the American University of Beirut, School of Medicine and post graduate training from University of Connecticut and Baylor College of Medicine. Her research interests include clinical vaccine development.

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Fungi: friend or foe? A mycobiome evaluation in children with autism and gastrointestinal symptoms

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Objective: Correlations have been made between GI symptoms and ASD severity, and the presence of gut inflammation and intestinal dysbiosis have been reported. There is limited evidence that Candida species are more prevalent in children with ASD, although many parents believe that their children may benefit from antifungal therapy. The objective of this study is to explore the potential differences in the gut mycobiome of children with ASD compared to neurotypical children

Study design: We enrolled 20 children with ASD and GI symptoms (ASD+GI), 10 children with ASD but no gastrointestinal symptoms (ASD-GI), and 20 neurotypical children (NT) of similar age. Fecal mycobiome taxa were analyzed from stool using ITS sequencing; gastrointestinal symptoms with the GI Severity Index (GSI); behavioral symptoms with the Social Responsiveness Scale -2 (SRS-2); and inflammation/immunity with serum dectin-1 and fecal calprotectin by ELISA.

Results: Neither the abundance of total fungi nor the number of fungal species (alpha diversity) differed between groups. Of the samples with identifiable fungi, Candida spp. were present in 4 of 19 (21%) ASD+GI, in 4 of 9 (44%) ASD-GI, and in 4 of 16 (25%) NT controls (overall p=0.42). Candida spp. did not correlate with increased behavioral scores or GI symptoms (p=0.38, p=0.5, respectively). Fecal calprotectin was normal in all but one child with ASD. Also, there was no significant difference in serum dectin-1 levels, suggesting no increased fungal immunity in children with ASD.

Conclusion: Our data suggest that fungi are present at normal levels in the stool of children with ASD, are not associated with gut inflammation, and may be commensal in nature.

Development of Small Intestinal Cell Engraftment in Mice

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Background & Aims: The replacement of diseased epithelial cells with healthy cells in the small intestine (SI) can be a radical treatment for several types of untreatable patients with epithelial dysfunction. Additionally, this replacement method may make it possible to establish new models of SI diseases with or without known etiology for understanding its pathophysiology and finding new therapeutic targets. However, there is no report regarding the functional/therapeutic replacement of SI epithelium with healthy or diseased SI cells in humans or animals. Here we aimed to create an innovative replacement method for the engraftment of SI organoids (SIOs) into the mouse SI.

Methods: The lumen of SI in wild-type mice was treated with ethylenediaminetetraacetic acid (EDTA) to remove the epithelium. After EDTA treatment, GFP-expressing normal SIOs were injected into the lumen of SI in wild-type mice, and their engraftment was verified histologically.

Results: The epithelial cells, but not stromal cells, in SI mucosa were peeled off by EDTA treatment. In addition, the injected GFP-expressing normal SIOs were engrafted into SI mucosa 3 months after injection, covering the area that lacked epithelium as a result of the introduced damage in recipient mice.

Conclusions: In preliminary studies, we established an orthotopic functional engraftment method for SIOs. Our results suggest that cultured SIOs might be a source of cells for replacement of SI epithelial cells or developing mouse models of its diseases.

Future plans: We will inject normal or diseased SIOs into the SI mucosa of wild-type or immunodeficient mice and investigate whether our engraftment can be a new therapeutic method and useful to develop novel mouse models for SI diseases.

Exercise-Induced Myokines as a Therapeutic Agent Against Colorectal Study: Developing MechanisticInsights

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Introduction: Exercise (physical activity) is shown to decrease CRC mortality. While the mechanisms are undoubtedly pleotropic, we have focused on the role of cytokines secreted by contracting muscles (termed "myokines"). However, given the complexity of the myokinome (~3000 molecules) and the potential of molecular interplay, identify the optimal candidates is challenging. In order to address this issue, we have developed a novel cell culture platform where we electrically contract mouse myotubules (C2C12 cells) to mimic exercise and use conditioned media to apply to CRC cells. In this study, we evaluate the impact of myokines on CRC gene expression in order to elucidate the molecular pathways involved in the anti-neoplastic effect of exercise.

Methods: Conditioned medium containing myokines was generated using C2C12 multinucleated myotubule contraction protocol. Differentiation of C2C12 cells generated myotubules which were stimulated with carbon electrodes using low-frequency electric pulse stimulation. The cells were stimulated in Krebs Ringer buffer and unstimulated control cells were left in buffer without electric impulse. After contraction (generally 6-8 h) buffer was filtered using 0.22 micron filter and centrifuged in Amicon Ultra centrifugal tubes (10KD molecular weight cut off fractions). *In vitro* produced myokines effect was studied on HT29 colon cancer cell line after 4 h and 24 hr treatment. Microarray based transcriptome profiling was performed using unstimulated control and stimulated myokine concentrated medium. Differentially expressed genes and pathway regulatory networks were identified. Enzyme- linked immunosorbent assay was performed to validate the upexpression of PDL1 with myokines treatment in HT29 cells.

Results and Discussion: Microarray technique was used in the present study explore the expression of 29635 genes with myokine treatment. The differential gene expression analysis showed 6239 genes which were differentially expressed between unstimulated and stimulated myokine treatment in HT29 cells. The two time points (4 h and 24 h) of myokine treatment was studied. 4 h and 24 h myokine treatment in HT29 cells showed upregulation of 4698 and 2935 genes respectively. On the other hand 1541 genes in 4 h and 3304 genes in 24 h myokine treatment was observed to be downregulated. Additionally, 3452 genes were commonly expressed between 4 h Unstimulated vs stimulated myokine treatment. However, 24 h un-stimulated vs stimulated myokine treatment reported 4548 genes which were commonly expressed between the groups. The differential gene expression analysis showed up-expression of euchromatin modification markers, higher nuclear euchromatin activity and downregulation of chromosome maintenance and segregation markers. Gene ontology analysis by The Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 showed downregulation of Wnt/ -Catenin, KRAS/MAPK, PI3K pathways and upregulation of apoptotic markers. It was interesting to observe an upregulation of PDL1 (CD274) by 3.8 fold change with 24 hr myokine treatment in HT29 cells. PDL1 protein upexpression by 2 fold change with unstimulated vs stimulated myokine treatment attests the microarray gene dataset The present study explores a better understanding of the novel therapeutic approach that attests the mechanistic insights of in- vitro produced myokines targeting PDL1.

Conclusion: In conclusion, this study explores an approach to study the effect of myokines in CRC at transcriptome- level. Current findings attests the clinical significance of exercise at molecular level. Modulation of signalling pathways by myokines can help explore cancer treatment strategies which can be combined with exercise, nutritional strategies and therapeutic interventions.

Characterization of genetic and epigenetic response to active Vitamin D with focus on in human duodenal organoids

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Vitamin D is a known chemo-preventative agent for colorectal cancer and a steroid hormone shown to induce cellular differentiation. Active form of vitamin D 1α, 25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] is a high affinity ligand for transcription factor VDR. It has been shown that Vitamin D treatment in normal intestinal tissue induces differential expression of more than 800 genes. Chromatin response to vitamin D treatment in normal human intestinal tissue remains unexplored. Our study aims to address this gap in genetic and epigenetic regulation of chromatin topology by vitamin D. We intend to perform an ATAC Seq in non-differentiated duodenal organoids for chromatin accessibility. The results from the study will be integrated with the transcriptional response data to understand pleiotropic impact of vitamin D treatment.

Microbes from non-human primates exposed to maternal high fat diet alter serotonin *in vitro*

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The impact of maternal high fat diet (mHFD) on child health extends beyond the neonatal period. In a non-human primate model, we have previously shown that offspring exposed to mHFD display persistent juvenile-onset anxiety and an altered gut microbial community. Since gut microbes can influence neurobehavior/neuroactivity via the gut-brain axis, we hypothesized that gut microbes from mHFD-exposed offspring will induce altered levels of intestinal serotonin *in vitro* via microbe-host interactions compared to microbes from offspring exposed to a maternal control diet.

Japanese macaques were fed mHFD or control diet during gestation and lactation. Both mHFD and control offspring were weaned at 6 months of age onto a control diet, and fresh stool was collected at 3 years of age. Small intestinal enteroids from adult wild-type B6 mice and adult humans were incubated with the macaque stool microbes from both perinatal diet groups. Gene expression of serotonin-relevant proteins (tryptophan hydroxylase-1 and Chromogranin A) and serotonin pathway metabolites (serotonin, tryptophan, and indoleacetic acid) in the supernatant were measured.

In humans, mHFD stool treatment increased serotonin measures in human duodenal, jejunal, and ileal enteroids. Specifically, we observe non-statistically significant trends towards increased serotonin in the supernatant of two duodenal and two jejunal enteroid lines, and a statistically-significant increase in one ileal enteroid line treated with mHFD filter-sterilized stool ($p=0.0039$). In contrast, mouse enteroids display a different serotonin pattern, where mHFD stool treatment increased serotonin measures in duodenal enteroids but decreased serotonin measures in jejunal enteroids. In mouse duodenal enteroids, we detect (1) increased serotonin in the supernatant of mouse duodenal enteroids ($p=0.0177$ with filter-sterilized mHFD stool, and $p=0.13$ with live mHFD stool) and (2) increased indoleacetic acid ($p=0.0344$ with live mHFD stool) with (3) no changes in tryptophan levels in the supernatant between mHFD and control treatments. In mouse jejunal enteroids, we measure (1) decreased serotonin in the supernatant (p-0.009 with filter-sterilized mHFD stool); (2) decreased gene expression of the rate-limiting enzyme in serotonin production, tryptophan hydroxylase-1 ($p=0.0312$ with mHFD heat-killed stool), and (3) decreased gene expression of the marker of serotonin-producing gut epithelial cells, Chromogranin A ($p=0.0324$ with mHFD heat-killed stool).

Our results indicate that stool effluents from mHFD-exposed offspring are capable of inducing changes in serotonin via host cells in the gut, even after 2.5 years of control diet feeding. We speculate that interactions between microbes and the host via are host-specific and crucial to programmed development of the gut-brain axis in primates.

Rotavirus activates intercellular calcium waves mediated by ADP signaling

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Rotavirus (RV) remains the leading viral cause of diarrheal disease in children worldwide. The life-threatening diarrhea from RV infection is potentially exacerbated by the release of signaling molecules from infected villus epithelial cells. RV increases cytosolic calcium in infected cells, which is necessary for RV replication and activation of secretory pathways. Thus, characterizing RV-induced calcium signaling is needed to understand RV pathogenesis. Increased signaling molecules, such as the RV enterotoxin NSP4, prostaglandins, and nitric oxide, have been observed during RV infection. However, the activation of signaling pathways from infected to uninfected cells has not been directly observed. Therefore, the signaling mechanisms that facilitate widespread dysregulation of fluid secretion leading to diarrhea remain undefined. To address this, we conducted live cell fluorescence imaging in cell lines and jejunum human intestinal enteroids (jHIEs) to measure calcium signaling during RV infection.

We generated African monkey kidney MA104 cells and jHIEs that stably express GFP-based genetically encoded calcium indicators to measure calcium dynamics during RV infection. These imaging studies revealed that RV significantly increases the number and magnitude of calcium transients during infection. Furthermore, we observed that single RV-infected cells triggered long-distance intercellular calcium waves (ICWs) that encompassed surrounding uninfected cells. Treatment with the ectoNTPase apyrase or the P2Y1 purinergic receptor inhibitor BPTU blocked the ICWs and decreased RV replication. We created a genetic knockout of the P2Y1 receptor in MA104 cells and jHIEs using CRISPR/Cas9, and there were reduced ICWs in RV-infected knockout cells. In RV-infected HIEs, treatment with apyrase and BPTU blocked the RV-induced increases in IL-1a, COX2, and iNOS expression, suggesting ADP signaling is upstream of prostaglandin and nitric oxide expression in RV infection. Furthermore, these inhibitors decreased RV-induced serotonin secretion, which exacerbates RV diarrhea and vomiting *via* the enteric nervous system, and reduced fluid secretion in the enteroid swelling assay. Finally, diarrhea severity in rhesus RV-infected neonatal mice was decreased when treated with P2Y1 blockers BPTU or MRS2500 compared to mock treatment.

Our studies demonstrate that RV-infected cells release extracellular ADP to activate calcium signaling in uninfected cells as ICWs. This purinergic signaling is important for RV replication, upregulation of additional signaling molecules, and activation of secretory pathways. This is the first observation that viruses can exploit purinergic signaling and ICWs to potentially amplify pathophysiological signaling important for diarrhea—a strategy that may be shared with other enteric viruses. Thus, our data points to purinergic signaling as a therapeutic target for developing host-directed, anti-diarrheal drugs.

Retrospective study of hepatitis a immunization rates in persons living with HIV at the Thomas Street Health Center and Harris Health Northwest HIV Clinic

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Background: Hepatitis A virus (HAV) and human immunodeficiency virus (HIV) share similar risk factors for infection including intravenous drug use and sexual transmission among men who have sex with men (MSM), resulting in more frequent HIV/HAV coinfection. The CDC has reported recent HAV outbreaks from person-to-person transmission among populations with these risk factors. This has raised concern for persons living with HIV (PLWH) who frequently suffer a more complicated course of HAV illness if infected. This has highlighted increased need for appropriate HAV prevention in PLWH. In the United States, low HAV vaccination rates in PLWH and additional risk factors for HAV acquisition have been described. This warrants further examination into HAV vaccination rates in PLWH.

Objectives: The primary objective of this study was to determine HAV vaccination rates among all PLWH in the study population regardless of other risk factors. Additionally, the study aimed to determine associations between vaccination and patient risk factors as well as demographic and clinical variables.

Methods: This IRB-approved (H-45873) retrospective chart review examined HAV immunization rates in PLWH presenting to Thomas Street Health Center and Harris Health Northwest HIV Clinics in Houston, Texas between January 1, 2010 and December 31, 2019. Patients were considered eligible for HAV vaccine if they were HAV IgG negative or never had this test performed and never received prior HAV vaccination. Kaplan-Meier curves summarized time to receiving 1 and 2 HAV vaccines. The cumulative incidence of receiving 1 and 2 HAV vaccines at 6, 12, and 24 months from entry to care was estimated. The log-rank test evaluated associations between subject characteristics and vaccination. Significant factors ($p<0.05$) were included in a multiple Cox proportional hazards (PH) regression analysis. A reduced Cox PH model was obtained by backwards elimination and forwards re-entering of variables.

Results: Out of 6,515 patients, 3,074 were eligible for HAV vaccination. At 6 months from entry to care, 6.3% of patients had received at least 1 dose of HAV vaccine, followed by 9.6% at 12 months, and 13.7% at 24 months. At 6 months from entry to care, 1.7% had received at least 2 doses of HAV vaccine, followed by 6.0% at 12 months, and 9.8% at 24 months. Over 24 months of follow-up, PLWH with Hispanic ethnicity were less likely to receive at least 1 dose of HAV vaccine (HR 0.59; 95% CI: 0.39, 0.90), while patients who were MSM (HR 1.48; 95% CI: 1.17, 1.87), those with a history of chronic hepatitis B (HR 3.74; 95% CI: 2.21, 6.35), and patients with a history of chronic hepatitis C (HR 1.88; 95% CI: 1.16, 3.06) were more likely to receive at least 1 dose of HAV vaccine. Over 24 months follow-up, Hispanic patients were also less likely to receive at least 2 doses of HAV vaccine (HR 0.51; 95% CI: 0.32, 0.82), while patients with a history of chronic hepatitis B (HR 6.60; 95% CI: 3.83, 11.37), chronic hepatitis C (HR 2.71; 95% CI: 1.62, 4.51), and MSM (HR 1.42; 95% CI: 1.07, 1.89) were all more likely to receive at least 2 doses of HAV vaccines.

Conclusion: In agreement with previous research, this study found that all PLWH had HAV vaccination rates below recommendations of the Advisory Committee on Immunization Practices. Hispanic PLWH were less likely to receive vaccination. The results warrant further study to identify effective solutions to the apparent gap in preventative care in this population.

The Role of Homeobox Genes in Conferring Intestinal Regional Identity

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Introduction: Homeobox (HOX) genes are known for their role in anterior-posterior patterning during development. As in other tissues, HOX genes are expressed in a spatial collinear fashion along the gastrointestinal tract. Ectopic expression of hoxd13, a posterior HOX gene, causes partial distalization of the developing avian proximal gut, implicating HOX genes in intestinal patterning and regional identity. Our unpublished data, in accord with others, shows that the crypt compartment, which houses stem cells necessary for intestinal epithelial renewal, retains intestinal regional-specific identity. The objective of this project is to determine the sufficiency of HOX genes in establish intestinal regional identity during intestinal development. In this study, three-dimensional embryonic stem cell-derived human intestinal organoids (HIOs) are being used as a mode of human intestinal development. In 2017 Munera et al. showed BMP2 treatment results in a distal (colonic) patterning of HIOs, while NOGGIN treatment results in a proximal (duodenum) patterning of HIOs. Here, an early time-course transcriptomic analysis has been performed between NOGGIN and BMP2 treated HIOs to determine the presence and role of HOX genes in establishing human intestinal regional identity.

Material and Methods: HIOs were derived from H9 embryonic stem cells and were treated with Activin A for 3 days to generate definitive endoderm. Subsequently, definitive endoderm was treated with FGF4 and Chir99021 with daily media changes for 4 days. On the 3rd and 4th day floating nascent spheres were collected and plated into Matrigel and cultured in HIO media containing NOGGIN or BMP2. RNA was collected from nascent spheres, and NOGGIN and BMP2 treated at spheres at 12, 24, 48 and 72 hours. Then, RNA-Seq Analysis was performed using a Kallisto-DeSeq2 pipeline.

Results: Principle Component Analysis on RNA-Seq data revealed clustering on NOGGIN vs BMP2 treated HIOs. NOGGIN and BMP2 treatments also showed dynamic upregulation of HOX genes during the first 72 hours of HIO formation. Previously reported early distal marker *SATB2* was confirmed to have early expression in BMP2 treated HIOs at 72 hours. Additionally, of the several HOX genes that are upregulated after BMP2 treatment, *HOXA7* and *HOXB8* were shown to be upregulated at every timepoint. *HOXA7* and *HOXB8* are also differentially upregulated in colonic enteroids (adult biopsy derived organoids) compared to duodenal enteroids. Hypergeometric Optimization of Motif EnRichment (HOMER) analysis was also performed showing the difference in enriched motifs between the NOGGIN and BMP2 treated groups.

Conclusions: Several genes were shown to be differentially expressed between the NOGGIN and BMP2 treated groups early on in proximal and distal HIO formation. *HOXA7* and *HOXB8* were shown to be upregulated early on in distal HIO formation, with continued expression in colonic enteroids. This suggests that *HOXA7* and *HOXB8* may play an early role in conferring a distal pattern in the intestine. Currently, the induced expression of *HOXA7* and *HOXB8* in HIOs is being performed in order to elucidate the role of these genes in conferring intestinal regional identity.

Pancreatic Stromal Gremlin 1 Expression during Pancreatic Tumorigenesis

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Background: Chronic pancreatitis (CP) is a major risk factor of pancreatic ductal adenocarcinoma (PDAC). How CP promotes pancreatic oncogenesis is unclear. A characteristic feature of PDAC is a prominent desmoplasia in the tumor microenvironment, composed of activated fibroblasts and macrophages. Macrophages can be characterized as M1 or M2, with tumor inhibiting and promoting functions, respectively. We reported that Gremlin1 (Grem1), a key pro-fibrogenic factor, is upregulated in the stroma of CP. The current study aimed to investigate the expression of Grem1 and correlation between Grem1 and macrophages within the pancreas during chronic inflammation and the development of PDAC.

Methods: Three commercial human pancreatic tissue microarrays were used, containing 11 cases of CP, 9 cases of pancreatic intraepithelial neoplasia (PanIN), and 98 cases of PDAC with pathological tumor stages 1-4. Grem1 mRNA *in situ* hybridization was performed and scored. Immunohistochemistry was performed using α-smooth muscle actin (SMA), CD68, and CD163 as markers of fibroblasts, total macrophages (M^{CD68+}), and M2 macrophages ($M2^{CD163+}$), respectively. The most densely stained area per case was imaged and quantified by investigators blinded to case identities.

Results: Grem1 mRNA *in situ* expression overlaps with α-SMA, indicating an exclusive expression of Grem1 by fibroblasts. These designated $Fibroblasts^{Grem1+}$ marginally increase from CP to PanIN to PDAC ($p=0.06$), increase with PDAC pathological tumor stages ($p<0.05$), and positively correlate with M^{CD68+} ($r=0.39$, $p<0.05$) and $M2^{CD163+}$ ($r=0.23$, $p<0.05$) cells in PDAC.

Conclusions: The increase of $Fibroblasts^{Grem1+}$ from CP to PanIN to PDAC, and with PDAC pathological tumor stages, suggests that Grem1 may have biomarker potential for PDAC progression. The positive correlation of $Fibroblasts^{Grem1+}$ and M^{CD68+} and $M2^{CD163+}$ in PDAC indicates that Grem1 may promote $M2^{CD163+}$ activation during PDAC development. Taken together, Grem1 may act as a novel link between chronic inflammation and PDAC. Further investigation on how $Fibroblasts^{Grem1+}$ activate $M2^{CD163+}$ is warranted, with aim of therapeutic development.

The dynamics of autophagy and mTORC1 in intestinal regeneration post-doxorubicin injury.

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Chemotherapy has many side effects, including the inflammation of mucus membranes termed mucositis. Patients commonly present with pain, vomiting and diarrhea causing high morbidity. Worsening symptoms reduce patient adherence to treatment and limit administration of therapeutic doses. There are no effective therapies to attenuate mucositis, and there is limited research on intestinal mucositis. Intestinal stem cell (ISC) damage is a common feature of murine intestinal mucosal damage by doxorubicin chemotherapy. However, the intestine has been shown to regenerate within seven days despite initial ISC loss. Pathways related to the regenerative process include those that drive cellular remodeling, such as autophagy, which is robustly induced by fasting. Fasting prior to doxorubicin chemotherapy administration has been shown to protect ISCs from DNA damage by activating autophagy. While feasible, the translatability of fasting is limited by the ability of ill patients to tolerate a fast. To maintain feasibility and improve translatability, we decided to focus on FDA-approved drugs that modulate autophagy. Rapamycin is a widely used drug that inhibits mTORC1, the major negative regulator of autophagy activity, thereby activating autophagy. To determine whether rapamycin could recapitulate the intestinally protective effects of fasting, mice were treated with rapamycin 24-hours prior to doxorubicin administration. Similar to fasting, rapamycin treated mice were resistant to body weight loss typically induced by injury. Histological analysis at the typical peak of doxorubicin-induced intestinal injury, demonstrated less disruption in intestinal morphology, a maintenance of the intestinal stem cell population, and increased proliferation seen in the intestinal crypts of fasted mice.

ACE2 and TMPRSS2 as early biomarkers in colon carcinogenesis: race-specific implications

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Background: The American Cancer Society has reported that African Americans possess a higher CRC incidence and mortality rate vs Caucasians. There is compelling evidence that this is driven at least partially through biological factors. Guda et al. has shown novel gene mutation specific to African American CRCs, highlighting biological differences in race in CRC and underscoring the need to delineate the mechanisms behind these. Covid19 has disproportionately affected African Americans, although the mechanisms are not completely elucidated. Biologically, several host proteins have been of particular interest as susceptibility targets. Angiotensin converting enzyme 1 (ACE2) acts as the membrane receptor and works in concert with transmembrane protease serine 2 (TMPRSS2) for viral entry. Recently there has been much attention on the impact of COVID and genetic vulnerability in cancers, where ACE2 and TMPRSS2 have been shown to be upregulated in CRCs (Hoang et. al., *Cancer Res Treat* 2020). Therefore, we wanted to assess the expression of ACE2 and TMPRSS2 in African Americans vs Caucasians as a biomarker for race and CRC risk.

Methods: Archived mucosal biopsies from colonoscopic biopsies of visually normal rectal mucosa were used for this study. A total of 145 samples were processed. Samples were classified as either control (no remarkable endoscopic findings) or from patients with adenomas (possessing tubular adenoma(s) >5mm in diameter and or sessile serrated adenomas). Total mRNA was isolated and subjected to real-time polymerase chain reaction for ACE2 and TMPRSS-2 analysis. GAPDH was used for normalization.

Results: Out of 145 patient samples, 82 of the samples came from African Americans, 63 from Caucasians. 58 out of all samples were classified as patients with adenomas, 34 coming from African American patients and 24 from Caucasians. Adenomal presence showed an induction of ACE2 mRNA (~50%, $p<0.13$) as well as TMPRSS2 (84%, $p<0.05$). When analyzing for race, African Americans showed a strong upregulation of ACE2 and TMPRSS2 (107%, $p<0.01$ and 105%, $p=0.13$ respectively). Caucasians with adenomas show no significant inductions of these markers vs their respected controls (ACE2 was downregulated ~2%, $p<0.04$; TMPRSS2 was upregulated 10%, $p<0.03$). Interestingly, African American control patients showed a lower expression of both markers, however comparing race and adenomal presence showed no significant differences.

Conclusion: We herein, for the first time to our knowledge, have shown that ACE2 and TMPRSS2 are upregulated in patients with adenomas, where in our study was specific by African Americans. Baseline expression of these genes showed a lower expression in African Americans vs Caucasians controls, however comparing race in adenoma patients showed no difference, suggesting that the role of these genes may be important in colon carcinogenesis in African Americans. Future studies investigating the molecular underpinnings behind ACE2 and TMPRSS2 in CRC risk may lead to biomarkers and therapeutic targets which can mitigate the racial disparities in CRC.

The hormonal therapeutic potential of probiotic Lactobacillus reuteri

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Lactobacillus reuteri is a well-used probiotic combating bone loss, colic, infections, and inflammation. Multiple strains with efficacy exist – in particular 6475 and 17938. Many of their probiotic effects are postulated to act through downregulation of inflammatory responses. Newer data, however, suggests that *L. reuteri* also affects gut hormones and social behavior. To characterize how *L. reuteri* mediates its beneficial effects through interactions with the gut epithelium and determine if it alters gut hormones, we performed transcriptomics on native organoids and on enteroendocrine enriched organoids treated with *L. reuteri* cell-free supernatants. Our data demonstrate that *L. reuteri* upregulates the transcription of many gut hormones including GIP, ghrelin, PYY, gastrin, CCK, and motilin. By performing a Luminex assay for select hormones, we confirm that *L. reuteri* stimulates secretion of GIP, ghrelin, and PYY. These results point towards *L. reuteri* causing widespread effects on hormone secretion from the gut epithelium and illustrate the power of this mighty microbe on host physiology.

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Bile acid effects on ileal contractility

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Background: Bile acids mediate intestinal motor functions through multiple receptor-mediated signaling pathways[1]. Bile acids endoscopically delivered to the intestine increase motor activity[2,3]. Bile acids bind to and activate the G-protein coupled receptor, TGR5, and the nuclear farnesoid X receptor (FXR), which are found in the GI tract and mediate intestinal motor, secretory, or sensory functions[4].

Previously, we induced early-life malnutrition in mice by administering a regional basic diet (RBD), an isocaloric (to a control diet) low-protein, low-fat, high-carbohydrate chow. RBD mice were underweight and stunted compared to control mice and metabolomic data in the RBD mice revealed multiple reduced fecal bile acid quantities compared to control mice[5]. Early studies enrolling children with protein-calorie malnutrition have described decreased conjugated bile acid quantities[6]. Few studies have examined bile acids actions *ex vivo* on isolated intestinal segments and none have explored the effects of bile acids in the healthy versus the malnourished intestine.

Objective: To determine the effect specific bile acids with varying bile acid receptor affinities exert on contractility in intestinal segments from healthy mice.

Methods: Intestinal (ileal) segments were isolated from healthy female mice. The intestine segments were everted to expose the intestinal apical membrane where bile acid transporters are located. The segments were treated with incrementally increased concentrations of commonly used and clinically relevant bile acids (i.e., ursodeoxycholic acid, deoxycholic acid, chenodeoxycholic acid, and cholic acid) in an *ex vivo* force transduction system to determine the effect each bile acid exerts on intestinal contractility.

Key Results: Ursodeoxycholic acid exerts a dose-dependent stimulatory contractile effect in the ileum. Deoxycholic acid exerts an opposite, inhibitory effect on contractility in the ileum at 100 uM concentration. Chenodeoxycholic acid and cholic acid demonstrate no overall effect on contractility in the healthy ileum segments.

Conclusions: Bile acids exert differing effects on intestinal contractility specific to the type of bile acid and its concentration. This study provides further insight into the role of bile acids in the intestine and may facilitate the development of targeted therapies for bile-acid deficient GI diseases.

Molecular Links between Fibroblasts and Macrophages in Pancreatic Ductal Adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is known for its desmoplastic microenvironment containing activated fibroblasts and macrophages. We reported that activated pancreatic fibroblasts secrete Gremlin1 (Grem1), a key pro-fibrogenic factor in chronic pancreatitis. Grem1 has been shown to be an endogenous inhibitor of macrophage migration inhibitory factor (MIF) in atherosclerotic disease. MIF stimulates classical activation of macrophages (M1) which are tumor-inhibiting. In contrast, alternatively activated macrophages (M2) are tumor-promoting. We reported that M2 positively correlate with Grem1 in PDAC. We hypothesize that upregulation of Grem1 during chronic pancreatitis blocks MIF, promoting M2 activation and pancreatic tumorigenesis. As a first step to test this hypothesis, we profiled expression patterns of these interrelated molecules in human PDAC.

Methods: A commercial human pancreatic tissue microarray containing 70 PDAC cases with pathological tumor stages 1-4 underwent Grem1 mRNA *in situ* hybridization, and immunohistochemistry (IHC) staining of α-smooth muscle actin (activated fibroblasts), MIF, CD68 (total macrophages), and CD163 (M2). The most densely stained area per case was imaged and quantified by two investigators blinded to case identities. MIF/CD163 co-staining was further performed and the most densely stained images of either MIF or CD163 per case were quantified. Data analysis was performed to identify correlations.

Results: MIF is mainly expressed in tumor cells, and Grem1 in activated fibroblasts. MIF is positively correlated with Grem1 in PDAC ($r=0.32$, $p<0.05$), but not correlated with CD68 or pathologic tumor stage. MIF showed an inverse trend with CD163, but was not significant. The subsequent MIF/CD163 co-staining confirmed a negative correlation between MIF and CD163 ($r=-0.29$, $p<0.05$).

Conclusion: The contrasting correlations, negative for MIF vs CD163, but positive for Grem1 vs CD163, suggest that Grem1 may block MIF activity to promote M2 activation in PDAC. Further investigation into the interaction between Grem1 and MIF, and its impact on M2 activation and pancreatic tumorigenesis is warranted.

Role of the microbiome in a novel model of gastroparesis

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Background: Gastroparesis, or delayed gastric emptying, has had an increasing healthcare burden with a doubling of pediatric admissions and a seven-fold increase in cost of related hospital admissions over the past decade. Delayed gastric emptying is observed in a broad range of undernourished states including small-for-gestational-age neonates, children with acute and profound weight loss, and adolescents with anorexia nervosa. Animal models are needed to elucidate causes of and potential therapies for disorders of gastric motility. We aimed to characterize a novel model of delayed gastric emptying induced by postnatal timed separation (TmSep) of mouse pups from lactating dams. We previously reported that TmSep pups have a dramatically altered microbiome. The objectives of this study are 1) to characterize this model of gastric dysmotility by studying the enteric nervous system (ENS), smooth muscle, and *ex vivo* contractility and 2) to investigate the effect of the microbiome by examining these parameters in mice raised in a germ-free environment.

Methods: Separation of pups from lactating dams for 12 hours per day was performed in both conventional (Conv) and germ-free (GF) housing. Control (Ctrl) pups nursed uninterrupted. On day-of-life 15, gastrointestinal tract was harvested 15 minutes after gavage of fluorescein isothiocyanate (FITC)-conjugated dextran to determine emptying into the small bowel and to examine gastric tissue for histopathology.

Results: Compared to Conv-Ctrl pups, Conv-TmSep mice were moderately underweight (4.5 vs 7.0 g, p<0.0001). Similarly, GF-TmSep mice were underweight compared to GF-Ctrl mice (3.6 vs 5.8 g, p<0.0001). Stomachs of TmSep mice in either environment were strikingly distended compared to their respective Ctrl mice (Figure 1). Gastric emptying was delayed in TmSep mice compared to controls in both standard housing (54% vs 70%, p=0.009) and GF environment (53% vs 74%, p=0.002) (Figure 2). The gastric smooth muscle layer (16.9 vs 30.4 μm, p=0.03) as well as mucosa (57.2 vs 108.5 μm, p<0.01) was thinner in TmSep mice versus Ctrls.

Conclusion: Thin smooth muscle in TmSep mice is a potential etiology of the delayed gastric emptying; alterations to the microbiome do not appear to be a causative factor in this model. Altered enteric nervous system, smooth muscle contractility, and neuro-hormonal signaling pathways also are under investigation as potential causes of gastroparesis in TmSep mice.

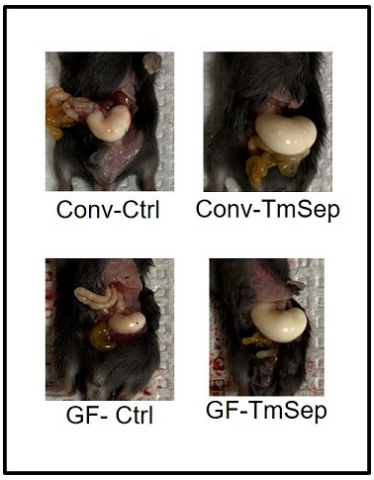

Figure 1: The stomachs of pup who undergo timed separation are larger in both conventional (Conv) and Germ-free (GF) environments compared to control (Ctrl) pups.

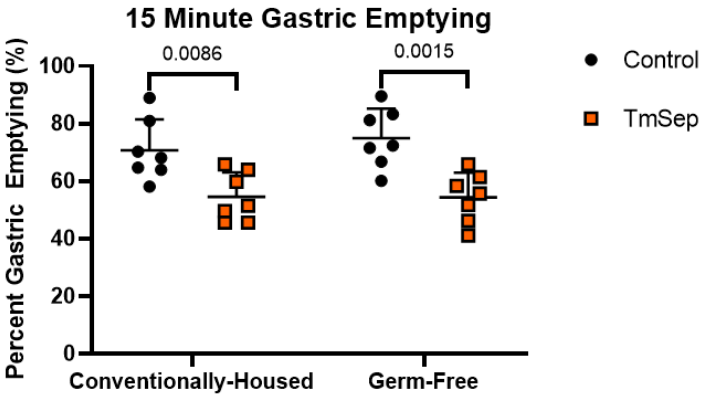

Figure 2: Gastric emptying measured by passage of FITC-dextran is delayed in both conventionally-housed and germ-free mice.

Exploring the interaction between rotavirus and the gut microbiota

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Background: Enteric viruses enter the host via the fecal-oral route and in the intestine, viruses encounter a dynamic community of microbes. Select intestinal microbes have been shown to bind viruses and inhibit infection. Viral adhesion to bacteria has been characterized with astrovirus, norovirus, and poliovirus, but few studies have addressed the interaction between rotavirus and bacteria. Rotavirus is a leading cause of diarrheal diseases in children, with an estimated 258 million cases and 128,500 deaths per year. As a result, identifying mechanisms by which microbes influence rotavirus infection remains an important question. We hypothesized that certain intestinal microbes would bind to rotavirus and potentially participate in infection.

Methods & Results: To address these questions, rotavirus-infected neonatal mice were examined for changes in bacterial community dynamics, host gene expression, and tissue recovery during infection. Profiling bacterial communities using 16S rRNA sequencing suggested significant and distinct changes in ileal communities in response to rotavirus infection, with no significant changes for other gastrointestinal (GI) compartments. 16S rRNA sequencing the ileum of neonatal mice demonstrated the gut microbiome was dominated by *Lactobacillus* (60%), followed by *Staphylococcus* (20%), *Escherichia* (15%), *Enterobacter* (3%), and *Bacteroides* (2%). Infection of neonatal pups with rotavirus significantly decreased ileal *Lactobacillus* (40%) and increased *Enterobacter* (10%), *Bacteroides* (7%), and *Akkermansia* (5%) after one day post-infection. Concomitant with the bacterial community shifts, we observed a loss of mucin-filled goblet cells in the small intestine at day 1, with recovery occurring by day 3. Rotavirus infection of mucin-producing cell lines and human intestinal enteroids (HIEs) stimulated release of stored mucin granules, similar to *in vivo* findings. *In vitro*, incubation of mucins with *Bacteroides* or *Akkermansia* members resulted in significant glycan degradation, which altered the binding capacity of rotavirus *in silico* and *in vitro*. Taken together, these data suggest that the response to and recovery from rotavirus-diarrhea is unique between sub-compartments of the GI tract and may be influenced by mucin-degrading microbes. To assess if any microbiota may bind to rotavirus, we fluorescently tagged commensal gut microbes *Bacteroides ovatus* ATCC 8384, *Bacteroides thetaioatomicron* ATCC 29148, *Ruminococcus torques* ATCC 2775, *Akkermansia muciniphila* ATCC BAA-835, *Escherichia coli* K12, *Lactobacillus reuteri* M27163, *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus* ATCC 4356, *Bifidobacterium longum* subsp. *infantis* ATCC 15697, *Bifidobacterium bifidum* ATCC 29521, *Prevotella copri* CB7 DSM 18205, *Clostridium sporogenes* DSM 795 ATC 3585, *Fusobacterium nucleatum polymorphum* ATCC 10953, *Enterococcus faecalis Symbioflor* DSM 16431, *Streptococcus thermophilus* ATTC 491, and *Faecalibacterium prausnitzii* A2-165. All microbes were adjusted to OD_{600nm} =1 and incubated with 10^7 PFU BFP-tagged rotavirus for 1 hr. After washing, adhesion was examined by fluorescence. Interestingly, only *L. acidophilus* was found to bind rotavirus.

Conclusions: Based on this data we speculate that select *Lactobacillus* can bind rotavirus and prevent rotavirus access to the epithelium. Decreased levels of *Lactobacilli* during infection may inadvertently promote infection. This data also points to the potential for *Lactobacillus* administration in minimizing infection and may provide a new strategy for rotavirus treatment.

Incidence and Determinants of Colorectal Cancers and Advanced Adenomas after a Negative Colonoscopy following a Positive Fecal Immunohistochemical Testing (FIT)

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Introduction: Serial fecal immunohistochemical testing (FIT) detects microscopic amounts of fecal blood and is widely used for colorectal cancer (CRC) screening with reported positive predictive value of 20.8% for detecting advanced adenomas. Moreover, there are cases where colon polyps are not found on colonoscopy with a positive FIT. We determined the incidence and determinants of CRC and advanced adenomas after a negative colonoscopy (i.e., no polyps found) in the setting of a positive FIT. **Methods:** We identified patients at Ben Taub and Lyndon B Johnson Hospitals who underwent a colonoscopy following a positive FIT between 06/2008 and 01/2013 using the Epic medical record database. All patients underwent medical record review to determine incident CRC and advanced adenomas (i.e., >1 cm, villous histology, high-grade dysplasia) in addition to demographic, endoscopic, and histopathology data. We compared incidence rates of CRC and advanced adenomas between those with no polyps found on index colonoscopy to those with polyps found and examined risk factors for polyps on index colonoscopy. **Results:** Of 2308 positive FIT patients who underwent colonoscopy, 132 (5.7%) had prevalent CRC, 6 (0.3%) had other gastrointestinal cancer, 43 (1.9%) had inflammatory bowel disease, 805 (34.9%) had adenomatous polyps, and 1322 (57.3%) had no CRC or polyps. Of the 2127 patients with and without polyps on index colonoscopy, 353 (16.6%) patients underwent a subsequent colonoscopy, and no cases of incident CRC were found. There were 27 cases of advanced adenomas among 1499 person-years follow-up time. Among those with polyps on index colonoscopy, the incidence of advanced adenomas was 2.24% per person-year compared to 0.85% per person-year in those with no polyps found on index colonoscopy (age-adjusted incidence rate ratio 2.94; 95% CI 0.90-9.66) (Figure 1). We found a trend towards an association between presence of future advanced adenoma and adenoma on index colonoscopy (OR 2.74, 95% 0.93-8.14). Predictors of polyps on index colonoscopy included age >50, male sex, birthplace within US, body mass index >25, smoking, alcohol use, family history of colon cancer, and withdrawal time >6 min (Table 1). **Conclusion:** We found no cases of incident CRC and 34% decreased risk of incident advanced adenomas in patients with a negative index colonoscopy following a positive FIT. Our study suggests a low likelihood of interval development of CRC or an advanced adenoma following a negative index colonoscopy. This confirms that a ten-year interval for subsequent colonoscopy is appropriate for patients with no polyps on colonoscopy after a positive FIT.

Figure 1. Cumulative incidence of advanced adenomas among those with and without polyps on index colonoscopy following a positive fecal immunohistochemical test (FIT)

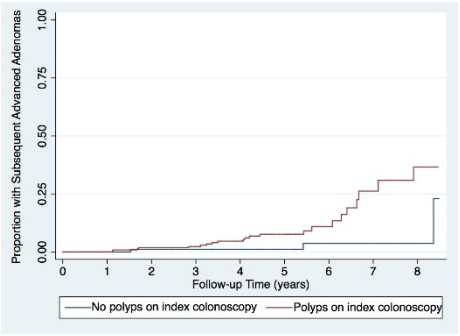

Table 1. Demographic, clinical, and procedural risk factors for presence of adenomatous polyps following a positive fecal immunohistochemical test (FIT) among 805 cases with and 1322 controls without polyps on index colonoscopy

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age (ref: <50 years)		
50-59	1.39 (0.95-2.02)	1.53 (1.03-2.27)
60-69	1.91 (1.30-2.81)	2.15 (1.44-3.22)
≥70	2.06 (1.28-3.32)	2.58 (1.56-4.27)
Sex (ref: Male)		
Female	0.60 (0.50–0.71)	0.63 (0.51-0.76)
Race/Ethnicity (ref: White)		
Hispanic	0.70 (0.53-0.93)	1.05 (0.73-1.53)
Black	0.91 (0.67-1.24)	0.90 (0.65-1.24)
Mixed	0.79 (0.50-1.26)	1.47 (0.84-2.55)
Marital Status (ref: Married)		
Divorced/Separated/Widowed	0.85 (0.69-1.05)	
Single	0.96 (0.78-1.20)	
Citizenship (ref: US Born)		
Naturalized/Legal Alien/Undocumented	0.67 (0.56-0.79)	0.66 (0.49-0.88)
BMI (ref: BMI <25)		
25 ≤ BMI < 30	1.26 (0.98-1.60)	1.30 (1.00-1.69)
BMI ≥ 30	1.26 (1.00-1.58)	1.43 (1.10-1.85)
Smoking status (ref: Never smoker)		
Current smoker	1.79 (1.42-2.26)	1.41 (1.07-1.84)
Former smoker	1.40 (1.12-1.74)	1.04 (0.82-1.33)
Alcohol status (ref: Never drinker)		
Current drinker	1.69 (1.35-2.11)	1.38 (1.07-1.78)
Former drinker	1.27 (0.83-1.95)	1.08 (0.69-1.70)
Diabetes (ref: No)		
Yes	1.17 (0.97-1.40)	
***Family Hx of Colon Cancer* (ref: No)**		
Yes	1.68 (1.10-2.56)	1.71 (1.10-2.66)
Aspirin Use (ref: No)		
Yes	1.21 (0.99-1.48)	
NSAID Use (ref: No)		
Yes	0.91 (0.76-1.10	
BBPS (ref: Inadequate)		
Adequate	1.62 (0.85-3.06)	1.85 (0.96-3.57)
Fellow Involvement (ref: No)		
Yes	0.94 (0.74-1.20)	
Withdrawal Time (ref: <6 minutes)		
6-10 minutes	1.63 (0.19-13.78)	1.45 (0.17-12.48)
>10 minutes	9.91 (1.25-78.70)	8.39 (1.04-67.54)

Parental versus enteral nutrition exacerbares liver injury in a neonatal pig model of obstructive cholestasis

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Purpose: Biliary atresia (BA) is a neonatal disease which results in the destruction of the extra-hepatic bile ducts. Infants with BA rapidly develop liver disease and will require liver transplant at some point in their life. The only available intervention is the Kasai procedure, a hepatoportoenterostomy, which can fail in greater than 30% of cases. In these infants, transplant is required within the first two years of life. Due to poor absorption of fat and fat soluble nutrients and increased metabolic requirements from progressive liver disease, many of these infants will have failure to thrive. Failure to thrive is associated with poorer transplant outcomes. To prevent this, parenteral nutrition (PN) is administered to improve growth and nutrient status. PN containing soy lipids are known to cause liver disease in infants, but whether the effect is accelerated in cases of BA is unclear. The goal of this study is to examine markers of liver injury in a neonatal piglet model of PN that has received bile duct ligation to mimic the effects of BA in the liver.

Methods: Term-age piglets (113 d gestational age) were delivered by caesarian section. Piglets were implanted with a jugular catheter for the administration of parenteral nutrition (TPN) containing soy lipid (Intralipid). Control piglets were implanted with an orogastric tube for feeding an enteral (ENT) piglet formula, Litter Life. The ENT and TPN piglets were then split into two groups, either receiving a bile duct ligation of the cystic and common bile ducts (BDL) or a sham incision (SHAM). TPN and ENT feeds were administered for 14 days.

Results: The piglets that were included in analysis for each group were: ENT-SHAM (n=8), ENT-BDL (n=5), TPN-SHAM (n=6), TPN-BDL (n=9). Piglets on TPN had lower growth rates than ENT pigs, independent of SHAM or BDL surgery ($p < 0.05$). Serum markers of liver injury were altered by BDL and TPN administration. Direct bilirubin levels in piglets were increased significantly ($p>0.001$) in all groups compared to the ENT-SHAM (0.05 ± 0.14 mg/dL). The direct bilirubin in the TPN-BDL (1.95 ± 0.13 mg/dL) was significantly higher ($p=0.03$) than the ENT-BDL (1.41 ± 0.19 mg/dL). The TPN-SHAM (1.44 ± 0.22 mg/dL) and ENT-BDL were nearly identical concentrations. The gamma glutamyl transferase was significantly higher ($p<0.05$) in the TPN-BDL (578.7 ± 58.4 U/L) vs. the ENT-BDL (346.8 ± 78.4 U/L) and vs. the TPN-SHAM (326.5 ± 101.2 U/L) group.

Conclusions: Parenteral nutrition administration to piglets with bile duct ligation increased markers of liver injury to a greater extent than bile duct ligation alone. This result suggests that use of soy-based lipid emulsions is not ideal for best-case outcomes of liver transplant. Future studies to determine if the effect is lipid-dependent (i.e. soy oil) or due to route of feeding (i.e. TPN) are necessary. An examination of PN with other lipid emulsions (fish oil, mixed oil, etc.) to optimize PN feedings in BA infants prior to liver transplant is warranted.

Does Microbiome Contribute to Immune Dysregulation in Common Variable Immunodeficiency?

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Background: Common Variable Immunodeficiency (CVID) is a B-cell defect defined by low immunoglobulins (IG), inadequate specific antibody response, and absent gut plasma cells. CVID patients present with recurrent infections. Around 60% have additional non-infectious complications (NIC) marked by autoimmunity and inflammation. Compared to patients who present with infections-only, NIC-CVID patients have atypical gut microbial composition (dysbiosis), impaired gut mucosal barrier, and less diverse gut microbes.

Hypothesis/Goals: Dysbiotic gut microbiome from NIC-CVID patients promotes mucosal immune dysregulation, and systemic inflammation. Our goal is to determine the impact of dysbiosis on intestinal and systemic inflammation in NIC-CVID, using fecal material transplant (FMT) from CVID patients to Germ-Free (GF) mice.

Methods: We randomized germ-free (GF) mice on C57Bl/6J background to receive fecal microbiota transplantation (FMT) from NIC, infections-only CVID, or healthy control. Thirty days following FMT, ½ of the mice were treated with IgG, and ½ will receive NS. Mice were singly housed after IgG treatment to avoid coprophagy effect. We collected feces at baseline, 30 days following FMT, 5- and 10-days following IgG or NS treatment. We measured immunoglobulin (Ig) isotypes using ELISA. 16srRNA gene sequencing was used for microbiome analysis.

Results: In this pilot study**,** GF(*C57Bl/6J)* mice (n=4/group) were orally gavaged (3 times over one week at 200µl/dose) from either NIC or infections-only CVID or healthy donors. Microbiome analysis showed proper engraftment from human to mice after 31 days, with significant difference in alpha diversity (Chao 0.0029) and beta diversity (P=0.011, weighted uniFrac PCoA) between NIC, infections-only and healthy donors. At baseline, GF mice had deficient serum IgA levels compared to WT, while serum IgG was not significantly different between WT and GF. Thirty days following FMT, all IG isotypes increased in GF mice. Ten days following a single dose of human-IgG, the Beta Diversity were significantly different between mice receiving FMT from NIC patients and not in other groups.

Conclusions: GF mice receiving FMT from CVID patients had significant differences in microbiome composition compared to FMT recipients from healthy controls. Human IgG treatment led to change in microbiome composition in NIC-FMT recipients, and not other groups. Higher serum IgG was detected in NIC/Infections-only FMT recipients, suggesting that those mice developed inflammatory status post-FMT. Together, microbiome transfer from NIC-CVID patients to GF mice might help model immune dysregulation observed in NIC-CVID.

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Novel genetic susceptibility candidates in granulomatous and non-granulomatous pediatric Crohn's disease

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Background: Non-caseating granulomas are a hallmark histopathological finding of Crohn's disease (CD). Studies have suggested that the presence of granulomas may indicate a more aggressive CD phenotype associated with a complicated clinical course, including stricturing and/or penetrating disease, need for biologic therapy, and need for surgery. As such, identification of genetic associations of granulomatous CD (GCD) may help elucidate disease pathogenesis, which in turn may optimize treatments and guide novel therapeutics to combat CD complications. There is relatively sparse genetic information known about CD subtypes, especially GCD. The aim of this study was to determine the extent of genetic variation between pediatric CD patients with and without a pathognomonic sub-mucosal granuloma detected at the time of diagnosis.

Methods: Whole-exome next-generation sequencing (WES) was performed on peripheral blood derived DNA from patients with GCD and non-GCD (NGCD). PLINK analysis was used to identify single nucleotide polymorphisms (SNPs) that were overrepresented in comparisons between groups, and subgroup allele frequencies were also compared to publicly available, large population-based genomic data in gnomAD. The potential deleteriousness of single nucleotide variants was determined by the CADD scoring tool.

Results: WES was completed for 17 patients with GCD and 19 with NGCD. There were no significant differences in baseline clinical characteristics, treatments, nor 1-year outcomes between the groups. Overlap analyses between PLINK- and gnomAD-generated SNPs revealed significant enrichment in SNPs associated with *HLA-DQA1, LILRA1, SAA2, PCDHB, HLA-B, NOD2,* and *IGH* shared by GCD and NGCD groups. In the meantime, GCD-specific [*HLA-B, MUC4*] and NGCD-specific [*HLA-B, ACOT9*] SNPs were sparse.

Conclusions: We are the first to examine WES-based genetic variation between treatment-naïve pediatric CD patients purely separated by the presence of a sub-mucosal epithelioid granuloma. While there were very few SNPs consistently differentiating between GCD and NGCD patients in our cohort using two distinct methodologies, we were able to identify several novel SNPs that were significantly enriched in pediatric CD patients compared to the control human genome. Our findings indicate that the genetic origin of GCD and NGCD is largely similar. This will require subsequent confirmation in larger but similarly scrutinized cohorts of patients.

Norovirus Infection in Cancer Patients Undergoing Chimeric Antigen Receptor T-cell Immunotherapy (CAR-T)

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Background: CAR-T is used to treat certain refractory hematological malignancies. B-cell aplasia and immunosuppression used to treat CAR-T side effects increase infection risk. Little data are available describing Norovirus (NoV) infections in CAR-T recipients. **Methods:** We reviewed the medical records of 134 patients with NoV diarrhea (identified by nucleic acid amplification test) between 2016-2019. Of these patients, nine received CAR-T prior to developing NoV. Here we describe their demographics, clinical characteristics, treatments, and complications. **Results:** The median age was 49 years (Table 1). Patients' underlying malignancies included Non-Hodgkin's lymphoma (4), acute lymphoblastic leukemia (3), chronic lymphocytic leukemia (1) and metastatic sarcoma (1). Prior to development of NoV, six patients had undergone hematopoietic stem cell transplant, and 1 had received checkpoint inhibitor therapy. Five patients experienced cytokine release syndrome after CAR-T, and 1 experienced CAR-T-related encephalopathy syndrome (Table 2). Two patients received interleukin-6 antagonist therapy, and one received high dose steroids. Time to diarrhea onset post-CAR-T cell infusion was variable(median 256days, IQR 26-523 days).Six had an absolute lymphocyte count< 1000/mm3 at diarrhea onset. Three had diarrhea for >14 days; median diarrhea duration in the other 6 patients was 4 days. Other GI complaints included abdominal pain (3), nausea (4), and vomiting (3). For NoV treatment, three received oral immunoglobulin, and 8 received Nitazoxanide. Complications included development of concomitant GI-GVHD(5), ileus (2), need for TPN (3), renal failure requiring dialysis (2), ICU stay (3), and death (2). Two patients were co-infected with other enteropathogens such as rotavirus, enteropathogenic and enteroaggregative *E.Coli* and *Clostridioides difficile.* Three patients with diarrhea lasting >14 days had serial samples collected over time; NoV shedding lasted 81-546 days. NoV was genotyped in 6 patients(Table 3) and included GII.2(2), GII.4(2), GII.6(1) and GII.12(1). **Conclusion:** NoV belonging to various genotypes is an important cause of acute and chronic diarrhea in patients receiving CAR-T cell therapy.

Table 1: Patient characteristics (N=9)

Demographics	**N(%)**
Age, median(range)(y)	49(13-69)
Male	5(55)
Caucasian	6(67)
Hispanic	3(33)
Type of malignancy	
Diffuse large B cell lymphoma	3(33)
Follicular lymphoma	1(11)
B cell acute lymphoblastic leukemia	2(22)
T cell acute lymphoblastic leukemia	1(11)
Chronic lymphocytic leukemia	1(11)
Metastatic sarcoma	1(11)
Clinical characteristics	
Chemotherapy received in prior 3 months	6(67)
Prior hematopoietic stem cell recipient	6(67)
Lab findings	
Lymphopenia <1000/mm3	6(67)
ANC <500/mm3	4(44)
Albumin, median(range, mg/dl)	3.5(2.7-4.1)
IgG<400mg/dl, receiving IVIg	8(89)*

*IgG level not documented for patient 9

Table 2: CAR-T related factors

CAR-T related factors	**N(%)**
Cyclophosphamide/Fludarabine conditioning	8(89)
Type of CAR-T	
Anti-CD19(CD4,CD8)	6(67)
CD8+ Cytotoxic T cells	1(11)
Cord blood Natural Killer cells	2(22)
CAR-T Toxicities	
Cytokine release syndrome	5(55)
CAR-T related encephalopathy syndrome	1(11)
Immune related colitis	1(11)

Table 3: NoV genotypes

NoV genotypes	**N(%)**
GII.2(p16)	2
GII.4(p31)	2
GII.6(p7)	1
GII.12(p16)	1

Evaluating Antiviral Agents for Human Noroviruses Using a Human Intestinal Enteroid Model

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Human norovirus (HuNoV) infections can result in chronic infections with serious morbidity and mortality in immunocompromised patients. While there are no FDA-approved medications for treating these infections, nitazoxanide, ribavirin, and enterally-administered pooled immunoglobulin (IVIG) are used off-label on the basis of expert opinion. Nitazoxanide and ribavirin show antiviral activity in a murine norovirus infection model and an *in vitro* replicon model of genotype GI.1 HuNoV RNA expression. However, these drugs have not been evaluated in infections with commonly circulating human norovirus strains. We used the human intestinal enteroid (HIE) system that supports the replication of several HuNoV strains to evaluate the antiviral activities of clinically available drugs, including bile acid sequestrants, acid sphingomyelinase (ASM) inhibitors, nitazoxanide, ribavirin, and IVIG. Antiviral activity was measured based on viral RNA replication 24 or 48 hours after infection of HIEs with or without drug treatment. Cell viability was measured to demonstrate that replication inhibition was not due to cytotoxicity to the HIEs across the therapeutic range of each compound. Antiviral activity was observed with bile acid sequestrants, IVIG and ASM inhibitors. Replication inhibition with nitazoxanide was variable with some cytotoxicity being observed. Ribavirin did not reduce virus replication at any tested concentration. Strain-specific responses were observed with some drugs. HIEs provide a pre-clinical platform to test antivirals against HuNoVs and develop therapeutics to treat norovirus disease.

The Effect of *Limosilactobacillus reuteri* on Maternal Separation Stress in Newborn Mice

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Background: Infantile colic is defined by the "rule of 3s": episodes of crying lasting more than 3 hours a day for more than 3 days a week for more than 3 weeks, resolving during the 3rd month of life, in an otherwise healthy infant. Colicky infants have gut microbial dysbiosis. Even though administration of probiotic *Limosilactobacillus reuteri* DSM 17938 (LR 17938) clinically appears to represent an effective treatment for infantile colic, its mechanism of action is still unknown. Infant crying is multifactorial that could be related to gut dysmotility, hormone alterations, behavioral factors, and/or an increased level of serotonin, and/or psychological factors including inadequate parent-infant interaction, maternal depression, and parental anxiety. Some have proposed reduced levels of melatonin, leading to sleep disturbance. Mice produce ultrasonic vocalizations (USVs) in a variety of social contexts throughout development and adulthood. USVs are whistle-like calls between frequencies of 30 and 90 kHz, which are robust, can be quantitatively analyzed, and may be elicited by quantifiable stimuli such as maternal separation stress.

Objectives: Currently, there are no established animal models for infantile colic. We aimed to gain insight into the mechanism of LR 17938 in improving infantile colic by developing a newborn colic-related animal model. We assessed USV and brain pain/stress gene expression in newborn mice exposed to maternal separation stress.

Methods: Pups were exposed to unpredictable maternal separation (MSU or SEP) or MSU combined with unpredictable maternal stress (MSU+MSUS or S+S), from postnatal days 5 to 14. USV calls and pain/stress/neuroinflammation-related genes in the brain were analyzed.

Results: We defined 10 different neonatal call patterns, none of which increased after MSU. Stress *reduced* overall USV calls. Orally feeding LR 17938 also did not change USV calls after MSU. However, LR 17938 markedly increased vocalizations in mice that were allowed to stay with their dams. LR 17938 modulated mRNA expression of brain genes related to stress and pain. The upregulated genes by LR 17938 were opioid peptides, kappa-opioid receptor-1 genes, and CD200, important in anti-inflammatory signaling. LR 17938 down-regulated CCR2 transcripts, a chemokine receptor, in the stressed neonatal brain.

Conclusions: We interpreted USV calls in newborn mice as "physiological calls" instead of "cries." The USV call patterns that we defined will be important in guiding future studies in other mouse strains. Oral feeding of probiotic *Limosilactobacillus reuteri* DSM 17938 after MSU did not change USV calls but the probiotic modulated cerebral gene expression favoring pain and stress reduction and anti-inflammatory signaling.

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Lighting the viral dark matter: revealing earth's cryptic genosphere through environmental sampling

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Bacteriophages (or phages) are abundant (estimated 10^{31} particles), diverse (in terms of their genome, morphology, and host), and ubiquitous. However, only a small number of phage genomes have been sequenced and around 60-80% of their sequences do not share homology with previously classified genes. Hence, phages represent the largest repository of undiscovered new biology and their parasitic lifestyle suggests that a portion of their gene intertwine with bacterial processes. The main objective of this study is to identify novel phage genes, and their corresponding protein function and structure, that supplant existing bacterial cell processes. To do this, wastewater, freshwater and seawater samples were collected around Austin and Houston, TX. Sludge, solids, and contaminants were removed via centrifugation. The viral fraction was recovered via mixed cellulose esters filter and chemical flocculation, detected with plaque assays and visualized with transmission electron microscopy. Lastly, DNA was successfully extracted, purified, and sequenced from all samples. Raw reads were analyzed via both the iVirus pipeline and MG-RAST, and a DNA library was constructed for functional screening.

Enteric neural crest cells (ENCCs) decrease human intestinal organoid (HIO) epithelial diversity

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Introduction: Short bowel syndrome (SBS) is a devastating disease that is increasing in prevalence in pediatric patients. If left untreated, SBS can result in dehydration, malnutrition, and ultimately, death. While modern therapeutic approaches have reduced mortality, morbidity and cost remain significant. Tissue-engineered intestine may provide a potential solution; however, the complex physiology and function of intestinal tissue has not been demonstrated in existing models. Human intestinal organoids (HIOs) provide a novel approach to generate intestinal tissue *in vitro* but lack some key components, such as the enteric nervous system (ENS). The ENS is critical for intestinal function. Previous studies have incorporated the ENS into HIOs with variable success. By co-culturing ENS-precursors, enteric neural crest cells (ENCCs), with HIOs at an early developmental timepoint we aimed to optimize the integration of ENS tissue into the HIO model.

Methods: HIOs and ENCCs were differentiated from human embryonic stem cells (hESCs) using previously published protocols. GFP-labeled hESCs were used for ENCC differentiation. HIOs were cultured for 28 days in either minigut (HIO) or EN-C (ENCC) media supplemented with growth factors: R-spondin 1, noggin, and EGF to determine to optimal media for co-cultures. HIOs alone, ENCCs alone, and combined HIOs and ENCCs (co-cultured HIOs+ENCCs group) were cultured for 28 days in minigut media. The HIOs alone and ENCCs alone cultures were combined (isolated HIOs & ENCCs group) for RNA isolation and analysis to control for the increased cell number in the co-cultured group. Epithelial, mesenchymal, vascular, and neuronal gene expression was analyzed by RT-qPCR. Epithelial genes were normalized to *CDH1* to control for variability in HIO growth. All other genes were normalized to *GAPDH*.

Results: Microscopy demonstrated a reduction in HIO size and budding with EN-C media compared to minigut media. *CHGA*, *MUC2*, *LYZ*, and *LGR5* were downregulated in EN-C media while *SI* was upregulated. Fluorescence microscopy confirmed that ENCCs survived in minigut media and integrated into the HIOs by day 28. Epithelial markers *HES1*, *CHGA*, *MUC2*, *LYZ*, *SI*, and *LGR5* were downregulated in HIOs co-cultured with ENCCs while neuronal markers *PHOX2B* and *TUJ1* were downregulated in ENCCs co-cultured with HIOs.

Conclusions: HIO growth and epithelial differentiation was reduced by EN-C media with the exception of enterocyte marker *SI*, which was upregulated. ENCCs survived in minigut media and integrated into HIOs. By day 28, ENCCs downregulated epithelial and vascular differentiation markers in HIOs. HIOs in turn, downregulate neuronal differentiation markers PHOX2B and TUJ1 while *ASCL1* and *EDNRB* were unchanged. CDH1 expression was unaffected by ENCC co-culture and microscopy does not show a reduction in HIO size, suggesting ENCCs reduce epithelial diversity, but not growth. Future studies will examine the effects of HIO+ENCC co-culture at earlier timepoints and determine if this result is due to competition for resources or developmental cues provided by the HIOs and ENCCs.

Genetic polymorphisms may differentiate between complicated pediatric small bowel versus colonic Crohn's disease

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Objectives: About 9% of pediatric Crohn's disease (CD) patients experience complications within 3 years from diagnosis in spite of anti-Tumor Necrosis Factor-alpha (anti-TNF) biologic treatment. Within 5 years, such complications may require surgical interventions in up to 20% of cases. Due to the relatively rare nature of these complicated pediatric CD cases within large CD cohorts, traditional genome wide association studies (GWAS) rarely capture this patient population. Our aim was to identify critical genetic associations of anti-TNF refractory complicated pediatric CD subtypes.

Methods: The study was approved by BCM IRB. Included patients had developed CD between the ages of 6 and 18. The Paris classification was used to place patients in the following categories: 1. Anti-TNF refractory *small bowel* CD (RSB-CD): L4b; L4b/B2; or L4b/B2B3 who had or were imminent to have small bowel resection; 2. Anti-TNF refractory *colonic CD* (RC-CD): L2 requiring ileal diversion; or L2/B2; or L2/B2B3 who had or were considered to receive colectomy or partial colonic resection. Whole-exome sequencing (WES) was performed from peripheral blood derived DNA. PLINK (https://www.cog-genomics.org/plink2/) was used to identify enriched single nucleotide polymorphisms (SNPs). The level of significance for exome wide differentiation was relaxed to $p<0.01$. The potential deleteriousness of single nucleotide variants was determined by CADD (https://cadd.gs.washington.edu/). Gene Ontology enRIchment anaLysis and visuaLizAtion tool (GORILLA) was used to compare gene lists associated with colonic enriched SNPs versus ileal enriched SNPs (http://geneontology.org/).

Results: In eight RSB-CD and 11 RC-CD cases, age at presentation, gender, ethnicity, and need for surgery (75% and 55%, respectively) did not significantly differ between the groups. There were 269 genes associated with 277 SNPs that had significantly ($p<0.01$) different allele variation between colonic vs ileal CD. Of these, 170 genes associated with 116 distinct SNPs had a CADD score of >10. Out of the top five SNP candidate associated genes, four (4/5 = 80%: *EFNA3, STEAP1B, DSG1,* and *CYP4F2*) have been already linked with Crohn's disease and/or colitis. GORILLA based investigation indicated that colonic CD associated genes were enriched ($p<0.001$) in biologic function relevant for lipid metabolic process (GO:0006629), small molecule metabolic process (GO:0044281), and organic substance metabolic process (GO:0071704) compared to ileal CD associated genes.

Conclusions: We have uncovered candidate genetic risk loci, which may differentially influence pediatric CD towards developing primarily small intestinal or colonic complications. The discovered loci hold significant potential as novel genetic modifiers, which may set the basis for risk assessment, prevention and personalized treatment against complicated pediatric CD.

Rotavirus NSP4 Viroporin Activity Mimics Endoplasmic Reticulum Ca^{2+} Release Events from Host Channels

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Rotavirus (RV) is the leading cause of life-threatening diarrheal disease in young children, and a hallmark of RV-infection is the elevation of cytosolic calcium ($[Ca^{2+}]$cyto) in the host cell. RV NSP4 is a viroporin in the endoplasmic reticulum (ER) that initiates global changes in $[Ca^{2+}]$cyto by releasing ER Ca^{2+}. During infection, this manifests as a dynamic increase in discrete Ca^{2+} signaling events. Using live Ca^{2+} imaging, we first have defined two distinct types of RV-induced Ca^{2+} signals. Early during infection, RV generates "Ca^{2+} puffs", which are low amplitude, subcellular ER Ca^{2+} signals phenotypically similar to ER release events by host inositol triphosphate receptor (IP3R). Late during infection, RV induces "intercellular Ca^{2+} waves", which are high amplitude Ca^{2+} signals that propagate from infected to uninfected cells by paracrine ADP signaling. Since Ca^{2+} puffs are only observed in RV-infected cells, we hypothesize they are produced by NSP4 viroporin-mediated release of ER Ca^{2+}. First, we found that RV Ca^{2+} puffs are not attenuated by triple knockout of host IP3R Ca^{2+} release channels. Next, we used reverse genetics to generate a panel of RVs with mutations in the NSP4 viroporin domain. Initial studies of these mutants found that the NSP4(N77A) mutant exhibits a significant delay in the onset of Ca^{2+} puffs and reduced total Ca^{2+} signaling per cell, but no delay in RV protein synthesis. Further, the NSP4(N77A) mutant displayed elongated Ca^{2+} puffs. This disruption in RV Ca^{2+} signaling correlated with a decrease in NSP4(N77A) replication. These data indicate that the NSP4 ion channel function of the viroporin domain gives rise to the Ca^{2+} puffs, which suggests that NSP4 is a viral mimic of host ER Ca^{2+} release channels, like IP3R. Continued characterization of NSP4-induced Ca^{2+} signaling will generate new mechanistic insights into how viroporins commandeer host Ca^{2+} signaling pathways for their benefit.

Human Intestinal Organoids as a Discovery Tool for Cronkhite-Canada Syndrome Pathogenesis

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Introduction: Cronkhite Canada Syndrome (CCS) is a rare polyposis syndrome for which the cause remains unknown. Because the disease is so rare (1 in 1 million), no standard of care exists. The disease is most prevalent in males and has an average age of onset at 60 years of age. The case presented is unique as the patient is female and diagnosed at a younger age.

Case Description/Methods: A 38-year-old woman of Asian (Laotian) descent presented in the gastroenterology clinic with fatigue, dizziness, alopecia, dysgeusia, and weight loss. Physical exam revealed onychodystrophy and hyperpigmentation of face and hands. Laboratory testing confirmed iron deficiency anemia with hypoproteinemia and hypoalbuminemia. Anti-gliadin antibodies were negative. A computed tomography scan of her abdomen revealed no significant abnormalities. Endoscopy revealed dozens of erythematous pedunculated polyps in the stomach, duodenum, and ileum while the colon had close to a dozen large pedunculated polyps. Pathology noted no adenomas or dysplasias. However, pathology did note edema, chronic and acute inflammation and prominent eosinophil content. A diagnosis of CCS was made. ***Our lab is the first to generate human intestinal organoids from a CCS patient.*** Organoids were generated from her stomach, duodenum, ileum, and colon biopsies using published methods. The CCS organoids grow faster, larger, and have unique morphologies compared to healthy controls. Cell type analysis also reveals an increased number of secretory cells in the colon and ileum.

Significance: Despite over 50 years of CCS cases, the etiopathogenesis and optimal treatment for CCS remains unknown. Our lab is the first to generate intestinal organoids from a CCS patient. Utilization of *ex vivo* organoid models is an important tool to help us understand disease mechanisms which still remain unknown. In the future we hope to use our organoids as a way to test potential treatments for CCS as no standard of care treatment exists.

SARS-CoV-2 infection and seroconversion in pediatric inflammatory bowel disease patients

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Background: As the Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to evolve, its influence on specific patient populations suffering from chronic disorders becomes increasingly important. Patients with inflammatory bowel disease (IBD) are commonly immunosuppressed with immunomodulators, biologics, and steroids. Therefore, IBD patients have been considered as a risk population for COVID-19. Yet, emerging epidemiologic data may indicate otherwise. It is still unclear, however, how COVID-19 infection affects IBD patients and how seroconversion against the virus might take place depending upon disease states and treatments. We describe a single center cohort of pediatric IBD patients with COVID-19, a subset of whom were tested for seroconversion subsequent to the laboratory test supported infection.

Methods and Results: The electronic medical records of pediatric IBD patients who tested positive for SARS-CoV-2 by nasopharyngeal swab-based PCR testing were included in the study. The clinical course of IBD, concurrent medications, COVID-19 related symptoms, SARS-CoV-2 testing date, and SARS-CoV-2 IgG antibody testing date and result were examined.
A total of 16 pediatric IBD patients at Texas Children's Hospital tested positive for SARS-CoV-2. Six (37.5%) patients were primarily tested due to close contact with a COVID-19 positive person, four (25.0%) due to surveillance, three (18.8%) due to symptoms, and three (18.8%) due to both symptoms and close contact with a COVID-19 positive person. Management was altered in only one of these patients (methotrexate was held for one week) in response to the positive COVID-19 test. Eight (50.0%) ultimately developed symptoms attributed to COVID-19 infection, including fever, sore throat, headache, fatigue, loss of taste, loss of smell, dizziness, cough, nausea, vomiting, abdominal pain, and/or diarrhea; eight (50.0%) were asymptomatic. No patients required hospitalization attributed to COVID-19. Of the 16 patients, 12 (75.0%) were tested for seroconversion. Seroconversion was tested between 2.1 to 18.9 weeks after initial positive SARS-CoV-2 PCR testing with a median of 8.1 weeks (IQR 4.0-12.8 weeks). Ten (83.3%) had positive SARS-CoV-2 IgG, of whom 7 (70.0%) had acute and resolved symptoms and 3 were asymptomatic. Therefore, while all symptomatic patients (7/7) had seroconversion, 3 out of 5 (60%) asymptomatic patients seroconverted.

Conclusions: We describe a cohort of pediatric IBD patients with COVID-19 whose disease course was not significantly affected. A large proportion of patients tested for seroconversion were found to mount a detectable IgG based immune response despite their medical immunosuppression. More research needs to be performed to evaluate the importance of seroconversion with relation to disease course andCOVID-19 reinfection in pediatric IBD patients.

Anti-viral resistance and phage counter adaptation to pandemic *E. coli*

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Background. Extraintestinal pathogenic *E. coli* (ExPEC), often multidrug-resistant (MDR), is a leading cause of urinary and systemic infections. The crisis of emergent MDR pathogens has led some to propose bacteriophage as a therapeutic. However, bacterial resistance to phage is a crucial blockade that we must understand to overcome. While phage-resistance has been explored in laboratory settings, they are poorly understood in therapeutic contexts.

Hypothesis. We hypothesize that phage-resistant isolates of *E. coli* will develop when exposed to phage in a model of murine sepsis, but at the expense of fitness costs that will make them less viable as pathogens.

Methods. We used three *E. coli* strains of sequence type (ST)131, a currently circulating pandemic strain of *E. coli* to develop resistant isolates to ϕHP3, a phage which has been used successfully with two single-use INDs. Using both a plate and murine sepsis model of phage exposure, we developed 21 resisters from the three parental strains. We then performed whole genome sequencing and assessed these resisters' fitness in biologically relevant conditions. We also developed a novel chemostat system which we used to generate an evolved phage isolate with restored infectivity in all LPS-truncated resisters.

Results. We found ExPEC rapidly develops resistance to ϕHP3. Whole genome sequencing of the resisters revealed truncations in genes involved in LPS biosynthesis, the outer membrane transporter *ompA*, or both; implicating them as receptors for this phage. Interestingly, resisters were attenuated in blood and demonstrated decreased virulence in a murine model of *E. coli* systemic infection. Several of the animal-derived resisters were also attenuated in urine, suggesting a greater hit to fitness under infection conditions. When evolved against a resister, ϕHP3 quickly regained efficacy against the target isolate and, strikingly, all the other resisters as well.

Conclusions. Our findings suggest that although resistance of pathogenic *E. coli* to our phage is inevitable, it comes at a fitness cost in its mammalian host, and new phage variants can be readily isolated by directed evolution.

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Retrospective Analysis Screening Colonoscopy in Otherwise Healthy 75 Years and Older Patients at MD Anderson Cancer Center

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Introduction: Adenomatous polyps of the colon are neoplastic growths that can become malignant. To reduce the incidence of colon cancer, guidelines have been developed to detect and remove adenomatous polyps before cancer develops. Overall, current guidelines recommend stopping screening at age 75. Some guidelines allow screening to continue provided that the patient wishes, and they are expected to live greater than 10 years. Faculty at MD Anderson Cancer Center tend to follow this later recommendation.

Objective: To examine the effect of the current MDACC colon cancer screening practices in patients 75 years and older to determine the adenomatous polyp and colon cancer detection rates and outcome in terms of colon cancer and all-cause mortality.

Methods: This was a retrospective chart review study that involved records of 5,665 patients, who had undergone colonoscopy at age 75 years or older, at MDACC between dates Jan. 5, 2001 and Jan. 1, 2020. Patients that underwent colonoscopy for diagnostic or therapeutic purposes were excluded. The study population included 415 patients that experienced a total of 430 colonoscopies, mean age 79years (range 75-92), who underwent screening colonoscopies at MDACC. Biomedical data was extracted from charts including total number with adenomatous polyps or adenocarcinoma as well as their outcomes, colon cancer mortality, and all-cause mortality.

Results: Adenomatous polyps or colon cancer was found in 52%; 95% CI 47%-57% (216 of 430). Adenomas were found in 44.4% CI 39.7-49.1%; 5.8% CI 3.6- 8.0% had adenocarcinomas. Finally, a total of 214 people were found to have no adenomas or adenocarcinoma on exam (49.8% CI 45.0-54.5%). The average age of an individual that underwent colonoscopy and had adenomas on exam was 79 years. The average age of death of a patient that had adenomas on colonoscopy was 79. The average age of death for someone that had adenocarcinoma was 77, and the average age of death for people with no adenomas or adenocarcinoma was 81.2. The death rate of someone with adenomas (6.8% CI 3.2-10.4%) was compared to the death rate of someone without adenomas on exam (7% CI 3.6-10.4%). Overall, this study delineated that there is a one in two chance that someone 75 years or older will have some type of colonic adenoma and a 6.8% chance of CRC. Since half the population examined were determined to have an increased risk of adenomas or cancer, screening should continue beyond the age of 75 years old.

Conclusion: Of the 216 CRC patients with adenomas, none are reported to have advanced to carcinoma during our observation period within 2001-2020. Therefore, the early detection of adenoma and their removal seems helpful in preventing adenocarcinoma.

Rotavirus degradation of DGAT1 causes increased viroplasm formation and viral yield

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Rotavirus (RV) infects enterocytes and enteroendocrine cells of the small intestine and causes life-threatening diarrhea. RV infection primarily targets infants and children and causes over 125,000 deaths annually. In infected cells, RV assembles viroplasms, cytoplasmic bodies for genome replication and initial particle formation. Viroplasm assembly requires viral proteins NSP2 and NSP5 in association with cellular proteins and lipid storage organelles called lipid droplets (LDs). LDs are vital to viroplasm formation and RV replication and their formation is induced during RV infection. Disruption of LD formation inhibits viroplasm assembly and virus replication. However, the cellular mechanism for lipid droplet formation as well as the RV mechanism for inducing LD formation are unknown. One essential step in LD formation is the synthesis of neutral lipids. DGAT1, an endoplasmic reticulum membrane protein, is the terminal enzyme for neutral lipid synthesis. During RV infection two forms of NSP2 are observed in infected cells, a cytoplasmically dispersed (dNSP2) and viroplasmic (vNSP2) form. We have observed that viral protein dNSP2 interacts with DGAT1 during infection. We hypothesized that dNSP2 interaction with DGAT1 triggers neutral lipid synthesis and subsequent viroplasm/LD formation. Although we initially predicted that DGAT1 expression or function would increase during RV infection, we observed the opposite effect. RV-infection leads to proteasome-mediated degradation of DGAT1. In cells with DGAT1-silenced or knocked out, RV infection produces a higher yield of infectious particles. RV infection increases viroplasm/LD formation and formation occurs earlier in DGAT1-silenced cells than in irrelevant siRNA-silenced cells. These finding suggest that RV mediated DGAT1 degradation may be the trigger for LD budding required for viroplasm/LD assembly. Future research will determine the interacting domains between dNSP2 and DGAT1, how DGAT1 is degraded by the proteasome, and whether DGAT1 degradation is the trigger for LD budding from the ER.

Abnormal phospholipids underlying malnutrition-associated steatosis

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Background: Malnutrition in early life often results in acute liver damage. Children with severe acute malnutrition and adolescents with anorexia nervosa are at high risk of liver damage in the form of steatosis. Similarly, small-for-gestational-age, underweight newborns are at increased risk of non-alcoholic fatty liver disease (NAFLD) later in childhood. Mechanisms by which malnutrition causes fatty liver disease – and more generally, mechanisms by which NAFLD occurs in lean individuals – are poorly understood. Phospholipids play major roles in the structure and function of lipid membranes. Phospholipids package triglycerides and cholesterol either for storage inside of cells as lipid droplets or for secretion as very low density lipoprotein (VLDL). More than half of the liver's total phospholipid content occurs as phosphatidylcholine (PC) and phosphatidylethanolamine (PE). PC and PE levels are tightly regulated by three complex enzymatic pathways: 1) biosynthesis of PC or PE; 2) degradation of choline (the substrate for PC synthesis); and 3) conversion of PE into PC. In healthy liver tissue, the molar ratio of PC/PE is maintained strictly between 1.5 and 2.0. Molar ratios outside of this range have been implicated in the pathogenesis of NAFLD. The aim of this study is to characterize abnormal lipid accumulation and phospholipid regulatory pathways in an early-life mouse model of malnutrition.

Methods: C57BL/6 mice were weaned to a low-protein low-fat chow or isocaloric control chow and livers were harvested at 8 weeks of age. Steatosis was visualized using frozen sections stained with oil red O and magnified at 200x; staining was quantified with ImageJ. Expression levels of enzymes participating in the three pathways that regulate PC and PE levels were assessed by western blot.

Results: Livers from malnourished mice exhibited profound macrovesicular steatosis, with 15-fold ($P = 0.029$) increased oil red O staining compared to livers from control mice. Malnourished livers contained reduced levels of one or more proteins in each of the three enzymatic pathways. These included the PC-synthesizing enzyme CTP:phosphocholine cytidyltransferase (28% decrease, $P = 0.009$); the choline-degrading enzymes aldehyde dehydrogenase 7 family member A1 (45% decrease, $P = 0.007$), betaine-homocysteine methyltransferase (48% decrease, $P=0.004$), and glycine N-methyltransferase (39% decrease, $P = 0.04$); and the PE-to-PC converting enzyme PE-methyltransferase (67% decrease, $P = 0.007$).

Conclusions: Macrovesicular steatosis is present by 8 weeks of life in mice subjected to early postnatal malnutrition. The malnourished liver contains reduced quantities of multiple enzymes that regulate PC and PE concentrations, suggesting that the PC/PE ratio may be abnormal. Restoration of PC and PE homeostasis warrants exploration as a potential therapeutic avenue to ameliorate malnutrition-induced fatty liver disease.

Defective Fe-S cluster biogenesis in malnutrition impairs heme and bile acid synthesis

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Background: Bile acids (BAs) are cholesterol derivatives synthesized by hepatocytes. BAs play indispensable roles in child growth by emulsifying dietary fats in the intestinal lumen and by acting as signaling molecules that regulate metabolism throughout the body. Malnourished children have impaired liver function including decreased BA synthesis, which causes fat malabsorption and multiple metabolic abnormalities. Using a low-protein low-fat diet (LPLFD) to model malnutrition in mice, we recently reported that decreased BA synthesis leads to decreased farnesoid-X-receptor (FXR) activation and decreased expression of FXR-dependent coagulation factors resulting in coagulopathy. Mechanisms underlying decreased BA synthesis in malnutrition remain unknown. The rate-determining enzyme in the classic pathway of BA synthesis, CYP7A1, uses cholesterol as a substrate and requires heme as an essential cofactor. LPLFD livers contain normal levels of CYP7A1 protein and 2-fold increased levels of cholesterol. These observations led us to speculate that most CYP7A1 in the malnourished liver is in the enzymatically inactive Apo-form (not bound to heme). Heme synthesis occurs in 8 enzymatic steps beginning with the TCA cycle product succinyl-CoA and ending with incorporation of iron into protoporphyrin rings by the enzyme ferrochelatase (FECH). Two of the 8 heme-synthesizing enzymes, δ-aminolevulenic acid dehydratase (ALAD) and FECH, require iron-sulfur (Fe-S) clusters as cofactors for stability and function. Similarly, 6 of the 8 TCA cycle enzymes that synthesize succinyl-CoA require Fe-S clusters. Fe-S cluster biogenesis requires both iron and sulfur-containing amino acids. Malnourished children and LPLFD mice have low circulating levels of sulfur-containing amino acids. Thus, we hypothesize that malnutrition impairs Fe-S cluster biogenesis, in turn leading to 1) reduced succinyl-CoA resulting from TCA cycle dysfunction, and 2) reduced ALAD and FECH levels and activity. These events decrease the synthesis of heme, causing decreased CYP7A1 activity and decreased BA synthesis in the malnourished liver.

Methods: C57BL/6 mice were maintained on LPLFD or isocaloric control chow. At 8 weeks of life livers was harvested for heme quantification and for western blots to measure expression levels of enzymes that synthesize Fe-S clusters and heme. AML12 mouse hepatocytes were maintained in special media mimicking LPLFD conditions, and *in vitro* BA synthesis was quantified by ELISA in the presence or absence of the sulfur-containing amino acids methionine and cysteine.

Results: LPLFD reduced levels of multiple enzymes that mediate Fe-S cluster biogenesis, including iron-sulfur cluster assembly scaffold protein IscU by 33% (P=0.006) and desulfurase-interacting protein 11 by 33% (P=0.038). LPLFD also reduced levels of FECH by 39% (P=0.001) and of lipoic acid synthase, which enables lipoylation of TCA cycle enzymes, by 68% (P=0.006). LPLFD reduced hepatocyte heme by 44% (P=0.002). We observed no apparent defect in iron storage based on normal levels of ferritin and iron regulatory proteins, thus implicating deficiency of sulfur-containing amino acids as the key underlying event. Indeed, impaired BA synthesis by AML12 cells in LPLFD media was restored completely by adding back methionine and cysteine.

Conclusions: The malnourished liver contains reduced levels of proteins that generate Fe-S clusters, reduced levels of heme-synthesizing enzymes that require Fe-S clusters, and reduced levels of heme, which is the essential cofactor for CYP7A1 activity and BA synthesis. Sulfur-containing amino acids positively regulate BA synthesis *in vitro*, instilling hope for new amino acid-based therapies to treat malnutrition-induced liver dysfunction and improve child growth.

Insulin-like growth factor-1 disturbances in a mouse model of global *Slc7a7* deficiency

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Lysinuric protein intolerance (LPI) is a severe inborn error of metabolism, characterized by urea cycle dysfunction, growth failure, osteoporosis, immune dysfunction and renal disease. LPI is caused by biallelic pathogenic variants in *SLC7A7*, which encodes the light subunit of the y^+LAT1 transporter, essential for intestinal absorption and renal reabsorption of arginine, lysine and ornithine (cationic amino acids). We recently published the generation of our *Slc7a7*$^{-/-}$ mouse model on a mixed C57BL/6 x 129/SvEv background that recapitulates the human disorder, including the biochemical phenotype, growth delay, and renal dysfunction. Disturbances in insulin-like growth factor-1 (IGF-1) and growth hormone (GH) disturbances have been reported in some individuals with LPI and has been hypothesized to contribute to the growth delay in this disorder.

Our objective was to investigate underlying disease mechanisms contributing to growth delay in *SLC7A7* deficiency. Using CRISPR technology, we developed a *Slc7a7*$^{-/-}$ mouse model on a mixed C57BL/6 x 129/SvEv F2 background, which harbors a deletion of exons 3 and 4 resulting in a premature frameshift mutation. Due to preweaning lethality and growth failure of *Slc7a7*$^{-/-}$ versus wild type (WT) mice, tissues were harvested at P14-18. We observed reduced hepatic RNA expression of *Igf1* in *Slc7a7*$^{-/-}$ mice versus WT littermates at P14-P18. However, we observed no consistent trends in the hepatic protein expression of IGF-1 *Slc7a7*$^{-/-}$ and WT littermates at P14-18. Plasma concentrations of IGF-1 were approximately 80% lower in *Slc7a7*$^{-/-}$ mice compared to WT littermates at P14-P18, using an enzyme-linked immunoabsorbent assay (ELISA). Importantly, we have previously reported low plasma concentrations of arginine, ornithine and lysine in our *Slc7a7*$^{-/-}$ mouse model, suggestive of cationic amino acid deficiency. Given that arginine is an IGF-1 secretagogue, we hypothesize that the growth delay in *Slc7a7*$^{-/-}$ mice may be due, in part, to disturbances in IGF-1 associated with arginine deficiency. In combination with a timed mating approach, pregnant *Slc7a7*$^{+/-}$ F1 mice were administered L-citrulline supplemented drinking water (1,000 mg/kg) or untreated drinking water throughout gestation. Embryos were harvested at E17.5. Preliminary data suggests that the body weights of *Slc7a7*$^{-/-}$ embryos harvested from pregnant mice that were treated with sterile water were approximately 19-25% lower compared to *Slc7a7*$^{+/-}$ and WT embryos, suggestive of intrauterine growth restriction. Interestingly, maternal L-citrulline supplementation was associated with a 15% reduction in the body weights of *Slc7a7*$^{-/-}$ embryos compared to *Slc7a7*$^{-/-}$ embryos that received maternal untreated drinking water. Regardless of genotype and treatment, the embryo to placenta weight ratios (an indirect measure of placental efficiency) were similar among groups. To test if the intrauterine growth restriction associated with *Slc7a7* deficiency can be improved by increasing circulating levels of IGF-1, intervention studies with maternal intraperitoneal injections of recombinant IGF-1 will be pursued.

The *Slc7a7*$^{-/-}$ mouse model demonstrates growth delay and possibly IGF-1 disturbances that are consistent with the human LPI disorder. Maternal L-citrulline supplementation did not improve intrauterine growth restriction in *Slc7a7*$^{-/-}$ embryos. Future studies to investigate the efficacy of maternal injections of recombinant IGF-1 on intrauterine growth restriction in *Slc7a7*$^{-/-}$ embryos are on-going.

SA-1 Knockdown induction cancer stem cell Warburg effect Markers: Potential Mechanism for Increased Colon Cancer Risk

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The role of chromatin modulators in colon carcinogenesis is becoming increasingly understood. The cohesin stromal antigen (SA-1) is important in gene expression via chromatin looping juxtaposing enhancers/promoters with initiation of transcription. While SA-1 is infrequently mutated, we have demonstrated that SA-1 expression is markedly decreased early in colon carcinogenesis and this is particularly accentuated in Africana Americans (Todoric et al., 2016). We know wanted to evaluate the mechanism of action. Intestinal stem cells (ISCs) number mirror CRC risk (Tomasetti C et al., 2017) whereas in frank tumors, cancer stem cells (CSCs) are thought to be involved in chemoresistance and thus poor prognosis. While ISCs and CSCs share stem cell markers (e.g. LGR5 and CD133) and metabolically may lead to Warburg physiology (preferential utilization of glycolysis). In this study, tested the hypothesis that SA-1 loss may lead to stem cell induction with or without metabolic changes

Methods: The HT-29 (1.5X105) cells were transiently transfected with SA1 siRNA (5 µM, Dharmafect) for 48 HPT. From each well, the transfected cells were processed individually in the same condition as replicates (Cuadrado et al., 2019). For RTPCR assay, the total RNA from SA1 knockdown HT-29 cells was isolated using TRIzol method. The RNA (0.1µg/ul) was reverse transcribed into cDNA using the High Capacity cDNA Reverse Transcription kit. The quantitative validation of the expression of targeted genes was performed by Fast Real-Time PCR System StepOne method. Further, the expression level was normalized to GAPDH (housekeeping gene) and determined as fold change. FACS analysis for protein expression, the conjugated LGR5 and CD133 antibody were titrated to detect the concentration (0.5 mg/mL and 0.125 mg/mL) to be used. The SA-1 KD HT- 29 cells were fixed with neutralized formalin (10%) for 10-15 min. The pellet was suspended in 1ml permeabilization buffer (1X) and centrifuged (1000 rpm, 4°C for 5 min). Sequentially, treated with LGR5 and CD133 (100 µl) for 30 min. Finally, suspended in 250 µL staining buffer and filtered to avoid the clumped cells. The sample was run on LSR Fortessa. The data was retrieved through Cellquest Pro software and analyzed by FLOWJO software package (Viny et al., 2019).

Results: We determine whether SA-1 modulation could lead stem cell phenotype and Warburg effect. As a result of transient transfection, 90% decrease in SA-1 gene with the p value of 0.015 was quantified. Interestingly, with regards to the successful SA-1 transient knockdown, the robust upregulation in LGR5 to about 383.2% (p value 0.00481) and CD133 to 144.7% (p value 0.1) in mRNA level were obtained through qPCR. FACS analysis confirmed upregulation of LGR5 and CD133 (34% and 11% respectively) and these more modest effects may be related to kinetics of transient transfection with the lag between mRNA and protein. We then assessed the role of SA-1 in Warburg effect. Previous studies have shown that earlyin colon carcinogenesis, there was elevation in a Warburg proteins including Glut-1, hexokinase 2 (HK-2), lactate dehydrogenase A (LDHA) and pyruvate kinase M (PKM) (Cruz, M.D et al., 2017). Therefore, the role of SA1 in colon cancer metabolism was understood with the expression of 190% (Glut1), 251% (HK2), 246% (LDHA), 40% (PKM) and their significant p values (0.008, 0.01, 0.01 and 0.4) correspondingly.

Conclusions: We demonstrate, for the first time, that SA-1 downregulation leads to induction of stem cells as indicated by both stem cell markers with indication of Warburg. Given the selective loss of SA-1 in African Americans, this may be a potential mechanism for racial disparities in CRCC.

Improving adherence to gastric intestinal metaplasia clinical practice guidelines among gastroenterologists at a U.S. academic institution

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Background: Gastric cancer (GC) is the 5th leading cause of cancer-related mortality worldwide. Endoscopic surveillance of gastric intestinal metaplasia (GIM) may lead to earlier GC detection. Recent guidelines from the American Gastroenterological Association (AGA) emphasize *Helicobacter pylori* treatment and surveillance after GIM diagnosis. Adherence to GIM guidelines among U.S. gastroenterologists is unknown. Our aim was to examine variation in management of GIM and acceptance of a standardized GIM protocol among gastroenterologists at a U.S. academic hospital. **Methods:** This was a pre- and post-intervention study. For the pre-intervention study, we randomly sampled 50 patients diagnosed with GIM on gastric biopsy from a histopathology database at the Michael E. DeBakey VA Medical Center (MEDVAMC) between 1/2016-12/2019. We abstracted *H. pylori* testing, endoscopy, and histopathology data on electronic medical record review. We developed a protocol for GIM management based on feedback from 14 gastroenterologists including endoscopic identification of GIM, GC risk factors, and surveillance recommendations based on AGA and European GIM guidelines (Figure 1). All gastroenterologists received education on the protocol, and the protocol was placed in each endoscopy room. For the post-intervention study, we surveyed 9 gastroenterologists and assessed change in GIM management in a separate cohort of 35 patients diagnosed with GIM between 4/2020-10/2020. **Results:** In 50 patients diagnosed with GIM prior to our intervention, GIM was endoscopically identified and gastric biopsy location was specified (i.e., antrum and corpus biopsies placed in separate jars) in only 8 patients (16%). Only 10 patients (20%) with GIM had a second *H. pylori* test in addition to histopathology, and subsequent gastric mapping biopsies were performed in 11 (22%). Among the 35 patients diagnosed with GIM post-intervention, gastric biopsy location was specified (i.e., antrum and corpus in separate jars) in 31 patients (91%) and additional *H. pylori* testing was recommended in 18 patients (53%). Furthermore, because gastric biopsies location and therefore extent of GIM was known in 91% of patients, gastric mapping biopsies were not necessary. Finally, among 9 gastroenterologists who participated in the intervention, familiarity with GIM guidelines increased from 33% to 77% with the intervention. Six gastroenterologists expressed greater comfort managing GIM (66%), and 7 stated that the protocol had a large impact on their clinical practice (77%). **Conclusions**: Practice guidelines regarding management of GIM are not consistently followed. We found that a standardized hospital protocol for GIM management and education of gastroenterologists increased adherence to *H. pylori* testing and GIM surveillance recommendations and increased comfort in managing GIM among gastroenterologists.

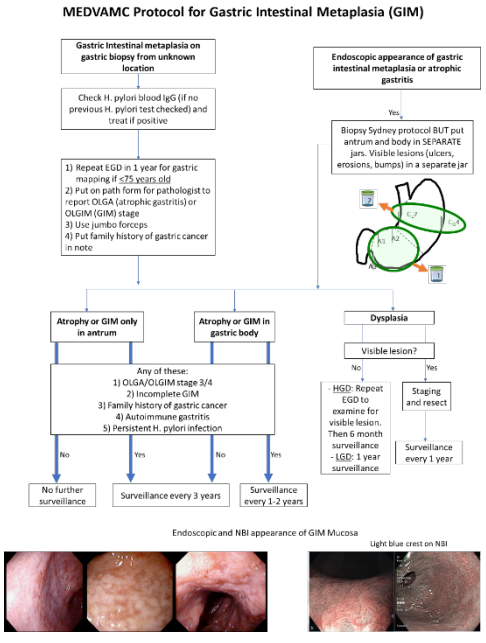

Figure 1. Michael E. DeBakey VA Medical Center Protocol for Gastric Intestinal Metaplasia Management adapted from 2020 American Gastroenterological Association and 2019 European Society of Gastrointestinal Endoscopy Guidelines.

Evaluation of the role of sphingosine-1-phosphate receptor 2 in bile acid-mediated replication of bile-dependent human noroviruses

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Human noroviruses (HuNoVs) are the leading cause of foodborne illness and acute viral gastroenteritis. Previously we reported that human intestinal enteroid (HIE) cells are permissive to infection with multiple HuNoV strains and that some strains (e.g., GII.3) replicate only in the presence of bile. Subsequently we found that hydrophobic bile acids (BAs) are an active component in bile required for GII.3 replication in jejunal HIEs. We aimed to determine how BAs were interacting with jejunal HIEs and the mechanism by which they promote infection of BA-dependent HuNoV strains. Using the highly effective conjugated BA, glycochenodeoxycholic acid (GCDCA), we show BA-dependent replication in HIEs is not mediated by detergent effects or classical farnesoid X receptor (FXR) or Takeda G-protein-coupled receptor 5 (TGR5) signaling. Instead, replication involves another G-protein coupled receptor (GPCR), sphingosine-1-phosphate receptor 2 (S1PR2). Interestingly, inhibition of S1PR2 only significantly reduces GII.3 and GII.17 (BA-required) infection but not GII.4 (BA-independent) infection, providing further demonstration of strain specific differences in HuNoV infection. GII.3 replication is also BA-dependent in ileal HIEs. S1PR2 inhibition during GII.3 infection of an ileal line also reduces replication indicating a common mechanism of BA-dependent infection among multiple segments of the small intestine. We found that GCDCA induces multiple cellular responses that promote GII.3 replication in HIEs, including (i) enhancing endosomal uptake, (ii) endosomal acidification and subsequent activity of endosomal/lysosomal enzyme acid sphingomyelinase (ASM), and (iii) enhancing ceramide levels on the apical membrane. In the presence of the S1PR2 inhibitor, BA-triggered endocytosis in HIEs is decreased indicating some of the infection-promoting effects of BA treatment require S1PR2. Together, our results support a model where BA-dependent HuNoV strains exploit rapid BA and S1PR2-mediated cellular endo-lysosomal dynamic changes to enter and replicate in HIEs. Our current studies are pursuing the mechanism by which BA activation of S1PR2 stimulates cellular changes such as increased endocytosis and regulates small intestinal biology.

The volume-regulated anion channel (VRAC) mediates intercellular calcium waves in rotavirus infection

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Globally, acute gastroenteritis is the second leading cause of mortality among children under five years old. Despite multiple vaccines, rotavirus (RV) is the most common etiology. RV remains a tremendous problem due to the lack of effective therapeutics to directly combat its pathogenesis. To allow for the development of such therapeutics, we must first improve our understanding of RV disease. One particularly puzzling aspect of RV pathogenesis is that infection of relatively few cells can drive severe up regulation of secretory activity throughout the entire intestinal epithelium. This suggests a role for paracrine signaling through which RV-infected cells augment the secretory activity of neighboring uninfected cells, but until recently no paracrine signal had been identified. In the Hyser lab, we recently identified ADP as a paracrine signal released from RV-infected cells. This ADP triggers intercellular calcium waves (ICWs) that spread through uninfected cells, dysregulating calcium (Ca^{2+}) signaling pathways to drive secretion. Blocking the ADP receptor P2Y1 reduces disease severity in mice, suggesting that this signaling is integral to RV pathogenesis. However, we have yet to determine how ADP is released from infected cells. In order to determine the ADP release pathway we performed a drug screen. We performed long-term live Ca^{2+} imaging of RV-infected monolayers of GCaMP6s-expressing cells and treated with inhibitors of various ADP release channels. By counting the number of Ca^{2+} spikes in uninfected neighboring cells either three (NB3) or five (NB5) cells away from the infected cells we can quantify the number of intercellular Ca^{2+} waves throughout infection. We found that inhibitors of the volume-regulated anion channel (VRAC) consistently reduced the number of intercellular Ca^{2+} waves, while inhibitors of connexin hemichannels, pannexins, maxi-anion channels, or vesicular exocytosis did not. To further test this finding we generated a line of HEK293 cells that express GCaMP6s and used CRISPR-Cas9 to knockout *LRRC8A*, the obligatory subunit of VRAC. Cells that lack LRRC8A, and therefore lack VRAC, showed a significant reduction in the number of intercellular Ca^{2+} waves during rotavirus infection, further implicating VRAC in RV-induced ADP release. VRAC is increasingly recognized for its role in a variety of pathological and physiological processes, but the mechanisms regulating its activation remain elusive. Our ongoing studies aim to use RV as a tool to better understand the intracellular pathways regulating VRAC activity. Furthermore, we plan to use human intestinal enteroids and the mouse model of RV diarrhea to evaluate VRAC as a therapeutic target and understand its role in secretory activity within the intestinal epithelium.

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Role of PLIN1 in Rotavirus Viroplasm/Lipid Droplet Formation

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Rotavirus (**RV**) infection causes severe gastroenteritis and dehydrating diarrhea in infants and young children under 5 years of age. RV infects mature enterocytes and enteroendocrine cells of the small intestine, leading to over 128,000 deaths annually. RV is a segmented double-stranded RNA virus that encodes for six structural proteins that comprise the virus particle and six non-structural proteins required for viral replication. RV replicates in viroplasms (**VI**), an intracellular compartment whose formation requires the non-structural proteins NSP2, NSP5, cellular proteins and lipid droplet (LD) components. Blocking LD formation in RV-infected cells significantly reduces VI formation and production of viral progeny. LDs are dynamic structures composed of a hydrophobic lipid core comprised of triglycerides (**TG**) and sterol esters surrounded by a phospholipid monolayer and the LD-associated protein perilipin (**PLIN1-5**). The PLIN proteins insert into the LD surface, providing physical stability to the droplet and act as a barrier to adventitious lipolysis of the TG core. The products of lipolysis are diacylglycerol (DAG) and fatty acids, which are involved in several metabolic processes, including beta oxidation for ATP production and phospholipid biogenesis. **However, it is unknown whether the PLIN proteins are required for LD/VI formation.** Because RV infection induces and requires LD formation as a platform for virus assembly and replication, this system can be used as a tool to explore PLIN protein regulation in LD formation and their roles during RV-induced pathogenesis. Our preliminary data demonstrate that RV infection induces PLIN1-coated LDs that colocalize with VI. PLIN1 is rapidly degraded by the proteasome in uninfected cells, but it is stabilized in RV-infected cells. These observations led us to explore whether NSP2 or NSP5 directly interacts with PLIN1 LDs during RV infection. Our coimmunoprecipitation results demonstrated that PLIN1 interacts with NSP2, suggesting that the NSP2-PLIN1 interaction may play a role in LD induction. The TG in the VI/LD also disappear over time during RV infection, suggesting that the phosphorylation of these PLIN1-coated LDs undergoes lipolysis. Lipidomic analysis of RV-infected cells demonstrates that phospholipid synthesis is upregulated, including phospholipids necessary for LD formation suggesting lipolysis of the LD contributes to phospholipid biogenesis. However, it is not known whether PLIN1 is required for LD/VI formation and how PLIN1-NSP2 interactions regulate lipolysis for phospholipid synthesis. Elucidating the mechanisms by which PLIN1 contributes to LD/VI formation will provide new insight for RV-induced pathogenesis and LD-associated pathologies.

Gut Bile Acid-FGF19 Signaling Is Lower in Preterm vs Term Neonatal Pigs

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Background: Reduced growth and poor response to enteral feeding are frequent comorbidities with preterm birth. Poor growth in preterm infants has been linked to poor digestion of dietary fats due to low hepatic bile acid production. Bile acids are also key regulators of metabolism and when secreted into the gut they activate the farnesoid X receptor (FXR) in ileal epithelial cells and trigger the secretion of fibroblast growth factor 19 (FGF19). FGF19 functions as a metabolic hormone with insulin-like actions that stimulate anabolic pathways, such as protein synthesis, and potentially growth. The aim of this study was to explore the how gestational age and feeding status affect bile acid pools, plasma FGF19 and FXR target genes involved in the FXR-FGF19 signaling in term and preterm pigs.

Methods: Thirty-two neonatal pigs were delivered at gestation days 105 (preterm) and 114 (term) via C-section. Some pigs were euthanized at birth and the remaining pigs were given total parenteral nutrition and fed a bolus meal of milk formula on day 3. Blood was collected hourly for 4 hours postfeeding and then tissue was collected on day 3.

Results: The total bile acid pool, including the liver, gallbladder, small intestinal tissue and contents and colon contents was greater in term than preterm pigs (59.8 vs 35.2 uMol/kg BW). Expression of hepatic enzymes involved in bile acid synthesis did not differ between preterm and term pigs. However expression of bile acid transporters NTCP and BSEP were lower in preterm pigs compared to term pigs. FGF19 expression was highest in the Ileum compared to the muscle, jejunum, liver, and hypothalamus, and greater in term than in preterm pigs. Plasma FGF-19 at birth and the response to feeding on day 3 was higher in term compared to preterm pigs.

Conclusions: Lower expression of hepatic bile acid transporters in preterm pigs, despite similar expression of bile acid synthesis enzymes, resulted in a smaller intestinal bile acid pool in preterm pigs. The smaller gut bile acid pool resulted in lower ileal FGF19 expression and plasma FGF19 levels in preterm pigs. Future studies are aimed at investigating whether lower circulating FGF19 concentrations impact growth and metabolism in preterm compared to term pigs.

Use of Androgen Lowering Medications Finasteride and Dutasteride Do Not Substantially Alter Risk of Incident HCV-Related Hepatocellular Carcinoma in Men

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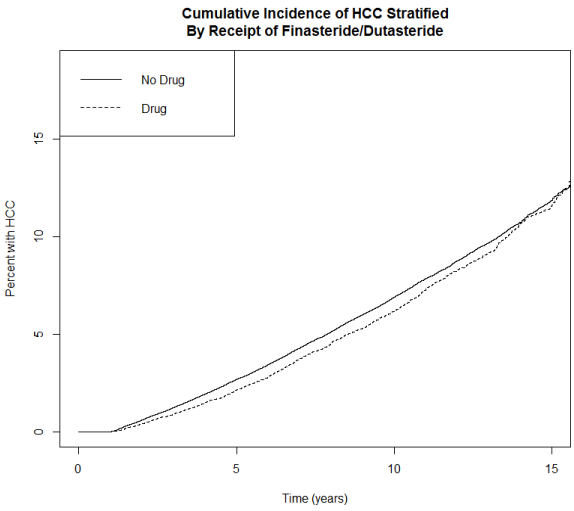
Background: Gender-defining differences in sex hormones are believed to contribute to the large male excess risk for hepatocellular carcinoma (HCC) across populations and etiologies. It is unknown if use of widely available 5-alpha reductase inhibitors (5AR-Is) finasteride and dutasteride, which lower potent androgen dihydrotestosterone (DHT) levels, most commonly used for treatment of benign enlarged prostate symptoms in aging men, alters risk of incident hepatitis C virus (HCV)-related HCC risk. **Methods:** We performed a retrospective population-based cohort study using nationwide Veterans Affairs (VA) healthcare databases (1/1/2002-12/31/2017). Eligible HCV+ male veterans were aged 18-80, without HCC, non-in situ prostate cancer or sex hormone modifying cancers or cancers treated with sex hormone targeting therapies (e.g., testicular, adrenal) at/pre-index date (date of first HCV+ code/lab in the study period), and not developing them or dying within the first year of follow-up. We used diagnostic codes, pharmacy, and labs to define and characterize: HCV (including if SVR achieved), hepatopathology (cirrhosis, FIB-4), and confounders—sociodemographic (race, age, marital status, homeless), comorbidities (obesity, hypertension, HIV, diabetes, HepB), utilization (enrollment time, insurance), other meds dispensed >=30 consecutive days (opioid antagonists like methadone, spiralactone, glucocorticosteroids, androgens), and risk factors (alcohol/opiod/substance abuse). We used the cancer registry or previously validated presence >=2 ICD codes in in-patient and out-patient visit files to identify HCC and other sex hormone modifying cancers, and the VitalStatus files for death. We calculated annual age-adjusted incidence of HCC for 5AR-I users and non-users, and compared Kaplan-Meier survival curves using the log-rank test. Multivariable extended Cox models were used to assess time-dependent association between finasteride/dutasteride use and incident HCC risk. **Results:** Our cohort consisted of 215,467 HCV+ men, with average age ~54 years, with 53% White non-Hispanic and 33% African-American, ~36% cirrhosis at baseline, with 18,063 (8.4%) used 5AR-I in the study period (>98% finasteride) with 5AR-I use greater than twice as common as use of supplemental androgen therapy. A total of 12,178 incident HCCs developed in our study cohort. 5AR-I users were significantly more likely to be older, African-American, & cirrhotic. Cumulative HCC incidence was slightly lower in finasteride /dutasteride users compared to non-users (6.87/1000 person years vs. 7.05). Log rank analysis indicated significant differences in Kaplan-Meier curves for finasteride/dutasteride users vs. non-users. (Figure 1) Time dependent use of Finasteride/Dutasteride was associated with significant 25% excess risk in univariable analysis (crude hazard ratio (HR)=1.26, 95% CI 1.17-1.35, P<0.001) that was reduced to 11% excess in fully adjusted multivariable model (HRadj=1.11, 95% CI: 1.04-1.19, p<0.003). **Conclusion:** Although our results are mixed, with significant slightly lower cumulative HCC incidence in HCV+ male veterans who used 5AR-Is yet significant slightly higher adjusted relative risk; collectively they suggest that 5AR-I use overall and use of the most widely prescribed 5AR-I, finasteride, are not associated with clinically meaningful differences in risk of subsequently developing HCC in HCV+ men. However, given the very low utilization of the more potent as well as more recently available 5AR-I, dutasteride, in our VA cohort, additional research is needed to validly and reliably establish if its association with HCC is similar to that observed with use of finasteride.



Profiling of pancreatic immune cell infiltration patterns in mouse acute pancreatitis

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Background: Acute pancreatitis (AP) is associated with significant morbidity and mortality. Approximately 50% of AP cases in the United States are alcohol-induced. Immune cells play critical roles during AP, however, a systemic evaluation of immune cell infiltration patterns in AP is lacking. In this study, we used multi-dimensional flow cytometry to profile infiltrating immune cells in the pancreas in several AP mouse models.

Methods: AP was induced in male adult C57BL/6 mice in three models: 1) Cerulein (CAE) model: CAE injection (50 μg/kg, ip, 9 hourly); 2) Alcohol + palmitoleic acid (POA) model: alcohol (1.32 g/kg, ip) and POA (4 mg/kg, ip, 1 hour apart) injection; 3) Alcohol + CAE (low dose) model: 5% alcohol liquid diet feeding for 2 weeks and CAE injection (50 μg/kg, ip, 3 hourly). Mice without treatment were used as baseline controls. All mice were euthanized 16 hours after AP induction. Primary pancreatic cells were prepared, and multi-dimensional flow cytometry was performed using following panels: Panel 1 (for innate immune cells and B cells): CD45, CD5, CD161, Ly6G, CD19, CD11b, I-A/I-E, Ly6C, CD21, CD35, CD23, CD11c; Panel 2 (for T cells and the subtypes): CD45, CD5, CD161, CD4, CD8a, CD44, CD62L, CD25.

Data and Results: CAE treatment induced an increase of several major innate immune cells (neutrophils 14.54-fold, monocytes 18.36-fold, eosinophils 13.08-fold, and dendritic cells 2.45-fold), and a decrease of follicular B cells (0.65-fold), T^{CD4+} cells (0.69-fold) and its several subtypes ($p<0.05$). Alcohol + POA treatment resulted in an increase of neutrophils (22.76-fold) and a decrease of T cells (0.58-fold) and several subtypes ($p<0.05$). The upregulation of monocytes induced by the low dose CAE was unexpectedly attenuated by alcohol feeding (8.66-fold vs 3.44-fold, $p<0.05$), and the downregulation of B cells by the low dose-CAE was opposed by alcohol feeding (0.07-fold vs 0.57-fold, $p<0.05$).

Conclusions: The pattern of increased innate and decreased adaptive immune cells was consistent in the pancreas in the CAE and Alcohol + POA models. Alcohol feeding opposed the low dose CAE effect on innate immune cells and B cells. Together, the immune profiling approach provides a better understanding of overall immune responses in AP in three different models, which may facilitate the identification of intervention windows and new therapeutic strategies.

Characterizing a new Mucin2 knockout mouse model

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Mucin 2 (MUC2) is a secretory protein expressed by goblet cells mainly in the colon and the small intestine. Known to be the most abundant intestinal mucin, one of its primary functions is to protect the intestinal epithelia, as well as providing a specialized microbial environment. It has been shown that MUC2 becomes attenuated in non-mucinous colorectal adenocarcinomas. With that being said, previous literature has linked the overexpression of MUC2 and MUC5AC with mucinous colorectal adenocarcinoma, a distinct subtype of adenocarcinoma in colorectal cancers (CRCs). However, the exact role MUC2 plays in mucinous colorectal adenocarcinomas remains unclear. The aim of this project was to successfully characterize a new *Muc2* knockout mouse model. CRISPR/Cas9 was used to target the first codon in *Muc2* for deletion. Genotyping was performed using Sanger sequencing to identify specific mutations, which identified two mutant lines, one with a 1-bp deletion and another with a 4-bp deletion at codon 1. Mice were further genotyped by Nco1 restriction enzyme digests to identify *Muc2* KO and *Muc2* (+/-). Tissue was collected from the small intestine and colon (n=4); total protein was extracted and quantified using a Pierce™ BCA Assay Kit. Western blots will be performed after protein quantification. Histological analysis using H&E, Alcian Blue, and PAS stains. Immunofluorescence using anti-MUC2 antibodies will be executed to further confirm the deletion of *Muc2*.

Reduced bile acid signaling contributes to hypertension development in spontaneously hypertensive stroke-prone rats

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Exciting recent findings have identified that the gut microbiota plays an essential role in blood pressure (BP) regulation. Studies from our lab and others have shown a causal role of gut dysbiosis in the development of hypertension in the spontaneously hypertensive stroke-prone (SHRSP) rat and several other animal models. One key mechanism by which the microbiota influences the host is through the generation/modification of metabolites. Among these metabolites, bile acids (BAs), are derived from the liver and modified by gut bacteria. Many BA species cross the gut epithelial barrier into the host circulation and influence inflammation, metabolism, and vascular function through the binding and activation of BA receptors, including TGR5.

We hypothesized that **disrupted BA signaling, as a result of gut dysbiosis, contributes to the development of hypertension.** By comparing 16s rRNA sequencing data from normotensive WKY and SHRSP cecal content, we found that SHRSP had a significant increase in the genus *Lactobacillus*, known to sequester BAs within its cytosol and reduce systemic BAs availability, when compared to WKY ($p<.05$). We also observed a significant reduction of several BAs in the systemic circulation of SHRSP as compared to WKY, including the TGR5 agonists, cholic acid (CA, 74% decrease), hyocholic acid (HCA, 77% decrease), and lithocholic acid (LCA, 74% decrease) ($p<.05$). We next supplemented WKY and SHRSP rats with 0.5% CA in the diet and measured systolic blood pressure (SBP) bi-weekly. After 15 weeks of treatment, systemic plasma was collected for BA analysis and endothelium-dependent dilation was assessed in the isolated aorta. CA supplementation considerably reduced SBP of SHRSPs, with an average decrease of 23 mmHg over the final 6 weeks of treatment ($p<.05$) compared to SHRSP controls. Chronic CA treatment also significantly improved vasodilatory response to increasing doses of acetylcholine (ACh) in the isolated aorta of SHRSPs ($p<.05$). Beta-diversity analysis of the cecal microbiota showed that CA treatment significantly altered the community makeup in WKY and SHRSPs. Of interest, CA treatment restored relative abundance of *Lactobacillus* in SHRSP to the level of WKY controls. In addition, CA supplementation significantly increased CA, HCA, and tauro-LCA in the systemic plasma of SHRSP ($p<.0001$). Next, we determined if BAs had their beneficial effects through activation of the BA receptor TGR5. Beginning at 6 weeks of age, SHRSPs were randomized into vehicle control or oleanolic acid (OA, 10 mg/kg IP daily), a selective TGR5 agonist, treatment groups. OA significantly decreased SBP by an average of 15 mmHg over the final 6 weeks of the treatment, compared to controls ($p<.05$). Furthermore, 15 weeks of OA treatment significantly improved vasodilatory response to increasing doses of ACh in isolated mesenteric arteries of SHRSPs ($p<.05$). Because systemic and neuronal inflammation also contributes to the development of hypertension, we examined the effects of TGR5 activation by OA treatment on inflammation in the gut and brain of SHRSPs. Using flow cytometry, we determined that OA treatment increased the percentage of anti-inflammatory Tregs and decreased pro-inflammatory T helper 17 cells in both cecum and brain of SHRSP ($p<.05$). OA treatment also significantly reduced interferon-γ^+ T cells in the ileum and cecum of SHRSP (stats). These data suggest an anti-inflammatory role of TGR5 signaling in the gut and brain. We conclude that reduced BA-mediated TGR5 signaling contributes to the development of hypertension in SHRSPs, and that activating TGR5 may be a potential therapeutic approach to attenuate vascular endothelial dysfunction, gut and brain inflammation, and associated hypertension.

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Pancreatic transcriptomic signatures during chronic pancreatitis recovery in cerulein mouse model

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Background: We have previously demonstrated that the pancreas can recover from chronic pancreatitis (CP) lesions in the cerulein-induced mouse model. To explore how pancreatic recovery is achieved at the molecular level, we used RNA-sequencing (seq) and profiled transcriptomes during CP transition to recovery.

Methods: CP was induced in C57BL/6 mice by cerulein (50 μg/kg, 5 ip injections/day, 3 days/wk) for 4 wks. Control mice received saline. Pancreata were harvested either 4 days (as CP and CON) or 4 wks (as CPR and CONR) after the last injection (n=4 mice/group). Total RNAs were prepared, RNA-seq was performed, and qPCR was conducted. The differentially expressed genes (DEGs) were determined by the Log2(fold change) > 1 and the false discovery rate (FDR) < 0.05. For gene set enrichment analysis, enriched pathways on the significant gene sets were identified by applying the GATHER algorithm and implemented in BETSY using pathway annotations from the MSigDB.

Results: We identified 3600 DEGs in CP and 166 in CPR, among which 132 overlapped between CP and CPR; 3468 were exclusive to CP and 34 exclusive to CPR, indicating that 4% DEGs persisted from CP injury to recovery and 34 DEGs emerged during CP recovery. We selected fibrosis relevant genes, *Col1a2*, *Fn1*, and *Tgfb1*, and found that all these fibrosis relevant genes increased in CP (>1-fold, adj p<0.005) and declined to control level in CPR. We also selected a known protective gene in CP, *Fgf21*, and demonstrated that *Fgf21* was suppressed in CP (4-fold, adj p=1.18E-28) and in CPR (1-fold, adj p=1.52E-05). qPCR validated these RNA-seq results. Gene set enrichment analysis identified top 20 gene sets from the shared DEGs between CP and CPR, which are mostly relevant to extracellular matrix and cancer biology, and top 10 gene sets from the specific DEGs to CPR, which are pertinent to DNA methylation and specific signaling pathways.

Conclusion: We identified a distinct set of DEGs in association with extracellular matrix and cancer cell activities to contrast CP and CPR. Once during ongoing CP recovery, DEGs relevant to DNA methylation and specific signaling pathways were induced to express. The DEGs shared between CP and CPR and the DEGs specific to CPR may serve as the unique transcriptomic signatures and biomarkers for determining CP recovery and monitoring potential therapeutic responses at the molecular level to reflect pancreatic histological resolution.

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Target Audience: physicians, fellows, residents, researchers and other health care providers who are interested in digestive diseases

Educational Objectives: At the conclusion of this live activity, participants should be better able to identify phages and viruses related to GI infection and injury, apply best practices and treatments for these infections, identify opportunities to apply this knowledge to the detection of these infections, and interpret the current research concerning phages, viruses, and digestive diseases.

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