THE GUT AS AN ENDOCRINE ORGAN

IMPLICATIONS FOR GI AND LIVER DISEASE

DDC
Texas Medical Center Digestive Diseases Center

11TH ANNUAL
Frontiers in Digestive Diseases Symposium

FEBRUARY 29, 2020

ONSTEAD AUDITORIUM
HOUSTON, TEXAS

About the Texas Medical Center Digestive Disease Center (DDC)

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

The DDC is federally funded (NIH P30DK056338) and designed to serve basic and clinical scientists at institutions within the Texas Medical Center, including Baylor College of Medicine, The University of Texas Health Science Center at Houston and the MD Anderson Cancer Center. The DDC is one of only 18 NIH-funded Digestive Diseases Research Core Centers in the country. Mary K. Estes, Ph.D., emeritus director and professor of molecular virology and microbiology at Baylor founded it in 1999.

The DDC Director is Hashem B. El-Serag, M.D., M.P.H., Margaret M. and Albert B. Alkek Chair of the Department of Medicine, and professor of gastroenterology and hepatology at Baylor College of Medicine. James Versalovic, M.D., Ph.D., professor and vice chair of pathology & immunology at Baylor College of Medicine and pathologist-in-chief and director of the Texas Children's Microbiome Center at Texas Children's Hospital, serves as DDC co-director. J. Marc Rhoads, M.D., gastroenterology division director and professor of pediatric gastroenterology at The University of Texas Health Science Center serves as Assistant Director.

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 particular strengths in the areas of gastrointestinal development, infection, and injury.

Contents

General Information

Symposium Program

DDC
Texas Medical Center Digestive Diseases Center

Visit the DDC online!

www.bcm.edu/research/centers/digestive-disease

Symposium Program at a Glance

7:15 am – 8:15 am

Breakfast / Onsite Registration

8:15 am – 8:30 am

Welcome Remarks

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

8:30 am – 9:15 am

"Glucagon-like Peptides in GI Function and Disease"

Jens J. Holst, M.D.
Department of Biomedical Sciences and
NNF Center for Basic Metabolic Research,
University of Copenhagen, Denmark

9:15 am – 9:45 am

"Intestinal serotonin: a multifunctional molecule for all seasons"

Michael Gershon, M.D.
Professor
Department of Pathology and Cell Biology
Columbia University, New York

9:45 am – 10:15 am

"Roles of FGF15/19 in regulating liver functions"

Grace Guo, MBBS, Ph.D.
Associate Professor
Rutgers University
Ernest Mario School of Pharmacy, New Jersey

10:15 am – 10:30 am

Coffee Break

10:30 am – 11:15 am

"The Bile Acid FXR-FGF19 gut liver axis: from cholestasis, to NASH and HCC"

Antonio Moschetta, M.D., Ph.D.
Professor of Internal Medicine
University of Bari Aldo Moro, Italy

11:15 am – 11:45 am

"Human-derived Bifidobacterium dentium modulates the mammalian serotonergic system and gut-brain axis"

Melinda Engevik, Ph.D.
Instructor
Department of Pathology
Baylor College of Medicine, Texas

11:45 am – 12:15 pm

"Gut hormone ghrelin in immunometabolism and ulcerative colitis"

Yuxiang Sun, M.D.
Associate Professor
Department of Nutrition and Food Science
Texas A &M University, Texas

12:30 pm – 1:30 pm

Lunch / Break-Out Sessions

Breakout Session #1
Grace Guo, MBBS, Ph.D.
(Room S3.8003, 3rd Floor)

Breakout Session #2
Jens Holst, M.D.
(Room S3.8014, 3rd Floor)

Breakout Session #3
Antonio Moschetta, M.D., Ph.D.
(Room S1.8331, 1st Floor)

Breakout Session #4
Michael Gershon, M.D.
(Room S5.8005, 5th Floor)

Breakout Session #5
Gary Wu, M.D.
(Onstead Auditorium, 3rd Floor)

1:30 pm – 3:00 pm

Poster Session, 1st Floor

3:00 pm – 3:15 pm

Poster Awards / Closing Remarks

Doug Burrin, Ph.D.
Pilot Feasibility Program Chair
TMC Digestive Diseases Center
Professor of Pediatrics, USDA-ARS

Texas Children's Hospital

Approved CME Activity

Directly provided by Texas Children's Hospital
Hosted by the Texas Medical Center Digestive Diseases Center
Saturday, February 29, 2020 | 8:00 am – 3:00 pm | Onstead Auditorium

"Glucagon-like Peptides in GI Function and Disease"
Jens J. Holst, M.D., Department of Biomedical Sciences and NNF Center for Basic Metabolic Research, The Panum Institute, University of Copenhagen

"The Bile Acid FXR-FGF19 gut liver axis: from cholestasis, to NASH and HCC"
Antonio Moschetta, M.D., Ph.D., Professor of Internal Medicine, University of Bari Aldo Moro

"Roles of FGF15/19 in regulating liver functions"
Grace Guo, MBBS, Ph.D., Associate Professor, Rutgers University, Ernest Mario School of Pharmacy

"Intestinal serotonin: a multifunctional molecule for all seasons"
Michael Gershon, M.D., Professor, Department of Pathology and Cell Biology, Columbia University

"Human-derived Bifidobacterium dentium modulates the mammalian serotonergic system and gut-brain axis"
Melinda Engevik, Ph.D., Instructor, Department of Pathology, Baylor College of Medicine

"Gut hormone ghrelin in immunometabolism and ulcerative colitis"
Yuxiang Sun, M.D., Ph.D., Associate Professor, Nutrition and Food Science, Texas A &M University

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TARGET AUDIENCE

Internal Audience, Physicians, Specialists Gastroenterology, Research in Digestive Diseases, Medical Students, Residents, Fellows, Any physician or researcher with interest in digestive diseases

EDUCATIONAL OBJECTIVES

At the conclusion of this live activity, participants should be better able to: (1.) Define infection and injuries that are a precursor to GI and Liver cancer, (2.) Apply best practices and treatments for infection and injury to avoid GI and Liver cancer; (3.) Identify opportunities to apply this knowledge to the detection of GI and liver cancer; and (4.) Interpret the current research concerning injury and infection as a precursor to cancer for better patient care

ACCREDITATION STATEMENT

This live activity has been planned and implemented in accordance with the accreditation requirements and policies of the Texas Medical Association through the joint providership of Texas Children's Hospital and Texas Medical Center Digestive Disease Center. Texas Children's Hospital is accredited by the TMA to provide continuing medical education for physicians.

CREDIT DESIGNATION

Texas Children's Hospital designates this live activity for a maximum of *4.50 AMA PRA Category 1 Credit(s)* ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE

All 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.

DDC Leadership

Hashem El-Serag, M.D., M.P.H.
Director
Baylor College of Medicine
hasheme@bcm.edu

James Versalovic, M.D., Ph.D.
Co-Director
Director, Functional
Genomics & Microbiome Core
Baylor College of Medicine
jamesv@bcm.edu

J. Marc Rhoads, M.D.
Assistant Director
UT Health Science Center
J.Marc.Rhoads@uth.tmc.edu

Douglas Burrin, Ph.D.
Pilot Feasibility Program Chair
USDA-ARS
doug.burrin@ars.usda.gov

Sara M. Tristan, B.S.
Administrator
Baylor College of Medicine
escamill@bcm.edu

Deborah Schady, M.D. Director,
Cellular & Molecular Morphology
Core
Baylor College of Medicine
schady@bcm.edu

Michael Mancini, Ph.D.
Co-Director, Cellular & Molecular
Morphology Core
Baylor College of Medicine
mancini@bcm.edu

Cecilia Ljungberg, Ph.D. Co-
Director, Cellular &
Molecular Morphology Core
Baylor College of Medicine
cecilial@bcm.edu

Lisa White, Ph.D.
Co-Director, Functional
Genomics & Microbiome Core
Baylor College of Medicine
lisaw@bcm.edu

Joseph Petrosino, Ph.D.
Co-Director, Functional
Genomics & Microbiome Core
Baylor College of Medicine
jpetrosino@bcm.edu

Sridevi Devaraj, Ph.D.
Co-Director, Functional
Genomics & Microbiome Core
Baylor College of Medicine
devaraj@bcm.edu

Noah Shroyer, Ph.D.
Director, GEMS Core
Baylor College of Medicine
Noah.Shroyer@bcm.edu

Mary K. Estes, Ph.D.
Co-Director, GEMS Core
Baylor College of Medicine
mestes@bcm.edu

Alton Swennes, D.V.M.
Co-Director, GEMS Core
Baylor College of Medicine
swennes@bcm.edu

Fasiha Kanwal, M.D., MSHS
Director, Study Design
& Clinical Research Core
Baylor College of Medicine
kanwal@bcm.edu

David Y. Graham, M.D.
Co-Director, Study Design
& Clinical Research Core
Baylor College of Medicine
dgraham@bcm.edu

Clinical Liaison Committee

Robert Bresalier, M.D.
Fasiha Kanwal, M.D., MSHS
J. Marc Rhoads, M.D.
Benjamin Shneider, M.D.

Internal Advisory Committee

Doug Burrin, Ph.D.
Hashem B. El-Serag, M.D., M.P.H.
Mary K. Estes, Ph.D.
David Y. Graham, M.D.
Cynthia Ju, Ph.D.
Geoffrey Preidis, M.D., Ph.D.
Deborah Schady, M.D.
Noah Shroyer, Ph.D.
Alton Swennes, D.V.M.
S. Thevananther, Ph.D.
James Versalovic, M.D., Ph.D.

External Advisory Committee

Anna Mae Diehl, M.D.
Duke University Medical Center, Durham

Robert Sandler, M.D., M.P.H.
University of North Carolina, Chapel Hill

Michael Helmrath, M.D.
Cincinnati Children's Hospital

Don W. Powell, M.D.
University of Texas Medical Branch

Deborah C Rubin, M.D.
Washington University of St. Louis

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

Symposium Directory

Attendees listed in alphabetical order by last name.

Saba Abdulsada, M.D.
Research Coordinator
Baylor College of Medicine
saba.abdulsada@bcm.edu

Masa Arimura, Ph.D.
Instructor
Baylor College of Medicine
arimura@bcm.edu

Shabba Armbrister, B.S.
Research Assistant
UT Health Science Center
shabba.armbrister@yahoo.com

Sriram Ayyaswamy, Ph.D.
Instructor
Baylor College of Medicine
ayyaswam@bcm.edu

Maya Balakrishnan, M.D.
Assistant Professor
Baylor College of Medicine
maya.balakrishnan@bcm.edu

Laura Beretta, Ph.D.
Professor
MD Anderson Cancer Center
lberetta@mdanderson.org

Nobel Bhasin, Ph.D.
Postdoctoral Fellow
Baylor College of Medicine
231157@bcm.edu

Erin Bolte, MSc
Student
Baylor College of Medicine
bolte@bcm.edu

Robert Bresalier, M.D.
Professor
MD Anderson Cancer Center
rbresali@mdanderson.org

Jim Broughman, Ph.D.
Staff Scientist
Baylor College of Medicine
broughma@bcm.edu

Doug Burrin, Ph.D.
Professor Pediatrics
USDA Children's Nutrition
Research Center
doug.burrin@usda.gov

Yanna Cao, M.D.
Associate Professor
UT Health Science Center
Yanna.Cao@uth.tmc.edu

Deepa Chakravarti, Ph.D.
Post-doctoral fellow
MD Anderson Cancer Center
dchakravarti@mdanderson.org

Somik Chatterjee, Ph.D.
Research Associate
Baylor College of Medicine
Somik.Chatterjee@bcm.edu

Bruno Chumpitazi, M.D., M.P.H.
Associate Professor
Baylor College of Medicine
chumpita@bcm.edu

Margaret Conner, Ph.D.
Associate Professor
Baylor College of Medicine
mconner@bcm.edu

Aaron Cox, Ph.D.
Instructor
Baylor College of Medicine
racox@bcm.edu

Sue Crawford, Ph.D.
Assistant Professor
Baylor College of Medicine
crawford@bcm.edu

Zach Criss, B.S.
Graduate Student
Baylor College of Medicine
zkcriss@bcm.edu

Heather Danhof, Ph.D.
Postdoctoral Fellow
Baylor College of Medicine
heather.danhof@bcm.edu

Joy Davis, B.S.
Medical Student
UT McGovern Medical School
joy.m.davis@uth.tmc.edu

Kali Deans, B.S.
Student
Baylor College of Medicine
deans@bcm.edu

Anna Mae Diehl, M.D.
Professor
Duke University
annamae.diehl@duke.edu

Bingning Dong, Ph.D.
Assistant Professor
Baylor College of Medicine
bd148049@bcm.edu

Madeline Drake
Student
UT McGovern Medical School
madeline.m.drake@uth.tmc.edu

Dave Durgan, Ph.D.
Asst. Professor
Baylor College of Medicine
durgan@bcm.edu

Price Edwards, M.D.
Clinical Fellow
Baylor College of Medicine
price.edwards@bcm.edu

Symposium Directory

Attendees listed in alphabetical order by last name.

Christoph Emontzpohl, Ph.D.
Post-Doc
UT Health Science Center
Christoph.Emontzpohl@uth.tmc.edu

Mindy Engevik, Ph.D.
Instructor
Baylor College of Medicine
melinda.engevik@bcm.edu

Kristen Engevik, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
kengevik@bcm.edu

Mary Estes, Ph.D.
Professor
Baylor College of Medicine
mestes@bcm.edu

Khalil Ettayebi, Ph.D.
Senior Staff Scientist
Baylor College of Medicine
ettayebi@bcm.edu

Nicole Fatheree, BBA
Researcher
UT Health Science Center
nicole.fatheree@uth.tmc.edu

Milton Finegold, M.D.
Emeritus Professor
Baylor College of Medicine
finegold@bcm.edu

Denise Francisco, M.D.
Fellow
Baylor College of Medicine
denise.francisco@bcm.edu

Jasmin Freeborn, B.A.
Research Assistant
UT Health Science Center
jasmin.freeborn@gmail.com

Loning Fu, Ph.D.
Associate Professor
Baylor College of Medicine
loningf@bcm.edu

Makoto Fukuda, Ph.D.
Assistant Professor
Baylor College of Medicine
fukuda@bcm.edu

Chunxu Gao, Ph.D.
Scientist
Baylor College of Medicine
cgao@bcm.edu

Michael Gershon, M.D.
Speaker
Columbia University
mdg4@cumc.columbia.edu

Ketan Ghaghada, Ph.D.
Assistant Professor
Baylor College of Medicine
ghaghada@bcm.edu

Annie Goodwin, M.D.
Instructor
Baylor College of Medicine
annieg@bcm.edu

David Y. Graham, M.D.
Professor
Baylor College of Medicine
dgraham@bcm.edu

Grace Guo, MBBS, Ph.D.
Speaker
Rutgers University
glg48@eohsi.rutgers.edu

Greg Guthrie, Ph.D.
Instructor
Baylor College of Medicine
gguthrie@bcm.edu

Darryl Hadsell, Ph.D.
Associate Professor of Pediatrics
Baylor College of Medicine
dhadsell@bcm.edu

Michael Helmrath, M.D.
Professor
Cincinnati Childrens
michael.helmrath@cchmc.org

Jens Holst, M.D.
Speaker
University of Copenhagen
jjholst@sund.ku.dk

Joseph Hyser, Ph.D.
Assistant Professor
Baylor College of Medicine
joseph.hyser@bcm.edu

Jong-Min Jeong, Ph.D.
Post-doctoral Fellow
UT Health Science Center
Jong-Min.Jeong@uth.tmc.edu

Cynthia Ju, Ph.D.
Professor
UT Health Science Center
changqing.ju@uth.tmc.edu

Umesh Karandikar, Ph.D.
Staff Scientist
Baylor College of Medicine
ukarandikar@gmail.com

Richard Kellermayer, M.D., Ph.D.
Associate Professor
Baylor College of Medicine
kellerma@bcm.edu

Natalia Khalaf, M.D., M.P.H.
Assistant Professor
Baylor College of Medicine
natalia.khalaf@bcm.edu

Symposium Directory

Attendees listed in alphabetical order by last name.

Anastasia Khodakova, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
khodakov@bcm.edu

Hyunseok Kim, M.D., M.P.H.
GI fellow
Baylor College of Medicine
hyunseok.kim@bcm.edu

KangHo Kim, Ph.D.
Assistant Professor
Baylor College of Medicine
kanghok@bcm.edu

Michihiro Kobayashi, M.D., Ph.D.
UT Health Science Center
michihiro.kobayashi@uth.tmc.edu

Suety Kwan, Ph.D.
MD Anderson Cancer Center
skwan1@mdanderson.org

Sharmi Lahiri, M.D., M.S.
Resident Physician
UT Health Science Center
sharmistha.lahiri@uth.tmc.edu

Rumi Lee, Ph.D.
Graduate Student
MD Anderson Cancer Center
rlee4@mdanderson.org

Miranda Lewis, B.S.
Graduate Student
Baylor College of Medicine
miranda.lewis@bcm.edu

Feng Li, Ph.D.
Assistant Professor
Baylor College of Medicine
fl3@bcm.edu

Shih-Ching (Roy) Lin, M.S.
Graduate Student
Baylor College of Medicine
sl18@bcm.edu

Hsiaoyun Lin, Ph.D.
Postdoc
Baylor College of Medicine
hsiaoyul@bcm.edu

Yuying Liu, Ph.D., Med
Associate Professor
UT Health Science Center
Yuying.Liu@uth.tmc.edu

Cecilia Ljungberg, Ph.D.
Assistant Professor
Baylor College of Medicine
cecilial@bcm.edu

Richard Lloyd, Ph.D.
Professor
Baylor College of Medicine
rlloyd@bcm.edu

Zhe Lyu, Ph.D.
Assistant Lab Director
Baylor College of Medicine
zlyu@bcm.edu

Mike Mancini, Ph.D.
Professor
Baylor College of Medicine

Andrea McAlester (Hill), Ph.D.
Postdoctoral Fellow
Baylor College of Medicine
mcaleste@bcm.edu

Eoin McNeill, Ph.D.
Postdoctoral Researcher
UT Health Science Center
emcneill@uth.tmc.edu

Firas Midani, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
Firas.Midani@bcm.edu

Toni-Ann Mistretta, Ph.D.
Biostatistician
Baylor College of Medicine
toniannm@bcm.edu

David Moore, Ph.D.
Professor
Baylor College of Medicine
moore@bcm.edu

Antonio Moschetta, M.D., Ph.D.
Speaker
University of Bari Aldo Moro
antonio.moschetta@uniba.it

Sanjay Nair, M.S.
UT Health Science Center
sanjay.nair@kcl.ac.uk

Maria Nunez, M.S., CCRP
Baylor College of Medicine
maria.nunez@bcm.edu

Numan Oezguen, Dr. rer. nat.
Instructor
Baylor College of Medicine
oezguen@bcm.edu

Antone Opekun, M.S., PA-C
Associate Professor
Baylor College of Medicine
aopekun@bcm.edu

Jennifer Padilla, B.S.
Research Technician II
Baylor College of Medicine
jpadilla@bcm.edu

Symposium Directory

Attendees listed in alphabetical order by last name.

Lei Pan, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
lei.pan@bcm.edu

Don Powell, M.D.
Emeritus Professor
UT Medical Branch
dpowell@utmb.edu

Marc Rhoads, M.D.
Professor of Pediatrics
UT McGovern Medical School
j.marc.rhoads@uth.tmc.edu

Wenly Ruan, M.D.
Fellow
Baylor College of Medicine
wenly.ruan@bcm.edu

Robert Sandler, M.D., M.P.H.
GI Division Chief, Emeritus
University of North Carolina
Chapel Hill
robert_sandler@med.unc.edu

Hashem El-Serag, M.D., M.P.H.
Chairman, Medicine
Baylor College of Medicine
hasheme@bcm.edu

Huanan Shi, B.S.
Graduate Student
Baylor College of Medicine
huanan.shi@hotmail.com

Guilherme Silva, M.D.
Medical Doctor
Baylor College of Medicine
katie.tatum@bcm.edu

Allison Speer, M.D.
Assistant Professor
UT McGovern Medical School
Allison.L.Speer@uth.tmc.edu

Jacob Perry, M.S.
Graduate Student
Baylor College of Medicine
jlperry@bcm.edu

Geoff Preidis, M.D., Ph.D.
Assistant Professor
Baylor College of Medicine
geoffrey.preidis@bcm.edu

Sara Di Rienzi, Ph.D.
Postdoc
Baylor College of Medicine
sara.dirienzi@bcm.edu

Deborah Rubin, M.D.
Professor of Medicine
Washington University
School of Medicine
drubin@wustl.edu

Deb Schady, M.D.
Associate Professor
Baylor College of Medicine
schady@bcm.edu

Monisha Shah, M.D.
Fellow
UT Health Science Center
monisha.shah.1@uth.tmc.edu

Zhongcheng Shi, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
zhongchs@bcm.edu

Betty Slagle, Ph.D.
Associate Professor
Baylor College of Medicine
bslagle@bcm.edu

Fabio Stossi, Ph.D.
Associate Professor
Baylor College of Medicine
stossi@bcm.edu

Tori Poplaski, B.A.
Graduate Student
Baylor College of Medicine
poplaski@bcm.edu

Eva Preisner, Ph.D.
Baylor College of Medicine
preisner@bcm.edu

Lisa Rivera, M.S.
PA Student
Baylor College of Medicine
wrlisa@gmail.com

Ergun Sahin, M.D., Ph.D.
Assistant Professor
Baylor College of Medicine
esahin@bcm.edu

Laura Schaefer, Ph.D.
Senior Staff Scientist
Baylor College of Medicine
ls6@bcm.edu

Jordan Shapiro, M.D.
Fellow
Baylor College of Medicine
jmshapir@bcm.edu

Rob Shulman, M.D.
Professor
Baylor College of Medicine
rshulman@bcm.edu

Krishnakant Soni, Ph.D.
Instructor
Baylor College of Medicine
ksoni@bcm.edu

Bridget Stroup, Ph.D., R.D.N.
Postdoctoral Associate Baylor
College of Medicine
stroup@bcm.edu

Symposium Directory

Attendees listed in alphabetical order by last name.

Yuxiang Sun, M.D., Ph.D.
Speaker
Texas A&M University
mdg4@cumc.columbia.edu

Alton Swennes, DVM
Associate Professor
Baylor College of Medicine
swennes@bcm.edu

Manasi Tamhankar, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
manasiajit.tamhankar@bcm.edu

Kai Li Tan, Ph.D.
Baylor College of Medicine
ktan@bcm.edu

Mimi Tan, M.D., M.P.H.
Assistant Professor
Baylor College of Medicine
mc2@bcm.edu

Valencia Tellis
Coordinator
Baylor College of Medicine
Valencia.Rose@bcm.edu

Victoria Tenge, B.S.
Graduate Student
Baylor College of Medicine
tenge@bcm.edu

S. (Thev) Thevananther, Ph.D.
Associate Professor
Baylor College of Medicine
sundarat@bcm.edu

Aaron Thrift, Ph.D.
Assistant Professor
Baylor College of Medicine
aaron.thrift@bcm.edu

Naomi Tjaden, M.D., Ph.D.
Resident
Baylor College of Medicine
tjaden@bcm.edu

Sara Tristan, B.S.
DDC Administrator
Baylor College of Medicine
escamill@bcm.edu

Sue Venable, B.S.
Lab Director
Baylor College of Medicine
svenable@bcm.edu

Jim Versalovic, M.D., Ph.D.
Professor
Baylor College of Medicine
jamesv@bcm.edu

Caitlin Vonderohe, DVM, Ph.D.
Baylor College of Medicine
vonderoh@bcm.edu

Yankai Wen, Ph.D.
Post-doctoral fellow
UT Health Science Center
Yankai.Wen@uth.tmc.edu

Theresa Nguyen Wenker, M.D.
Fellow
Baylor College of Medicine
thn1@bcm.edu

Donna White, Ph.D., M.P.H.
Assistant Professor
Baylor College of Medicine
dwhite1@bcm.edu

Gary Wu, M.D.
Professor
University of Pennsylvania
gdwu@pennmedicine.upenn.edu

Anthony Xu, M.D.
Resident
Baylor College of Medicine
anthony.xu@bcm.edu

Long Xu, Ph.D.
Postdoctoral fellow
UT Health Science Center
Long.Xu@uth.tmc.edu

Li Yang, Ph.D.
Postdoc Associate
Baylor College of Medicine
231382@bcm.edu

Yang Yang, Ph.D.
Postdoctoral Fellow
UT Health Science Center
Yang.Yang@uth.tmc.edu

Momoko Yoshimoto, M.D., Ph.D.
Associate Professor
UT Health Science Center
Momoko.Yoshimoto@uth.tmc.edu

Joan Yu
Student
Baylor College of Medicine
joany@bcm.edu

Fan Zhang, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
Fan.Zhang@bcm.edu

Bojun Zhang, Ph.D.
Postdoctoral Associate
Baylor College of Medicine
bojun.zhang@bcm.edu

Speakers

JENS J. HOLST, M.D.
University of Copenhagen

Dr. Jens Juul Holst is a professor in the Department of Biomedical Sciences and affiliated with the Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen, Denmark. He is head of a research group that focuses on obesity and type 2 diabetes, especially with the aim of mapping hormonal disorders and the possibilities of treatment based on hormones. He has also taken part in developing a wide range of drugs used in treatment of type 2 diabetes.

Dr. Holst's research concentrates on appetite regulation and hormones that regulate metabolism (digestion).

A. MOSCHETTA,M.D., PH.D.
University of Bari Aldo Moro

Dr. Antonio Moschetta is Professor of Internal Medicine at the University of Bari Aldo Moro in Bari, Italy. He received his M.D. from the University of Bari Aldo Moro, Italy, in 1997 and his Ph.D. from Utrecht University, the Netherlands, in 2001. He was research associate at HHMI in UTSW Dallas in the department of pharmacology.

Dr. Moschetta's research focuses on the relationship between nutrients, hormones and disorders related to the gut–liver axis, with a special emphasis on the role of lipid-related transcriptional programs in liver and intestinal disease. He has been awarded several prizes including the David Williams Award from the Aspen Lipid Conference, the Rising Star in Gastroenterology and Hepatology from the United European Gastroenterology Week (UEGW), and the Richard E. Weizman Award from the Endocrine Society.

GRACE GUO, MBBS, PH.D.
Rutgers University

Dr. Grace Guo is an Associate Professor at the Department Pharmacology and Toxicology in the Ernest Mario School of Pharmacy of Rutgers University and a Research Scientist at the NJ VA Medical Center. She obtained her MBBS degree from the West China University of Medical Sciences in 1993 and a PhD degree from the University of Kansas Medical Center in 2001, as well as post-doctoral training at the NCI, NIH in 2004.

Dr. Guo's research focuses on determining the effects of bile acid mediated intestine-liver cross-talk on liver metabolism and pathogenesis and the underlying molecular mechanisms, especially following disruption of endogenous homeostasis and exposure to xenobiotic chemicals.

MICHAEL GERSHON, M.D.
Columbia University

Dr. Michael Gershon is a Professor of Pathology and Cell Biology at Columbia University. He is an internationally renowned physician scientist with almost 400 published peer-reviewed papers, which have relevance to disorders of GI motility and the initial observation in the gut of intrinsic sensory nerve cells that trigger propulsive motor activity.

Dr. Gershon also discovered that the serotonin transporter (SERT) is expressed by enterocytes (cells that line the lumen of the gut) as well as by enteric neurons and is critical in the termination of serotonin-mediated effects. He has identified roles in GI physiology that specific subtypes of serotonin receptor play and he has provided evidence that serotonin is not only a neurotransmitter and a paracrine factor that initiates motile and secretory reflexes, but also as a hormone that affects bone resorption and inflammation.

MELINDA ENGEVIK, PH.D.
Baylor College of Medicine

Dr. Mindy Engevik is currently an Instructor of Pathology at Baylor College of Medicine. She received her Ph.D. degree in Molecular and Cellular Physiology at the University of Cincinnati in 2014. She is also a 2019 DDC pilot feasibility awardee.

Dr. Engevik's research focuses on the interaction between the gut microbiota and secretory cells, such as goblet and enterochromaffin cells. Her interests include delineating how microbes manipulate the host to promote colonization.

YUXIANG SUN, M.D., PH.D.
Texas A&M University

Dr. Yuxiang Sun, Associate Professor in the department of Nutrition and Food Science at Texas A&M University, is an expert on "hunger hormone" ghrelin. She received her M.D. from Beijing Medical University in China and her Ph.D. from the University of Manitoba in Canada. She completed her postdoctoral fellowship at Baylor College of Medicine.

Dr. Sun's research focuses on glucose-homeostasis, energy-homeostasis, lipid metabolism, neuroendocrine regulation, pathogenesis and pathophysiology of obesity, diabetes, inflammation, and aging. She generated the first ghrelin knockout mice, and discovered ghrelin's novel roles in diabetes, thermogenesis and macrophage polarization. Her laboratory uses state-of-the-art tools to study ghrelin in energy sensing, intake, and expenditure. Her work suggests that ghrelin might be a promising drug target for obesity, diabetes, inflammation, and aging.

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Baylor College of Medicine
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Assistant Professor
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University of Texas Health Science Center
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"Cellular and Molecular Morphology"
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The Cellular and Molecular Morphology Core provides expertise, equipment and procedures relevant to GI research, makes available its specialized laboratory facilities to GI researchers, and develops new tests that may be useful in clinical and basic research.

Major core services include histology, immunohistochemistry, RNA in situ hybridization, mRNA probe generation, frozen sections for enzyme histochemistry, immunofluorescent antibody studies, live and fixed cell confocal, deconvolution microscopy and super resolution microscopy (SIM and STORM), and transmission electron microscopy, quantitative morphometric analysis, high throughput microscopy and high content analysis, laser capture microdissection for molecular genetic analyses, and digital images for internet communication and publication.

"Functional Genomics and Microbiome"
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The Functional Genomics and Microbiome Core stimulates research in infection and injury states affecting the intestine and liver. Services provided by the core include training the conduct of functional genomics and metagenomics relevant to GI research, consultation on experimental design of gene expression (mRNA) studies and assistance with analysis of genomic profiling data, providing mammalian gene expression, cytokine/transcription factor/signaling pathway arrays, and gut microbial profiling/metagenomics to DDC members at discounted prices, and facil analysis and bio-informatics strategies with functional genomics and microbiome datasets

"Gastrointestinal Experimental Model Systems (GEMS)"
Core D
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The Gastrointestinal Experimental Model Systems (GEMS) Core is organized to encompass an enteroid/organoid subcore and a gnotobiotic subcore. This core offers turnkey access to organoids/enteroid technologies to TMC-DDC researchers. This includes samples (enteroids, organoids), reagents (specialized growth media, etc.), training, and consultative expertise. The core also provides access to gnotobiotic facilities and animals, training and consultative expertise.

"Clinical Research & Study Design"
Core E
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The Study Design & Clinical Research Core promotes the use of appropriate study design, statistical analyses, and interpretation for clinical and basic science investigators; assists these investigators in acquiring clinical specimens to facilitate their research; and assists investigators in designing and performing translational research. The primary two functions are to provide epidemiological and biostatistical support for design and analysis, and to provide investigators with access to the clinical specimens required for their basic and translational research activities.

Colorectal polyps in patients with cirrhosis

Abdulsada, Saba M.[1]; Hassan, Manal[1]; Ismail, Mohamed S.[1]; Patel, Kalpesh[1]; Jalal, Prasun K.[1]

1. Surgery, Baylor College of Medicine, Houston, TX, United States.

Background: Studies suggested that patients with non-alcoholic fatty liver disease (NAFLD) are at increased risk of colorectal polyps (CRP). We aim to investigate the CRP characteristics in patients with cirrhosis compared with normal population.

Method: Between 2013 and 2018, 640 cirrhotic patients were referred for colonoscopy. 430 (67%) patients underwent screening colonoscopy. Collected data were compared with 430 consecutive cases with screening colonoscopy who were referred to the same center between 2018-2019; cases with a history of underlying liver disease were excluded. The association between CRP and epidemiological/clinical factors were assessed by multivariate logistic regression analysis. Odds ratio (OR) and 95% confidence interval (95% CI) was estimated after adjustment for significant confounding factors.

Results: The overall prevalence of CRP was significantly higher in cirrhotic patients (285/430, 66.3%) than in non-cirrhotic patients (254/430, 59%), P =.01. Cirrhotic patients had significantly higher no. of polyps with large size (≥10 mm), recto-sigmoidal in origin, and serrated type than non-cirrhotic patients; (31.9% vs. 22.8%, P=.018); (63.9% vs. 44.9%, P<.001); and (46.7% vs. 31.1, P<.001), respectively. However, adenomatous polyps are significantly more in non-cirrhotic patients than in cirrhotic patients (70.1% vs. 55.1%, P<.001). Univariate risk assessment showed the presence of cirrhosis, NAFLD, metabolic syndrome (MS), and cigarette smoking were significantly associated with CRP. The estimated crude ORs (95% CI) were 1.4 (1.1-1.8), 2.0 (1.3-3.0), 1.6 (1.2-2.2), and 1.7(13-23) respectively. However, multivariate analysis showed that MS and cigarette smoking, not cirrhosis, are independently associated with increased risk of CRP. The estimated age sex and race adjusted ORs (95% CI) were 1.5 (1.1-2.1) and 1.7 (1.3-2.4) respectively. MS was associated with an increased risk of adenomatous polyps: OR (95% CI) was 1.5 (1.1-2.1), P =.01 after adjustment for cirrhosis, age sex, race and smoking. Cigarette smoking, female gender, and cirrhosis were significantly associated with serrated polyps (P<.05): ORs (95% CI) were 1.8 (1.2-2.4), 1.6 (1.2-2.3), and 1.6 (1.2-2.3).

Conclusion: Smoking and MS are significant risk factors for CRP. MS is a risk factor for adenomatous polyps. Cirrhosis, female gender, history of cigarette smoking are at increased risk for serrated polyps.

Development of Small Intestinal Engraftment in Mice

Sumimasa Arimura[1], Zachary Keith Criss II[1], Clarissa Estrella[1], Jihye Yun[2], and Noah Freeman Shroyer[1]

[1]Department of Medicine Section of Gastroenterology
[2]Department of Molecular and Human Genetics

Background & Aims: The replacement of disease-causing epithelial cells with healthy cells in small intestine 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 small intestinal diseases with or without known etiology for understanding its pathophysiology and finding new therapeutic targets. Here we aimed to create an innovative replacement method for the engraftment of small intestinal organoids (SIOs) into mouse small intestine.

Methods: The lumen of small intestine 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 small intestine in wild-type mice, and their engraftment was verified histologically.

Results: The epithelial cells, but not stromal cells, in small intestinal mucosa were peeled off by EDTA treatment. In addition, the injected GFP-expressing normal SIOs were engrafted into small intestinal mucosa 7 days 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 engraftment method for small intestinal organoids. Our results suggest that cultured SIOs might be a source of cells for replacement of small intestinal epithelial cells or developing mouse models of its diseases.

Future plans: We will inject human normal or disease-causing SIOs into mouse small intestinal mucosa and investigate whether our engraftment can be a new therapeutic method and useful to develop novel mouse models for small intestinal diseases.

Gender disparities in the prevalence of nonalcoholic fatty liver disease: a systematic review and meta-analysis of population based studies

Parth Patel[1], Sydney Dunn-Valadez[1], Vinshi Khan[2], Hiba Ali[1], Laith H Elserag[2], Ruben Hernaez[3], Yan Liu[2], Hashem B. El-Serag[1,3,4], Fasiha Kanwal[2,4] and Maya Balakrishnan[3]

(1) Internal Medicine, Baylor College of Medicine, (2) Section of Gastroenterology and Hepatology, Baylor College of Medicine, (3) Department of Medicine, Section of Gastroenterology and Hepatology, Baylor College of Medicine, (4) Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E Debakey VA Medical Center

Background: Nonalcoholic fatty liver disease (NAFLD) is the leading cause for liver disease worldwide Male gender confers greater risk for most chronic liver diseases including hepatitis B, hepatitis C, and alcoholic liver disease but it is unclear whether this is the case for NAFLD as well. The findings of epidemiologic studies have varied with some reporting a nearly two fold increased risk of NAFLD among men compared to women and others reporting no significant NAFLD risk associated with gender. We conducted a systematic review and meta-analysis to examine gender differences in NAFLD prevalence

Methods: We searched Pubmed, MEDLINE, Embase, and Cochrane library from inception to 12/2017 for only population-based studies reporting the prevalence of NAFLD diagnosed by liver imaging or liver enzymes among adults (age>18 years). We excluded papers with no original data, animal studies, inability to determine gender-based prevalence, that excluded participants with metabolic risk factors, or failed to exclude viral hepatitis and/or alcohol related liver disease among participants in the study population. We used random-effects models to calculate point estimates (and 95% confidence intervals) of prevalence and pooled relative risk ratios for NAFLD by gender

Results: Of 8201 studies 24 population-based studies were included the final analysis with a total sample size of 105,406 NAFLD was diagnosed using ultrasound (n=18), aminotransferases (n=5), and MRI (n=1) The study populations included 56,412 women and 48,994 men, had a mean age of 47 4 years, mean BMI of 25 4 kg/ m2, and diabetes prevalence of 16 73% NAFLD prevalence was 22 98% (95%CI 22 73-23 23) in the overall population; 19 96% (95% CI 19 23-20 71%) among women and 26 45% (95% CI 25 69-27 22%) in men Based on random effect model the risk ratio of NAFLD in women compared to men was 0 74 (95% CI 0 61-0 89) (See Forest plot - Figure 1)

Conclusion: In our systematic review of population based studies, men had approximately a 25% higher risk of NAFLD compared to women This gender related risk of liver disease is not as high as observed in other liver diseases related to viral hepatitis or alcohol The reasons for the increased risk of NAFLD among men requires further study.

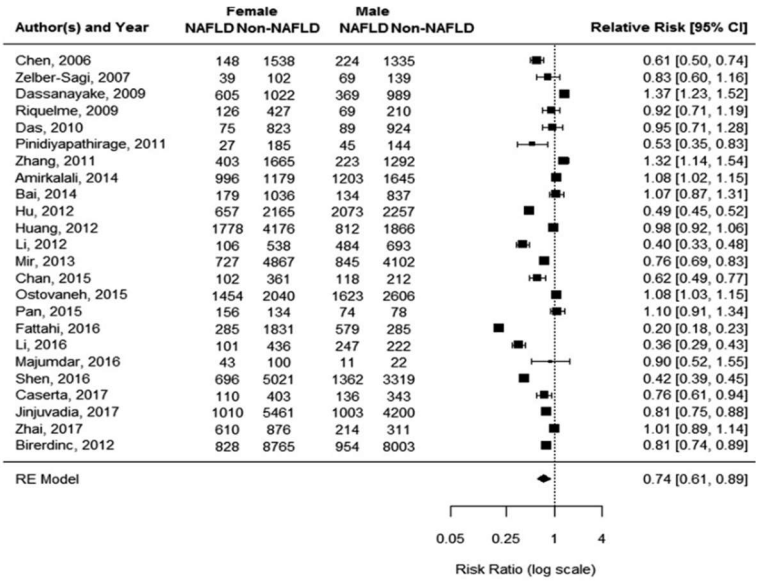

Figure 1: Forest plot with random effect model risk ratio of NAFLD in female compared to male

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

Nobel Bhasin, Criss Zachary Keith, Clarissa Estrella, Noah Freeman Shroyer
Department of Medicine Section of Gastroenterology and Hepatology

Baylor College of Medicine
Houston, Texas

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.

Molecular Links between Fibroblasts and Macrophages in Pancreatic Ductal Adenocarcinoma

M. Drake[1], B. Yang[1], J. Davis[1], M. Younes[2], Y. Cao[1], and T.C. Ko[1]

[1]Department of Surgery, [2]Department of Pathology & Laboratory Medicine, UTHealth

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.

Pancreatic Stromal Gremlin 1 Expression during Pancreatic Tumorigenesis

J. Davis[1], M. Younes[2], T.C. Ko[1], and Y. Cao[1]

[1]Department of Surgery, [2]Department of Pathology & Laboratory Medicine, UTHealth

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 Role of Homeobox Genes in Conferring Intestinal Regional Identity

Zachary K. Criss II, Yuan-Hung Lo, Ph.D., Noah Shroyer, Ph.D.

Baylor College of Medicine, Department of Medicine

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.

Inhibition of TRAP1 accelerates DNA damage under oxidative stress

Dabral, Prerna[1]; Lai, Lisa[2]; Bronner, Mary P.[3]; Valentine, John F.[4]; March, Jordon K.[4]; Brentnall, Teresa[2]; Pan, Sheng[5]; Chen, Ru[1]

1. Department of Medicine-Gastroeneterology, Baylor College of Medicine, Houston, TX, United States, 2. University of Washington School of Medicine, Seattle, WA, United States, 3. Huntsman Cancer Institute/University of Utah, Salt Lake City, UT, United States, 4. University of Utah School of Medicine, Salt Lake City, UT, United States, 5. University of Texas at Houston Health Science Center, Houston, TX, United States

Ulcerative colitis (UC), an inflammatory bowel disease characterized by chronic and recurrent inflammation of the colon, is associated with an increased susceptibility to colorectal cancer. The chronic inflammatory response in UC results in the production ROS that can cause oxidative damage to DNA, proteins and lipids, leading to tumor initiation. Previous research from our group has used proteomics based approach to report the upregulation of a mitochondrial protein, Tumor necrosis factor receptor-associated protein 1(TRAP1) in UC-associated colorectal cancer and its role in neoplastic progression. TRAP1 functions as an anti-oxidant and protects against oxidative stress, apoptosis and DNA damage. In this study, we investigated the roles of TRAP1 in modulation of cellular response to oxidative stress in colon cells. We observed that inhibition of TRAP1 through TRAP1-specific inhibitor, Gamitrinib-triphenylphosphonium (G-TPP), resulted in DNA damage, which was accompanied by a significant decrease in cellular proliferation. In addition, downregulation of TRAP-1 using siRNA led to deregulation of multiple pathways, including RNA metabolism, apoptosis and ATF4 pathways which have been linked to DNA damage. Together, these results indicate that inhibition of TRAP1 accelerates DNA damage through deregulation of multiple pathways.

The dynamics of autophagy and mTORC1 in intestinal regeneration.

Deans KK[1], Chen MS, and Shroyer NF

1 Department of Medicine, Baylor College of Medicine, Houston, Texas 77030, USA.

BACKGROUND: Chemotherapy is used to treat cancer by indiscriminately targeting rapidly dividing cells. Mucositis, or inflammation of the gastrointestinal epithelium, is a major side effect of many chemotherapy agents, including Doxorubicin, causing high morbidity in patients. While thousands of patients suffer from the debilitating gastrointestinal side effects of chemotherapy, there are no preventative treatments for mucositis. Recently, mouse models have been developed to further understand the effects of chemotherapy on the gastrointestinal tract. The Doxorubicin injury model established that rapidly dividing intestinal stem cells are especially sensitive to chemotherapy injury leading to substantial deterioration of intestinal epithelial integrity. While it remains unclear how the stem cell population is restored, it has been demonstrated that terminally differentiated cells can de-differentiate to reestablish the integrity of the intestinal epithelium. One of these cells is the Paneth cell. Several laboratories including our own, have developed Paneth cell lineage tracing techniques to study their plasticity. Our laboratory has shown that Paneth cells begin expressing markers of proliferation 24 to 48 hours, express stem cell markers at 72 hours, and subsequently generate all types of epithelial cells 7 days following Doxorubicin injury. The mechanisms driving Paneth cell de-differentiation are still being elucidated. We propose that autophagy and mTORC1 pathways play a dynamic role in intestinal regeneration following doxorubicin injury. **METHODS:** Outbred wild type mice were treated with 20mg/kg of Doxorubicin and sacrificed 1, 2, 3, 4,6, and 7 days following intraperitoneal injection. Overall health was assessed by body weight. Crypt viability, a marker of tissue damage, was measured by H&E stains and immunohistochemistry. Autophagy and mTORC1 markers were assessed, in intestinal crypt isolates, by immunoblot. Autophagy occurs in three major phases, initiation marked by ULK1 phosphorylation, membrane formation marked by the conjuation of LC3I to LC3II, and fusion of autophagosome and lysosome. ULK1 has several phosphorylation sites that positively and negatively regulate autophagy initiation. AMPK stimulates autophagy by phosphorylating serine-555. mTORC1 inhibits autophagy by phosphorylating serine-757. Furthermore, autophagy flux can be estimated in vivo by quantifying levels of SQSMT1. Similar to LC3, SQSMT1 is incorporated into the growing autophagosome, however, it is degraded at a higher rate. Low levels of SQSMT1 are associated with increased autophagy activity. Each of these markers was measured to assess autophagy activity. To examine the mTORC1 pathway, we measured the phosphorylation of S6 ribosomal protein, a key mediator of downstream protein translation. **RESULTS:** Body weight declined as much as 30% by 7 days despite substantial improvements in crypt viability. Greatest tissue damage was seen at day 3 post injury. Phosphorylation of ULK1 (S757) increased from day 4 to day 7, indicative of a later mTORC1 inhibition of autophagy. Phosphorylation of ULK1 (S555), associated with increased autophagy activity, significantly decreased at day 3 compared to day 7. There was a similar decrease in both LC3 I and II from day 2 to day 3. SQSMT1 significantly decreased at day 2 compared to days 4 and 6. Interestingly, there was no time specific change in mTORC1 activity as measured by the p-S6RP. **CONCLUSION:** Similar to previous reports, following doxorubicin injury, the intestinal epithelium experiences the greatest degree of intestinal damage around days 2 and 3 post-injury. The epithelium then shows substantial recovery by day 7. However, body weight does not correlate with the improvement in intestinal morphology. Consistent trends were not seen among markers of autophagy. This could be due to a change in autophagy flux. Finally, the lack of change in mTORC1 activity as measured by p-S6RP protein was surprising. Previous immunohistochemical data demonstrated that mTORC1 activity increased substantially from day 1 to day 7. Next steps include the assessment of autophagy and mTORC1 markers by immunofluorescence and immunohistochemistry, in addition, to the modulation of autophagy prior to doxorubicin injury.

A novel animal model of gastroparesis

Edwards, Price T[1]. Soni, Krishnakant[1]. Halder, Tripti[1]. Conner, Margaret[2]. Preidis, Geoffrey A[1].

1. Section of Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, 2. Department of Molecular Virology and Microbiology, Baylor College of Medicine

Background: Gastroparesis, or delayed gastric emptying, occurs in 24.2 per 100,000 adults. Although the prevalence is unknown in the pediatric population, the cost of hospital care for children with gastroparesis has risen dramatically over the last decade. Gastroparesis 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. Undernutrition creates a cycle of physiologic disturbances, including delayed gastric emptying, that make catch-up growth difficult. Animal models are needed to further elucidate causes of and potential therapies for malnutrition-associated gastroparesis. We aimed to characterize a novel model of gastroparesis induced by early postnatal malnutrition.

Methods: Malnutrition was induced by timed maternal separation (TmSep) of pups from lactating dams for 12 hours per day. Control mouse pups nursed uninterrupted. On day-of-life 15, a gastric gavage of fluorescein isothiocyanate-conjugated dextran was administered, and the gastrointestinal tract was harvested 30 minutes later. Percent gastric emptying was determined by quantifying fluorescence throughout the gastrointestinal tract. H&E-stained sections were imaged on an Eclipse 90i microscope, and thickness of muscularis propria and mucosa was measured by a blinded observer using NIS Elements (Nikon).

Results: Compared to control pups, malnourished mice were moderately underweight, mean 4.45 ± 0.1 g versus 6.96 ± 0.2 g ($p < 0.0001$). On gross examination, stomachs of TmSep mice were strikingly distended compared to control mice. Gastric emptying was impaired in TmSep versus controls (87.3% versus 97.0%, $p=0.023$). The gastric smooth muscle layer was thinner in TmSep mice versus controls, mean 16.9 ± 5.3 μm versus 30.4 ± 8.8 μm ($p=0.03$).

Discussion: We present a novel model of malnutrition-associated gastroparesis induced by timed separation of mouse pups from lactating dams. We further highlight thinning of the gastric smooth muscle layer as a potential etiology that warrants further investigation, although we cannot yet rule out potential contributions from an altered enteric nervous system, gut microbiota, or neuro-hormonal signaling pathways. Defining the underlying pathophysiology may create opportunities for new therapeutic interventions for gastroparesis in children.

Validation of the Early detection Screening (HES) Algorithm in a Multi-etiology Kaiser Permanente Northern California (KPNC) based Cirrhosis Cohort

Hashem B El-Serag, Douglas A. Corley, Israel Christie, Peter Richardson, Donna L. White, Jessica Davila, Fasiha Kanwal, Nabihah Tayob

Background: We previously developed and refined the HCC Early detection Screening (HES) algorithm in cohorts of patients with cirrhosis in the national VA Healthcare System. HES includes current AFP, age, platelets, ALT, and rate of change from previous AFP value within the past year, and cirrhosis etiology. In this analysis, we validated the algorithm's ability to improve the likelihood of early HCC detection in a community-based cohort of patients with cirrhosis of any etiology being cared for KPNC healthcare system. **Methods:** The cohort included patients with cirrhosis who were actively enrolled between 1/1/1997 and 12/31/2014. The cohort included patients with at least one AFP test after the cirrhosis index date and had ALT and platelet laboratory tests performed within 6 months prior to AFP. HES discrimination performance was evaluated compared to AFP alone in early stage (stage 1 (localized) for both SEER and AJCC classification) HCC cases. Patient-level sensitivity within T months was defined as % HCC cases with at least one positive screen within T months prior to diagnosis. The screening-level false positive rate (FPR) was defined as % positive screening results more than T months prior to HCC diagnosis. The 95% bias-corrected bootstrap percentile confidence intervals were estimated for patient-level sensitivity at 10% screening-level FPR. We also evaluated the HES algorithm with respect to PPV, NPV and the number of HCC cases detected per 1000 CT/MRI that are triggered by HES algorithm. The added utility of HES algorithm over concurrent ultrasound was examined in 242 patients who eventually developed HCC. **Results:** The study cohort included 6,330 controls and 1,102 (709 early stage HCC) HCC cases. Most patients were men (62.4%) and non-Hispanic whites (52.4%). Risk factors were HCV (37.3%), NAFLD (21.6%), alcoholic liver disease (19.1%), and HBV (15.7%). HES algorithm improved sensitivity for detecting early stage HCC cases by 5.18-8.58 percentage points compared to AFP alone over the range of T considered ($p<0.002$). Within 6 months prior to clinical diagnosis with early stage HCC, sensitivity was 51.20%; a 5.18 percentage point improvement compared to AFP alone, 46.02% ($p=0.0015$). The estimated PPV for early stage HCC increased from 11.80% to 13.65% ($p<0.0005$) and the NPV increased by 98.18% to 98.30% ($p=0.03$) using AFP alone and HES algorithm, respectively. HES algorithm could have detected 18 additional early stage HCC cases (16% increase) compared to AFP alone ($p<0.0005$). HES algorithm had a positive screening result in 56%, 43% and 33.9% in 50, 142 and 245 screening occasions within 6 months, 1 year and 2 years prior to HCC diagnosis, respectively, where no nodules were detected on ultrasound. **Conclusions:** HES algorithm demonstrated a significant absolute 5.18 percentage point improvement in sensitivity for detecting early HCC compared to AFP alone 6 months prior to clinical diagnosis.

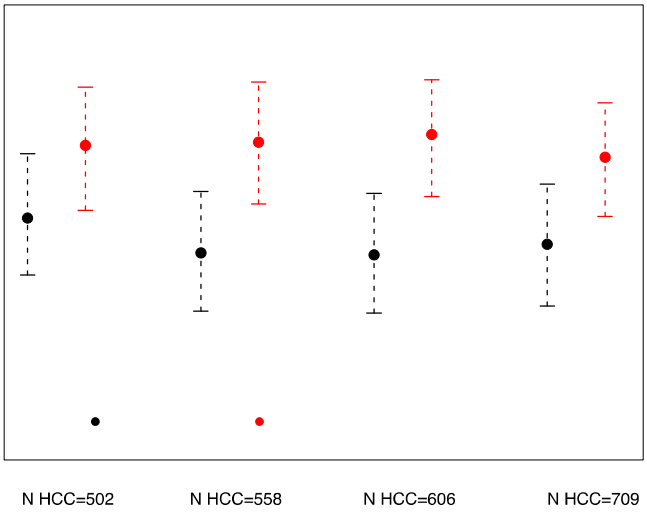

Figure: Patient-level sensitivity corresponding to 10% screening-level false positive rate for T=6, 12, and 24 months prior to HCC diagnosis and at any time prior to HCC diagnosis (Ever) and the associated 95% bootstrap percentile intervals in early stage HCC cases.

The Performance of the Early detection Screening (HES) Algorithm for Early Detection of Hepatocellular Carcinoma (HCC). A Prospective Cohort Phase 3 Biomarker Study in the United States

Hashem B El-Serag, Fasiha Kanwal, Abeer Alsarraj, Ruben Hernaez, Nabihah Tayob

Background: We previously developed and refined the HCC Early detection Screening (HES) algorithm in retrospective cohorts of patients with cirrhosis of any etiology in the national VA Healthcare System. HES includes current AFP, age, platelets, ALT, and rate of change from previous AFP value within the past year. In this analysis, we validated the HES algorithm's ability to improve the likelihood of early HCC detection in a prospective VA HCC surveillance cohort and compared it to AFP, AFP-3, DCP and GALAD score. **Methods:** We conducted a phase 3 biomarker study (prospective-specimen collection, retrospective-blinded-evaluation) during 08/2014-10/2018. We enrolled patients with cirrhosis and no prior HCC in a 6-month surveillance program consisting of liver imaging (mostly ultrasound) and AFP. HCC was diagnosed according to American Association for the Study of Liver Diseases (AASLD) criteria. ALT and platelets were measured in every visit. Blood samples were prospectively collected every 6 months and were analyzed for AFP, AFP L-3, and DCP in a retrospective blinded fashion. We calculated patient-level sensitivity and screening-level false positive rate (FPR) for detecting HCC for AFP, AFP L-3, DCP, the GALAD score, which combined the 3 biomarkers with age and gender, and the HES algorithm. For easier comparisons, we calculated sensitivity at a fixed FPR of 10%. Controls were patients with cirrhosis under surveillance who did not develop HCC. **Results:** We analyzed 1,431 total study visits for 513 controls and 49 HCC cases that developed after enrollment in the surveillance cohort. We restricted the analysis to study visits prior to or at HCC diagnosis. We further restricted controls to only those with consistently negative liver imaging results, and to those with ALT and platelets measured in all study visits. The mean age of the overall cohort was 63 years and 98% were men. Cirrhosis etiology was HCV in 72%, alcohol 60%, and nonalcoholic fatty liver disease in 22%. At the time of diagnosis, the mean tumor size was 2.1 cm (standard deviation, SD 0.9), and 69% of patients had only one HCC nodule. The sensitivity of each of AFP, AFP-3 and DCP were low and comparable. GALAD score had higher sensitivity than each of triple markers. However HES (which does not so far incorporate AFP-3 or DCP) yielded a similar sensitivity to GALAD, and 6 percentage points higher than AFP alone (Table). **Conclusions:** In a HCC surveillance cohort of patients with cirrhosis from different etiologies, the use of HES algorithm results in a considerable improvement over AFP alone in the sensitivity for HCC detection with no added testing or cost. This improvement rivals that of GALAD score, which uses AFP-3 and DCP in addition. We are now investigating the possible additional yield to HES from adding AFP-3 and DCP.

Table. Patient-level sensitivity corresponding to 10% screening-level false positive rate for T=6, and 12 months prior to HCC diagnosis and at any time prior to HCC diagnosis (Ever)

	HCC within 6 months (N HCC: 33)	HCC within 12 months (N HCC: 42)	HCC ever (N HCC: 49)
AFP	0.33	0.36	0.43
AFP-L3	0.36	0.40	0.41
DCP	0.33	0.33	0.33
GALAD	0.42	0.45	0.49
HES algorithm	0.39	0.40	0.49

Intestinal epithelial and immune cell response to enteric virus-induced paracrine purinergic signaling

Kristen A. Engevik[1], Alexandra Chang-Graham[1], Melinda A. Engevik[2], Jacob L. Perry[1], Joseph M. Hyser[1]

1. Department of Molecular Virology and Microbiology, Baylor College of Medicine
2. Department of Immunology and Pathology, Baylor College of Medicine

Calcium (Ca2+) is a ubiquitous messenger that influences numerous cellular processes, and therefore Ca2+ signaling is tightly regulated by cells. Ca2+ signaling dysregulation results in severe and potentially life-threatening diseases, which is exemplified by rotavirus (RV) infection. RV is an enteric virus that causes life-threatening diarrhea in children, resulting in ~198,000 deaths each year. Pathophysiological consequences of RV infection are widely studied, yet host Ca2+ signaling pathways and the mechanisms by which RV exploits them to cause diarrhea remain incompletely characterized. We have found that RV infection increases Ca2+ signaling both within infected enterocytes and in surrounding uninfected cells through paracrine signaling. This manifests as intercellular Ca2+ waves that originate from the infected cell and propagates through uninfected cells mainly through ADP and the P2Y1 receptor. We hypothesized that ADP purinergic signaling would activate Ca2+ dependent pathways in various intestinal cell types, including goblet cells, enteroendocrine cells and macrophages. We found that P2Y1-mediated signaling was critical for activation of secretory epithelial cells, including induction of serotonin secretion of enterochromaffin cells and mucus secretion from goblet cells in human intestinal enteroids (HIEs) and mucin-producing cell lines. In monkey kidney MA104, RV-infection chemoattracted RAW and bone-marrow derived macrophages, which also harbor the P2Y1 receptor. This effect was blunted by pharmacological inhibitors of the P2Y1 receptor. Consistent with our *in vitro* findings, we observed that murine RV infection promoted secretion of serotonin, mucin and accumulation of macrophages. These effects of minimized in the presence of P2Y1 inhibitors and in P2Y1 knock out mice. Collectively these findings point to the role of purinergic signaling and Ca2+ waves in the pathophysiology of RV-infection. Understanding the role ADP signaling via P2Y1 receptor plays in RV will provide mechanistic insights into the homeostatic function of purinergic signaling in the GI tract.

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Fecal *Collinsella* abundance is negatively associated with toxin A/B production in cancer patients with *Clostridioides difficile*

Denise Francisco, MD[1,2], Adilene Olvera, MPH MLS (ASCP)[2], Liangliang Zhang[3], Eduardo Yepez Guevara, MD[2], Kevin W. Garey, PharmD[4], Christine Peterson[3], Kim-Anh Do[3], Ryan Dillon MSc[5], Robert Jenq[6], Pablo C. Okhuysen, MD[1,2]

[1]Section of infectious Diseases, Baylor College of Medicine, Houston, Texas, [2]Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, Texas.
[3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, [4]University of Houston College of Pharmacy, Houston, Texas, [5]Merck & Co., Inc., Kenilworth, NJ, USA
[6]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Background
The detection of *C. difficile* (CDI) by nucleic acid amplification test (NAAT) with negative toxin enzyme immunoassay (EIA-) is difficult to interpret in cancer patients. Markers that differentiate true infection from colonization, and are associated with clinical outcomes are needed. We hypothesized that the microbiome composition and inflammatory fecal markers in EIA- patients differed from those who are EIA+ and were associated with disease severity and recurrence.

Methods
We studied the fecal microbiome composition (16s rRNA, V3) of 147 cancer patients with CDI diagnosed by a two-step testing algorithm. Clinical data, CDI bacterial quantity (BQ) by qPCR and markers of intestinal inflammation (calprotectin, lactoferrin, IL-1β and IL-8) were analyzed. Data was stratified according to cancer type [hematologic (H) n=49, solid tumor (ST) n=66, or stem cell transplant (SCT) n=32].

Results
Demographic characteristics and symptoms were similar between the three groups. At baseline, species diversity by Shannon index was similar in all three groups regardless of EIA detection and did not correlate with clinical presentation, response to therapy or recurrence. Microbiome composition did not correlate with inflammatory response except in H in whom a higher diversity correlated with increased IL-8 ($p=0.021$) and calprotectin ($p=0.01$) levels. At the genus level across all strata and when compared to EIA- cases, EIA+ cases presented with a higher abundance of *Peptoclostridium* ($p=0.0008$) which correlated with CDI BQ qPCR (log of BQ/mg 2.38 ± 1.49 vs 0.92 ± 1.28, $p < 0.001$). In contrast, EIA- cases had a higher abundance of *Collinsella* ($p=0.001$). SCT patients carried fewer *Peptoclostridium* when compared to other groups, whereas all three patient groups carried similar amounts of *Collinsella*. The relative abundance of *Peptoclostridium* and *Collinsella* was not associated with response to therapy, or fecal markers of inflammation. Principal component analysis did not demonstrate differences between the three groups studied.

Conclusion
In this study, the presence of *Collinsella*, a known butyrate and bile salt hydrolase producer, was associated with the lack of CDI toxin A/B production. Loss of *Collinsella* may represent a novel risk factor for active CDI.

Antimicrobial stewardship and *Helicobacter pylori*: A new beginning

David Y. Graham, M.D.

VA Medical Center and Baylor College of Medicine, Houston, TX. USA

H. pylori required more than 20 years before it was accepted as an infectious rather than a gastroenterology disease. Originally therapy was developed by trial and error as if cure was impossible and there was a placebo response (i.e., as a GI diseases such as constipation). Successful regimens, defined as cure ≥95% of susceptible infections in adherent subjects, were developed but were continued even after antimicrobial resistance had greatly reduced their effectiveness. Antimicrobial stewardship one uses only drugs for which the infection is susceptible, at optimum dose, formulation, dosing interval, dosing frequency, and duration. Infectious disease therapies typically achieve close to 100% cures and comparative trials use non-inferiority trial designs in which both regimens achieve high cure rates. In contrast, traditional H. pylori trials often used an ineffective regimen with unoptimized antibiotic combinations. Consents are uninformed when patients are denied knowledge that one comparator is known to be no longer effective. Meta-analyses combine studies with different drugs, drug combinations, and treatment durations in populations often with high and unmeasured resistance and declare better of two very poor results a winner. Treatment regimens (drugs, doses, durations) have been defined by Pharma rather than by results. Now that H. pylori has been defined as an infectious disease, we face new challenges including re-education of clinicians and investigators regarding the established infectious disease treatment paradigms. Following the well-established trail blazed by the infectious disease community we can change from enriching Pharma and their speakers and get about curing patients and eliminating disease.

Parenteral versus enteral nutrition exacerbates liver injury in a neonatal pig model of obstructive cholestasis

Greg Guthrie[1], Barbara Stoll[1], Marko Rudar[1], Sanjiv Harpavat[2], Douglas Burrin[1]

[1]USDA-ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, United States, [2]Baylor College of Medicine, Department of Pediatrics, Section Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, United States

Objectives and Study: Biliary atresia (BA) is a neonatal disease that results in the destruction of the extra-hepatic bile ducts. The current treatment for BA is the Kasai procedure, a hepatoportoenterostomy, which fails in 30% of cases and results in liver transplant. Infants with BA have poor bile flow into the intestine. This limits absorption of fat and fat-soluble nutrients and increased metabolic requirements from progressive liver disease, many of these infants will have failure to thrive or poor transplant outcomes. Parenteral nutrition (PN) is administered in some of these infants to optimize nutrient status and improve growth. PN containing soy lipids are associated with increased risk of cholestatic liver disease in infants, but whether the effect is accelerated in cases of BA is unknown. The goal of this study is to quantify the effect of enteral and parenteral nutrition on serum markers of liver injury in a neonatal pig model of obstructive cholestasis to mimic the effects of BA on liver injury. We measured fibroblast growth factor 19 (FGF-19), a gut hormone that functions as a negative feedback on hepatic bile acid synthesis.

Methods: Term-age piglets (113 d gestational age) were delivered by caesarian section and implanted with a jugular catheter for the administration of parenteral nutrition (TPN) containing soy lipid (Intralipid). Pigs were also implanted with an orogastric tube for feeding an enteral (ENT) pig formula. The ENT and TPN piglets were then randomized to receive either 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 d.

Results: Direct bilirubin levels were increased (p>0.001) in all groups compared to the ENT-SHAM (0.05 ± 0.14 mg/dL). Direct bilirubin was higher in the TPN-BDL (1.95 ± 0.13 mg/dL) than the ENT-BDL (1.41 ± 0.19 mg/dL), whereas TPN-SHAM (1.44 ± 0.22 mg/dL) and ENT-BDL were not different. Serum gamma glutamyl transferase was higher 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) groups. Serum and hepatic bile acids increased in all groups compared to ENT-SHAM. Serum bile acids were also higher in the TPN groups compared to the ENT-BDL. Bile acid content in the small intestine was highest in the ENT-SHAM (3280 ± 570 nmol/g content) and markedly lower in the ENT-BDL (75.4 ± 21.9 nmol/g content) and the TPN-BDL (125.6 ± 32.7 nmol/g content). As expected, plasma FGF-19 concentration was high in the ENT-SHAM (6829 ± 1051 pg/mL) and undetectable in most ENT-BDL (229 ± 148 pg/mL) pigs. However, unexpectedly plasma FGF19 was also high TPN-BDL (9187 ± 2959 pg/mL) pigs.

Conclusion: In a novel model of neonatal obstructive cholestasis, markers of cholestatic liver injury were higher parenteral versus enterally-fed pigs. The high serum bile acid levels in TPN-BDL pigs occurred despite higher plasma concentrations of FGF-19 suggesting an uncoupling of its suppression of hepatic bile acid synthesis. Our results suggest that PN with soy-based lipid emulsions compared to enteral formula feeding may accelerate liver disease in infants with BA. Future studies are warranted using multi-component lipid emulsions to test whether this effect of PN is lipid-dependent or mainly due to mode of feeding (i.e. TPN vs ENT).

Depletion and enrichment of phytosterols in soybean oil lipid emulsions directly associate with cholestasis in preterm PN-fed pigs

Greg Guthrie[1], Barbara Stoll[1], Shaji Chacko[1], Candace Style[2], Mariatu Verla[2], Oluyinka Olutoye[2], Deborah Schady[3], Douglas Burrin[4]

[1]USDA-ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, United States, [2]Baylor College of Medicine, Department of Pediatric Surgery, Houston, United States, [3]Baylor College of Medicine, Department of Pathology, Houston, United States, [4]USDA-ARS Children's Nutrition Research Center, Department of Pediatrics, Section Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, United States

Objectives and Study: The long-term administration of parenteral nutrition (PN) containing pure soybean oil lipid emulsions is suggested as a contributing factor for developing parenteral nutrition associated cholestasis in infants. The multifactorial reasons for the development of cholestasis are poorly understood, yet clinical reports have shown a correlation between plasma phytosterols and direct bilirubin levels. Currently, there is no defined toxic level of plant phytosterols in PN. We aimed to test whether depletion of phytosterols from soybean oil lipid emulsions prevent the development of cholestasis. This study used preterm pigs to compare three pure soybean oil preparations with low, normal, and high phytosterol enrichment to determine if phytosterols specifically contribute to the cholestasis when the PN lipid intake is constant. **Methods**: Piglets were delivered by caesarian section 7 d preterm and implanted with jugular catheters for administration of PN. Three lipid emulsions were prepared from soybean oil containing 30% (depleted, DEP), 100% (Intralipid, normal phytosterol concentration NP), and 150% (enriched, ENR) total phytosterol concentration. Piglets received either enteral nutrition or total PN containing equal lipid intakes (5 g/kg*d-1, representing 1.2 times the maximum human dose of 4 g/kg*d-1) from either the DEP, NP, or ENR emulsions. During and at the end of 21 d of treatment, blood and tissue samples were collected for analysis. **Results**: At the end of the study, plasma and liver phytosterol concentrations were significantly ($p < 0.05$) higher in NP compared to ENT and DEP groups and in the ENR group compared to all groups. Serum direct bilirubin was higher ($p < 0.05$) in the NP (1.39 ± 0.22 mg/dL) and ENR (1.61 ± 0.38 mg/dL) groups compared to ENT (0.05 ± 0.01 mg/dL) and the DEP (0.35 ± 0.03 mg/dL) groups but did not exceed the reference value defined as cholestasis in human infants (direct bilirubin level ≥ 2.0 mg/dL). A similar significant ($p < 0.05$) increase was observed in serum bile acids, which was unexpectedly higher in the NP (43.8 ± 3.31 μM) than in the ENR (35.0 ± 1.69 μM) group compared to ENT (4.15 ± 0.64 μM) and DEP (7.03 ± 1.91 μM). Serum gamma glutamyl transferase was higher in the ENR (244.3 ± 133.1 U/L) piglets ($p < 0.05$) and in the NP (173.2 ± 154.3 U/L) piglets compared to DEP (51.7 ± 7.6 U/L) and ENT (27.6 ± 3.64 U/L) piglets. There were significant correlations between serum cholestasis markers and plasma phytosterol concentrations. All PN lipid groups showed evidence of mild hepatic steatosis, but no change in hepatic expression of proinflammatory cytokines or farnesoid X receptor target genes. **Conclusion**: The increase in serum direct bilirubin was lower in the depleted group vs the lipid emulsions with normal or enriched phytosterol content, but below direct bilirubin level ≥ 2 mg/dL defined as cholestasis in infants. We demonstrated a strong positive correlation between serum markers of cholestasis and plasma phytosterol concentrations but not liver inflammatory cytokine expression. The mechanisms associated with phytosterol-mediated injury deserve further evaluation. Overall, our results provide additional evidence that phytosterols in soybean oil emulsions are linked to an increase in serum markers of cholestasis in preterm PN-fed pigs.

Male Sex Hormones are Associated with Presence, Severity and Mortality in Males with Non-alcoholic Fatty Liver Disease: A Prospective Cohort Study

Hyun-seok Kim, Aaron P. Thrift, Ruben Hernaez, Maya Balakrishnan, Yamini Natarajan, Fasiha Kanwal, Hashem B. El-Serag Baylor College of Medicine, Houston, TX 77027

Background: Many studies have reported the association between low male sex hormone levels and metabolic syndrome. However, it is not clear whether male sex hormones correlate with the presence, severity or prognosis of nonalcoholic fatty liver disease (NAFLD). We hypothesized that circulating male sex hormone levels may be associated with the severity and mortality of NAFLD, using nationally representative data. **Methods:** We obtained data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988-1994. NAFLD was defined by ultrasonographic detection of hepatic steatosis in the absence of other known causes of liver disease (i.e., hepatitis B and C infection, alcohol abuse) and categorized as normal, mild, moderate, or severe steatosis. Severity of hepatic fibrosis was determined by the NAFLD fibrosis score (NFS). Four circulating sex hormones were measured using morning fasting samples: testosterone (ng/mL), estradiol (pg/ml), sex hormone binding globulin (SHBG) (nmol/L), and 3-alpha androstanediol glucuronide (3-AAG) (ng/ml). Free androgen index (%) was calculated by as testosterone/SHBG X 100. Participants were passively followed up for mortality, identified by death certificate underlying or contributing causes, by linkage to National Death Index records through 2015. We used survey-weighted generalized logistic regression to evaluate the association between male sex hormone levels and each of fibrosis severity of NAFLD and mortality risk estimated in survey-weighted cox-regression survival analyses. **Results:** A total of 950 male participants met our inclusion/exclusion criteria and had complete data available for analysis. Among those, 295 people (28%) had NAFLD: 97 with mild (34.5%), 149 with moderate (49.2%), and 49 with severe steatosis (16.2%). Compared to non-NAFLD controls, NAFLD patients had significantly lower testosterone and SHBG levels but not with estradiol and 3-AAG levels (testosterone: 5.70± 0.09 in control vs 4.58 ± 0.12 in NAFLD, p=0.04; SHBG: 38.9 ± 1.07 in control vs 32.1 ± 1.13 in NAFLD, p=0.03) after adjusting for demographic and metabolic risk factors. Testosterone and SHBG levels were also significantly inversely associated with the degree of steatosis after adjusting for demographic and metabolic risk factors (Table 1). Among participants with NAFLD, there were 145 (53.8%) with low NFS (<-1.455), 120 (39.3%) with intermediate NFS, and 30 (6.9%) with high NFS (>0.676). Free androgen index was inversely associated with the severity of hepatic fibrosis (18.6 ± 1.15 in low NFS, 13.9 ± 0.92 in intermediate NFS, 11.6 ± 1.03 in high NFS, trend p= 0.03). After median-follow up duration of 20.6 years, 295 deaths were observed (104 in NAFLD and 191 in non-NAFLD). Free androgen index was inversely associated with all-cause mortality only in NAFLD participants (adjusted HR: 0.93 [0.88-0.99], p= 0.02), but not in non-NAFLD participants (adjusted HR 0.99 [0.90-1.10], p-value 0.93) after adjusting for demographic and metabolic risk factors and fibrosis severity. **Conclusion:** The presence and severity of NAFLD patients was associated with lower serum testosterone and SHBG level. In addition, testosterone/SHBG ratio could be a mortality prognostic marker in male NAFLD patients.

Table 1. Sex hormone level by degree of NAFLD (steatosis) on liver ultrasound findings

	No NAFLD (n=655)	NAFLD Mild (n=97)	NAFLD Moderate (n=149)	NAFLD Severe (n=49)	unadjusted p-value	Limited model p-value*	Full model p-value#
			Total				
testosterone	5.70 ± 0.09	5.12 ± 0.18	4.26 ± 0.13	4.42 ± 0.37	<0.0001	0.00138	0.05
E2	37.1 ± 0.89	35.3 ± 1.42	35.6 ± 1.02	35.9 ± 2.07	0.157	0.333	0.290
SHBG	38.9 ± 1.07	34.8 ± 1.90	29.4 ± 1.45	34.7 ± 3.65	0.002	0.0006	0.037
androstanediol	14.0 ± 0.52	14.5 ± 1.16	15.4 ± 2.45	12.0 ± 1.85	0.909	0.677	0.859

* adjusted for age, race
\# adjusted for age, race, hypertension, diabetes, dyslipidemia, waist to hip ratio

Table 2. Mortality by male sex hormones in NAFLD (N=295; 104 deaths)

		Multivariate HR (95% CI)	p-value
Free androgen index (per 1 unit)		0.93 [0.88-0.99]	0.02
Age group,	20-39	Ref	
	40-59	7.92 [2.84-22.1]	<0.001
	≥60	20.4 [6.62-62.6]	<0.001
NFS category,	low	Ref	
	Intermediate	1.01 [0.53-1.95]	0.99
	High	2.09 [1.00-4.36]	0.05
Race,	Whites	Ref	
	Blacks	0.95 [0.52-1.73]	0.81
	Hispanics	0.28 [0.11-0.71]	<0.01
	Other race	0.44 [0.05-3.83]	0.47
Waist to hip ratio,	Low tertile/Intermediate tertile	Ref 1.75 [0.48-6.41]	0.40
	High tertile	2.10 [0.55-7.96]	0.28
Education,	<College	Ref	
	>=College	0.62 [0.29-1.36]	0.24
Household income,	low	Ref	
	Middle	0.81 [0.33-1.96]	0.64
	High	0.52 [0.30-0.90]	0.02
Insurance status,	No	Ref	
	Yes	0.36 [0.11-1.19]	0.09
Smoking status,	Never	Ref	
	Former	1.58 [95% CI: 0.76-3.28]	0.22
	Current	2.92 [95% CI: 1.18-7.26]	0.02

Karnofsky Performance Status of Underweight Compared to Obese Nonalcoholic Steatohepatitis at Liver Transplantation in the United States

Mohamed Saleh Ismail, M.D., MSc, Baylor College of Medicine

Background and Aims: The Karnofsky performance status scale (KPS) is used for assessment of functional abilities of liver transplant (LT) candidates. Based on published literature, the KPS is an independent predictor of graft and patient survival after LT. We aimed at assessing the KPS in different BMI categories calculated at LT among patients with nonalcoholic steatohepatitis (NASH). **Method:** Using the large United Network for Organ Sharing (UNOS) database, adult patients underwent LT from 01/2002 to 12/2017 were included. Patients were categorized into underweight (BMI <18.5 kg/m^2, n=24), lean (BMI 18.5 - <25 kg/m^2, n=514), overweight (BMI 25 - <30 kg/m^2, n=1235), obese I (BMI 30 - <35 kg/m^2, n=1470), obese II (BMI 35 - <40 kg/m^2, n=1052) and obese III (BMI ≥40 kg/m^2, n=486). Among each BMI category, patients were grouped into low (10-40%), intermediate (50-70%) and high (80-100%) KPS groups based on KPS scores at time of LT. **Results:** Underweight patients have significantly low KPS at time of transplant compared to other BMI categories (*P* <.0001). Underweight patients were more likely to receive hemodialysis one week before transplant and be on life support at time of transplant compared to other BMI categories (*P* =.004 and *P* <.001, respectively). However, these same underweight patients have significantly higher patient and graft survival compared to other BMI groups (*P* <.001). The KPS at 1-year follow-up after LT was markedly improved in underweight patients and was comparable to other BMI categories (*P* =.3). **Conclusion:** Underweight patients with NASH have significantly better post-LT outcomes even if they have low KPS at time of transplant.

Table:

	Number (%)						
Characteristic	Underweight (n=24)	Lean (n=514)	Overweight (n=1235)	Obese I (n=1470)	Obese II (n=1052)	Obese III (n=486)	*P* value
Mean (±SD) age at LT, years	55.0 ± 12.5	59.8 ± 8.7	60.1 ± 7.8	58.8 ± 7.7	57.3 ± 7.9	55.2 ± 8.5	**.0001**
Male	9 (37.5)	233 (45.3)	685 (55.5)	778 (52.9)	583 (55.4)	247 (50.8)	**.001**
White	17 (70.8)	425 (82.7)	1031 (83.5)	1250 (85.0)	930 (88.4)	394 (81.1)	**.0001**
Dialysis one week before transplant	7 (31.8)	116 (23.0)	227 (18.6)	245 (16.8)	179 (17.3)	116 (24.2)	**.004**
On life support at transplant	6 (25)	48 (9.3)	89 (7.2)	114 (7.8)	83 (7.9)	59 (12.1)	**.001**
Functional status at transplant							**.0001**
Low KPS	15 (62.5)	266 (52.6)	535 (44)	676 (47.4)	469 (46.1)	250 (52.6)	
Intermediate KPS	6 (24.9)	190 (37.7)	506 (41.6)	545 (38.1)	411 (40.5)	166 (34.9)	
High KPS	3 (12.5)	49 (9.7)	174 (14.4)	206 (14.4)	136 (13.4)	60 (12.6)	
Functional status at last follow-up							.3
Low KPS	3 (27.3)	67 (20.9)	129 (17)	165 (19)	109 (19.1)	58 (21.1)	
Intermediate KPS	1 (9.1)	59 (18.3)	141 (18.6)	176 (20.3)	115 (20.2)	42 (15.3)	
High KPS	7 (63.7)	195 (60.8)	488 (64.4)	525 (60.6)	344 (60.6)	174 (63.6)	
Mean (±SD) patient survival, days	1722 ± 1188	1355 ± 1140	1467 ± 1196	1549 ± 1231	1630 ± 1301	1534 ± 1215	**.001**
Mean (±SD) graft survival, days	1722 ± 1188	1350 ± 1138	1465 ± 1197	1546 ± 1230	1629 ± 1300	1534 ± 1214	**.001**

Probiotics differentially affect the gut immunity, microbial community and its associated metabolites in mice with Treg-deficiency-induced autoimmunity

Yuying Liu[1], Thomas K. Hoang[1], Christopher M. Taylor[2], Baokun He[1], Sinyoung Park[1], Jasmin Freeborn[1], Meng Luo[2], Xiangjun Tian[3], Dat Q. Tran[1], Stefan Roos[4], and J. Marc Rhoads[1]

[1]Department of Pediatrics, Divisions of Gastroenterology, The University of Texas Health Science Center at Houston McGovern Medical School, Houston, TX, [2]Department of Microbiology, Immunology & Parasitology, Louisiana State University School of Medicine, Children's Hospital, New Orleans, Louisiana, [3]Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, [4]Department of Microbiology, Uppsala BioCenter, Swedish University of Agricultural Sciences, Sweden

Background: Regulatory T (Treg) cells play a pivotal role in immune tolerance. Treg-deficiency causes a lethal, $CD4^+$T cell-driven autoimmune disease, called IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, with X-linked inheritance) in humans and scurfy (SF) mice. Feeding *Lactobacillus reuteri* DSM 17938 (LR 17938) to SF mice can reprogram the gut microbiota and markedly reduce disease progression, prolonging the mouse's lifespan from < 1 month to > 4 months. However, the specificity of LR17938 to differentiate with other probiotics in these effects is unknown. **Objectives:** To determine whether the therapeutic probiotic effect on SF mice is specific to LR17938 and to compare gut immune modulation, microbiota and plasma metabolites in SF mice treated with different probiotics. **Methods:** Probiotics were selected to assess the effects of SF survival including LR 17938, *L. rhamnosus* GG (LGG), *Bifidobacterium breve* 46u01b (BB), and *L. acidophilus* DDS (La DDS). We gavage fed 10^7 cfu/day to SF mice daily, starting on d13 after the SF phenotype was identified. Mesenteric lymph nodes (MLNs) and terminal ileum (INT) were collected for analysis of immune cells (T cells and dendritic cells) by flow cytometry. Cecal contents and blood were collected on d22 (before weaning) for microbiota analysis by 16s rRNA gene sequencing and plasma global metabolomics (Metabolon). **Results:** Male SF mice demonstrated scaly, crusty skin on ears and tails on d13 of age and died by d28 with a lymphoproliferative syndrome. Oral gavage of each of 3 probiotics, LR 17938, LGG, and BB prolonged the survival of SF mice, while La DDS was ineffective. LR17938 and BB were more effective than LGG. Probiotic LR and BB reduced inflammatory T cells locally (MLN) and systemically (blood) in SF mice. All three probiotics reduced inflammatory dendritic cells (DCs) and increased tolerogenic DCs in the intestinal mucosa of SF mice. All probiotics restored the gut microbial alpha diversity, but they differentially modulated the relative abundance of bacteria. Specifically, LR 17938 increased the relative abundances of *Oscillospira, Rumminococcaceae, RF32,* and *Desulfovibrio* while reducing *Bacteroides, Enterobacteriaceae,* and *Akkermansia.* BB increased *Prevotella* and *Rumminococcaceae while reducing Bacteriodes, Parabacteroides and Enterobacteriaceae.* LGG increased *Rikenellaceae, Allobaculum, RF32, and Sutterella,* while reducing *Bacteroides and Enterobacteriaceae.* Metabolomics revealed substantial differences among 696 metabolites when comparing SF, WT and SF+probiotics. However, similar changes of many metabolites in SF mice were seen, regardless of whether SF mice were treated with LR17938, LGG, or BB. Of importance, treatment of SF mice with LR17938 and BB reversed SF-associated decrease in inosine. This was notable, because we previously showed that inosine reduces inflammation in SF mice via interaction with the adenosine A_{2A} receptor. **Conclusions:** 1) Probiotics modulate immune responses, and different probiotics produce different changes in the colonic microbial community in the setting of enteropathy with systemic inflammation. 2) There are similarities in the metabolic signature of different probiotics with anti-inflammatory actions when comparing a lactobacillus with a bifidobacterium.

Lactobacillus reuteri reduces the severity of experimental autoimmune encephalomyelitis in mice by modulating gut microbiota

Yuying Liu[1], Baokun He[1], Thomas K. Hoang[1], Xiangjun Tian[2], Christopher M. Taylor[3], Eugene Blanchard[3], Meng Luo[3], Meenakshi B. Bhattacharjee[4], Jasmin Freeborn[1], Sinyoung Park[1], Jacob Couturier[5], J. William Lindsey[6], Dat Q. Tran1, and J. Marc Rhoads[1*]

Departments of [1]Pediatrics, Division of Gastroenterology, [4]Pathology and Laboratory Medicine, [5]Internal Medicine, Division of Infectious Diseases, and [6]Neurology, the University of Texas Health Science Center at Houston-McGovern Medical School, Houston, TX, [2]Department of Bioinformatics & Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, [3]Department of Microbiology, Immunology & Parasitology, Louisiana State University, School of Medicine, New Orleans, Louisiana

Background: The gut microbiome plays an important role in immune function and has been implicated in multiple sclerosis (MS). However, how to modulate microbiota to prevent or treat MS remain largely unknown. Probiotic *Lactobacillus reuteri* DSM 17938 (LR 17938) has anti-inflammatory effects in mouse models of neonatal necrotizing enterocolitis and Treg-deficiency-induced autoimmune disease. LR 17938 in these models modulated gut microbiota and microbiota-associated metabolites to inhibit T_H1 and T_H2 differentiation and their-associated cytokines, significantly ameliorating the severity of these diseases. An *in vitro* study indicated that LR 17938 inhibits the differentiation of naïve $CD4^+$ T cells into T_H17 and T_H1 cells. Hypothesis: LR 17938 may modulate microbiota and inhibit T_H1 and T_H17-mediated inflammation in a mouse model of MS. **Objectives:** We determined the effect of LR 17938 on experimental autoimmune encephalomyelitis (EAE) mouse model, a widely used animal model of MS, a model that is primarily mediated by T_H17 and T_H1 cells. **Methods:** EAE was induced in female C57BL/6J mice (10 week-old) by using the Hooke Kit™ MOG35-55/CFA Emulsion PTX kit (Hooke Laboratory). Briefly, mice were immunized with an emulsion of myelin oligodendrocyte glycoprotein peptide (MOG35-55) in complete Freund's adjuvant (CFA) by subcutaneous injection into two different sites on each hind flank, followed by intraperitoneal administration of pertussis toxin (PTX) in PBS after 2 h MOG35-55 immunization. Then PTX was given again on the following day. Each mouse was orally feeding either LR 17938 in MRS (10^8 cfu/day, 100 µl) or MRS medium (100 µl), daily, from d0 to d20 after immunization. Clinical EAE scores evaluated on scale 0 (normal), 1 (limp tail), 2 (limp tail+weakness of hind legs), 3 (limp tail+complete paralysis of hind leges), 4 (limp tail+complete hind leg+partial front leg paralysis), to 5 (spontaneously rolling in the cage). Stool samples were analyzed by 16s rDNA sequencing. Spinal cords were stained with H&E, CD3, and CD68. We isolated plasma and PBMCs from blood. ELISA detected cytokine levels in plasma, and *in vitro* stimulation and cell proliferation assays for PBMCs and splenocytes. **Results:** We discovered that LR 17938 treatment reduced T_H1/T_H17 cells and their associated cytokines IFN-γ/IL-17 in EAE, inhibiting the development of EAE. We also showed that the loss of diversity in gut microbiota induced by EAE was largely restored by LR 17938 treatment. Taxonomy-based analysis of gut microbiota showed that the "beneficial" genera *Bifidobacterium*, *Prevotella*, and *Lactobacillus* were negatively correlated with clinical EAE severity, whereas the genera *Anaeroplasma, Rikenellaceae*, and *Clostridium* were positively correlated. Notably, LR 17938 treatment altered the relative abundances of these EAE-associated taxa in mice. **Conclusions:** Probiotic LR 17938 changed gut microbiota to modulate immune responses in EAE, making it a novel candidate in future studies to modify the severity of MS.

Lipid Dysregulation of Immune Mediated Intestinal Epithelial Healing

Andrea A. Hill, Myunghoo Kim, Daniel F. Zegarra-Ruiz, Michael C. Renfroe, Kendra Norwood, Hyo Won Song, Wan-Jung Wu, Dasom Kim, Ming-Ting Tsai, Fatima Saldana Morales, Angela M. Major and Gretchen. E Diehl.

Baylor College of Medicine, Houston, TX, United States

It is clear that long-term exposure to high fat diets (HFD) results in obesity and systemic inflammation and can exacerbate many disorders, including inflammatory bowel disease (IBD). However, the direct effect of lipids on tissue homeostasis and repair remain undefined. We show here that short term exposure to HFD results in reduced barrier repair after intestinal epithelial damage with increased accumulation of apoptotic neutrophils. After barrier breach, neutrophils are recruited to clear invading bacteria, after which they undergo apoptosis followed by uptake by tissue macrophages in a process termed efferocytosis. Efferocytosis initiates a pro-repair program, including upregulation of the anti-inflammatory cytokine IL-10. We find dietary lipids directly interfere with macrophage recognition and uptake of apoptotic cells, and subsequent IL10 production, after intestinal damage by blocking interactions between apoptotic cells and the efferocytosis receptor CD36, which also binds dietary lipids. Overexpression of IL-10 rescues repair defects after HFD, but not if epithelial cells lack the IL-10 receptor, highlighting the key role of IL-10 in barrier repair. These findings demonstrate a previously unidentified mechanism by which dietary lipids, a risk factor for intestinal disease, can directly interfere with homeostatic processes required to maintain tissue integrity.

Integration of enteric neural crest cells into human intestinal organoids

McNeill EP[1], Sequeira D[1], Speer AL[1]

McGovern Medical School at UTHealth, Corresponding author: Allison L. Speer, Department of Pediatric Surgery, McGovern Medical School at UTHealth, 6431 Fannin St. MSB 5.254, Houston, TX 77030, E-mail: Allison.L.Speer@uth.tmc.edu

Background: The prevalence of intestinal disorders leading to short bowel syndrome is increasing. Current therapies are inadequate. Tissue-engineered intestine may be a potential solution. However, the complex physiology of the intestine makes it difficult to accurately recapitulate. Improving our knowledge of intestinal development and function is critical to overcome this challenge. The recent development of human intestinal organoids (HIOs) provided new insights into intestinal development and function but does not fully mimic the complexity of the intestines as it lacks an enteric nervous system (ENS). We hypothesize that this issue can be addressed by co-culturing early gut spheroids with enteric neural crest cells (ENCCs) prior to HIO formation, resulting in the generation of HIOs that more accurately recapitulate intestinal tissue due to the developmental cues provided by the ENS.

Methods: Human embryonic stem cells (hESCs) expressing green fluorescent protein (GFP) were differentiated into ENCCs under chemically defined conditions using a recently published protocol. Immunofluorescent (IF) staining was performed for SOX10, TUJ1, GFAP, and BLBP. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed for HOX3B, HOX5B, and PAX3. ENCCs were then mixed with day 4 gut spheroids differentiated from hESCs and co-cultured in matrigel droplets. Fluorescence microscopy was performed to analyze ENCC survival and migration within the co-cultures.

Results: ENCC differentiation was confirmed by positive IF for SOX10, an ENCC lineage marker and qRT-PCR for vagal neural crest cell (NCC) markers HOX3B, HOX5B, and ENCC lineage marker PAX3. The ENCCs successfully differentiated to both neuronal and glial lineages, as confirmed by positive IF for neuronal marker TUJ1, and glial markers GFAP and BLBP. Following co-culture, microscopy confirmed that the ENCCs migrate and integrate with early gut spheroids during HIO generation.

Conclusion: This preliminary data suggests that ENCCs co-cultured with gut spheroids survive and integrate with the spheroids.

Gut hormonal secretion due to microbial fermentation of carbohydrates in pediatric IBS patients.

Firas S. Midani[1,3], Heather A. Danhof[1,3], Robert J. Shulman[2], Bruno P. Chumpitazi[2], Robert A. Britton[1,3].

[1]Department of Molecular Virology and Microbiology, [2]Department of Pediatrics, [3]Alkek Center for Microbiome and Metagenomics Research, Baylor College of Medicine.

Hallmarks of many diet-associated ailments include both alterations in the gut microbiome and abnormalities in gut hormonal secretion. One such ailment is irritable bowel syndrome (IBS), a functional gastrointestinal disorder affecting approximately 11% of people worldwide. The vast majority of IBS patients find certain foods worsen their gastrointestinal symptoms. In a subset of patients, a low fermentable carbohydrate diet improves symptoms. Patients who benefit from a diet low in fructans (commonly ingested fermentable carbohydrates) also differ in gut microbiome composition from ones who do not. We hypothesized that dietary fructans worsen gastrointestinal symptoms in a subset of children with IBS by both altering gut microbiome composition and affecting gut microbial modulation of hormonal secretion by enteroendocrine cells. We cultured stool from two children, one fructan-sensitive and one fructan-tolerant, in bioreactors optimized for the cultivation of human gut microbes. After a short equilibration period, bioreactors were supplemented with either fructose, a fructan (inulin), or water (control). Bioreactor cultures were analyzed for differences in gut microbial composition, short-chain fatty acid production, and their effect on gut hormonal secretion using an enteroid model enriched for enteroendocrine cells. In this pilot experiment, we identified differential microbial responses to fermentable carbohydrates, in terms of composition, production of short-chain fatty acids, and modulation of serotonin secretion from enteroendocrine enriched enteroids. We plan to repeat our approach with a larger sample size to confirm these initial findings. If confirmed, we speculate there may be similar crosstalk between diet, gut microbiome, gut hormonal secretion, and gastrointestinal symptoms in other disorders beyond IBS.

The prevalence of non-*Helicobacter pylori* related gastric cancer is increasing

Theresa H. Nguyen[1], Niharika Mallepally[1], Tariq Hammad[1], Aaron P. Thrift[2, 3], Hashem B. El-Serag[1], Mimi C. Tan[1]

[1]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, [2]Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, [3]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA

Background: Gastric cancer is the fifth leading cause of cancer-related mortality globally. Gastritis related to *Helicobacter pylori* (*H. pylori*) infection is thought to be the most important causal factor for non-cardia gastric cancer. *H. pylori* negative gastritis has been described, but its prevalence among patients with gastric cancer is unknown. The aim of this study was to examine the prevalence of *H. pylori* infection among those with newly diagnosed gastric adenocarcinoma.

Methods: This was a retrospective cohort study of consecutive, newly diagnosed patients with non-cardia gastric adenocarcinoma at the Michael E. DeBakey VA Medical Center in Houston, Texas from 2007 to 2018. We performed a structured review of the medical records to verify the diagnosis of gastric adenocarcinoma on histopathology and the date of diagnosis. *H. pylori* infection positivity was defined by the presence of *H. pylori* bacteria on histopathology including special staining (i.e., Genta, Giemsa, and immunohistochemical staining), positive serum *H. pylori* antibody serology, positive stool *H. pylori* antigen, or positive urea breath test at the time of, prior to, or after gastric adenocarcinoma diagnosis. We used Poisson regression to examine the number of cases of non-*H. pylori* related non-cardia gastric cancer based on year of diagnosis (2007-2010, 2011-2014, 2015-2018).

Results: There were 91 consecutive patients with confirmed incident non-cardia gastric adenocarcinoma diagnosed between November 2007 and October 2018. Most were men (N=87, 95.6%) and black (N=47, 51.6%), and the mean age at diagnosis was 68.0 years (SD 10.8). In addition to gastric cancer biopsy histopathology, 73 patients had at least one additional test for *H. pylori* infection; these included *H. pylori* antibody serology (n=31), non-cancer gastric biopsy histopathology without special staining (n=45), and histopathology with special staining (n=41). None had testing by stool *H. pylori* antigen or urea breath test. The overall prevalence of *H. pylori* infection in the study cohort was 35.2% (n=32). Among those with an additional test for *H. pylori* infection (n=73), the prevalence of *H. pylori* related gastric cancer was 43.8% (n=32). Prevalence rates of non-*H. pylori* related gastric cancer rose slightly from 57.9% in 2007-2010 to 60.0% in 2011-2014 to 73.2% in 2015-2018 (p-value for trend=0.44).

Discussion: The prevalence of *H. pylori* negative non-cardia gastric adenocarcinoma is high, comprising up to 64.8% of all cases. This finding suggests there may be other important causal factors for gastric adenocarcinoma in a US population.

Contemporary prevalence and predictors of *Helicobacter pylori* infection in a U.S. population

Frederick B. Peng[1], Theresa H. Nguyen[2], Ikenna Emelogu[1], Niharika Mallepally[1], Yan Liu[2,5], Aaron P. Thrift[3,4], Hashem B. El-Serag[1,5], Mimi C. Tan[2]

[2]Section of Gastroenterology and Hepatology, [1]Department of Medicine, Baylor College of Medicine, Houston, Texas, [3]Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas, [4]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, [5]Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E DeBakey Veterans Affairs Medical Center

Background: *Helicobacter pylori* infection leads to most peptic ulcers and gastric cancer cases. The prevalence of *H. pylori* has been declining overall but there is no current screening strategy in the U.S. to identify and treat patients with *H. pylori* infection. The purpose of our study was to identify the prevalence and predictors of *H. pylori* infection among patients undergoing upper endoscopy with gastric biopsies for any indication in the Harris County Hospital System in Houston, TX. **Methods:** We identified all consecutive patients undergoing upper endoscopy with gastric biopsies for any indication from two hospitals in the Harris County Hospital System in Houston, TX during 1/2015-12/2016. We abstracted demographic, lifestyle, laboratory, endoscopic, and histopathologic data from the electronic medical record to evaluate previous as well as active *H. pylori* infection seen on gastric biopsy. We determined the overall as well as sex and race/ethnic specific prevalence of *H. pylori* infection. We evaluated associations between demographic, lifestyle, and endoscopic features with *H. pylori* infection in logistic regression models and reported as odds ratios (OR) and 95% confidence intervals (CI). **Results:** Of 943 patients who underwent gastric biopsies, 376 were men (39.9%) with mean age 53.0 years (SD 11.6 years). Most were Hispanics (51.1%) or bla cks (26.0%) with a small proportion of whites (11.1%). The overall prevalence of *H. pylori* infection was 52.8% (n=498), which was highest among Hispanics (60.2%), blacks (51.0%), and Asians (52.3%) compared to whites (21.9%). Predictors of *H. pylori* included race (vs. white, black adjOR 3.76, 95% CI 2.19-6.45; Hispanic adjOR 5.31, 95% CI 3.14-9.00; Asi an adjOR 3.96, 95% CI 1.93-8.11) and proton pump inhibitor use (adjOR 1.50, 95% CI 1.10-2.05). Female sex was protective for *H. pylori* infection (adjOR 0.65, 95% 0.47-0.91). Gastric polyps identified on endoscopy were associated with the absence of *H. pylori* (OR 0.57, 95% CI 0.37-0.88). There were no significant associations with age, BMI, family history of gastric cancer, tobacco use, or alcohol use. **Conclusion:** In this contemporary U.S. cohort of patients undergoing endoscopy with gastric biopsies, the overall prevalence of *H. pylori* infection is very high (52.8%). Black, Hispanic, and Asian race were associated with high *H. pylori* infection, while men were at increased risk of developing this infection. These findings call for developing a *H. pylori* screening strategy in certain high-risk U.S. populations.

Table: Associations of demographic and lifestyle predictors and endoscopic findings with *Helicobacter pylori* infection. Odds ratios (OR) and 95% confidence intervals (CI) reported.

	Univariate OR	95% CI	Multivariate OR	95% CI
Age				
< 40	ref	ref	ref	ref
40-60	1.03	0.70-1.52	1.10	0.73-1.65
> 60	1.18	0.77-1.81	1.28	0.82-2.02
Sex				
Male	ref	ref	ref	ref
Female	0.91	0.70-1.20	**0.65**	**0.47-0.91**
Ethnicity/Race				
White	ref	ref	ref	ref
Black	**3.71**	**2.19-6.28**	**3.76**	**2.19-6.45**
Hispanic	**5.38**	**3.28-8.85**	**5.31**	**3.14-9.00**
Asian	**3.91**	**2.00-7.65**	**3.96**	**1.93-8.11**
BMI (kg/m²)				
< 18	0.57	0.22-1.48	0.67	0.24-1.84
18-24.9	ref	ref	ref	ref
25-29.9	1.09	0.78-1.52	0.98	0.68-1.41
>=30	1.19	0.87-1.63	1.12	0.78-1.59
Family history of gastric cancer	0.99	0.57-1.71	0.93	0.52-1.65
Current smoking status				
Never smoked	ref	ref	ref	ref
Current smoker	0.78	0.56-1.08	1.11	0.74-1.66
Former smoker	0.82	0.60-1.12	0.86	0.60-1.24
Alcohol drinking status				
Never drank	ref	ref	ref	ref
Current smoker	0.93	0.69-1.25	0.93	0.65-1.33
Former smoker	0.61	0.37-1.02	0.75	0.42-1.34
Medication use				
PPI use	**1.67**	**1.26-2.21**	**1.50**	**1.10-2.05**
H2RA use	1.13	0.86-1.49		
Aspirin use	1.14	0.86-1.50		
NSAID use	1.29	1.00-1.68	1.25	0.94-1.67
Indication for endoscopy				
Acid reflux	0.95	0.68-1.32		
Dyspepsia	1.31	1.00-1.72	1.27	0.94-1.72
GI bleeding	0.90	0.59-1.37		
Anemia	0.97	0.71-1.32		
Suspected *H. pylori*	1.56	0.88-2.75		
Endoscopic finding				
Gastritis/erythema	0.87	0.67-1.13		
Gastric ulcer	0.81	0.56-1.18		
Duodenal ulcer	1.12	0.67-1.89		
Gastric polyp	**0.57**	**0.37-0.88**		
Atrophic gastritis	0.78	0.40-1.53		
Mass/cancer	1.14	0.42-3.09		

BMI: body mass index; PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist; NSAID: non-steroidal anti-inflammatory drug

An unusual cause of hematochezia: anorectal inflammatory myoglandular polyp

Frederick B. Peng[1], Mimi C. Tan[2]

[2]Section of Gastroenterology and Hepatology, [1]Department of Medicine,
Baylor College of Medicine, Houston, Texas

Introduction: Colorectal polyps are an unusual cause of hematochezia and usually result from overlying ulcerations on adenomas or cancers. Non-adenomatous polyps, such as inflammatory polyps, may be a rare cause of gastrointestinal bleeding. Here, we present a case of a patient with painless hematochezia found to be originating from a bleeding anorectal inflammatory myoglandular polyp related to rectal prolapse.

Case Description: A 51-year-old man with alcohol abuse and hepatitis C presented with fatigue and light-headedness along with 7-8 years of small volume painless hematochezia with bowel movements. He endorsed straining with bowel movements and something protruding from his anus that he would push back in. On physical exam, he was hemodynamically stable with a normal abdominal exam and a rectal exam revealing a palpable rectal mass without overt signs of bleeding. His lab work was notable for a hemoglobin of 5.5 g/dL. Magnetic resonance imaging (MRI) of the pelvis revealed rectal wall thickening and enhancing mass abutting the anal sphincter (Figure 1). Colonoscopy revealed left-sided diverticulosis without bleeding and an ulcerated, vascular mass in the anal canal, best seen on retroflexion (Figures 2, 3). Biopsies of the mass were consistent with an inflammatory myoglandular polyp thought to result from intermittent rectal prolapse. The mass was resected via transanal excision with complete resolution of hematochezia.

Discussion: Inflammatory myoglandular polyps are rare, non-neoplastic pedunculated polyps that are predominantly incidental findings during enemas or endoscopy but can present with hematochezia. While concentrated mostly in the distal colon, they can be seen in the descending and transverse colon as well. The etiology remains unknown, but there may be an association with mucosal prolapse and sigmoid diverticulosis. Specifically, it is hypothesized that chronic trauma from intestinal peristalsis may distort colonic crypt architecture, which results in muscularization of the lamina propria. This leads to subsequent redundancy and passive venous congestion that contributes to prolapse of these lesions. Generally, symptomatic inflammatory myoglandular polyps require endoscopic or surgical resection, which is curative. In this case, given the patient's symptoms along with the size and location, surgical management was indicated.

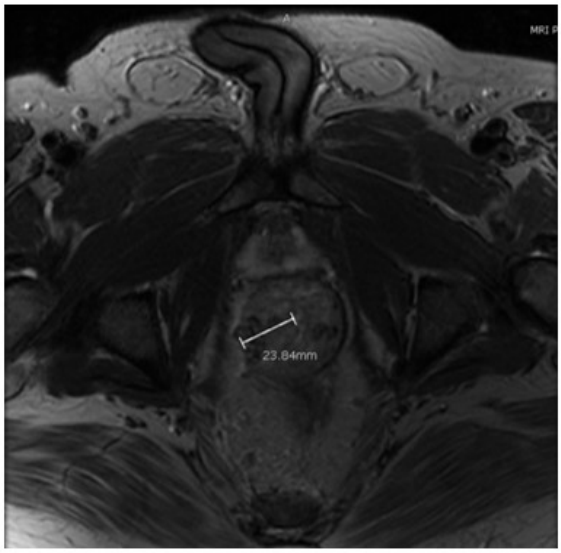

Figure 1. Magnetic resonance imaging (MRI) Pelvis revealing circumferential wall thickening of the inferior rectum measuring up to 2.4 cm in diameter with associated enhancement.

Characterizing the role of rotavirus nsp4 virporin activity in aberrant calcium signaling and virus replication

Jacob L. Perry, Alexandra L. Chang-Graham, Alicia C. Strtak, Long Tran, Jeanette M. Criglar, Mary K. Estes, and Joseph M. Hyser, Baylor College of Medicine, Houston, Texas

Calcium signaling is used by all cells to regulate cellular functions. Rotavirus is the leading cause of life-threatening diarrheal disease in young children and a hallmark of rotavirus is the elevation of cytosolic calcium. This is caused by nonstructural protein 4 (NSP4), an endoplasmic reticulum (ER)-targeted viroporin that dysregulates host calcium by releasing ER calcium stores. Recently, we determined that rotavirus elevates cytosolic calcium through hundreds of discrete calcium signals. Further, we observed a pattern to the calcium signals, in that they are initially low amplitude signals that progressively increase during infection. This suggests that rotavirus may induce distinct types of calcium signals. To determine whether localization and amplitude of the calcium signals change over time, we used live imaging to characterize the calcium signals induced by rotavirus infection. Three distinct signal types were identified: **Sparks:** low amplitude, perinuclear calcium fluxes occurring early during infection; **Global Spikes:** high amplitude calcium fluxes involving the whole rotavirus-infected cell occurring ~1-2 hours after the Sparks; **Intercellular Waves:** high amplitude calcium fluxes involving the rotavirus-infected and neighboring cells occurring after the Sparks. Since the calcium Sparks occur early during infection, we predict they are important for rotavirus replication. The perinuclear pattern of the calcium Sparks suggest these are the release of ER calcium, which could be caused by NSP4 viroporin activity or host channels, such as inositoltriphosphate-3-receptors (IP3R). To determine which channel causes Sparks, we generated a panel of recombinant rotaviruses with mutations in the NSP4 viroporin domain, and we used CRISPR-Cas9 to engineer cells lacking IP3R3, the most abundant isoform expressed in MA104 cells. We will use these tools to dissect the molecular mechanism of the Sparks. Characterizing how the calcium Sparks regulate early stages of rotavirus replication will give us insight into the role viroporins play in the life cycle of viruses.

Coagulopathy in malnourished mice is sexually dimorphic and regulated by nutrient-sensing nuclear receptors

Geoffrey A. Preidis[a], Krishnakant G. Soni[a], Ji Ho Suh[a], Tripti Halder[a], Kang Ho Kim[b], Jong Min Choi[b], Feng Li[b], Sridevi Devaraj[c], Margaret E. Conner[d], Cristian Coarfa[b], Sung Yun Jung[b], and David D. Moore[b,*]

[a]Section of Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston,TX; [b]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX; [c]Department of Pathology, Baylor College of Medicine, Houston, TX; [d]Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX

Liver dysfunction including coagulopathy is a prominent feature of protein-energy malnutrition. To identify mechanisms underlying malnutrition-associated coagulopathy, we administered low-protein low-fat diet (LPLFD) to suckling dams and examined hepatic transcription and plasma coagulation indices in young adult weanlings. LPLFD worsened body composition parameters to a greater extent in males versus females. Transcriptional profiles suggested opposing effects of nutrient-sensing receptors, namely peroxisome proliferator-activated receptor-α (PPARα) target induction and farnesoid X receptor (FXR) target repression. Coagulopathy, with decreased synthesis of fibrinogen and factor 11 (F11), was observed in malnourished males but not females. PPARα-deficient mice were not coagulopathic. Furthermore, FXR agonist increased and PPARα agonist decreased transcription of fibrinogen and F11 in primary mouse hepatocytes. A DNA regulatory element was identified in the fibrinogen and F11 genes, and opposing effects of FXR and PPARα were confirmed with luciferase assays. However, ChIP-qPCR did not identify PPARα enrichment on either gene in malnourished mice; instead, hepatic PPARα protein was markedly diminished in malnourished males and in healthy and malnourished females. In contrast, malnourished males exhibited loss of FXR binding on fibrinogen and F11, and this finding was associated with loss of hepatocyte peroxisomes, which contribute to bile acid biosynthesis, and decreased hepatic concentrations of deoxycholate, an FXR ligand.

Conclusion: LPLFD affects liver function more severely in males than in females. Malnourished males are coagulopathic and exhibit decreases in hepatocyte peroxisome numbers, hepatic deoxycholate, FXR binding to DNA regulatory elements on fibrinogen and F11, and coagulation factor synthesis. These effects are abrogated both in female mice which have low baseline levels of PPARα, and in PPARα-deficient animals, suggesting that coagulation factor synthesis is regulated by host nutritional status in a sex-specific manner through nutrient-sensing nuclear receptors.

Early postnatal malnutrition causes gastrointestinal dysmotility that is sexually dimorphic

Krishnakant G Soni,* Peace Dike,* Ji Ho Suh,* Tripti Halder,*
Price T. Edwards,* Margaret E. Conner,† & Geoffrey A. Preidis*

*Section of Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX †Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX

Background: Slow gastrointestinal (GI) transit is observed in states of malnutrition including anorexia nervosa, small for gestational age newborns, and severe acute malnutrition. Mechanisms underlying malnutrition-associated GI dysmotility are unknown, due in part to lack of animal models. This study sought to characterize dysmotility associated with early postnatal malnutrition in multiple mouse models, and to gain insight into associated GI pathophysiology.

Methods: Neonatal mice were malnourished by timed separation from dams starting at five days of life. Alternatively, isocaloric low-protein, low-fat chow was administered to dams, with malnourished neonates tested at two weeks (pups) or weaned to the same chow and tested at two months (young adults). We assessed total GI transit time by carmine red gavage, colonic motility by rectal bead latency, and both gastric emptying and small intestinal motility by calculating the distribution of fluorescein isothiocyanate (FITC)-conjugated dextran. Intestinal segments were assessed *ex vivo* for tone and contractility with force transduction, and for permeability with an Ussing chamber. Histologic measurements were obtained from H&E-stained sections, and fecal microbial communities were characterized by 16S sequencing.

Key Results: Both models of neonatal malnutrition and young adult malnourished males exhibited moderate weight loss, stunting, and abnormal stomachs upon gross inspection; however, young adult females were less profoundly affected by the malnourished diet. Both pup models of malnutrition exhibited decreased mean geometric center of progression of the gavaged bolus of fluorescent dye, whereas gastric emptying was significantly impaired only in maternally separated pups and in malnourished young adult females. Pups malnourished by maternal separation had markedly atrophic gastric mucosa and muscularis externa. Compared to healthy controls, malnourished young adult males had increased longitudinal smooth muscle tone in the duodenum, as well as exaggerated responses to cholinergic stimulation in both duodenum and proximal colon. Similarly, malnourished male duodenum and proximal colon demonstrated increased permeability to a 4 kDa marker. Intriguingly, healthy and malnourished females were not different with respect to intestinal tone, contractility, and permeability. Microbial community richness and diversity, as well as abundance of Firmicutes and Bacteroidetes, varied by malnutrition model and by sex. There was a striking increase of *Muribacter muris*, a member of the phylum Proteobacteria, in both neonatal models of malnutrition.

Conclusions & Inferences: Multiple models of early postnatal malnutrition produced delayed upper GI transit. Timed maternal separation dramatically changes the gross and histologic appearance of the neonatal stomach, and malnutrition affects young adult males more severely than females. Malnourished young adult males (but not females) exhibit increased intestinal tone and contractile responses, as well as increased barrier permeability. Microbiota alterations are associated with each of these phenomena. These models will facilitate future studies to identify mechanisms underlying malnutrition-associated GI dysmotility and sex-specific regulation of GI physiology.

Characterizing human intestinal communities for suppression of *Clostridioides difficile*

E.C. Preisner[1], J.M. Auchtung[2], and R.A. Britton[1]

1. Department of Molecular Virology and Microbiology, Baylor College of Medicine
2. Department of Food Science and Technology, University of Nebraska-Lincoln

Antibiotics disturb the healthy gut microbiome and its function, thus providing pathogens such as *Clostridioides difficile* a niche to colonize and cause disease. *C. difficile* is the leading cause of hospital-acquired infections today, with nearly half a million cases per year and approximately 29,000 deaths directly linked to *C. difficile* infection (CDI). Approximately 30% of patients that suffer from CDI can have multiple episodes of recurrence and one treatment option, fecal microbial transplantation (FMT), is the most effective method of stopping the recurrence cycle. FMTs are thought to restore the homeostasis within the gut environment that resists *C. difficile*; however, human FMTs have yet to be regulated by the Food and Drug Administration (FDA) and may pose safety concerns to human health due to their complex composition of bacteria, archaea, viruses, helminths and fungi. While FMTs are an effective therapy for recurring CDI, there are initial indications that acute and chronic disease can be transferred to patients via FMT and the long-term effects on human health are unknown. The focus of this study was the development of a safe, defined, and simple microbial community that can be used to combat CDI. Using mini bioreactor arrays several human fecal samples were screened for *C. difficile* invasion resistance. Through further dilution and rescreening for invasion resistance, two simple fecal communities were identified. Illumina Miseq sequencing and analysis revealed that these microbial communities consist of 15-20 members. An *in vivo* model of CDI was conducted in Humanized microbiota mice (^{Hmb}mouse) where mice were treated with the simplified communities prior to infection with a clinically relevant ribotype of *C. difficile* (ribotype 027). Results demonstrated that treatment protected against CDI by delaying symptoms and weight loss by one day and reduced *C. difficile* load measured in feces. Post recovery period of the initial infection, a relapse of CDI was induced by intraperitoneal injection of clindamycin. Mice that were treated with the simplified communities in the initial infection did not show a loss in body mass and had significantly lower *C. difficile* load in the relapse period of CDI. Overall results from *in vitro* and *in vivo* studies showed that simplified communities resisted *C. difficile* invasion and reduced CDI severity overall. In conclusion, the simplified microbial communities may serve as a therapeutic alternative to FMT treatment in CDI.

Lactobacillus reuteri secretes γ-Glutamylcysteine to suppress pro-inflammatory driven reactive oxygen species in human intestinal epithelium

Wenly Ruan, M.D.[1], Melinda Anne Engevik Ph.D.[2], Alexandra Chang-Graham[3], Heather Danof[3], Robert Britton[3], Joseph Hyser[3], James Versalovic[2]

[1]Pediatric Gastroenterology, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, United States;[2]Pathology & Immunology, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, United States; [3]Molecular Virology & Microbiology, Baylor College of Medicine, Houston, Texas, United States

Background: The intestinal epithelium is continually exposed to potential inducers of reactive oxygen species (ROS), including pro-inflammatory cytokines and microbial stimuli. Normally, ROS levels in epithelial cells are maintained at low levels via antioxidant compounds such as γ-glutamylcysteine and glutathione. However, dysregulation of ROS can lead to intestinal inflammation and contribute to inflammatory bowel disease (IBD). Many factors contribute to ROS levels including the gut microbiome. Some gut microbes possess the enzymatic machinery to produce antioxidants whereas others can dysregulate levels of ROS. Our model microbe, *Lactobacillus reuteri* (ATCC PTA 6475), has been demonstrated to reduce intestinal inflammation in mice models. It contains the genes encoding two distinct GshA-like glutamylcysteine ligases (GshA and GshA2). We hypothesize that *L. reuteri* can secrete γ-glutamylcysteine to suppress ROS, minimize NFκB activation and regulate secretion of epithelial cytokines. **Methods & Results**: *L. reuteri* was grown in a fully defined media LDM4, and conditioned media was analyzed with liquid chromatography-mass spectrometry (LC-MS). *L. reuteri* was found to generate γ-glutamylcysteine, with the greatest quantities measured after 16 hours of incubation. Consistent with LC-MS results, *L. reuteri* had increased expression of *gshA* and *gshA2* mRNA after 16 hours incubation. To determine if *L. reuteri* secreted products can enter the intestinal epithelial cells, all cysteine containing products including γ-glutamylcysteine were fluorescently tagged and then incubated with HT29 cell monolayers. γ-glutamylcysteine was demonstrated to enter intestinal epithelial cells based on microscopy. In addition, glutathione levels were examined via a ThiolTracker assay, and we demonstrate that *L. reuteri* secreted γ-glutamylcysteine is able to increase the amount of intracellular glutathione levels. To determine if *L. reuteri* secreted products or γ-glutamylcysteine alone could suppress pro-inflammatory cytokine driven ROS and IL-8 secretion, human colonic HT29 cells were treated with IL-1β or hydrogen peroxide. *L. reuteri* metabolites significantly suppressed IL-8 production in a dose-dependent manner. IL-8 was also suppressed by γ-glutamylcysteine and N-acetylcysteine. *L. reuteri* secreted products also reduced activity of the NFκB promoter as determined by a luciferase reporter assay in HT29 cells. In addition, we examined the ability of *L. reuteri* conditioned media to mitigate ROS in MA-104 cells (monkey kidney epithelial cell line) transfected with the pHyPer-dMito mitochondria-localized ROS sensor. *L. reuteri* as well as γ-glutamylcysteine and glutathione suppressed ROS activation by hydrogen peroxide. We generated γ-glutamylcysteine deficient mutants by targeted mutagenesis of GshA genes, and these mutant *L. reuteri* strains had a diminished ability to suppress IL-8 production and ROS. To confirm the ability of *L. reuteri* metabolites to suppress pro-inflammatory cytokines, we also examined IL-1β and hydrogen peroxide driven IL-8 production in human jejunum enteroid monolayers. WT *L. reuteri* metabolites, but not *ΔgshA, ΔgshA2* or ΔgshA/A2 mutants, suppressed IL-8 in human enteroids. **Conclusions**: Together these data indicate that *L. reuteri* secretes γ-glutamylcysteine which can enter the intestinal epithelial cells and modulate epithelial cytokine production. It acts through suppression of ROS and NFκB which then decreases IL-8 production. We are able to demonstrate this in both HT 29 cells and human jejunum enteroids which are more physiologically relevant. These experiments highlight a prominent role for ROS intermediates in microbiome:mammalian cell signaling processes involved in immune responses and intestinal inflammation.

Intermittent fasting lowers blood pressure in a rat model of hypertension by modulating the gut microbiota

Huanan Shi, Taylor Abo-Hamzy, Robert M. Bryan and David J. Durgan

Baylor College of Medicine

Hypertension (HT) is a common and dangerous condition that affects 1 in 3 American adults and contributes to approximately 1000 death per day. Studies have demonstrated that disruption of the gut microbiota, termed gut dysbiosis, plays a causal role in the development of HT in animal models and patients. Chronic inflammation is a key component in the development of HT. Additionally, the gut microbiota has been shown to modulate the host inflammatory response. Recent studies revealed that intermittent fasting alters the gut microbiota and reduces host inflammation. Thus, we hypothesized that every-other-day-fasting (EODF) would attenuate elevations in blood pressure (BP) by maintaining a healthy gut microbiota and reducing systemic inflammation. Five-week old spontaneously hypertensive stroke prone (SHRSP) rats and normotensive Wistar Kyoto (WKY) rats were randomized to be fed *ad lib* or on EODF for 10 weeks. BP was measured weekly, and tissues and cecal content were collected at the end of the study. We found that ten-weeks EODF was able to prevent elevations of systolic BP (SBP) in SHRSP compared to *ad lib* fed SHRSP (n=6-8, $p<0.05$). We next examined the effects of EODF on the composition of the gut microbiota. Principle coordinate analysis showed that EODF significantly altered the overall composition of both WKY and SHRSP microbiota (WKY $p<0.01$, SHRSP $p<0.009$). Abundance of the phylum Proteobacteria, which includes a number of pathogenic genera, was significantly increased in SHRSP *ad lib* as compared to WKY *ad lib* (18% vs. 4%, $p<0.05$). EODF significantly reduced the abundance of Proteobacteria in SHRSP ($p<0.05$). These alterations in the gut microbiota were associated with elevated markers of inflammation (*ifn-γ*, *tlr2*) in the gut wall of SHRSP *ad lib* versus WKY *ad lib* (genotype main effect $p< 0.05$ for *ifn-γ* and *tlr2*), which were reduced by EODF (diet main effect $p< 0.01$ for *ifn-γ* and *tlr2*, and SHRSP Con vs SHRSP EODF $p<0.01$). To examine the direct effects of the EODF altered microbiota on BP regulation and eliminate the confounding variable of fasting periods, we transplanted the microbiota of SHRSP *ad lib* and SHRSP EODF rats by oral gavage into germ free rats. We found that germ free rats transplanted with SHRSP *ad lib* microbiota had a significantly higher SBP as compared to those transplanted with SHRSP EODF microbiota (n=6-7, $p<0.01$). Gut microbiota communicate with the host through the production of metabolites that interact with gut epithelium locally or with distant tissues after absorbed into circulation. Thus, we performed non-targeted metabolomics on cecal and plasma contents of WKY and SHRSP *ad lib* and EODF groups. Preliminary analysis indicates that sphingolipid metabolism might underlie the beneficial effects of EODF. EODF significantly reduced the concentration of pro-inflammatory sphinganine, sphingosine and ceramides in cecum and increased the concentration of anti-inflammatory dihydroceramides in plasma. These studies will help us understand the mechanisms underlying gut dysbiosis-induced HT and provide insight for potential therapeutic approaches.

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Childhood chronic abdominal pain and sucrase-isomaltase immunohistochemistry expression

Darren J. Strong, PA-SIII: Bruno P. Chumpitazi, MD, MPH;
Zoe R. Wilhelm, BS; Alexander P. Opekun; Antone R. Opekun, MS, PA-C*

Baylor College of Medicine

Background: Of the childhood functional gastrointestinal disorders (FGIDs), there are four childhood functional abdominal pain disorders (FAPDs) which include: functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraines, and functional abdominal pain – not otherwise specified (FAP–NOS). Under Rome IV criteria, FAPDs constitute a positive, symptom-based diagnosis with symptoms present at least four days per month for two months before diagnosis (six months before diagnosis of abdominal migraines), with symptoms not being attributed to another medical condition. The etiology of FAPDs stems from a complex interplay of biological, psychological, and social factors with the unifying consensus that all FAPDs feature a disorder of gut-brain interaction. Of the multiple proposed pathophysiological processes that lead to FAPDs, the role of disaccharidase deficiency, specifically sucrase-isomaltase (SI), is explored in this study because of the considerable symptom overlap between carbohydrate maldigestion, congenital sucrase-isomaltase deficiency (CSID) and FGIDs, including FAPDs. SI deficiency is currently primarily diagnosed using the Dahlqvist Method, the standard enzyme activity assay for small intestinal brush border enzyme activity determinations. However, due to the variability of in vivo biopsy sampling and difficulties with in vitro sample processing, other assessments of intestinal enzymes including immunohistochemistry (IHC) are being investigated.

Objectives: The objectives of this study were to 1) Explore the relationship between SI expression via immunohistochemistry and SI activity as measured by Dahlqvist assays; 2) Explore the relationship between SI expression and FAPD symptoms.

Methods: This study was a retrospective case series of 99 patients (ages 2-19) who underwent EGD biopsy and had duodenal mucosal enzymes sent for disaccharidase activities via the Dahlqvist Method from January 2016 through December 2018. The detection of SI IHC was performed on stored paraffin blocks where SI expression was measured as a pixel intensity of 3,3'-diaminobenzidine (DAB) conjugation with an enzyme-tagged secondary antibody indirectly bound to mucosal SI. This IHC SI enzyme expression, expressed as a ratio of DAB SI: Villi Nucleus Count, was compared with SI Dahlqvist activities accessed in chart review. IHC SI expression was also associated with symptoms, including a symptom composite score based on the number of symptoms present out of eight assessed symptoms and to abdominal pain frequency.

Results: IHC SI expression correlated with SI enzyme activity, r=0.23, for both sucrase and palatinase activities (p=0.024 and p=0.023 respectively). IHC SI expression correlated with symptom composite score, r=0.24 (p=0.016). Patients with constipation and more frequent abdominal pain had higher IHC SI expression values (p=0.002 and p=0.042 respectively) while patients with diarrhea had lower values (p=0.029). There were no relationships identified between lactase, sucrase, maltase, or palatinase activity and any symptom.

Conclusions: There is a low positive relationship between IHC SI expression and SI activity. In children with chronic abdominal pain, SI expression measured via IHC was increased in those with constipation and more frequent abdominal pain while decreased in those with diarrhea. These relationships were not seen in SI activity. These data suggest that with optimization of the IHC method for SI detection, IHC may serve as a more clinically relevant method evaluating SI expression.

A global *Slc7a7* knockout mouse model recapitulates human lysinuric protein intolerance

Bridget M. Stroup,[1] Ronit Marom,[1] Xiaohui Li,[1] Chih-Wei Hsu,[2] Cheng-Yen Chang,[3] Brian Dawson,[1] Ingo Grafe,[1] Yuqing Chen,[1] Ming-Ming Jiang,[1] Denise Lanza,[1] Jennie Rose Green,[1] Qin Sun,[1,4] J. P. Barrish,[5] Safa Ani,[1] Audrey Christiansen,[2] John Seavitt,[1] Mary Dickinson,[2] Arthur Beaudet,[1] Luan D. Truong,[6] Farrah Kheradmand,[3] Jason Heaney,[1] Brendan Lee,[1] Lindsay C. Burrage.[1, 7]

[1]Department of Molecular and Human Genetics, [2] Department of Physiology and Biophysics, [3]Department of Medicine-Pulmonary, Baylor College of Medicine; [4]Baylor Genetics; [5]Department of Pathology, Texas Children's Hospital, Baylor College of Medicine; [6]Department of Pathology and Genomic Medicine, Houston Methodist Hospital; [7]Texas Children's Hospital.

Lysinuric protein intolerance (LPI) is an inborn error of metabolism caused by biallelic pathogenic variants in *SLC7A7*, which encodes the light subunit of the y^+L amino acid transporter (y^+LAT1) for intestinal absorption and renal reabsorption of arginine, lysine, and ornithine (cationic amino acids). LPI is a severe disorder that presents with diverse phenotypes, including growth delay, urea cycle dysfunction, renal disease, osteoporosis and immune dysfunction.

Our objective was to generate a new mouse model of LPI to investigate disease mechanisms. We generated a global *Slc7a7*$^{-/-}$ knockout mouse model using CRISPR/Cas9 technology that results in a frameshift mutation with homozygous deletion of exons 3 and 4. Perinatal lethality in *Slc7a7*$^{-/-}$ mice was observed on three genetic backgrounds, but survival improved on a 129 Sv/Ev x C57BL/6 F2 background. Regardless, tissues were harvested at P14-18 due to reduced survival and growth failure of *Slc7a7*$^{-/-}$ versus wild type (WT) mice on the 129 Sv/Ev x C57BL/6 F2 background. Consistent with human LPI, *Slc7a7*$^{-/-}$ mice exhibited reduced plasma concentrations and increased urinary excretion of the cationic amino acids. In the renal cortex, *Slc7a7*$^{-/-}$ mice demonstrated loss of brush border and increased lipid vacuolation and secondary lysosomes in the proximal tubules, based on hematoxylin and eosin (H&E) staining and electron microscopy, which, in combination with aminoaciduria, suggests proximal tubular dysfunction. Delayed renal development was observed such that glomeruli demonstrated increased Bowman's space and podocytes with cuboidal morphology. Interestingly, *Slc7a7*$^{-/-}$ mice also demonstrated delayed development of the liver and lungs with increased number and size of hematopoietic aggregates in the liver and reduced alveolargenesis in the lungs, based on H&E staining. Although x-ray imaging demonstrated reduced mineralization in the spines of both male and female *Slc7a7*$^{-/-}$ mice, micro-computed tomography analyses of the L_4 vertebrae revealed a reduction in trabecular bone mass in male (37% decrease), but not female, *Slc7a7*$^{-/-}$ mice compared to male and female WT littermates. Interestingly, the trabecular structures in L_4 vertebrae of *Slc7a7*$^{-/-}$ mice at P14-18 more closely resembled the L_4 vertebrae of WT mice at P5 than P14-18, which suggests delayed skeletal development. H&E stained spleen sections showed possible expansion of the red pulp in *Slc7a7*$^{-/-}$ mice. In addition to altered splenic structures, *Slc7a7*$^{-/-}$ mice showed 94% and 23% increases in the percentages of neutrophils and lymphocytes in whole blood, respectively, which may suggest altered immune function.

In conclusion, we demonstrate that our *Slc7a7*$^{-/-}$ mouse model recapitulates the biochemical phenotype LPI, in addition to other characteristic phenotypes, such as growth failure, delayed organ development, renal disease, osteoporosis, and immune dysfunction. This mouse model may be a useful tool for future investigations of LPI pathology.

The enteric nervous system drives intestinal epithelium differentiation through a nonsynaptic signaling mechanism

Kai Li Tan[1], Sarah E Blutt1, George Van Buren[2], Mary K Estes[1]

1. Department of Microbiology and Virology, Baylor College of Medicine, 2. Department of Surgery, Baylor College of Medicine

The enteric nervous system (ENS), an autonomic and intrinsic nervous system, governs various intestinal functions including gastrointestinal (GI) transit, sensory and endocrine activities. While the role of the ENS in regulating smooth muscle contraction is widely known, its interactions with the mucosa remain elusive. Recently, a study showed that a subtype of the intestinal epithelium, the enteroendocrine cells (EECs) form synapses with the vagal nerves, suggesting that there is direct communication between the epithelium and the nervous system. Nevertheless, many questions remain unanswered, including (1) Is there direct crosstalk between the intestinal epithelium and the ENS, (2) Isthe mode of communication- synaptic, endocrine, paracrine or cellcell contact, and (3) What are the biological functions of the interactions? To explore these unanswered questions, in vivo models can be overly complicated due to the presence of other cell types. Therefore, I propose using a simple, two-cell population in an ex vitro co-culture system to address the interactions between the ENS and the intestinal epithelium.

To this end, I developed a layered 3D co-culture method. In this co-culture system, primary mouse ENS are isolated and first cultured at the base of a well. Subsequently, mouse intestinal epithelial 3D organoids (enteroids) are suspended in a drop of low percentage matrigel directly above the ENS. This co-culture method is novel, as it prevents initial mixing of the ENS and the enteroids, but allows both cell populations to freely interact with each other, which is key to probe for any close-range communication, including synaptic, paracrine and cell-cell contact signaling.

After a few days in co-culture, neurites extend towards and form contacts with the enteroids, with a subset of nerve terminal ends at the EECs, suggesting possible synaptic formation. To examine if the ENS affects the epithelium in any way, I performed quantitative PCR (qPCR) on the epithelial layer and found that enteroids cultured with the ENS have elevated levels of secretory cell-specific transcripts along with a decrease in absorptive enterocyte-specific transcript. These results suggest that the ENS drives epithelial differentiation towards the secretory lineage. In addition to mRNA levels, there is an increase in the number of EECs in enteroids that are physically in contact with the ENS, compared to enteroids cultured alone or enteroids in co-culture that do not contact the ENS. This result suggests that the ENS drives epithelial secretory lineage differentiation through close range interaction. This observation is conserved in human cells as well, as co-culture using human-derived tissue shows that human ENS drives epithelial differentiation in a similar manner. Further experiments indicate that the ENS-mediated epithelial differentiation is independent of neural activity, as inhibiting action potential in neurons does not change the observation, suggesting that the influence ENS exerts on IE differentiation is not via synaptic connection, but through close range paracrine signaling or cell-cell contact.

In conclusion, a layered 3D co-culture method I established indicates that the ENS and the epithelium can directly communicate, and the ENS influences epithelial differentiation through a non-synaptic signaling mechanism. Further work will focus on identifying the molecular mechanism(s), as well as the ENS and epithelial subtypes involved in this process.

Missed opportunities for screening or surveillance among patients with newly diagnosed non-cardia gastric adenocarcinoma

Mimi C. Tan [1], Theresa H. Nguyen [1], Niharika Mallepally [1], Tariq Hammad [1], Hashem B. El-Serag [1], Aaron P. Thrift [2,3]

[1]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, [2]Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, [3]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA

Background: There are known risk factors for non-cardia gastric adenocarcinoma, and endoscopic surveillance of preneoplastic lesions has been associated with the early detection of gastric adenocarcinoma. We determined possible missed opportunities for the detection and subsequent surveillance of preneoplastic conditions in a cohort of patients with gastric adenocarcinoma.

Methods: We conducted a retrospective cohort study among consecutive, newly diagnosed patients with non-cardia gastric adenocarcinoma from 11/2007 to 10/2018 at the Michael E. DeBakey VA Medical Center in Houston, Texas. We performed structured medical record review for gastric adenocarcinoma risk factors (non-White race [i.e., Black, Hispanic, Asian], smoking, alcohol, *Helicobacter pylori* infection, gastric ulcers, family history of gastric cancer), past endoscopic and gastric biopsy history and histopathological findings. We evaluated the indications for the gastric adenocarcinoma diagnosing endoscopy (diagnostic, surveillance, incidentally found) and identified the proportions of all patients with missed opportunities for screening and surveillance based on risk factors and presence of preneoplastic lesions. Associations between receipt of prior endoscopy and cancer-related outcomes (cancer stage, receipt of treatment, survival) was determined using logistic regression models.

Results: Among 91 patients diagnosed with gastric adenocarcinoma, 87 (95.6%) were men and 29 (31.9%) were White, with mean age at diagnosis of 68.0 years (SD 10.8). The cancer diagnosing endoscopy was done for diagnostic indications in 89.0%, surveillance of preneoplastic gastric lesions in 2.2%, and cancers were found incidentally in 8.8%. Dyspepsia (29.6%), iron deficiency anemia (27.2%) and gastrointestinal bleeding (27.2%) were the most common diagnostic indications. Most patients had at least one risk factor for gastric cancer (N=79, 86.8%), and 42 (46.2%) had 2 or more risk factors. The most common risk factors included smoking (76.9%), non-White race (67.0%) and alcohol use (59.3%). Twenty patients (22.0%) had at least 1 endoscopy performed at a median 2.4 years prior to gastric cancer diagnosis. Of 14 patients who had previous gastric biopsies, 7 had high risk lesions (6 intestinal metaplasia; additional 1 gastric ulcer) but only 2 underwent surveillance endoscopy with gastric biopsies. Receipt of prior endoscopy was not associated with significant differences in cancer stage, receipt of treatment, or survival.

Conclusion: Most patients with gastric adenocarcinoma had at least 1 known risk factor but never had prior screening/surveillance endoscopy and therefore could represent missed opportunity for prevention or early detection. Among the few with known prior preneoplastic lesions, endoscopic surveillance with gastric biopsies was not consistently performed, representing another missed opportunity.

Demographic, lifestyle and dietary risk factors for gastric intestinal metaplasia among us veterans

Niharika Mallepally[1], Aaron P. Thrift[3,4], Mohamad Othman[2], Hashem B. El-Serag[1,5], Mimi C. Tan[2]

[2]Section of Gastroenterology and Hepatology, [1]Department of Medicine, Baylor College of Medicine, Houston, Texas, USA. [3]Section of Epidemiology and Population Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA, [4]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA, [5]Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA

Background: The risk of non-cardia gastric cancer is increased in the presence of gastric intestinal metaplasia. The purpose of this study was to determine risk factors for both the presence and severity of gastric intestinal metaplasia among a non-immigrant United States population.

Methods: We used data from a cross-sectional study of 2244 patients randomly sampled and invited to endoscopy from primary care clinics (n=569) and endoscopy clinics (n=1675) at the Michael E. DeBakey VA Medical Center in Houston, Texas between 2/2008 and 8/2013. All patients completed standardized lifestyle and symptom questionnaires, a 110-item Food Frequency Questionnaire and underwent endoscopy with gastric mapping (5-7 standardized biopsies). Presence and severity of gastric intestinal metaplasia was determined by two GI pathologists and defined as intestinal metaplasia on any non-cardia gastric biopsy; extensive gastric intestinal metaplasia was defined as involving both antrum and corpus. Multivariate logistic regression models were used to examine the determinants and magnitude of associations among demographic, lifestyle, and dietary factors with the presence and severity of gastric intestinal metaplasia.

Results: We identified 431 cases with gastric intestinal metaplasia and 1813 controls without gastric intestinal metaplasia. The prevalence of gastric intestinal metaplasia was 21.6% and 18.4% among participants recruited from primary care clinics and endoscopy clinics, respectively. Compared to controls, cases were older on average (62.1 vs. 59.9 years), more likely to be male (97.0% vs. 90.8%), current smokers (34.5% vs. 28.1%), *Helicobacter pylori* positive (52.9% vs. 25.0%) but less likely Non-Hispanic White (NHW) (41.1% vs. 61.0%). Older age (per 1 year increase, AdjOR, 1.04; 95%CI, 1.03-1.06), male sex (AdjOR, 2.13; 95%CI, 1.17-3.88), non-White race/ethnicity (vs. NHW: Hispanic, AdjOR, 2.40; 95%CI, 1.67-3.46; Black, AdjOR, 1.88; 95%CI, 1.46-2.42), current smoking (AdjOR, 1.93; 95%CI, 1.39-2.67), and *H. pylori* infection (AdjOR, 2.89; 95%CI, 2.30-3.63) were independently associated with risk of gastric intestinal metaplasia. We did not find significant associations with dietary intake of fruits (tertile 3 vs 1 OR, 1.41; 95%CI 0.96-2.08), vegetables (OR, 1.02; 95%CI 0.69-1.52), fat (OR, 0.83; 95%CI 0.51-1.35), sodium (OR, 0.92; 95%CI 0.56-1.50), or vitamin C (OR, 1.18; 95%CI 0.79-1.79) with gastric intestinal metaplasia. In a subset of 116 patients with extensive gastric intestinal metaplasia, the strength of association was stronger with older age, male sex, race/ethnicity, and smoking.

Conclusion: Older age, male gender, race/ethnicity, and smoking were the non-endoscopic factors associated with gastric intestinal metaplasia in a non-immigrant US population, while dietary factors were not. These factors remained significant after adjusting for *H. pylori* status.

Using artificial intelligence in diagnosis of esophageal squamous cell neoplasia: a post-hoc study of high-resolution microendoscopy (hrme) image interpretation

Mimi C. Tan[1], Sheena R. Bhushan[1], Kalpesh K. Patel[1], Tariq Hammad[1], Anam Khan[1], Sunina Nathoo[1], Rehman Sheikh[1], Hyunseok Kim[1], Jessica Bernica[1], Niharika Mallepally[1], Fan Zhang[2], Xueshan Wang[2], Xinying Yu[3], Zhengi Li[3] , Guiqi Wang[3], Sharmila Anandasabapathy[1]

[1]Department of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas
[2]Department of Gastrointestinal Medicine, The First Hospital of Jilin University, Changchun, Jilin, China, [3]Department of Endoscopy, Cancer Institute and Hospital, The Chinese Academy of Medical Sciences, Beijing, China

Background: High-resolution microendoscopy (HRME) is a low-cost, portable device producing subcellular epithelial images to detect esophageal squamous cell neoplasia (ESCN). A limitation of any microendoscopic technology in underserved settings with high rates of ESCN (e.g., China, Iran, South Africa) is the need for expert interpretation. We developed a fully automated HRME image analysis software to distinguish neoplastic from benign mucosa. The aim of this study was to evaluate the accuracy and confidence of expert and novice endoscopists in HRME image interpretation with and without input from an automated software to detect ESCN.

Methods: High quality HRME images from 130 consecutive patients in the US and China undergoing ESCN screening and surveillance were used. All HRME images were interpreted by the software as neoplastic or non-neoplastic using an abnormal nuclear density cut-off of 218. All endoscopists (6 experts, 7 novices) underwent standardized training in HRME image interpretation and were tested on 199 HRME images. They interpreted the image as neoplastic or non-neoplastic (pre-software read) and reported the confidence level of their interpretation. All endoscopists were then given the automated software interpretation and again asked their interpretation (post-software read) and confidence level. The endoscopists were aware of the software performance throughout the testing (sensitivity 73%, specificity 80%). All HRME imaging sites were biopsied and consensus histopathology was reached by two expert GI pathologists blinded to the HRME results. Diagnostic accuracy of pre- and post-software reads were calculated and mean difference between the two reads was compared using paired t-test.

Results: Overall, the endoscopists had a pre-software read sensitivity of 84.3% (95% CI 79.5%-89.1%), specificity 75.0% (95% CI 71.9%-78.1%), and accuracy 81.1% (95% CI 78.0%-84.2%). On the post-software read, the endoscopists had a sensitivity of 84.8% (95% CI 82.1%-87.5%; change from pre- to post-software read p=0.75), specificity 80.1% (95% CI 77.6%-82.6%; p=0.002), and accuracy of 83.1% (95% CI 81.9%-84.4%; p=0.13). There was **no significant difference** in pre-and post-software read among experts, **but a significant increase in specificity was seen among novices**. When endoscopists had high confidence, there was no significant change in sensitivity and specificity pre- and post-software. Whereas with low confidence, the specificity increased from 58.0% to 71.0% (p=0.004) without significant change in sensitivity.

Conclusion: We found that integrating an automated software image analysis increased the specificity of novice endoscopists in detecting ESCN. Given the high sensitivity but low specificity of Lugol's iodine screening for ESCN, our study suggests that software-assisted microendoscopy may be useful for screening in underserved settings.

Trends in cure rates among Medicare insured patients with hepatocellular carcinoma: a population-based study

Aaron P. Thrift, Xiangjun Gu, Hashem B. El-Serag

Department of Medicine, Baylor College of Medicine, Houston, TX

Background: There have been several advances in the treatment of hepatocellular carcinoma (HCC). Nonetheless, except for a small proportion of patients, most HCC patients still receive only palliative treatment. Even for HCC patients treated with curative intent, cure may not be achieved. The changes over time in the proportions of HCC patients cured are unclear.

Methods: We identified patients diagnosed with HCC from 1994-2007 in the SEER-Medicare database. HCC patients were followed from date of diagnosis until death or December 31, 2012. Curative intent treatment was defined as receipt of liver transplantation or surgical resection. Patients were grouped according to year of diagnosis and we calculated the 5-year observed (and relative) survival rates and percent receiving curative intent treatment. Survival curves were estimated for each group using the Kaplan-Meier method and compared statistically using the log-rank test. We estimated Hazard ratios (HR) and 95%CIs using Cox regression.

Results: We identified 10,826 HCC patients with median age 75 years. The majority of patients were male (62.2%) and 59.7% were non-Hispanic white (13.6% Hispanic, 7.5% Black, 12.2% Asian). 5-year survival rates were 7.9% (95%CI, 6.1%-9.9%), 9.8% (95%CI, 8.1%-11.7%), 9.8% (95%CI, 8.6%-11.1%), 13.0% (95%CI, 11.7%-14.3%) and 16.0% (95%CI, 14.4%-17.6%) for patients in cohorts 1994-96, 1997-99, 2000-02, 2003-05, and 2006-07, respectively. After adjusting for age at diagnosis, patients diagnosed in 2006-07 had 31% lower risk of 5-year mortality than patients diagnosed in 1994-96 (HR, 0.69; 95%CI, 0.64-0.75). The percent of patients receiving curative intent treatment increased from 10.9% in 1994-96 to 23.4% in 2006-07 ($p<0.001$). Only 5.2% (95%CI 4.7-5.8) of patients who did not receive curative treatment were alive after 5 years compared with 36.7% (95%CI 34.5-38.9) among patients who received curative intent therapy (HR for receipt of curative treatment adjusted for age, 0.30; 95%CI, 0.28-0.32). After additionally adjusting for receipt of treatment, more recent cohorts had significantly lower risk of 5-year mortality (2006-07 vs. 1994-96; HR, 0.78; 95%CI, 0.72-0.84). We observed greater relative improvement in 5-year survival rates over time in patients who did not receive curative treatment (3.7% in cohort 1994-96 vs. 7.3% in cohort 2006-07; log-rank test p-value<0.001) than among patients who received curative intent therapy (39.0% in cohort 1994-96 vs. 41.7% in cohort 2006-07; log-rank test p-value=0.0673).

Conclusions: The proportion of patients 65 years or older cured of HCC, while increased over time remains very small and highly correlated to receipt of liver transplantation and surgical resection. Given the limited availability of liver transplant and limited eligibility for surgical resection, finding curative HCC therapies remains a critical area of need.

miR-302 contributes to the gene regulatory network of enteric neural crest cells

Naomi E. Butler Tjaden[1,2], Angelina S. Bortoletto[1], Rachel Keuls[1], Ronald J. Parchem[1], Noah F. Shroyer[1]

1. Baylor College of Medicine, Houston, Texas, USA, 2. Pediatrician-Scientist Training and Development Program, Baylor College of Medicine, Houston, Texas, USA.

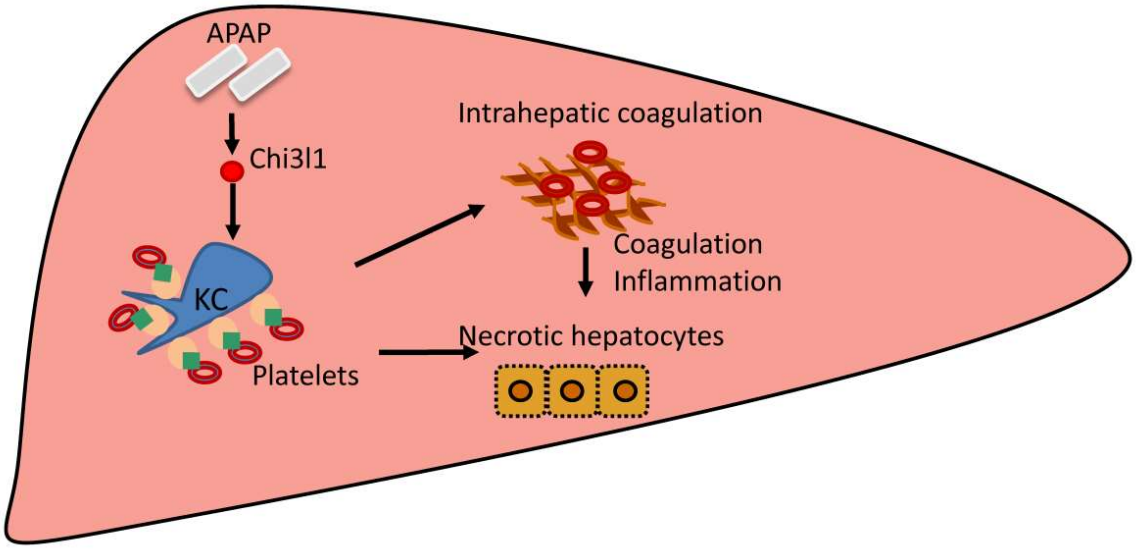
Hirschsprung disease (HSCR) is the most common congenital enteric neuropathy, resulting from incomplete colonization of the enteric nervous system (ENS) by enteric neural crest cells (ENCCs). Though numerous genes, including microRNAs have been identified that contribute to ENCC biology, there are still large gaps in our knowledge regarding the pathogenesis of this complex and devastating disease. There is hope that in the future, HSCR will be treated with cell therapy instead of extensive surgical resections, however for this to be a reality, the basic biological processes governing ENCC specification, proliferation, migration and differentiation must be understood. This project investigates the role of miR-302 in ENS development in an *in vivo* mouse model to understand the role for miR-302 in the gene regulatory network (GRN) of ENCC development. Deletion of this microRNA (as assessed in miR-302a-d$^{-/-}$ mice) leads to a frank neurocristopathy mid-gestation: mouse embryos deficient in *miR-302* display gross peripheral and ENS defects; notably, near-absence of vagal nerve development. EDNRB is upregulated in *miR-302* knockout mice, suggesting an important role for miR-302 in the gene regulatory network (GRN) of ENCC development. miR-302 is an evolutionarily conserved miRNA that is required during early embryonic development, known to play a role in regulating neural progenitors by suppression of precocious differentiation. These studies will provide valuable insights into the pathogenic mechanisms of miR-302 deficiency, as well as miR-302 contributions to the ENCC GRN controlling normal ENS colonization.

The role of chitinase 3-like-1 in Kupffer cell-mediated hepatic platelet recruitment during acute liver injury

Zhao Shan[1], Constance Lynn Atkins[1], Meng Wang[1], Yankai Wen[1], Dechun Feng[2], Chun Geun Lee[3], Jack Angel Elias[3,4], William Martens Lee[5], Bin Gao[2], Cynthia Ju[1,*]

1. Department of Anesthesiology, UTHealth McGovern Medical School, Houston, TX, USA, 2. Laboratory of Liver Disease, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA, 3. Molecular Microbiology and Immunology, Brown University, Providence, Rhode Island, New Haven, CT, USA, 4. Division of Medicine and Biological Sciences, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island, New Haven, CT, USA 5. Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Thrombocytopenia is frequently observed in patients with acute liver failure. This observation is consistent with the findings that during acute liver injury, platelets are recruited to the liver and contribute to liver damage. However, the underlying mechanism of the hepatic platelet accumulation is poorly understood. We uncovered a critical role of Kupffer cells (KCs) in this process using murine models of acute liver injury, as KC-depletion inhibited platelet recruitment into the liver after mice were challenged with acetaminophen (APAP). Our studies also revealed a key molecular mechanism mediating this function of KCs. The data showed that whereas platelets were rapidly recruited to the liver after injury in wild-type mice, very few platelets were found in the liver of mice with chitinase 3-like-1 (Chi3l1) deletion. Similar to platelet-depletion, Chi3l1-deletion also dramatically attenuated APAP-induced liver injury. Moreover, administration of recombinant Chi3l1 could normalize hepatic platelet accumulation and the phenotype in Chi3l1$^{-/-}$ mice after APAP challenge. In conclusion, we uncovered a novel molecular pathway involved in hepatic platelet recruitment and demonstrated the feasibility and potential of targeting Chi3l1 in treating APAP-induced acute liver injury.



Use of androgen lowering medications finasteride and dutasteride do not substantially alter risk of incident hcv-related hepatcellular carcinoma in men

Donna L. White[1,2], Peter Richardson[2], Israel Christie[2], Sarah Plew[2], Li Jiao[1,2], Hashem B. El-Serag[1,2], Fasiha Kanwal[1,2], and Jennifer R. Kramer[2]

1. Department of Medicine, Section of Gastroenterology and Hepatology, Michael E. DeBakey VA Medical Center and Baylor College of Medicine, 2. Michael E. DeBakey Health Services Research Center of Excellence (IQuESt)

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) finestaride and dutasteride which lower androgen levels and are often prescribed to treat benign enlarged prostate symptoms alter 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, prostate cancer or adrenal/testicular/hypothalamic disorders at/pre-index date (date of first HCV+ code/lab), and not developing them or dying in first year, with >=12-month follow-up. We used diagnostic codes, pharmacy, and labs to define: HCV (and 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 to identify HCC and competing risk prostate cancer, and VitalStatus files for death. Multivariable 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 an 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% finestaride), and xxx incident HCCs developing. 5AR-I users were significantly more likely to be older, African-American, & cirrhotic. A total of 12,178 incident HCCs occurred. Cumulative HCC incidence was lower in finestaride /dutasteride users compared to users (6.87/1000 person years vs. 7.05). Log rank analysis indicated significant differences in Kaplan-Meier curves for finestare/dutasteride users vs. non-users. Time dependent use of Finestaride/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 (HRradj=1.11, 95% CI: 1.04-1.19, p<0.003).

Conclusion: Although our results are mixed with slightly higher cumulative incidence in non-users, but slightly higher adjusted relative risk in users; collectively, our results suggest that use of these widely prescribed medications are not associated with clinically meaningful differences in HCC risk in HCV+ males.

Association between dietary fat intake and the colonic gut microbiota in humans

Anthony Xu[1], Donna L. White[1, 3,] David Graham[1,4,] Hashem B. El-Serag[1,3,4,]
Joseph F. Petrosino[2], Li Jiao[1,3,4]

1. Department of Medicine; Baylor College of Medicine; 2. Alkek Center for Metagenomics and Microbiome Research; Baylor College of Medicine; 3. Center for Innovations in Quality, Effectiveness and Safety; 4. Michael E. DeBakey VA Medical Center;

Background: High-fat diets have been associated with systemic diseases in humans, as well as alterations in gut microbiota in animal studies. However, the influence of dietary fat intake on the gut microbiota in humans is largely unknown.

Aim: We examined the association between self-reported intake of total fat (TF), saturated fat (SF), trans-fat (TrF), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and the composition and structure of the colonic mucosa adherent gut microbiota in polyp-free individuals.

Methods: This cross-sectional study included 33 adult men and 1 woman who found to have endoscopically normal colon, and 97 snap frozen colonic mucosal biopsies were obtained. Microbial DNA was extracted and subsequently amplified and sequenced for the 16S rRNA V4 region using the Illumina MiSeq platform. The UPARSE and SILVA database was used for operational taxonomic unit (OTU) classification. Energy-adjusted diet data were collected using 2005 Block Food Frequency Questionnaire. Higher vs. lower intake was categorized using the median intake in participants. Alpha microbial diversity was examined by linear regression. Beta-diversity was examined using the Weighted UniFrac as a distance matrix and by principal coordinates analysis. The relative abundance of the bacterial taxa was compared based on fat intake using the Mann–Whitney test. False discover rate (FDR) *P*-values < 0.05 indicated statistical significance. We conducted the negative binomial regression analysis to examine the association between bacterial count and fat intake adjusting for age, ethnicity, body mass index, healthy eating index, smoking status, alcohol consumption, and colon segment.

Results: The bacterial alpha diversity did not differ by fat intake. The beta diversity differed significantly by SF (P=0.013). Higher TF and PUFA intake were related to a higher relative abundance of *Sutterella* (P<0.01) and *Acidaminococcus* (P< 0.05). Higher MUFA was related to higher abundance of *Roseburia* (P<0.05). Higher SF and TrF intake were related to a higher abundance of *Tyzzerella* and a lower abundance of Lachnospiraceae Unco8782 (P<0.05). Higher SF was also related to a higher abundance of *Fusobacterium,* and a lower abundance of Lachnospiraceae Unc94789. These associations were confirmed in multivariable analyses.

Conclusions: The structure of colonic mucosa adherent gut microbiota was associated with the amount and type of dietary fat intake in polyp-free individuals. Greater intake of TF, MUFA and PUFA was associated with increased *Sutterella, Roseburia,* and *Acidaminococcus.* Greater intake of unhealthy fats such as TrF and SF was associated with increased *Fusobacterium* or *Tyzzerella,* and decreased *Lachnospiraceae* Unco8782 or Unc94789. The functional significance of these bacteria in systemic disease should be investigated further.

Eosinophils attenuate hepatic ischemia reperfusion injury through an interleukine-33-ST2 signaling axis

Yaochun Wang[1,7,&], Yang Yang[1,&], Meng Wang[1,&], Shuhong Wang[1,8], Jong-Min Jeong[1], Long Xu[1], Shizuo Akira[2], Jared M. Brown[3], Sean P. Colgan[4], Wasim Dar[5], J. Steve Bynon[5], Holger K. Eltzschig[1], Elizabeth A. Jacobsen[6], Cynthia Ju[1]*

[1]Department of Anesthesiology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA. [2]Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan. [3]School of Pharmacy, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [4]Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [5]Department of Surgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA. [6]Division of Allergy, Asthma and Clinical Immunology, Mayo Clinic Arizona, Scottsdale, AZ, USA. [7]Present address: Center for Translational Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. [8]Present address: Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

Eosinophils are a myeloid cell subpopulation that mediate type 2 T helper cell host immune responses. Unexpectedly, we identified a rapid accumulation of eosinophils in human liver grafts following hepatic transplantation. No eosinophils were detectable in healthy liver tissues. Studies with genetic models of eosinophil deficiency (PHIL or ΔdblGata1 mice) or antibody-mediated eosinophil-depletion revealed exacerbated injury following hepatic ischemia and reperfusion. Adoptive transfer of bone marrow-derived eosinophils normalized liver injury of eosinophil-deficient mice and reduced hepatic ischemia and reperfusion injury in wild-type mice. Mechanistic studies combining genetic and adoptive transfer approaches identified a critical role for interleukin (IL)-33 signaling, via suppression of tumorigenicity (ST2) on eosinophils, in the production of IL-13 and in the hepato-protection against ischemia reperfusion-induced injury. Together, these studies provide new insight into a novel mechanism of eosinophil-dependent liver protection that could be targeted therapeutically to improve outcomes of patients undergoing liver transplantation.

Characterizing a new Mucin2 knockout mouse model

J. Yu, Z. Criss, K. Deans, N. Shroyer Ph.D.

Baylor College of Medicine, Department of Medicine

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*.

Cholic acid attenuates systemic hypertension in spontaneously hypertensive rats

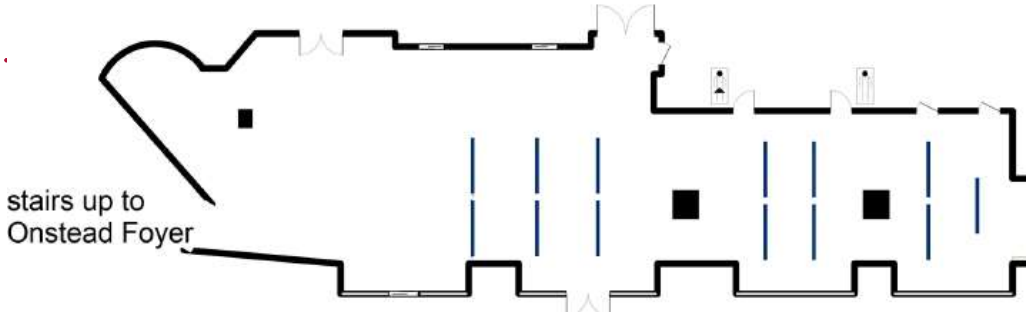
Bojun Zhang, Sriram Ayyaswamy, Robert M Bryan, David J Durgan

Baylor College of Medicine

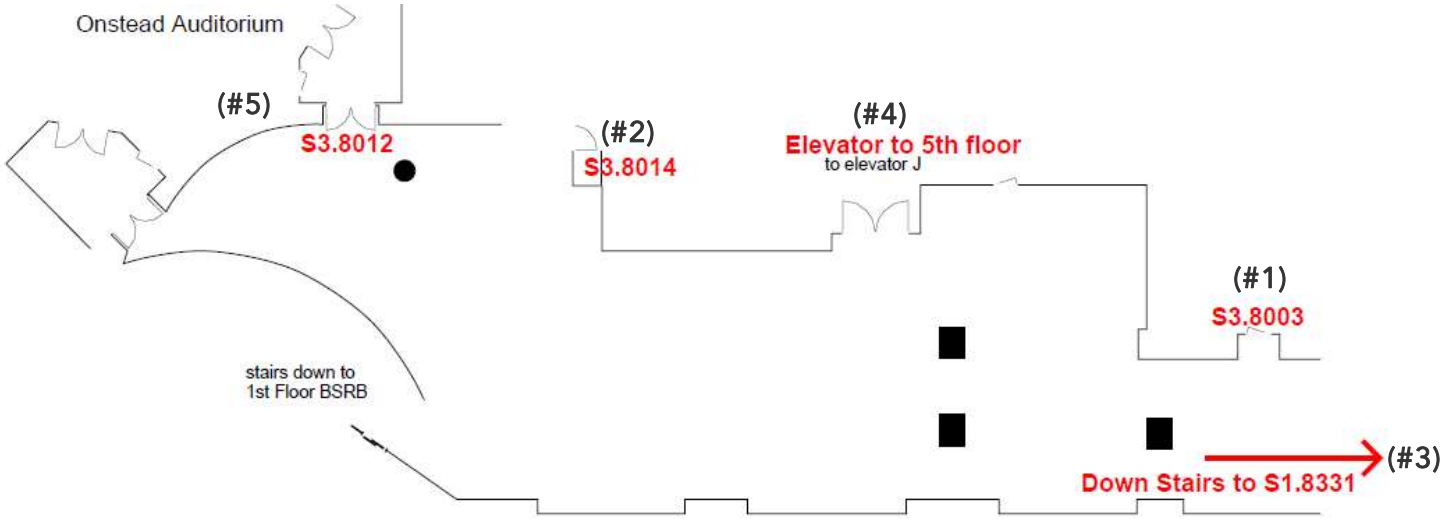
Gut dysbiosis, defined as a pathological imbalance of the gut microbiota, is associated with hypertension in humans and animal models. Recent studies have demonstrated a cause and effect relationship between gut dysbiosis and hypertension in several animal models. However, our understanding of the mechanisms linking gut dysbiosis to blood pressure (BP) regulation of the host is still lacking. One key mechanism by which the microbiota influences the host is through the generation/modification of metabolites, such as bile acids (BAs). BAs, which serve to emulsify fats, are derived from the liver, released into the gut, and further modified by bacteria into a variety of primary and secondary BAs species. These primary and secondary BAs diffuse into the systemic circulation, disperse throughout the body, and act as hormones by stimulating BA receptors. BA signaling has been shown to influence many pathways involved in BP regulation, including systemic inflammation and vascular function. Thus, we hypothesized that **gut dysbiosis contributes to the development of hypertension by reducing bile acid signaling.** By comparing 16s rRNA sequencing data from normotensive WKY and spontaneously hypertensive stroke prone rat (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 ($p<.05$). Additionally, we observed a significant reduction in 9 of 18 plasma BAs in SHRSPs, as compared to WKY. This included a 77% reduction in cholic acid (CA), a primary BA. We next examined the effects of CA supplementation on systolic BP (SBP) in WKY and SHRSP. Starting at 6 weeks old, WKY and SHRSP were fed control or control + 0.5% CA diet for 16 weeks. SBP was measured weekly. At 22 wks, rats were euthanized, and the thoracic aorta was isolated to examine endothelial function by aortic ring assay. Cecal content was collected for 16s rRNA sequencing and BA measurements. CA treatment restored CA and hyocholic acid in SHRSP plasma to similar levels of that observed in WKY control plasma. Furthermore, CA treatment decreased SBP by 18 ±7mmHg at 20 weeks in SHRSP ($p<.05$) but had no effect on SBP in WKY rats. Acetylcholine-induced vasodilation of the aorta was significantly impaired in SHRSP control as compared to WKY control. Interestingly, CA supplementation significantly improved endothelium-dependent vasodilation in the aorta of SHRSP rats similar to that in WKY rats ($p<.0005$). 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. We conclude that reduced BA signaling contributes to the development of hypertension in SHRSP, and that CA treatment may be a potential therapeutic approach to attenuate vascular endothelial dysfunction and associated hypertension.

Event Map

Posters will be located on the 1st Floor of BSRB.



Onstead Auditorium (S3.8012) is located on the 3rd Floor.



Breakout Session Locations:

Breakout Session (#1)
Grace Guo, Ph.D.
3rd Floor
Room S3.8003

Breakout Session (#2)
Jens Holst, M.D.
3rd Floor
Room S3.8014

Breakout Session (#3)
Antonio Moschetta, M.D., Ph.D.
1st Floor
Room S1.8331

Breakout Session (#4)
Michael Gershon, M.D.
5th Floor
Room S5.8005

Breakout Session (#5)
Gary Wu, M.D.
3rd Floor
Onstead Auditorium

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