Seattle Children's Hospital Division of Pediatric Gastroenterology and Hepatology

2023 - 2024

UNIVERSITY of WASHINGTON

UW Medicine

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Scarlett Laboratory

Scarlett Laboratory

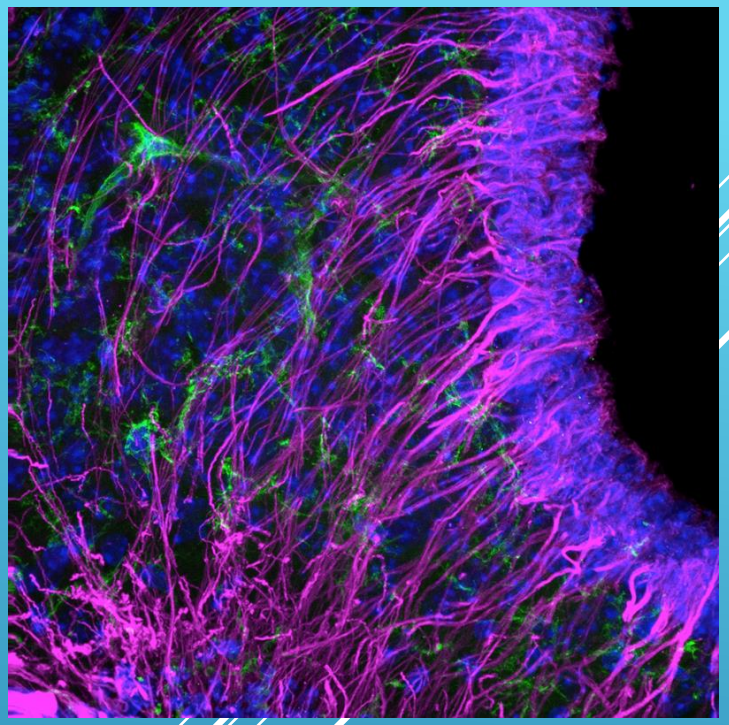
Goal: Investigate the integrated mechanisms whereby the brain and periphery regulate glucose and energy homeostasis and identify how defects in these systems contribute to diabetes and obesity pathogenesis.

1. Personnel: 4 PI's (2 senior, 1 mid, 1 junior), 1 clinical research fellow, 3 PhD post-doctoral fellows, 7 technicians, lots of undergraduates
2. Funding: Combination of NIH, DoD, Biotech and Foundational grants
3. Equipment and Resources: Histochemical, Biochemical, Surgical, Transcriptomics, Photometry.

https://uwmdi.org/labs/scarlett-laboratory/

NEUROCIRCUITS THAT REGULATE ENERGY HOMEOSTASIS

Cutting edge photometry, immunohistochemical and biochemical techniques to study the cells and extracellular matrix of the brain



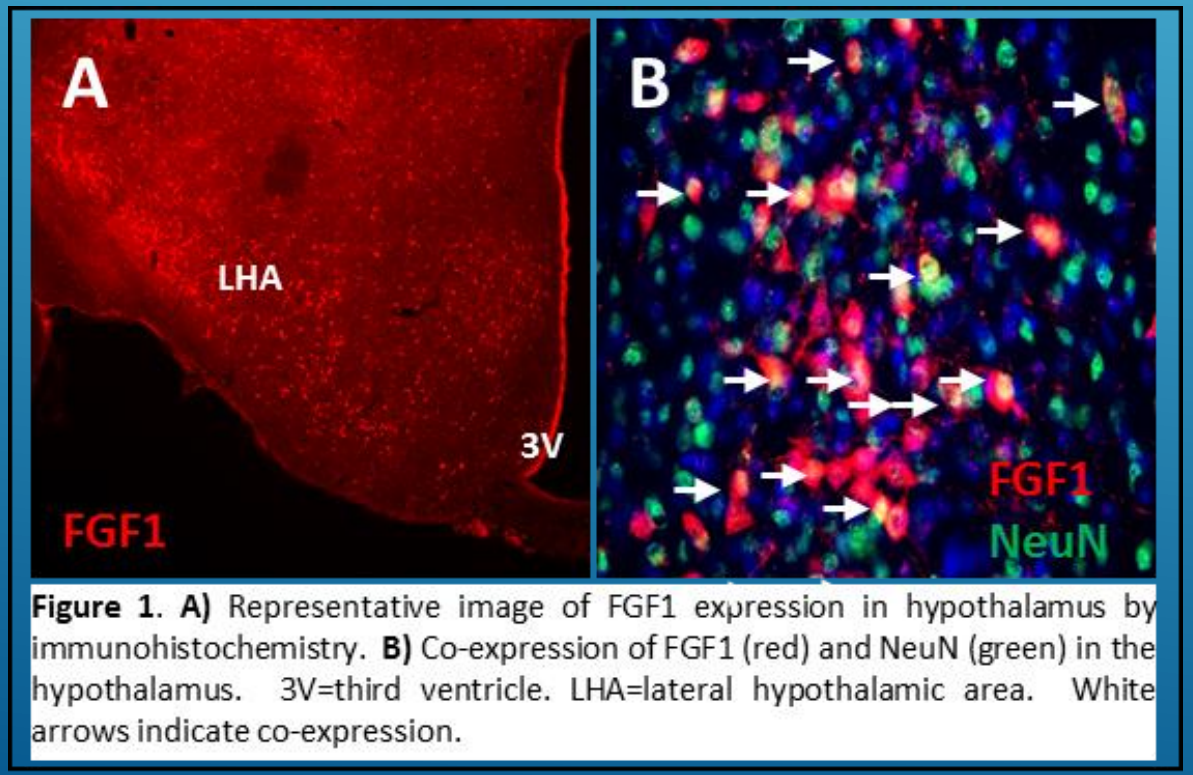
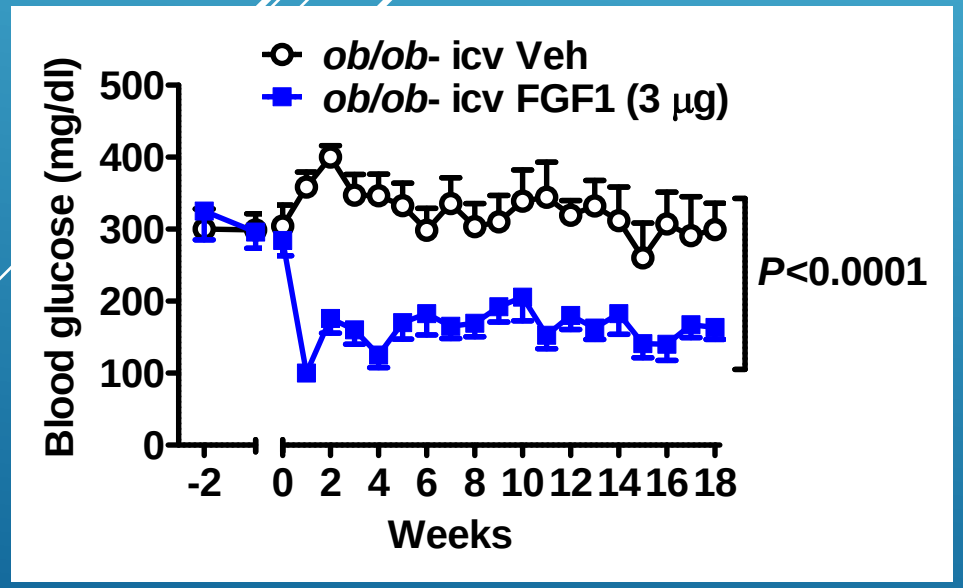
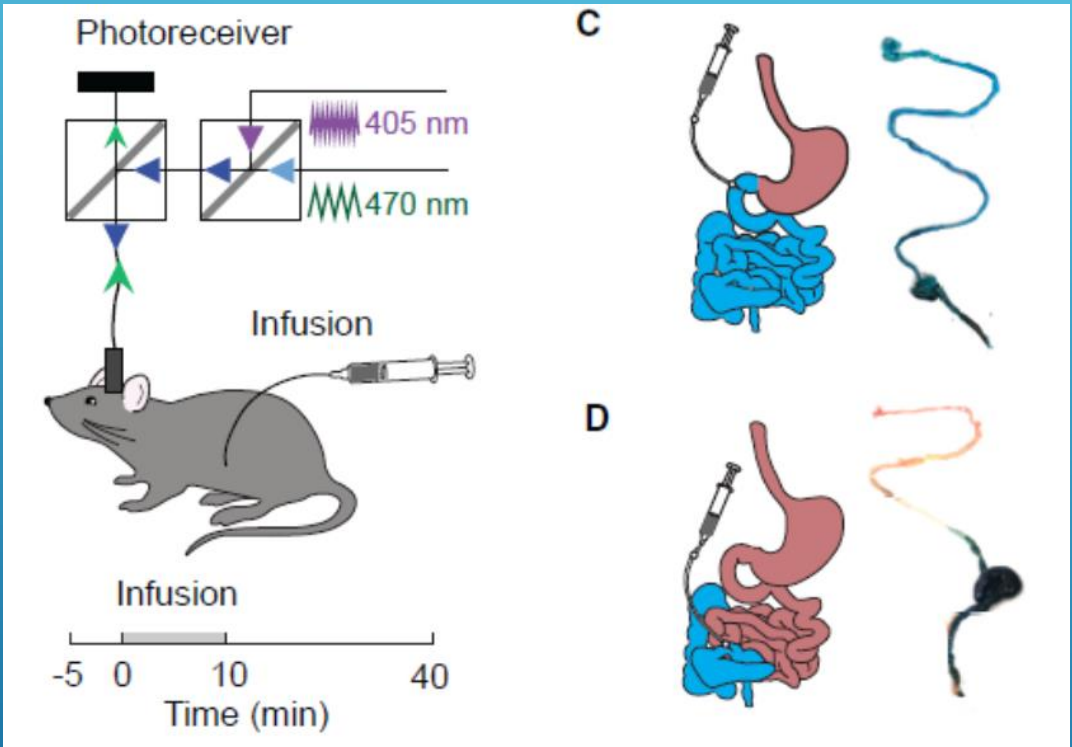


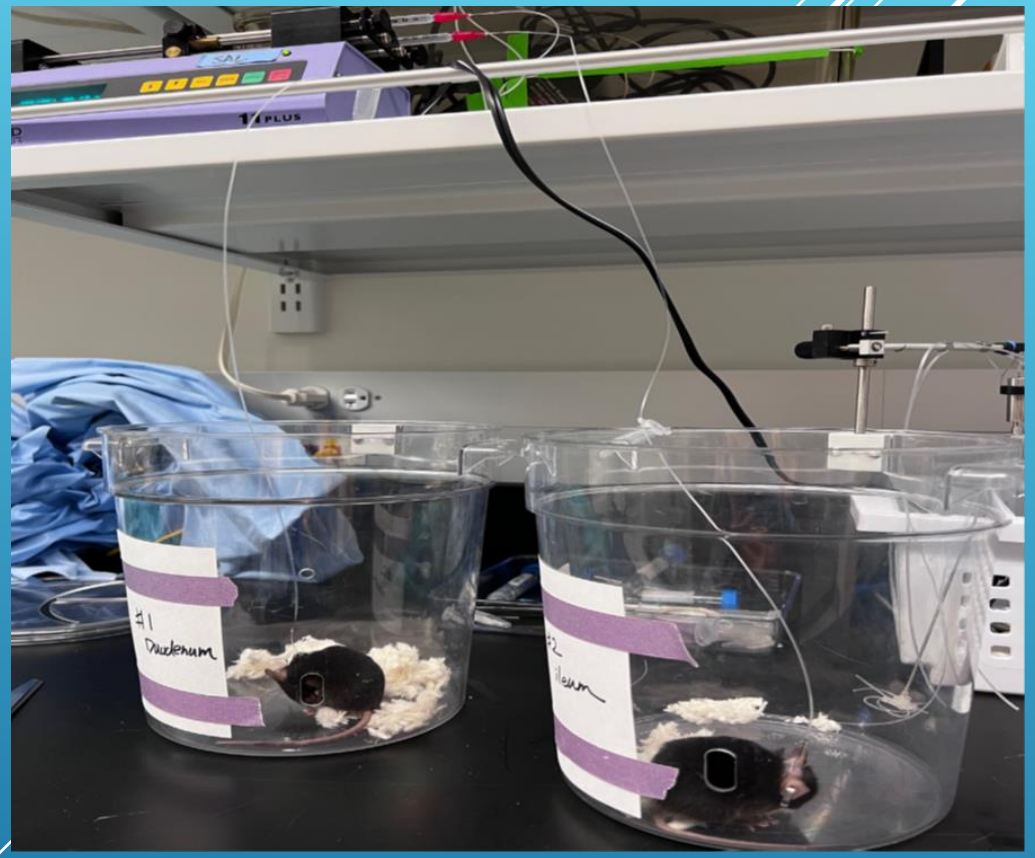
Figure 1. A) Representative image of FGF1 expression in hypothalamus by immunohistochemistry. **B)** Co-expression of FGF1 (red) and NeuN (green) in the hypothalamus. 3V=third ventricle. LHA=lateral hypothalamic area. White arrows indicate co-expression.



GUT-BRAIN SIGNALING



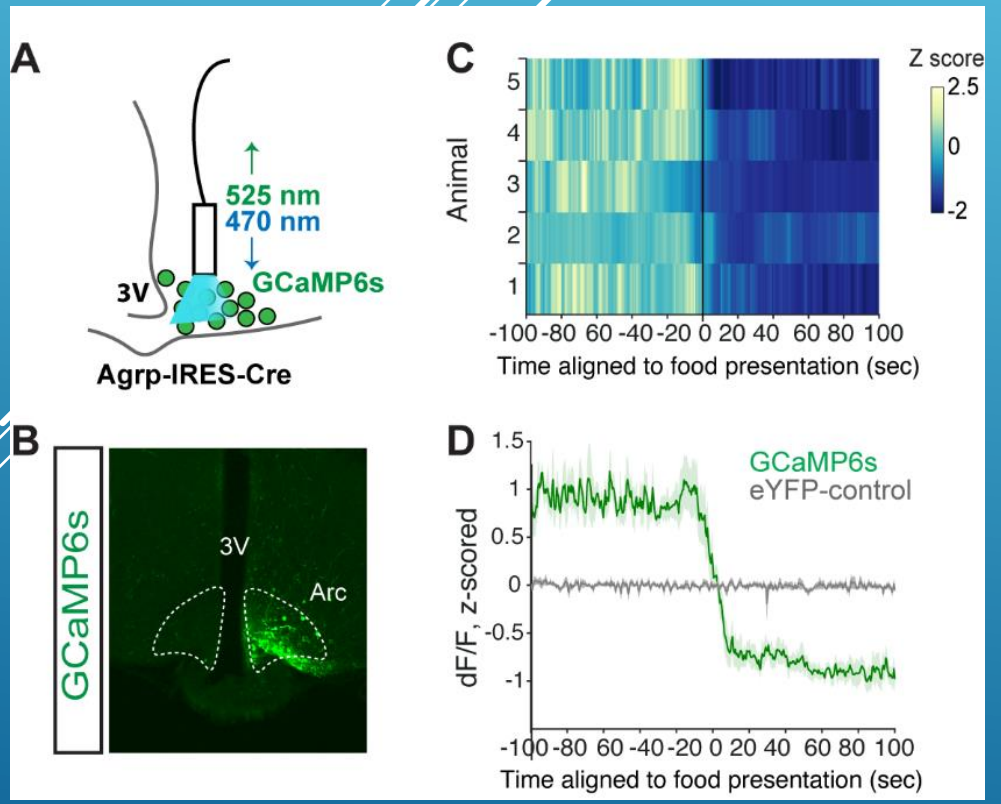
Targeted placement of catheters in the gastrointestinal tract to activate specific anatomical components



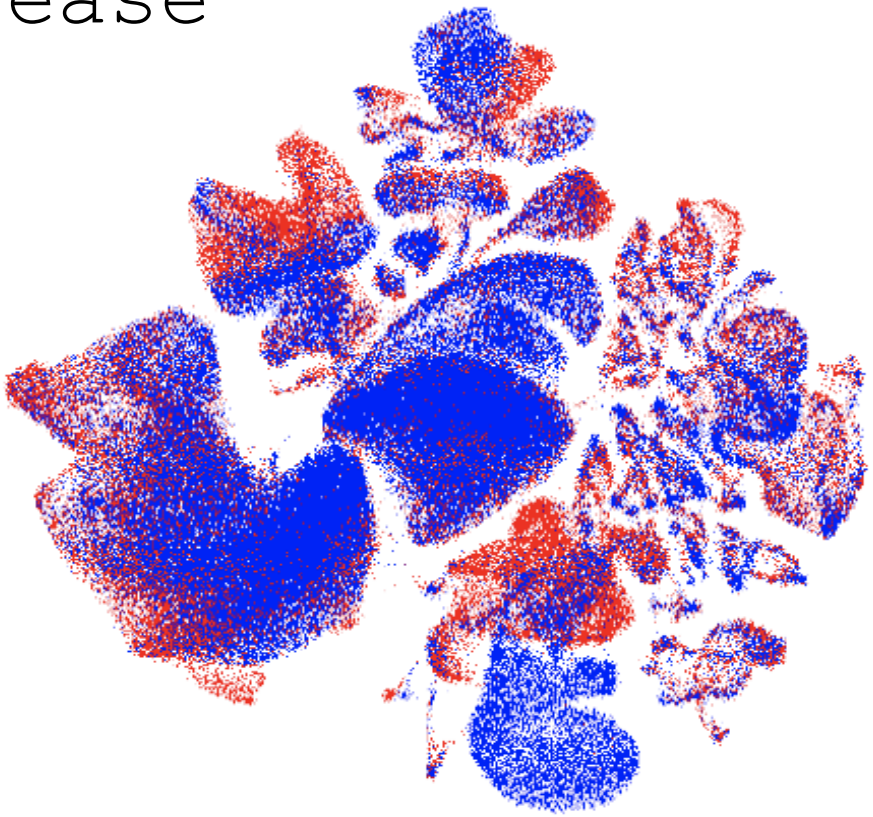
Live, in-vivo infusion of nutrients or compounds into the gastrointestinal tract with simultaneous monitoring of neural activity

CYSTIC FIBROSIS RELATED DIABETES

Combining intestinal infusion of nutrients with live, in-vivo recording of hypothalamic neurons to investigate the role of dysfunctional brain-gut signaling in CFRD



Of Single Cells and Mucosal Disease



Hengqi (Betty) Zheng MD
Assistant Professor of Pediatrics

Betty Zheng MD
@DrBettyZheng

https://www.linkedin.com/in/hengqi-betty-zheng-b49bba34/

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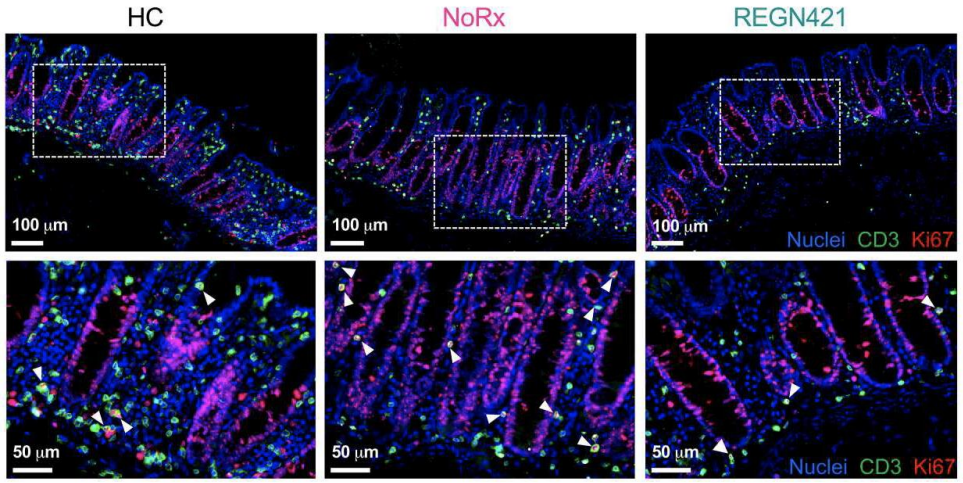
About my research

- My approach to research is embedded in the concept of **team science** (collaboration of bench, clinical, and technological elements).

- I am trained as a pediatric gastroenterologist (from Seattle Children's GI graduated from fellowship in 2016) and focused on enhancing translational research by applying established and new immunological techniques and ideas.

- Pediatric mucosal diseases are not fully understood and the application of new single-cell omic techniques can aid in identifying targets of therapy and response.



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GRAFT VERSUS HOST DISEASE

Notch signaling drives intestinal graft-versus-host disease in mice and nonhuman primates

Victor Tkachev[1,2,3,4†], Ashley Vanderbeck[5,6†], Eric Perkey[5,7†], Scott N. Furlan[8], Connor McGuckin[2,3,4], Daniela Gómez Atria[2‡], Ulrike Gerdemann[2,3,4], Xianliang Rui[2,3,4], Jennifer Lane[2,3,4], Daniel J. Hunt[9], Hengqi Zheng[9], Lucrezia Colonna[9§], Michelle Hoffman[8], Alison Yu[9], Riley Outen[5], Samantha Kelly[5], Anneka Allman[5], Ute Koch[10], Freddy Radtke[10], Burkhard Ludewig[11], Brandon Burbach[12], Yoji Shimizu[12], Angela Panoskaltsis-Mortari[13], Guoying Chen[14], Stephen M. Carpenter[14‖], Olivier Harari[14], Frank Kuhnert[14], Gavin Thurston[14], Bruce R. Blazar[13], Leslie S. Kean[2,3,4†*], Ivan Maillard[5†*]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GRAFT VERSUS HOST DISEASE

Spatiotemporal single-cell profiling reveals that invasive and tissue-resident memory donor CD8$^+$ T cells drive gastrointestinal acute graft-versus-host disease

Victor Tkachev[1*], James Kaminski[1,2†], E. Lake Potter[3†], Scott N. Furlan[4†], Alison Yu[1], Daniel J. Hunt[1], Connor McGuckin[1], Hengqi Zheng[5], Lucrezia Colonna[4‡], Ulrike Gerdemann[1], Judith Carlson[5§], Michelle Hoffman[4], Joe Olvera[1], Chris English[6], Audrey Baldessari[6], Angela Panoskaltsis-Mortari[7], Benjamin Watkins[8], Muna Qayed[8], Yvonne Suessmuth[8], Kayla Betz[1], Brandi Bratrude[1], Amelia Langston[8], John T. Horan[8], Jose Ordovas-Montanes[2,9,10], Alex K. Shalek[2,11,12], Bruce R. Blazar[7], Mario Roederer[3], Leslie S. Kean[1*]

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06736-7 OPEN

Evidence for persistence of the SHIV reservoir early after MHC haploidentical hematopoietic stem cell transplantation

Lucrezia Colonna[1,2], Christopher W. Peterson[3,4], John B. Schell[1,11], Judith M. Carlson[1], Victor Tkachev[1], Melanie Brown[1], Alison Yu[1], Sowmya Reddy[3], Willi M. Obenza[3], Veronica Nelson[3], Patricia S. Polacino[5], Heather Mack[5], Shiu-Lok Hu[5,6], Katie Zeleski[1], Michelle Hoffman[1], Joe Olvera[5], Scott N. Furlan[1,2], Hengqi Zheng[1,2], Agne Taraseviciute[1,2], Daniel J. Hunt[1], Kayla Betz[1], Jennifer F. Lane[5,7], Keith Vogel[5], Charlotte E. Hotchkiss[5], Cassie Moats[5], Audrey Baldessari[5], Robert D. Murnane[5], Christopher English[5], Cliff A. Astley[5], Solomon Wangari[5], Brian Agricola[5], Joel Ahrens[5], Naoto Iwayama[5], Andrew May[5], Laurence Stensland[8], Meei-Li W. Huang[8], Keith R. Jerome[8,9], Hans-Peter Kiem[3,4,10] & Leslie S. Kean[1,2,4,12]

Published in final edited form as:
Sci Transl Med. 2017 September 20; 9(408): . doi:10.1126/scitranslmed.aan3085.

Combined OX40L and mTOR blockade controls effector T cell activation while preserving Treg reconstitution after transplant

Victor Tkachev[1,*], Scott N. Furlan[1], Benjamin Watkins[1,3], Daniel J. Hunt[1], Hengqi Betty Zheng[1], Angela Panoskaltsis-Mortari[2], Kayla Betz[1], Melanie Brown[1], John B. Schell[1], Kat Zeleski[1], Alison Yu[1], Ian Kirby[4], Sarah Cooley[2], Jeffrey S. Miller[2], Bruce R. Blazar[2], Dunca Casson[4], Phil Bland-Ward[4], and Leslie S. Kean[1,*]

Single-cell Omic Clinical Trials I led/lead

(1) PREDICT – scRNA-seq in pediatric IBD and GI GVHD

(2) Healthy Endoscopy – scRNA-seq in healthy comparison

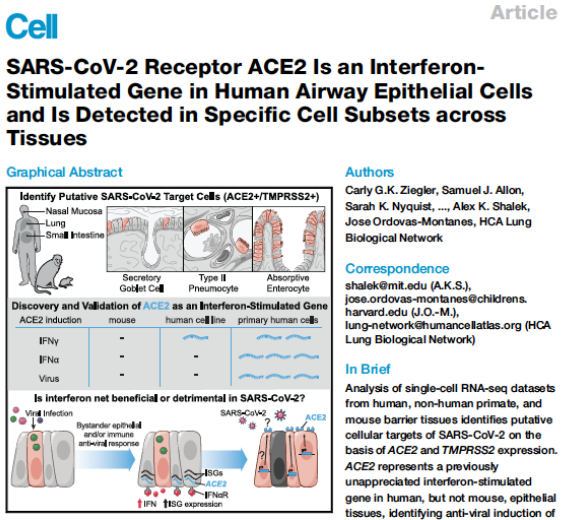
(3) STRIDE Seattle – spatial transcriptomics/multiomics in pediatric IBD

TITLE

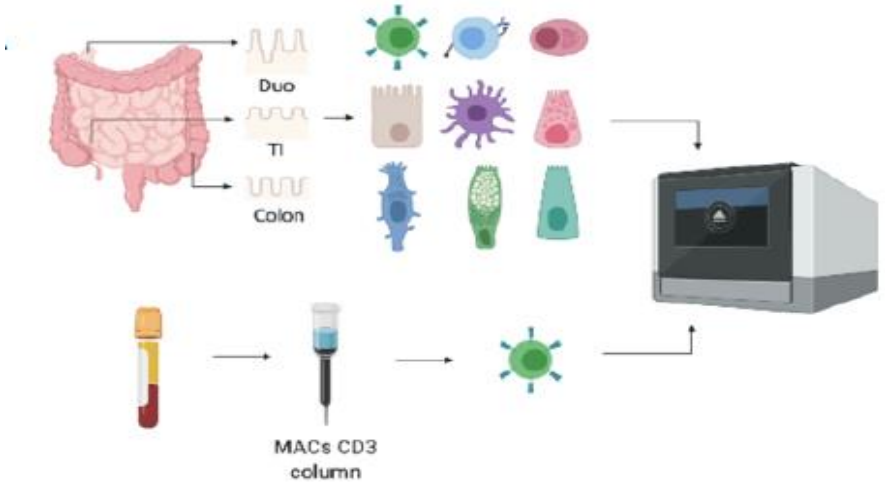
Concerted changes in the pediatric single-cell intestinal ecosystem before and after anti-TNF blockade

AUTHORS

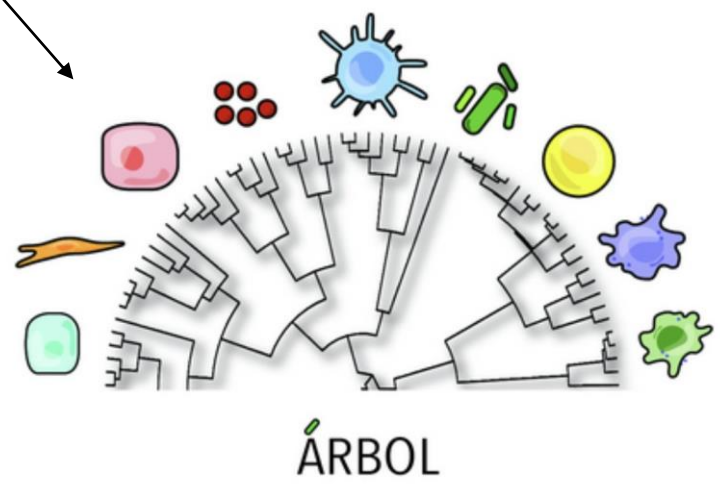
Hengqi Betty Zheng[1,*], Benjamin A. Doran[2,3,4,5,6,7,*], Kyle Kimler[2,3,4,5,6,7,*], Alison Yu[2,*], Victor Tkachev[2], Veronika Niederlova[3,5,6,8], Kayla Cribbin[2], Ryan Fleming[2], Brandi Bratrude[2], Kayla Betz[2], Lorenzo Cagnin[2], Connor McGuckin[2], Paula Keskula[2], Alexandre Albanese[2], Maria Sacta[3], Joshua de Sousa Casal[3,6,9], Ruben van Esch[10], Andrew C. Kwong[3,6], Conner Kummerlowe[4,5,6,7], Faith Taliaferro[3,6], Nathalie Fiaschi[11], Baijun Kou[11], Sandra Coetzee[11], Sumreen Jalal[11], Yoko Yabe[11], Michael Dobosz[11], Matthew F. Wipperman[11], Sara Hamon[11], George D. Kalliolias[11], Andrea Hooper[11], Wei Keat Lim[11], Sokol Haxhinasto[11], Yi Wei[11], Madeline Ford[1], Lusine Ambartsumyan[1], David L. Suskind[1], Dale Lee[1], Gail Deutsch[12], Xuemei Deng[12], Lauren V. Collen[3], Vanessa Mitsialis[3,13], Scott B. Snapper[3,13,14], Ghassan Wahbeh[1], Alex K. Shalek[4,5,6,7,9,14,15,#], Jose Ordovas-Montanes[3,5,6,9,16,#,^], Leslie S. Kean[2,17,#]

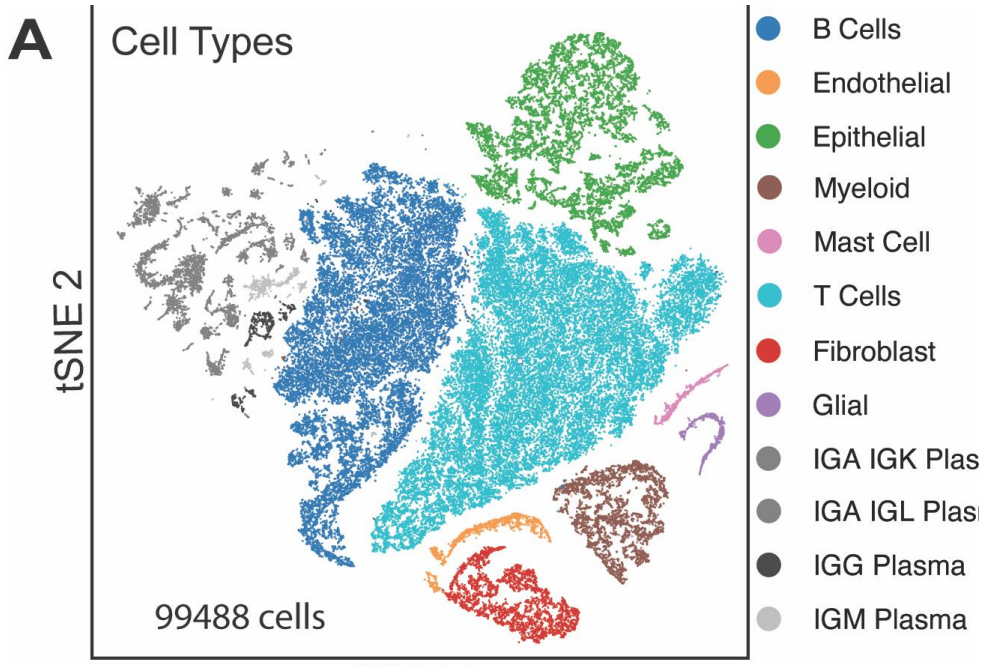


(1) PREDICT: NIH Clinical Trials.gov ID: NCT03369353
(2) The Healthy Endoscopy Study: NIH Clinical Trials.gov ID: NCT04369963



Naïve to treatment pediatric IBD patients with 3 years of clinical and sample follow up





Single Cell transcriptomics in GI tissue and blood

Zheng H et al. Preprint medRxiv. 2021.

https://github.com/jo-m-lab/ARBOL

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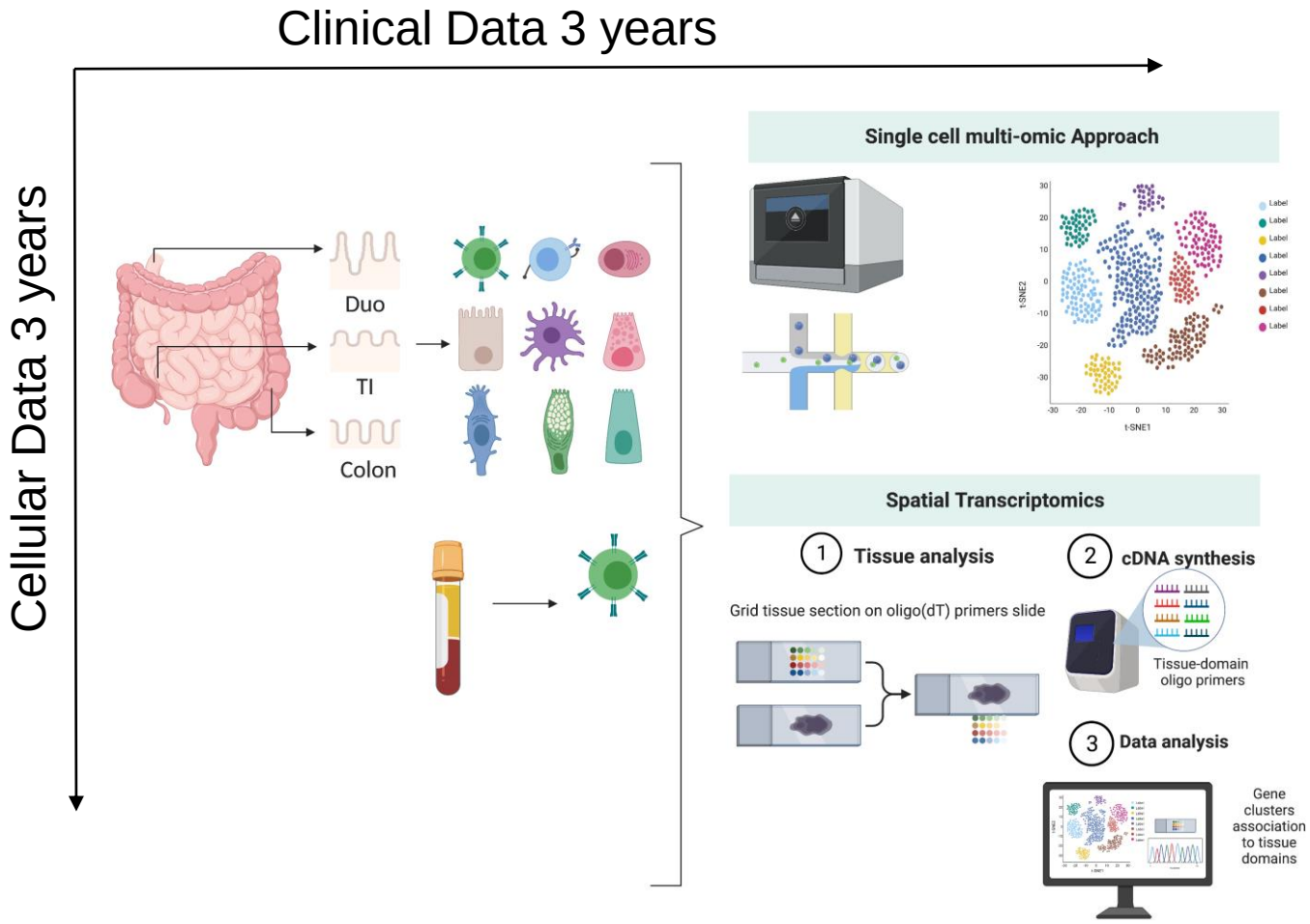
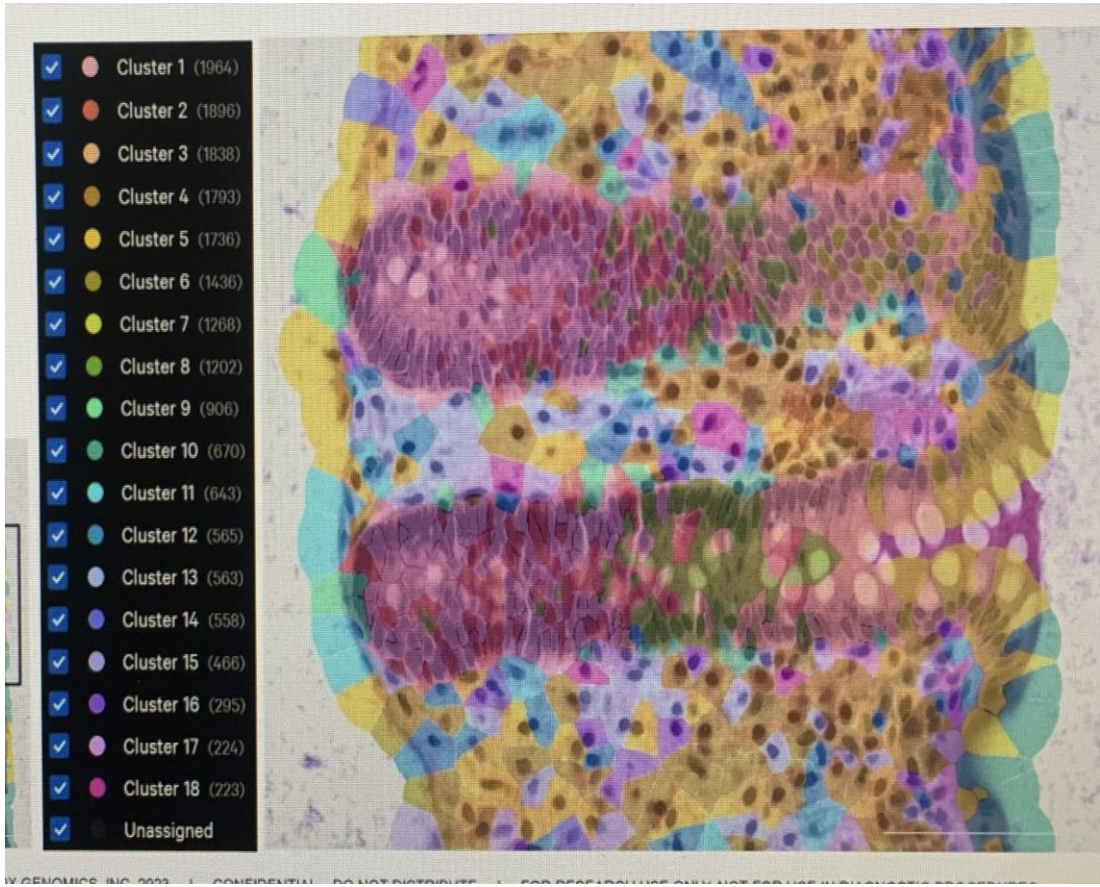
(3) STRIDE-Seattle: Local collaboration with the Allen Institute looking at spatial transcriptomics and multi-omic approaches





Very Early Onset IBD (VEO-IBD)

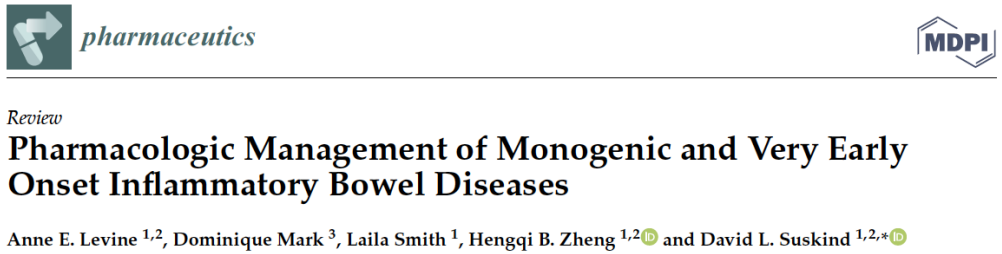
- Ongoing collaboration with SCH Immunology group
- Multiple publications on VEO-IBD (2 first author fellows!)


Pediatric Drugs
https://doi.org/10.1007/s40272-022-00503-4

REVIEW ARTICLE

Linking Genetic Diagnosis to Therapeutic Approach in Very Early Onset Inflammatory Bowel Disease: Pharmacologic Considerations

Anne E. Levine[1,2] · Hengqi B. Zheng[1,2] · David L. Suskind[1,2]


pharmaceutics

MDPI

Review

Pharmacologic Management of Monogenic and Very Early Onset Inflammatory Bowel Diseases

Anne E. Levine [1,2], Dominique Mark [3], Laila Smith [1], Hengqi B. Zheng [1,2] and David L. Suskind [1,2,*]


frontiers in Immunology

MINI REVIEW
published: 26 May 2021
doi: 10.3389/fimmu.2021.675186

The Growing Need to Understand Very Early Onset Inflammatory Bowel Disease

Hengqi B. Zheng[1,2*], M. Teresa de la Morena[2,3] and David L. Suskind[1,2]

- PI on Novatis MAS825 International clinical trial for NLRC4-GOF patients
  - 3 month old (youngest on trial) from SCH

Thank you

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An antiracism curriculum for pediatric liver transplant teams

Hannibal Person, MD

Seattle Children's®

Background:

Racism is an individual, interpersonal, and structural process that produces inequities in opportunity and outcomes for people based on their race

Racism is a public health problem

Healthcare providers have been shown to have racial bias

Diversity has been shown to enhance medical educational and improve patient outcomes

Racial disparities in pediatric liver transplant (PLTx)

- Pre-transplant mortality
- Exception point application
- Graft failure rates
- Morbidity

Socioeconomic and other SDOH only partially explain these differences

Rosenblatt et. al., 2021; Ebel et. al., 2022; Wadhwani et. al., 2022; Hsu et. al., 2015
Came & Griffith, 2018; Hoffman et. al., 2016; Johnson et. al., 2016; Johnson et. al., 2017; Saha et. al., 2008; Leveist & Pierre, 2014

Bias Reduction in Medicine (BRIM):

Early educational intervention for gender bias with evidence-basis

- Allows faculty to become more aware of their own implicit sex and gender biases and the benefits of bias reduction
- Introduces them to the underlying constructs of gender and sex bias
- Provides evidence-based strategies to self-regulate sex and gender bias

Participant feedback and department climate assessment showed significant improvements

Carnes et. al., 2012; Carnes et. al., 2015

BRIM Pediatrics+

Modification of BRIM
- Antiblack racism
- Pediatrics-specific
- Increased cognitive and other antiracism skills
- Individual antiracism action planning
- Team antiracism action planning (structural)

Plan for enactment across all faculty at SCH

Observational study:
- Participant experience, perception of participation in antiracism
- Enactment/completion of antiracism action plans
- Institutional inclusion metrics
- *Patient experience and outcomes (CDHE)*

Currently completing pilot divisions (GI, NDV, and Palliative Care/Bioethics)

BRIMP+LTx

Modification of BRIMP+ to be PLTx specific

- PLTx-specific racial disparities literature
- Relevant clinical scenarios
- Relevant individual and team antiracism action plans

Hypothesis: More specialty-specific education will enhance learner experience and outcome beyond the BRIMP+ skills and team-based approach

Collaboration with SPLIT

Participants:

- PLTx teams (recruited via SPLIT Advocacy Committee) from North America
- Pilot team and then broader recruitment

Intervention:

- BRIMP+LTs (4, 2-hours workshops with pre- and post-work)

Other Projects:

1. Endoscopy ergonomic health pilot (with Dr. Elizabeth Reznikov – GI Fellow)
2. GI patient-provider communication educational intervention (with SCH CONNECT)
3. DBGI registry for Gut-Brain Health Program/IB-Stim registry

Research Projects: **Ghassan Wahbeh**

- Active:
  - Vedolizumab for pediatric IBD
  - Tofacitinib for pediatric UC
  - Ozanimod for pediatric UC
  - Develop Registry: Anti TNF safety database
  - Rare Complications of Paediatric IBD – Registry
- Upcoming:
  - Ozanimod for pediatric CD
  - Guselkumab, mirikizumab for pediatric CD
- Recently closed
  - AK002 for Adolescents with EOE

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Inflammatory Bowel Disease Center

CSW/QI/New upcoming projects

- Clinical Standard Work:
  - Inpatient management of Acute severe colitis
  - Inpatient management of perianal fistulizing Crohn’s Disease
  - Inpatient management of internally fistulizing Crohn’s Disease

- Small Bowel Ultrasound in IBD disease evolution

Lee Research Program

Inflammatory Bowel Disease

- Focus: The role of diet in inflammatory bowel disease pathogenesis
- Current studies:
  - RE-EEN: Multicenter study evaluating conventional formula vs whole-food home-blended smoothie as EEN
  - Epidemiology: Dietary exposures on IBD course
    - Prospective study using 24h dietary recall to assess relationship between dietary exposures and disease relapse
  - Food additive exposures in IBD

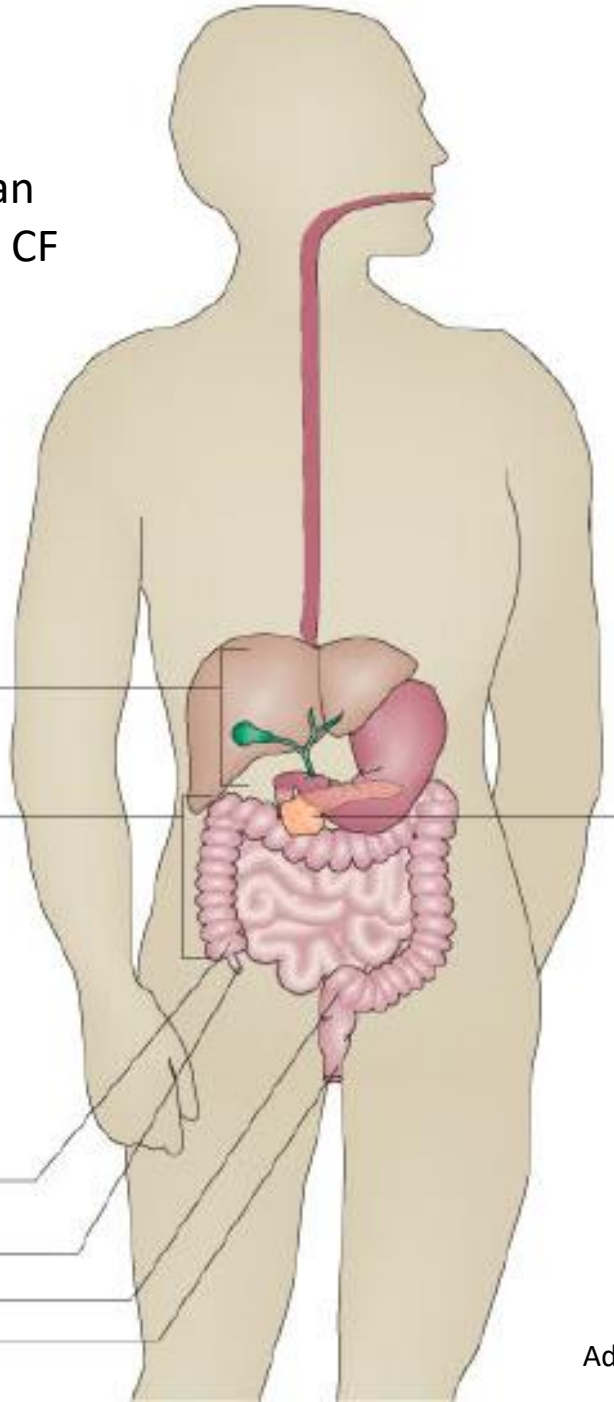
Celiac Disease

- Focus:
  - Lab markers in celiac disease
  - Gluten exposure
  - Food insecurity
- Current studies:
  - Evaluating predictive value of TTG IgA at T1DM diagnosis
  - Nutritional intake in children with celiac
  - Relative cost of GF diet vs conventional diet
  - Serological vs biopsy diagnosis of celiac
  - Creation of Celiac Disease Registry

Cystic Fibrosis-GI Manifestations

Nicole Green, MD

GI complications have become an increasing cause of morbidity in CF patients



Hepatobiliary tract
- Biliary cirrhosis
- Gallbladder disease
- Malignancies
- Portal venopathy
- Drug induced liver injury (DILI)

Gastrointestinal tract
- Atresia
- Intussusception
- Gastroesophageal reflux
- Dysbiosis
- Inflammation
- Malignancy
- MI
- DIOS
- Appendiceal abscess
- Constipation
- Rectal prolapse

Pancreas
- Exocrine pancreatic insufficiency
- Pancreatitis
- Malignancy

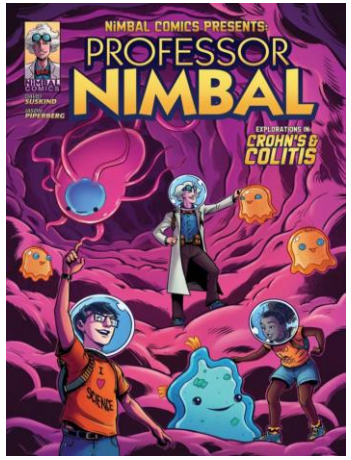
Adapted from Ooi et al., *Nature Reviews* 2016

Research Projects

- Feasibility of **dietary intervention to influence gastrointestinal symptoms and microbiome** in pediatric patients with cystic fibrosis

- Prospective Study of Ultrasound to **Predict Hepatic Cirrhosis in CF Patients (PUSH)**

- Comparison of **GI microbiome in CF patients with and without advanced liver disease**. Compare potential **shits in microbiome after starting Trikafta modulator therapy**



Dietary Therapy in IBD: From the Microbiome and Beyond

David Suskind M.D.
Professor of Pediatrics
Division of Gastroenterology
University of Washington
Seattle Children's Hospital

14-year-old boy with 3 months of abdominal pain, loose stools, and weight loss.

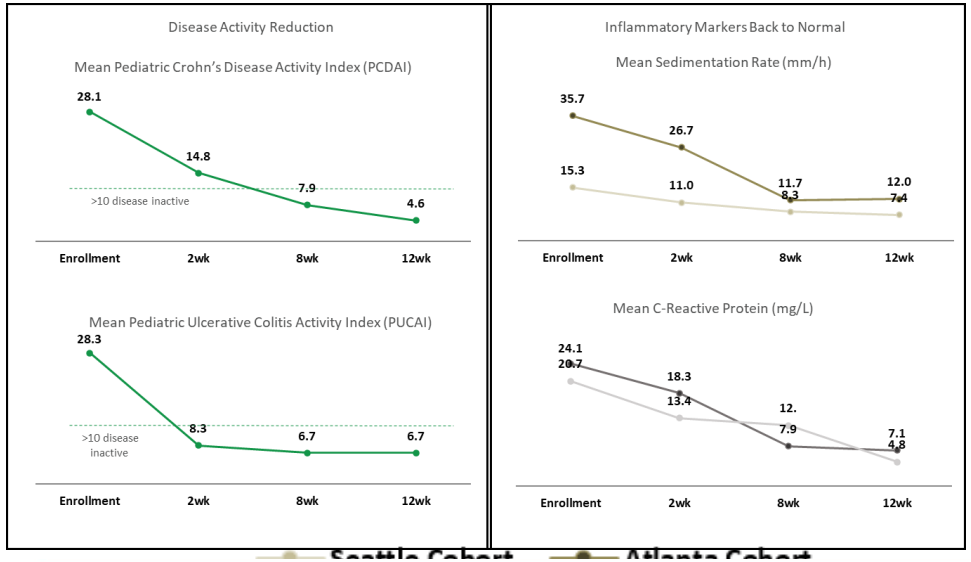
- Anemic with elevated CRP
- EGD/Colonoscopy c/w Crohn's disease
- Family wanting to avoid medication

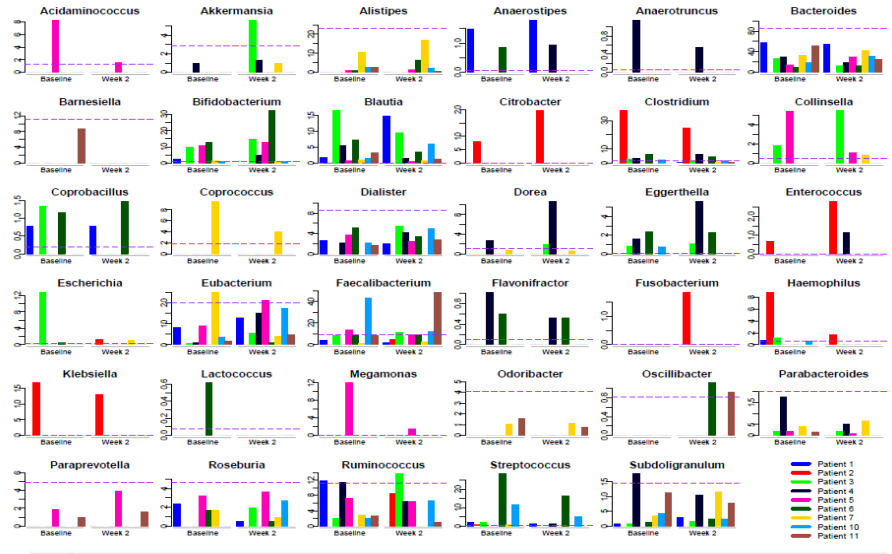
- EEN to SCD
- Clinical remission and laboratory remission for over 3 years
- Endoscopy/Colonoscopy completely normal
  - Normal histology

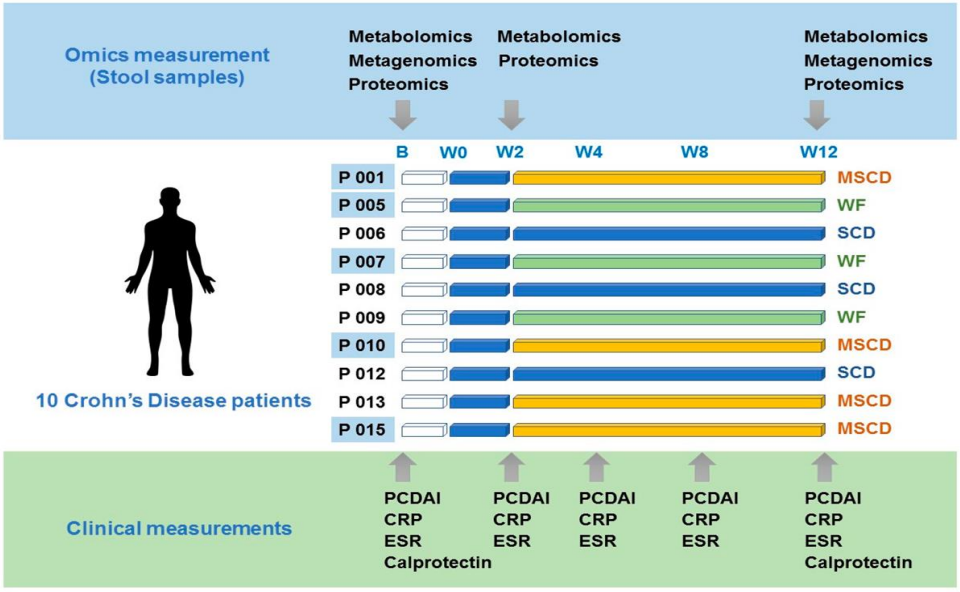
20+ clinical studies have shown the efficacy of treating IBD with diet

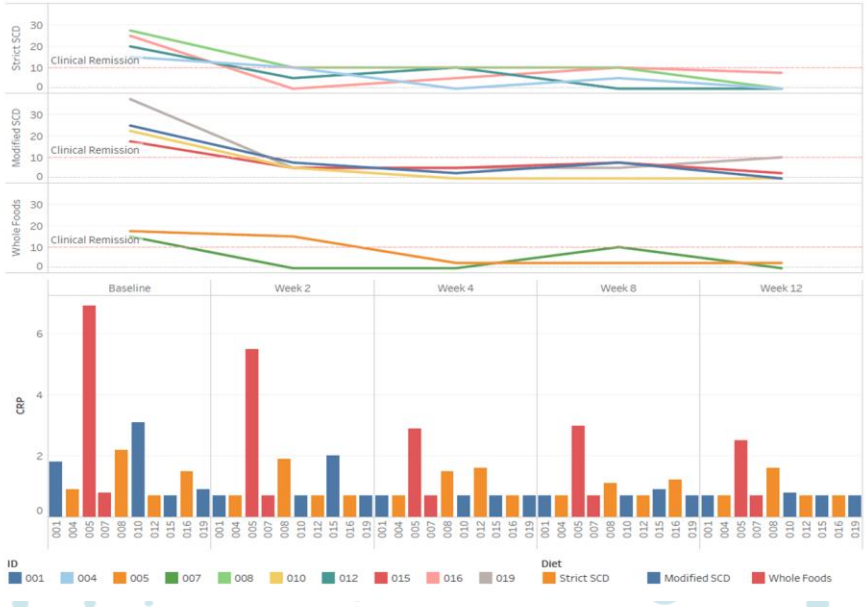
Suskind et al. JCG 2018 Feb; 52(2): 155–163

2 cohorts (n = 12); SCD as the sole treatment of IBD patients









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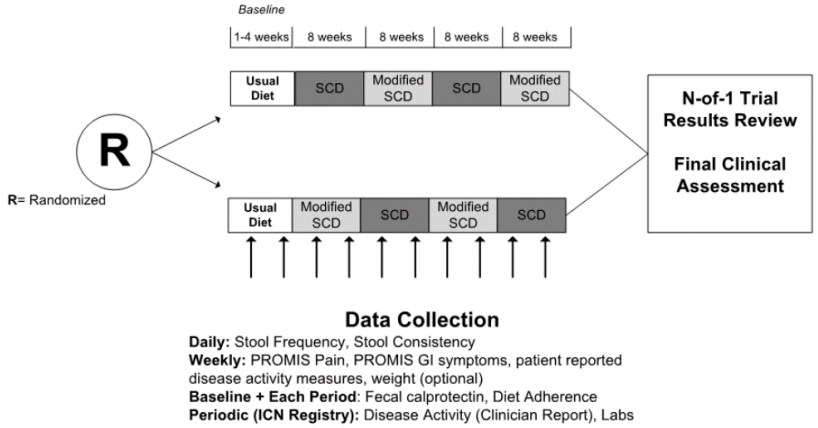
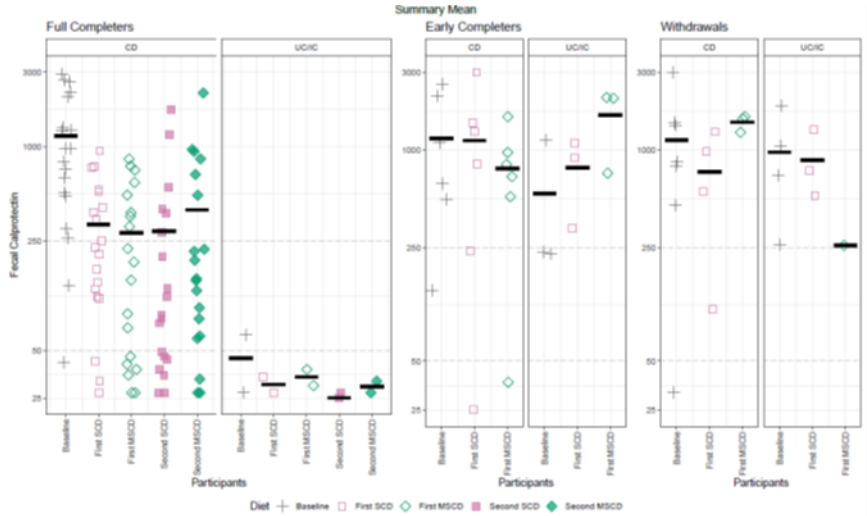




Longitudinal Assessment of Nutritional Intervention in Inflammatory Bowel Disease Health Outcomes (LAND HO)

Event	Study Time Point				
	Baseline	Follow-up	Annually	Endoscopy	Completion
IBD standard Labs	■	■		■	■
Blood for banking	■	■			■
Stool Metabolomics	■	■			■
Stool Microbiome	■	■			■
Urine	■	■			■
Biopsy Samples				■	
Dietary Recall	■	■			■
IMPACT III	■		■		■
EAT-26	■		■		■
PROMIS Anxiety	■ □		■ □		■ □
PROMIS Depression	■ □		■ □		■ □

Patient ■ Parental □

Liver Research

Pamela Valentino, MD

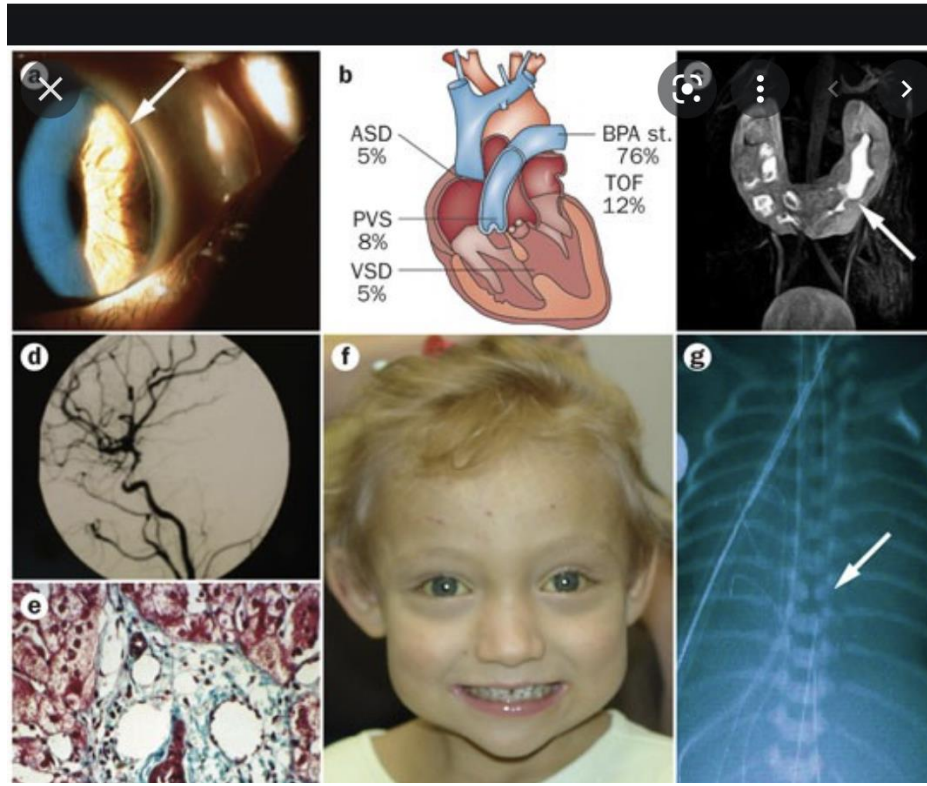
Evelyn Hsu, MD

Niviann Blondet, MD

Katelyn Saarela, MD




Liver Disease Research in Children



Kids with Acute Liver Failure

TRIUMPH
Treatment for Immune Mediated Pathophysiology

Babies with Jaundice

ChiLDReN
The Childhood Liver Disease Research Network
including the Cystic Fibrosis Liver Disease Network

Odevixabat in BA patients

Maralixibat in BA, PFIC, Alagille patients

Kids with Autoimmune Liver disease

A-LiNK

Transplant Outcomes

STARZL NETWORK
for Excellence in Pediatric Transplantation

Social Determinants of Health in Liver Transplantation

SRTR SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

SPLIT
Society of Pediatric Liver Transplantation

Allocation Research

Original Clinical Science—Liver

Impact of Acuity Circles on Outcomes for Pediatric Liver Transplant Candidates

Douglas B. Mogul, MD, PhD,[1] Emily R. Perito, MD, MAS,[2] Nicholas Wood, PhD,[3] George V. Mazariegos, MD,[4] Douglas VanDerwerken, PhD,[3] Samar H. Ibrahim, MBChB,[5] Saeed Mohammad, MD,[6] Pamela L. Valentino, MD, MSc, FRCP(C),[7] Sommer Gentry, PhD,[3] and Evelyn Hsu, MD[8]

Allocation to pediatric recipients around the world: An IPTA global survey of current pediatric solid organ transplantation deceased donation allocation practices

Stefany Hernández Benabe[1] | Irini Batsis[2] | Anne I. Dipchand[3] | Stephen D. Marks[4] | Mignon I. McCulloch[5] | Evelyn K. Hsu[6]

[1]AdventHealth, Orlando, Florida, USA

[2]Mount Sinai School of Medicine, New York, USA

[3]The Hospital for Sick Children, Toronto, Ontario, Canada

[4]NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London Great Ormond Street

Abstract

Background: There has not been a comprehensive global survey of pediatric-deceased donor allocation practices across all organs since the advent of deceased donor transplantation at the end of the 20th century. As an international community that is responsible for transplanting children, we set out to survey the existing landscape of allocation. We aimed to summarize current practices and provide a snapshot overview

Ethics and Health Disparities

An ethical analysis of obesity as a contraindication to pediatric liver transplant candidacy

Emily R. Berkman [1,2,3,*], Evelyn K. Hsu [4], Jonna D. Clark [1,2,3], Mithya Lewis-Newby [2,3,5], André A.S. Dick [6], Douglas S. Diekema [2,3,7], Aaron G. Wightman [2,3,8]

[1] *Division of Pediatric Critical Care Medicine, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[2] *Division of Bioethics and Palliative Care Medicine, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[3] *Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute, Seattle, Washington, USA*
[4] *Division of Pediatric Gastroenterology and Hepatology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[5] *Division of Cardiac Critical Care, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[6] *Division of Transplantation, Section of Pediatric Transplantation, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[7] *Division of Pediatric Emergency Medicine, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA*
[8] *Division of Pediatric Nephrology, University of Washington School of Medicine, Seattle Children's Hospital Seattle, Washington, USA*

EDITORIALS www.jpeds.com • THE JOURNAL OF PEDIATRICS

Addressing Racism in Pediatric Liver Transplantation: A Moral Imperative

In this volume of *The Journal*, Shifman et al use longitudinal data from the Scientific Registry of Transplant Recipients and the Health Resources and Services Administration database of primary care health professional shortage areas (HPSA) to characterize the association between living in primary care shortage areas and graft failure or death for pediatric liver transplant recipients.[1] They studied a

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Our Community Needs to Address Racial and Ethnic Health Inequities in Pediatric Liver Transplantation

We continue to fail non-White children along every step of their transplant journey. They are sicker at the time of transplant referral, have a higher risk of dying while awaiting transplantation.

Innovative interventions and multicenter studies in Intestinal Failure

Danielle Wendel, MD

Seattle Children's®

Intestinal Failure Projects

Current Projects

- Use of sodium bicarbonate locks for prevention of central line-associated blood stream infection
- Teduglutide post-marketing registry (multicenter)
- A prospective prevalence study in adolescent and adult patients dependent on parenteral nutrition to assess the incidence of intestinal failure associated liver disease (IFALD) (multicenter)
- International intestinal failure registry (multicenter)
- QoL in intestinal failure (local and multicenter)

Future Projects

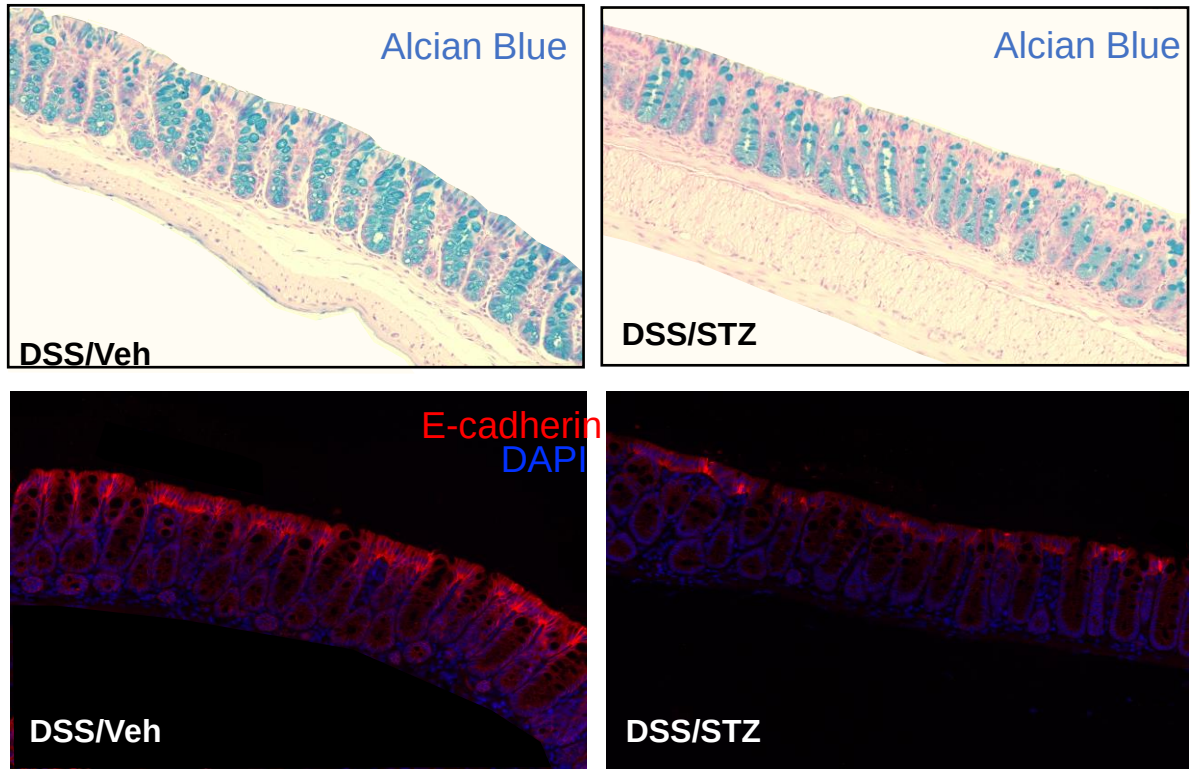
- Nutritional intake in children with history of intestinal failure who are enterally autonomous
- School readiness and QoL for intestinal failure patients and families
- Multicenter trial of SMOF lipids in pediatrics

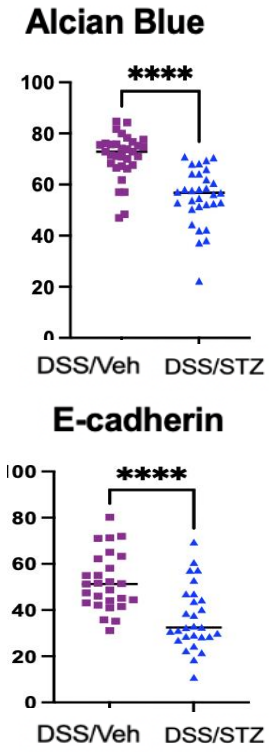
And More!!!

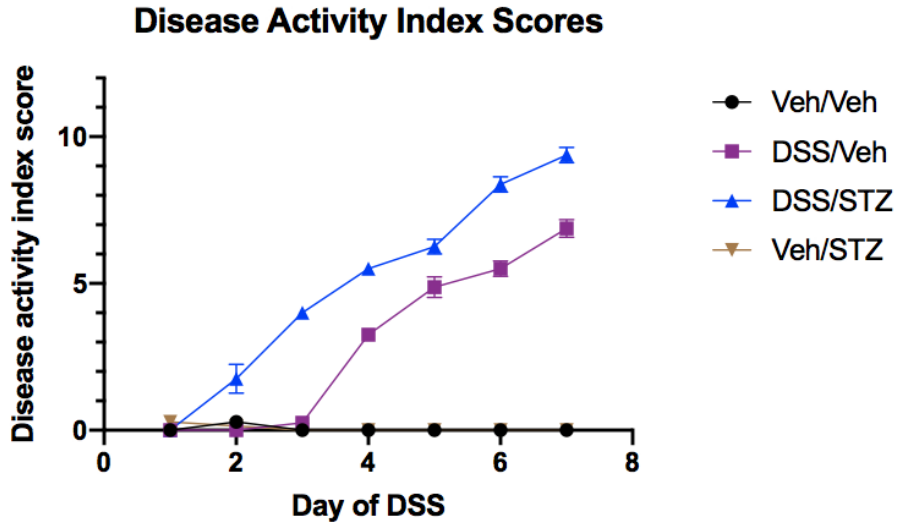
Seattle Children's®

Intestinal barrier function in metabolic health and inflammatory bowel disease

Kendra Francis, MD Clinician Researcher

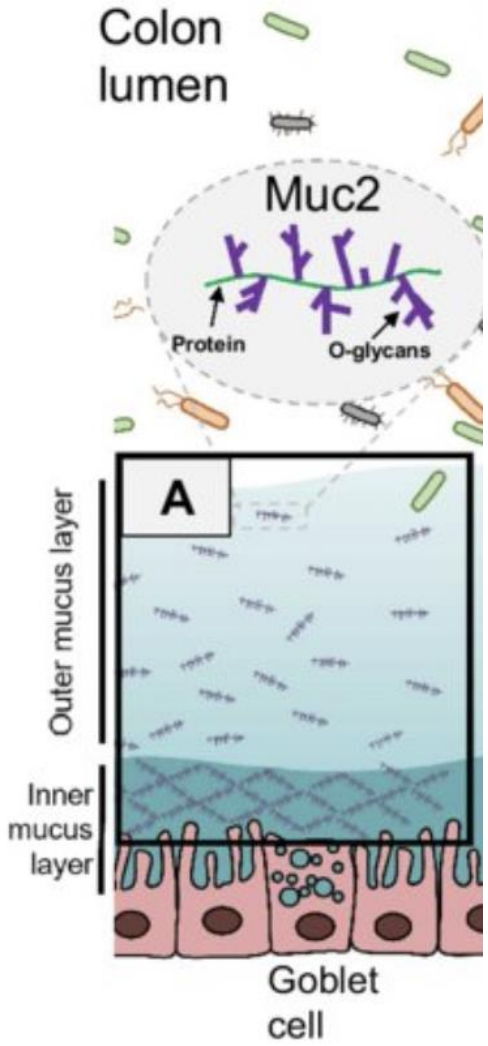


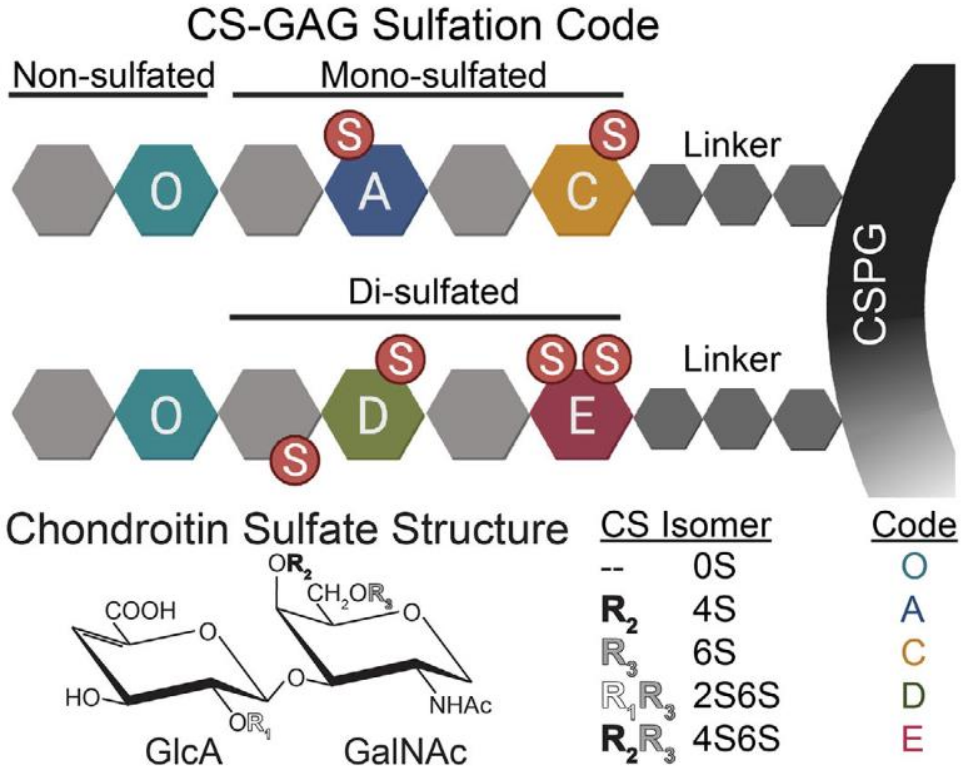




In the setting of diet-induced obesity, diabetes worsens intestinal barrier function and IBD outcomes

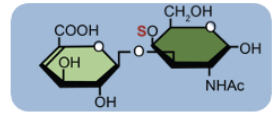
Extracellular Matrix in IBD:
Chondroitin Sulfate Glycosaminoglycan Code





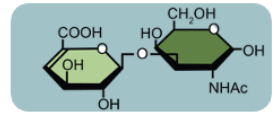
Matrix Stability

ΔA (4S-CS)



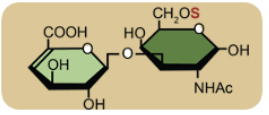
Diffusion

ΔO (0S-CS)

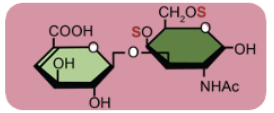


Inflammation

ΔC (6S-CS)

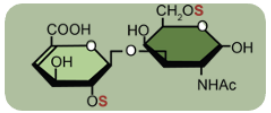


ΔE (4S6S-CS)

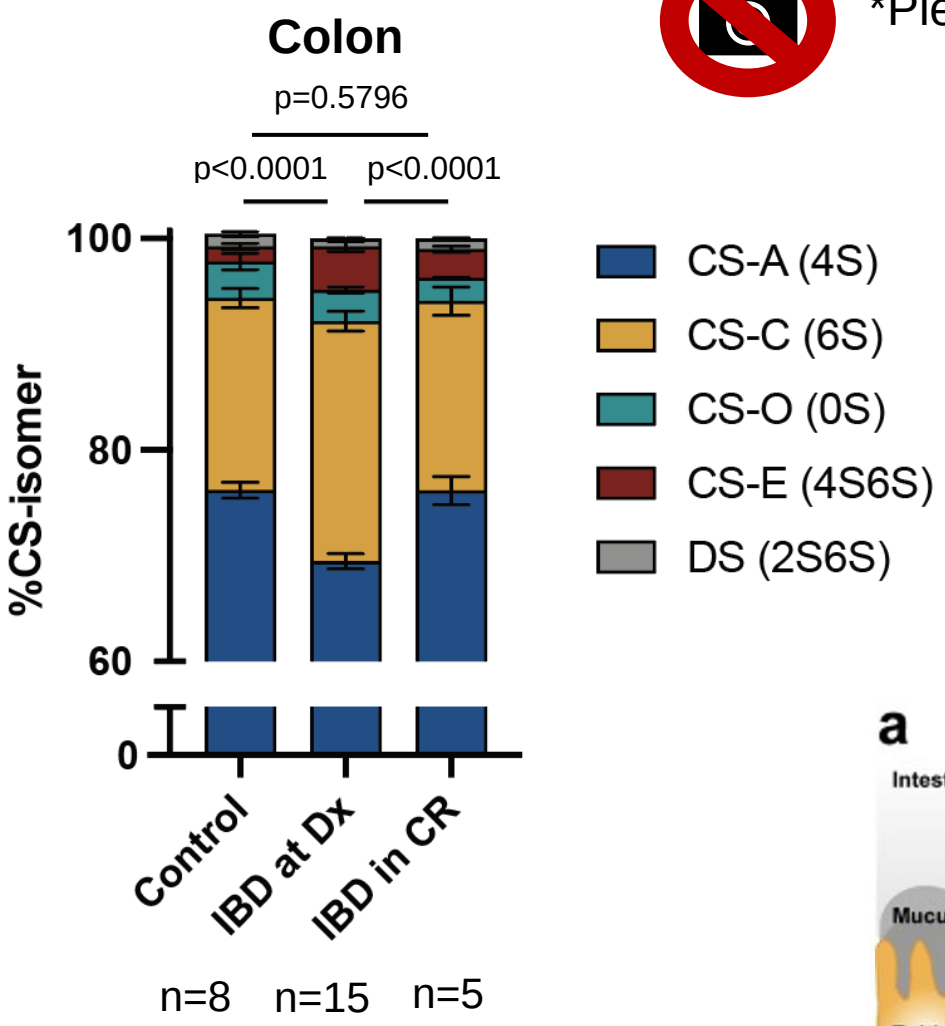


Tissue regeneration

ΔD (2S6S-CS)



Kendra Francis, MD Clinician Researcher



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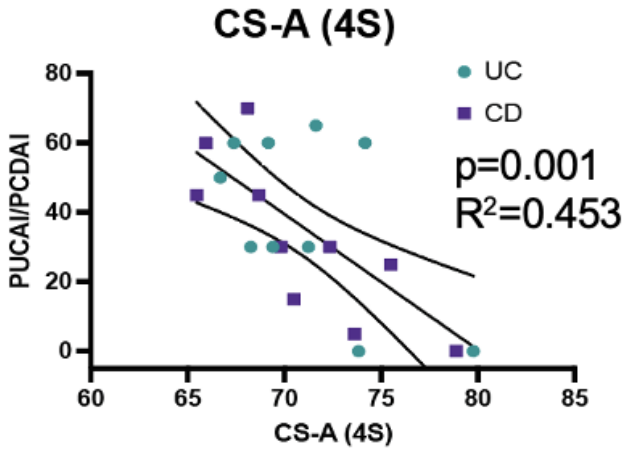

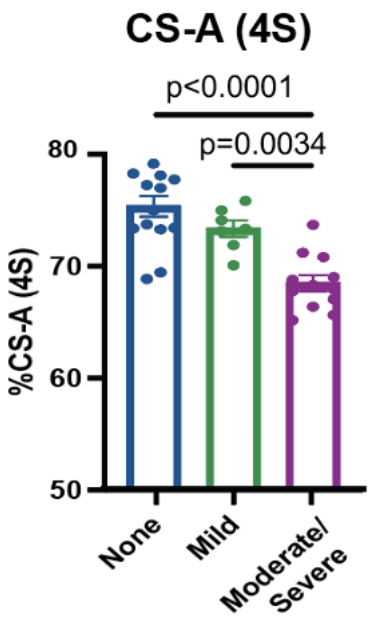

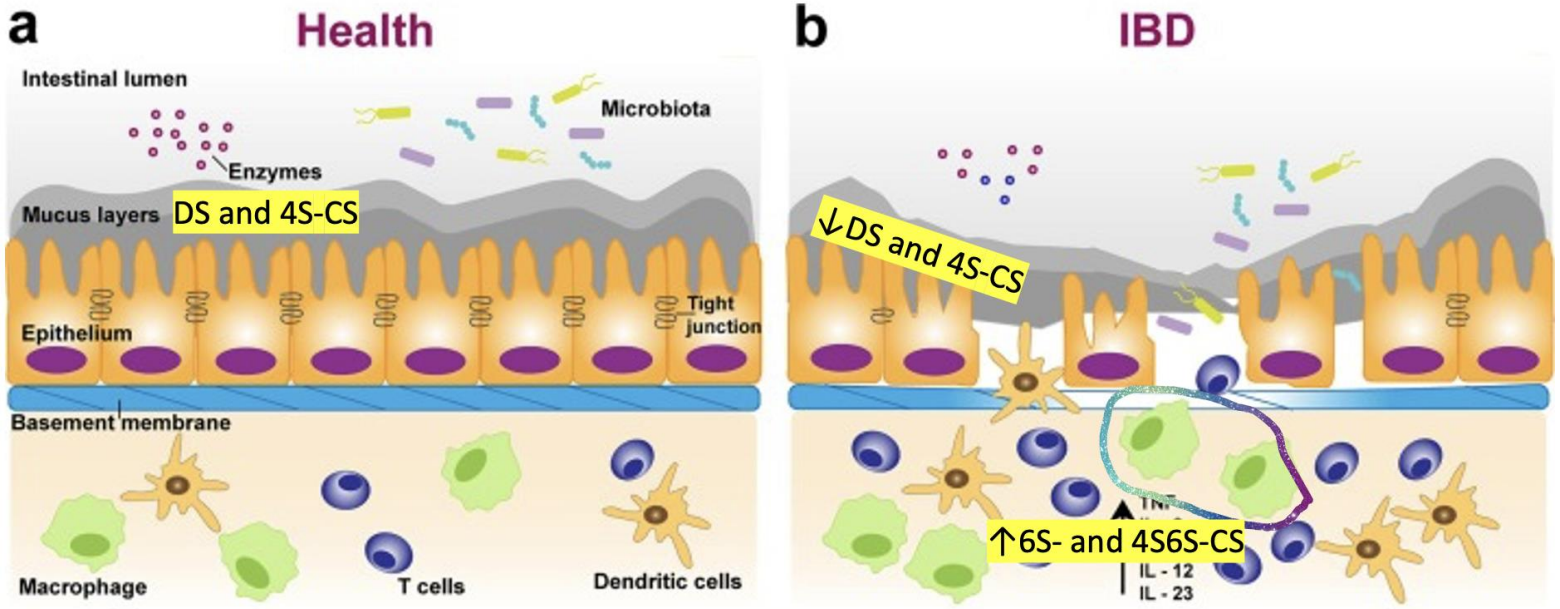

Kendra Francis, MD Clinician Researcher

Seattle Children's Airway and Esophageal Center

Multidisciplinary Aerodigestive Program

and

Tracheoesophageal Fistula/Esophageal Atresia Clinic

Michael K. Pickens, D.O., F.A.A.P.
Associate Professor of Pediatrics
Division of Gastroenterology
GI Medical Director of the Aerodigestive Program

- CARE Study (Congenital Anomalies Research Exploration):
  - This is a multicenter study with Columbia University, Boston Children's Hospital, and Cincinnati Children's Hospital and a collaboration with Pediatric Gastroenterology and Pediatric Surgery at SCH.
  - This study was created to improve our understanding of the genetic causes of birth defects.
  - Collecting saliva samples, blood samples, and tissue to evaluate for genetic mutations associated with TEF/EA congenital anomalies.
- Quality of Life Outcomes in TEF/EA Population:
  - Collaborative study with Pediatric Gastroenterology and Pediatric Surgery.
  - Enrolling 50 of our 168 patients and using PedsQOL Survery.
- A single center's retrospective study on TEF/EA Population and Outcomes:
  - Collaborative study between Pediatric Gastroenterology and Pediatric Surgery.
  - Aimed at looking at the possible associations between healthcare disparities and outcomes in TEF/EA patients.

Eosinophilic Associated Gastrointestinal Disorders (EGID)

Pediatric Gastroenterology Division

Michael K. Pickens, D.O., F.A.A.P.
Associate Professor of Pediatrics
Division of Gastroenterology
GI Medical Director of the Aerodigestive Program

- ENGAGE Study – Dupilumab for Eosinophilic Gastritis with or without Eosinophilic Enteritis:
  - Industry Sponsored Study with Regeneron and Sanofi.
  - Phase 2 Randomized Study.
  - Will have Phase 3 Arm to it as well.
- Emerging Therapeutics in Eosinophilic Gastrointestinal Disorders in Pediatrics:
  - Focusing on targeted biologic therapies: IL-4/IL-3 inhibitors, IL-5 inhibitors, anti-Siglec 8, anti-integrins, anti-TNF alpha, mast cell stabilizing medications.
- A retrospective single center study on Eosinophilic Esophagitis Treatment and Outcomes:
  - Comparing PPI, Dietary Therapy, and Swallowed Steroids.
- Eosinophilic Esophagitis and Healthcare Disparities:
  - Using Peds Quality of Life Questionnaire.
  - Evaluating racial differences, obstacles to access of care, and socioeconomic distribution.