UNIVERSITY OF ALBERTA

DEPARTMENT OF MEDICINE
FACULTY OF MEDICINE & DENTISTRY

ME2 MAJUMDAR RESEARCH & QUALITY IMPROVEMENT DAY

& QI DAY

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SCIENTIFIC ABSTRACTS

FULL ABSTRACTS ENCLOSED

Ajibulu, Lekan (Medical Student)
Case report: “Simpleness”: a qualitative description study exploring patient perspectives on the barriers and facilitators of using digital health tools to self-manage inflammatory bowel disease
Supervisor: Dr. Karen Wong (Gastroenterology)

Aliy, Jokha (Graduate Student)
Plant-derived extracellular vesicles and their potential role in the microbiome and bacterial infections
Supervisor: Dr. Carlos Cervera (Infectious Diseases)

Armbruster, Marie (Graduate Student)
Limited nesting as a preclinical model to study the psychoneuroimmunology of post-partum depression: A comparison of two mouse strains.
Supervisor: Dr. Paul Forsythe (Pulmonary Medicine)

Beghin, Justine (Graduate Student)
Probing potential therapeutic targets of Influenza’s polymerase using an aptameric approach
Supervisor: Dr. Vanessa Meier-Stephenson (Infectious Diseases)

Burgar, Jordyn (Graduate Student)
Implementing Physiotherapist-Pharmacist Collaborative Care for Knee OA: Methodological Insights from a Community-Based Pragmatic RCT
Supervisor: Dr. Ross Tsuyuki (Cardiology)

Carr, Alice (Postdoctoral Fellow)
Changes In Kidney Function After Islet Transplantation Using Calcineurin Inhibitor-Based Immunosuppression In A Single-Centre Cohort In Canada Over 20 Years
Supervisor: Dr. Peter Senior (Endocrinology & Metabolism)

Charlton, Maddison (Graduate Student)
Correlating biophysical properties of TDP-43 aggregates with clinical phenotypes in amyotrophic lateral sclerosis
Supervisor: Dr. Valerie Sim (Neurology)

Dembele, Kléouforo-Paul (Postdoctoral Fellow)
Nanotubes mediated mitochondria transfer from normal to cancer cells promotes Mesenchymal-to-Epithelial Transition (MET) required for metastasis in cancer
Supervisor: Dr. Evangelos Michelakis (Cardiology)

Elsayed, Manar (Graduate Student)
Validation of Administrative Data Case Definitions of Immune Checkpoint Inhibitor-associated Inflammatory Arthritis
Supervisor: Dr. Carrie Ye (Rheumatology)

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Gao, Yunfeng (Postdoctoral Fellow)
Increased effector memory RA T cells after resolution of recurrent Clostridioides difficile infection: a preliminary study
Supervisor: Dr. Dina Kao (Gastroenterology)

Hamie, Angela (Graduate Student)
Advancing BCMA-Targeted CAR NK Therapy Using Lipid Nanoparticle mRNA Delivery
Supervisor: Dr. Michael Chu (Hematology)

Jarvis, Catherine (Graduate Student)
An Analysis of Patient Recovery and Opinions on Driving Post Transcatheter Aortic Valve Insertion (TAVI): The TAVI-D Study
Supervisor: Dr. Robert Welsh (Cardiology)

Karthivashan, Govindarajan (Research Fellow)
Therapeutic window of native PLGA nanoparticles in the 5xFAD mouse model of Alzheimer's disease
Supervisor: Dr. Satyabrata Kar (Neurology)

Kornuta, Claudia (Postdoctoral Fellow)
PAR-2 activating peptide as mucosal adjuvant improves immune cell recruitment to the lymph nodes and activation
Supervisor: Dr. Harissios Vliagoftis (Pulmonary Medicine)

Leung, Dixon (Resident)
Exploring Hereditary Hemorrhagic Telangiectasia: How Rectal Bleeding Led to a New Diagnosis
Supervisor: Dr. Dilini Vethanayagam (Pulmonary Medicine)

Liu, Shania (Postdoctoral Fellow)
Why do patients stop taking their glucagon-like peptide-1 receptor agonists?
Supervisor: Dr. Ross Tsuyuki (Cardiology)

Lubachowski, Mathew (Graduate Student)
Anaphase Promoting Complex Activation with C43-4 Peptide Reduces Aberrant Substrate Accumulation in Aging and Aging Associated Diseases
Supervisor: Dr. Troy Harkness (Geriatric Medicine)

Ma, Chen Hsiang (Resident)
Guideline Directed Medical Therapy in Heart Failure Patients with Advanced Chronic Kidney Disease: A Prospective Study from the Heart Function Clinic Registry
Supervisor: Dr. Gavin Oudit (Cardiology)

MacKay, Scott (Resident)
Multifaceted STRIDE II-Based Monitoring for Inflammatory Bowel Disease Advanced Therapy Starts
Supervisor: Dr. Brendan Halloran (Gastroenterology)

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Mandal, Shivani (Graduate Student)
Chronic airway inflammation drives sex-specific changes in behaviour, neuroinflammation and gut microbiota
Supervisor: Dr. Paul Forsythe (Pulmonary Medicine)

Mann-Nuttel, Ritu (Postdoctoral Fellow)
Cultured human Pulmonary neuroendocrine cells stimulated with House dust mite allergen activate Innate lymphoid cells 2 and classic Dendritic cells
Supervisor: Dr. Paul Forsythe (Pulmonary Medicine)

Marriott, Hazel (Graduate Student)
Altered upper airway alarmin cytokine expression in response to biologic treatment in severe asthma
Supervisor: Dr. Paige Lacy (Pulmonary Medicine)

Nabavi Rad, Ali (Graduate Student)
Donor Microbiota Induced Complement Component 3 (C3) Production Contributes to Fecal Microbiota Transplantation (FMT) Efficacy in Patients with Recurrent Clostridioides Difficile Infection (rCDI)
Supervisor: Dr. Dina Kao (Gastroenterology)

Nanoa, Joseph (Graduate Student)
Activation of the Glycolytic Enzyme Triose Phosphate Isomerase is a Viable Therapeutic Strategy to Improve Ex-Situ Heart Perfusion: Implications For Cardiac Transplantation
Supervisor: Dr. Gopinath Sutendra (Cardiology)

Omkar, Ayushi (Graduate Student)
Behaviour change techniques in e-Health interventions for older and/or frail/sarcopenic adults: A systematic review and meta-analysis
Supervisor: Dr. Puneeta Tandon (Gastroenterology)

Osness, Emma (Graduate Student)
Markerless Motion Capture Parameters Associated with Fall risk and/or frailty: A Scoping Review
Supervisor: Dr. Puneeta Tandon (Gastroenterology)

Patel, Kinjal (Clinical Fellow)
Improving Cirrhosis Identification: Evaluation of ICD-10 Codes and Development of a Hybrid Algorithm for Enhanced Accuracy in Alberta's Healthcare System
Supervisor: Dr. Puneeta Tandon (Gastroenterology)

Paul, Pallabi (Postdoctoral Fellow)
Native PLGA nanoparticles inhibit Tau seed-induced Amyloid β1-42 aggregation: Implications of cross-seeding in Alzheimer's disease pathology
Supervisor: Dr. Satyabrata Kar (Neurology)

Piao, Jiyuan (Graduate Student)
From snails to mammals: discovery of an activator of the evolutionarily conserved PHLPP1 that promotes features of quiescence and hibernation in mouse cells and hearts
Supervisor: Dr. Evangelos Michelakis (Cardiology)

Rahemtulla, Kahir (Resident)
Comorbid Heart Failure and Short-Term Outcomes After Hospitalization for AECOPD
Supervisor: Dr. Mohit Bhutani (Pulmonary Medicine)

Raiesdana, Somayeh (Postdoctoral Fellow)
A pilot randomized trial on the usability and safety of an app (MyIBDDiet) to improve the self-management of anti-inflammatory diet for individuals with inflammatory bowel disease: Protocol
Supervisor: Dr. Karen Wong (Gastroenterology)

Rullay, Alisha (Graduate Student)
Prospective evaluation of diaphragm structure and function in double lung transplant recipients with baseline lung allograft dysfunction
Supervisor: Dr. Kieran Halloran (Pulmonary Medicine)

Rullay, Alisha (Graduate Student)
Health-related quality of life and exercise capacity in double lung transplant recipients with baseline lung allograft dysfunction
Supervisor: Dr. Kieran Halloran (Pulmonary Medicine)

Rullay, Alisha (Graduate Student)
Predicting baseline lung allograft dysfunction in double lung transplant recipients based on pre-and peri-operative characteristics
Supervisor: Dr. Kieran Halloran (Pulmonary Medicine)

Seyyedi, Noorossadat (Graduate Student)
p53 associated de novo activation of VWF expression in tumor cells
Supervisor: Dr. Nadia Jahroudi (Hematology)

Shagani, Thisairajah (Graduate Student)
Does steatotic liver disease influence treatment response and clinical outcomes in primary biliary cholangitis?
Supervisor: Dr. Ellina Lytvyak (Preventive Medicine) & Dr. Aldo Montano-Loza (Gastroenterology)

Shaheen, Mohamed (Postdoctoral Fellow)
Effects of dietary intake of stool donors and recipients of fecal microbiota transplantation on the gut bacterial diversity and clinical outcomes in recurrent Clostridioides difficile infection
Supervisors: Dr. Dina Kao (Gastroenterology)

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Sharma, Rahul (Resident)
Characterizing Patient Reported Outcome Measure Descriptions for Clinical Trials in Dialysis Registered on ClinicalTrials.gov
Supervisor: Dr. Sofia Ahmed (Nephrology)

Shreekumar, Devika (Graduate Student)
Management of obesity in a multimorbid patient population with chronic liver and gastrointestinal diseases is effective, safe and improves quality of life
Supervisor: Dr. Ellina Lytvyak (Preventive Medicine)

Shreekumar, Devika (Graduate Student)
PSC-specific prognostic scores associated with graft loss and overall mortality in recurrent PSC after liver transplantation
Supervisor: Dr. Ellina Lytvyak (Preventive Medicine)

Skoreyko, Jessica (Graduate Student)
Targeting Hepatitis B virus's cccDNA through repurposed GQ-binding ligands
Supervisor: Dr. Vanessa Meier-Stephenson (Infectious Diseases)

Suandork, Tanya (Research Fellow)
Homologous composition of plant- and human-derived extracellular vesicles (EVs) suggests a potential dietary origin of circulating plasma EVs
Supervisor: Dr. Carlos Cervera (Infectious Diseases)

Sun, Ning (Research Fellow)
Metabolic remodeling and Abnormal Mitochondrial Signaling in Primary Biliary Cholangitis
Supervisor: Dr. Andrew Mason (Gastroenterology)

Syed, Hussain (Graduate Student)
Machine Learning Predicts Response to Obeticholic Acid Therapy and Prognostic Pathways linked with Primary Biliary Cholangitis
Supervisor: Dr. Andrew Mason (Gastroenterology)

Tejay, Saymon (Graduate Student)
Tumour Initiated Purinergic Signalling Can Promote Cardiomyocyte RBFOX1 Degradation and Increase the Risk for Developing Cardiotoxicity from DNA Damaging Anticancer Agents
Supervisor: Dr. Gopinath Sutendra (Cardiology)

Tyagi, Varalika (Graduate Student)
SARS-COV-2 Prevention & Infection rates in SOT and Caregivers enrolled in TREAT-COVID
Supervisor: Dr. Dima Kabbani (Infectious Diseases)

Tyagi, Varalika (Graduate Student)
Norovirus and Sapovirus associated chronic diarrhea in SOT: Does Viral load correlate with severity of symptoms?
Supervisor: Dr. Dima Kabbani (Infectious Diseases)

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Umar, Narmeen (Resident)
Concomitant sarcopenia and myosteatosis in cirrhosis patients is associated with longer recovery and mortality after liver transplantation
Supervisors: Dr. Aldo Montano-Loza and Dr. Ellina Lytvyak (Gastroenterology)

van Lierop, Lisa (Graduate Student)
Long-term effectiveness and safety of ustekinumab dose escalation in patients with moderate-to-severe ulcerative colitis: a multicenter retrospective cohort study
Supervisor: Dr. Frank Hoentjen (Gastroenterology)

van Lierop, Lisa (Graduate Student)
Long-term outcomes of extended versus conventional adalimumab dose interval for patients with Crohn's disease in stable remission: 3-year follow-up of the randomized controlled LADI trial
Supervisor: Dr. Frank Hoentjen (Gastroenterology)

Waly, Doaa (Postdoctoral Fellow)
HBRV Seroprevalence and Immune Reactivity in Breast Cancer and Autoimmune Disease Patients
Supervisor: Dr. Andrew Mason (Gastroenterology)

Whitman, Brendan (Postdoctoral Fellow)
Composition and influence of Lyophilized Fecal Microbiota Transplantation (LFMT) or Lyophilized Sterile Fecal Filtrate (LSFF) on the human gut metaproteome following treatment of recurrent Clostridioides difficile infection
Supervisor: Dr. Dina Kao (Gastroenterology)

Zhang, Yongneng (Postdoctoral Fellow)
A critical contribution of cardiac myofibroblasts in RV failure and the role of UCP2 SNPs in the predisposition to RV decompensation in pulmonary arterial hypertension
Supervisor: Dr. Evangelos Michelakis (Cardiology)

Scientific Research Abstracts

“Simpleness”: a qualitative description study exploring patient perspectives on the barriers and facilitators of using digital health tools to self-manage inflammatory bowel disease

Lekan Ajibulu, BSc (Hons), Kaitlyn Delaney Chappell, MSc, Cynthia H. Seow, MBBS (Hons), Karen J. Goodman, PhD, Karen Wong, MD
Supervisor: Dr. Karen Wong

INTRODUCTION
Inflammatory Bowel Disease (IBD) is a chronic condition requiring ongoing self-management and frequent healthcare interactions. Digital health tools, such as MyIBDToolkit, can enhance disease management by providing real-time data and improving care coordination. However, there is limited evidence on patient perspectives regarding barriers and facilitators to their adoption.

METHODS
A qualitative descriptive study was conducted to explore patient experiences with MyIBDToolkit. Participants with a confirmed IBD diagnosis were recruited from clinics in Alberta, Canada. Virtual semi-structured interviews were conducted between June and July 2024. Thematic analysis was used to identify key themes, and member checking ensured credibility.

RESULTS
Eighteen participants were interviewed, reaching thematic saturation. Patients found MyIBDToolkit useful for tracking symptoms and improving communication with providers. However, key barriers included the burden of data entry, privacy concerns, and inconsistent engagement with the tool. Variability in provider adoption also affected patient experiences.

CONCLUSIONS
While digital health tools like MyIBDToolkit can enhance IBD self-management, addressing usability, privacy, and provider engagement is essential. Integrating patient feedback into tool development may improve adoption and long-term sustainability in chronic disease management.

“Simpleness”: A Qualitative Description Study Exploring Patient Perspectives on the Barriers and Facilitators of Using Digital Health Tools to Self-Manage Inflammatory Bowel Disease

Ajibulu et al., 2024 | *Inflammatory Bowel Disease*

AIM: evaluation of the patient-reported barriers and facilitators to the adoption of digital health tools in the context of IBD management.

METHODS

Study Design: Qualitative Description

Study Population: Participants > 18 years of age with IBD

Intervention: Semi-structured interviews about the use of digital health tools to self-manage their IBD

Results: 18 interviews conducted

Participant Outcomes

How would your care improve?

- Enhanced Monitoring for Patients
- Enhanced Monitoring for Providers
- Proactive and Streamlined Care

What are some of your challenges or concerns?

- Continued use of Digital Tool
- Engagement and Adoption
- Privacy Concerns

Barriers & Facilitators

Usability

- User Friendly interface
- Written and pre-made responses
- Technical Support
- Streamlined information

Accessibilty

- Mobile Accessibility
- Integration with existing digital health tools
- Offline Access
- Financially Feasible

This study highlights both the benefits and challenges of implementing digital health tools for IBD management, emphasizing the importance of addressing usability, engagement, and privacy concerns. Future efforts should focus on refining these tools with patient input to enhance their adoption and effectiveness across diverse populations.

Plant-derived extracellular vesicles and their potential role in the microbiome and bacterial infections

Jokha Aliy, Tanya Suandork, Carlos Cervera
Supervisor: Dr.Carlos Cervera

INTRODUCTION

The finding of plant starch-derived nanoparticles (SNPs) in the urine of healthy participants and ascitic fluid of cirrhotic patients prompted us to review their role in the human microbiome, as these were most of the bacteria-like structures found in bacteria DNA-rich fluids. We found most SNPs contain a lipidic bilayer membrane, similarly to human extracellular vesicles (EVs). The purpose of this study was to investigate their role in the human microbiome and their potential implication in bacterial infections.

METHODS

To visualize the expel of SNPs from starch granules upon hydration, we fixed dry starch granules using epoxy resin on 0.13 mm thick glass coverslip mounted on cell culture plates. Live microscopy was done using an EVO M5000 microscope. SNPs were obtained by hydration of common alimentary legumes and pseudograins (lentil, chickpea and quinoa) and centrifugation. DNA extraction was done by phenol:chloroform protocol to undergo 16S sequencing. Cell culture experiments were performed using HeLa cells. Cell imaging was done using a Leica Stellaris 8 confocal microscope (cell imaging core facility).

RESULTS

We observed SNPs originated from starch granules in different starchy plants. The Amplicon Sequence Variants (ASV) identified from the pellet were mostly composed of chloroplast and mitochondrial DNA. A small proportion of bacterial sequences was also identified (Actinobacteriota, Bacteriodota, Firmicutes and Proteobacteria, among others), while cultures only grew different Bacillus spp. SNPs (or plant EVs) were endocytosed by cells, acquiring the host cell membrane upon endocytosis. We found plant EVs competent for bacterial DNA translocation. By transformation with different bacterial DNA we could induce intracellular bacterial aggregates.

CONCLUSIONS

Plants mitochondria and chloroplasts are common in the human diet. Their ability to translocate DNA may contribute to our knowledge of the human microbiome and bacterial infections

Limited nesting as a preclinical model to study the psychoneuroimmunology of post-partum depression: A comparison of two mouse strains.

Marie Armbruster, Shivani Mandal, Ritu Mann-Nuttel, Paul Forsythe
Supervisor: Dr. Paul Forsythe

INTRODUCTION

Postpartum depression (PPD) is a mood disorder that affects the ability of a mother to engage with and care for their infant. Stress exposure is a major predisposing factor for PPD, while immune factors may also influence development of this disorder. Here we assessed the limited nesting paradigm (LN) as a potential model to investigate the relationship between stress and the immune system in PPD in two mouse strains.

METHODS

Dams (C57BL6J, BALB/cJ) and pups were exposed to LN from post-natal day 3-9, while controls had standard cages. Maternal behaviour was determined over the LN period followed by assessment of self-care behaviour using the splash test. Gene expression in brain regions and the peripheral immune profile were characterized. Unpaired t-test or Mann Whitney test were performed for statistical analyses.

RESULTS

LN exposure increased negative maternal behaviour ($p=0.0039$, $n=10\text{-}11$) and decreased active nursing ($p=0.0165$) in C57BL6J, but did not significantly alter these behaviours in BALB/cJ dams. Self-care behaviour was unaltered by LN in C57BL6J while BALBC/cJ exhibited decreased frequency of grooming ($p=0.0362$, $n=9\text{-}10$). In association with altered maternal behaviour, C57BL6J dams had lower expression of BDNF in the prefrontal cortex ($p=0.0021$) and increased expression of oxytocin ($p=0.0018$), oxytocin receptor ($p=0.0010$) and vasopressin ($p=0.0087$) in the hypothalamus, changes that were absent in BALB/cJ dams. LN increased T regulatory cells in C57BL6J mice ($p=0.0014$) while Th17 cells were decreased ($p=0.0524$), but BALB/cJ LN mothers only demonstrated a decrease in Th17 ($p=0.0077$).

CONCLUSIONS

LN results in increased aggression towards pups in C57BL6J mice, associated with brain circuitry and immune alterations while maternal behaviour and associated brain circuitry was unaltered in BALB/cJ. Overall, our study indicates that LN in C57BL6J mice may be a useful model to study the neuroimmune relationships in certain aspects of PPD while BALB/cJ mice may provide some insight into resistance to post-partum stress.

Probing potential therapeutic targets of Influenza's polymerase using an aptameric approach

Justine Beghin, Kira Sviderskaia, Kuldeep Kaur, Lorne Tyrrell, and Vanessa Meier-Stephenson
Supervisor: Dr. Vanessa Meier-Stephenson

INTRODUCTION

Influenza viruses cause an annual estimate of >1 billion infections and 500,000 deaths worldwide and remains a leading concern for pandemic potential. The viral genome is comprised of eight segments, each with an attached viral polymerase (FluPol) that facilitates both replication and transcription. These processes are essential and highly conserved among influenza strains, making them promising therapeutic targets. One approach for novel therapeutic development is through aptamer screening. Aptamers are short, stable oligonucleotides that fold into distinct shapes to allow selective target binding, without prior knowledge of binding sites. Can an aptamer-based approach be used to develop a small molecule therapeutic that binds to and decreases activity of FluPol?

METHODS

The FluPol complex of Influenza B (for initial optimization of the strategy) was produced using the Spodoptera frugiperda 9 (Sf9) insect cell line in the MultiBac system and purified using affinity column chromatography. Fluorescent-based in vitro replication and transcription functional assays were performed to test protein functionality after purification. The complex was then subjected to systematic evolution of ligands by exponential enrichment (SELEX) experiments to determine aptamer hits that can bind FluPol. FluPol paired with top aptamer hits will undergo replication and transcription assay testing to determine if their binding results in an impact on FluPol's function.

RESULTS

Production and purification of FluPol has been successful. The presence of the three subunits has been confirmed via SDS-PAGE and protein agarose; and functionality testing confirms the FluPol is functional. The first replicate of SELEX has been completed, and sequencing of the final aptamer pool is underway. Once sequences are determined, binding and functional assays of aptamer-FluPol complexes will be performed.

CONCLUSIONS

Using an aptamer-based SELEX approach provides an unbiased strategy to probe for therapeutic target sites in new and emerging pathogens, including influenza viruses.

Implementing Physiotherapist-Pharmacist Collaborative Care for Knee OA: Methodological Insights from a Community-Based Pragmatic RCT

Dr. Ross Tsuyuki, PharmD, MSc; Dr. Allyson Jones, PT, PhD; Jill Hall, BScPharm, ACPR, PharmD; Dr. Claire Barber, MD, PhD, FRCPC; Dr. Doug Klein, MD, CCFP, MSc
Supervisor: Dr. Ross Tsuyuki

INTRODUCTION

Early knee osteoarthritis (OA) is often underdiagnosed, with many individuals relying on over-the-counter medications. As highly accessible healthcare providers in the community, pharmacists can screen for OA and facilitate multidisciplinary care. This study proposes a pharmacist-physiotherapist collaborative model to manage early stage knee OA. We discuss the methodological challenges in assembling this pragmatic randomized control trial (RCT) in the community for OA care.

METHODS

The objective of the primary study is to evaluate the effectiveness of a 3-month pharmacist-physiotherapist collaboration in reducing pain and functional limitations in early knee OA patients. A prospective, pragmatic RCT is conducted across urban and rural Alberta in pharmacies partnered with local physiotherapy clinics. A total of 125 patients will be randomized to either the intervention or usual care group. The intervention includes a comprehensive pharmacist assessment, medication review, and referral to physiotherapy for an evidence-based group exercise program for knee OA. The usual care group receives a brief pharmacist assessment, non-prescription recommendations, and an education pamphlet. Usual care participants may opt into the intervention at 3 months. Follow-up occurs at 3 and 6 months post-intervention.

RESULTS

Outcomes will be assessed using OA disease-specific measures, self-management measures, physiotherapy adherence, and patient-reported satisfaction. We encountered a few methodological challenges. Careful consideration was required to decide whether to randomize at the participant or site level. Additionally, maintaining the participation of usual care participants necessitated a delayed intervention option. Lastly, a lack of tools for communication and collaboration for non-physicians led to the development of a platform for data collection and documentation, as well as a survey to measure clinician collaboration.

CONCLUSIONS

Addressing these challenges provides insights into implementing pragmatic RCTs in community settings. Findings may inform future healthcare models that enhance accessibility, self-management, and quality of life for individuals with chronic conditions like OA.

Changes In Kidney Function After Islet Transplantation Using Calcineurin Inhibitor-Based Immunosuppression In A Single-Centre Cohort In Canada Over 20 Years

Alice L. J. Carr, Ph. D; Braulio A. Marfil-Garza, Ph. D; Ying Ling, MD; Richard A. Oram, Ph. D; Tolulope O. Olateju, MD; Anna Lam, MD; Khaled Dajan, MD; Blaire Anderson, MD; Doug O'Gorman, BSc; Tatsuya Kin Ph. D; David Bigam, MD; Sofia B. Ahmed MD;
Supervisor: Dr. Peter Senior

INTRODUCTION
INTRODUCTION
Islet transplantation alone (ITA) is an established treatment for severe hypoglycemia in type 1 diabetes, requiring nephrotoxic, calcineurin-based immunosuppression. The long-term effects of ITA on kidney function, including impact of successive infusions, existing reduced function or sex, remain unclear.

METHODS
METHODS
We analysed data from 223 adults receiving ITA (41% male) at the University of Alberta Hospital between 1999-2019, evaluating kidney function by estimated glomerular filtration rate (eGFR). Mixed-effects models assed eGFR slopes overtime (ml/min/1.73m-2/year), stratified by sex and baseline eGFR. Acute eGFR changes were assessed within 3 months per infusion. Risks of Stage 3b and Stage 4 chronic kidney disease (CKD) or greater were evaluated using Cox and Fine-Grey regression.

RESULTS
RESULTS
Overall, eGFR declined rapidly in the first-year post-transplant (-11.52 [95% CI -13.92,-8.9]), which attenuated before stabilising beyond 5 years (1-5y: -3.12 [95% CI -3.84,-2.28]; 5-20y: -1.08 [95% CI, -1.80,-0.36]). Females experienced greater first-year declines in eGFR than males (-14.79 [95% CI -17.92,-11.66] vs. -6.75 [95% CI -10.49,-3.01];p=0.0012) with similar decline subsequently. Risk of Stage 4 CKD or greater was significantly higher for females (SHR 6.66 [95% CI 1.32,33.33];p=0.023). Individuals with baseline eGFR <60 ml/min/1.73m-2 (established CKD) had less initial eGFR decline, (-3.99 [95% CI -13.31,5.33] vs. -12.03 [95% CI -14.57,9.49];p=0.1) but were at increased risk of progression to Stage 4 CKD or greater (SHR 54.5 [95% CI 8.03,369];p<0.0001). Female sex, established CKD, more acute kidney injuries in the first year and older age were independent risk factors for Stage 3b CKD.

CONCLUSIONS
CONCLUSIONS
While ITA with initiation of calcineurin-based immunosuppression induces rapid first-year eGFR decline, decline slows significantly beyond 5 years. Sex and pre-existing kidney function are key factors in long-term outcomes, which may guide risk-benefit discussions for ITA candidates and may inform sex-specific immunosuppression strategies to enhance safety and outcomes. Calcineurin-free immunosuppression remains an urgent need.

Correlating biophysical properties of TDP-43 aggregates with clinical phenotypes in amyotrophic lateral sclerosis

Maddison Charlton, Satish Nemani, Leonardo Cortez, Helen Huang, Valerie Sim
Supervisor: Valerie Sim

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a clinically heterogeneous disease, varying in upper and lower motor neuron involvement, onset region (limb vs. bulbar), and progression rate. Despite the variability, most ALS cases share a common pathology: cytoplasmic inclusions of transactive response DNA binding protein 43 kDa (TDP-43). Whether pathology arises from TDP-43 mislocalization, aggregation, or both remains unclear. TDP-43 aggregates also appear in frontotemporal dementia (FTD) and LATE, with evidence suggesting distinct TDP-43 conformations in the pathology of FTD versus ALS. These may influence disease phenotype similarly to prion strain effects. We propose using prion strain-typing methods to assess whether TDP-43 aggregates from different disease phenotypes have distinct biophysical properties, including size distribution and seeding efficiency.

METHODS

We are comparing the biophysical properties of TDP-43 aggregates from ALS and LATE
brain regions. As pathological TDP-43 is cytoplasmic, we use protocols to isolate both normal and phosphorylated TDP-43 (pTDP-43) using pTDP-43-specific antibodies. Size distributions are determined using asymmetric flow field-flow fractionation (AF4). Seeding properties are assessed via real-time quaking-induced conversion (RT-QuIC) using whole brain homogenates, cytoplasmic fractions, and purified samples with a truncated TDP-43 substrate.

RESULTS

We have successfully optimized protocols for isolating pathological TDP-43 after extensive testing of various conditions. Current efforts are focused on preparing samples for RT-QuIC to evaluate seeding efficiency.

CONCLUSIONS

Following RT-QuIC, samples will undergo AF4 to determine aggregate sizes. We will then analyze additional ALS cases with different onset regions to explore correlations between TDP-43 structure and clinical phenotype. This may provide insights into disease mechanisms and guide therapeutic development.

Nanotubes mediated mitochondria transfer from normal to cancer cells promotes Mesenchymal-to-Epithelial Transition (MET) required for metastasis in cancer

Kléouforo-Paul DEMBELE, Alois Haromy, Yuan-Yuan Zhao, Jiyuan Piao, Yongsheng Liu, Gopinath Sutendra, Evangelos D. Michelakis
Supervisor: Dr. Evangelos D. Michelakis

INTRODUCTION

Tumor metastasis is often incurable and fatal. To metastasize, cancer cells receive signals from their microenvironment to initiate Epithelial to Mesenchymal Transition (EMT). But to form metastatic colonies, EMT cells must undergo MET to regain an epithelial phenotype, a less well understood process than EMT. We recently published how mitochondrial signals remodel the cytoskeleton during EMT and how the mitochondrial enzyme Pyruvate Dehydrogenase (PDH) promotes histone acetylation. Here, we hypothesize that uptake of mitochondria via nanotubes by cancer cells from the microenvironment cells, triggers epigenetic changes leading to an induction of MET, promoting colonization, in accordance to the local metabolic environment.

METHODS

We used lentiviral technology to generate stable cells with fluorescent mitochondria and established coculture models of lung cancer with liver epithelial cells. Standard and advanced techniques, including high-resolution microscopy, Fluorescence-Activated-Cell-Sorting, Seahorse-Metabolic assay, Chromatin-immunoprecipitation, Western blot, and RT-qPCR, were used to explore our hypothesis.

RESULTS

We found that EMT cells, with higher γ-tubulin levels, had significantly more, larger and longer nanotube connections, allowing them to uptake intact mitochondria/PDH from liver epithelial cells. We demonstrated that uptake of intact mitochondria not only significantly enhances the metabolic activity of cancer cells, but also boosts the MET/EMT hybrid state (E-Cadherin, N-Cadherin, Snail), stress/colonization marker expression (ATF4, NRF2), as well as acetylation process (ac-H3, PDH, P300). Interestingly, in cocultured cancer cells, we found elevated histone acetylation at the promoter region of ATF4. Moreover, a specific γ-tubulin inhibitor significantly prevents nanotube formations, mitochondria uptake and strongly decreases the expression of acetylation actors and ATF4 without obviously affecting the hybrid state.

CONCLUSIONS

These findings suggest that the cancer microenvironment promotes change in cancer cells phenotype, and γ-tubulin-enriched nanotubes are required in intact mitochondria/PDH transfer and acetylation to trigger epigenetic changes that facilitate MET process to colonize the distant organ.

Validation of Administrative Data Case Definitions of Immune Checkpoint Inhibitor-associated Inflammatory Arthritis

Manar Elsayed, Zoe Hsu, Carrie Ye.
Supervisor: Dr. Carrie Ye

INTRODUCTION
Immune checkpoint inhibitors (ICIs) are used for treating numerous malignancies by blocking the intrinsic inhibitors of immunity. However, they may have off-target effects called immune-related adverse events (irAEs). ICI-inflammatory arthritis (ICI-IA) is one of the most common rheumatic irAEs (Rh-irAEs). To date, there are no validated ICD-code-based administrative database case definitions of ICI-IA. This study aims to validate ICD-code-based case definitions for identifying ICI-IA.

METHODS
We conducted a retrospective cohort study using the Alberta CanRIO database of patients with Rh-irAEs, linked to provincial administrative health data. ICI-IA was defined as a new onset of at least one swollen joint or synovitis on imaging following ICI exposure, without another cause or pre-existing IA. We used ICD-9 and ICD-10 codes that represent IA. Seven primary algorithms of different combinations of outpatient and hospitalization codes were tested for sensitivity and specificity. Results were further evaluated stratified by sex.

RESULTS
A total of 228 patients were included in the final analysis: 100 with ICI-IA and 128 without. Sensitivity across all algorithms tested ranged from 3.8 (95% CI: 0.1, 7.5) to 86.7 (95% CI: 80.2, 93.2), while specificity ranged from 89.4 (95% CI: 84.0, 94.9) to 99.2 (95% CI: 97.6, 100.0). The algorithm requiring ≥1 outpatient IA ICD code achieved the best balance of sensitivity(86.7, 95% CI: 80.2, 93.2) and specificity (89.4, 95% CI: 84.0, 94.9). Including inpatient-based algorithms and the NACRS database did not improve performance. Moreover, performance was similar between sexes.

CONCLUSIONS
A simple outpatient-based algorithm showed good sensitivity and specificity at identifying ICI-IA cases, which can be used to conduct population-level studies on ICI-IA.

Increased effector memory RA T cells after resolution of recurrent Clostridioides difficile infection: a preliminary study

Yunfeng Gao, Chelsea McDougall, Rose Franz, Karen Wong, Dina Kao
Supervisor: Prof. Dina Kao

INTRODUCTION

Fecal microbiota transplantation (FMT) is the most efficient therapy for recurrent Clostridioides difficile infection (rCDI); however, the mechanisms underpinning its efficacy remains poorly understood. Bacterial engraftment and bacterially derived metabolites are thought to be key mechanisms. Emerging evidence suggests that FMT not only restores microbiome diversity but also directly influences host immune responses. We aimed to interrogate the dynamic changes of CD4+ T cells following resolution of rCDI.

METHODS

We utilized longitudinally collected samples from a randomized clinical trial which compared lyophilized FMT (LFMT) and lyophilized sterile fecal filtrate (LSFF) to prevent rCDI. The success rate of preventing rCDI assessed at week 8 was 87.9% in the LFMT group and 65.3% in the LSFF group. Peripheral blood mononuclear cells (PBMC) were collected at week 0, week 1, and week 8 from 3 successfully treated patients in the LFMT group and 4 in the LSFF group. To profile immunophenotypical changes in CD4+ T cells, flow cytometry staining was performed.

RESULTS

We found that 2/3 (66%) in the LFMT group and 1/4 (25%) in the LSFF had increased Effector memory RA T cells (EMRAs: CD4+, CD45RA+ , CD62L-, CD45RO-) accompanied by decreased naïve T cells (CD4+, CD45RA+, CD62L+, CD45RO-) in total CD4+ T cells, and no significant changes were observed in Central Memory T cells (CD4+, CD45RO+, CD62L+), Effector Memory T cells (CD4+, CD45RO+, CD62L-) and transitional B cells (CD19+, CD24highCD38high) populations. These preliminary results suggest that donor microbiota-induced host immune response mediated by EMRAs may play a vital role in establishing microbial homeostasis and colonization resistance.

CONCLUSIONS

Our preliminary finding shows the host-microbial interaction through EMRAs may play a key role in efficacy underpinning FMT in rCDI.

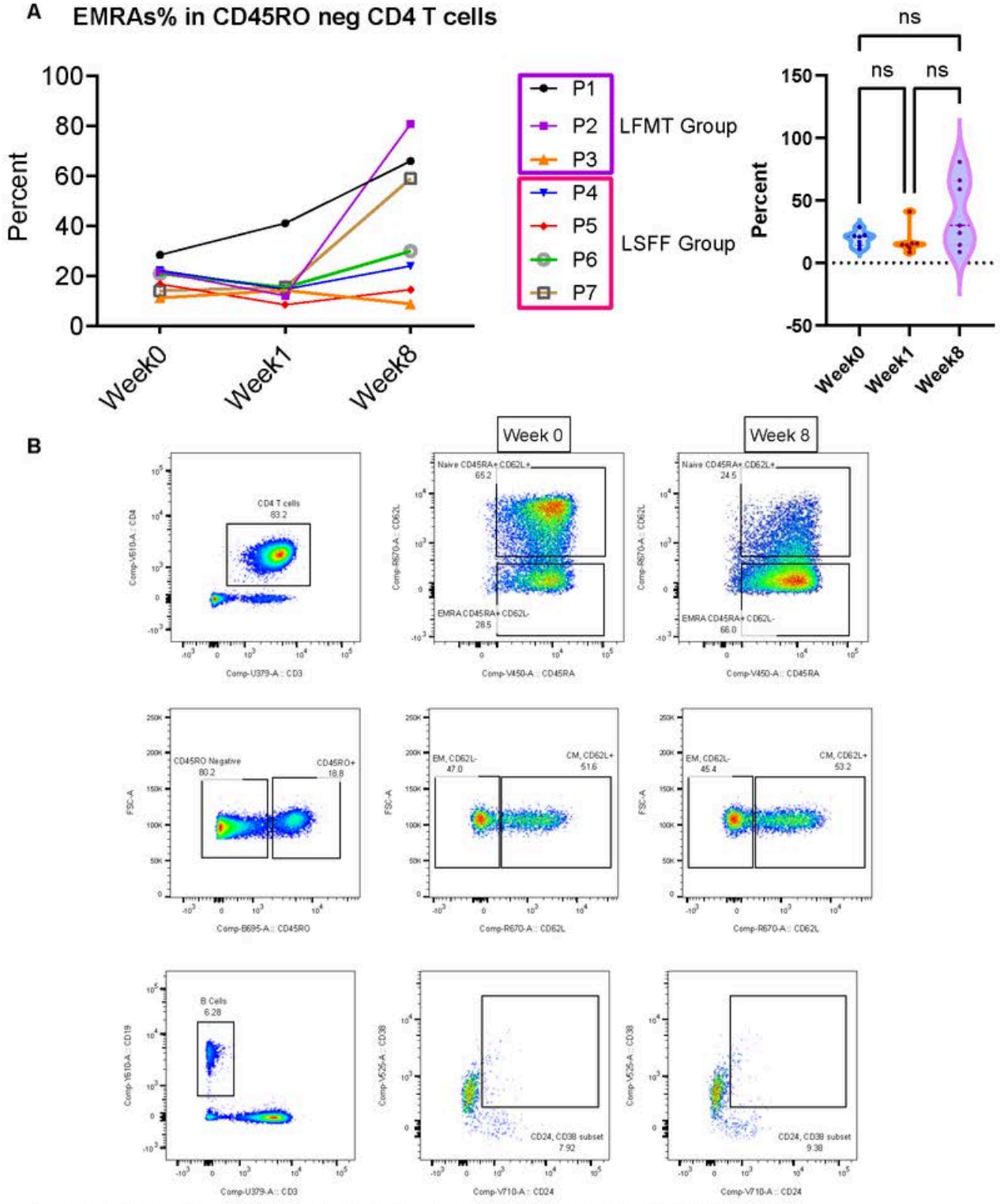

Figure 1, Dynamic changes of CD4+ T cells in patients derived PBMCs.
(***A***) The temporal dynamics of EMRAs within patients' peripheral $CD4^+$, $CD45RO^-$ T cells of rCDI patients receiving LFMT versus LSFF. P1-P3 represent patients receiving LFMT treatment, and P4-P7 represent patients receiving LSFF treatment. (***B***) The inverse relationship between naïve and EMRA following successful treatments. These panels illustrate representative data from flow cytometry results, with an increased proportion of EMRA cells ($CD4^+$, $CD45RO^-$, $CD62L^-$, $CD45RA^+$) accompanied by the decreased proportion of naïve T cells ($CD4^+$, $CD45RO^-$, $CD62L^+$, $CD45RA^+$) from base-line to week 8. No statistical differences observed in Central Memory T cells ($CD4^+$, $CD45RO^+$, $CD62L^+$), Effector Memory T cells ($CD4^+$, $CD45RO^+$, $CD62L^-$) and transitional B cells ($CD19^+$, $CD24^{high}CD38^{high}$) populations.

Advancing BCMA-Targeted CAR NK Therapy Using Lipid Nanoparticle mRNA Delivery

Angela Hamie, Bee Tan, Justine Lai, Carina-Debes Marun, Xiuxing Hu, Curtis Hodge, Twinkle Joy, Glen Jickling, Pankaj Tailor, Michael Chu
Supervisor: Michael Chu

INTRODUCTION

Chimeric Antigen Receptor (CAR) T cell therapy has demonstrated promise in treating multiple myeloma (MM), however, it carries risks including T cell malignancies, high relapse rates, cytokine release syndrome (CRS), and neurotoxicity. Viral vector-based delivery methods pose additional risks, including immune reactions and insertional mutagenesis. Alternatively, CAR-Natural Killer (NK) cells offer a safer option, with reduced toxicity and the potential for "off-the-shelf" use without HLA matching. Furthermore, lipid nanoparticles (LNPs) provide a non-viral, cost-effective method for delivering therapeutic mRNAs, enabling safe, efficient, and scalable production for CAR therapies.

METHODS

Anti-BCMA mRNA CAR constructs, consisting of a single-chain fragment variable (scFv) IgH recognizing BCMA, CD8 transmembrane domain, 4-1BB intracellular signaling domain, and CD3ζ chain, were encapsulated in LNPs (Nano spark precision instrument) and transfected into NK cells isolated from patient and healthy donors. LNP's were characterized for size, polydispersity index and encapsulation efficiency. mRNA LNP delivery efficiency was assessed using fluorescent microscopy and flow cytometry. Functional assays will evaluate the cytotoxicity of modified NK cells against BCMA-expressing MM cell lines (RPMI 8226 and KMS12).

RESULTS

A combination of lipid 5, β-Sitosterol, DSPC, and PEG 2000 (50:38:10:2) demonstrated superior transfection efficiency in primary NK cells compared to traditional ionizable lipids such as SM102, MC-3, and cholesterol. 40-60% GFP mRNA transfection efficiencies were achieved in patient-derived NK cells expanded in vitro over 7-10 days. Anti-BCMA CAR expression was confirmed via flow cytometry, western blot, and fluorescent microscopy. Current studies are evaluating the killing efficiency of the modified NK cells against MM cell lines.

CONCLUSIONS

Optimized mRNA LNP encapsulation allowed for high transfection efficiencies in primary NK cells, confirming the feasibility of this non-viral approach for CAR therapy. This safer alternative to viral vector-based CAR-T therapy supports the development of allogenic CAR-NK therapies as a promising treatment for MM, with the potential to improve cancer patient outcomes.

An Analysis of Patient Recovery and Opinions on Driving Post Transcatheter Aortic Valve Insertion (TAVI): The TAVI-D Study

Catherine R. Jarvis, Pishoy Gouda, Justin Ezekowitz, Benjamin Tyrrell, Robert C. Welsh
Supervisor: Dr. Robert C Welsh

INTRODUCTION

Transcatheter aortic valve insertion (TAVI) is heralded for being minimally invasive and having a shorter recovery when compared to surgical aortic valve replacement (SAVR). In 2023, the Canadian Cardiovascular Society (CCS) published a one-month driving guideline for TAVI and SAVR. A 2024 Canadian physician survey study showed overwhelming support for a shorter TAVI guideline.

METHODS

An observational clinical assessment of TAVI patient recovery was conducted from June 2024 to January 2025 at the Mazankowski Alberta Heart Institute. Enrolled post-TAVI (30-90 days) patients also completed a 17-question survey examining one-month recovery and opinions on driving.

RESULTS

The study included 111 participants. 96.4% received transfemoral (TF) TAVI. All patients (n=20) requiring pacemaker insertion were symptomatic at ≤1 week post procedure except one at two weeks. 65% (n=13/20) of pacemaker-requiring patients were implanted during TAVI admission. Re-admission for pacemaker insertion occurred 71.4% (n=5) within two weeks and 28.6% (n=2) after three weeks, a calculated on-the-road risk of harm to population, where risk of harm = TD x SCI x V x AC (TD: fractional time individual spends driving, SCI: likelihood of cardiac incapacitation incidence, V: vehicle type, and AC: probability of cardiac incapacitating event incidence while driving causing a fatal/injury-related motor vehicle incident at 2%), of 0.0014%, well below the established CCS threshold of 1%. 95% of pacemaker patients had pre- and/or post-TAVI conduction abnormalities; one patient did not, developing new right bundle branch block (RBBB) and requiring pacemaker insertion seven days post TAVI, a 0.0002% on-the-road risk (Figure). 52.3% expressed that a one-month driving restriction was ‘too long’.

CONCLUSIONS

We propose shortening post-TAVI driving guidelines to 48 hours (alternatively one week) for patients with successful uncomplicated TF TAVI without pre-existing and/or new post-TAVI conduction disturbances and two weeks for those with known conduction abnormalities. Modified guidelines encouraged when patient and public safety are of concern.

Therapeutic window of native PLGA nanoparticles in the 5xFAD mouse model of Alzheimer's disease

Govindarajan Karthivashan, Istuti Gupta and Satyabrata Kar
Supervisor: Satyabrata Kar

INTRODUCTION

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is characterized by extracellular beta-amyloid (Aβ) plaques, intracellular neurofibrillary tangles, neuroinflammation, and progressive neuronal loss in specific brain regions. Current treatments offer limited symptomatic relief and do not address the underlying pathology. Poly(lactic-coglycolic acid) (PLGA) nanoparticles have emerged as promising nanocarriers for drug delivery across the blood-brain barrier. However, the intrinsic therapeutic potential of native (drug-free)PLGA nanoparticles remains largely unexplored. Based on our previous findings demonstrating their diagnostic and therapeutic potential in the 5xFAD mouse model of AD, this study investigated the therapeutic window of native PLGA following chronic intracerebroventricular(icv) administration.

METHODS

5xFAD transgenic and wild-type mice received chronic icv infusions of native PLGA or artificial cerebrospinal fluid (CSF) for 28 days via mini-osmotic pumps. Cognitive function, Aβ plaque burden, $A\beta_{1-40/42}$ and amyloid precursor protein (APP) levels, and microglial activation were assessed on day 28 (end of treatment), and at 15- and 30-days post-treatment.

RESULTS

Behavioral assessments (Y-maze and novel object recognition) revealed significant cognitive improvements in PLGA-treated 5xFAD mice, persisting up to 15 days post-treatment
and declining by day 30. Immunohistochemical and biochemical analyses showed reduced Aβ
plaque load and levels of soluble $A\beta_{40/42}$, APP as well as its cleavage products (α-CTF and β-CTF)up to day 15 and then returned by 30 day post-treatment. PLGA treatment also reduced microglial activation, indicated by Iba1 levels and morphology. Notably, the activated microglial lysosomal marker CD68 was found to be elevated until day 15, suggesting enhanced Aβ clearance, but returned to baseline by day 30.

CONCLUSIONS

Native PLGA nanoparticles confer transient therapeutic benefits in AD pathology, with effects lasting up to 15 days post-treatment and diminishing thereafter. These results
underscore their potential as a novel, nanotherapeutic strategy for AD, which needs to be validated using further study.

PAR-2 activating peptide as mucosal adjuvant improves immune cell recruitment to the lymph nodes and activation in a prime-boost influenza vaccination model

Claudia Alejandra Kornuta, Gang Zhou, Kevin Kane and Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Protease-Activated Receptor 2 (PAR-2) is a G protein-coupled receptor that can be activated by synthetic peptides known as PAR-2 activating peptides (AP). We developed a novel mucosal vaccination strategy against Influenza A Virus (IAV) using AP as an adjuvant. This model employs IAV virosomes, which contain virion surface proteins hemagglutinin and neuraminidase but no viral genetic material. Previously, AP enhanced protection against lethal IAV infection when co-delivered with IAV virosomes intranasally (i.n.) in a murine prime-boost model. However, the mechanism of the AP adjuvant effect remains unknown. We hypothesize that AP enhances early immune cell recruitment and promotes antigen presentation in lymph nodes.

METHODS

Cell recruitment to the lungs and mediastinal lymph nodes (mLNs) of C57BL/6 mice following i.n. prime and booster delivery of AP, virosome, virosome+AP, or PBS were analyzed by flow cytometry of cells recovered from digested lungs and mLNs. CFSE was delivered i.n. to track cell migration from lung to mLNs.

RESULTS

An early pro-inflammatory profile was detected in the lungs of the virosome+AP group, characterized by higher frequency of inflammatory monocytes (iMono). CD86 expression was increased in CD11b+ and CD11b- dendritic cells (DCs) and macrophages, and MHCII expression was increased in iMono at one day post-booster (1dpb). MLNs in virosome+AP group showed increased size and higher numbers of lymphocytes and DCs at 1dpb. Elevated frequencies of $CD3^{+}$ $CD103^{+}$ cells— tissue-resident T cells marker —and early B cell activation markers were also observed. Tracking of $CFSE^{+}$ cells from the lung to the mLNs revealed that most of the recruited cells were lymphocytes and $CD11b^{-}$ DCs in the virosome or virosome+AP groups.

CONCLUSIONS

AP acts as a mucosal adjuvant by promoting a pro-inflammatory lung environment, enhancing immune cell recruitment from the lungs to the regional lymph nodes, and facilitating the presentation of IAV virosome antigens, thereby improving the immune response to vaccination.

Exploring Hereditary Hemorrhagic Telangiectasia: How Rectal Bleeding Led to a New Diagnosis

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Supervisor: Dilini Vethanayagam

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by telangiectasia and visceral arteriovenous malformations (AVMs). Key genes involved in HHT include ENG, ACVRL1, SMAD4, GDF2, EPHB4, and RASA1, which affect signaling pathways crucial for maintaining vascular endothelial integrity. The diagnosis of HHT is commonly guided by The Curaçao Diagnostic Criteria.

METHODS

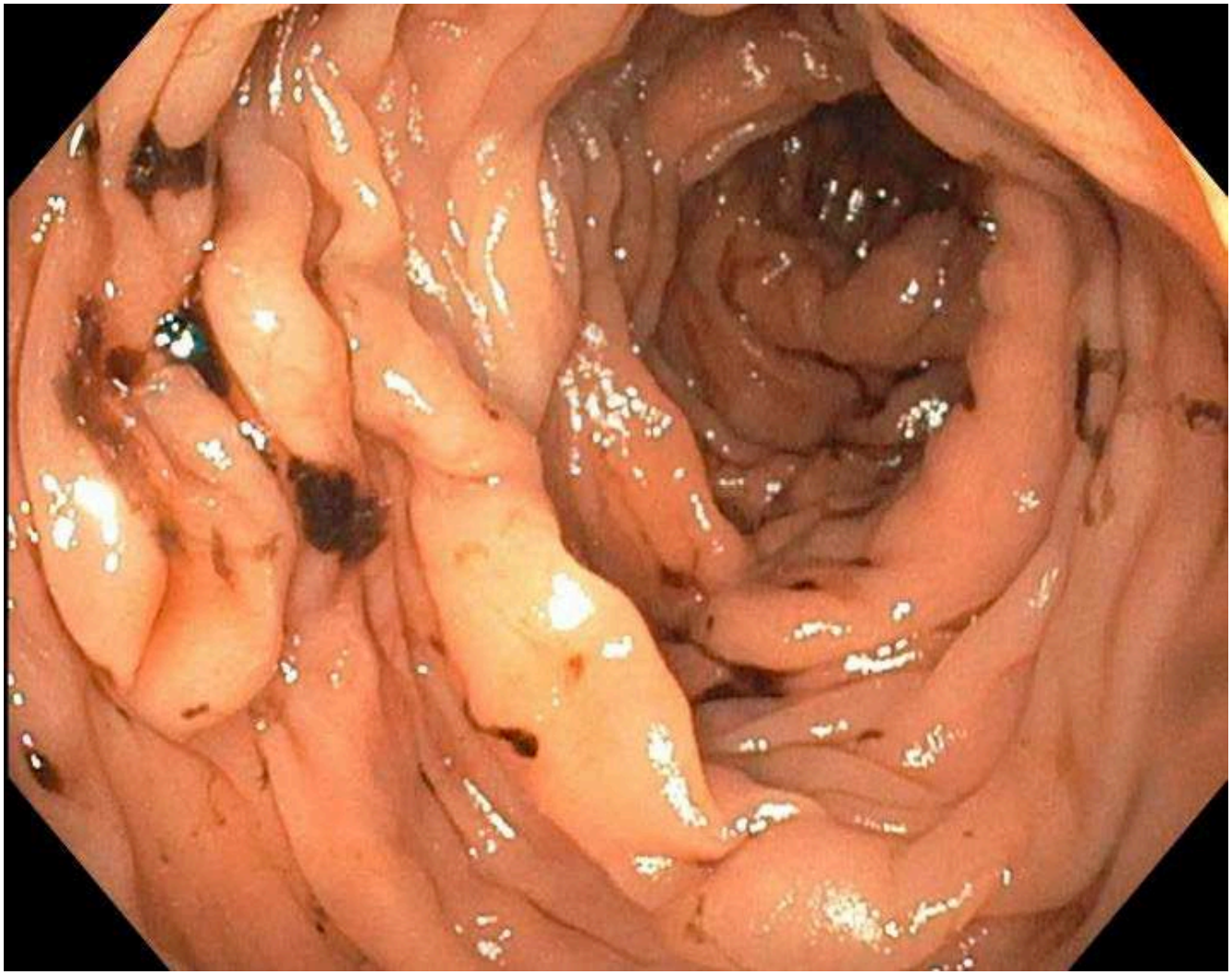
We report the case of a patient with suspected HHT who presented with recurrent gastrointestinal bleeding.

RESULTS

A 33-year-old male from a rural community in Alberta (Canada) presented with a one-day history of rectal bleeding. His past medical history was significant for recurrent epistaxis since age 8, a previous gastrointestinal bleed, and a laparotomy at the age of 15 where pathology revealed small intestinal vascular malformations. His family history was strongly suggestive of HHT, as his mother had undergone a partial colectomy at the age of 28 due to bowel telangiectasias and had been followed by Hematology for over 40 years, although no formal HHT diagnosis was ever made. In this patient, colonoscopy, esophagogastroduodenoscopy, and push enteroscopy, did not identify any culprit lesions (Figure). However, a subsequent CT enterography revealed AVMs in the distal ileum and venous malformations in the jejunum. A video capsule endoscopy was then performed, which showed non-bleeding telangiectasias in the small bowel. Based on the clinical picture, the patient was assessed to have possible HHT by The Curaçao Diagnostic Criteria. He was managed with IV iron and octreotide. Upon discharge, he was referred to the Edmonton HHT clinic. Molecular genetics for HHT has been non-diagnostic. Despite this, his clinical diagnosis of possible HHT remains likely, and he will continue to require screening for the multisystem complications associated with AVMs.

CONCLUSIONS

HHT remains under-recognized and under-diagnosed. Maintaining a high level of suspicion is critical, and incorporating a multidisciplinary approach can help reduce morbidity and mortality.



Why do patients stop taking their glucagon-like peptide-1 receptor agonists?

Shania Liu, Genieve Wong, Pavneet Mavi, Stephanie Gysel, Daniel Burton, Neire Monteiro, Derek Durocher, Ross Tsuyuki
Supervisor: Ross Tsuyuki

INTRODUCTION
Type 2 diabetes and obesity are among leading causes of morbidity and mortality worldwide. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective for the management of type 2 diabetes and overweight or obesity, but effectiveness of therapy is compromised by high rates of non-persistence. The objective of this study was to examine the reasons for non-persistence to GLP-1 agonist therapy among patients with obesity and/or diabetes.

METHODS
A cross-sectional study was conducted at four community pharmacies in Alberta, Canada. Pharmacy dispensing records of GLP-1RAs were screened between January 2023 and June 2024. Adults who were non-persistent to GLP-1RA therapy (defined as a treatment gap of more than 90 days). Eligible patients were invited to participate in a 4-item telephone survey to confirm non-persistence and identify reason(s) for non-persistence. The primary outcome was the patient-reported reason(s) for GLP-1RA non-persistence. Patient-reported reason(s) for non-persistence were transcribed verbatim and coded independently by two authors (patients could report more than one reason).

RESULTS
Among 651 patients assessed for eligibility using pharmacy dispensing records, the presumed non-persistence rate to GLP-1 agonist therapy was 47% (308/651). Of these patients, 91 consented to participate in telephone surveys. In this cohort, the GLP-1RA was prescribed for obesity in 40%, diabetes for 25%, and both obesity and diabetes in 35%. Semaglutide was the GLP-1RA in 89% of cases. Main reasons for non-persistence to GLP-1 agonist therapy included medication shortages (n=24/91; 26%), adverse effects (n=20/91; 22%), medication cost (n=16/91; 18%), perceived ineffectiveness (7%, n=6/91), life circumstances (5%, n=5/91), and changes to lifestyle to manage weight/A1C resulting in the participant to no longer require GLP-1 RA therapy (2%, n=2/91).

CONCLUSIONS
About half of patients prescribed GLP-1RAs are non-persistent after 90 days. Patient-reported reasons for stopping their medication included medication shortages, adverse effects, and cost.

Anaphase Promoting Complex Activation with C43-4 Peptide Reduces Aberrant Substrate Accumulation in Aging and Aging Associated Diseases

Mathew Lubachowski, Troy Harkness
Supervisor: Troy Harkness

INTRODUCTION

The Anaphase Promoting Complex (APC) regulates cell cycle progression, but also influences aging hallmarks such as genomic instability, loss of proteostasis, cellular senescence, and disrupted energy metabolism. These processes are also dysfunctional in aging associated diseases like Hutchinson's Gilford progeria syndrome and cancer. Previous research in our lab has shown APC impairment and substrate accumulation in such conditions, and identified an APC activating peptide (C43-4) via yeast two-hybrid screen. This activator could restore APC function in aging, and related diseases, improving outcomes. I hypothesize APC dysfunction and substrate accumulation exists in aged cells, progeria patient cells, and drug-resistant cancer cells, but that C43-4 restores APC function and reduces APC substrates.

METHODS

I compared abundances of APC substrates using western blotting in; young, passage 20, and old, passage 40, 2DD primary human foreskin fibroblasts; Hutchinson's Gilford progeria syndrome patient derived and healthy parental control fibroblasts; and MDA-MB-231 or MCF7 human breast cancer cells either treated with doxorubicin or drug naïve. Cells were either transfected with a C43-4 expression vector, or treated with synthesized peptide. Cancer cell survival, when challenged with doxorubicin in the presence or absence of the peptide, was assayed using MTT or trypan blue exclusion.

RESULTS

Known APC substrates are increased in aged fibroblast, progeria fibroblasts, and drug-resistant breast cancer cells. Survival of cancer cells decreased when challenged with doxorubicin in the presence of C43-4. Finally, I am currently evaluating APC substrate levels in response to peptide treatment.

CONCLUSIONS

The APC regulates cell cycle progression, and influences multiple hallmarks of aging and associated diseases. Reduction of aberrant APC substrate accumulation using peptide C43-4 has the potential to improve aging associated diseases and promote healthier aging. Moving forward I will show that C43-4 not only reduces APC substrates, but also markers of aging and associated disease states.

Guideline Directed Medical Therapy in Heart Failure Patients with Advanced Chronic Kidney Disease: A Prospective Study from the Heart Function Clinic Registry

Chen Hsiang Ma, Arthur Qi, Luke Gagnon, Ben Vandermeer, Aminu Bello, Gavin Y Oudit
Supervisor: Gavin Oudit

INTRODUCTION
Managing heart failure patients with comorbid advanced chronic kidney disease (CKD) presents significant challenges, often resulting in suboptimal utilization of goal-directed medical therapy (GDMT) and worse cardiovascular outcomes. This study compares comorbidities and GDMT utilization among patients with stage 4-5 CKD in an outpatient, multidisciplinary cardiology clinic.

METHODS
The HFC registry enrolled patients referred to the Mazankowski Heart Institute between 2018 and 2023, utilizing recent cardiac imaging and outpatient creatinine measurements for heart failure subtype and CKD stage stratification. Baseline comorbidities and outpatient medication data were obtained from chart review.

RESULTS
Our cohort included 1379 patients with a median age of 68, and 29% identified as female. Patients with CKD stage 4-5 constituted 9.0% (124 patients). Those with advanced CKD exhibited a higher burden of comorbidities, including hypertension (82.3% vs 56.2%), diabetes mellitus (65.3% vs. 36.3%), and ischemic heart disease (58.9% vs. 48.2%), compared to heart failure patients with CKD stage 3 or higher. Moreover, baseline GDMT utilization was lower in patients with advanced CKD, including RAAS inhibitors (71.0% vs 93.5%), beta-blockers (88.7% vs. 94.0%), MRA (34.7% vs. 73.2%), and SLGT2i (7.3% vs. 16.0%). Rates of HFpEF were higher in patients with advanced CKD (38.7% vs. 26.3%), while rates of HFrEF were higher in patients with non-advanced CKD (54.2% vs. 39.5%).

CONCLUSIONS
Significant gaps persist in GDMT utilization among advanced kidney disease patients, highlighting the lack of evidence for this highly comorbid population. Further research is needed to assess the impact of current GDMTs in advanced CKD patients.

Multifaceted STRIDE II-Based Monitoring for Inflammatory Bowel Disease Advanced Therapy Starts

Scott MacKay, Denise Parsons, Sami Hoque, Frank Hoentjen, Levinus Dieleman, Michal Gozdzik, Karen Kroeker, Karen Wong, Todd McMullen, Farhad Peerani, & Brendan Halloran
Supervisor: Dr. Brendan Halloran

INTRODUCTION

Inflammatory Bowel Disease (IBD) outreach monitoring has demonstrated cost-effectiveness and reduced healthcare utilization. IBD STRIDE-II guidelines recommend monitoring patient-reported outcomes (PRO's), fecal calprotectin (FCP), C-reactive protein (CRP), and endoscopy to determine if patients achieve therapeutic targets. Previous monitoring in the literature obtained PRO's alone, which risks undertreating asymptomatic inflammation in spite of elevated flare and colorectal cancer risk. Our monitoring protocol closely monitors biomarkers and PRO's for new advanced therapy start patients.

METHODS

Patients complete 24 weeks of outreach monitoring with PRO's on day 0 and 7 then every 2 weeks. Labs are collected at baseline and weeks 4, 8, 12, 16, and 24. FCP is collected at baseline and weeks 8, 16, and 24. Treating gastroenterologists receive two granular clinical results summaries.

RESULTS

75 protocol patients on the following therapies: ustekinumab (n = 31), risankizumab (n = 17), tofacitinib (n = 14), upadacitinib (n = 10), vedolizumab (n = 2), and infliximab (n = 1) were monitored. 51 patients (68.0%) failed 1+ prior advanced therapies and 13 (17.3%) had prior IBD surgery. 7 (9.3%) switched therapy before 24 weeks due to lack of response. 1 (1.3%) had an adverse drug event. 64 patients (85.3%) complied with all FCP collections and 73 (97.3%) completed 95+% of PRO's. Per STRIDE-II criteria, 47 patients (62.7%) demonstrated clinical response during 24 weeks and 25 (33.3%) achieved remission by 24 weeks. 15 (20.0%) received steroids, 9 (12.0%) presented to emergency, and 5 (6.7%) were hospitalized for IBD during monitoring.

CONCLUSIONS

Our proactive protocol provides real-world clinical response data to clinicians and facilitates responsive disease management. Patients were highly compliant with serial PRO, FCP, and labs collection. In future, we will compare protocol patients to standard of care managed patients to assess if the protocol reduces healthcare utilization and improves patient outcomes.

Chronic airway inflammation drives sex-specific changes in behaviour, neuroinflammation and gut microbiota

Shivani Mandal, Marie Armbruster, Ritu Mann-nuttel, Paul Forsythe
Supervisor: Paul Forsythe

INTRODUCTION

Depression is a common co-morbidity with asthma and worsens disease outcomes, yet the mechanistic relationship between disorders is unclear. Both asthma and major-depressive-disorder have been associated with gut microbiome disruptions. We hypothesize that chronic allergic airway inflammation induces central neuroinflammation and behavioural changes, which are associated with alterations in the gut microbiota.

METHODS

6-week-old male and female C57BL/6 mice (n=14/group) were exposed to house-dust-mite (HDM) extract or PBS for eight weeks. Lung inflammation was assessed using histology and bronchoalveolar-lavage cell counts. Depressive-like behaviour was evaluated using splash (grooming) and tail suspension test (behavioural despair). Hypothalamic bulk-RNA sequencing and small intestine 16S sequencing was performed. In the hippocampus, neuroinflammation was assessed by quantifying mast cells and expression of Glial-Fibrillary Acidic Protein (GFAP; astrocyte activation marker) and Ionized calcium Binding Adaptor protein (IBA1; microglial activation marker). Statistical analyses used unpaired t-tests or Mann-Whitney tests (mean ± SEM).

RESULTS

HDM exposure induced lung remodelling and eosinophilia ($p<0.001$) in both sexes, confirming chronic airway inflammation. In males, this was accompanied by hypothalamic gene changes linked to inflammation, mitochondrial and glial dysfunction, and synaptic deficits. HDM males also had signs of neuroinflammation with increased mast cell counts ($p=0.038$) and higher microglial activation (IBA1;$p=0.025$) in the hippocampus. Females had minimal hypothalamic gene changes but increased astrocyte activation (GFAP;$p=0.026$) in the hippocampus. Correspondingly, only males showed behavioural despair ($p=0.004$), while both males and females had reduced grooming ($p=0.004$[males]; 0.033[females]). Similarly, 16S analysis revealed a shift in gut microbiota composition in HDM males ($p=0.01$) with changes characteristic of depression and inflammation, but not in females.

CONCLUSIONS

Neuroimmune and gut microbiome responses to chronic allergic airway inflammation are sex-specific, with greater brain function and behaviour disruption in males. This study highlights potential gut-brain-immune interactions relevant to asthma comorbidities and the importance of sex-informed approaches to developing treatment strategies.

Cultured human Pulmonary neuroendocrine cells stimulated with House dust mite allergen activate Innate lymphoid cells 2 and classic Dendritic cells

Ritu Mann-Nuttel, Nami Shrestha, Yingqi Wu, Harissios Vliagoftis and Paul Forsythe
Supervisor: Dr. Paul Forsythe

INTRODUCTION

Pulmonary neuroendocrine cells (PNEC) have recently gained attention as rare airway epithelial cells that amplify allergic asthma responses. PNEC derived mediators such as Calcitonin gene-related peptide (CGRP) have been shown to activate Innate lymphoid cells 2 (ILC2) in a murine asthma model. Studying human PNEC function has been challenging due to a lack of suitable cell isolation methods. Here used our novel in vitro human PNEC model and investigated the effect of supernatant from PNEC stimulated with House dust mite allergen (HDM) on ILC2 and classic dendritic cell (cDC) activation.

METHODS

PNEC enriched cultures were generated from primary bronchial/tracheal epithelial cells (ePNEC) in transwells. Successful differentiation of neuroendocrine cells was evaluated with qRT-PCR and immunohistochemistry. In all experiments, standard (PNEC deficient) human bronchial/tracheal epithelial cells served as controls. At day 60 of culture, ePNEC were challenged with HDM for 24h and supernatant was subsequently used to stimulate PBMC-derived Lin- CD45+ CRTH2+ IL13+ IL5+ ILC2 and Lin- CD11cint CD141+ cDC1, Lin- CD11cint CD1c+ cDC2. ILC2 and DC cell activation was assessed with flow cytometry.

RESULTS

Supernatant from HDM stimulated ePNEC induced an 60% increase in ILC2 cells expressing IL13 and IL5 compared to control. Further, the activation markers MHCII and CD86 were significantly upregulated in cDCs cells exposed to mediators from HDM stimulated PNEC.

CONCLUSIONS

Here we demonstrate, for the first time, that HDM stimulates human PNEC to release mediators that activate ILC2 and cDCs. These results highlight or novel model as an effective tool for investigating neuro-endocrine immune interactions in the human airway and that will contribute to a deeper understanding of PNEC biology in asthma development and severity.

Altered upper airway alarmin cytokine expression in response to biologic treatment in severe asthma

Marriott H, Duchesne M, Okoye I, Moolji J, Adatia A, Lacy P
Supervisor: Paige Lacy

INTRODUCTION

Secretion of alarmin cytokines thymic stromal lymphopoietin (TSLP), interleukin(IL)-25, and IL-33, heralds the onset of the asthma inflammatory cascade. Our group has shown that TSLP and IL-25 are elevated in nasal epithelia of severe asthmatics. We hypothesize nasal alarmin cytokine expression decreases in response to biologic therapies targeting eosinophils and TSLP.

METHODS

Nasal brushings collected from candidates for biologic therapy upon presentation with severe asthma and at three month follow up were analyzed for intracellular expression of alarmin cytokines by flow cytometry and analyzed using a Fortessa-SORP cytometer with FlowJo version 10.10. Biologic therapy included mepolizumab, benralizumab, and tezepelumab according to clinical guidelines. At each visit clinical characteristics including asthma control questionnaire (ACQ)-6 were recorded. Impulse oscillometry was measured using a Thorasys Tremoflo C-100 device, and Fractional exhaled Nitric Oxide was measured using NiOX device according to guidelines.

RESULTS

At three-month follow-up visits, patients were found to have a reduction in nasal TSLP, IL-25 and Il-33 expression with mean fold changes of -8.64 ± 7.43, -6.78 ± 3.27 and -5.043 ± 4.14 (mean ± standard deviation, n=21), respectively. The fold change in TSLP expression was found to correlate with reduction in ACQ-6 score (Spearman $r=-0.674$, $p<0.05$), suggesting improvements in asthma control may be connected to expression of TSLP. No significant relationship was found between alarmin cytokines and other clinical parameters

CONCLUSIONS

Biologic therapy reduced expression of TSLP, IL-25 and IL-33, regardless of biologic administered. This reduction was detected as early as two doses after therapy initiation, suggesting nasal cytokine expression may provide insight into early responses to biologic. As alarmin cytokine expression was reduced in all groups, biologic therapy may feed back to the epithelium, regardless of where along the inflammatory cascade it acts. Future work will elucidate the mechanisms of this feedback and the implications it has for the airway epithelium.

Donor Microbiota Induced Complement Component 3 (C3) Production Contributes to Fecal Microbiota Transplantation (FMT) Efficacy in Patients with Recurrent Clostridioides Difficile Infection (rCDI)

Ali Nabavi Rad, Mohamed Shaheen, Chelsea McDougall, Rose Franz, Karen Wong, Dina Kao
Supervisor: Dr. Dina Kao

INTRODUCTION
Fecal microbiota transplantation (FMT) is the most effective therapy for patients with recurrent Clostridioides difficile infection (rCDI), yet the mechanisms of action remain poorly understood. Luminal complement component 3 (C3) provides host defense against intestinal infection. Basal C3 level is induced and influenced by the presence and composition of commensal gut microbiota. We hypothesize that C3 induced by FMT may contribute to FMT efficacy. We aimed to evaluate the changes in gut C3 levels following success outcomes from rCDI patients who received either lyophilized FMT (LFMT) or lyophilized sterilized fecal filtrate (LSFF), and correlated these results with stool microbial composition analysis.

METHODS
Stool samples from 40 rCDI patients (23 in LFMT and 17 in LSFF group) at baseline (W0) and 8 weeks (W8) after successful treatment were chosen for C3 analysis. The concentrations of C3 in stool samples was measured with Human Complement C3 ELISA kit. Bacterial community compositions of the stool samples were determined by 16S rRNA gene sequencing.

RESULTS
Bacterial community assembly showed distinct trajectories between LFMT- and LSFF-treated patients. Both groups had reduced Enterobacteriaceae and increased Lachnospiraceae. However, recovery of Ruminococcaceae, Bacteroidaceae, Rikenellaceae, and Coriobacteriaceae was seen in the LFMT but less pronounced or absent in the LSFF group. At 8 weeks, LFMT group demonstrated statistically significant increase in C3 levels (mean= 79.96 ng/g at W0 versus 176.67 ng/g at W8, p= 0.00038) compared to the LSFF group (mean= 96.57 ng/g at W8) which remained unchanged from baseline (mean= 103.85 ng/g at W8, p= 0.74).

CONCLUSIONS
LFMT was more efficient in correcting the gut microbiome alterations in rCDI, shifting microbiomes towards that of healthy donors. Ruminococcaceae, Bacteroidaceae, Rikenellaceae, and Coriobacteriaceae from the donor microbiota may play a role in inducing gut C3 production in rCDI patients following successful intervention, which may be one of the mechanisms underpinning the FMT efficacy.

Variable	LFMT (n=23)	LSFF (n=17)
Female, N (%)	18 (78.3%)	8 (47.1%)
Age, mean (SD), y	52.9 (17.7)	59.2 (20.3)
Ethnicity, caucasian (%)	19 (82.6%)	15 (88.2%)
rCDI duration before FMT, mean (SD), m	3.9 (1.3)	5.2 (2.0)
Episodes of rCDI before FMT, mean (SD)	3.4 (0.6)	3.8 (1.0)

Table 1. Participant baseline characteristics. N, number of participants; SD, standard deviation.

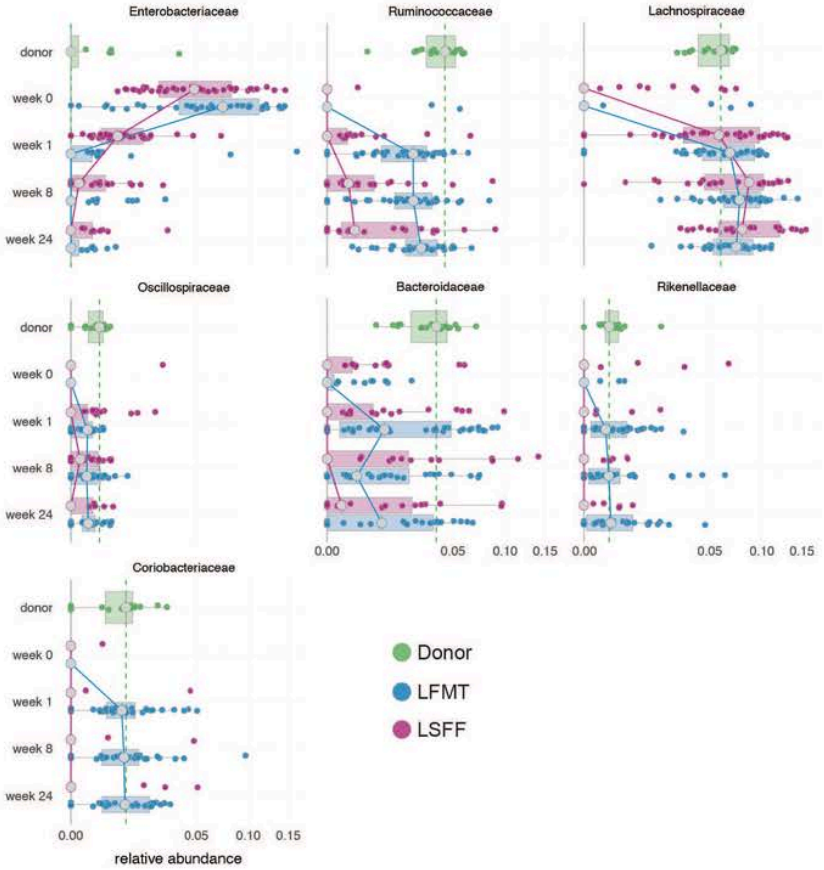


Figure 1. The relative abundance of certain gut bacteria at the family level in donors and 83 rCDI patients at 0, 1, 8, and 24 weeks following treatment with LFMT or LSFF.

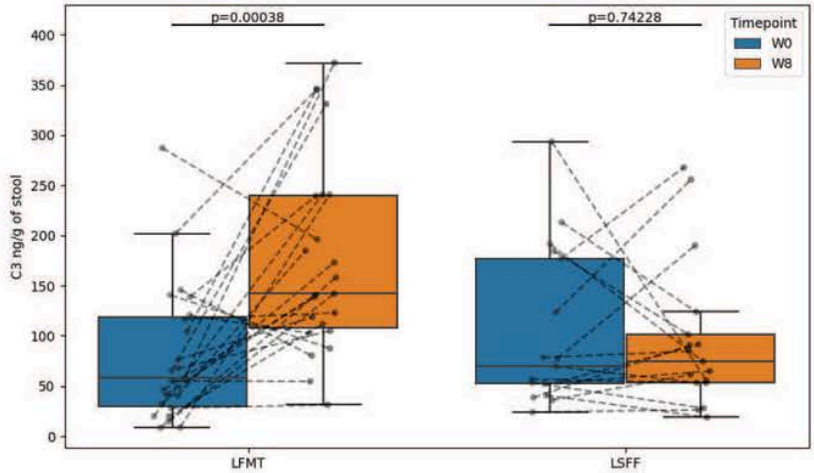


Figure 2. Gut complement C3 level (ng per g of stool) in rCDI patients at baseline (W0) and 8 weeks (W8) following successful intervention with LFMT or LSFF.

Activation of the Glycolytic Enzyme Triose Phosphate Isomerase is a Viable Therapeutic Strategy to Improve Ex-Situ Heart Perfusion: Implications For Cardiac Transplantation

Joseph Nanoa, Sanaz Hatami, Saymon Tejay, Maria Areli Lorenzana, Yuan Yuan Zhao, Liyan Zhang, John Ussher, Gary Lopaschuk, Seyed Amirhossein Tabatabaei-Dakhili, Evangelos Michelakis, Darren Freed, Gopinath Sutendra
Supervisor: Dr. Gopinath Sutendra

INTRODUCTION

Cardiac transplantation remains the gold standard therapy for end-stage heart failure; however, many patients die awaiting a transplant, partly due to the limited supply of available useable donor hearts. Normothermic ex-situ heart perfusion (ESHP, i.e., heart in a box) is a novel method to preserve and increase the available time of usable donor hearts (for transplantation), but its function declines after ~7hrs by a yet unknown mechanism. We hypothesized the decrease in cardiac function from ESHP may be due to a decrease in the metabolic flux from glucose (a prominent metabolic fuel) to pyruvate, the substrate for oxidative phosphorylation in the mitochondria, required for ATP synthesis and optimal cardiac performance.

METHODS

Cardiac-specific ZNF281 overexpression mice were used to assess the role of ZNF281 on cardiomyocyte function. ZNF281 Interfering Molecule (ZIM) was developed to inhibit the interaction of ZNF281 with triose phosphate isomerase (TPI).

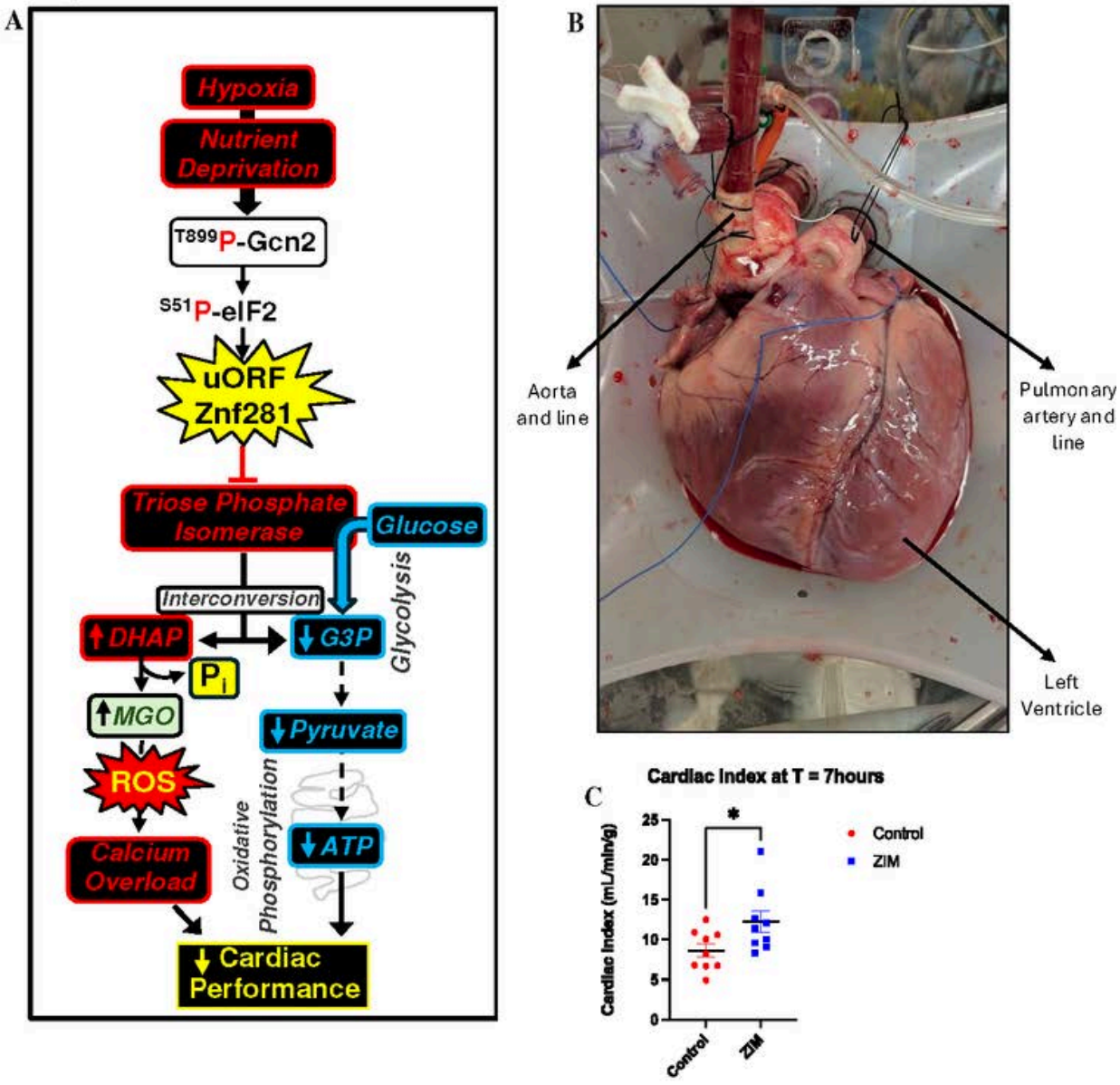
RESULTS

We found that upon explantation, the integrated stress response pathway is activated, which results in the acute cytoplasmic translation of the stress-response Zn2+ finger protein ZNF281. We found that ZNF281 (in cardiomyocytes from cardiac-specific ZNF281 overexpression transgenic mice) can preferentially bind the glycolytic enzyme triose phosphate isomerase (TPI), decreasing its enzymatic activity and the levels of its glycolytic product glyceraldehyde-3-phosphate (G3P), an intermediate that can eventually increase the levels of pyruvate, and subsequently mitochondrial ATP. At the same time inhibition of TPI increases the levels of a toxic glycolytic byproduct, methylglyoxal (MG), that can promote calcium overload and inefficient contractility. Disruption of ZNF281 and TPI interaction with ZIM (a novel compound that our team generated), promotes complete glucose metabolism (and ATP production) and significantly improves ESHP function at 7hrs and beyond.

CONCLUSIONS

Our findings provide an alternative technology for increasing the donor pool of useable hearts, that is desperately needed.

Figure A



A, Our proposed mechanism suggests that once the heart is explanted it will be exposed to several physiologic stresses, including hypoxia and nutrient deprivation. These stresses will activate the stress response kinase Gcn2 that can phosphorylate the translation initiation factor eIF2. Phosphorylation of eIF2 can increase the acute translation of ZNF281, a Zn2+ finger protein that can bind and inhibit the glycolytic enzyme triose phosphate isomerase (TPI). Inhibition of TPI can result in a decrease in glyceraldehyde-3-phosphate (G3-P), a glycolytic substrate for pyruvate and subsequently generation of ATP. In addition, inhibition of TPI will increase the levels of DHAP that can spontaneously break down into inorganic phosphate and the toxic glycolytic byproduct methylglyoxal (MGO). MGO can increase reactive oxygen species (ROS) and calcium overload. Collectively, the calcium overload and the decrease in ATP will result in decreased cardiac performance. **B**, picture of the ex-situ heart perfusion setup where the aorta and pulmonary artery are cannulated and ex-situ cardiac function is measured by electrical probes. **C**, Perfusion of an ex-situ heart (after explantation) and treatment with a ZNF281 Interfering Molecule (named ZIM) that disrupts the binding between ZNF281 and TPI preserves cardiac function up to 7hrs after explantation, compared to vehicle-treated ex-situ heart.

Behaviour change techniques in e-Health interventions for older and/or frail/sarcopenic adults: A systematic review and meta-analysis

Ayushi Omkar, Jennifer Bertrand, Chikku Sadasivan, Julian Mansour, Emma Osness, Liz Dennett, Ben Vandermeer, Victor Ezeugwu, Puneeta Tandon
Supervisor: Dr. Puneeta Tandon

INTRODUCTION
Behaviour change techniques (BCTs) are fundamental components of eHealth interventions aimed at promoting physical activity. These techniques may be particularly important for individuals who face additional challenges with eHealth, such as those with frailty, sarcopenia or advanced age. Identifying effective BCTs in these groups could improve eHealth physical activity outcomes. This systematic review aims to examine BCTs used in randomized controlled trials (RCTs) of eHealth physical activity interventions targeting older adults (mean age ≥ 60 years), or those with frailty or sarcopenia.

METHODS
We searched six databases (MEDLINE, Embase, CINAHL, CENTRAL, PsycINFO, Scopus) for RCTs from 1990–2024 on eHealth interventions targeting physical activity, performance, quality of life, or daily living in adults ≥60 or those with sarcopenia/frailty. Studies that exclusively used virtual-reality, wearable devices, or telephone-based interventions were excluded. A meta-analysis will assess pooled effect sizes of each study's clinical effectiveness, and meta-regression will explore how BCT number, type, or category influence outcomes.

RESULTS
Of 69 studies reviewed so far, 26 focused on older adults, and the rest on sarcopenia or frailty in chronic conditions like cardiovascular/metabolic disease (n=20) and cancer patients or survivors (n=13). The most frequent BCTs were social support (n=63), environmental cues (n=61), behaviour feedback (n=57), self-monitoring (n=56), and health consequence info (n=55). Most interventions targeted physical activity alone (n=37), or combined it with nutrition (n=14) or mental wellness (n=11). Delivery methods included web platforms (n=32), mobile apps (n=28), and wearables (n=30).

CONCLUSIONS
Preliminary findings suggest that social support, environmental changes, and behaviour feedback are the most common BCTs in eHealth physical activity interventions for older adults or those with sarcopenia/frailty. Next steps will assess their effectiveness in improving activity, function, and quality of life, informing future intervention design.

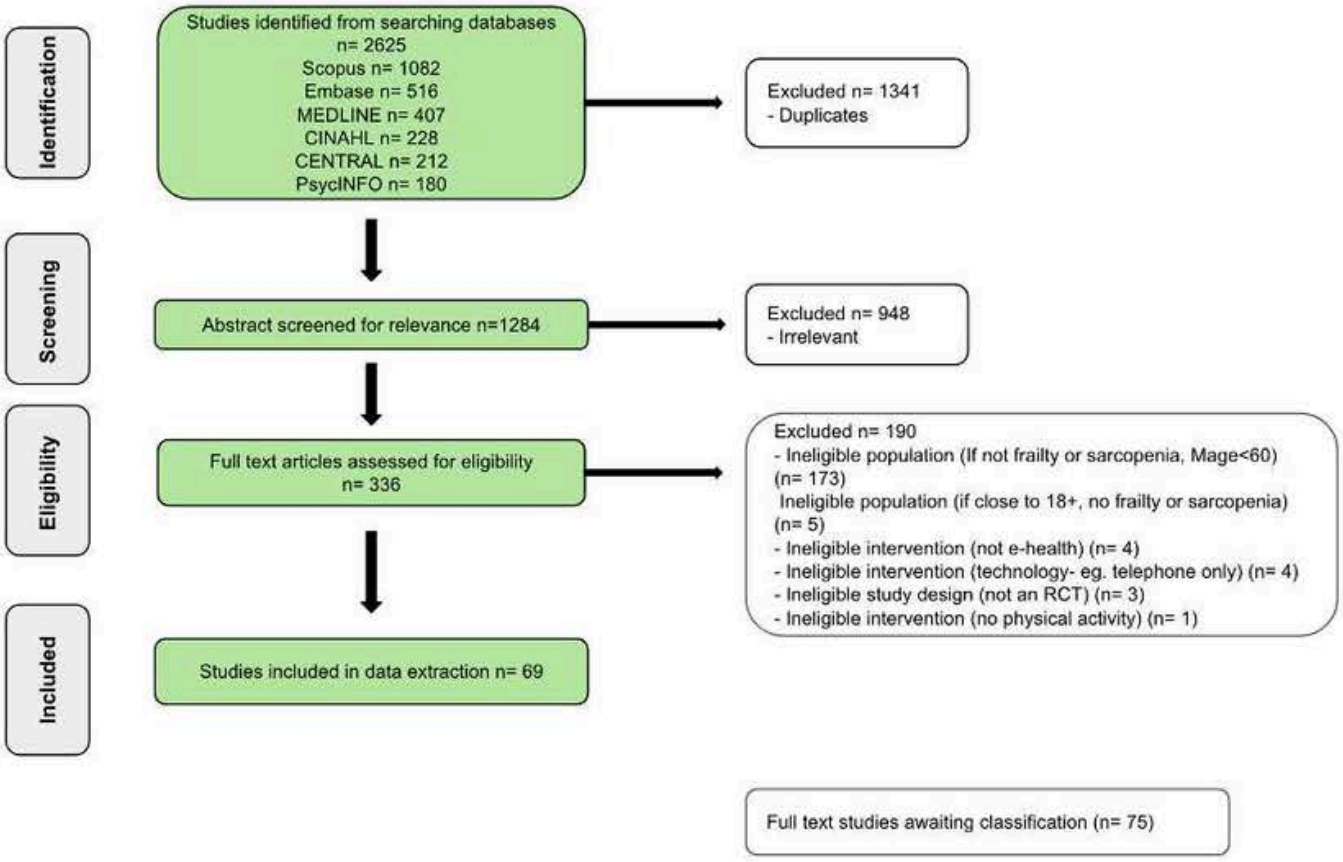


FIGURE 1: Flow diagram of study selection.

Markerless Motion Capture Parameters Associated with Fall risk and/or frailty: A Scoping Review

Emma Osness, Serena Isley, Jennifer Bertrand, Victor Ezegwu, Elizabeth Dennett, Jack Bates, Nathan Van Decker, Alexis Stanhope, Naomi Dolgoy, Ayushi Omkar, Puneeta Tandon
Supervisor: Puneeta Tandon

INTRODUCTION
Fall risk and frailty are highly prevalent in individuals with chronic disease. Current assessments often rely on subjective interpretation and in-person evaluation, limiting accessibility. Advances in markerless motion capture (MMC) offer potential for remote, in-home measurement, but the motion parameters associated with fall risk and frailty have not been systematically summarized. Identifying key parameters could enhance digital health tools by increasing efficiency and objectivity.

METHODS
A search was conducted in October 2024 across MEDLINE, Embase, Scopus, and CINAHL. A health sciences librarian developed the search strategy with clinical input. The search was limited to English, with no date restrictions. Two reviewers independently screened articles, with a third resolving disagreements. Reference lists of included papers were also searched, yielding two additional studies. Eligible studies assessed adults using MMC and compared results to validated fall risk and/or frailty assessments.

RESULTS
Forty studies met inclusion criteria: 31 focused on fall risk, 7 on frailty, and 2 on both. Most participants were community-dwelling older adults. The Microsoft Kinect was the most commonly MMC device. The average age was 75.8 years (SD = 8.7), and 42% were male. Studies extracted an average of 22.8 features (range: 2–148). Gait analysis was the most frequent movement assessment, used in 13 studies. For frailty, the only parameters identified in multiple studies (n=2) were degradation of speed, power reduction, and elbow flexion time, all measured during a 20-second arm flexion-extension test. For fall risk, the parameters identified commonly (n=5) included gait speed, stride length, and step width, extracted during gait analysis.

CONCLUSIONS
Digital biomarkers for frailty remain under-researched, with only 17% of studies addressing it directly. Most studies analyzed a limited range of kinematic parameters, underscoring the need for broader investigation into movement-based biomarkers. Future research should expand the scope of analysis to improve early detection and intervention.

Improving Cirrhosis Identification: Evaluation of ICD-10 Codes and Development of a Hybrid Algorithm for Enhanced Accuracy in Alberta's Healthcare System

Kinjal Patel, Mayur Brahmania, Grace T Wang, Mathew Daniel, Samina Khan, Mohamed Abdalla, Puneeta Tandon
Supervisor: Puneeta Tandon

INTRODUCTION

Cirrhosis is a global health concern contributing to high morbidity, mortality, and hospitalizations. The Cirrhosis Care Alberta initiative aims to standardize cirrhosis management through order sets and Our Practice Advisories (OPAs) integrated into the Connect Care (CC) electronic medical record (EMR) system. However, inconsistent documentation and underutilization of EMR problem lists hinder accurate cirrhosis identification, leading to missed clinical decision support opportunities. This study evaluated a published ICD-10 code set (Shearer et al., 2022) and developed an enhanced algorithm integrating administrative and EMR data for better cirrhosis identification. The algorithm's performance was evaluated across four Alberta healthcare sites.

METHODS

We evaluated the consensus ICD-10 codes in a cohort of 719 chart-review patients. A novel cirrhosis identification algorithm was developed using ICD-codes from the consensus set, recorded in either administrative data (Discharge Abstract Database, DAD) or EMR problem lists (Connect Care). The algorithm was tested in a cohort of 913 patients admitted to gastroenterology or internal medicine services at four healthcare sites over 3-13 weeks (including two rural and urban sites). Sensitivity and specificity were assessed against chart reviews (gold standard).

RESULTS

The validation of consensus codes yielded positive predictive values consistent with previous studies. Sensitivity and specificity of cirrhosis identification using administrative data alone (DAD) were 76.2% and 97.7%, respectively. Using EMR data (Connect Care) alone, sensitivity was 85.3% and specificity 97.5%. Combining both data sources, the algorithm achieved sensitivity of 86.2% and specificity of 97%. Site variability was observed, with lower sensitivity at rural sites (70% and 78.6%), likely due to differences in coding practices.

CONCLUSIONS

A combined administrative and EMR-based algorithm offers a robust method for identifying cirrhosis patients across diverse healthcare settings. It may improve OPA activation, clinician use of order sets, and facilitate the creation of a cirrhosis registry for quality improvement and research.

Table 1: Summary Table of sensitivities and specificities of each coding algorithm as broken down by site.

Population	Algorithm	Specificity (%)	Sensitivity (%)
Overall (n=913)	DAD	97.74	76.15
	CC	97.49	85.32
	DAD or CC	97	86.24
University of Alberta Hospital (n=172)	DAD	97.71	77.14
	CC	99.24	88.57
	DAD or CC	97.71	91.43
Foothills Medical Centre (n=371)	DAD	97.9	88.89
	CC	96.11	91.67
	DAD or CC	96.11	91.67
High River Health Centre (n=171)	DAD	98.14	60
	CC	99.38	70
	DAD or CC	98.14	70
Red Deer Regional Hospital (n=199)	DAD	97.08	64.29
	CC	97.08	78.57
	DAD or CC	97.08	78.57

Native PLGA nanoparticles inhibit Tau seed-induced Amyloid β1-42 aggregation: Implications of cross-seeding in Alzheimer's disease pathology

P.S. Paul, A. Khalili, J-Y. Cho, H. Wille, and S. Kar
Supervisor: Satyabrata Kar

INTRODUCTION

Tau and amyloid β (Aβ) proteins play critical role in the development and progression of Alzheimer's disease (AD) pathology, the prevalent cause of dementia affecting elderly population. Evidence suggests a reciprocal cross-seeding mechanism where Aβ aggregates not only induce tau aggregation, but tau seeds can also promote aggregation of Aβ peptide, thus accelerating disease progression. We have previously demonstrated that native poly(lactic-co-glycolic acid) (PLGA) nanoparticles, which constitute a family of FDA approved biodegradable polymers used in delivering drugs in a variety of diseases, can inhibit Aβ-induced tau aggregation. However, the effect of PLGA on tau seed-induced Aβ aggregation has not been explored. This study investigates whether native PLGA can prevent Aβ aggregation initiated by pathological tau seeds.

METHODS

We used a variety of biophysical techniques including thioflavin-T fluorescence kinetic (ThT) assay, dynamic light scattering (DLS), fluorescence microscopy and transmission electron microscopy (TEM) to examine the effects of native PLGA on tau seed-induced Aβ aggregation.

RESULTS

Our results showed that seed of 0N4R tau can induce aggregation of 1-20μM Aβ1-42 in a dose-dependent manner as evident by ThT kinetic assay, DLS, fluorescence imaging and TEM analysis. Interestingly, native PLGA nanoparticles (5, 10 and 20μM) without conjugation with any drug/agent attenuated Aβ1-42 aggregation as a function of increasing concentrations. Additionally, Aβ1-42 aggregation trigger by a different tau isoform (i.e., 2N4R tau), which is involved in the formation of characteristic neurofibrillary tangles associated with AD brains, was also decreased by native PLGA nanoparticles.

CONCLUSIONS

Native PLGA nanoparticles effectively suppress tau seed-induced Aβ1-42 aggregation, highlighting their ability to disrupt pathological cross-seeding mechanisms in AD pathology. This extends not only their role in inhibiting tau driven Aβ pathology, but also their potential implication in the treatment of AD pathology.

From snails to mammals: discovery of an activator of the evolutionarily conserved PHLPP1 that promotes features of quiescence and hibernation in mouse cells and hearts.

Jiyuan Piao, Yongneng Zhang, Yuan-Yuan Zhao, Patrick Hannington, Amir Tabatabaei-Dakhili, John Ussher, Gopinath Sutendra, Evangelos Michelakis
Supervisor: Evangelos Michelakis

INTRODUCTION

Hibernation and aestivation are dormancy states in many animals, sharing common features with cellular quiescence, involving a metabolic and signaling rewiring that offers a remarkable resistance to stress, including that from ischemia during dormancy, or reperfusion when exiting from it. In contrast, non-hibernating/aestivating species, including humans, are vulnerable to both ischemia and ischemia-reperfusion (IR) injury. We identified a circulating small molecule putative dormancy-inducing factor in a snail aestivation model, we synthesized it chemically and because it specifically activates its only target, PHLPP1, we named it SNail Activator of PHLPP1 (SNAP). PHLPP1 is a phosphatase at the intersection of biology's two richest signaling fuel-sensing networks, mTOR and AMPK. SNAP dephosphorylated PHLPP1's targets p-AKT and p-S6K and induced dormancy in snails indistinguishable from natural aestivation; and quiescence in ischemic mice fibroblasts (reversible cell-cycle exit, inhibition of protein synthesis and apoptosis and increased autophagy). Under ischemia, PHLPP1 and p-AKT translocated to mitochondria, and in vitro and ex vivo IR models showed that in mice cardiomyocyte and perfused hearts SNAP was cardioprotective by preventing the inhibition of pyruvate dehydrogenase activity and glucose oxidation through inhibiting mitochondrial AKT; and by promoting autophagy through inhibiting cytoplasmic S6K. SNAP may be an evolutionary-lost dormancy inducer that through its effects on the widely conserved AKT and S6K, acutely increases the threshold of tolerance to fuel-deprivation, inducing quiescence and a hibernation-like state in mice cells and hearts. The relevance of this first direct therapeutic application of hibernation biology in a non-hibernating species, may range from extending the shelf-life of the IR injury-vulnerable donated transplant organs to astronaut hibernation in ultra-long space travel.

METHODS

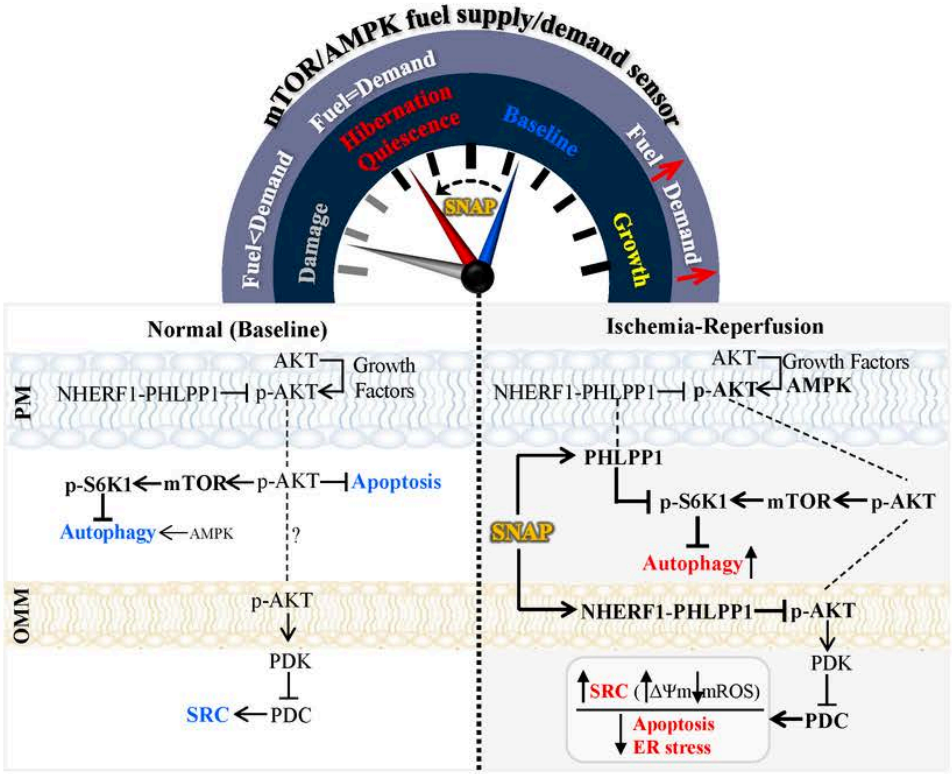
Kindly refer to the introduction section for reference.

RESULTS

Kindly refer to the introduction section for reference.

CONCLUSIONS

Kindly refer to the introduction section for reference.



PM: Plasma membrane. OMM: Outer membrane of mitochondria.

Comorbid Heart Failure and Short-Term Outcomes After Hospitalization for AECOPD

K. Rahemtulla, G. Lam, C. Wen, S. Moitra, M. Stickland, JA. Ezekowitz, J. Weatherald, M. Bhutani
Supervisor: Dr. Mohit Bhutani

INTRODUCTION

Heart Failure (HF) is common in patients with chronic obstructive pulmonary disease (COPD). The impact of concomitant HF on outcomes in patients hospitalized for an acute exacerbation of COPD (AECOPD) is uncertain.

METHODS

This was a population-based cohort study of all patients hospitalized for an AECOPD in Alberta, Canada between September 2018 to December 2019 using linked administrative databases with a diagnosis of COPD at discharge. The exposure of interest was a diagnosis of HF based on a validated ICD-10 algorithm, defined as 1 inpatient or 2 ambulatory heart failure visits within 1 year of each other anytime within the 5 years prior to the index admission for AECOPD.1 The primary outcome was 30-day all-cause hospital readmission. Secondary outcomes were 30-day all-cause emergency department (ED) visits and all-cause 90-day mortality post-discharge. We used Poisson regression and Cox proportional hazards regression to compare outcomes between patients with and without HF.

RESULTS

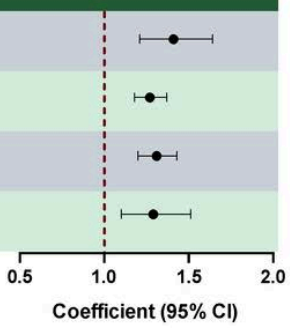
Of 8463 patients hospitalized with an AECOPD, the median age was 74 years, 49.8% were female, and 33.3% of patients had concomitant HF. The 30-day all-cause readmission, ED visit, and 90-day mortality rates were significantly higher in patients with HF (see Figure 1).

CONCLUSIONS

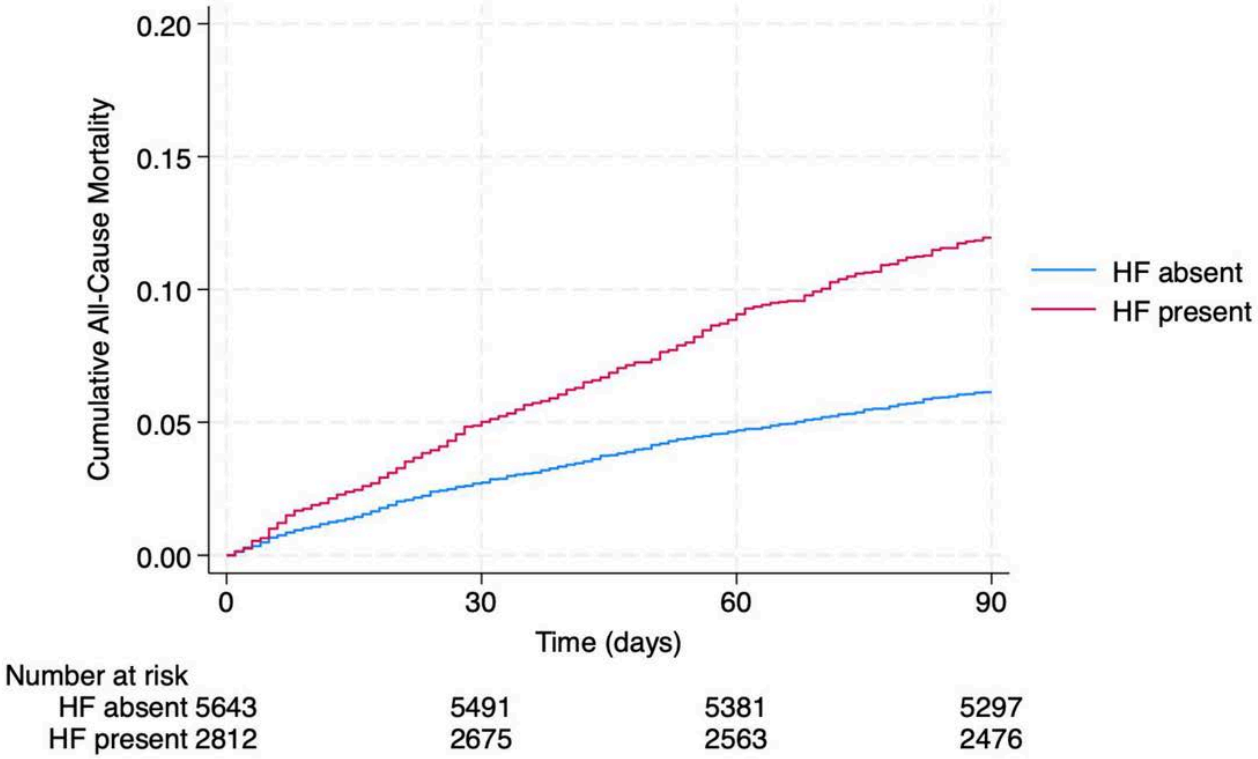
Comorbid HF is associated with increased short-term risk of all-cause readmission, ED visits, and death in patients following hospitalization for an AECOPD. Further research will identify whether medical optimization of both COPD and HF at the time of discharge impacts the short-term risk.

Rahemtulla et al., Figure 1A

Outcomes	AECOPD, no HF (n=5643)	AECOPD + HF (n=2812)	Coefficient (95% CI)
Total hospital readmission in 30-days [a]	517	333	1.41 (1.21, 1.64)
Total ED visits in 30-days [a]	2085	1315	1.27 (1.18, 1.37)
>1 ED visit in 30 days (%) [b]	1095 (19.4%)	728 (25.9%)	1.31 (1.20, 1.43)
All-cause mortality in 90-days (%) [c]	346 (6.1%)	336 (12.0%)	1.29 (1.10, 1.51)



Rahemtulla et al., Figure 1B



A pilot randomized trial on the usability and safety of an app (MyIBDDiet) to improve the self-management of anti-inflammatory diet for individuals with inflammatory bowel disease: Protocol

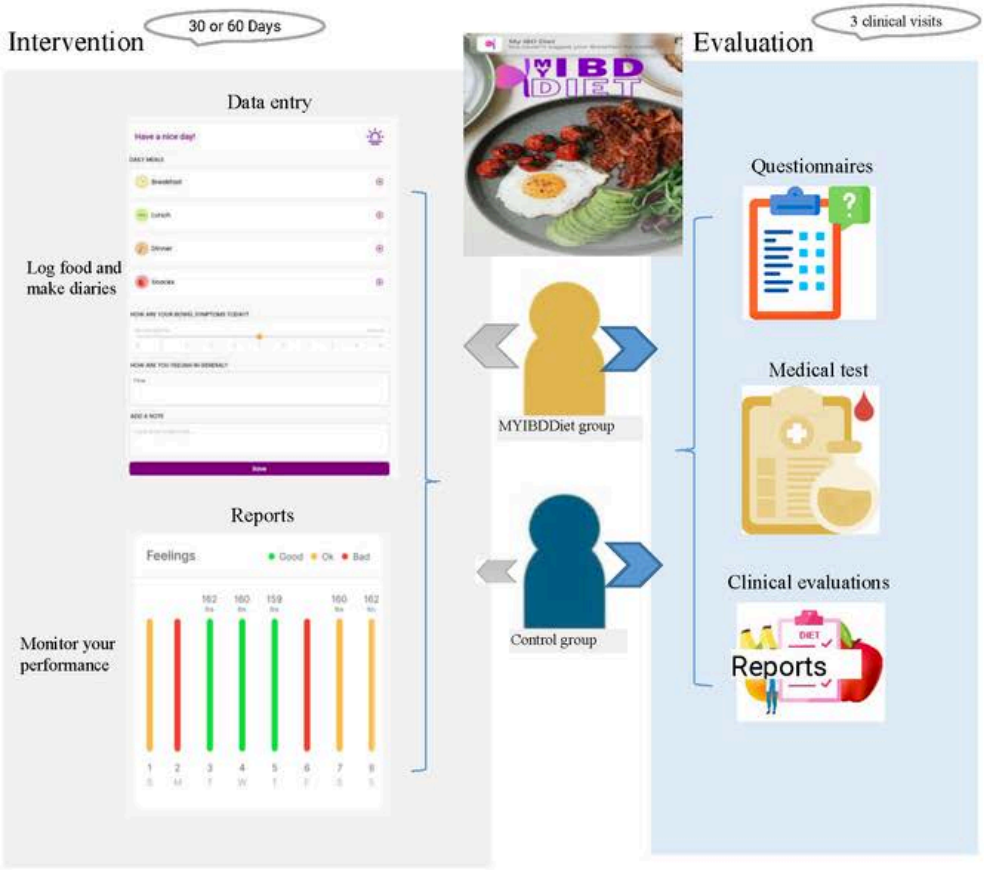
Somayeh Raiesdana, Kendall VanDiepen, Lekan Ajibulu , Karen Wong*
Supervisor: Dr. Karen Wong

INTRODUCTION
Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract. The role of diet in the management of IBD is increasingly recognized with recent guidelines providing concrete dietary recommendations. Although mobile health apps targeting diet and lifestyle habits in IBD are emerging, few are designed for self-management and few have been evaluated for effectiveness.

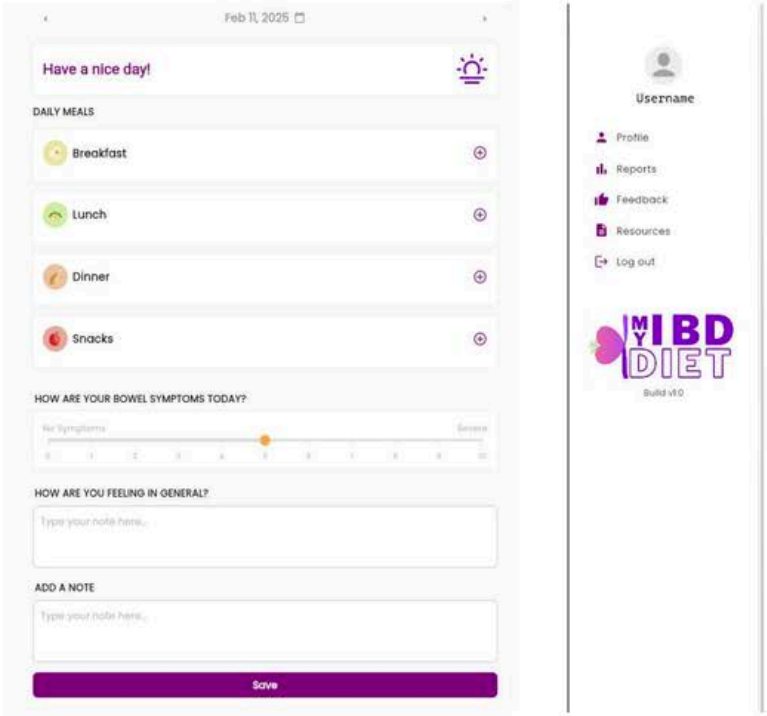
METHODS
We have co-designed a diet education app (MyIBDDiet) with and for IBD patients with the aim of improving the diet quality of users. The app features food intake tracking, including preparation methods, added fats, and food processing levels, with instant messaging feedback on whether to consume an item more or less often. The symptom-tracking feature further helps patients correlate their feelings with dietary choices. Additionally, the app offers educational resources and videos on anti-inflammatory eating, fiber and the microbiome, food additives, emulsifiers, and practical restaurant substitutions.

RESULTS
The primary outcomes of the study are the acceptability, usability, and safety of the app. Secondary outcomes include clinical efficacy, evaluated by changes in diet quality, healthy eating index, IBD-disease activity, and quality of life.
Members of our patient advisory council, including individuals with Crohn’s disease and ulcerative colitis, have evaluated the app's design and resources and confirmed the app for usability and acceptability. The app has been refined based on their needs and preferences, as well as feedback from a group of nutrition experts at the University of Alberta Hospital.

CONCLUSIONS
Data from both arms of this clinical trial will be analyzed using descriptive statistics to evaluate how daily food logging and receiving feedback through an evidence-based diet app can support IBD patients in self-managing their diet.
The pilot data generated can inform the design of an adequately powered randomized trial and future mobile app development and evaluation by providing a framework for evaluation of clinical effectiveness.



Graphical representation of study design; The left column displays the app's log and reporting interfaces, while the right column outlines the evaluation steps during clinical visits.



Shows the overall view of the home menu of the app

Prospective evaluation of diaphragm structure and function in double lung transplant recipients with baseline lung allograft dysfunction

Alisha Rullay, Karina Kaur, Jonathan Liu, Zachary Guenther, Alim Hirji MD MSc, Rhea Varughese MD MSc, Dale Lien MD, Justin Weinkauf MD MSc, Laura van den Bosch MD, Jayan Nagendran MD PhD, Ann Crockett, Jason Weatherald MD MSc, Gavin Low MD, Kieran Hallora
Supervisor: Dr. Kieran Halloran

INTRODUCTION

Baseline lung allograft dysfunction (BLAD) is a physiologic state in lung transplant recipients where lung function fails to normalize and is associated with an increased risk of death and potentially chronic lung allograft dysfunction. One potential contributor could be the diaphragms, which can have reduced function post-operatively due to phrenic nerve injury, ventilation-associated atrophy, or medication effects. We hypothesized BLAD would be associated with changes in diaphragm structure and function at 3-months post-transplant.

METHODS

We tested diaphragm function in patients who underwent lung transplant from June 2023 to May 2024 via ultrasonography and mean inspiratory pressure (MIP) measurements at 3-months post-transplant. We measured diaphragm thickness, thickening fraction, and excursion during tidal, deep, and sniff breath maneuvers. We compared values in patients with BLAD - defined as failure of forced expiratory volume in 1 second and forced vital capacity to reach 80% of recipient reference values on two tests done 3 weeks apart - to those with normal function using Wilcoxon rank sum tests and linear regression.

RESULTS

We included 56 patients, mainly transplanted for interstitial lung disease (69%), 28 (50%) of whom met criteria for BLAD. Patients with BLAD had lower MIP ($p=0.0499$) and lower diaphragm excursion on deep breathing ($p=0.0407$) and sniff test ($p=0.0321$). There were no differences in thickness or thickening fraction. BLAD remained associated with both MIP ($p=0.0313$) and deep breath excursion ($p=0.0028$) even after adjustment for primary disease and severe primary graft dysfunction.

CONCLUSIONS

BLAD is associated with lower diaphragm function but not structure at 3-months post-transplant. This suggests muscle function could be contributing to BLAD pathogenesis in some cases. We are planning follow-up measurements at 1-year post-transplant in this cohort to assess the dynamics of diaphragm function and BLAD over time.

Health-related quality of life and exercise capacity in double lung transplant recipients with baseline lung allograft dysfunction

Alisha Rullay BSc, Karina Kaur BSc, Jennifer Holman PT, Laura van den Bosch MD, Justin Weinkauf MD, Jayan Nagendran MD PhD, Rhea Varughese MD MSc, Alim Hirji MD MSc, Dale Lien MD, Jason Weatherald MD MSc, Kieran Halloran MD MSc
Supervisor: Dr. Kieran Halloran

INTRODUCTION
Baseline lung allograft dysfunction (BLAD) after lung transplant is associated with an increased risk of dying, but the association with health-related quality of life (HRQL) and exercise capacity is not known. We hypothesized that BLAD would be associated with reduced HRQL and six-minute walk distance (6MWD) at 1-year post-lung transplant.

METHODS
We analyzed patients who underwent lung transplant in our program 2004 to 2018 who completed 1-year Short Form 36 (SF-36) questionnaires and 6MWD testing. We defined BLAD as failure of both forced expiratory volume in 1 second and forced vital capacity to reach > 80% predicted of a healthy reference population's lung function on two consecutive tests > 3 weeks apart. We tested the relationship between BLAD status and SF-36 physical component summaries and 6MWD using linear regression, adjusting for age at transplant, sex at birth, and primary lung disease.

RESULTS
264 patients were included, 96 (36%) of whom met criteria for BLAD. Patients with interstitial lung disease as indication for transplant, and those who received older, female, and heavy smoking donors were at increased risk of BLAD. Figure 1 displays the unadjusted SF-36 PCS and 6MWD scores stratified by BLAD status. BLAD was associated with lower SF-36 scores (p=0.0025) and 6MWD (p=0.0008) at 1-year post-transplant in adjusted linear regression models.

CONCLUSIONS
BLAD was associated with reduced HRQL and 6MWD scores at 1-year post-lung transplant in adjusted models. This suggests that poor post-transplant lung function could be contributing to lower HRQL and exercise capacity in lung recipients, and worthy of further exploration in terms of causes, prevention strategies, and treatments.

Predicting baseline lung allograft dysfunction in double lung transplant recipients based on pre-and peri-operative characteristics

Alisha Rullay BSc, Karina Kaur BSc, Alim Hirji MD MSc, Rhea Varughese MD MSc, Jason Weatherald MD MSc, Laura van den Bosch MD, Dale Lien MD, Justin Weinkauf MD, Patrick Gauthier PhD, Kieran Halloran MD MSc
Supervisor: Dr. Kieran Halloran

INTRODUCTION

Baseline lung allograft dysfunction (BLAD) is a physiologic state in lung transplants (LTx) where lung function does not reach normal post-transplant levels and is associated with poorer survival and potentially more chronic lung allograft dysfunction (CLAD). We sought to determine whether BLAD could be predicted using pre-transplant recipient, donor, and operative variables.

METHODS

We analyzed patients who underwent double LTx in 2004-2020. We defined BLAD as failure of forced expiratory volume in 1 second and forced vital capacity to reach > 80% of recipient reference values for two consecutive tests > 3 weeks apart at any time post-LTx. We tested a comprehensive list of recipient, donor, and operative variables (figure 1A) chosen based on biologically plausible association with BLAD. We excluded early outcomes - i.e. primary graft dysfunction - as these may be on the causal pathway between risk factor and BLAD. Variables with >5% missing data were handled with K nearest neighbors imputation. We constructed a final multivariable logistic model using 30-fold cross-validation and lasso reduction for feature selection.

RESULTS

We included 669 double LTx recipients, 42% of whom met criteria for BLAD. Of the analyzed variables, interstitial lung disease, donor female-to-recipient-male sex match, bridging on mechanical ventilation, donor age, and donor heavy smoking history were most associated with an increased risk of BLAD, while obstructive lung disease, non-bridging status, and Caucasian recipient ethnicity were associated with reduced BLAD risk. All associations are depicted in figure 1B. Model performance assessed using cross-validation with 30-folds was reasonable, with a median area-under-the-curve of 0.68.

CONCLUSIONS

BLAD after LTx can be predicted using only pre- and peri-operative factors with reasonable performance, and the highest ranked associations provide some insight into potential mechanisms of BLAD physiology.

p53 associated de novo activation of VWF expression in tumor cells

Noorossadat Seyyedi, Tiffany Lo, Parnian Alavi, Manijeh Pasdar, Nadia Jahroudi
Supervisor: Nadia Jahroudi

INTRODUCTION

Expression of the pro-coagulant protein von Willebrand Factor (VWF) under physiological condition is exclusively restricted to endothelial cells and megakaryocytes. However, its de novo expression is detected in some cancer cells of non-endothelial/megakaryocytic origin and may promote their metastatic potential. We have previously demonstrated VWF expression in the osteosarcoma cell line SAOS2, but not in KHOS cells, with the transcriptional repressor NF-IB and the activator GATA6 implicated in the regulation of its expression. NF-IB has been reported to be a target of tumor suppressor p53, one of the most frequently mutated genes in cancer. We have previously shown that the dual adhesion and signaling protein plakoglobin (PG) can restore the tumor suppressor function of some p53 mutants. We hypothesized that p53 mutations induce de novo activation of VWF, potentially through targeting NF-IB and potentially GATA6, while plakoglobin interaction with mutant p53 reverses this effect.

METHODS

p53- and plakoglobin-null H1299 cells were transfected with p53- [WT, conformational, or contact mutants], with or without plakoglobin, and assessed for VWF, NF-IB, and GATA6 expression by qRT-PCR, western blot, and immunofluorescence assays. Co-immunoprecipitation examined p53-NF-IB interactions, while chromatin immunoprecipitation determined NF-IB recruitment to the VWF promoter. Human Protein Atlas and the TP53 database were surveyed to explore the correlation of NF-IB and p53 mutation with VWF expression in cancer cells.

RESULTS

Specifically conformational mutant p53 expression in H1299 induced VWF expression. It also upregulated GATA6 expression and disrupted NF-IB association with the VWF promoter. PG co-expression all these effects. Database searches demonstrated that VWF expression is associated with either downregulating mutation of NF-IB gene (53%) and/or conformational mutant p53 expression (~32%).

CONCLUSIONS

Our study revealed a novel mechanism by which mutant p53 could contribute to de novo activation of VWF expression through interfering with VWF transcriptional regulatory factors, while plakoglobin reverses this effect.

Effects of dietary intake of stool donors and recipients of fecal microbiota transplantation on the gut bacterial diversity and clinical outcomes in recurrent Clostridioides difficile infection

Mohamed Shaheen, Anissa Armet, Chelsea McDougall, Rose Franz, Karen Wong and Dina Kao
Supervisor: Dr. Dina Kao

INTRODUCTION

Fecal microbiota transplantation (FMT) is currently the most effective treatment for preventing recurrent Clostridioides difficile infection (rCDI), achieving clinical success rates of 80–90%. This success is largely driven by the modulation of recipient gut microbiota by of donor-derived organisms. Diet plays a central role in shaping gut microbial diversity and composition, therefore, understanding how diet influences microbiota restoration may offer opportunities to improve FMT outcomes. This study aimed to evaluate dietary intake and quality in FMT donors and recipients and to examine associations of diet with bacterial community in the context of rCDI treatment.

METHODS

Twenty rCDI patients received oral capsule FMT from one of two donors and were assessed at baseline (W0), Week 1, and Week 8 (W8). Clinical success was defined as no recurrence of CDI at W8. Dietary intake data were collected using one day and three days 24-hour dietary recalls during collecting stool samples from recipient and donor respectively. Dietary quality was assessed using the Healthy Eating Index. Stool samples were analyzed using 16S rDNA sequencing to characterize bacterial community composition, and associations between diet and microbiota were examined.

RESULTS

The overall clinical success rate was 95%. Dietary intake patterns among FMT recipients were highly variable. Compared to Donor-32 FMT recipients, Donor-35 recipients had lower caloric intake and more closely aligned dietary patterns with their donor, except for one participant who experienced treatment failure. At W8, compared to W0, recipients showed increased bacterial diversity, enrichment of beneficial taxa, and reductions in pathobionts. Higher HEI scores were associated with higher gut microbial diversity, and donor-recipient dietary alignment appeared to enhance microbiota restoration in recipients (Figure 1).

CONCLUSIONS

Healthy dietary patterns and donor-recipient dietary alignment may improve FMT efficacy. These findings highlight the potential benefit of incorporating dietary assessment into donor selection and recipient counseling in clinical practice.

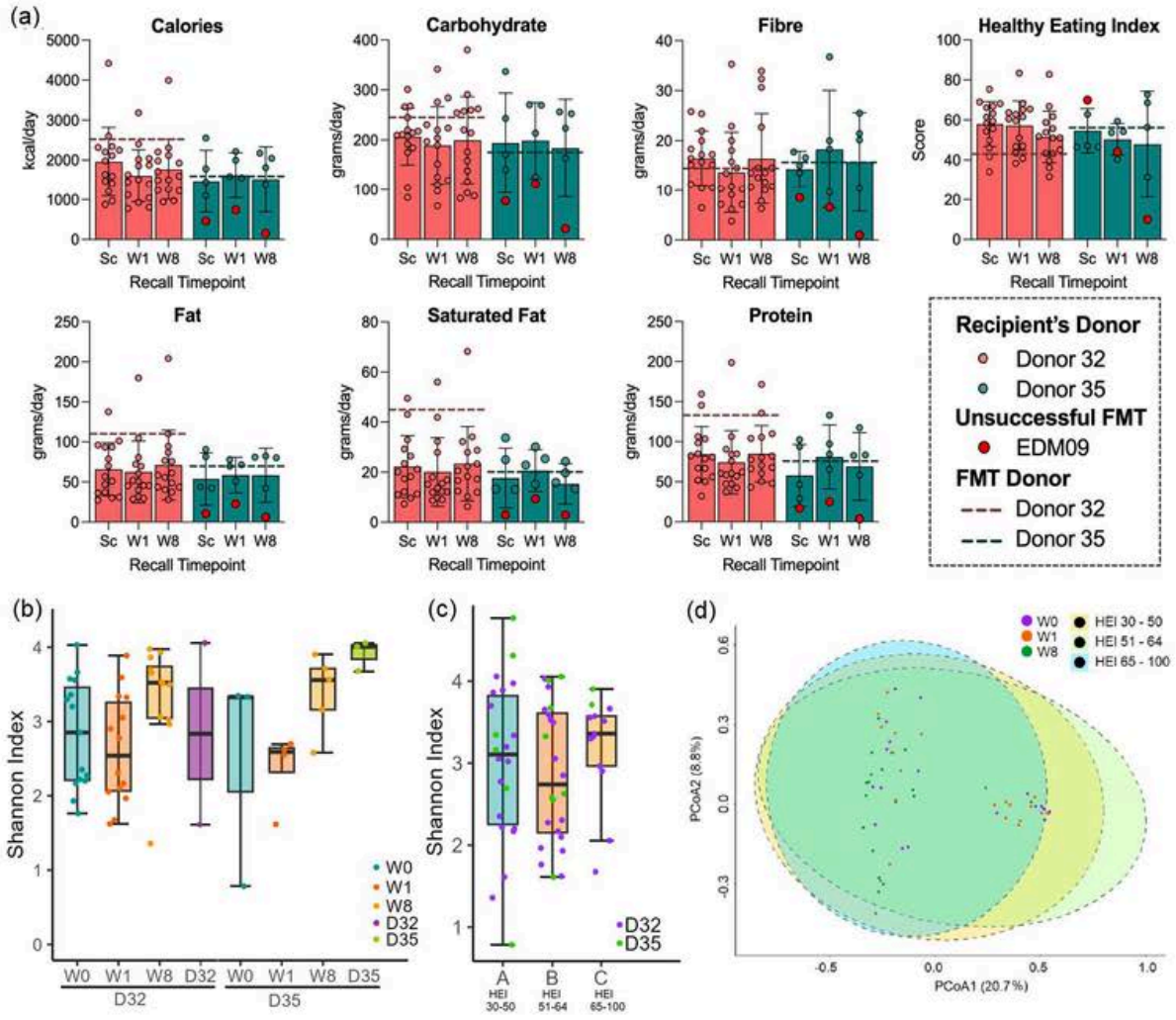


Figure 1. Dietary intake and bacterial diversity indices of Fecal Microbiota Transplantation (FMT)-donor and recipients in recurrent *Clostridioides difficile* infection at baseline (W0) and post-treatment (W1 and W8). (a) Bar plots show mean ± standard deviations of dietary component intake, individual dots represent FMT recipients corresponding to their respective donors. Dotted lines located across the bars represent the average intake of the two FMT donors. (b) Bacterial alpha diversity indices (Shannon) of patients and the donors. (c) Bacterial Shannon diversity indices of FMT recipients based on their Healthy Eating Indices (HEI). A higher Shannon index was observed with a higher HEI (65-100)($p < 0.5$). (d) Bacterial beta diversity indices (Bray-Curtis dissimilarity index) demonstrated a clustering of W8 samples (clinical success cases with restoration of beneficial bacteria) within the higher HEI group, suggesting a potential link between HEI and restoration of beneficial gut bacteria.

Characterizing Patient Reported Outcome Measure Descriptions for Clinical Trials in Dialysis Registered on ClinicalTrials.gov

Rahul Sharma,1 Badal S.B. Pattar,2,3 Annalijn I. Conklin,4,5 David Collister,1,6,7 Sandra M. Dumanski,2,3,7,8 Aminu Bello,1,7 Bill Wang,9 Sofia B. Ahmed1,6,7
Supervisor: Dr. Sofia Ahmed

INTRODUCTION

Background The importance of patient-centered outcomes is increasingly recognized in kidney care, particularly in management of kidney failure with dialysis.

Objectives To determine how frequently patient-reported outcome measures (PROMs) are reported in randomized controlled trials of dialysis.

METHODS

Clinical trials registered on ClinicalTrials.gov were searched until November 28 2024. Randomized controlled trials with the term “dialysis” (e.g., hemodialysis, peritoneal dialysis) listed as an intervention or treatment were included. Data on inclusion of pre-specified core (e.g., life participation, fatigue, pain) and non-core (e.g., itch/skin, mobility, impact on family and friends) PROMs as defined by the international Standardized Outcomes in Nephrology were extracted. Results of included studies were synthesized in a descriptive manner.

RESULTS

Of 369 randomized clinical trials identified, 242 met inclusion criteria. Hemodialysis-only was the dialysis intervention or treatment in the majority of studies (70%); the remainder of studies included peritoneal dialysis-only (25%) or mixed dialysis (hemodialysis or peritoneal dialysis) (5%) interventions or treatments. Sixty percent of studies (n=145) did not include a pre-specified PROM. Forty percent of studies (n=97) (hemodialysis-only, n=71, 29%; peritoneal dialysis-only, n=21, 9%; mixed dialysis, n=5, 2%) included at least one PROM as a pre-specified outcome. Within hemodialysis-only studies including pre-specified PROMs, 76% reported both core and non-core PROMs, while 24% reported only non-core PROMs. Within peritoneal dialysis-only studies reporting PROMs, 68% reported both core and non-core PROMs, 5% reported only core PROMs, 23% reported only non-core PROMs. Within mixed dialysis studies, 60% reported both core and non-core PROMs and 40% reported only non-core PROMs.

CONCLUSIONS

Less than half of recent and ongoing randomized controlled trials in dialysis include PROMs as a pre-specified outcome. Given the increasing complexity of the growing dialysis population, greater focus on PROMs is needed in research to optimally inform person-centered, goal-directed dialysis.

PSC-specific prognostic scores associated with graft loss and overall mortality in recurrent PSC after liver transplantation

Ellina Lytvyak, Dennis Wang, Devika Shreekumar, Maryam Ebadi, Yousef Alrifae, Andrew Mason, Aldo J. Montano-Loza
Supervisor: Dr. Ellina Lytvyak

INTRODUCTION
Primary sclerosing cholangitis (PSC) is a progressive liver disease with no treatment apart from liver transplantation (LT). After LT, patients can develop recurrent PSC (rPSC). The United-Kingdom (UK-PSC) and Amsterdam-Oxford (AOPSC) scores are used as prognostic models for PSC outcomes. We aimed to assess these scores as predictive tools for graft loss and overall mortality in rPSC.

METHODS
We evaluated 67 people who developed rPSC. Using Cox regression models, we quantified associations between UK-PSC and AOPSC scores and graft loss and overall mortality. Cut-offs were established using receiver operator characteristic analysis and the highest Youden index.

RESULTS
Both UK-PSC and AOPSC scores were independently associated with graft loss (hazard ratio [HR] 2.43; $p<0.001$) and HR 3.45; $p<0.001$), respectively), but only the UK-PSC score was independently associated with overall mortality (HR 2.63; $p=0.009$). The probability of overall graft survival was 72% at 5 years, and 47% at 10 years (Figure 1a). Individuals with UK-PSC ≥-4.2 (6.1±0.8 vs. 14.7±1.0 years; $p=0.001$), AOPSC score ≥2.4 with age at recurrence (5.4±1.3 vs. 12.0±1.1 years; $p<0.001$) and AOPSC score with age at diagnosis ≥2.2 (4.8±0.8 vs. 11.8±1.6 years; $p=0.014$) had shorter graft survival (Figure 1b-d). Patients with severe cholestasis had shorter graft survival compared to those without severe cholestasis (5.0±1.0 vs. 12.3±1.1 years; $p<0.001$; Figure 1e). Individuals with UK-PSC ≥-3.6 (9.1±1.8 vs. 15.5±1.6 years; $p=0.009$), AOPSC score ≥3.0 with age at recurrence (7.8±2.1 vs. 14.5±2.0 years; $p=0.047$) and AOPSC score ≥2.9 with age at diagnosis (6.1±2.4 vs. 14.5±1.6 years; $p=0.002$) had shorter overall survival.

CONCLUSIONS
UK-PSC score at rPSC predicts both graft loss and overall mortality, while AOPSC scores using either age at rPSC or at diagnosis along with severe cholestasis predict graft loss in people with rPSC. These easy-to-administer tools can be utilized in clinical practice to identify high-risk rPSC patients and guide decisions about monitoring/interventions.

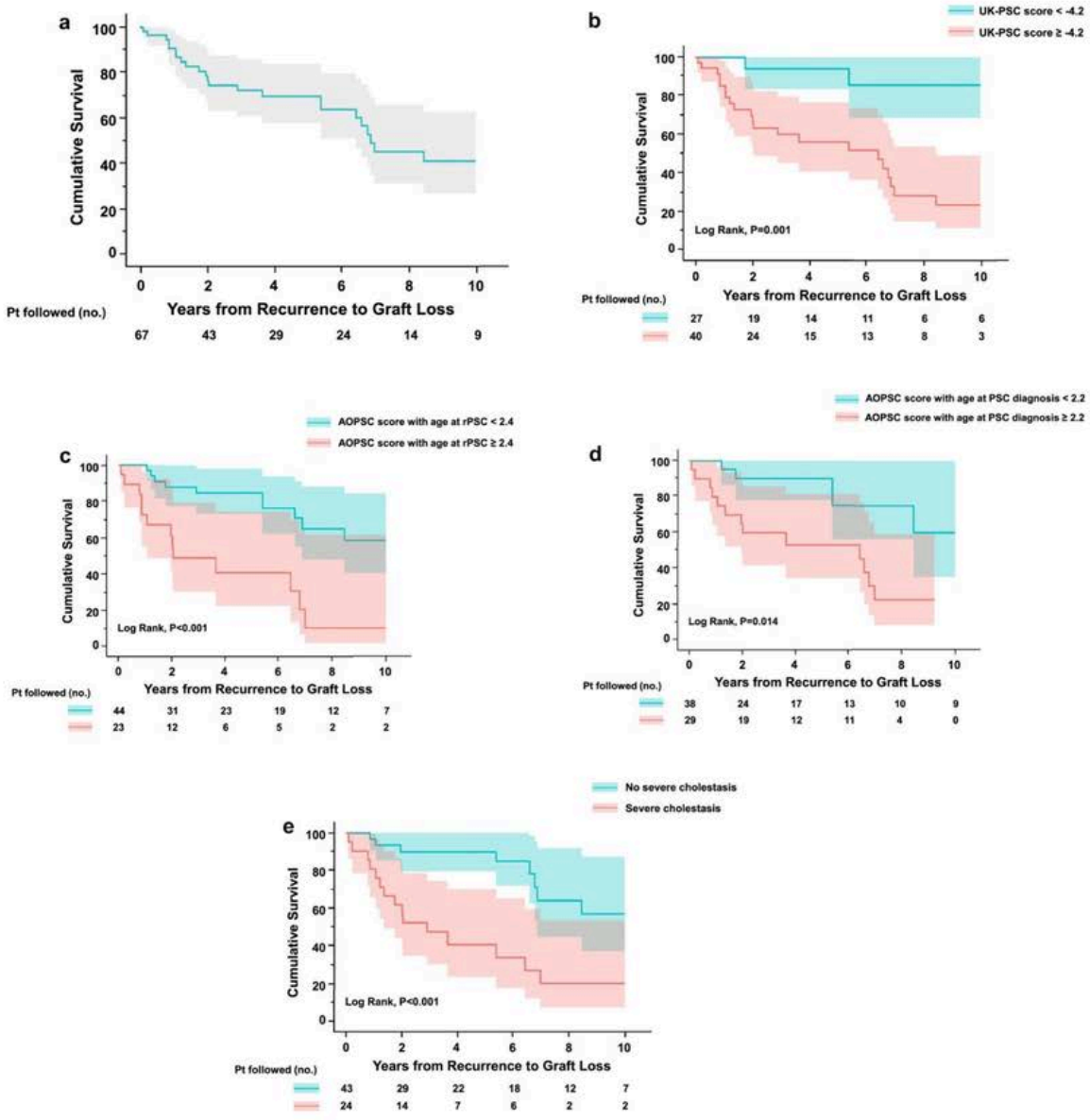


Figure 1. (a) Cumulative probability of overall graft survival from onset of recurrent primary sclerosing cholangitis (*r*PSC). **(b)** Cumulative probability of graft survival from onset of *r*PSC in patients with United-Kingdom-PSC (UK-PSC) score ≥−4.2 or <−4.2. **(c)** Cumulative probability of graft survival from onset of *r*PSC in patients with Amsterdam-Oxford PSC (AOPSC) score with age at *r*PSC ≥2.4 or <2.4. **(d)** Cumulative probability of graft survival from onset of *r*PSC in patients with AOPSC score with age at PSC diagnosis ≥2.2 or <2.2. **(e)** Cumulative probability of graft survival from onset of *r*PSC in patients with or without severe cholestasis.

Management of obesity in a multimorbid patient population with chronic liver and gastrointestinal diseases is effective, safe and improves quality of life

Ellina Lytvyak, Devika Shreekumar, Shagani Thisairajah, Olexandr Troshyn, Aldo J. Montano-Loza
Supervisor: Dr. Ellina Lytvyak

INTRODUCTION

Obesity is often overlooked and unmanaged in patients with chronic liver and gastrointestinal diseases (CLGI). We aimed to evaluate the effectiveness and safety of obesity management in this complex multimorbid population and its impact on quality of life.

METHODS

A longitudinal prospective cohort study was conducted at the Bariatric Medicine Clinic, University of Alberta, with patients with CLGI managed and unmanaged in the clinic. Clinical, laboratory data, percent of total weight loss (%TWL) and Chronic Liver Disease Questionnaire (CLDQ) scores were collected.

RESULTS

Baseline characteristics of 125 managed patients are presented in Table 1. Unmanaged patients (n=38) did not differ by demographic and clinical features. At 12 months, managed patients had -11.1% %TWL compared to 3.5% weight gain in unmanaged ($p=0.006$; data not shown). Over 62% of managed patients were on weight-loss medications (WLM) and 38%–solely on lifestyle modifications (LS). At 6 months, %TWL was -11.3±6.8%, -5.1±7.2% vs. -0.2±1.6% for WLM, LS vs. unmanaged, respectively ($p<0.001$; Figure 1a). At 12 months, managed patients on WLM had a total weight loss of -14.1% compared to -5.8% on LS and 3.5% weight gain among patients not managed at the Bariatric Medicine Clinic ($p<0.05$; Figure 1a). There was no worsening in either liver, renal function, vitamin, micronutrients or protein status among managed patients. Managed patients had improvements in the CLDQ total score and all CLDQ domains (activity, emotional function, worry, abdominal symptoms, systemic symptoms and fatigue) from baseline to 6 months (Figure 1b).

CONCLUSIONS

Both lifestyle and pharmacological management of obesity in multimorbid patients with CLGI is effective, safe, and results in improved quality of life. Weight loss should be closely supervised to ensure a patient-centred, evidence-based, comprehensive approach, constant monitoring and recommendations that are tailored to the patient’s complex health conditions and unique needs.

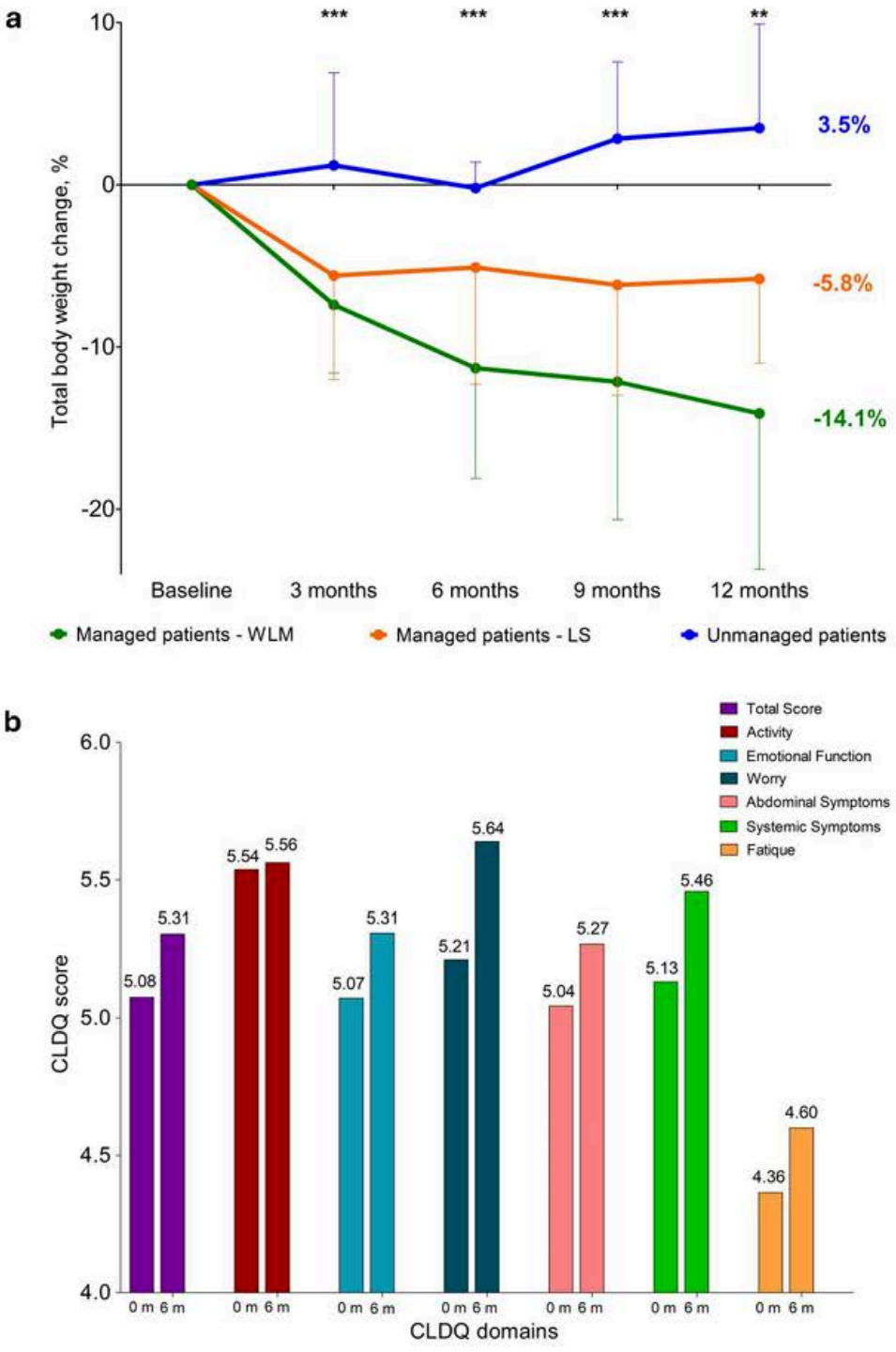


Figure 1. (a) Body weight changes over time, depending on the intervention, %, mean ± SD. **(b)** Chronic Liver Diseases Questionnaire (CLDQ) score changes over time in managed patients, mean.

Targeting Hepatitis B virus's cccDNA through repurposed GQ-binding ligands

Jessica Skoreyko, Emma Kasinyabo, Kira Sviderskaia, Hoa Le, Vannessa Meier-Stephenson
Supervisor: Dr. Vanessa Meier-Stephenson

INTRODUCTION

Hepatitis B virus (HBV) chronically infects ~300 million individuals worldwide, increasing the risk of complications like hepatocellular carcinoma. The chronicity of this virus is due to the establishment and persistence of the covalently closed circular DNA (cccDNA) in the livers of those chronically infected. Because cccDNA binds host nuclear factors like histones, the similarity to the host genome makes targeting and clearing the cccDNA challenging. Consequently, a cure for chronic HBV infections has yet to be found. With the discovery of a highly conserved G-quadruplex (GQ) within the precore promoter (PCP)- a vital promoter for the genetic code of all progeny virus- a novel target to bind the cccDNA may be possible. Mutations that disrupt this GQ formation led to a reduction in viral transcripts. Therefore, we hypothesize that with repurposing GQ-binding ligands from the cancer field, we can interfere with the transcription and production of progeny viruses.

METHODS

GQ-binding ligands (TMPyP4, BRACO19, PhenDC3) were assessed for their toxicity via an alamarBlue assay. The activity of the PCP in the presence of these GQ-binding drugs was investigated through a luciferase assay. To assess the impact of these ligands on the virus's lifecycle, 2ug of 1.3mer HBV plasmid was transfected into HepG2-NTCPs. After 4 hours, 2 days, and 4 days post-transfection, cells were harvested to assess viral markers (via immunofluorescence, ELISA and qPCR).

RESULTS

The presence of GQ-binders shows minimal toxicity to the cells at doses and times used. In the luciferase reporter assays, the presence of GQ-binders appears to enhance the activity of the PCP. However, in initial 1.3mer HBV transfection studies, there appears to be inhibition by TMPyP4 but minimal inhibition by BRACO19 or PhenDC3.

CONCLUSIONS

These ligands appear to impact viral activity. However, further assessment into their mechanism of action needs to be explored, including any off-target impacts in the cell.

Homologous composition of plant- and human-derived extracellular vesicles (EVs) suggests a potential dietary origin of circulating plasma EVs

Tanya Suandork, Jokha Aliy, Mizan Rahman, Carlos Cervera
Supervisor: Carlos Cervera

INTRODUCTION

Extracellular vesicles (EVs) are described as lipid bilayer-enclosed particles secreted by cells and implicated in intercellular communication. While extensively studied in humans, the knowledge on morphology, composition, and origin of plant EVs remain less characterized. Our research explores the shared and distinct features of human and plant EVs, with particular attention to their composition.

METHODS

We used transmission electron microscopy (TEM) to characterize plant-derived EVs. We used Alcian blue staining and immunofluorescence to detect the presence of glycosaminoglycans (GAGs), proteoglycans (PGs), and sialic acid. We used acridine orange to stain the lipid bilayer membranes. EVs surface markers (CD63, CD9, and CD81) and other constitutive proteins were evaluated by Western blot (WB).

RESULTS

Starch nanoparticles (SNPs) were obtained from various starchy plants (chickpea, lentil, beans, rice, and quinoa). TEM revealed the presence of lipid bilayer membranes, suggesting that a substantial portion of these SNPs may correspond to plant-derived EVs with 3 size categories (1-2 µm, 500 nm, and 100 nm). These structures exhibit positive staining with acridine orange, indicating the presence of cardiolipin in the membrane. All SNPs stained positively with Alcian blue and wheat germ agglutinin (WGA), suggesting the presence of GAGs and sialic acid, respectively. Immunofluorescence confirmed the presence of perlecan, keratan sulfate (KS) and heparan sulfate (HS), with KS further validated by WB. We detected the presence of plant mitochondrial (COX4 and GDC-H), chloroplast (TIC40 and CSD2), and thylakoid (Cytochrome f and NdhB) proteins by WB in EVs obtained from the plasma of four healthy participants.

CONCLUSIONS

Plant and human-derived EVs exhibit several homologies. The detection of plant chloroplast and mitochondrial proteins in human EVs suggests that a proportion of these vesicles may originate from dietary sources.

Metabolic remodeling and Abnormal Mitochondrial Signaling in Primary Biliary Cholangitis

Ning Sun, Hussain Syed, Filip Wysokinski, Olaide Ugbechie, Doaa Waly, Seyed Sajjad Zadian, Varinder Verma, Andrew L. Mason
Supervisor: Andrew Mason

INTRODUCTION

Cholangiocytes from primary biliary cholangitis (PBC) patients aberrantly express increased pyruvate dehydrogenase complex-E2 subunit (PDC-E2), which is thought to result in loss of tolerance to mitochondrial proteins and produce anti-mitochondrial antibodies (AMA). To better understand these changes, we have studied the metabolism in PBC cholangiocytes and found increased glycolysis linked with altered mitochondrial respiration. Herein, we addressed the hypothesis that a glycolytic-shift and metabolic remodeling occur systemically both in cholangiocytes and the peripheral blood of PBC, which in turn leads to an increased PDC-E2 expression.

METHODS

We used RNAseq to compare transcriptomic changes in PBC patients' whole blood versus healthy controls to gain a wider perspective of the systemic changes in PBC patients' metabolism. We especially focused on studying glycolysis and mitochondrial respiration pathways by Gene Ontology enrichment analysis. We also investigate whether HIFα pathway activation was involved in the metabolic remodeling of cholangiocytes. Then, we focused on evaluating the mitochondrial-DNA replication by using quantitative PCR. We also evaluated the mitochondrial membrane potential and PDC-E2 expression in PBMC of PBC versus healthy controls and MAFLD by immunocytochemistry.

RESULTS

We found evidence of increased glycolysis and altered mitochondrial respiration pathway with an upregulated mitochondrial-encoded OXPHOS gene expression and a downregulated nuclear-encoded OXPHOS gene expression in peripheral blood from patients with PBC as compared to healthy subjects. These gene expression changes were accompanied by increased mt-DNA replication and hyperpolarized mitochondria in PBC peripheral blood. Some specific cholangiocytes from PBC patients' were characterized by activated HIF1α signalling. Finally, the overexpression of the mitochondrial autoantigen PDC-E2 was predominantly observed with hyperpolarized mitochondria in PBMC of patients with PBC.

CONCLUSIONS

These findings support the hypothesis that the abnormal mitochondrial signalling characterized by hyperpolarized mitochondria induces compensatory mitochondrial biogenesis linked with the overexpression of mitochondrial autoantigens in PBC.

Machine Learning Predicts Response to Obeticholic Acid Therapy and Prognostic Pathways linked with Primary Biliary Cholangitis

Hussain Syed, Ning Sun, Doaa Waly, Varinder Verma, David Shapiro, Mary Erickson, Kathy Siminovitch, Mohammed S. Osman , Andrew L. Mason
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary Biliary Cholangitis (PBC) is a chronic cholestatic liver disease. Ursodeoxycholic acid (UDCA) is used as the first-line therapy while obeticholic acid (OCA) is approved as second-line treatment for patients with inadequate responses. Evidence suggests that oxidative stress and DNA damage in biliary epithelial cells (BECs) may trigger autophagy, leading to cellular senescence or apoptosis, which contributes to inflammation and fibrosis. However, the relationship of these processes with prognosis remains unclear. Current prognostic tools focus on clinical endpoints but do not capture pathway-level differences that distinguish prognoses. We developed a machine learning (ML) model using transcriptomic data from peripheral blood to predict response and identify pathways involved in PBC pathogenesis.

METHODS

Patients enrolled in the POISE clinical trial for OCA and a prospectively collected independent cohort were used to develop the model. ML selection identified 1200 candidate genes which were mapped to pathways using IPA. These were refined using a genetic algorithm to generate an 81 gene panel which was trained on POISE End-of-Treatment (n=53), tested on the POISE baseline (n=88) and validated on the prospective cohort (n=63). RNA-seq from BECs of PBC (n=4) vs non-cholestatic controls (n=5) were compared against peripheral blood RNA-seq to identify overlap.

RESULTS

The model performed well in the baseline-testing [AUROC 0.84] and validation [AUROC 0.89] cohorts, outperforming alkaline phosphatase and bilirubin. Dysregulated pathways captured OCA activity as an FXR agonist with inhibition of bile acid synthesis, inflammation, and fibrosis [$p<0.05$]. Top dysregulated pathways identified autoimmune inflammation, immune regulation, epithelial-mesenchymal transition, integrated stress response and metabolic signaling [$p<0.005$]. These prognostic pathways were also mirrored in the BEC of PBC patients.

CONCLUSIONS

The ML model outperformed traditional biomarkers and revealed pathways driving disease progression. Notably, peripheral blood signatures reflected pathological changes in the biliary epithelium. These findings advance our understanding of PBC and support a more targeted investigative approach.

Figure 1

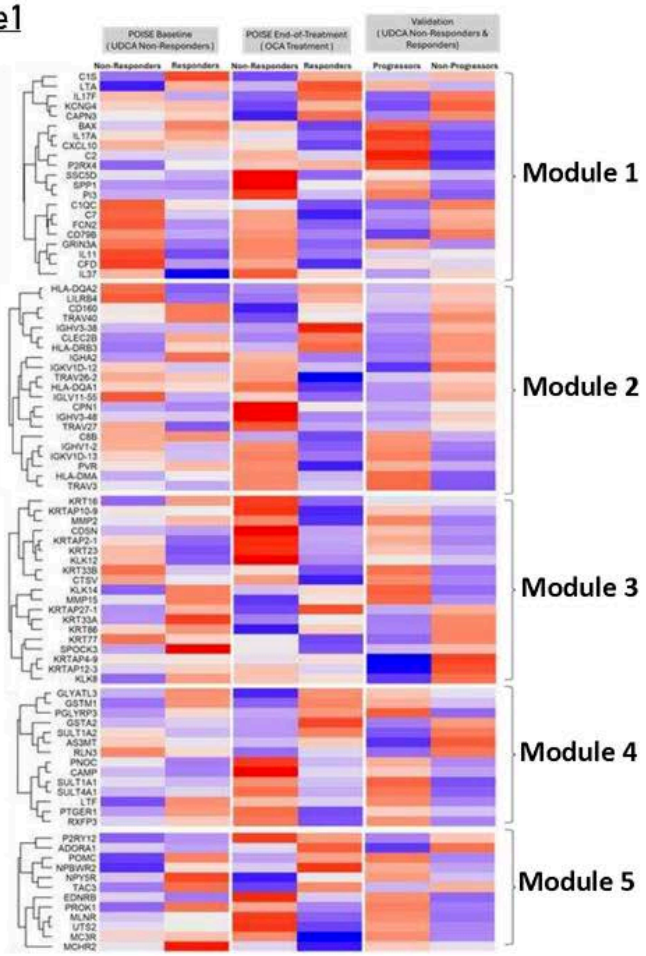


Figure 1. Ingenuity Pathway Analysis (IPA) of genes identified as prognostically relevant to PBC progression by machine learning model. Prognostically relevant genes dysregulated in the top 10 most enriched pathways as identified by IPA were showcased in a heatmap showing changes in the POISE Baseline, POISE end-of-treatment and prospectively collected validation datasets. The hierarchical clustered genes were organized in modules as 1 [autoimmune related inflammation], 2 [immune regulation], 3 [epithelial-mesenchymal transition], 4 [integrated stress response] and 5 [metabolic signaling]

Figure 2

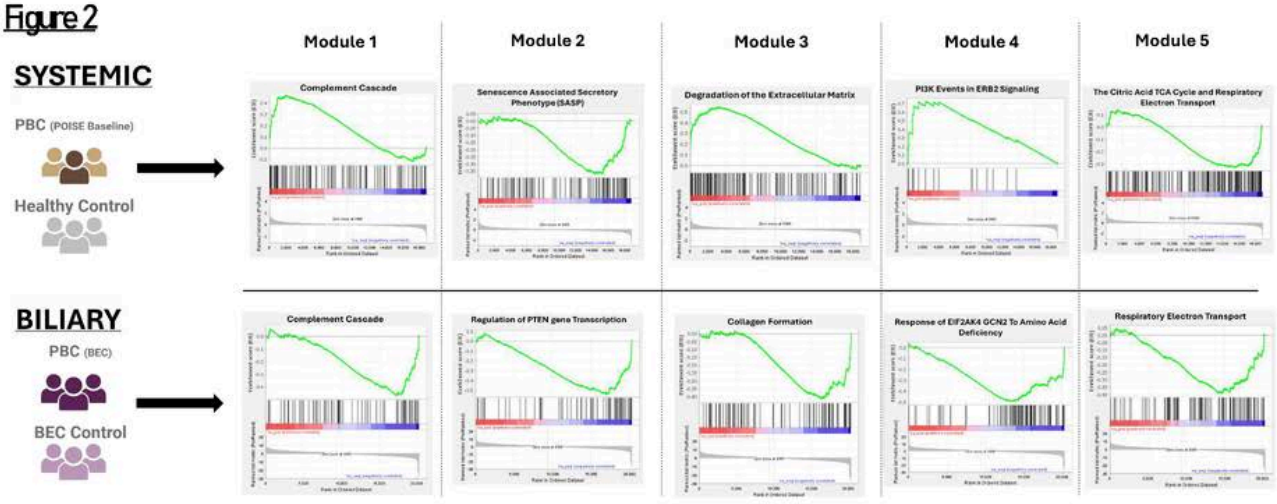


Figure 2. Gene set enrichment analysis (GSEA) comparing systemic and liver-specific pathways illustrates shared biological processes and gene expression trends between peripheral blood and liver-specific datasets. These included autoimmune related inflammation, immune regulation, epithelial-mesenchymal transition, integrated stress response and metabolic signaling.

Tumour Initiated Purinergic Signalling Can Promote Cardiomyocyte RBFOX1 Degradation and Increase the Risk for Developing Cardiotoxicity from DNA Damaging Anticancer Agents

Saymon Tejay, Maria Areli Lorenzana-Carillo, Guochang Huang, Seyed Amir Hussein Tabatabaei, Yuan Yuan Zhao, Farah Eaton, Michelle Mendiola Pla, Dawn E Bowles, Ian D Patterson, Edith Pituskin, John R Ussher, Evangelos Michelakis and Gopinath Sutendra
Supervisor: Dr. Gopinath Sutendra

INTRODUCTION

It is well established that cancer cells secrete numerous signalling factors affecting distant normal tissues such as skeletal muscle or adipose tissue break down by tumour necrosis factor (TNFa) and lipid mobilizing factor (LMF) respectively. What remains unclear is if tumour secreted factors (TSFs) can initiate a signalling cascade in cardiomyocytes to render these cells more susceptible to cell death and cardiotoxicity after DNA damaging chemotherapy treatment, a common adverse side effect.

METHODS

Clinically relevant tumour xenotransplant mice were used to identify TSFs in the serum and their effect on the myocardium. Serum samples were collected from breast cancer patients in the placebo arm of the MANTICORE trial prior to chemotherapy and development of cardiotoxicity. We generated cardiomyocyte-specific RBFOX1-deficient mice and assessed myocardial signalling and heart function (via echocardiography) prior to and after chemotherapy (anthracycline) treatment. Human chemotherapy induced cardiotoxicity myocardial biopsies were used to translate mechanistic findings.

RESULTS

We found that tumour secreted inosine and hypoxanthine were significantly elevated in the serum of lung cancer mice and breast cancer patients that developed cardiotoxicity. Mechanistically, we found that tumour secreted inosine and hypoxanthine can bind and activate the A2A receptor on cardiomyocytes, activating CAMKIIδ, which phosphorylates the postnatal mRNA splicing factor RBFOX1 on threonine-197, resulting in its caspase-dependent degradation. Loss of RBFOX1 initiates cardiomyocyte immaturity and epigenetic remodeling, promoting a more open chromatin state and accessible chromatin that increases susceptibility to DNA damage and cell death when treated with DNA damaging or intercalating anticancer agents. RBFOX1- deficient male and female mice develop significant cardiotoxicity when treated with low dose doxorubicin (commonly used DNA intercalating chemotherapy). RBFOX1 loss correlated with cell death markers (P53, cleaved caspase 9) in anthracycline-mediated cardiotoxicity patients.

CONCLUSIONS

This work identified a potential biomarker (inosine/ hypoxanthine) and mechanism for susceptibility to cardiotoxic anti-cancer drugs in preclinical models and patients.

Does steatotic liver disease influence treatment response and clinical outcomes in primary biliary cholangitis?

Ellina Lytvyak, Aldo J Montano-Loza, Bettina Hansen, Eugene Wong, Laurent Lam, Pierre Antoine Soret, Sara Lemoinne, Gideon M. Hirschfield, Aliya Gulamhusein, Albert Pares, Ignasi Olivas, Shagani Thisairajah, on behalf of the Global PBC Registry
Supervisor: Dr. Ellina Lytvyak & Dr. Aldo Montano-Loza

INTRODUCTION

Primary biliary cholangitis (PBC) is a rare life-long liver disease, with a prevalence in Canada of 318 cases per million. Its concomitance with steatotic liver disease (SLD) is inevitable as the latter affects over one-third of the population. Controlled attenuation parameter (CAP) via vibration-controlled transient elastography (VCTE) is a reliable measure for assessing SLD. This international multicentre study evaluates whether SLD affects treatment response and clinical outcomes in PBC.

METHODS

From the GLOBAL PBC international registry, 820 patients with at least one CAP value were retrospectively analyzed. SLD was defined as CAP≥280 dB/m. Patients with prior liver transplantation (LT) or hepatocellular carcinoma (HCC) were excluded. The biochemical response was assessed using Paris-2, Toronto, and GLOBE score criteria, while deep response was defined as normal alkaline phosphatase (ALP) and Bilirubin<0.6xULN. Clinical outcomes were estimated using Cox regression analysis.

RESULTS

Among the 820 patients included, 88.9% were females, and 22.7% had SLD. Patients with SLD had a higher BMI and higher frequencies of diabetes mellitus and hypertension. They also had similar liver stiffness measurement and frequency of cirrhosis by VCTE, but had lower FIB-4 and APRI scores than those without SLD. SLD patients achieved higher response rates according to Paris-2 (62.9% vs 47.1%) and Toronto criteria (70.8% vs 53.5%), GLOBE score (79.0% vs. 69.6%), ALP normalization (43.8% vs 30.6%), and deep response (30.2% vs 17.0%), all $p<0.05$. Over a median follow-up of 7.6±6.4 years, 6.0% developed hepatic decompensation (HD), 0.2% HCC, 2.0% required a LT and 3.9% died.

CONCLUSIONS

In PBC patients, the presence of SLD evaluated with CAP by VCTE is common but does not seem to have a negative impact on response to treatment and clinical outcomes.

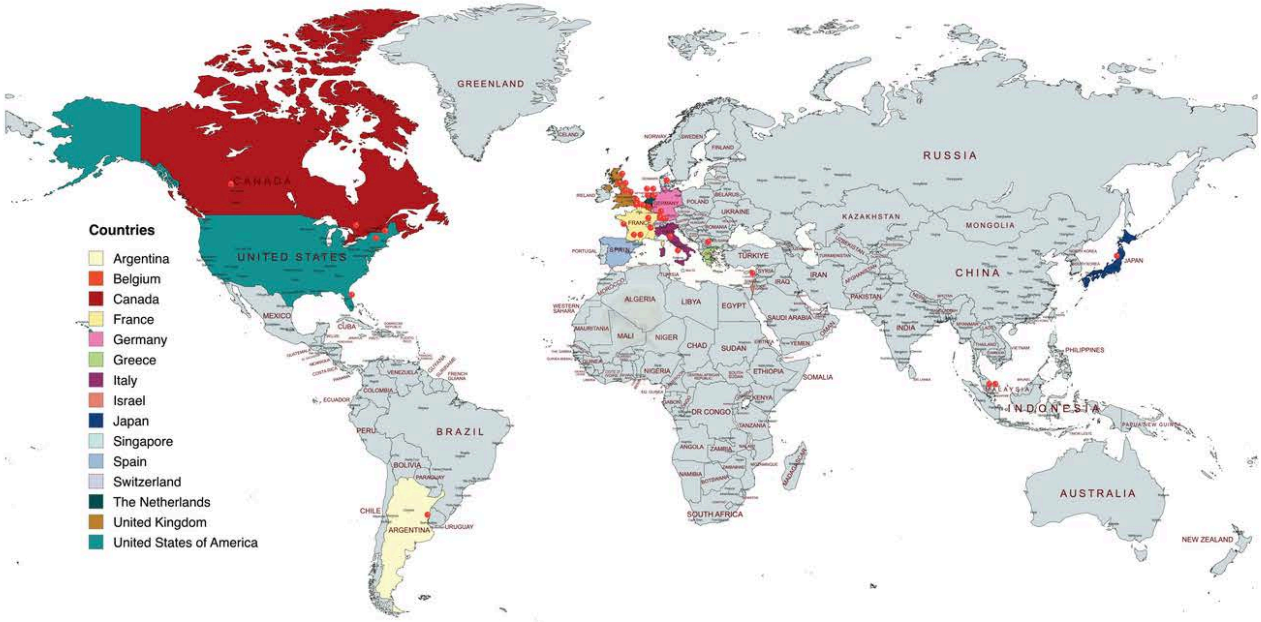


Figure 1. Geographic distribution of participating centers.

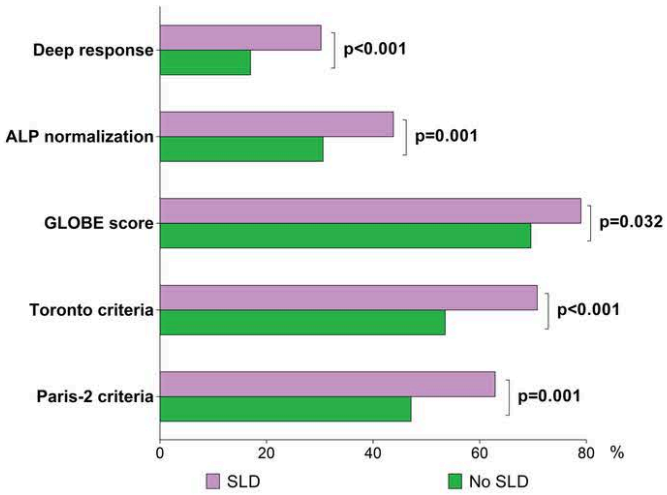


Figure 2. Comparison of treatment response rates in PBC patients with and without SLD.

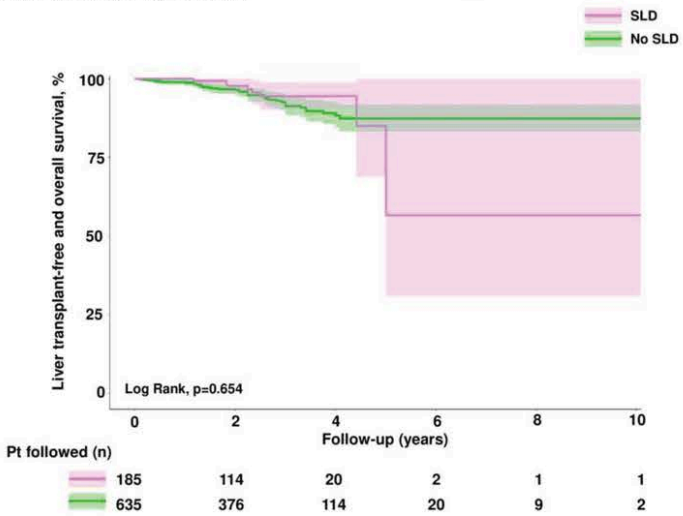


Figure 3. Cumulative liver transplant-free and overall survival in PBC patients with and without SLD.

Table 1. Baseline characteristics of PBC patients included in the study.

Centers included	37
Patients included	820
Female, % (n)	88.9 (729)
Age at PBC diagnosis, years, mean±SD	53.9±12.7
Age at the time of VCTE, years, mean±SD	61.6±12.0
SLD, % (n)	22.7 (186)
Follow-up period (years), mean±SD	7.6±6.4
Clinical outcomes, % (n)	
Hepatic decompensation	6.0 (49)
Hepatocellular carcinoma	0.2 (2)
Liver transplantation	2.0 (16)
Death	3.9 (32)

Table 2. Treatment response and clinical outcomes in PBC patients with and without SLD.

Characteristics	**SLD**	**No SLD**	**p-value**
BMI, kg/m²	31.7±6.4	25.6±5.0	**<0.001**
Diabetes type 2, %	25.8	7.9	**<0.001**
Hypertension, %	45.8	26.8	**<0.001**
LSM, kPa, mean±SD	13.7±14.5	11.4±12.1	0.073
LSM≥14.0 kPa, % (n)	24.5	19.0	0.129
FIB-4 score, mean±SD	1.6±1.3	2.1±1.9	**0.001**
APRI score, mean±SD	0.52±0.48	0.72±0.99	**<0.001**

SARS-COV-2 Prevention & Infection rates in SOT and Caregivers enrolled in TREAT-COVID

Varalika Tyagi, Kimberly Robertson, Geetha Sanmugalingham, Tanya Suandork, Judith Rho, Dr.Patricia Gongal, Dr. Dima Kabbani, TREAT-COVID Study Group, TREAT-COVID Group investigators, TREAT-COVID Group coordinators
Supervisor: Dr. Dima Kabbani

INTRODUCTION

Solid organ transplant recipients (SOTRs) are at increased risk of severe respiratory viral infections. Although early in the pandemic, COVID 19 vaccination rates were high in SOTRs, it is unclear if this is still the case in 2024-2025 nor whether SARS-Cov-2 still causes severe disease in SOTRs compared to other respiratory viruses.

METHODS

TREAT-COVID, a prospective multicenter study, with adult and pediatric SOTRs and their Caregivers (Ca), assesses the clinical, mental health, and economic burden of COVID-19 and other respiratory viruses. At each center, participants self enroll on an online platform and enter data through questionnaires every 3 months for up to 2 years. Data is also collected through medical chart reviews.

RESULTS

Between September 2024 and March 2025, 438 adult SOTRs and 79 Ca were enrolled and completed baseline questionnaires. Demographics are presented in the table. Organ transplant type: 36% kidney, 25% liver, 22% lung, 8.4% heart, 2% kidney-pancreas and 5.4% other. COVID-19 prevention: 96% of SOTRs and 94% of Cas received at least two doses of COVID-19 vaccine. COVID-19 booster vaccination rates for 2024/25 were 50% and 66% for SOT and Cas respectively. COVID-19 was common prior to 2024 with 65% of SOTRs experiencing COVID-19 before enrollment, among them 39% had multiple infections with treatment administered to 60% of SOTRs for the first and second infection. Remdesivir was the most common treatment. Since enrollment 5 SOTRs have had COVID-19, 1 has had RSV, 1 has had influenza and 2 have had enterovirus/rhinovirus.

CONCLUSIONS

Participants enrolled have a diverse demographic and organ-type composition. SOTRs had very high vaccination rates but only 50 % of SOTRs received a COVID-19 booster vaccine in 2024. Continued enrollment/data collection will provide insight into other respiratory viruses vaccination and infection rates.

Demographics		**SOT N=438 (%)**	**Caregivers N=79 (%)**
Age, median (IQR)		59 (46-67)	
Sex	M	229 (52)	25 (32)
Gender	M	227 (52)	25 (32)
	W	185 (42)	51 (65)
	Two-Spirited	1	
	NA	25 (6)	3 (3.8)
Race			
	White-North American	301 (68.7)	65 (82.3)
	White- European	31 (7.1)	4 (5.1)
	Indigenous	12 (2.7)	2 (2.5)
	Asian- East/South/South-East	20 (4.5)	3 (3.8)
	Middle Eastern	8 (1.6)	
	Latin American	5 (1.1)	1 (1.3)
	Other	17 (3.8)	
	No Response/Prefer not to answer	44 (9.92)	4 (5)
Job Status			
	Retired	155 (35.4)	35 (44.3)
	Full time employment	113 (25.8)	29 (36.7)
	Disability	40 (9.1)	
	Part time employment	18 (4.1)	5 (6.3)
	No Response/Prefer not to answer	64 (14.6)	4 (5.1)
Immunosuppression			
	Prednisone	261 (59.6)	
	Tacrolimus	251 (80.1)	
	Cyclosporine	24 (5.5)	
	Mycophenolate	240 (54.8)	
	Azathioprine	30 (6.8)	
COVID 19 vaccinations			
	None	7/223 (3)	3/64 (3)
	2 vaccines	10/223 (4.4)	10/64 (16)
	3 vaccines	23/223 (10)	6/64 (9)
	≥ 4 vaccines	183/223 (82)	44/64 (69)
	Booster is 2024	109/216 (50)	38/57 (67)
Evusheld			
	Not eligible	114/438 (26)	
	Not received	134/324 (41)	
	1 dose	27/324 (8)	
	2 doses or higher dose	51/324 (18)	
	Unknown	113/324 (35)	

Norovirus and Sapovirus associated chronic diarrhea in SOT: Does Viral load correlate with severity of symptoms?

Varalika Tyagi, Dr. Linnet Immeraj, Dr. Judy Qiu, Dr. Emily Christie, Dr. Kieran Halloran, Dr. Carlos Cervera, Dr. Lily Pang, Dr. Dima Kabbani
Supervisor: Dr. Dima Kabbani

INTRODUCTION

Norovirus (NoV) and Sapovirus (SapV) in solid organ transplant recipients (SOTRs) are highly prevalent and cause chronic diarrhea and prolonged viral shedding. This study aims to evaluate the relationship between clinical severity and stool NoV/SapV-viral load (VL), and clinical and virologic response to different therapeutics.

METHODS

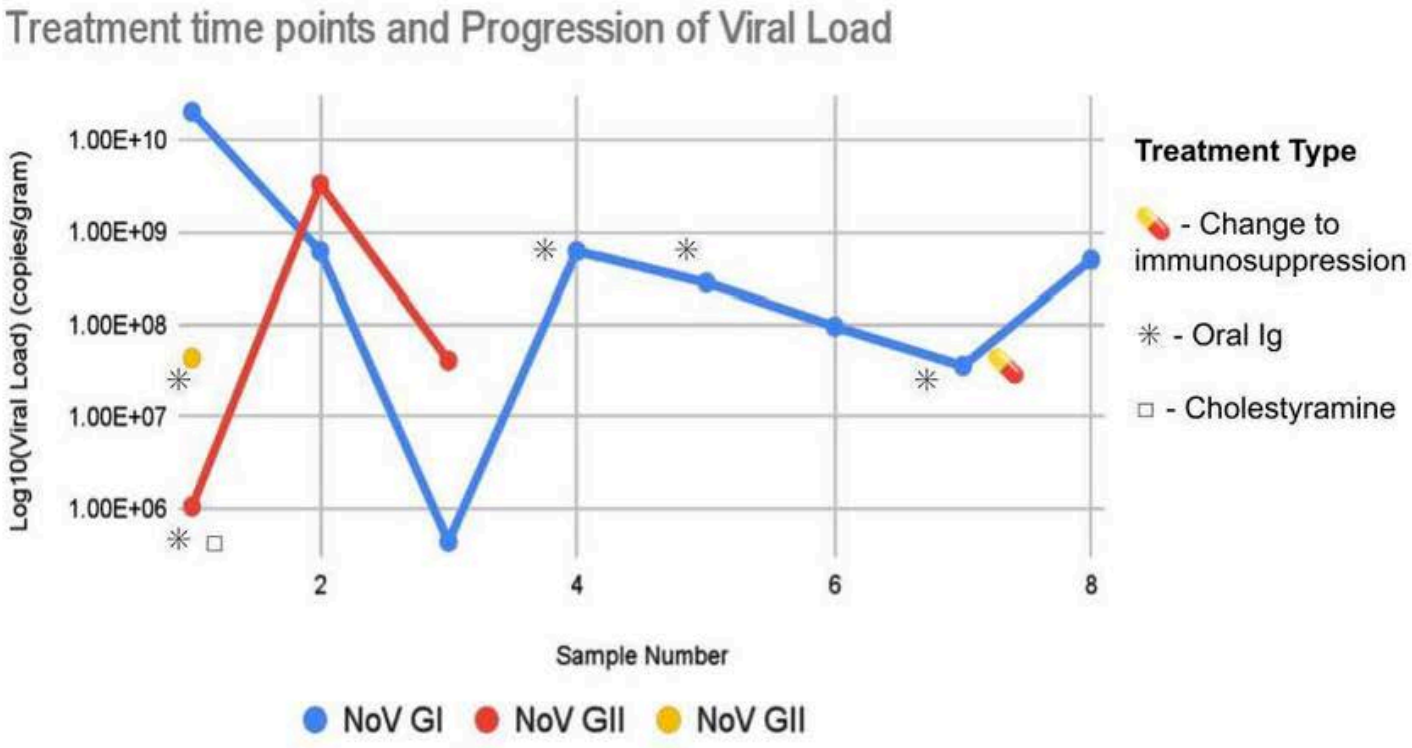
Single center prospective study of adult (>18) SOTRs diagnosed with NoV or SapV. Stool samples were collected at regular intervals. RNA extracts were prepared from 10% weighted-stool samples and subjected to RT-PCR to obtain cDNA (complementary DNA) and quantified using digital PCR (dPCR) assays. Total viral copies per reaction were calculated and converted per gram of stool for each sample. Clinical assessments were performed through questionnaires and chart review. Patients were followed for up to 2 years.

RESULTS

Since November 2023, 6 SOTRs (3 lungs, 3 kidney) were enrolled and provided at least one stool sample, median age 58.5, 83% M, with following viruses: NoV GI (1), NoV GII (3) and SapV (2). Diarrhea lasting >14 days was seen in 5/6 SOTRs. Treatment included oral immunoglobulin 3/6, cholestyramine 1/6, modification in immunosuppression 3/6, antimotility 4/6, IV hydration 3/6. In the 2 SOTRs with SapV, symptoms resolved between 1-1.5 months, and follow-up VL in stool was negative. In NoV SOTRs, stool VL ranged from 1.05E+06 to 2.05E+10 copies/gram at enrollment and diarrhea lasted from 14 days-14 months, with NoV remaining positive in stools despite improvement of symptoms in 3. Figure demonstrates VL change in NoV in 3 SOTRs.

CONCLUSIONS

Preliminary data suggests a high burden of gastrointestinal symptoms and viral shedding in SOTRs with NoV. Continued enrollment and sample collection will provide insight into the relationship between stool VL, virus type and clinical symptoms.


Treatment time points and Progression of Viral Load
Log10(Viral Load) (copies/gram)
1.00E+10
1.00E+09
1.00E+08
1.00E+07
1.00E+06
2
4
6
8
Sample Number
NoV GI
NoV GII
NoV GII
Treatment Type
- Change to immunosuppression
- Oral Ig
- Cholestyramine

Concomitant sarcopenia and myosteatosis in cirrhosis patients is associated with longer recovery and mortality after liver transplantation

Ellina Lytvyak, Devika Shreekumar, Shagani Thisairajah, Maryam Motamedrad, Narmeen Umar, Norberto Sanchez-Fernandez, Alessandro Parente, Norman M. Kneteman, Khaled Dajani, Blaire Anderson, David Bigam, A M James Shapiro, Aldo J Montano-Loza
Supervisor: Dr. Aldo Montano-Loza and Dr Ellina Lytvyak

INTRODUCTION

Sarcopenia (low muscle mass) and myosteatosis (pathological fat accumulation in muscle) are well-established predictors of worse outcomes in patients with cirrhosis. Still, their impact on the post-liver transplantation (LT) course is unknown. We aimed to assess the association between sarcopenia and myosteatosis and recovery time and negative outcomes in patients who underwent LT.

METHODS

We evaluated patients with cirrhosis who underwent LT and had computed tomography (CT) imaging performed within three months before LT. Body composition analysis was assessed using Slice-O-Matic software (V4.2; Tomovision) to measure the skeletal muscle index (SMI) in cm2/m2 and muscle radiodensity in Hounsfield Units (HU). Sarcopenia was defined as SMI<39 cm2/m2 in females and <50 cm2/m2 in males. Myosteatosis was defined as mean skeletal muscle radiodensity <28 HU for females and <33 HU in males. Cox regression models were built to estimate and measure associations between skeletal muscle abnormalities and post-LT clinical outcomes.

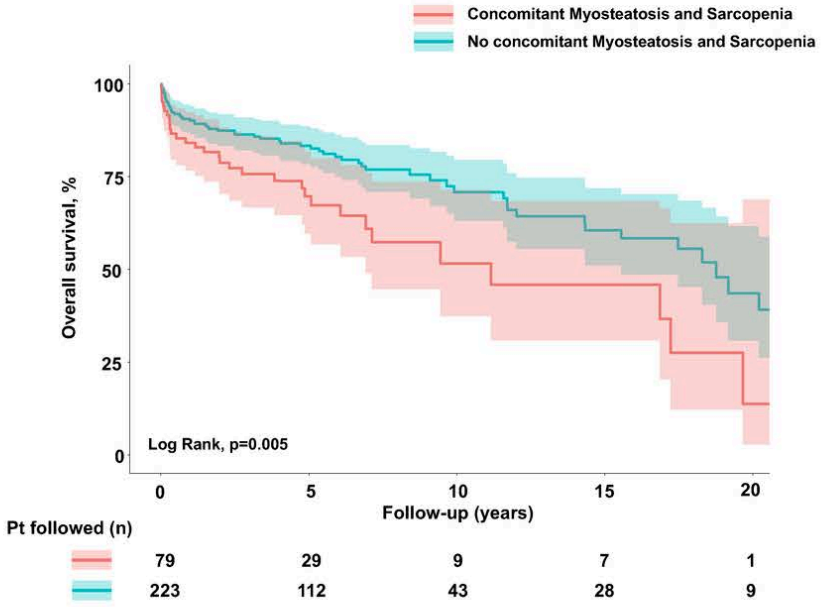
RESULTS

302 patients were included (67.9% were males, mean age at LT of 51.6 years, MELD score at LT of 21.2). The main indications for LT were alcohol liver disease (38.4%), hepatitis C (28.1%), autoimmune liver diseases (19.2%), and metabolically-associated steatotic liver disease (7.6%). Concomitant sarcopenia and myosteatosis were present in 26.2%. After LT, patients with concurrent sarcopenia and myosteatosis tended to have longer post-LT ICU median length of stay (LOS) (4 vs 3 days) and substantially longer post-LT hospital LOS (28 vs 20 days). In addition to this, had worse 1- & 5-year post-LT survival (Fig 1a). The association between concurrent sarcopenia and myosteatosis and overall mortality remained significant after adjusting for age, sex and MELD score at LT (Fig 1b).

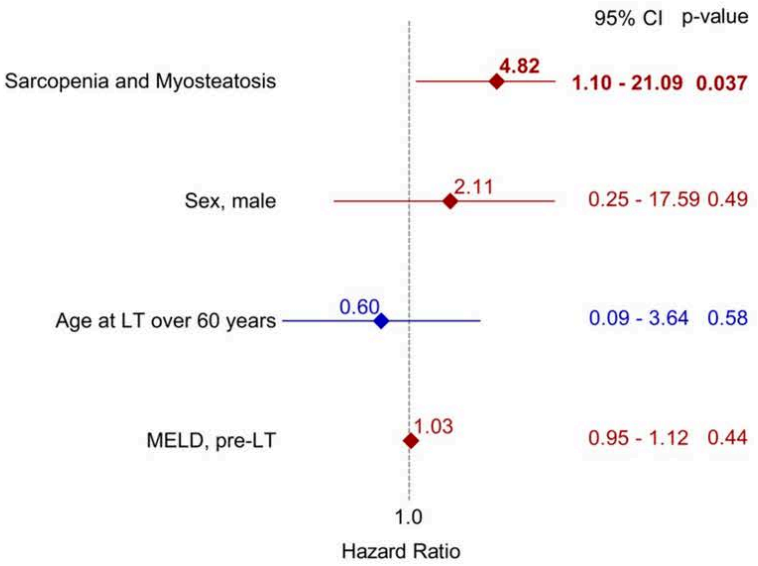
CONCLUSIONS

Concurrent sarcopenia and myosteatosis affect over a quarter of patients with cirrhosis who received LT and are associated with longer recovery and worse post-LT survival. This objective assessment could be implemented as a futility indication for LT.

1a) Post-liver transplantation survival in patients with concomitant sarcopenia and myosteatosis vs no concomitant sarcopenia and myosteatosis



1b) Forest plot based on multivariate analysis based adjusted hazard ratios



Long-term effectiveness and safety of ustekinumab dose escalation in patients with moderate-to-severe ulcerative colitis: a multicenter retrospective cohort study

Lisa M.A. van Lierop, Larissa Albino, Ryan Rosentreter, Pepijn W.A. Thomas, Cathy Lu, Jesse Siffledeen, Karen I. Kroeker, Christopher Ma, Farhad Peerani, Brendan Halloran, Daniel Baumgart, Levinus Dieleman, Lillian Du, Frank Hoentjen, and Karen Wong
Supervisor: Prof. Frank Hoentjen

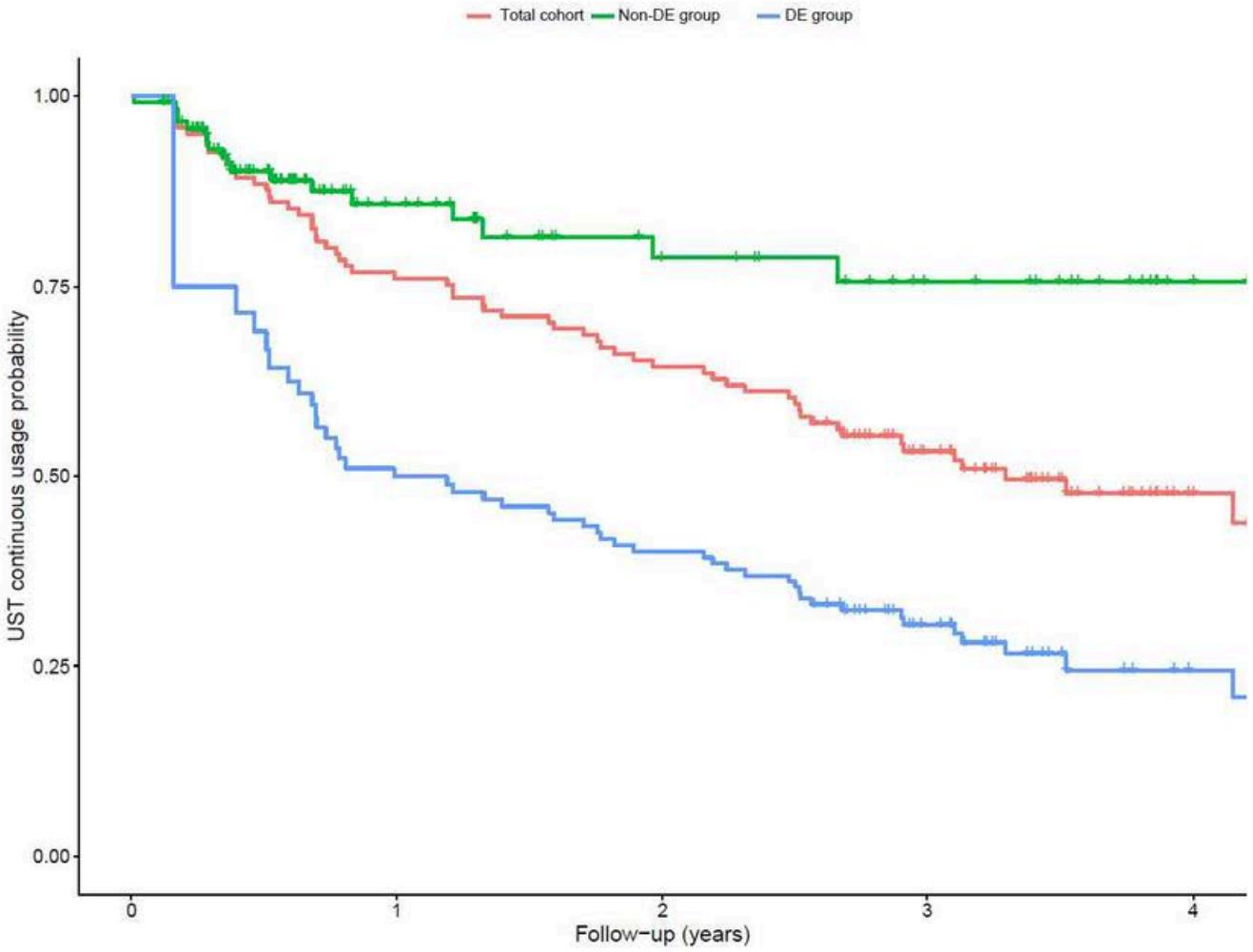
INTRODUCTION
Ustekinumab dose escalation (DE) may be an effective strategy to recapture clinical response in patients with ulcerative colitis (UC). The aim of this study was to assess the real-world long-term effectiveness and safety outcomes following ustekinumab DE in patients with moderate-to-severe UC.

METHODS
This multicenter retrospective cohort study included patients with moderate-to-severe UC who received at least one IV induction ustekinumab dose between January 2016 and November 2021. We compared ustekinumab DE to no DE, examining clinical, biochemical, and endoscopic disease outcomes. The primary endpoint was corticosteroid-free clinical remission (partial Mayo score ≤ 2 without systemic corticosteroids) at the end of follow-up. Cox-proportional hazards regression analysis was performed for factors associated with time to DE, and a Kaplan-Meier plot was created for visualizing drug persistence probabilities.

RESULTS
We enrolled 121 patients. Eighty-one patients (67%) underwent DE during a median follow-up of 141 weeks. Corticosteroid-free clinical remission at the end of follow-up was achieved for 53.1% (DE group) and 57.5% (non-DE group). Discontinuation rates were 54.3% (DE group) versus 42.5% (non-DE group), mainly due to a lack of effectiveness. Two patients discontinued ustekinumab for adverse events. Ustekinumab persistence probability after 2 years was 40% (DE group) versus 79% (non-DE group) (Figure 1).

CONCLUSIONS
Our results indicate that DE is a commonly used method for optimizing ustekinumab treatment in moderate-to-severe UC. While DE appears safe, effectiveness and drug persistence beyond 2 years are limited.

Figure 1: Kaplan-Meier plot for probabilities of continued ustekinumab during follow-up in years. The green (upper) line represents the non-DE group, the red (middle) line represents the entire cohort, and the blue (bottom) line represents the DE group.



Long-term outcomes of extended versus conventional adalimumab dose interval for patients with Crohn's disease in stable remission: 3-year follow-up of the randomized controlled LADI trial

Lisa M.A. van Lierop, Monique J.C. Devillers, C. Janneke van der Woude, Annemarie C. de Vries, and Frank Hoentjen
Supervisor: Prof. Frank Hoentjen

INTRODUCTION
In the randomized controlled LADI trial we showed that a subset of patients with Crohn's disease (CD) maintained clinical remission following extension of the adalimumab dose interval. The aim of this study was to evaluate the long-term clinical outcomes for LADI trial participants who extended the adalimumab interval to 3 or 4 weeks compared to conventional dosing.

METHODS
We enrolled adult CD patients in biochemical and corticosteroid-free clinical remission on adalimumab 40 mg every 2 weeks. The intervention group extended dosing to 3-4 weeks if in remission at week 24. Controls maintained the 2-week interval. Long-term follow-up data >48 weeks was collected from 2017 to 2023. The primary endpoint of the current study was the proportion of patients in corticosteroid-free clinical remission (Harvey Bradshaw Index ≤4 or remission per Physician Global Assessment) at year 3 while maintaining the assigned adalimumab interval at baseline (control: 40 mg every 2 weeks; intervention: 40 mg every 3 or 4 weeks).

RESULTS
Data was extracted for 143/174 initially randomized subjects (intervention group: n=95; control group: n=48). In the intervention group, 30/95 (31.6%) patients maintained de-escalation at 3 years (7 on a 3-week interval, 23 on a 4-week interval). The primary endpoint was achieved in 28/95 (29.5%) at year 3. Twenty-eight patients re-escalated to 40 mg every 2 weeks, of which 24 were in corticosteroid-free clinical remission at year 3. In addition to 4 subjects in each group that stopped adalimumab for stable remission, another 19 patients (13.3%) discontinued adalimumab at year 3.

CONCLUSIONS
Long-term follow-up of the LADI trial showed that nearly one-third of patients in the intervention group was in remission after persistent de-escalation of adalimumab therapy at year 3, while another 25% recaptured remission after dose re-escalation. In the control group, over half of patients maintained remission on adalimumab every 2 weeks.

Long-term outcomes of increased versus conventional adalimumab dose interval for patients with Crohn's disease in stable remission: 3-year follow-up of the randomized controlled LADI trial

Figures and Tables

Figure 1: Sankey plot of adalimumab dosing intervals up to 3 years categorized by randomization group

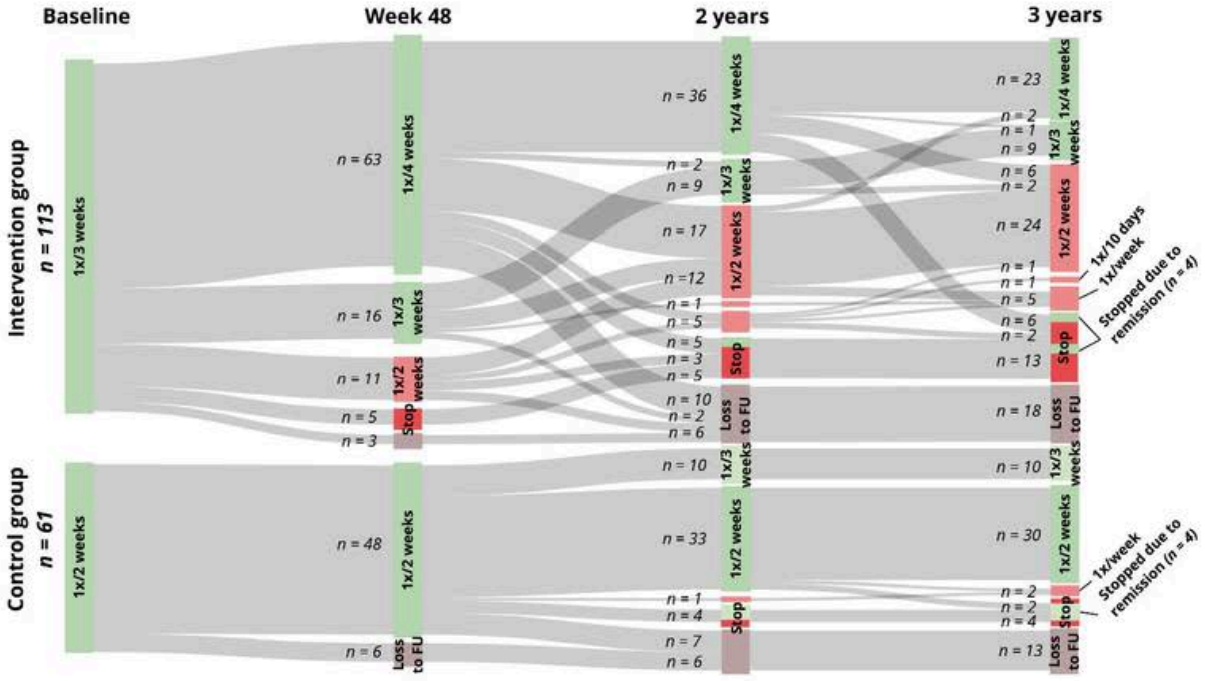


Table 1: Baseline characteristics

Demographics	Intervention group (n=95)	Control group (n=48)	p-value
Age, years	40.7 (32.2 – 49.3)	44.1 (31.0 – 53.6)	0.457
Sex			0.681
• Female	47 (49.5)	22 (45.8)	
• Male	48 (50.5)	26 (54.2)	
BMI, kg/m^2	23.7 (21.7 – 26.5)	24.6 (22.5 – 27.8)	0.139
Smoking status			0.048
• Active	15 (15.8)	9 (18.8)	
• Never	43 (45.3)	30 (62.5)	
• Ex-smoker	37 (38.9)	9 (18.8)	

Disease history			
Concomitant immunosuppressants	17 (17.9)	12 (25.0)	0.318
Disease duration, years	13.6 (7.1 – 20.6)	11.8 (5.5 – 21.7)	0.599
Remission duration, years	2.7 (1.4 – 5.7)	2.4 (1.4 – 4.9)	0.993
Time on adalimumab, years	4.9 (2.4 – 7.0)	3.4 (1.9 – 7.2)	0.395
Previous IBD therapy			
• Infliximab	43 (45.3)	19 (39.6)	0.517
• Adalimumab	14 (14.7)	5 (10.4)	0.472
• Vedolizumab	1 (1.1)	0	1.000
• Ustekinumab	0	0	
Previous IBD-related surgery	51 (53.7)	22 (45.8)	0.375
Montreal classification			
Age at diagnosis			0.319
• A1	13 (13.7)	5 (10.4)	
• A2	71 (74.7)	33 (68.8)	
• A3	11 (11.6)	10 (20.8)	
Disease extent			0.078
• L1: ileal	20 (21.1)	8 (16.7)	
• L2: colonic	19 (20.0)	18 (37.5)	
• L3: ileocolonic	56 (58.9)	22 (45.8)	
• L4: upper disease	15 (15.8)	4 (8.3)	0.299
Disease phenotype			0.994
• B1: non-stricturing, non-penetrating	56 (58.9)	28 (58.3)	
• B2: stricturing	21 (22.1)	11 (22.9)	
• B3: penetrating	18 (18.9)	9 (18.8)	
• p: perianal disease	29 (30.5)	14 (29.2)	0.867
Biochemical disease activity			
Fecal calprotectin, µg/g	29.0 (15.0 – 65.0)	30.5 (16.0 – 60.0)	0.559
C-reactive protein, mg/L	1.3 (1.0 – 3.0)	2.0 (1.0 – 3.0)	0.859
Therapeutic drug monitoring			
Adalimumab drug concentration	9.7 (6.9 – 11.8)	10.0 (6.5 – 12.0)	0.970
Anti-adalimumab antibodies	1 (1.2)	0	1.000

Data are median (IQR) or *n* (%).

Table 2. Adverse events per randomization group

Adverse event category and type	**Intervention group (n=14)**	**Control group (n=9)**
Infections	**6**	**4**
Upper respiratory tract	1	1
COVID-19	3	1
Gastro-intestinal tract	1	0
Dental	1	1
Urinary tract	0	1
Malignancies	**2**	**1**
Melanoma	0	1
Breast	1	0
Esophageal	1	0
Skin lesions	**2**	**3**
Lichen planus	1	0
Fungal infection	1	0
Carbuncle	0	1
Other	0	2
Injection site reactions	1	0
Other	**3**	**1**
Severe fatigue	1	0
Eye-related	2	0
Elevated liver enzymes	0	1

HBRV Seroprevalence and Immune Reactivity in Breast Cancer and Autoimmune Disease Patients

Doaa Waly, Olaide Oyegbami, Varinder Madhav Verma, Seyed Sajjad Zadian, Hussain Syed, Ning Sun, Naveen Bassapa, Anil Joy John Mackey, Andrew Mason. Supervisor: Waly

INTRODUCTION

Human Betaretrovirus (HBRV) is the human counterpart of mouse mammary tumor virus, a cause of breast cancer, lymphoma, and renal cancer in mice. HBRV has been identified in patients with various cancers and autoimmune diseases but is not widely accepted as a human pathogen. To strengthen this association, we developed a ligation-mediated PCR assay with massively parallel sequencing to detect HBRV proviral integrations in primary biliary cholangitis (PBC) patients' biliary epithelium and those with autoimmune hepatitis. Subsequently, analyzing 87 breast cancer and control samples, we found 179 HBRV insertions in 31% of breast cancer samples, 7% of lymph node metastases, and 6% of control breast samples, suggesting a link between HBRV and breast cancer, warranting further investigation into its oncogenic role.

METHODS

We developed an HBRV Env ELISA assay, revealing ~10% seroprevalence in breast cancer and PBC patients versus 2% in controls. Due to insensitivity, we created cellular immune assays to detect HBRV infection. HBRV Gag and Env peptides were mapped using two sequential ELISpot assays: the first screened matrix peptide pools, and the second tested individual peptides from positive pools.

RESULTS

Using peptides mapping, 43% of patients were positive. Two pools of immunodominant HBRV peptides were derived for IGRA and ELISpot assays, showing increased reactivity in breast cancer patients. Testing HBRV reactivity in 63 breast cancer patients and 46 controls, we found significantly higher reactivity in cancer patients (48% vs. 4.3%; $p<0.002$).

CONCLUSIONS

Using HBRV cellular immune assays, we gained insight into immune checkpoint inhibitor (ICI) side effects. For example, 50% of autoimmune hepatitis patients have HBRV infection. We tested HBRV-related cancer patients for reactivity after developing ICI hepatitis. To date, we have identified HBRV-positive patients treated with ICI who developed hepatitis or PBC-like disease, suggesting ICI side effects may be linked to reactivation of cellular immunity associated with oncogenic HBRV.

Composition and influence of Lyophilized Fecal Microbiota Transplantation (LFMT) or Lyophilized Sterile Fecal Filtrate (LSFF) on the human gut metaproteome following treatment of recurrent Clostridioides difficile infection

Brendan Whitman, Chelsea McDougall, Rose Franz, Karen Wong, Dina Kao
Supervisor: Dina Kao

INTRODUCTION

Fecal microbiota transplantation (FMT) is an approved and highly effective therapy for preventing recurrent Clostridioides difficile infection (rCDI). Although the gut microbial compositional shifts occurring after FMT have been profiled, the functional pathways have remained difficult to ascertain. Stool metaproteomics offers the opportunity to investigate the composition of donor stool based treatments and the host-microbial interactions underpinning FMT efficacy in rCDI.

METHODS

We compared metaproteomes of human feces collected longitudinally from patients before and after successful treatment in a randomized clinical trial comparing efficacy of conventional lyophilized FMT (LFMT) and a lyophilized sterile fecal filtrate (LSFF), devoid of live bacteria, to understand gut microbiome functional changes dependent on the introduction of intact microbes. We also utilized metaproteomics to profile the investigational products (IP) LFMT and LSFF.

RESULTS

First, analysis of the IPs revealed that while LSFF is depleted of bacterial proteins, both are rich in host derived proteins. These include mucins, immunoglobulins, and immune system modulators (Table 1). Second, examination of patient gut metaproteomes revealed that while LFMT results in a higher diversity of bacterial taxa similar to donors, both treatments result in gut metaproteomes that increase in protein diversity and converge in function(Figure 1). In both treatment cohorts, a striking decrease in Klebsiella and a corresponding increase in Blautia genera was observed after rCDI resolution, implicating these taxa in the antagonism or promotion of gut homeostasis, respectively.

CONCLUSIONS

These results illuminate that an often-ignored aspect of FMT, host derived proteins and polypeptides, are highly abundant in both LFMT and LSFF IPs and may contribute to positive clinical outcomes in treating rCDI. Furthermore, the commonalities observed in patient stool metaproteomes following LSFF or LFMT administration suggest that donor microbiota engraftment may not be required for restoring gut functional homeostasis. These observations require further validation.

Table 1. Top 25 most abundant proteins in each of lyophilized fecal microbiota transplant and lyophilized sterile fecal filtrate investigative products. *LFQ* label-free quantification

Product Category	Gene Name	Organism	Protein Description	LFQ Intensity	Product Category	Gene Name	Organism	Protein Description	LFQ Intensity
LFMT	CELA3A	Homo sapiens	Chymotrypsin-like elastase family member 3A	3.17E+10	LSFF	PRSS2	Homo sapiens	Trypsin-2	1.94E+10
LFMT	PRSS2	Homo sapiens	Trypsin-2	1.01E+10	LSFF	IGKC	Homo sapiens	Immunoglobulin kappa constant	1.76E+10
LFMT	CTRC	Homo sapiens	Chymotrypsin-C	7.96E+09	LSFF	-	Roseburia faecis	Ig-like domain-containing protein	6.18E+09
LFMT	AMY2A	Homo sapiens	Pancreatic alpha-amylase	5.00E+09	LSFF	-	Clostridia	Hypothetical protein	4.33E+09
LFMT	-	Roseburia faecis	Ig-like domain-containing protein	4.99E+09	LSFF	-	Clostridia	Hypothetical protein	4.20E+09
LFMT	IGHA1	Homo sapiens	Immunoglobulin heavy constant alpha 1	4.24E+09	LSFF	FCGBP	Homo sapiens	IgGFc-binding protein	4.16E+09
LFMT	PRSS1	Homo sapiens	Serine protease 1	3.87E+09	LSFF	KLK1	Homo sapiens	Kallikrein-1	3.62E+09
LFMT	PLA2G1B	Homo sapiens	Phospholipase A2	3.18E+09	LSFF	SI	Homo sapiens	Sucrase-isomaltase, intestinal	3.23E+09
LFMT	FCGBP	Homo sapiens	IgGFc-binding protein	3.06E+09	LSFF	MGAM	Homo sapiens	Maltase-glucoamylase	3.20E+09
LFMT	-	Clostridia	Hypothetical protein	3.04E+09	LSFF	CST4	Homo sapiens	Cystatin-S	2.79E+09
LFMT	IGKC	Homo sapiens	Immunoglobulin kappa constant	2.92E+09	LSFF	-	Clostridia	ATPases associated with a variety of cellular activities	2.67E+09
LFMT	-	Clostridia	Rhs family protein	2.17E+09	LSFF	IGHA1	Homo sapiens	Immunoglobulin heavy constant alpha 1	2.54E+09
LFMT	gap	Clostridia	Type I glyceraldehyde-3-phosphate dehydrogenase	2.07E+09	LSFF	CST1	Homo sapiens	Cystatin-SN	2.44E+09
LFMT	ppdK	Clostridia	Belongs to the PEP-utilizing enzyme family	2.05E+09	LSFF	-	Clostridia	Hypothetical protein	2.44E+09
LFMT	flaE	Clostridia	Bacterial flagella	1.99E+09	LSFF	-	Hominilimicola sp.	Beta strand repeat-containing protein	2.35E+09
LFMT	MGAM	Homo sapiens	Maltase-glucoamylase	1.89E+09	LSFF	GAPDH	Homo sapiens	Glyceraldehyde-3-phosphate dehydrogenase	2.19E+09
LFMT	CTRB2	Homo sapiens	Chymotrypsinogen B2	1.78E+09	LSFF	DPP4	Homo sapiens	Dipeptidyl peptidase 4	2.17E+09
LFMT	fliC	Clostridia	Bacterial flagella	1.77E+09	LSFF	IGHA2	Homo sapiens	Immunoglobulin heavy constant alpha 2	2.10E+09
LFMT	PNLIP	Homo sapiens	Pancreatic triacylglycerol lipase	1.76E+09	LSFF	PRSS1	Homo sapiens	Serine protease 1	1.80E+09
LFMT	ppdK	Clostridia	Phosphoenolpyruvate synthase pyruvate phosphate dikinase	1.65E+09	LSFF	CDHR2	Homo sapiens	Cadherin-related family member 2	1.65E+09
LFMT	KRT1	Homo sapiens	Keratin, type II cytoskeletal 1	1.53E+09	LSFF	-	Clostridia	Rhs family protein	1.53E+09
LFMT	-	Clostridia	Solute-binding protein	1.52E+09	LSFF	MUC2	Homo sapiens	Mucin-2	1.50E+09
LFMT	SI	Homo sapiens	Sucrase-isomaltase, intestinal	1.48E+09	LSFF	CEACAM5	Homo sapiens	Carcinoembryonic antigen-related cell adhesion molecule 5	1.45E+09
LFMT	CPB1	Homo sapiens	Carboxypeptidase B	1.38E+09	LSFF	SERPINA1	Homo sapiens	Alpha-1-antitrypsin	1.26E+09
LFMT	fliC	Clostridia	Bacterial flagella	1.30E+09	LSFF	-	Clostridia	ABC Transporter	1.25E+09

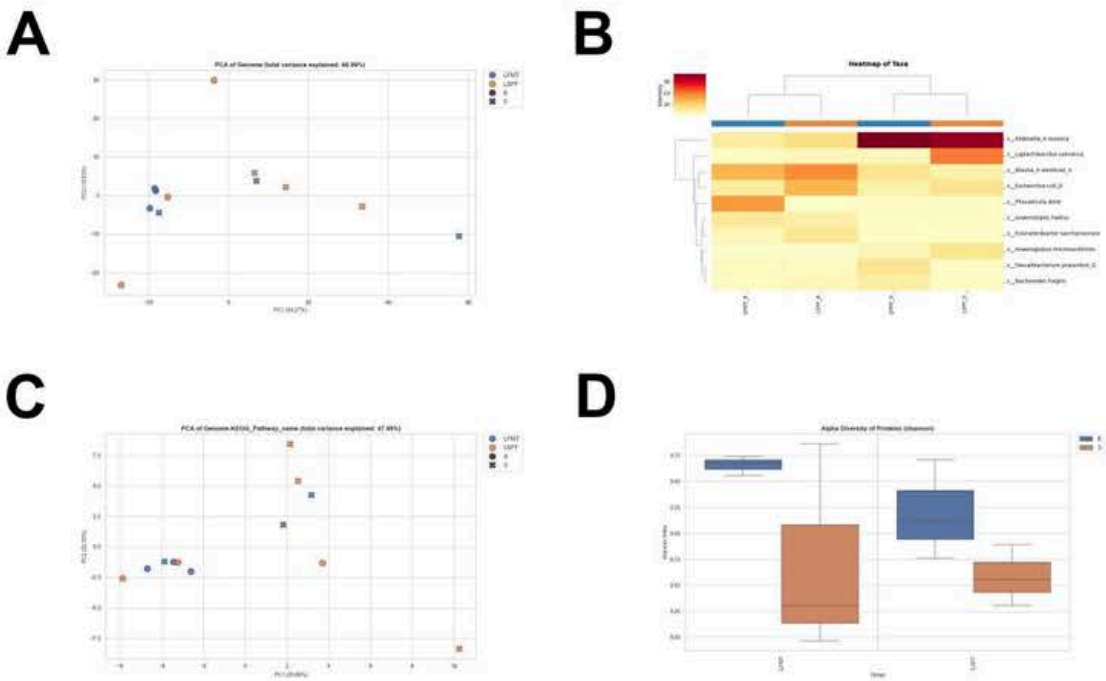


Figure 1. Metaproteomics reveals distinct taxa and taxa-function trends of patient gut microbiomes after treatment with lyophilized FMT or SFF. A) Principal component analysis of six patients before (0) and eight weeks (8) after treatment (n=12, n=6 per treatment group) shows dissimilarity in total microbial taxa profiles for LSFF and LFMT at both timepoints. B) Heatmap of most abundant bacterial taxa show pronounced changes for *Klebsiella* and *Blautia* for LFMT and LSFF treatment. C) Principal component analysis examining KEGG function clustering reveals a convergence in metaproteomes after LFMT or LSFF treatment. D) Alpha diversity as calculated by Shannon index for a total of 7895 orthologous protein groups all patient samples before and after transplantation. For all graphs, a minimum of 3 peptides was the threshold for detection of taxa or taxa-function.

A critical contribution of cardiac myofibroblasts in RV failure and the role of UCP2 SNPs in the predisposition to RV decompensation in pulmonary arterial hypertension

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INTRODUCTION

The mechanism driving the transition from compensated right ventricular hypertrophy (cRVH) to decompensated RV (dRV) in pulmonary arterial hypertension (PAH) is unknown. We hypothesized that a transition from cardiac fibroblasts (cFB) to cardiac myofibroblasts (cMFB) underlies this mechanism. Decreased mitochondrial calcium (mCa++) promotes cMFB differentiation (from cFB). Methylation of mCa++ uptake 1 (MICU1) and lack of UCP2 (uncoupling protein 2, a component of the mCa++ uniporter complex) decrease mCa++.

METHODS

In a monocrotaline-rat PAH model, we measured the RV pressure from isolated perfused hearts and sarcomere shortening from isolated RV cardiomyocytes. In cohorts (n=78) of patients with PAH, the correlation between UCP2 loss-of-function SNP (rs659366) and RV function was measured.

RESULTS

In isolated hearts, RV systolic pressure was lower in dRV but in isolated cardiomyocytes (CM), contractility (sarcomere shortening) was not, pointing to a non-cardiomyocyte difference. The number of cMFB was dramatically increased in dRV compared to Control and cRVH. Mitochondrial respiration was lower in dRV cMFB than cRVH cFB. mCa++ was progressively decreased from Control to cRVH to dRV c(M)FB, while it was not different in CM. The MICU1 methyltransferase (PRMT1) levels and MICU1 methylation were increased but the expression of UCP2 was decreased from Control to cRVH to dRV c(M)FB (but not CM). In human RV tissues (from autopsy or biopsy), dRV had increased number of cMFB compared with Control and cRVH. Cytoplasmic PRMT1 was increased from Control to cRVH, while UCP2 was decreased from cRVH to dRV c(M)FB. In patient cohorts (n=78) with PAH undergoing both catheterization and echocardiography, carriers of this germline UCP2 SNP had decreased TAPSE compared to non-carriers that had similar PA pressure.

CONCLUSIONS

Our data point to a change of cell identity (cFB to cMFB) in the RV as the basis of RV decompensation. UCP2 SNPs may be promising biomarkers for RV failure in PAH patients.

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