Research DAY 2019

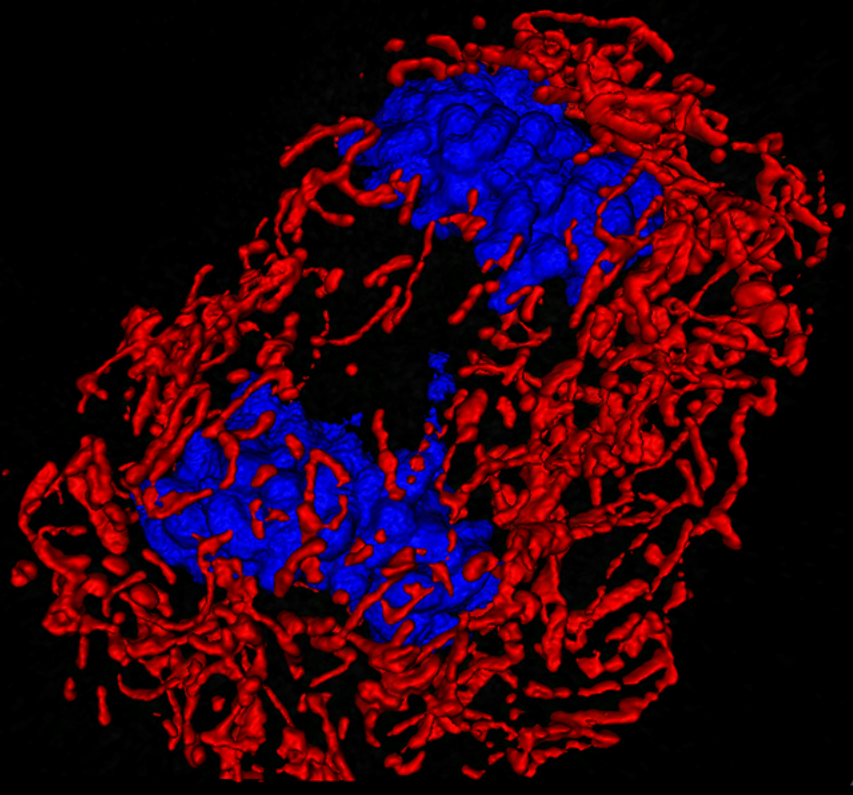
Department of Medicine

Tuesday, June 25, 2019

Classroom D, WMC 2F1.04

8:00 a.m. - 4:00 p.m.

Keynote Speaker:
Dr. Lewis E. Kay, O.C., PhD
Professor of Molecular Genetics, Biochemistry and Chemistry
University of Toronto
Recipient of the 2017 Canada Gairdner International Award



POSTER PRESENTATIONS

John W. Scott Library

All Day Viewing

BARBARA J. BALLERMANN

Department of Medicine
Chair

Research has been the life-blood of the Healing Arts in all cultures and throughout history. We continue this tradition in the Department of Medicine, always with the goal of better clinical care. In 2018 members of this Department contributed over 800 research papers to the literature. The work spans the spectrum from molecule to patient and from patient to health systems. Research is central to what we do – is the foundation of medicine.

With some help from their supervisors, most of the Department's research work is actually done by residents, graduate students and postdoctoral fellows – and this work is showcased today. The Department of Medicine graduate program is one of the largest at this University with 102 graduate students and 22 postdoctoral fellows, and 378 residents in our core and subspecialty programs. Nearly all trainees are involved in research at some level.

The trainees who are presenting the work today have put a lot of effort into their presentations, and many of them will take their findings to national and international conferences. You can help them by showing how much you value their effort, you can get a preview of what will be published by this Department in the near future, and by chatting with the presenters, you can add your ideas to this ongoing research.

As is the case every year, the oral abstracts will be presented in Classroom D, and posters will be shown in the lower level of the John W. Scott Library (lunch is served). This year, I would like to welcome two guest adjudicators for the oral presentations:

Lewis E. Kay, O.C., PhD, Professor, Department of Biochemistry, University of Toronto.

John Ussher, PhD, Assistant Professor, Department of Pharmacy and Pharmaceutical Sciences, University of Alberta

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LEWIS E. KAY O.C. PhD

Guest Oral Adjudicator

Professor of Molecular Genetics, Biochemistry, and Chemistry at the University of Toronto and a Senior Scientist at the Hospital for Sick Children. He received his B.Sc. in Biochemistry from the University of Alberta in 1983 and his Ph.D. in Biophysics from Yale University in 1988, pursuant to which he spent three years as a postdoctoral fellow in Chemical Physics at the NIH. Appointed Assistant Professor at the University of Toronto in 1992, he was promoted to Professor just three years later. In 2012, in honour of his scholarly achievements, he was named University Professor by the University of Toronto, the highest academic distinction bestowed by the institution.

Professor Kay's extraordinary research cuts across the interface of physical chemistry and medical sciences. His work focuses on transforming the techniques of nuclear magnetic resonance (NMR) spectroscopy as applied to the study of large proteins and their complexes, in particular those that are involved in health and disease. Indeed, his innovative contributions to biomolecular NMR spectroscopy have actually defined the field, with a profound impact on essentially all aspects of biomolecular NMR. NMR methods established by Professor Kay now allow for the study of protein complexes in the one million Da molecular weight range. He has applied these ground-breaking techniques to study the proteasome, the nucleosome, p97, and protein machines involved in disaggregation that serve as critical targets for drug discovery. In addition, Professor Kay has developed and advanced NMR methods used to study protein dynamics and how these dynamic properties change upon ligand binding or folding.

In related accomplishments, Professor Kay has improved methods to study protein folding, and has applied these new techniques to study protein aggregation in numerous disease-related systems. The strength of his curiosity-driven research has led to a reliable framework by which to explore sparsely-populated, transiently-formed conformations of proteins that are implicated in protein function and disease. He now applies this methodology to a wide spectrum of protein systems.

Professor Kay has published close to 450 research papers, including several cited more than 1,000 times. His work has earned approximately 50,000 citations and his h-index exceeds 100. He has been identified by ISI as being among the top 0.5 percent of authors in chemistry in the world (since 2005). The tools developed in his laboratory are disseminated freely, used extensively worldwide, and have far-reaching impact not only for current research, but also for future discoveries.

Professor Kay is a Fellow of both the Royal Society of London and the Royal Society of Canada. In 1997, he was appointed an International Research Scholar of the Howard Hughes Medical Institute, and since 2000, he has held a Canada Research Chair in Proteomics, Bioinformatics and Functional Genomics. Included among numerous awards he has received are the Anfinson Award from the Protein Society, the Khorana Prize of the Royal Society of Chemistry, the Founders Medal of the International Society of Magnetic Resonance in Biological Systems, the Steacie Award of the Canadian Society for Chemistry, and the Flavelle Medal of the Royal Society of Canada. Most recently, he was named a Canada Gairdner International Award laureate (2017); he received the Nakanishi Prize from the American Chemical Society (2018); and was awarded Canada's most prestigious science prize, the Gerhard Herzberg Canada Gold Medal for Science and Engineering (2018).

John Ussher arried out his PhD training with Dr. Gary Lopaschuk at the University of Alberta, where we acquired expertise in the molecular regulation of cardiac energy metabolism, with a specific focus on pharmacologically increasing cardiac malonyl CoA content to treat ischemic heart disease.

Following his PhD training, John trained with Dr. Daniel Drucker at the Lunenfeld-Tanenbaum Research Institute (Toronto) to acquire extensive expertise in incretin biology. During this fellowship, he discovered that the cardioprotective properties of incretin hormones were mediated via indirect actions on peripheral tissues other than the heart.

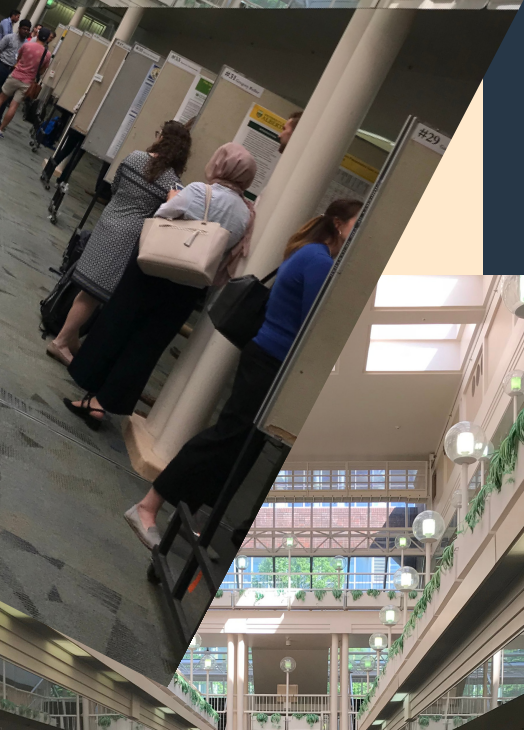
In November 2014, John returned to the University of Alberta with the Faculty of Pharmacy and Pharmaceutical Sciences, where his lab investigates the mechanisms by which obesity perturbs energy metabolism in various peripheral tissues (e.g. skeletal muscle, liver, heart, etc.). Furthermore, his lab uses both mouse genetics and pharmacological approaches to determine whether these alterations may represent a plethora of novel targets to prevent and/or reverse obesity-related type 2 diabetes and cardiovascular disease.

Some of the specific projects our lab is currently exploring include the following; (1) optimizing the heart's ability to metabolize sugars to reduce heart disease risk in type 2 diabetes, (2) understanding how skeletal muscle ketone body metabolism influences insulin sensitivity and blood sugar control in obesity and/or type 2 diabetes, and (3) elucidating the cellular/molecular actions by which the ketogenic diet impacts whole body health.

JOHN USSHER PhD

Guest Oral Adjudicator

Assistant Professor, Department of Pharmacy and Pharmaceutical Sciences, University of Alberta



Meeting at a Glace

8:00 AM	Welcome Address
8:10 AM	Keynote Speaker
8:45 AM	Oral Presentations
10:00 AM	Break
10:15 AM	Oral Presentations
11:45 AM	Lunch
1:45 PM	Translational Research Fellowship Award
2:15 PM	Oral Presentations
3:35 PM	Award Ceremony

SCORING CRITERIA

Oral & Poster Presentations

1=Poor, 5= Excellent

- Clarity and Justification of the Research Questions/Hypothesis
- Appropriateness of the Methods Used to Answer the Questions/Hypothesis
- Validity and Relevance of the Results to the Questions/Hypothesis
- Quality of the Discussion and Conclusion
- Innovation Impact
- Visual Layout and Visual Impact
- Oral Response to Adjudicator's Question(s)

Prizes!

The top scoring oral & poster presentations will be awarded ***$500*** at the Award Ceremony as follows:

1st Prize: Oral Presentation
Runner Up: Oral Presentation

1st Prize: Poster Presentation
Runner Up: Poster Presentation

Paul Man Award

The Paul Man Award is in honor of Dr. Paul Man, Division Director of Pulmonary Medicine from 1986 to 2001 for his exceptional contribution to translational research. Valued at $500.

Translational Research Fellowship Award

The purpose of this fellowship award is to provide a trainee from the Department of Medicine for dedicated research (basic and clinical) done within the Department a stipend towards their salary here at the University of Alberta. Valued at $24,000.

PAST RECIPIENTS

2018

ABDUL KALAM AZAD
SUPERVISOR: ALLAN MURRAY
FGD5 Regulates VEGF Receptor-2 Coupling to PI3 Kinase and Receptor Recycling

2017

RANIA SOUDY
SUPERVISOR: JACK JHAMANDAS
Cyclic AC253, a novel amylin receptor antagonist, improves cognitive deficits in a mouse model of Alzheimer's disease

2016

BRANDON MILLAN & HEEKAK PARK
SUPERVISOR: KAREN MADSEN
Fecal Microbial Transplants Reduce Antibiotic-Resistant Genes in Patients with Recurrent Clostrdium Difficile Infection

2015

ROXANNE PAULIN
SUPERVISOR: EVANGELOS MICHELAKIS
Sirtuin 3 Deficiency Is Associated with Inhibited Mitochondrial Function and Pulmonary Arterial Hypertension in Rodents and Humans

2014

STACEY REINKE
SUPERVISOR: CHRIS POWER
Implementation of metabolomics strategies in multiple sclerosis

2013

PETER DROMPARIS
SUPERVISOR: EVANGELOS MICHELAKIS
Pioglitazone reduces angiogenesis by altering mitochondrial function and reducing hypoxia inducible factor-1 activation

2012

VAIBHAV PATEL
SUPERVISOR: GAVIN OUDIT
Loss of ACE2 Exacerbates Diabetic Cardiovascular Complications and Leads to Systolic and Vascular Dysfunction: A Critical Role of the Ang II/AT1 Receptor Axis

MORNING ORAL PRESENTATIONS

845AM

Kerolous Messeha, Graduate Student
Supervisor: Andrew Mason
Studying the Immune Effects of Betaretrovirus infection in the NOD.c3c4 mouse model of Primary Biliary Cholangitis

900AM

Xueyi Chen, Graduate Student
Supervisor: Gavin Oudit
Cardiac PI3Kalpha Mediates Infarct Healing and Cardiac Remodeling by Regulating Angiogenic Responses and Cardiomyocyte Survival

915AM

Aris Boukouris, Graduate Student
Supervisor: Evangelos Michelakis
The neuronal protein CRMP2A is a novel survival factor and determines cell fate in cancer cells undergoing diverse metabolic stresses

930AM

Amy Kirkham, Postdoctoral Fellow
Supervisor: Ian Paterson
Beta-blockers preserve left ventricular myocardial and right ventricular ejection fraction during trastuzumab for breast cancer relative to ACE-inhibitors and placebo

945AM

Zhao Wu Meng, Subspecialty Resident
Supervisor: Mang Ma
Using Fibrosis 4 Index to Triage Elevated Liver Enzymes in Asymptomatic Patients Without Viral Hepatitis

MORNING ORAL PRESENTATIONS

1015AM

Sotirios Zervopoulos, Graduate Student
Supervisor: Evangelos Michelakis
A novel non-canonical pathway of nuclear entry of proteins lacking a nuclear localization sequence

1030AM

Ali Nomani, Subspecialty Resident
Supervisor: Khurshid Khan
Microemboli during Transcranial Doppler Ultrasonography in patients with subarachnoid hemorrhage

1045AM

Arunima Sivanand, Graduate Student
Supervisor: Robert Gniadecki
Neoantigens in mycosis fungoides: whole exome sequencing discovery of immunotherapeutic targets

1100AM

Hannah Cherniawsky, Graduate Student
Supervisor: Christopher Paul Venner
Lenalidomide Maintenance Positively Impacts Outcomes in Multiple Myeloma Without Negative Impacts In Relapse: An Analysis Of Real World Data From The Myeloma Canada Research Network National Patient Database

1115AM

Nariman Sephervand, Graduate Student
Supervisor: Justin A. Ezekowitz
High versus Low SpO2 oxygen therapy in patients with acute Heart Failure: HiLo-HF Pilot trial

1130AM

ThucNhi Dang, Subspecialty Resident
Supervisor: Clarence K. Wong
INCREASING FIT CUT-OFFS INCREASES RATES OF MISSED HIGH-RISK LESIONS ON COLONOSCOPY WITHOUT DECREASING NUMBER NEEDED TO SCOPE

AFTERNOON ORAL PRESENTATIONS

215PM

ALISON CLIFFORD
ASSISTANT PROFESSOR
RHEUMATOLOGY

Alison Clifford, MD trained at Dalhousie University, where she completed medical school, Internal Medicine and Rheumatology residencies. She then went on to do a 2 year combined clinical and research vasculitis fellowship at the Center for Vasculitis Care and Research at the Cleveland Clinic in Cleveland, USA. She joined the Department of Medicine at the University of Alberta in 2016 as an Assistant Professor of Rheumatology. She is a member of CanVasc, the Canadian network for vasculitis research. She has a dedicated vasculitis clinic, and conducts research on the role of imaging in large vessel vasculitis.

235PM

TORU TATENO
ASSISTANT PROFESSOR
ENDOCRINOLOGY

Dr. Tateno has focused his clinical and research interest in pituitary tumors. He was born in the centre of Tokyo, Japan, and he received MD from Tokyo Medical and Dental University. He finished clinical training and PhD under supervision of Dr. Hirata at Tokyo Medical and Dental University. He then completed postdoctoral and clinical fellowships at the University of Toronto before joining the University of Alberta. He reported gene expression patterns in pituitary tumors, the roles of FGFR4 SNP in pituitary tumor development and hormone regulation, and a novel mouse model of pituitary adenoma. He also reported several cases with endocrine tumors including pituitary tumor, IGF-II producing tumor, ectopic ACTH syndrome, etc. Recently, he presented his work regarding the roles of L-type amino acid transporter 1 in pituitary tumors at the annual meeting of the Endocrine Society in 2019. He also works as academic lead of the pituitary team at the University of Alberta.

Dr. Tateno and his wife, Tae, have two children. He enjoys tennis and cello in his spare time.

AFTERNOON ORAL PRESENTATIONS

255PM

STEPHANIE THOMPSON
ASSISTANT PROFESSOR
NEPHROLOGY

Stephanie Thompson is an Assistant Professor in the Division of Nephrology. She completed her clinical Nephrology training and her Internal Medicine training at the University of Alberta. She subsequently obtained a PhD in Epidemiology through the School of Public Health at the University of Alberta. Dr. Thompson's research interests include trials that test lifestyle interventions in people with chronic kidney disease, with a focus on exercise and developing strategies on how to increase the adoption of exercise into the care of people with chronic kidney disease. She is also interested in examining how behavioural interventions and technology can be used to promote patient engagement in self-care. Dr. Thompson's methodological interests include the design and conduct of clinical trials, qualitative research, and the evaluation of healthcare delivery. She has received funding from the University Hospital Foundation and The Canadian Institute of Health Research.

315PM

JASON PLEMEL
ASSISTANT PROFESSOR
NEUROLOGY

Jason Plemel began his training in the laboratory of Dr. Wolfram Tetzlaff where he completed his Doctorate. There he investigated two separate strategies to improve white matter regeneration: transplantation of precursor cells to replace lost oligodendrocytes and cell culture to find novel targets to improve remyelination. During Dr. Plemel's postdoctoral work he studied the contribution of microglia following myelin injury in the laboratories of Dr. Peter Stys and Dr. Wee Yong. His interdisciplinary project investigated mechanisms of how immune cells respond to primary degeneration and developed a new tool to image cell death and injury using spectral microscopy. In his new faculty appointment at the University of Alberta, Dr. Plemel and his laboratory will investigate how microglia play an important role in the regeneration of injured white matter, but also how microglia can induce injury to white matter during different disease conditions.

AFTERNOON POSTER PRESENTATIONS

#1
Abhishek Dahal, Graduate Student
Supervisor: Satyabrata Kar
Role of Tau Protein in Kainic Acid-induced Animal Model of Temporal Lobe Epilepsy

#2
Abul Kalam Azad, Graduate Student
Supervisor: Allan Murray
Investigating the role of endothelial cell-specific p110β isoform of PI3K as a potential target for anti-angiogenic therapy

#3
Aishwarya Iyer, Graduate Student
Supervisor: Robert Gniadecki
Cutaneous T-cell lymphoma is a genetically and clonotypically heterogeneous

#4
Ali Nomani, Subspecialty Resident
Supervisor: Khurshid Khan
Cerebral Air Embolism with Endovascular Thrombectomy in Acute Ischemic Stroke: The Need for Site-Specific Protocols for CAE at Comprehensive Stroke Centers

#5
Ammar Hassanzadeh Keshteli, Graduate Student
Supervisors: Levinus Dieleman & Karen Madsen
Ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) have distinctive serum metabolomic fingerprints versus UC patients without PSC

#6
Anas Alrohimi, Core Internal Medicine Resident
Supervisor: Ken Butcher
Early apixaban treatment after transient ischemic attack and acute ischemic stroke does not result in hemorrhagic transformation

#7
Andrea Johnson, Core Internal Medicine Resident
Supervisor: Elaine Yacyshyn
Giant Cell Myocarditis: Fifteen-year case series of a single institution

AFTERNOON POSTER PRESENTATIONS

#8

Andrea Johnson, Core Internal Medicine Resident
Supervisor: Alison Clifford
Intracranial vascular involvement in Takayasu's arteritis: common or not?

#9

Andrew Masoud, Graduate Student
Supervisor: Allan Murray
Apelin promotes vascular repair following immune-mediated injury through directing tip-cell differentiation

#10

Andrew Schmaus, Graduate Student
Supervisor: Satyabrata Kar
Thermal response of amyloidogenic elements in cultured N2a cells: potential relevance to Alzheimer's Disease pathology

#11

Andrew Castle, Postdoctoral Fellow
Supervisor: David Westaway
Development of CRISPR-Cas9-based gene drive approaches to prion disease resistance

#12

Andrew MacDonald, Core Internal Medicine Resident
Supervisor: Constantine Karvellas
Use of the Molecular Adsorbent Recirculating System (MARSÂ®) in Acute Liver Failure - A Multicentre Experience

#13

Anish Nikhanj, Graduate Student
Supervisor: Gavin Y. Oudit
The Use of Cardiac Resynchronization Therapy in Type 1 Myotonic Muscular Dystrophy Patients with Left Bundle Branch Block

#14

Arafat Alam, Graduate Student
Supervisor: Cynthia Wu & Linda Sun
Survival pattern among venous thromboembolism (VTE) patients with hematologic malignancy in Alberta, Canada from 2002 to 2015

AFTERNOON POSTER PRESENTATIONS

#15
Asmaa Basonbul, Graduate Student
Supervisor: Joseph Brandwein
BCL-2 Inhibitor Venetoclax Enhances Temozolomide Sensitivity in AML

#16
Aya Lafta, Graduate Student
Supervisor: Branko Braam
Fluid volume overload and vascular stiffness in hemodialysis patients

#17
Bohyung Min Min, Core Internal Medicine Resident
Supervisor: Meena Kalluri
Comparison of Palliative Care Practices in Idiopathic Pulmonary Fibrosis

#18
Brittany Kula, Core Internal Medicine Resident
Supervisor: Wendy Sligl
A retrospective review of Pseudomonas aeruginosa infection in a quarternary intensive care unit: epidemiology, outcomes, and antimicrobial susceptibilities: 2013-2016

#19
Bruno Saleme, Graduate Student
Supervisor: Evangelos Michelakis
Novel mechanism for transcription-independent translation of selective proteins under acute cellular stress, involving mRNA demethylation

#20
Carissa Beaulieu, Core Internal Medicine Resident
Supervisor: Cynthia Wu
The appropriateness of HIT testing at the University of Alberta

#21
Christen Klinger, Graduate Student
Supervisor: Joel B. Dacks
Paralagous expansion of membrane trafficking factors played key roles during the evolution of apicomplexan parasites

AFTERNOON POSTER PRESENTATIONS

#22

Christopher Wang, Core Internal Medicine Resident
Supervisor: Vincent Bain
De-novo Donor Specific Antigen Formation in Liver Transplants: Risk Factors for Development and Impact on Graft Survival

#23

Daniel Sawler, Subspecialty Resident
Supervisor: Linda Sun
Time from suspected thrombotic thrombocytopenic purpura to initiation of plasma exchange in Alberta, Canada and impact on survival: a 10-year provincial retrospective cohort study

#24

David Page, Core Internal Medicine Resident
Supervisor: Lalit Saini
Effect of Imatinib on relapse rates and survival in philadelphia chromosome positive acute lymphoblastic leukemia post-allogeneic stem cell transplantation

#25

Deepa Krishnaswamy, Core Internal Medicine Resident
Supervisor: Kumaradevan Punithakumar
A Novel 4D Semi-Automated Algorithm for Volumetric Segmentation in Echocardiography

#26

Eddie Liu, Core Internal Medicine Resident
Supervisor: Brendan Halloran
GI BLEED DUE TO CHRONIC LYMPHOCYTIC LEUKEMIA INFILTRATION IN THE SMALL BOWEL

#27

Eduardo Reyes-Serratos, Graduate Student
Supervisor: Dean Befus
Levels of human Calcium-binding protein, spermatid-associated 1 (hCABS1) in saliva are positively associated to psychosocial stress and can be analyzed in a high-throughput manner

#28

Mohammad Ashif Rahman, Subspecialty Resident
Supervisor: Frances Carr
Using the Confusion Assessment Method (CAM) Tool to screen for delirium amongst hospitalized inpatients - a Quality Improvement Initiative

AFTERNOON POSTER PRESENTATIONS

#29

Gina Sykes, Graduate Student
Supervisor: Glen Jickling
Age-Associated Immune Alterations in Patients with Ischemic Stroke

#30

Grace Lam, Subspecialty Resident
Supervisor: Winnie Leung
Changing the Paradigm: A National Prospective Multi-Centered Study to Validate a Novel Algorithm for Cystic Fibrosis (CF)-related Diabetes (CFRD) Screening

#31

Hiatem Abofayed, Graduate Student
Supervisor: Andrew Mason
Comparison of cellular immune responses to human betaretrovirus versus autoimmune responses to mitochondrial antigens in patients with primary biliary cholangitis

#32

Hussain Syed, Graduate Student
Supervisor: Andrew Mason
Investigating TCR-VB repertoire expression profiles in Primary Biliary Cholangitis patients for evidence of Human Betaretrovirus Superantigen Activity

#33

Jenny Lu-Song, Core Internal Medicine Resident
Supervisor: Meena Kalluri
Cost analysis of end of life care in idiopathic pulmonary fibrosis

#34

Jesse Stach, Core Internal Medicine Resident
Supervisor: Sander Veldhuyzen Van Zanten
Acute Upper Gastrointestinal Bleeding: Evaluating Physician Practices in the Emergency Department

#35

Jimmy Guo, Core Internal Medicine Resident
Supervisor: Levinus Dieleman
EMERGING THERAPEUTIC TARGETS FOR INFLAMMATORY BOWEL DISEASE-COLORECTAL CANCER: Case Study Analysis

AFTERNOON POSTER PRESENTATIONS

#36

Kahir Rahemtulla, Graduate Student
Supervisor: Vivian Mushahwar
AN ALTERNATIVE PROPHYLAXIS FOR DEEP VEIN THROMBOSIS USING INTERMITTENT ELECTRICAL STIMULATION

#37

Katelynn Madill-Thomsen, Graduate Student
Supervisor: Philip Halloran
Automated histology lesion interpretation in kidney transplant biopsies shows that pathologists often deviate from Banff

#38

Kevin Yen, Core Internal Medicine Resident
Supervisor: Fang Ba
Patient-Centered Decision-Making Algorithm for Deep Brain Stimulation Surgery in Parkinson's Disease

#39

Khadija Alzahrani, Graduate Student
Supervisor: Harissios Vliagoftis
German Cockroach Extract Proteolytic Activity Down-regulates Interleukin-13 Dependent Eotaxin-3 (CCL26) Expression in Airway Epithelial Cells

#40

Laura van den Bosch, Core Internal Medicine Resident
Supervisor: Meena Kalluri
A Multidimensional Dyspnea Scale To Characterize Episodic Breathlessness In Interstitial Lung Disease

#41

Lily Lin, Graduate Student
Supervisors: Nee Khoo, Darren Freed & Evangelos Michelakis
Rapid leaflet expansion is the main adaptive change to maintain tricuspid valve (TV) competency from detrimental remodeling: a three-dimensional echocardiography (3DE) study in a novel chronic right ventricular (RV) pressure and volume loaded piglet model

#42

Lindsey Russell, Graduate Student
Supervisor: Dina Kao
Serial fecal microbiota transplant plus fidaxomicin in treating severe or fulminant Clostridioides difficile infection

AFTERNOON POSTER PRESENTATIONS

#43

Lingyu Xu, Graduate Student
Supervisor: Ian Paterson
A Novel 3-Dimentional technique in Measuring pericoronary epicardial adipose tissue radiodensity

#44

Lingyu Xu, Graduate Student
Supervisor: Ian Paterson
Cardiac remodeling predicts outcome for patients with stable heart failure: a serial cardiac magnetic resonance imaging study

#45

Mahsa Mohseni, Graduate Student
Supervisor: Joseph Brandwein
Combination of siRNA and Chemotherapeutic Agents in Acute Leukemic Cells

#46

Matthew Anaka, Core Internal Medicine Resident
Supervisor: Simron Singh (University of Toronto)
Understanding neuroendocrine tumour patient treatment preferences using discrete choice experiments

#47

Matthew Anaka, Core Internal Medicine Resident
Supervisor: Jennifer Spratlin
Goals of care designation associated with improved survival and indicators of quality end-of-life care in pancreatic cancer (PC) patients (pts) undergoing palliative chemotherapy

#48

Nadia Daniel, Graduate Student
Supervisor: Harissios Vliagoftis
The role of growth factor deprivation in PAR-2 regulation and autophagy induction in the airway epithelium

#49

Nariman Sepehrvand, Graduate Student
Supervisor: Justin A. Ezekowitz
External validation of the H2F-PEF model in diagnosing patients with heart failure and preserved ejection fraction

AFTERNOON POSTER PRESENTATIONS

#50

Nilanjani Premraj, Graduate Student
Supervisor: Levinus Dieleman
CAN PREBIOTICS AND/OR DIETARY CHANGES REDUCE LEAKY GUT IN HEALTHY FIRST-DEGREE RELATIVES OF CROHN'S PATIENTS?

#51

Parnian Alavi, Graduate Student
Supervisors: Nadia Jahroudi & Jayan Nagendran
Aging is associated with increased von Willebrand factor expression

#52

Peter (Yuan) Zhang, Core Internal Medicine Resident
Supervisor: Miriam Shanks
Left Ventricular Thrombus Detection by Echocardiography After Acute Myocardial Infarction and the Incidence of Stroke

#53

Qi Wu, Postdoctoral Fellow
Supervisor: Satyabrata Kar
Characterization of Exosomes-derived from Cholesterol Accumulated Astrocytes and its Significance in Alzheimer's Disease Pathology

#54

Rachel Jeong, Core Internal Medicine Resident
Supervisor: Ngan Lam
Kidney Function, Albuminuria, and the Risk Of Hemorrhage and Thrombosis After Kidney Transplantation

#55

Ravi Homenauth, Subspecialty Resident
Supervisor: Karen Kroeker
WAIT TIMES FOR IBD SURGERY IN EDMONTON: 50% ARE WAITING TOO LONG

#56

Raymond Chu, Core Internal Medicine Resident
Supervisor: Elaine Yacyshyn
A Ten-Year Retrospective Review of Temporal Artery Biopsy Lengths in Alberta

AFTERNOON POSTER PRESENTATIONS

#57

Reed Sutton, Graduate Student
Supervisor: Karen Kroeker
ADHERENCE TO GUIDELINES AND BEST PRACTICES FOR IBD FLARE MANAGEMENT AND CORTICOSTEROID ADMINISTRATION: A RETROSPECTIVE CHART REVIEW

#58

Reed Sutton, Graduate Student
Supervisor: Karen Kroeker
Management of Inflammatory Bowel Disease Patients with Clinical Care Pathways Reduces Emergency Department Utilization

#59

Sabitha Rajaruban, Graduate Student
Supervisor: Karen Madsen
CONSUMPTION OF REFINED SUGAR RAPIDLY DECREASES MICROBIAL DIVERSITY AND ENHANCES SYSTEMIC RESPONSE TO MICROBIAL STIMULI

#60

Saima Rajabali, Graduate Student
Supervisor: Adrian Wagg
Using community based participatory approach in clinical trials involving older adults - Lessons from SHAPES

#61

Sarah Younus, Research Associate
Supervisor: Meena Kalluri
Comparison of MRC breathlessness scale to a novel multidimensional dyspnea scale (MDDS) for clinical use

#62

Selynne Guo, Core Internal Medicine Resident
Supervisor: Darryl Rolfson
Perceptions of Frailty Amongst Older Adults

#63

Shivani Upadhyaya, Core Internal Medicine Resident
Supervisor: Anna Oswald
Resident mental models and experiences of the initial implementation of Competence By Design (CBD)

AFTERNOON POSTER PRESENTATIONS

#64

Steven Willows, Postdoctoral Fellow
Supervisor: Andrew Mason
Investigating an infectious etiology for altered metabolism in biliary epithelial cells of patients with primary biliary cholangitis

#66

Tayyaba Zehra, Graduate Student
Supervisor: Branko Braam
EXPERIMENTAL CHRONIC KIDNEY DISEASE REDUCES STRENGTH OF TGF- SYNCHRONIZATION AND IMPAIRS AUTOREGULATION

#67

Victoria Sarban, Graduate Student
Supervisor: Miriam Shanks
Multi-view Three-Dimensional Fusion Echocardiography System in Patients with Cardiac Resynchronization Therapy Devices

#68

Yazid Al Hamarneh, Research Associate
Supervisor: Ross Tsuyuki
Pharmacist Prescribing and Care Improves Cardiovascular Risk, But What Do Patients Think? A sub-study of the RxEACH study.

#69

Yazid Al Hamarneh, Research Associate
Supervisor: Ross Tsuyuki
Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the RxEACH study

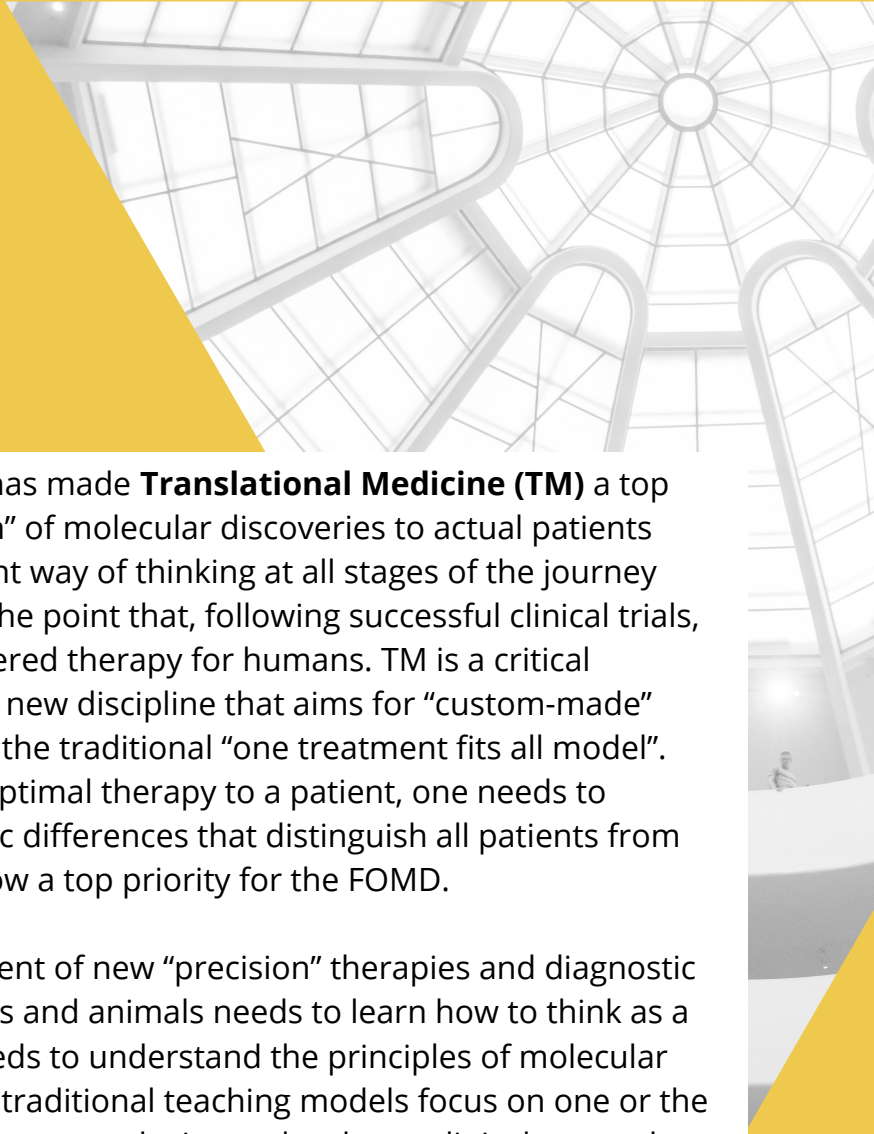
#70

Yongneng Zhang, Graduate Student
Supervisor: Evangelos Michelakis
A novel cardiac fibroblast-cardiomyocyte paracrine mechanism in the hypertrophied right ventricle in pulmonary hypertension

#71

Yusra Batool, Graduate Student
Supervisor: Glen Jickling
Differential immune activation in patients with acute ischemic stroke and admission blood pressure greater than 185/110 mm Hg

MSC IN MEDICINE (TRANSLATIONAL MEDICINE)



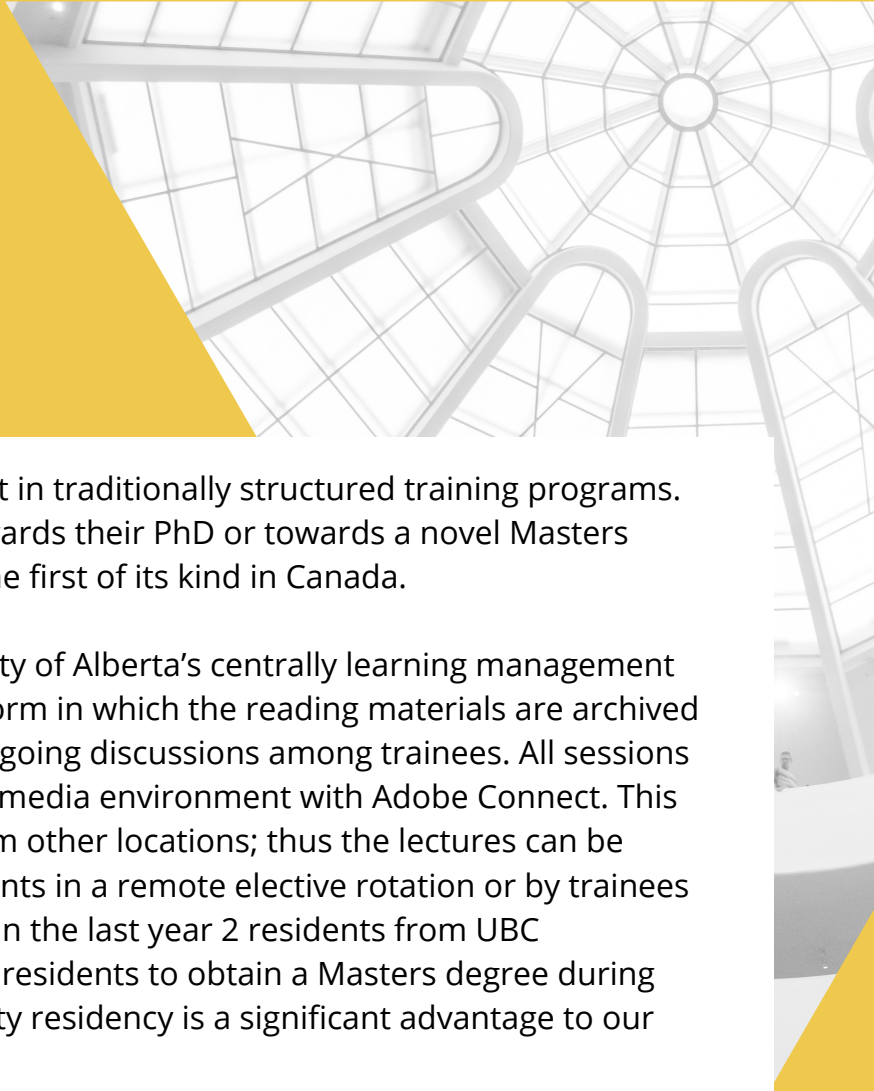
The Department of Medicine (DOM) has made **Translational Medicine (TM)** a top priority. TM facilitates the "translation" of molecular discoveries to actual patients and populations. It requires a different way of thinking at all stages of the journey from a discovery in an animal lab to the point that, following successful clinical trials, the government approves the discovered therapy for humans. TM is a critical component of **Precision Medicine**, a new discipline that aims for "custom-made" therapies for patients, as opposed to the traditional "one treatment fits all model". This is because in order to apply an optimal therapy to a patient, one needs to understand the molecular and genetic differences that distinguish all patients from one another. Precision Medicine is now a top priority for the FOMD.

The need: To optimize the development of new "precision" therapies and diagnostic tests, a researcher studying molecules and animals needs to learn how to think as a clinician; and a clinical researcher needs to understand the principles of molecular research. This is challenging because traditional teaching models focus on one or the other, with the learners following either an exclusive molecular or clinical research career track. Although all recognize the importance of TM, there are surprisingly few examples of training programs worldwide aiming to teach this new discipline to future medical researchers and leaders.

The action: Four years ago, the DOM launched and since then supports a novel training program, teaching the attitudes and skills required to excel in TM. This is the first training program of its kind in Canada and one of few in the world.

The innovations: The TM program attracts trainees from very diverse backgrounds and levels of training. Rather than teaching principles of basic or clinical research of specific diseases, the program teaches integrative and overarching concepts and skills to address the many challenges of bringing a molecular discovery to patients with diverse diseases. Since nothing needs to be "memorized", the final exams are "open book". Teaching objectives include, among others, new ways to design animal experiments or clinical trials compatible with PM, strategies to attract funding including grant writing skills, effective ways to communicate cross-disciplinary research findings, understanding of regulatory rules and "quality control" principles in preclinical and clinical research.

MSC IN MEDICINE (TRANSLATIONAL MEDICINE)



Most of these principles are not taught in traditionally structured training programs. The trainees can either get credits towards their PhD or towards a novel Masters Program with “specialization in TM”, the first of its kind in Canada.

The program uses eClass, the University of Alberta’s centrally learning management system. eClass provides a digital platform in which the reading materials are archived as well as an out-of-class forum for ongoing discussions among trainees. All sessions are recorded through the eClass multimedia environment with Adobe Connect. This allows “live” streaming of sessions from other locations; thus the lectures can be attended interactively online by residents in a remote elective rotation or by trainees from other Universities. For example, in the last year 2 residents from UBC completed the program. The ability of residents to obtain a Masters degree during busy core Internal Medicine or specialty residency is a significant advantage to our clinical training programs.

The progress: A total of 72 learners have registered to the program so far. Of these, some took credits for their PhD and some participated as “open access” students. Of the 42 trainees that participated in the Masters track, there were 2 junior faculty members, 14 graduate students and 26 residents from core and 10 specialty residency programs. To complete the Masters requirements a submission of a thesis is required. So far 11 trainees have obtained their Master’s with specialization in TM degree.

The TM program is a major investment of the DOM, with many of its faculty contributing over the years. Currently, the program is directed by Evangelos Michelakis, MD, Gopinath Sutendra, PhD, Glen Jickling, MD, PhD and Eleni Karageorgos.

Studying the Immune Effects of Betaretrovirus infection in the NOD.c3c4 mouse model of Primary Biliary Cholangitis

Kerolous S. Messeha, Dr. Andrew L. Mason

INTRODUCTION

A human betaretrovirus (HBRV) has been characterized in patients with primary biliary cholangitis (PBC). The virus shares between 93% to 98% nucleotide similarity with the mouse mammary tumor virus (MMTV). Retroviruses are known to suppress host immune responses by the presence of immunosuppressive domains (ISDs) in the envelop (Env) portion. These ISDs have been shown to inhibit lymphocyte proliferation and promote secretion of IL-10, an immunoregulatory cytokine. In vivo, we investigated whether MMTV Env protein harbors an ISD with similar immunoregulatory characteristics. Then, we addressed the hypothesis that B cells in the NOD.c3c4 mouse model produce IL-10 as a result of MMTV infection

METHODS

Splenocytes from healthy mice C57Bl/6 and BALB-C were used. ELISA and proliferation assays were used to detect the levels of IL-10 secretion and assess the ability of the identified ISDs to inhibit lymphocyte proliferation respectively. Flowcytometry was used to assess the role of B cells in response to MMTV infection. Splenocytes from infected NOD.c3c4 & healthy C57Bl/6 were stained for MMTV-infected B cells secreting IL-10.

RESULTS

ISDs significantly promoted higher secretion of IL-10. In the proliferation assays, there was reduction in proliferation of $p < 0.01$ and $p < 0.001$ (95% CI) in BALB-C and C57Bl/6 respectively. NOD.c3c4 mice had a significant expansion of B cells secreting IL-10 compared to C57B/6 with $P < 0.001$, CI > 95%.

CONCLUSIONS

MMTV masks the immune response by ISDs via inhibiting lymphocytes proliferation and promoting IL-10 secretion. Moreover, MMTV- infected B cells have a manifest role in the development of a PBC like picture in NOD.c3c4 mice as more B cells secreting IL-10 were found in NOD.c3c4 compared to healthy mouse strains. This study reveals a part of the immune response to MMTV. Further work should be done to assess the effect of blocking IL-10R on rendering PBC progression.

Supervisor: Dr. Andrew Mason

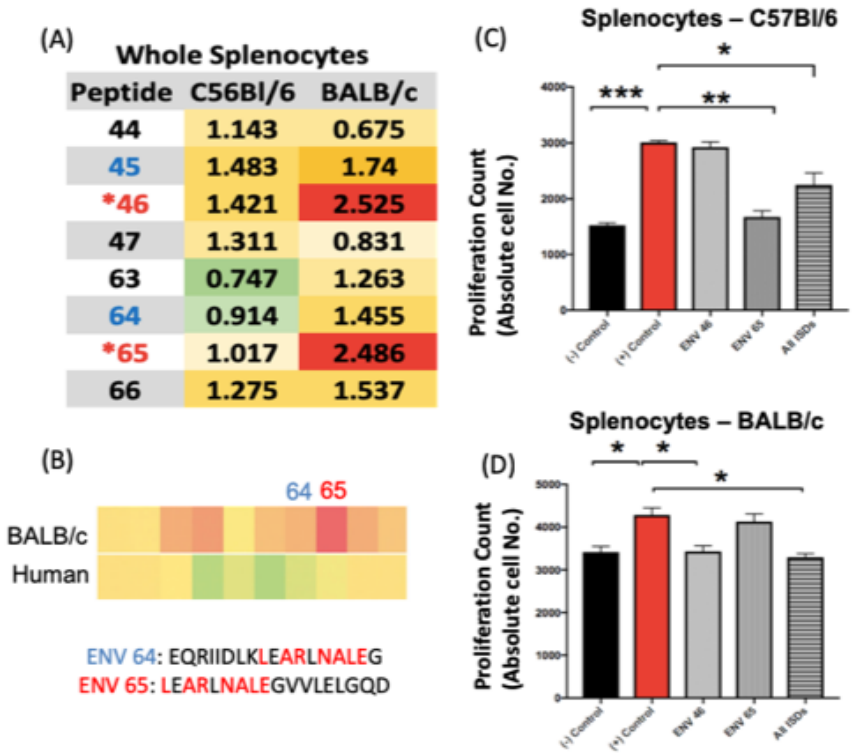


Figure 1. *(A) Heatmap showing marked IL-10 secretion (pg/ml) in C57Bl/6 and BALB/c in response to two ISDs (46, 65). (B) There are amino acids overlap in transmembrane ISDs ENV 64 and ENV 65 from human and mice respectively. (C) The graph shows a marked reduction in lymphocytes proliferation by using ENV 65 and both identified ISDs in C57B/6 with p<0.001 and p<0.01 (D) The graph shows a marked reduction in lymphocytes proliferation by using ENV 46 and both identified ISDs in BALB/c with p<0.01*

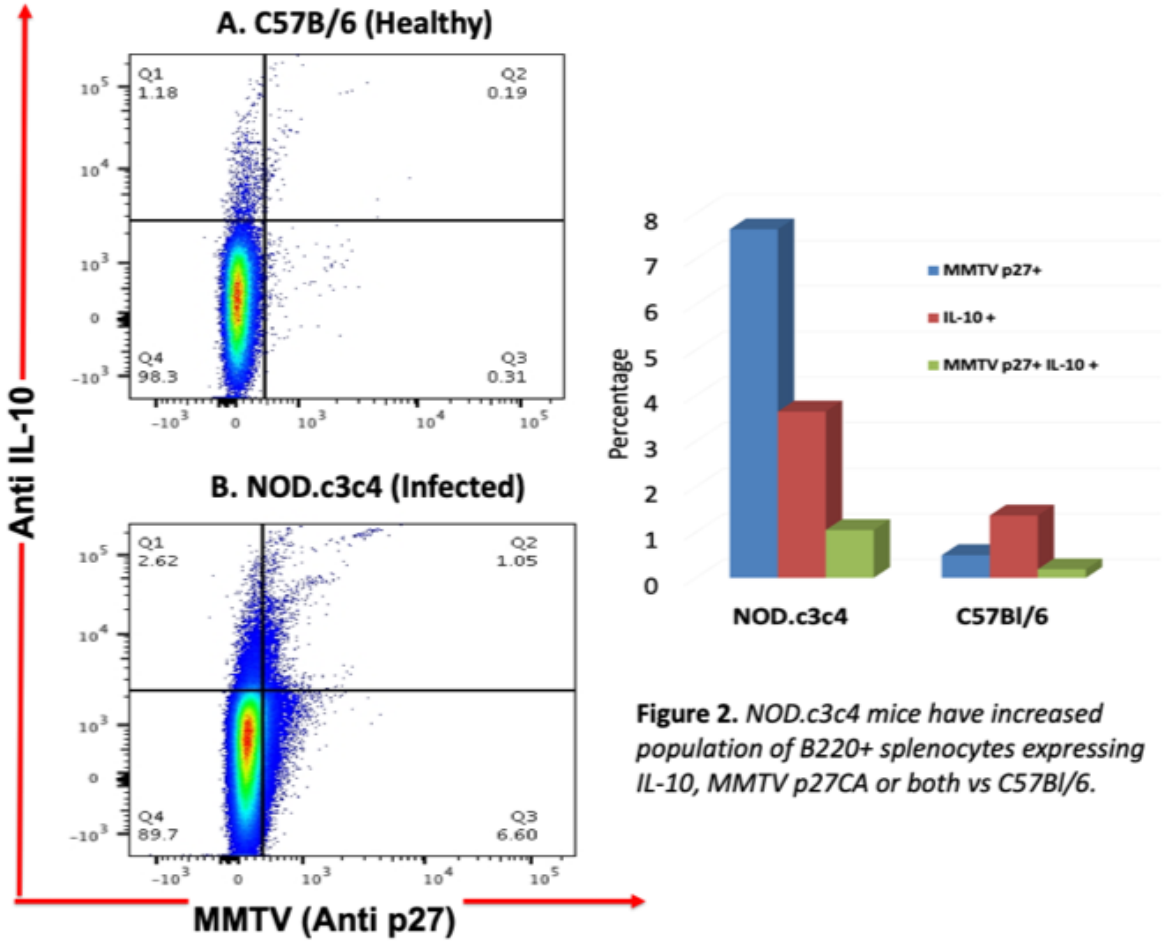


Figure 2. *NOD.c3c4 mice have increased population of B220+ splenocytes expressing IL-10, MMTV p27CA or both vs C57Bl/6.*

Cardiac PI3Kalpha Mediates Infarct Healing and Cardiac Remodeling by Regulating Angiogenic Responses and Cardiomyocyte Survival

Xueyi Chen, Pavel Zhabyeyev, Abul K. Azad, Wang Wang, Jessica DesAulnier, Allan G. Murray, Zamaneh Kassiri, Bart Vanhaesebroeck, and Gavin Y. Oudit

INTRODUCTION
Phosphoinositide 3-kinase alpha (PI3Kalpha) is a lipid kinase controlling multiple signaling pathways to regulate cell survival, growth, proliferation, and metabolism, which have been explored as an attractive therapeutic target for various diseases, such as cancer, thrombosis, and others. As PI3Kalpha inhibitor-BYL719 is in clinical trials displaying a tolerable safety profile, we decided to explore the potential consequences of PI3Kalpha inhibition in a leading cause of global deaths-coronary artery disease.

METHODS
WT mice treated with BYL719 and mice with genetically-modified, endothelial (alphaTie2) or cardiomyocyte (alphaCre) specific loss of PI3Kalpha function were used in the study. Ligation of left anterior descending coronary artery to mimic myocardial infarction (MI) or sham surgery was performed on 12-week-old mice. Cardiac function was assessed using echocardiography. Cardiac histological changes and signaling pathways alteration were examined by immunofluorescence staining and Western blot respectively. Human umbilical vein endothelial cell (HUVEC) culture and adult murine cardiomyocyte isolation were performed to assess the effects of BYL719 on cellular level.

RESULTS
PI3Kalpha catalytic subunit (p110alpha) was upregulated in human and murine hearts after MI. With Pharmacological PI3Kalpha inhibitor, mice displayed aggravated post-MI cardiac remodeling with significantly decreased cardiac function, increased the rate of apoptotic cell death, and decreased vascular density in the ischemic area compared to controls. Using genetic approaches, we demonstrated that mice without endothelial- or cardiomyocyte-PI3Kalpha function showed deteriorated post-MI cardiac function, which was associated with suppressed endothelial cell survival and proliferation and enhanced post-MI apoptotic cell death ratio respectively. In vitro experiments showed that PI3Kalpha specific inhibition suppressed HUVEC pro-angiogenic Akt/eNOS signaling and enhanced hypoxia-triggered isolated adult murine cardiomyocyte death.

CONCLUSIONS
PI3Kalpha is a critical mediator of cardiomyocyte survival and vascular repair after myocardial infarction. Thus, activation of cardiac PI3Kalpha may represent a novel therapeutic strategy for MI, whilst the use of PI3Kalpha inhibitor causes potential harm to the ischemic heart.

Supervisor: Dr. Gavin Oudit

The neuronal protein CRMP2A is a novel survival factor and determines cell fate in cancer cells undergoing diverse metabolic stresses

Aristeidis Boukouris, Bruno Saleme, Sotirios Zervopoulos, Gopinath Sutendra, Evangelos Michelakis

INTRODUCTION

The remarkable ability of cancer cells to survive severe metabolic stress (lack of nutrients and oxygen) is incompletely understood. We hypothesized that cancer cells may respond to different types of metabolic stress by a common novel pathway.

METHODS

We exposed various cancer cell types to diverse metabolic stresses including hypoxia, glucose starvation and global mitochondrial inhibition (using ethidium bromide, electron transport chain inhibitors and knockdown of Sirt3, a mitochondrial deacetylase inhibitor). We performed unbiased proteomic analysis (2D gel electrophoresis and mass spectrometry) as well as standard molecular techniques and assays including CRISPR and transcriptomics.

RESULTS

We found a strong induction (mRNA and protein) of the Collapsin Response Mediator Protein-2A (CRMP2A) in all metabolic stresses, associated with a parallel decrease in the levels of the master transcription factor c-Myc. Decreasing DNA methylation (known to be regulated by products of mitochondrial metabolism) with a methyltransferase inhibitor (5-aza) also induced CRMP2A suggesting that DNA methylation may be involved in a c-Myc-dependent CRMP2A regulation at stress (c-Myc is known to repress its targets in a methylation-dependent manner). Acute loss of CRMP2A (siRNA) significantly increased apoptotic cell death within 48 hours suggesting that it is an essential survival factor. Transcriptomics between cells treated with 2 different CRMP2A siRNAs and CRISPR-treated cells (i.e. a sustained CRMP2A loss) showed a common induced group of 10 genes, all related to epithelial-to-mesenchymal transition (EMT) markers. Additional studies in CRISPR cells confirmed induction of EMT proteins (e.g. Snail, Slug, N-cadherin) and an EMT-compatible phenotype (cell elongation).

CONCLUSIONS

CRMP2A, a protein previously only described in neurons, has important cell fate-determining properties in cancer. CRMP2A is ubiquitously induced under different metabolic stressors. Acute loss of CRMP2A deprives cells of an essential survival factor and causes death, while sustained/permanent loss forces cells to undergo an EMT phenotypic switch, a known death-escaping mechanism that promotes metastasis.

Supervisor: Dr. Evangelos Michelakis

Beta-blockers preserve left ventricular myocardial and right ventricular ejection fraction during trastuzumab for breast cancer relative to ACE-inhibitors and placebo

Amy A. Kirkham, Edith Pituskin, Richard B. Thompson, John R. Mackey, Sheri Koshman, Davinder Jassal, Marshall Pitz, Mark J. Haykowsky, Joseph J. Pagano, Kelvin Chow, Larissa J. Vos, Sunita Ghosh, Gavin Y. Oudit, Justin A. Ezekowitz, D. Ian Paterson

INTRODUCTION

Trastuzumab therapy for breast cancer causes a drop in left ventricular (LV) ejection fraction (EF). MANTICORE-101–Breast is a randomized placebo-controlled trial that previously reported that both beta-blockers (BB) and ACE-inhibitors (ACEI) attenuated the LVEF drop occurring with placebo (PL) during trastuzumab treatment, but BB were more effective. This secondary analysis was performed to determine if the protective effects of BB extend to LV myocardial function (global longitudinal strain, GLS), right ventricular (RV) function and left atrial (LA) volume.

METHODS

Cardiac magnetic resonance imaging was performed before, after four trastuzumab treatments (3MO), and after all 17 trastuzumab treatments (12MO) in n=94 (BB=31, ACEI=33, PL=30) women with breast cancer. ANCOVA with adjustment for baseline was used to compare the change in variables at both time points between groups.

RESULTS

At 12MO, heart rate was reduced in BB and mean arterial pressure and systemic vascular resistance were reduced in ACEI (all $p<0.05$ relative to other groups, Table 1). The deterioration of GLS in PL was prevented at both time points only by BB ($p<0.01$, Figure1). The GLS change in BB was greater than in ACEI at both time points ($p<0.01$, Figure 1). At 3MO, the drop in RVEF was similar to that previously reported in LVEF (-6±1 vs -7±1) in PL, and this was prevented by BB (-1±1, $p<0.01$), but not ACEI (-4±1, $p=0.13$). There were no group differences in RVEF at 12MO. LA indexed volume was increased in all groups at both times.

CONCLUSIONS

In the short-term (3MO), BB has protective effects on biventricular function during trastuzumab treatment for breast cancer, including LV GLS. By 12MO, BB caused an increase in GLS beyond baseline. By completion of trastuzumab, the drop in RV function appears to resolve regardless of group. LA volume increases with trastuzumab with no effect of BB or ACEI.

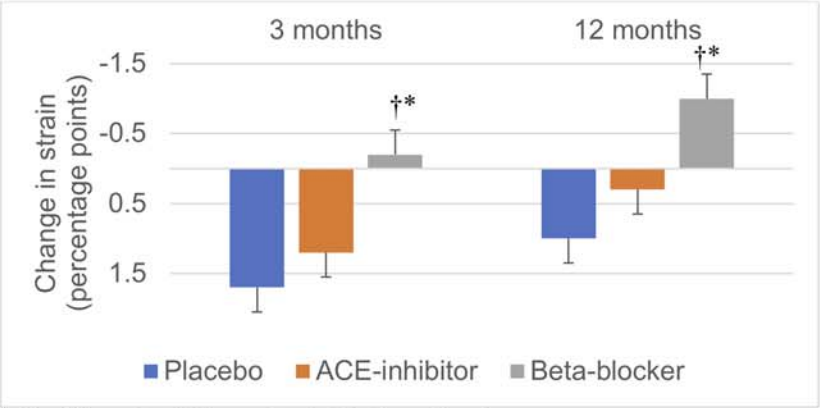
Supervisor: Dr. Ian Paterson

Table 1: Comparison of 3-month and 12-month changes in cardiac function and hemodynamics for treatment with beta-blocker vs ACE-inhibitor vs placebo

	Placebo n=30	Beta-blocker n=31	ACE-inhibitor n=33	p-value
Resting heart rate (bpm)				
3 months	5±2	-5±2†*	5±2	**<0.01**
12 months	-4±2	-13±2†*	-5±2	**<0.01**
Mean arterial pressure (mmHg)				
3 months	0±2	-6±2*	-9±2*	<0.01
12 months	-1±2	-3±2	-7±2*	0.04
Systemic vascular resistance (dynes/sec/cm^5)				
3 months	-18±42	-36±42†	-185±40*	**<0.01**
12 months	82±56	106±55†	-73±53*	**0.04**
LVEF (%)				
3 months	-7±1	-4±1*	-4±1*	<0.01
12 months	-6±1	-1±1†*	-3±1*	<0.01
RVEF (%)				
3 months	-6±1	-1±1*	-4±1	**<0.01**
12 months	-2±1	-1±1	0±1	0.39
Left atrial volume (mL/m^2)				
3 months	3±1	4±1	6±1	0.30
12 months	5±2	7±2	6±2	0.65

Data are marginal mean ± standard error change from baseline with adjustment for baseline
* Significantly different ($p<0.05$) than placebo
† Significantly different ($p<0.05$) than ACE-inhibitor

Figure 1: Comparison of changes in left ventricular global longitudinal strain between groups. At 3 months, the beta-blocker prevented the negative change, and by 12 months, had increased strain from baseline.



* Significantly different ($p<0.05$) than placebo
† Significantly different ($p<0.05$) than ACE-inhibitor

Using Fibrosis 4 Index to Triage Elevated Liver Enzymes in Asymptomatic Patients Without Viral Hepatitis

Zhao Wu Meng, Lucas Janz, Tracy Davyduke, Mang Ma

INTRODUCTION

Current guidelines suggest that an extensive panel of biochemical workup should be performed for all asymptomatic patients with elevated aminotransferases, which is resource intensive and costly. The Fibrosis 4 (FIB4) Index for Liver Fibrosis is a scoring system validated for staging liver disease in HCV and NAFLD. We sought to assess FIB4 index as a tool in identifying the subset of patients with asymptomatic AST/ALT elevation that would not benefit from an extensive biochemical workup.

METHODS

An established database of consecutive referrals to our tertiary care center for elevated aminotransferases was accessed. The study extended from November 18th, 2016 to August 9th, 2018. Criteria for acceptance were 1) Age 16-50 2) abnormal ALT/AST or fatty liver on U/S 3) no existing chronic liver disease. Within our referral database, we sought to assess those individuals with a FIB4 index of <1.30 and had negative HBV/HCV status. Our primary outcome is the proportion of patients diagnosed with NAFLD. Secondary outcomes include the proportion of patients with abnormal biochemical workup that led to another diagnosis.

RESULTS

Out of 451 identified patients, 337 (74.7%) were male. Median age was 39 (IQR 32-46), and median BMI was 30.7 (IQR 27.9-35.2). 377 (84.2%) consumed <10 alcoholic drinks/week. Median FIB4 Index was 0.72 (0.56 – 0.92). Final diagnosis included NAFLD (86.3%), alcoholic liver disease (1.8%), mixed alcohol/NAFLD (7.5%), and normal ALT (3.1%). The rest of the patients (1.33%, n=6) had sarcoidosis (2), PBC (1), hemosiderosis (1), Gilbert's syndrome (1), and steroid use (1). In our population of 451 patients who had FIB4 <1.3, extensive biochemical testing changed the management of 1 patient.

CONCLUSIONS

For patients with asymptomatic elevation in AST/ALT and a clinical suspicion of NAFLD, Fibrosis-4 index is an effective tool in identifying those patients who do not require initial extensive biochemical workup.

Supervisor: Dr. Mang Ma

A novel non-canonical pathway of nuclear entry of proteins lacking a nuclear localization sequence

Zervopoulos SD, Haromy A, Boukouris AE, Sutendra G and Michelakis ED

Introduction: The only known mechanism for protein entry into the nucleus is through nuclear pores (NPs; size-restricting channels on the nuclear membrane), after recognition of their nuclear localization sequence (NLS) by carriers/chaperones. But some proteins can enter the nucleus despite lacking a NLS and a large size that physically restricts passage through NPs, suggesting a yet undiscovered entry mechanism. The mitochondrial enzyme pyruvate dehydrogenase complex (PDC) is such a protein. We have described its nuclear entrance, with the involvement of Hsp70 under certain proliferative stimuli, producing nuclear acetyl-CoA for histone acetylation (Sutendra et al, Cell, 2014) and we now studied its nuclear entry.
Methods: We studied A549 lung cancer cells and foreskin fibroblasts with electron and super-resolution confocal microscopy, also using transfection with PDC and lamin constructs bound to fluorescent proteins (allowing live imaging), co-immunoprecipitation and the proximity ligation assay (PLA).
Results: Upon exposure to proliferative stimuli, we found a mitochondrial subpopulation (pMito) forming a perinuclear ring. Some pMito formed distinct contact points with the nuclear envelop (NE) and live imaging revealed pMito releasing PDC in areas without NPs. PDC released out of mitochondria was associated with lamin A (LMNA) which forms the inner nuclear membrane (co-IPs, PLA). Because the NE is an extension of the endoplasmic reticulum (ER), we hypothesized that pMito tether onto the NE through mitofusin 2 (MFN2), previously described to mediate mitochondria-to-ER tethering. We found MFN2 on the NE and siRNA-mediated loss of MFN2 or LMNA decreased nuclear PDC. Supported by additional data we propose a novel pathway for nuclear PDC entry, shown in the Figure.
Conclusion: The proposed novel pathway for PDC's nuclear entry, can be extended to other proteins lacking NLS. Its pharmacologic targeting could be utilized in conditions that NLS-less proteins enter the nucleus, like cancer, where various metabolic enzymes affect gene transcription through epigenetic alterations.

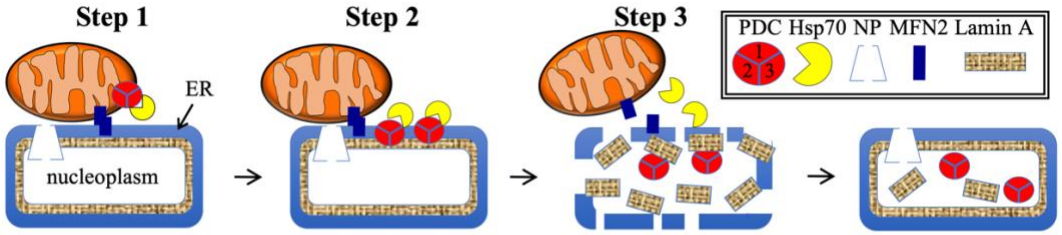


Fig: The 3 steps of PDC's entry into the nucleus. Step 1 involves the tethering of mitochondria onto the nuclear envelope (NE) through MFN2-rich contact points. During the second step, Hsp70 deposits PDC on lamin A, which is disassembled during the beginning of mitosis and reforms at the end of it in the daughter cells.

Microemboli during Transcranial Doppler Ultrasonography in patients with subarachnoid hemorrhage

Ali Nomani, Asif Butt, Maher Saqqur, Carol Derksen, Ashfaq Shuaib, Khurshid Khan,

INTRODUCTION
Microembolic signals have been reported during Transcranial Doppler (TCD) monitoring in patients with subarachnoid hemorrhage (SAH). The source and of these microemboli and their relation to onset of vasospasm and development of infarcts is undetermined.

METHODS
Retrospective data for patients with aneurysmal subarachnoid hemorrhage admitted to University of Alberta Hospital (UAH) undergoing TCD assessment were analyzed. Mean flow velocities (MFVs) were analyzed before the appearance and after disappearance of microemboli respectively. In addition, presence or absence of vasospasm on catheter angiogram was compared to occurrence of microemboli. Furthermore, association of infarcts with microemboli and endovascular coiling or surgical clipping was analyzed.

RESULTS
Of 26 patients with microemboli, 18 (69.2%) were females. Mean age was 52.2 ± 1.3 years. Seventeen (65.4%) underwent coiling, 8 (30.8%) surgical clipping and one had unsuccessful procedure. Four (23.5%) of 17 who underwent coiling had luminal coil protrusion. There was no significant correlation between the vasospasm on catheter angiogram and presence of microemboli. There was no association between high MFVs and occurrence of microemboli. In 11 (91.6 %) of 12 patients with infarcts, microemboli were detected in the vessels corresponding to the site of infarction.

CONCLUSIONS
There is no correlation between MFV and occurrence of microemboli. There is an association between the vascular territory of Delayed Cerebral Ischemia (DCI) and occurrence of microemboli, however the causal relationship is yet to be determined.

Supervisor: Dr. Khurshid Khan

Figure 2: TCD views of one of the patients showing Microemboli

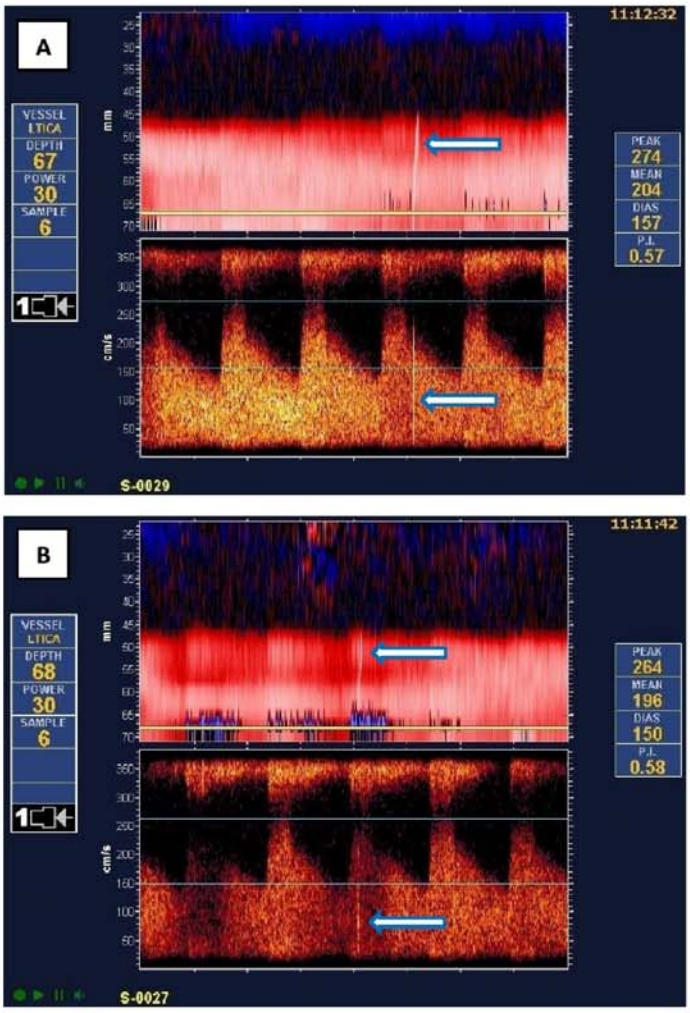


Figure 2: Arrowheads show occurrence of microemboli

Neoantigens in mycosis fungoides: whole exome sequencing discovery of immunotherapeutic targets

INTRODUCTION

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, has a dismal prognosis in advanced stages. The success of immune checkpoint inhibitors (ICI) in treating advanced malignancies has not extended to MF. There is an urgent need to identify predictive biomarkers, and to advance immunotherapies in MF. Neoantigens are 'new' peptides, generated by somatic mutations in tumour cells, that evoke an immune response. As tumour-specific markers, neoantigens are an attractive immunotherapeutic target. A high neoantigen burden across multiple cancers has been associated with higher overall survival after ICI treatment. Neoantigens have never previously been studied in MF, and our objective was to characterize their identity and number in MF.

METHODS

9 samples (3 plaques, 3 tumours, 3 controls) were selected from ongoing analysis of 108 whole exome sequences (WES) at 200X depth. RNA-seq was available for 3 samples, and used to validate expression of predicted peptides. Bioinformatics pipelines utilized included Mutect2 for mutation calling, OptiType for HLA typing and MuPeXi to predict peptides (8-11 amino acids long) and binding affinities to HLA types.

RESULTS

An average of 3303 non-synonymous mutations were identified, resulting in 5907 putative neoantigens. 569 were strong binders (<0.05%rank), 1244 intermediate binders (<0.15%rank) and 4094 weak binders (<0.5%rank). 83% of predicted peptides were expressed according to available RNA-seq.

CONCLUSIONS

We describe the use of WES with high sequencing depth to successfully identify neoantigens in MF for the first time. MF has a high tumour mutation burden, resulting in a large number of putative neoantigens. The paradoxically poor response to ICI may be attributed to challenges in using T-cell based therapies to target T-cell malignancies, and intratumour genetic heterogeneity resulting in subclonal neoantigens. This suggests a role for the development of immunotherapies targeting specific neoantigens.

Supervisor: Dr. Robert Gniadecki

Lenalidomide Maintenance Positively Impacts Outcomes in Multiple Myeloma Without Negative Impacts In Relapse: An Analysis Of Real World Data From The Myeloma Canada Research Network National Patient Database

Cherniawsky, H., Kukreti, V., Reece, D., Masih-Khan, E., McCurdy, A., Jimenez-Zepeda, V., Sebag, M., Song, K., White, D., Stakiw, J., LeBlanc, R., Reiman, A., Aslam, M., Louzada, M., Kotb, R., Gul, E., Atenafu,, E., Venner, C.

INTRODUCTION
Randomized trials have demonstrated the positive impact of lenalidomide maintenance (LM) on survival in multiple myeloma (MM) following autologous stem cell transplant (ASCT). However, real-world data is lacking. Through the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB) we examined the impact of LM at a national level.

METHODS
We retrospectively analyzed patients from the MCRN CMM-DB treated with bortezomib-based induction and ASCT who began treatment prior to January 2016 based on intention-to-treat with LM. Primary outcomes included overall (OS) and progression free survival (PFS). Secondary outcomes included depth of response, 2nd PFS and PFS 2. Lastly, we compared outcomes of 21/28 days versus 28/28 days dosing.

RESULTS
Data from 1,256 patients across 10 Canadian centers was included (723 with LM and 533 without). Median follow-up in the LM group was 49 months and 45 months in the non-LM group. The median OS favoured LM (Not reached vs 98 months, $p < 0.0001$, figure 1a) as did PFS (58 months vs 35 months, $p < 0.0001$, figure 1b). Median second PFS of relapsed patients was similar between LM and non-LM patients (12 months vs 16 months, $p=0.07$, figure 1c). Median PFS2 favoured of LM (not reached vs 68 months, $p < 0.01$, figure 1d). A 28/28 days (n=356) versus a 21/28 (n=257) days LM dosing schedule showed no difference in estimated 5-year OS (81% vs 80% respectively, $p = 0.66$) or 5-year PFS (47% and 52% respectively, $p = 0.75$).

CONCLUSIONS
Through MCRN CMM-DB we present one of the largest real-world cohorts demonstrating the dramatic impact of LM on OS, PFS and depth of response. LM did not demonstrate a negative effect on outcomes in second-line therapy. An abridged 21/28 day dosing strategy did not negatively impact survival endpoints. Overall, this data supports the use of LM in the frontline management of MM.

Supervisor: Dr. Christopher Paul Venner

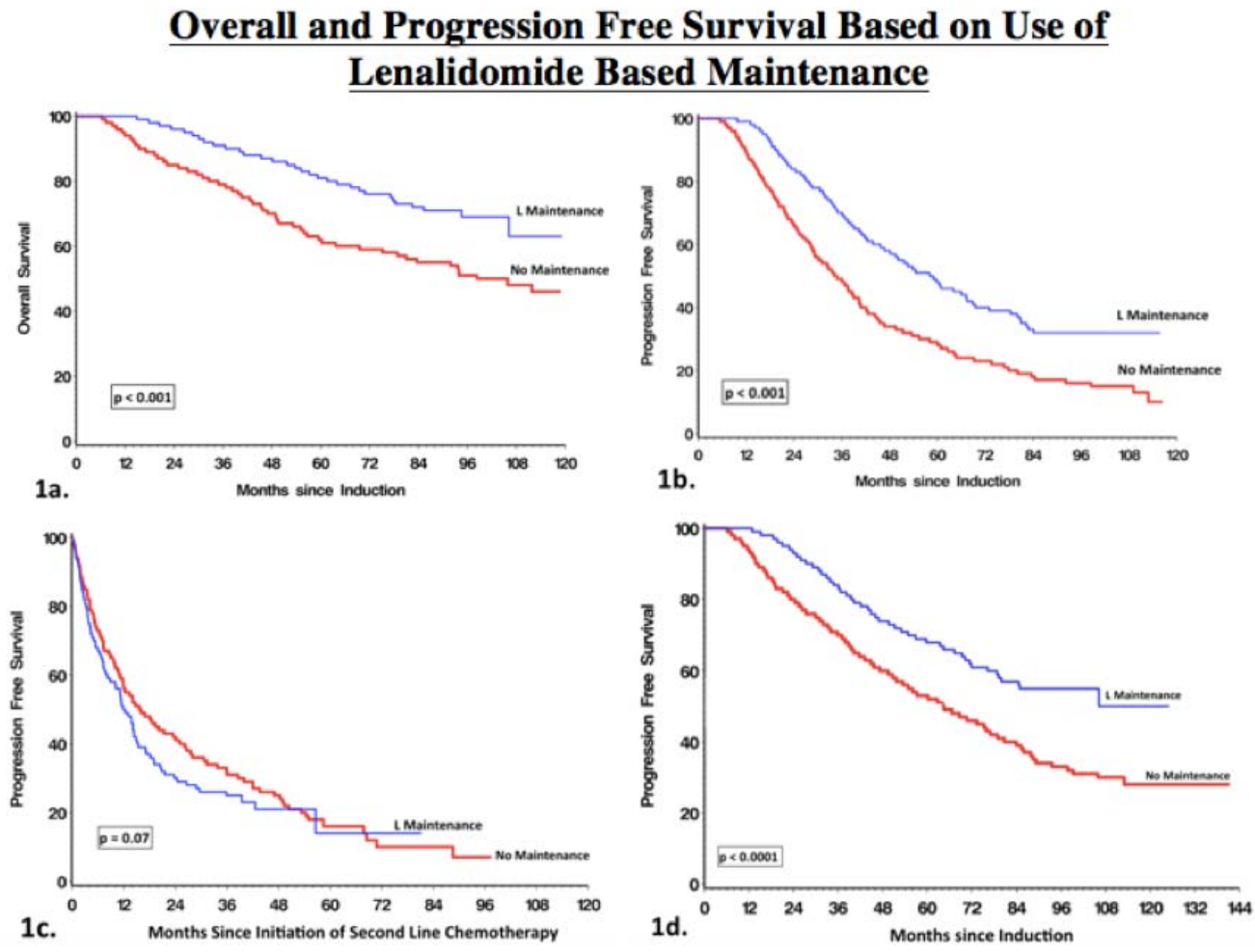


Figure 1. Overall (1a) and progression free (1b) survival is improved with the use of lenalidomide based maintenance at the level of statistical significance. Second progression free survival (1c) and PFS 2 (1d) also demonstrate there is no negative effect of lenalidomide on survival outcomes of second line therapy.

High versus Low SpO2 oxygen therapy in patients with acute Heart Failure: HiLo-HF Pilot trial

Nariman Sepehrvand, Wendimagegn Alemayehu, Brian H. Rowe, Finlay A. McAlister, Sean van Diepen, Michael Stickland, Justin A. Ezekowitz

INTRODUCTION
Most patients with acute heart failure (HF) are treated with supplemental oxygen in the emergency department (ED). There is an ongoing debate regarding the role that oxygen plays in the treatment of patients with HF. We investigated the effect of oxygen titrated to a high versus low pulse oximetry target in patients hospitalized with HF.

METHODS
In a pilot, open-label, randomized controlled trial, 50 patients admitted for the treatment of acute HF were enrolled in the ED. Patients were randomized to either a high SpO2 (>=96%) or low SpO2 (90-92%) and oxygen was manually titrated to the pre-specified target ranges for 72 hours. The primary endpoint was the change in NT-proBNP from randomization to 72 hours, and key secondary endpoints included dyspnea by visual analogue scale (VAS), patient global assessment (PGA), peak expiratory flow (PEF) and clinical outcomes through 30 days.

RESULTS
The median age was 73 years; 42% were female and 70% had a prior history of HF. Pre-randomization SpO2 was similar between groups. The change in NT-proBNP at 72 hours was -823.4 (-1578.0, -148.2) and -247.5 (-705.0, -41.8) pg/ml in the high and low SpO2 groups, respectively (p=0.46) (Table). Accounting for the baseline NT-proBNP values, the 72-hour to baseline NT-proBNP ratio was comparable between groups (0.7 vs 0.6; p=0.51). The change in VAS, PGA, and PEF from baseline to 72-hour were similar between treatment arms. In-hospital all-cause mortality (4.0% vs. 8.0%, p=0.50), and 30-day HF readmission rates (20.0% vs. 8.0%, p=0.21) were not different between the high and low SpO2 arms.

CONCLUSIONS
In this pilot study, no differences were observed in the primary outcome or patient symptoms between high and low SpO2 targets. Further RCTs with larger sample size are warranted to determine the comparative efficacy of treatment with supplemental oxygen in patients with acute HF.

Supervisor: Dr. Justin A. Ezekowitz

Table. Study endpoints

	High SpO_2 target (n=25)	Low SpO_2 target (n=25)	p-value
Baseline NT-proBNP, pmol/L	1890.5 (712.5, 3522.0)	1213.5 (515.0, 3219.0)	0.45
72-hour NT-proBNP, pmol/L	766.2 (535.6, 1455.0)	1201.0 (473.2, 2026.0)	0.72
Δ NT-proBNP, pmol/L	-823.4 (-1578.0, -148.2)	-247.5 (-705.0, -41.8)	0.46
72h to baseline NT-proBNP ratio	0.7 (0.3, 0.8)	0.6 (0.5, 0.9)	0.51
Δ Dyspnea VAS, mm	10.0 (5.0, 25.0)	10.0 (7.0, 20.0)	0.86
Δ PGA, mm	5.0 (0.0, 20.0)	10.0 (0.0, 15.0)	0.91
Δ PEF, L/min	52.5 (20.0, 90.0)	42.5 (25.0, 67.5)	0.52

NT-proBNP: N-terminal pro-BNP; PEF: peak expiratory flow; PGA: patient global assessment; SpO_2: peripheral oxygen saturation level; VAS: visual analogue scale;

INCREASING FIT CUT-OFFS INCREASES RATES OF MISSED HIGH-RISK LESIONS ON COLONOSCOPY WITHOUT DECREASING NUMBER NEEDED TO SCOPE

ThucNhi T. Dang, Jerry T. Dang, Daniel Sadowski, Richard Sultanian, Clarence K. Wong

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and carries a high mortality rate. The fecal immunochemical test (FIT) is a CRC screening tool that is used across Canada as the standard for CRC screening in the average-risk population. Each province sets a different FIT threshold but it is unknown what the optimal FIT cut-off should be or what specific high-risk lesions (HRL) the FIT detects. Objectives: (1) determine correlation between numerical FIT and CRC and HRL and (2) determine correlation between numerical FIT and different types of HRLs.

METHODS

All patients aged 50-74 years old who had a positive FIT (≥75 ng/mL) who subsequently underwent colonoscopy as part of the Edmonton SCOPE program were identified. Demographic data and colonoscopy findings were collected. HRL were defined as: polyp size ≥1 cm, ≥3 polyps that were tubular or sessile serrated adenomas (SSA), villous pathology, high-grade dysplasia (HGD), or CRC. Numerical FIT data were then extracted and correlated with CRC and HRL.

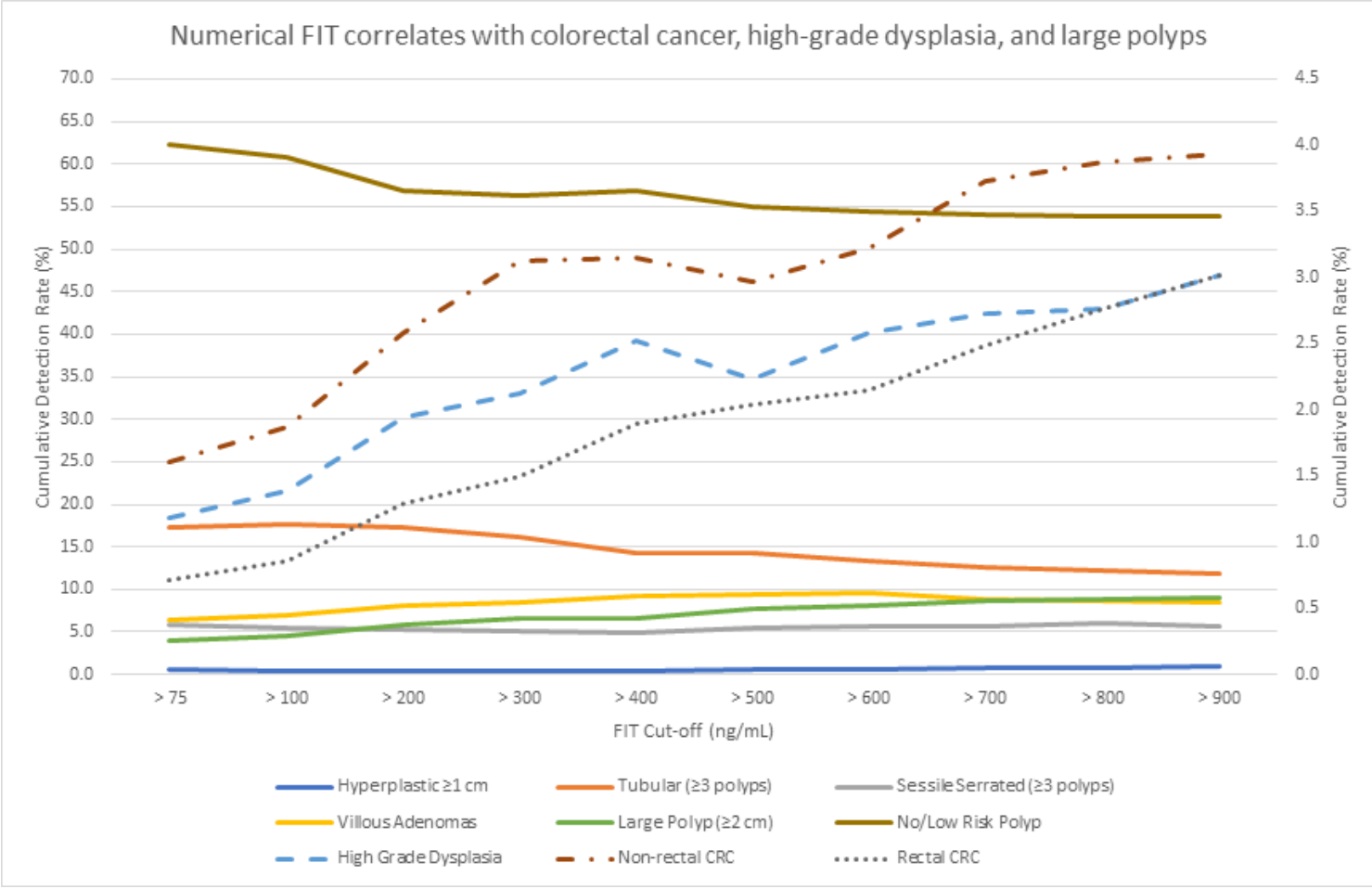
RESULTS

A total of 2369 patients were identified. Multivariable analysis, adjusting for age, sex, and family history, revealed each increase of 50 ng/mL resulted in a 3% increase in CRC or HRL on colonoscopy. Increased numerical FIT correlated with increased CRC as well as HGD and larger polyps (?2 cm) but not with large hyperplastic polyps, villous polyps, tubular adenomas, or SSAs (Figure 1). Between a cut-off of ≥75 ng/mL to ?200 ng/mL there was an increase of CRC miss rates of 23.6% and HRL miss rates of 47.7%. Number needed to scope (NNS) decreased by an average of 2.8 scopes for each increase in 25 ng/L for CRC but decreased minimally for HRL.

CONCLUSIONS

Increasing the FIT cut-off value increases both CRC and HRL miss rates but only minimally decreases number needed to scope

Supervisor: Dr. Clarence K. Wong


Numerical FIT correlates with colorectal cancer, high-grade dysplasia, and large polyps
Cumulative Detection Rate (%)
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
> 75
> 100
> 200
> 300
> 400
> 500
> 600
> 700
> 800
> 900
FIT Cut-off (ng/mL)
Hyperplastic ≥1 cm
Tubular (≥3 polyps)
Sessile Serrated (≥3 polyps)
Villous Adenomas
Large Polyp (≥2 cm)
No/Low Risk Polyp
High Grade Dysplasia
Non-rectal CRC
Rectal CRC

Role of Tau Protein in Kainic Acid-induced Animal Model of Temporal Lobe Epilepsy

Abhishek Dahal and Satyabrata Kar

INTRODUCTION

Kainic acid (KA) is an analogue of the excitatory neurotransmitter glutamate that when injected systemically into adult rats can trigger seizures and neuronal loss in a manner that mirrors the neuropathology of human mesial temporal lobe epilepsy (mTLE). However, mechanisms responsible for the neuronal loss remains elusive. Some earlier studies have indicated that the tau protein, which is critical in the development of Alzheimer's disease, may have a role in triggering the seizures and/or loss of neurons associated with mTLE. However, the cellular site or the mechanism by which tau can influence mTLE pathology remains unclear. Thus, we evaluated the role of tau in KA-induced animal model of mTLE.

METHODS

Adult male rats were injected intraperitoneally with either KA (12mg/kg) or normal saline. Control and KA-treated rats were euthanized at 12 hr, 2 and 12 days following treatment and their hippocampal brain regions were processed to evaluate loss of neurons, activation of astrocytes and level/expression of total, phospho- and cleaved-tau using western blotting and immunohistochemistry.

RESULTS

We observed that KA administration evoked seizures and progressive loss of neurons and activation of astrocytes in the hippocampal region of the brain. Interestingly the level/expression of astrocytic markers GFAP and vimentin, but not glutamine synthetase, are increased in KA-treated rats, suggesting different subsets of astrocytes are differentially affected following KA treatment. The level/expression of total and to some extent phospho-tau are elevated in KA-treated rats. Additionally, we observed that the level and expression of caspase-cleaved tau in astrocytes were markedly increased in the hippocampus of KA-treated rats.

CONCLUSIONS

Our results indicate that KA-induced seizures not only differentially affect astrocytes but also increase the levels/expression of tau that can influence the development mTLE pathology.

Supervisor: Dr. Satyabrata Kar

Investigating the role of endothelial cell-specific p110β isoform of PI3K as a potential target for anti-angiogenic therapy

Abul K Azad, Pavel Zhabyeyev, Gavin Y Oudit, Ronald B Moore, Allan G Murray.

INTRODUCTION

Angiogenesis-inhibitor drugs targeting VEGF-signalling to endothelial cell (EC) are used to treat various cancers. However, tumors become resistant to this therapy due to the recruitment of alternative growth factors, acting via cognate EC receptor tyrosine kinases (RTK) or g-protein coupled receptors (GPCR), to cue neo-angiogenesis. In ECs, PI3 kinase p110β isoform is uniquely coupled to both RTKs and GPCRs. EC-specific p110β inactivation impairs angiogenic sprouting and tip cell marker gene expression in vitro. These data indicate that p110β mediates pro-angiogenic signals. We hypothesize that EC PI3-β activity mediates tumor angiogenesis escape from sunitinib therapy.

METHODS

Mouse Lewis lung carcinoma (LLC1) or B16F10 melanoma cells were implanted subcutaneously in EC-specific p110β knockout (ECβKO) or control mice. Sunitinib (40mg/kg/day) treatment was initiated when the tumors reach 200 mm3, and all mice were euthanized at 1500 mm3. Second, to model metastasis, B16F10 cells were injected intravenously in ECβKO or control mice, treated with sunitinib for 20 days. Pimonidazole was administrated 1 hour before euthanasia.

RESULTS

EC-specific p110β loss with sunitinib treatment decreases growth of LLC1 and B16F10 melanoma lines in comparison to sunitinib-treated control mice. Similarly, EC p110β loss with sunitinib decreases B16F10 metastases in the lung, and the overall tumor area in lung cross-section, vs control mice. Further, primary and metastatic tumors had a marked decrease in CD31-positive microvessels in ECβKO vs control mice, accompanied by a significant reduction in tip cell marker gene expression. Surprisingly, pimonidazole-positive hypoxic area in the tumors was normalized in ECβKO vs control mice.

CONCLUSIONS

Our findings here demonstrated that EC-specific inactivation of p110β decreases primary tumor growth and tumor metastasis accompanied by decreased tumor vasculature and tip cell gene expression, but normalization of tumor blood flow. Inhibition of endothelial p110β may be useful as adjuvant therapy, and may facilitate delivery and/or response of the tumor to conventional chemotherapy agents.

Supervisor: Dr. Allan Murray

Cutaneous T-cell lymphoma is a genetically and clonotypically heterogeneous

Aishwarya Iyer, Dylan Hennessey, Sandra O'Keefe, Jordan Patterson, Weiwei Wang, Gane Ka-Shu Wong and Robert Gniadecki

INTRODUCTION

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) primarily arising in the skin. Early diagnosis is difficult as the histology overlaps with features of inflammatory skin diseases. Even when the diagnosis is established there are no prognostic markers that predict whether the disease will be aggressive or indolent. Lastly, there are no curative treatments and MF will invariably relapse even after aggressive chemotherapy.

METHODS

The main objective of this study is to address the presence of intratumor heterogeneity in MF. To determine whether MF is a monoclonal process we performed laser microdissection of atypical tumor cells in skin biopsies and performed simultaneous whole exome (WES) and transcriptome sequencing (WTS) to identify the T-cell clonotypes and the genetic architecture of the samples.

RESULTS

Multiple clonal and subclonal cell population was observed within individual tumor/plaque sample, based on the single nucleotide variations (SNV) and copy number aberrations (CNA) providing evidence of intratumor genetic heterogeneity. Also, T-cell receptor oligoclonality was observed for the sequences obtained from WES, indicating the presence of multiple tumor T-cells along with reactive T-cells.

CONCLUSIONS

Intratumor heterogeneity is correlated with the prognosis of solid cancers and their response to immunotherapy. Heterogeneity in CTCL does not only provide better insights into tumor origin and disease progression but may also be a source of prognostic biomarkers.

Supervisor: Dr. Robert Gniadecki

Cerebral Air Embolism with Endovascular Thrombectomy in Acute Ischemic Stroke: The Need for Site-Specific Protocols for CAE at Comprehensive Stroke Centers

Ali Nomani, Anas Alrohimi, Asif Butt, Rene Van Dijk, Muzaffar M Siddiqui

INTRODUCTION

Background: Cerebral air embolism is a rare condition but carries potential catastrophic complications after endovascular interventions. Management is frequently limited to high flow oxygen, hyperbaric oxygen therapy, symptomatic management and conservative measurements. Recently, endovascular techniques to treat large vessel occlusion caused by an air embolus have been reported.

METHODS

Case: We describe a case and neuroimaging of a patient with acute ischemic stroke who underwent unsuccessful Endovascular Thrombectomy. Shortly after the procedure, the patient developed sudden worsening of the pre-existing neurological deficits and was found to have extensive cerebral air emboli as a potential complication of combination stent retriever and aspiration device treated with hyperbaric oxygen.

RESULTS

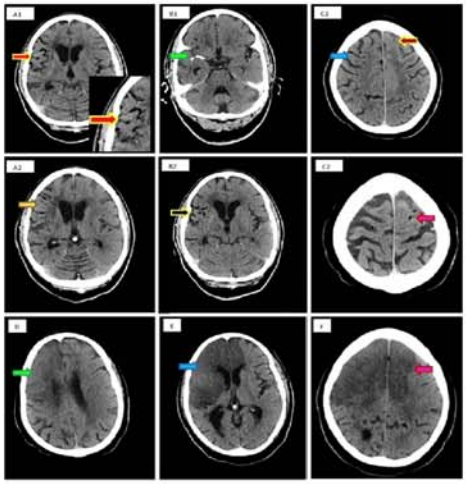
Aim: By this article, we aim to present a comprehensive review of diagnosis, suspicion thresholds, mechanisms, treatment strategies with stratification and site-specific protocols for stroke centers for managing cerebral air embolism by proposing an algorithmic approach.

CONCLUSIONS

We propose an algorithm for systematic approach towards diagnosing, stratifying and treating Cerebral Air Embolism in context of Endovascular Thrombectomy in Stroke.

Supervisor: Dr. Khurshid Khan

Figure 1: Follow up CT scans. **A1** (with magnification in lower right highlighting serpiginous hypo density in intracranial



vasculature characterizing the "air angiogram" appearance)**, A2, B1 and B2:** Plain CT Head showing air emboli in distribution of right MCA, **C1 and C2:** Plain CT Head showing air emboli in distribution of right and left ACA), **D and E:** Plain CT Head showing infarcts in distribution of right MCA and ACA. **F:** Plain CT Head showing infarct in distribution of left ACA.

Figure 2: Map outlining the hyperbaric chamber sites and the Comprehensive Stroke Centers in Canada. represents hyperbaric sites; ● represents hospitals with Comprehensive Stroke Centre Status.

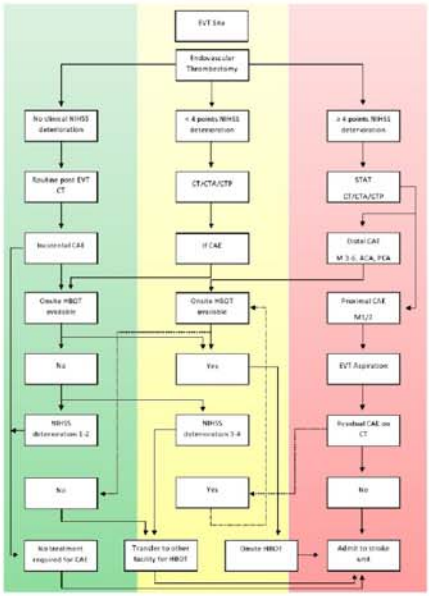


Figure 3: Suggested algorithm for systematic approach towards diagnosing, stratifying and treating Cerebral Air Embolism in context of Endovascular Thrombectomy in Stroke.

Ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) have distinctive serum metabolomic fingerprints versus UC patients without PSC

Ammar Hassanzadeh Keshteli, Richa Chibbar, Rupasri Mandal, David Wishart, Karen Madsen, Levinus Dieleman

INTRODUCTION
Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver and biliary tract disease that is strongly associated with inflammatory bowel disease, especially ulcerative colitis (UC). It is still unknown why some UC patients develop PSC or why UC patients with PSC are at higher risk of colorectal cancer. In the present study, we aimed to compare the serum metabolomic profiles of UC patients with or without PSC in order to explore the underlying pathophysiological mechanisms and to identify PSC-related biomarkers.

METHODS
Serum samples were collected from a group of adult UC patients with confirmed diagnosis of PSC and a group of UC patients without PSC who were matched for several demographic and clinical characteristics. Metabolomic assessment was done using nuclear magnetic resonance spectroscopy.

RESULTS
Forty-nine UC patients were recruited (24 with PSC and 25 without PSC). Their mean age was 42.9 years (SD: 15.6) and 62% of them were men. Forty-seven (94%) patients had a history of pan-colitis and 20% of them were on biologic medications. Fifty-three metabolites were identified and quantified in serum samples. In a multivariate analysis, serum metabolome of UC patients with PSC were found to be significantly distinctive from those without PSC (Figure 1). Increased 2-oxoglutaric acid and L-glutamic acid and decreased malonic acid were the most important metabolic changes in UC patients with PSC that could differentiate them from UC patients without PSC.

CONCLUSIONS
This is the first study indicating that metabolomic profiling in UC patients can discriminate between patients with and without PSC. Interestingly, the discriminatory metabolites are involved in host cellular energy metabolism, as well as amino acid and fatty acid metabolism and are likely involved in PSC pathogenesis and its complications in UC.

Supervisor: Dr. Levinus Dieleman, Karen Madsen

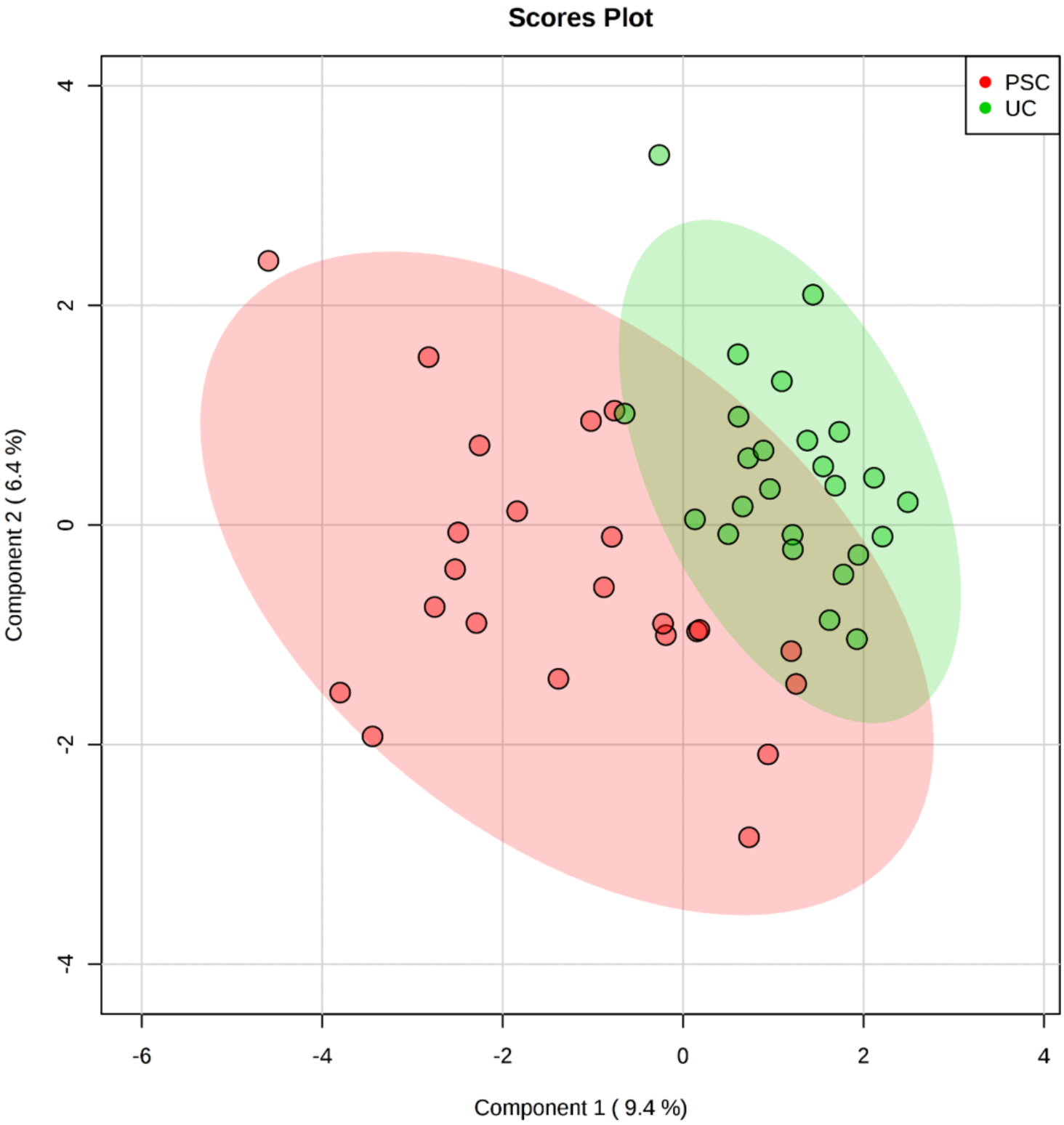


Figure 1. Partial least squares discriminant analysis plot showing a separation between ulcerative colitis patients with primary sclerosing cholangitis (PSC) and without PSC using their serum metabolic profiles ($P<0.001$).

Early apixaban treatment after transient ischemic attack and acute ischemic stroke does not result in hemorrhagic transformation

Anas Alrohimi, MBBS and Ken Butcher, MD, PhD

INTRODUCTION
The optimal timing of anticoagulation after stroke in Atrial Fibrillation (AF) patients is unknown. Patients are at risk for recurrent stroke, but also Hemorrhagic Transformation (HT). There are limited safety data of direct oral anticoagulants initiation within 14 days of ischemic stroke/TIA, as these patients were excluded from phase III trials.

METHODS
A prospective, open label study for AF patients treated with apixaban ≤14 days of ischemic stroke/TIA onset. CT scans prior to and 7 days after apixaban initiation were assessed centrally for HT. The primary endpoint was symptomatic HT. Secondary outcomes included any HT at day 7, systemic hemorrhage, and recurrent ischemic events within 90 days.

RESULTS
85 patients, with a mean age of 79 ±11 years were enrolled. Median (IQR) infarct volume was 6 (1–14) ml. Median time from index event onset to apixaban initiation was 3 (1–6) days, and median baseline NIHSS was 3 (1–10). The number of days between symptom onset and apixaban initiation was directly correlated with the infarct volume (r=0.272, P=0.02). Pre-treatment HT was present in 13 patients (10 HI1, 3 HI2). On follow-up CT scan, incident HT was present in 2 patients, 5 patients had stable HT, and resolving HT was evident in 7 patients. No patients developed symptomatic HT. Infarct volume was a predictor of HT (OR= 1.1 [1.05–1.18], P <0.001). All 2 (100%) patients with incident HT were functionally independent (mRS=0-2) at 90 days, which was similar to those without HT (82%, p=0.328). Recurrent ischemic events occurred within 90 days in 12 patients, 3 of which were associated with severe disability (mRS= 3-5) and 4 were associated with death.

CONCLUSIONS
Early apixaban treatment did not precipitate symptomatic HT after stroke. Asymptomatic HT was associated with larger baseline infarct volumes. Early recurrent ischemic events may be clinically more important than HT.

Supervisor: Dr. Ken Butcher

Giant Cell Myocarditis: Fifteen-year case series of a single institution

Andrea Johnson, Holger Buchholz, Lindsey Carter, Brian Chiu, Leslie T Cooper, Roderick MacArthur, Nathan Puhl, Derek Townsend, Elaine Yacyshyn

INTRODUCTION

Giant cell myocarditis (GCM) is a severe and rapidly progressing inflammatory disease of the heart. It is rare with limited published literature. Multicenter GCM disease registry (n=63) describe an average age of 42.6 years (range 16-69), with historic median survival of 5.5 months from symptom onset. GCM is a pathological diagnosis, characterized by mixed inflammatory infiltrate with multifocal necrosis and multinucleated giant cells.

METHODS

Keyword search of the local pathology database identified cases of GCM over the last 15 years at the University of Alberta. With ethics approval, chart review was completed via paper charts and electronic records.

RESULTS

Nine patients were identified with two excluded with alternate diagnoses. Of the seven patients remaining, there were four males (57%) and average age of presentation was 39.6 years (range 22-61).

All GCM patients developed heart failure; most presentations (86%) were rapidly progressive with fulminant heart failure within two months of symptom onset. Three patients required VAD (ventricular assist device), one of which later progressed to transplant. A total of five patients received heart transplants, three urgently.

Four patients were diagnosed with GCM upon transplant, and did not receive prior immunosuppressive therapy. Three patients were diagnosed via endomyocardial biopsy, and received various immunosuppressive therapies (including steroids, tacrolimus, mycophenolate mofetil, thymoglobulin).

Two patients were lost to follow up at 2 months, but the remaining five patients were alive one year after presentation, with known survival ranging from 1-16 years. No recurrence was seen after transplant.

CONCLUSIONS

This study characterized seven cases of GCM in the last 15 years at our institution. Trends in age and presentation are consistent with published literature. Survival is challenging to analyze as most patients were lost to follow up; however, survival appears to be longer than historical reports. This could be due to improved diagnostics, management or therapeutics. Further evaluation of this rare condition is necessary to better understand future treatments.

Supervisor: Dr. Elaine Yacyshyn

Intracranial vascular involvement in Takayasu's arteritis: common or not?

Andrea Johnson, Derek J Emery, Alison H. Clifford

INTRODUCTION

Takayasu's Arteritis (TAK) is a large-vessel vasculitis of unknown etiology resulting in aneurysms, stenoses and occlusions of the aorta and its branches. Involvement of the intra-cranial vessels is believed to be uncommon, but has not been well studied. Review of the literature suggests 11.2% of TAK patients may develop intracranial disease, but there is high variability. We aimed to determine the prevalence of intracranial vascular lesions in TAK patients seen by Rheumatologists at the University of Alberta.

METHODS

We retrospectively reviewed clinical records of patients diagnosed with TAK by any Rheumatologist at the University of Alberta between 2012-2018. Neuroimaging studies were reviewed by a single Neuroradiologist.

RESULTS

Of 24 patients identified, 2 were excluded with alternate diagnoses, leaving 22 patients with TAK in this study. Of these, 19 were female (86.4%), with an average age at diagnosis of 32.2 years (range 13-63). The most common symptoms at disease presentation were: limb claudication (31.8%), headache (31.8%), stroke (27.3%), and vision change (22.7%). On exam, patients had documented loss of pulse (40.9%), asymmetric blood pressure (36.3%) and bruits (31.8%). Extracranial lesions were most commonly identified in the extracranial carotid arteries (54.5%), thoracic aorta (50%), and subclavian arteries (50%). Vascular imaging findings included wall thickening (59.1%), stenosis (50%), occlusion (27.3%) and aneurysms (22.7%). Thirteen of 22 patients had available baseline imaging of the intracranial vessels. Intracranial vascular lesions were found in 4 patients (18.2% of all patients). Initial treatment included steroids (90.9%), and majority received concomitant steroid-sparing agents (68%).

CONCLUSIONS

Intracranial vessel involvement in TAK may be more common than previously suspected. In our institution, intracranial vascular lesions were identified in 18.2% of all Takayasu's patients. Gaining an improved understanding of the true frequency of intracranial involvement will be important to aid in appropriately monitoring these young patients for disease activity. Prospective study is needed.

Supervisor: Dr. Alison Clifford

Apelin promotes vascular repair following immune-mediated injury through directing tip-cell differentiation

Andrew G. Masoud1, Jiaxin Lin2,3, Maikel A. Farhan1, Conrad Fischer4, Lin F. Zhu2, Hao Zhang1,5, Banu Sis6, Zamaneh Kassiri7, Ronald B. Moore2, Daniel Kim1, Colin C. Anderson2,3, John C. Vederas4, Benjamin A. Adam6, Gavin Y. Oudit1,5, Allan G. Murray1*

INTRODUCTION

Chronic allograft vasculopathy (CAV) injury of the transplanted hearts' vasculature jeopardizes long-term graft/patient survival. This injury is mitigated by a poorly characterized repair response, involving the same cues of vascular development. Endothelial cells (ECs) undergoing angiogenesis in the embryo differentiate to specialized phenotypes (e.g. the lead/tip cell in vascular sprouts) with characteristic gene expression. While in the adult, pro-angiogenic tip-cell cues' role in the established vasculature' repair is largely unknown.

Apelin, a tip-cell gene, participates in vascular repair from myocardial infarction and kidney glomerular microvasculature injury. We hypothesize that Apelin is an autocrine growth cue that sustains vascular repair and mitigates immune injury.

METHODS

CAV was induced via transplanting male Apelin-/y (knockout; KO) or Apelin+/y (wild type; WT) hearts into female mice, to elicit a HY-minor histocompatibility antigen-directed cell-mediated allo-immune response against donor hearts. Heart grafts were harvested two or six weeks after transplantation. We characterized intima area, mid to large-sized arterial EC loss, microvessel density, inflammatory cellular infiltration using Immunohistochemistry-IHC, tip-cell genes in mice and human explants with CAV (myocardium and coronaries), Apelin's effect on monocytes-EC interaction, and graft-harboring mice treatment with apelin(17) analogue.

RESULTS

Apelin-/y donor hearts showed i) increased circumference area of endothelial loss ($1.4 \pm .1$ vs $0.4 \pm .1\%$; 1.9 ± 0.2 vs $0.5 \pm 0.1\%$; $P<0.05$) and microvasculature rarefaction (Fig 1a); ii) intima expansion in conduit arteries (Fig 1b); iii) enhanced inflammatory cellular infiltration (Fig 1c); IV) downregulated tip-cell genes (e.g. Esm1, Fig 1d) and apelin(17) treatment reduced maladaptive vascular repair in vivo, and lowered the EC-adherent monocytes in vitro (Fig 1e).

CONCLUSIONS

Apelin loss: blunts repair and worsens CAV endothelial injury of the whole graft-nourishing vascular tree. Apelin repel mononuclear leukocytes trafficking to the graft.

Apelin treatment mitigated maladaptive vascular repair. Thus, Apelin is a potential pharmacotherapeutic target for immune-mediated vascular injury in the adult.

Supervisor: Dr. Allan Murray

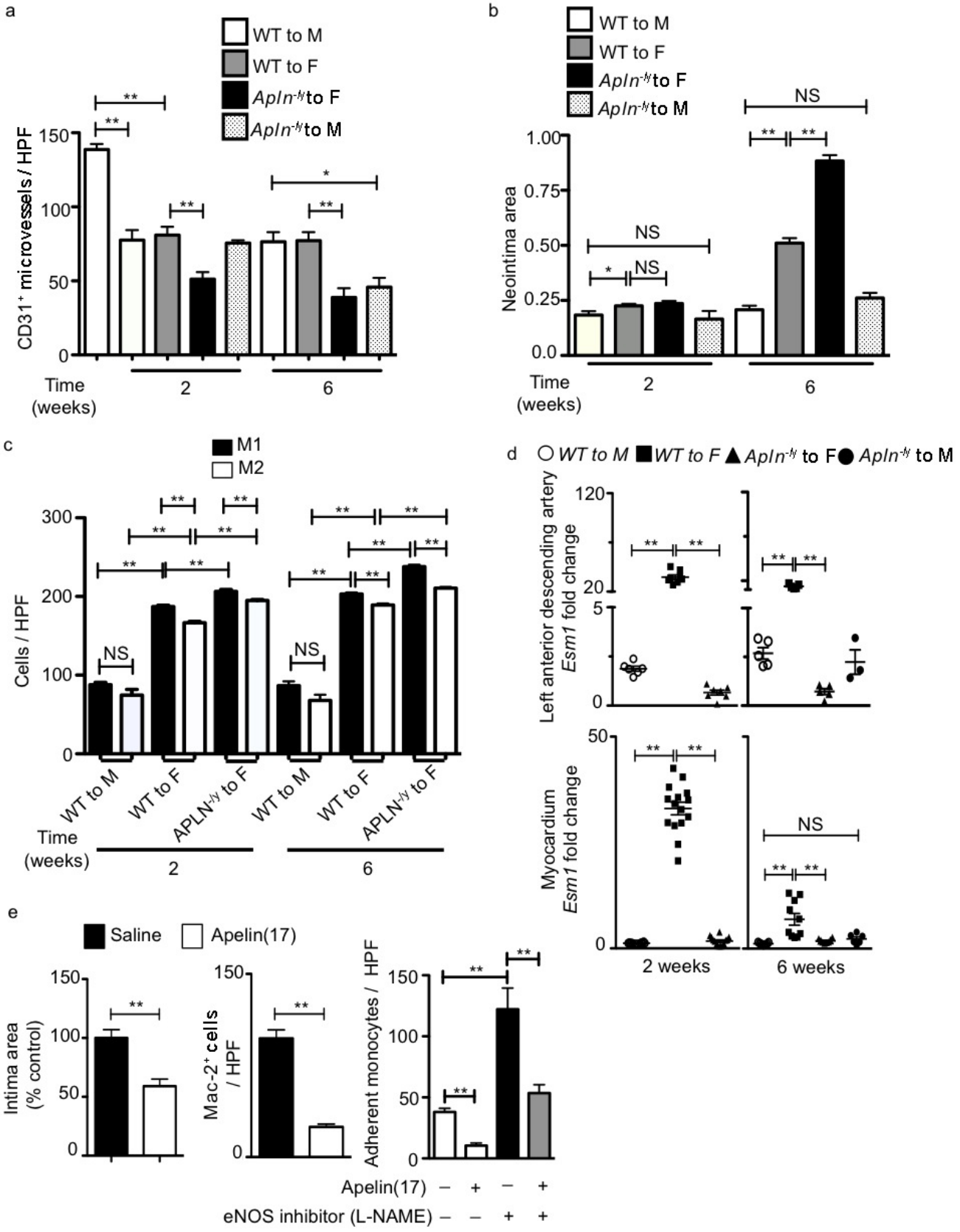


Figure.1: a) Microvessel density quantitation, b) Intimal thickness quantitation, c) M1 vs M2 Macrophages quantitation, d) *Esm1* relative fold-change quantitation and e) Apelin17 rescue of intimal thickness, inflammatory macrophages infiltrate and *in vitro* human monocytes-HUVECs adhesion quantitation, respectively, in the experimental mice groups (n=4-15). NS= non-significant, *P<0.05 and **P<0.01 via ANOVA or Mann-Whitney test, whenever indicated (Graphpad Prism)

Thermal response of amyloidogenic elements in cultured N2a cells: potential relevance to Alzheimer's Disease pathology

Andrew Schmaus and Satyabrata Kar

INTRODUCTION

Alzheimer's Disease (AD), the most prevalent cause of dementia in the elderly population, is characterized by the accumulation of tau-positive neurofibrillary tangles (NFTs) and amyloid-? (A?) containing extracellular plaques in the diseased brain. These aggregates correlate to the neurodegeneration and loss of cognitive function seen in AD. While a subset of AD is associated with mutations of specific genes such as the amyloid precursor protein (APP), the vast majority of cases are sporadic, for which the primary risk factor is age. Recent studies have indicated that body temperature may have a role in protein aggregation and development of pathological features associated with AD. Thus, in the current project, we aim to evaluate how temperature can influence the pathological features associated with AD brains at the cellular level.

METHODS

We used wild-type murine neuroblastoma (N2a) and Swedish APP mutant N2a cells to investigate the effects of low, normal and high temperature on the production and secretion of A?-related peptides from its precursor APP by western blotting, ELISA, and immunocytochemistry. Additionally, we evaluated how temperature can influence cell viability that may contribute to neurodegeneration in AD pathology.

RESULTS

Our results show an inverse relationship between temperature and APP processing leading to production of A?-related peptides such as ?/?-C-terminal fragments of APP. The secretion of A? peptides as well as typical clearance routes via the endolysosomal system are also found to be altered in a temperature dependent manner. Additionally, we showed that hypothermic condition can significantly decrease cell viability.

CONCLUSIONS

Our results obtained so far indicate that thermal response may directly influence AD-related pathology by regulating the production/secretion of AD-associated molecules.

Supervisor: Dr. Satyabrata Kar

Development of CRISPR-Cas9-based gene drive approaches to prion disease resistance

Andrew R. Castle, Serene L. Wohlgemuth, and David Westaway

INTRODUCTION

Prion diseases are fatal, transmissible, neurodegenerative disorders of mammals that depend upon posttranslational conversion of the cellular glycoprotein PrPC, encoded by Prnp, into a disease-associated conformation. One example is chronic wasting disease (CWD), which is threatening cervid populations in the US and Canada. Moreover, zoonotic transmission of CWD remains a concerning possibility. As an alternative to as-yet-unsuccessful vaccine approaches, we propose using CRISPR-Cas9-based gene drive technology to promote the spread of null Prnp alleles, thereby eliminating prion disease susceptibility from cervid populations. We are performing proof-of-principle experiments to validate this approach using rodent models.

METHODS

For initial cell experiments, Cas9 and murine Prnp guide RNAs (gRNAs) were delivered by plasmid transfection and T7E1 assays were used to detect Prnp disruptions in pooled genomic DNA. To test whether sequences could be recombined into the Cas9 cleavage site, a donor plasmid containing a fluorescent reporter sequence flanked by homology arms of ~800 bp was co-transfected into N2a cells alongside the Cas9-gRNA expression plasmid. Junction fragments were amplified from pooled genomic DNA and were sequenced to confirm precise integration. For in vivo experiments, Cas9-gRNA complexes were electroporated into fertilized mouse oocytes. Prnp disruptions in the pups obtained were detected by sequencing.

RESULTS

Co-expression of Cas9 and Prnp gRNAs in RK13 cells generated detectable indels within the Prnp coding sequence. Subsequent in vivo testing of one of these gRNAs resulted in mouse pups with heterozygous Prnp disruptions. Finally, we showed in N2a cells that a fluorescent reporter sequence could be integrated precisely into the Cas9 cleavage site within Prnp.

CONCLUSIONS

We successfully disrupted Prnp in cell culture and in vivo using CRISPR-Cas9, and demonstrated that exogenous sequences can be recombined into the cleavage site. Work is ongoing to utilize inducible forms of Cas9 as gene brake mechanisms and to generate transgenic mice expressing Cas9 from germline-specific promoters.

Supervisor: Dr. David Westaway

Use of the Molecular Adsorbent Recirculating System (MARS®) in Acute Liver Failure – A Multicentre Experience

Andrew J. MacDonald, Brianne M. Shropshire, Jody C. Olson & Constantine J. Karvellas

INTRODUCTION

Acute liver failure (ALF) is a fulminant disease characterized by acute hepatic injury in combination with hepatic encephalopathy (HE) and impaired hepatic synthetic function. Despite maximal medical therapy, ALF carries high mortality, with liver transplantation representing the only definitive management strategy. Studies have demonstrated a beneficial effect on HE and hemodynamics; however, the role of the Molecular Adsorbent Recirculating System (MARS) in transplant-free survival remains in question.

METHODS

This study primarily aimed to describe the ALF population receiving MARS therapy at two large North American tertiary hospitals. Secondary outcomes included change in hemodynamic and biochemical parameters post-MARS treatment, and survival to intensive care unit (ICU) discharge and hospital discharge. As part of a large retrospective case series, all ALF patients receiving MARS therapy between January 2009 and January 2019 were identified through existing databases and reviewed. Paired mean differences for pre- and post-MARS parameters were calculated using Student's t-test.

RESULTS

Forty-seven patients (mean age 39.74 years; 22 males and 25 females) were treated with MARS (mean 1.96 runs; range 1-4; mean 15.10 total hours), with acetaminophen/paracetamol toxicity representing the most common ALF etiology (n=21). Following MARS therapy, patients displayed increased mean arterial pressure (+5.53mmHg; p=0.14), with no significant increase observed in vasopressor requirements. Serum bilirubin (-16.13?mol/L; p=0.39), INR (-1.24; p=0.001), creatinine (-53.59?mol/L; p=0.0001), ammonia (-61.88mmol/L; p=0.001), and lactate (-1.53mmol/L; p=0.11) decreased following MARS treatment. Overall, 14 patients underwent orthotopic liver transplantation (29.79%), with one patient dying intra-operatively. Twenty-seven patients survived to ICU discharge (57.45%; mean ICU length of stay 15.81 days), with 26 surviving to hospital discharge (55.32%; mean hospital length of stay 31.88 days).

CONCLUSIONS

Among patients with ALF, MARS therapy improves hemodynamics and trends biochemical variables towards normalization. A larger case-control study is required to evaluate any potential survival advantage (currently ongoing).

Supervisor: Dr. Constantine Karvellas

The Use of Cardiac Resynchronization Therapy in Type 1 Myotonic Muscular Dystrophy Patients with Left Bundle Branch Block

Anish Nikhanj, Soori Sivakumaran MD, Haran Yogasundaram MD, Harold Becker MD, Shane Kimber MD, Zaeem A. Siddiqi MD, PhD, Gavin Y. Oudit MD, PhD

INTRODUCTION

Type 1 myotonic muscular dystrophy (DM1) is an autosomal dominant-inherited disease associated with a high burden of atrial and ventricular arrhythmias, and conduction delays. Patients with DM1 show markedly reduced LV systolic function in the presence of LBBB. We demonstrate that CRT device intervention is critical in this group of patients to delay the progression of heart disease.

METHODS

DM1 patients were recruited to the Neuromuscular Multidisciplinary Clinic established at the Kaye Edmonton Clinicwhere they received concurrent care from specialist physicians and allied healthcare professionals. In collaboration with the Mazankowski Alberta Heart Institute, DM1 patients were evaluated based on their: 1) medical history and clinical examinations; 2) initial diagnostic testing including 12-lead electrocardiogram (ECG) and cardiac diagnostic imaging; 3) follow-up 12-lead ECG and echocardiogram studies of patients receiving CRT devices.

RESULTS

Our DM1 cohort consisted of 64 patients, which showed a high burden of atrial and ventricular arrhythmias, with reduced systolic function. 12 (19%) patients presented with LBBB and nine of these patients received a CRT pacemaker device, resulting in biventricular pacing and an improved median LVEF from 37.3% to 45.8% (P=0.007) captured by echocardiogram, following device intervention.

CONCLUSIONS

We demonstrate that CRT device intervention improves left ventricular systolic function in patients with DM1 with LBBB. CRT device intervention should therefore be implemented as a standard therapy in DM1 patients with similar presentation to delay the progression of heart disease.

Supervisor: Dr. Gavin Y. Oudit

Survival pattern among venous thromboembolism (VTE) patients with hematologic malignancy in Alberta, Canada from 2002 to 2015

Arafat Alam, Mohammad Karkhaneh, Linda sun, Cynthia Wu

INTRODUCTION
Nearly 20% of all newly identified cases of VTE is associated with cancer. Hematologic malignancies are at increased risk of developing VTE. We aimed to identify the prevalence of hematologic malignancy in VTE patients and compare the survival between VTE patients with or without hematologic malignancy.

METHODS
Using linked administrative data and a validated algorithm we identified adult VTE cases in Alberta, Canada from 2002 to 2015. Subjects having ICD-10 code for hematologic cancer within one year before and after the VTE index event were further identified. Cox proportional hazard regression model was applied to estimate the hazard ratio (HR) of death.

RESULTS
We identified 47,824 VTE patients. Of them 32,544, 13,487 and 1,793 cases were diagnosed as deep vein thrombosis (DVT), pulmonary embolism (PE), and both DVT & PE respectively. Of all VTE cases, 902 (1.9%) patients had hematologic malignancies. Lymphoma, leukemia, myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN) and plasma cell dyscrasia accounted for 55.2%(498), 9.3% (84), 6.8% (61), 17.8%(161) and 10.9% (98) of the hematologic malignancy cases respectively. The prevalence of hematologic malignancy was comparable between men and women (51.2% vs 48.8%). 54.1% of the VTE patients with hematologic malignancy died during the study period compared to 20.3% of those without hematologic malignancy. The HRs of death among VTE patients with lymphoma, leukemia, MDS, MPN and plasma cell dyscrasia were 2.87 (95%CI:2.54-3.24), 4.02 (2.99-5.41), 2.26 (1.65- 3.08), 1.87 (1.46- 2.39), 3.32(2.62- 4.20), respectively, which were significantly higher than that of VTE patients without them, adjusted for age, sex, and age as a time dependent covariate.

CONCLUSIONS
Lymphoma is the most common hematologic malignancy in VTE patients. VTE patients with any type of hematologic malignancy have an increased risk of death compared to those without them.

Supervisor: Dr. Cynthia Wu, Linda Sun

Table 1: Cox proportional Hazard regression analysis of mortality among patients with venous thromboembolism by hematologic malignancies in Alberta, Canada (2002-2015)

	Hazard ratio (95% CI) [a]			
	VTE Type [b]			
Hematologic Malignancy Type	DVT [c]	PE [d]	DVT&PE	Overall VTE [b]
Lymphoma	2.47 (2.12 – 2.88)	3.79 (3.01 – 4.64)	3.11 (1.76 – 5.47)	2.87 (2.54 – 3.24)
Leukemia	3.68 (2.54 – 5.34)	4.88 (2.99 – 7.97)	12.33 (1.74 – 87.59)	4.02 (2.99 – 5.41)
Myelodysplastic syndrome	2.33 (1.56 – 3.49)	1.94 (1.15 – 3.28)	8.04 (2.01 – 32.14)	2.26 (1.65 – 3.08)
Myeloproliferative neoplasm	1.58 (1.14 – 2.18)	2.59 (1.79 – 3.83)	1.57 (0.39 – 6.29)	1.87 (1.46 – 2.39)
Plasma cell dyscrasia	3.72 (2.72 – 5.01)	2.74 (1.85 – 4.06)	4.00 (1.50 – 10.67)	3.32 (2.62 – 4.20)
VTE, no malignancy [e]	1:00	1:00	1:00	1:00

a: hazard ratios calculated by controlling covariates of age, sex, and age was considered as a time-dependent variable in the model b: venous thromboembolism c: deep vein thrombosis; d: pulmonary embolism; e: VTE cases with no Hematologic malignancy

BCL-2 Inhibitor Venetoclax Enhances Temozolomide Sensitivity in AML

Asmaa Basonbul, MSc

INTRODUCTION

Introduction:
Temozolomide (TMZ) is an alkylating agent, which adds a methyl group to O6 position of guanine, resulting in mismatch pairing with double strand breaks leading to apoptosis. The DNA repair enzyme O6-methylguanine methyltransferase (MGMT) enhances cell resistance to TMZ. BCL-2 is an anti-apoptotic protein preventing cell to death. Venetoclax (Venet) is a small molecule, which promotes apoptosis through inhibition of BCL-2. The objective of this study is evaluated the ability of the BCL-2 inhibitor Venet to enhance TMZ sensitivity in acute myeloid leukemia (AML) cells.

METHODS

Methods:
AML bone marrow blast cells were collected from AML patients. KG1, MV4-11 and MOLM13 AML cell lines were chosen. Western blot was used to measure MGMT and BCL-2 expression. The Cells were incubated with TMZ 5, 10, 15, 20, 50 and 100 uM in combination with a fixed concentration of Venet. After 2 days, cell viability and apoptosis assays were performed using spectrophotometry and flow cytometry, respectively. Synergy was evaluated by the Chou-Talalay method.

RESULTS

Results:
Cells expressing high MGMT demonstrated strong resistance to TMZ; however, co-incubation with 1 uM Venet resulted in a marked enhancement of sensitivity to TMZ. Venet 2.5 nM alone inhibited cell growth by approx. 50% in highly expressed BCL-2, MV4-11 and MOLM13. This dose in combination with TMZ markedly increased the cytotoxicity with nearly 100% inhibition at 100uM TMZ. A synergistic effect was demonstrated in all cell lines with combination index (CI) < 1. Cells overexpressed annexin V and propidium iodide (PI) apoptotic marker after drug combination in all cell lines. Most AML patient samples which were resistant to TMZ became sensitized in combination with 1 uM Venet.

CONCLUSIONS

Conclusion:
Venetoclax enhances TMZ sensitivity and induces cytotoxicity, in MGMT overexpressing cells. The drug combination design on animal model should be evaluated. Moreover, explored the relationship mechanism between the two inhibitors.

Supervisor: Dr. Joseph Brandwein

Fluid volume overload and vascular stiffness in hemodialysis patients.

Aya Lafta, Judy Ukrainetz, Branko Braam

INTRODUCTION
Fluid overload (FO) and arterial stiffness are risk factors for cardiovascular events in hemodialysis (HD) patients. The relationship between FO and arterial stiffness in HD patients has not established yet. We hypothesized that FO is associated with a high arterial stiffness using pulse wave velocity (PWV) and augmentation index (AIx).

METHODS
We have enrolled 20 fluid overloaded and 19 non fluid overloaded HD patients; 26 healthy subjects were evaluated as controls. Fluid status was assessed by bio-impedance spectroscopy. Arterial stiffness (Arteriograph24TM) measurements were taken on a pre-dialysis day for 24-hours, followed by 5-hour measurements starting 30 minutes before and ending 30 minutes after the mid-week HD session. In healthy controls, a 5-hour measurement of PWV and AIx was performed as time control.

RESULTS
Average age of HD patients was 56 ± 14 and 46 ± 15 years in the healthy subjects. Fluid status was -0.1 ±0.7L, and 3.6 ±2.3L, 0.1 ±0.5L, in healthy subjects, FO and non-FO HD patients, respectively. As anticipated, PWV and AIx were higher in HD patients compared to healthy controls. FO was not associated with a higher PWV (10.0 ±1.5 vs 10.3 ± 1.9 m/s) in patients with and without FO, respectively. No clear changes in PWV or AIx were observed over 24h preceding and during HD run. A negative linear relationship between UF rate and a decrease in PWV over the dialysis run was not significant ($P > 0.05$).

CONCLUSIONS
The study shows that PWV and AIx were higher in HD patients than in healthy subjects. Surprisingly, there was no difference in PWV/AIx between the two HD groups. Based on study results, the effects of fluid status on arterial stiffness might be obscured by more medication use in FO patients. An additional interventional study would be needed to further delineate the relationship between fluid status and arterial stiffness.

Supervisor: Dr. Branko Braam

Comparison of Palliative Care Practices in Idiopathic Pulmonary Fibrosis

Meena Kalluri, Sarah Younus, Bohyung Min, Onofre Moran-Mendoza, Ingrid Harle, Huzaifa Adamali, Shaney Barratt, Michelle Molares, Naomi Rippon

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and fatal lung disease characterized by lung scarring. This leads to heavy symptom burden and impaired quality of life (QOL). Clinical practice guidelines recommend integrated palliative care and advanced care planning (ACP). However, a well-defined model of palliative care for patients with advanced lung disease does not currently exist. We compare the Kaye Edmonton Clinic (KEC) IPF clinic and the North Bristol Trust clinic in terms of each model's unique approach to palliative care (PC) and impact. Specifically, KEC uses a Multidisciplinary Collaborative care model (MDC) to deliver integrated palliative care, and the Bristol clinic team uses a palliative multidisciplinary discussion model.

METHODS

Electronic medical records of deceased adult ILD patients from each of the two sites were reviewed (January 2017-October 2018) and analyzed to describe various models of PC.

RESULTS

The mean age at death was 72 years (n=40) and 75% of patients were male. Thirty-three patients (83%) of patients had IPF and seven (18%) non-IPF ILD diagnoses. PC was initiated in 100% of patients 16 months (mean) before death (range: 50 months). PC was defined as symptom assessment, management (n=40; 73% on opiates, 45% BZD, 85% O2) and ACP. Forty (100%) patients had symptoms assessed, using the MDDS (KEC) and ILD screening tools (Bristol). Ninety percent (36) had symptoms managed using opiates/BZD/O2. Nineteen patients (48%) had ACP discussions. Location of death was known in 33 patients and not recorded in 7. Fourteen patients died at home, 15 in hospital, 3 in hospice and 1 in another location. Seventy-three percent of patients died at their preferred location (n=11).

CONCLUSIONS

Two distinct PC delivery models were reviewed in terms of: the integration of PC results in early assessment and management of symptoms; consistent ACP documentation; and high concordance between preferred and actual location of death, a marker of good end of life care.

Supervisor: Dr. Meena Kalluri

	#IPF Dx	#non-IPF ILD Dx	PC (mean months before death)	# Symptom Assessment	# Symptom Management	# ACP	Preferred location of death (LOD)	% Concordance between actual and preferred LOD
KEC	13	7	18.3	20	17 (Opiates/BZD/O2)	16	Home (8)	63% (5/8)
Bristol	20	0	14.5	20	19 (Opiates/BZD/O2/antitussives)	3	Home (3)	100% (3/3)
Total	33	7	16.4	40	36	19	11	73% (8/11)

Table 1: Comparison of PC and ACP in ILD patients undergoing the KEC MDC model vs the Bristol Trust MDD model.

A retrospective review of Pseudomonas aeruginosa infection in a quarternary intensive care unit: epidemiology, outcomes, and antimicrobial susceptibilities: 2013-2016.

Brittany Kula, Wendy I Sligl, Darren Hudson

INTRODUCTION
Pseudomonas aeruginosa (PA) is known for causing infection in the intensive care unit (ICU) and as multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains become more prevalent, there is need for ongoing review of prevalence, susceptibilities and factors affecting patient outcomes. The objectives were to determine patient characteristics and 30-day mortality in patients admitted to a quaternary-care ICU and infected with PA.

METHODS
Patients with PA during ICU admission from 2013-2016 were reviewed retrospectively. Independent predictors of mortality were analyzed using multivariate logistic regression.

RESULTS
140 patients were actively infected with PA. 7 had incomplete data. Mean patient age was 55.4 years (range 18-87, SD 18.4), and 62% were male. Common admission types were medical (71%) and surgical (20%), with the remainder trauma or neurological (9%). Mortality was 23% at 30 days.
The average APACHE II score at admission was 19.4 (range 1-53, SD 9.8). 126 patients (90%) required invasive ventilation for a mean of 12.9 days (SD 16.8 days). 102 patients (73%) required vasopressor support for a mean 4.2 days (SD 6.2 days) and 27 (19%) required initiation of renal replacement therapy. The average ICU length of stay was 19.8 days.
The most common specimens were respiratory (66%) followed by urinary (10%), skin/soft tissue (11%), blood (5%), gastrointestinal (2%) and surgical (5%). The incidence of sensitive specimens was 82%, MDR 14% and XDR 4%. Empiric antimicrobial therapy was adequate in 69% of cases. On multivariate analysis liver disease (OR 6.2, 95% CI 1.5-25.7), malignancy (OR 5.0, 95% CI 1.5-17.3) and higher APACHE II scores (OR 1.1, 95% CI 1.0-1.1), were independently associated with higher 30-day mortality.

CONCLUSIONS
PA in the ICU is associated with high mortality and is most commonly isolated from the respiratory tract. Existing malignancy, liver disease and higher APACHE II score at admission were independently associated with higher mortality.

Supervisor: Dr. Wendy Sligl

novel mechanism for transcription-independent translation of selective proteins under acute cellular stress, involving mRNA demethylation

Bruno Saleme, Aristeidis Boukouris, Sotirios Zervopoulos, Gopinath Sutendra, and Evangelos Michelakis

INTRODUCTION

Cells shut off protein translation after exposure to major acute stress, to conserve energy (protein translation is the cell's most energy-demanding function) and commence damage repair to survive. While translation is inhibited, cells selectively translate Stress Responsive Proteins (SRPs) immediately (minutes) and without involving gene transcription, using pre-existing mRNAs, via largely unknown mechanisms. We hypothesized that methylation tags on pre-existing mRNAs of SRPs cue this selective translation.

METHODS

Stable-Isotope Labeling of Amino acids in Cell-culture (SILAC, allowing the identification of newly synthesized versus pre-existing proteins), mass spectrometry, RNA sequencing, methylation-induced crosslinking immunoprecipitation (miCLIP), immunoblots and qRTs were used in control versus stressed A549 cancer cells (DNA damaging UV exposure).

RESULTS

To confirm the transcription-independent translation of candidate SRPs, we found increased p53 and ATF4 protein levels within 20 minutes after stress, without an increase in their mRNA levels and without evidence of resistance to protein degradation. This was sustained with inhibited transcription, but lost with ribosome inhibition. Using SILAC, we found that ~40 proteins involved in cellular repair and reprograming, were induced 2-23 fold within 20 minutes after UV, while their mRNA levels remained unchanged. These proteins showed significant baseline methylation at 5'UTR of their mRNAs, which was reduced after UV, suggesting that 5'UTR methyl- tags signal translation in stress. Inhibition of Fat Mass and Obesity Associated Protein (FTO), an RNA demethylase, impaired the ability to acutely translate SRPs after UV and survive, suggesting that FTO may mediate stress-induced mRNA demethylation.

CONCLUSIONS

Here we describe for the first time the simultaneous use of SILAC, RNA sequencing, and miCLIP to identify SRPs and the mRNA tags that predict their translation under acute stress. The transcription-independent selective SRP translation in stress is facilitated by an FTO-dependent 5'UTR mRNA de-methylation and is critical for early adaptation to stress and cell survival.

Supervisor: Dr. Evangelos Michelakis

The appropriateness of HIT testing at the University of Alberta

Carissa Beaulieu , Bradley Rutherford, Mohammad Karkhaneh, Cynthia Wu

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication affecting hospitalized patients treated with heparin. There are validated clinical tools to predict the clinical likelihood of HIT (such as the 4T's score). Failure to use these results in inappropriate HIT testing. Our study aimed to determine how often inappropriate testing was performed at the University of Alberta.

METHODS

We obtained ethics approval to perform a retrospective chart review on 500 charts. Data collected included demographics, clinical parameters at the time of HIT testing, HIT assay results, adverse events, and treatment. 4T's scores were calculated retrospectively and confirmed where available.

RESULTS

To date, we have reviewed 44 patients who underwent HIT testing. Of those patients 24 (54.5%) were male, with an average age of 64 years. Two patients (4.5%) had probability scores performed by the admitting service. 25 (56.8%) had retrospective 4T's scores in the low-risk category, 17 (38.6%) intermediate, and 1 (2.3%) in the high-risk category. HIT testing revealed 4 positive functional assays (9.0%). Two (4.5%) were ultimately negative for HIT, and 2 equivocal on lumiaggregometry. Twenty-nine (65.9%) patients had anticoagulation stopped when HIT was suspected. Four (9%) patients in total were started on non-heparin anticoagulation. Seven (15.9%) patients developed thrombosis, and 11 (25%) had bleeding events.

CONCLUSIONS

It is clear that use of validated pretest probability tools for HIT are underutilized and inappropriate testing is common. Only a very small number of patients with suspected HIT are confirmed to have HIT. Additionally, the patients in our cohort have a high rate of thrombotic and hemorrhagic complications irrespective of HIT test results. Appropriate assessment of suspected HIT can decrease unnecessary testing and treatment alterations.

Supervisor: Dr. Cynthia Wu

Paralagous expansion of membrane trafficking factors played key roles during the evolution of apicomplexan parasites

Christen M. Klinger, Elena Jimenez-Ruiz, Leandro Lemgruber, Markus Meissner, and Joel B. Dacks

INTRODUCTION
Apicomplexan parasites rely on specialized secretory organelles, micronemes and rhoptries, to sustain asexual infection in hosts. The formation of these organelles is mediated by the membrane-trafficking system (MTS), the set of cellular machinery responsible for regulated movement of material between organelles. Theoretical mechanisms of organelle evolution posit that novel organelles evolve, in part, by paralagous duplication and divergence of identity-encoding MTS machinery. As Apicomplexa possess canonical endomembrane organelles, we hypothesized that they have evolved additional (novel) MTS paralogues concurrently with micronemes and rhoptries.

METHODS
Standard homology searching methods, combined with a unique phylogenetic pipeline, were used to identify and classify MTS paralogues in Apicomplexa and outgroup taxa for comparison. Functional studies of select paralogues in the model apicomplexan Toxoplasma gondii used endogenous gene tagging, gene disruption, phenotypic characterization, and super-resolution structured illumination microscopy.

RESULTS
We identify 18 paralogues encoded in Apicomplexa and some close outgroup taxa, but absent from the rest of eukaryotes (novel), spanning multiple MTS families. Three of these belong to the ADP-ribosylation-factor(ARF)-like (Arl) family, including one paralogue that is only found in Apicomplexa. Endogenous gene tagging of all three (ArlX1, X2, and X3) reveal unique localization patterns throughout the parasite. ArlX3, predicted to be essential by a previous whole-genome screen, was chosen for further analysis. Conditional knockdown of ArlX3 blocks parasite growth by affecting the three main steps of the asexual cycle. Further analysis revealed mis-localization of multiple microneme and rhoptry resident proteins and Golgi fragmentation.

CONCLUSIONS
We identify novel MTS paralogues that arose during apicomplexan evolution. Characterization of an essential novel paralogue, ArlX3, revealed a putative role in post-Golgi trafficking of microneme and rhoptry resident proteins. Our results are entirely consistent with the hypothesized role of novel paralogues in organellogenesis, and are important for understanding the evolution of eukaryotes, including some of the world’s deadliest parasites.

Supervisor: Dr. Joel B. Dacks

De-novo Donor Specific Antigen Formation in Liver Transplants: Risk Factors for Development and Impact on Graft Survival

Christopher Wang, Aldo J. Montano-Loza, Patricia Campbell, Vincent Bain

INTRODUCTION
Antibody mediated rejection is an area of keen interest in solid organ transplants but its role in liver transplants remains poorly defined. Donor-specific antibodies (DSA) have emerged as potentially relevant biomarkers in predicting graft survival and function. The aim of this pilot study was to determine the risk factors associated with de-novo DSA formation and to evaluate its role clinical outcomes after liver transplantation.

METHODS
This single-center retrospective study compiled data on liver transplants performed between 2005 and 2018 in Edmonton, Canada. The presence of DSA was determined using single antigen flow beads until 2009 and by Luminex thereafter. Potential predictors of DSA formation were evaluated using Cox proportional hazard models. Graft survival estimates were obtained using the Kaplan-Meier method, and comparisons between patient groups were conducted using the log-rank test.

RESULTS
94 patients had measurements of HLA antibodies both before and after transplantation. In this cohort, 23 patients (24%) tested negative on initial cross-match before transplant but developed new antibodies against either Class I or Class II molecules post-transplant. Evaluation of potential predictors of de-novo antibody formation revealed no significant differences. However, patients who underwent transplantation for autoimmune liver disease (PBC, PSC and autoimmune hepatitis) had a higher risk of antibody formation (HR=2.55, 95% CI=1.11-5.88, P=0.02). The mean graft survival time in patients with de-novo antibody formation was lower than those with no change in antibody status but this difference was not clinically significant (P=0.21).

CONCLUSIONS
Patients who received a transplant for autoimmune liver disease had a higher risk of developing new Class I or II HLA antibodies post-transplant. In this preliminary report, development of DSA did not impact on graft survival. A standard approach to DSA monitoring is required to better understand its prevalence and impact in liver transplantation.

Supervisor: Dr. Vincent Bain

Time from suspected thrombotic thrombocytopenic purpura to initiation of plasma exchange in Alberta, Canada and impact on survival: a 10-year provincial retrospective cohort study

Daniel Sawler, Arabesque Parker, Julien Ferland, Jacqueline Karathra, M Dawn Goodyear, & Haowei (Linda) Sun

INTRODUCTION
Acquired thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) with significant morbidity and mortality. Guidelines recommend initiating plasma exchange (PLEX) within 4-8 hours of suspected TTP diagnosis. Real-world performance is unknown, and it is unclear whether PLEX delays beyond 8 hours increases mortality. This study assessed the time from suspected TTP to PLEX and whether PLEX delayed >8 hours from suspected diagnosis is an independent predictor of death.

METHODS
This 10-year retrospective study included adults ?18 years presenting with suspected TTP (TMA, thrombocytopenia, no obvious alternative causes) to apheresis centres in Alberta, Canada (2008-2017). Patients were classified as confirmed TTP if ADAMTS13 activity <10%. Survival curves were generated using Kaplan-Meier estimates, differences were compared using log-rank test. Association between delayed PLEX and risk of death was assessed by univariate and multivariable Cox proportional hazards regression.

RESULTS
138 individuals had 159 presentations of suspected TTP including 125 (79%) new presentations and 34 relapses, with acquired TTP confirmed in 68 presentations. Median time to PLEX initiation was 8.3 hours (IQR 4.3-13.7). Only 55% of patients with delayed PLEX received temporizing plasma infusions. At a median follow-up of 3 years, 50 individuals (36%) died, including 7 (14%) with confirmed TTP. There was no significant difference in 30-day survival between early vs. delayed PLEX (Figure 1, p=0.20). Only malignancy-associated TMA (hazard ratio HR 7.1, p<0.0001) was associated with increased risk of death on univariate regression. Early PLEX was not associated with lower risk of death in confirmed TTP in univariate and multivariable regression (adjusted HR 0.64, 95%CI 0.1-2.9, p=0.57).

CONCLUSIONS
Delayed initiation of PLEX >8 hours occurred in 50% of suspected TTP cases in our study, although it was not predictive of mortality. Confirmation with prospective studies is required to evaluate the impact of delayed PLEX on morbidity, mortality and healthcare utilization.

Supervisor: Dr. Linda Sun

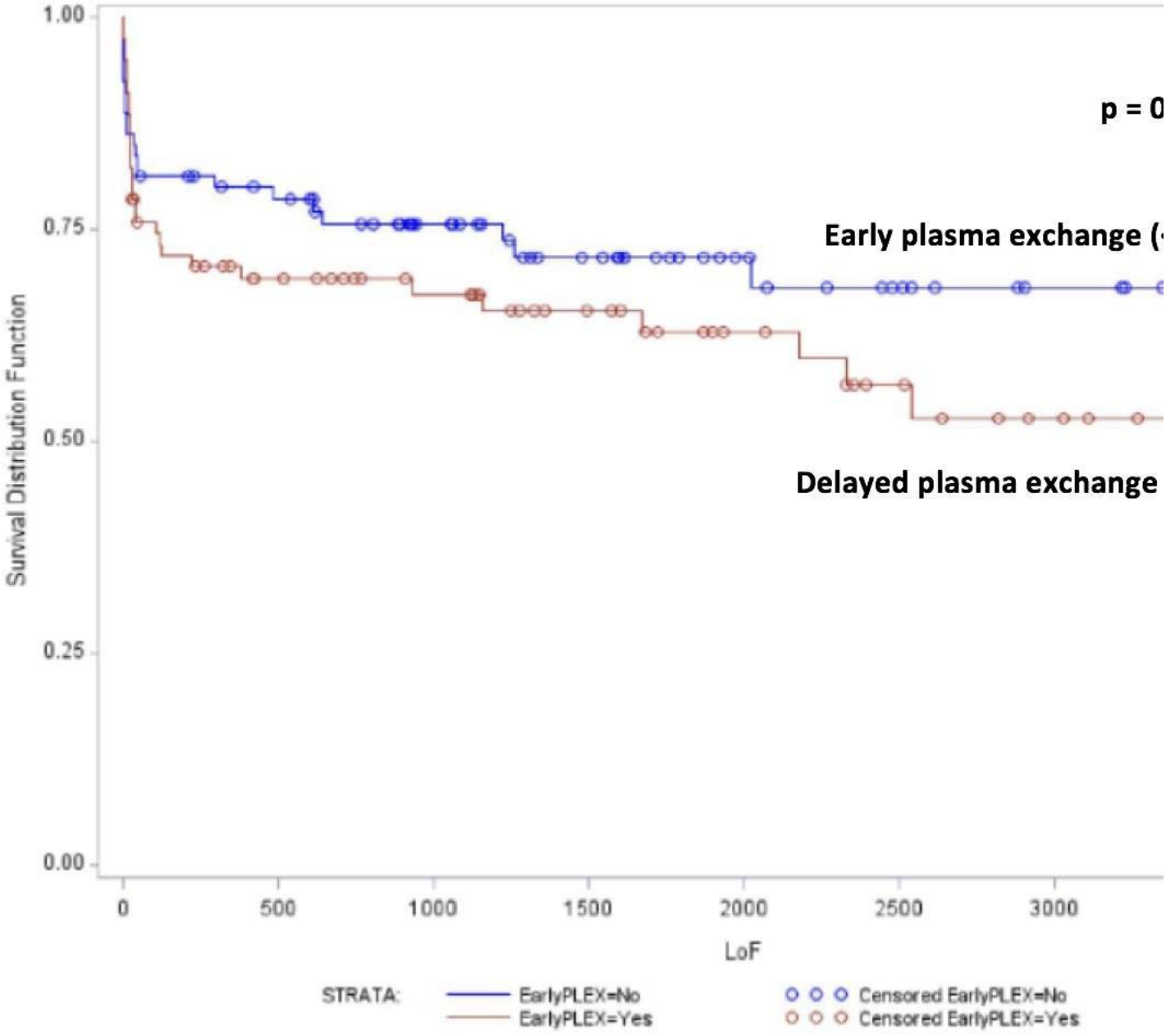


Figure 1. Kaplan-Meier curves of overall survival, according to time from suspected TT plasma exchange (Early ≤8 hours vs delayed > 8 hours)

Effect of Imatinib on relapse rates and survival in philadelphia chromosome positive acute lymphoblastic leukemia post-allogeneic stem cell transplantation

David Page, Lalit Saini

INTRODUCTION

Philadelphia chromosome positive acute lymphoblastic leukemia (Ph-ALL) traditionally carried a poor prognosis prior to the creation of Imatinib, a tyrosine kinase inhibitor targeting the oncogenic protein resulting from the Philadelphia chromosome. Given the positive effect on remission rates during induction, the question has been raised whether this drug would be effective for Ph-ALL patients post-allogeneic transplant. Given the heterogeneity of data from studies analyzing this question we sought to undertake a meta-analysis of the data to see if any conclusion could be drawn from using this drug in this context.

METHODS

We performed a search strategy of the literature to collect papers studying TKIs in Ph-ALL post allogeneic transplant. These studies were then reviewed for relevance to our question, and any data relating to overall-survival (OS), disease-free-survival (DFS) and relapse rates (RR) was pulled from these papers and subjected to meta-analysis. We also studied our analyzed papers for quality to assess this question.

RESULTS

Of 1356 unique citations we found 7 papers answering this question. After meta-analysis we found the hazard ratio (HR) for OS was 0.621 (95% CI 0.353-1.093, p=0.099), the HR of patients for RR was 1.275 (95% CI 0.724 – 2.243, p=0.4), and the HR for DFS was 0.784, (95% CI 0.248 – 1.766 p=0.557). We found the quality of our papers was low, due to predominantly lack of control groups in papers collected.

CONCLUSIONS

Given the data resulted from our meta-analysis failed to achieve significance we would give a recommendation of caution in the use of these drugs post-transplant. There are compelling theoretical reasons both for and against the use of this drug in this setting. There is insufficient data to answer this question through meta-analysis, pointing to the need for a prospective randomized control trial to determine the efficacy and safety of Imatinib in the post-transplant population.

Supervisor: Dr Lalit Saini

A Novel 4D Semi-Automated Algorithm for Volumetric Segmentation in Echocardiography

Deepa Krishnaswamy, Abhilash Hareendranathan, Tan Suwatanaviroj, Pierre Boulanger, Harald Becher, Michelle Noga, and Kumaradevan Punithakumar

INTRODUCTION

3D echocardiography is a non-invasive and cost-effective imaging modality used to assess cardiac function. Cardiologists often assess left ventricular function by annotating the endocardial borders, where metrics such as ejection fraction are calculated. Delineation of contours is time-consuming and prone to repeat reliability errors. Disadvantages of current segmentation methods include the inability to produce anatomically feasible results, and the need for extensive manual interaction. The goal is to develop a fast and reproducible algorithm with minimal user interaction that addresses the above concerns.

METHODS

The proposed approach involves obtaining 3D segmentations at end diastole and end systole, where contours are propagated over time to obtain the full 3D+T segmentation of the left ventricle. To obtain volumetric delineation of the left ventricle at end-diastole, a set of angular 2D slices were generated automatically using a user-defined axis of the chamber. The 3D delineation was obtained using a diffeomorphic registration approach, given manual segmentations in two orthogonal 2D angular slices. The process is repeated for end systole, where a subset of the dense contours is propagated over time to obtain the full 3D+T segmentation. A modification of the approach involves propagating the two manual segmentations over the entire cardiac cycle and then performing individual 3D segmentation per frame.

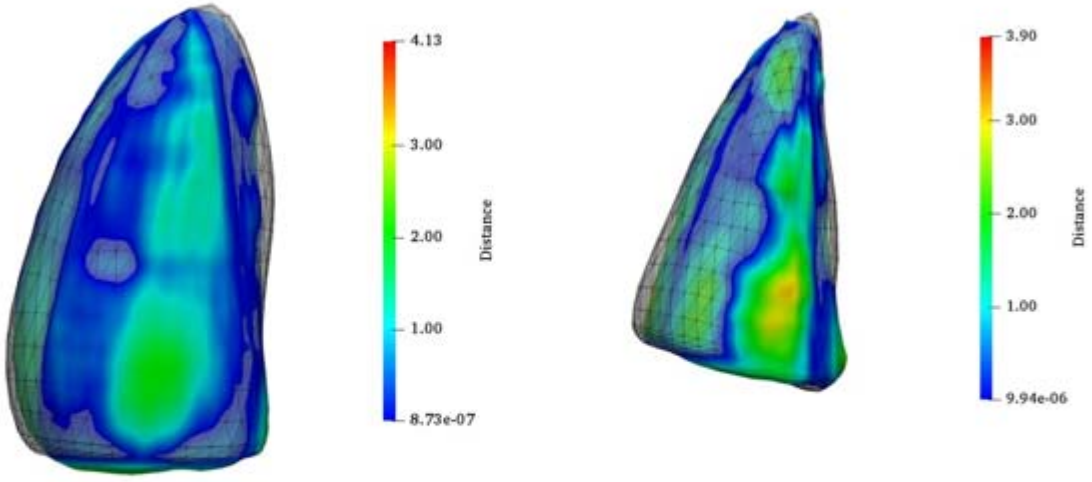
RESULTS

The proposed methods were compared quantitatively to expert manual segmentations over 18 patient datasets from the Mazankowski Alberta Heart Institute, Edmonton, AB. The methods yielded overall Dice scores of 0.93 (0.02) and 0.92 (0.02) respectively. The corresponding Hausdorff distance values were 4.86 (1.47) mm and 4.89 (1.52) mm for the two methods.

CONCLUSIONS

The study proposes two novel approaches for 3D+T segmentation of the left ventricle in echocardiography images. It relies on minimal user interaction and does not depend on prior geometrical knowledge while yielding segmentation results with high conformance with expert delineation.

Supervisor: Dr. Kumaradevan Punithakumar



Displaying the mean absolute distance metric in mm between method 1 of the proposed approach and the ground truth reference segmentation for end diastole (left) and end systole (right)

GI BLEED DUE TO CHRONIC LYMPHOCYTIC LEUKEMIA INFILTRATION IN THE SMALL BOWEL

Eddie Liu, Amit Dhillon, Sergio Zepeda-Gomez, Brendan Halloran

INTRODUCTION

Patients with leukemic infiltrates in the gastrointestinal tract are usually asymptomatic but may present with abdominal pain, diarrhea, or GI bleeding. We aim to report a case of GI bleed caused by chronic lymphocytic leukemia (CLL) infiltrating the small bowel.

METHODS

Case report and review of literature.

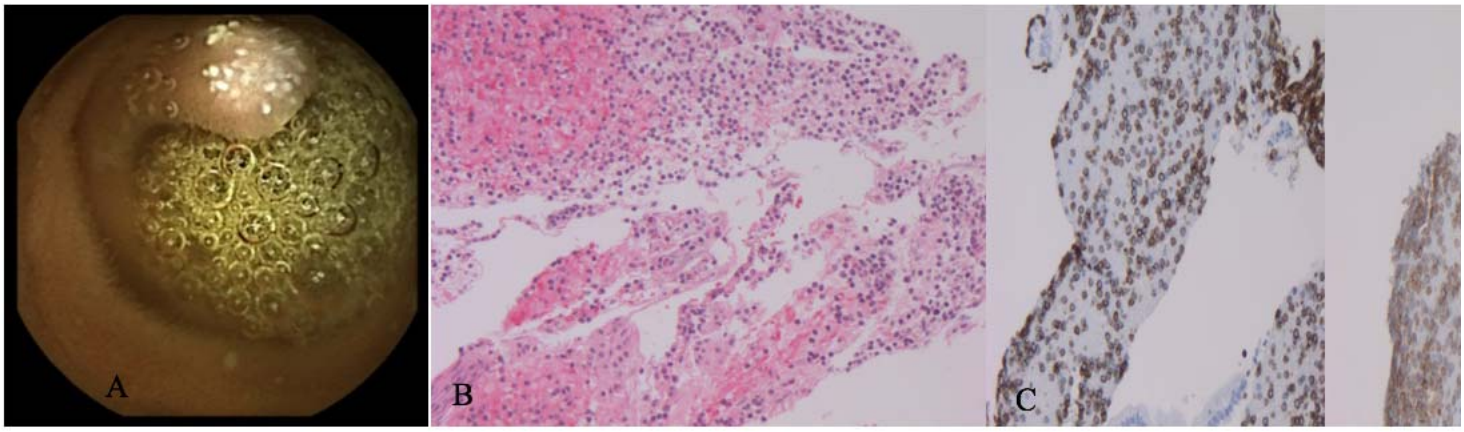
RESULTS

An 89-year-old man presented with a 2-week history of melena stool, intermittent left lower quadrant abdominal pain and worsening fatigue. Hemoglobin was decreased to 60 g/L from a baseline of 111 g/L 2 months ago. White blood cell (WBC) was 238 x 109/L with lymphocytic predominance. which was similar to baseline levels. Esophagogastroduodenoscopy and colonoscopy did not reveal source of bleeding. Video capsule endoscopy showed multiple small bowel lymphangiectasia. The lesion at 14% appeared to have a centralized erosion which might have been the culprit lesion (Figure 1A). These lesions were biopsied using double balloon enteroscopy. Tissue histology showed fragments of monotonous lymphocytic cell population (Figure 1B) which were positive for CD5, CD20 and CD23 in keeping with CLL infiltration (Figure 1C). LMWH was stopped and he began treatment with ibrutinib, this led to resolution of his GI symptoms.

CONCLUSIONS

CLL is the most prevalent form of leukemia in adults, complications are usually associated with intrinsic immune dysfunction resulting in infection, anemia, and thrombocytopenia. CLL has been reported to infiltrate throughout the GI tract, however clinically significant GI infiltration by CLL is rare. The few cases reported in the literature are limited to the terminal ileum and proximal colon causing GI bleed, abdominal pain and obstruction. This case shows that CLL can also affect multiple segments of the small bowel to cause overt GI bleed, likely due to formation of lymphangiectasia or vascular ectasia. Although CLL in the small bowel is rare, physicians should consider this in formulating a differential diagnosis in patients with CLL and unexplained GI bleeds.

Supervisor: Dr. Brendan Halloran


A
B
C

Levels of human Calcium-binding protein, spermatid-associated 1 (hCABS1) in saliva are positively associated to psychosocial stress and can be analyzed in a high-throughput manner

Eduardo Reyes-Serratos, Marcelo Marcet-Palacios, Thomas Ritz, David Rosenfield, A. Dean Befus

INTRODUCTION

hCABS1 is a potential stress biomarker. Using Western blot (WB), we observed that levels of a 27kDa form of hCABS1 were positively correlated with stress, while forms <27kDa were associated with resilience to stress. Because WB requires large quantities of antibody and sample and is time-consuming, we investigated whether Wes™ technology, a high-throughput immunoprobing platform would be a more efficient methodology and validate our WB observations.

METHODS

Participants were subjected to the Trier Social Stress Test (TSST), an acute stress-inducing validated method. During the test, participants answered stress questionnaires at 6 time points at which saliva samples were collected. We analyzed blinded saliva samples in Wes™ using two hCABS1 polyclonal antibodies (pAb), H1.0 and H2.0 (fig.1) reactive with distinct regions of hCABS1 and studied the association between hCABS1 levels and stress. We verified pAb specificity using an over-expression cell lysate control (OEL) and its negative control (NCL) in Wes™ and WB.

RESULTS

WB analyses of OEL and NCL indicate that H2.0 recognizes both hCABS1 (confirmed by Mass Spectrometry [MS]) and another protein(s). H1.0 is specific to hCABS1. In Wes™, both pAb show specific reactivity to OEL, congruent with MS, and no reactivity to NCL.
Wes™ using H2.0 detects a 35kDa form of hCABS1 in saliva homologous to the 27kDa form detected in WB (matrices are different between Wes™ and WB, molecular weight variations are ±20%). H1.0 Wes™-analyzed TSST saliva samples encounter a 60kDa form with no apparent association to stress.

CONCLUSIONS

Our data on OEL and NCL suggest that Wes™ is more specific than WB, favouring our decision to transition into Wes™ as a high-throughput, quantitative assay of hCABS1 levels in saliva. Wes™ replicated our observations in WB when using pAb H2.0 in TSST saliva samples. Additional studies are needed using H1.0 to determine if the H1.0-detected proteins are associated with stress.

Supervisor: Dr. Dean Befus

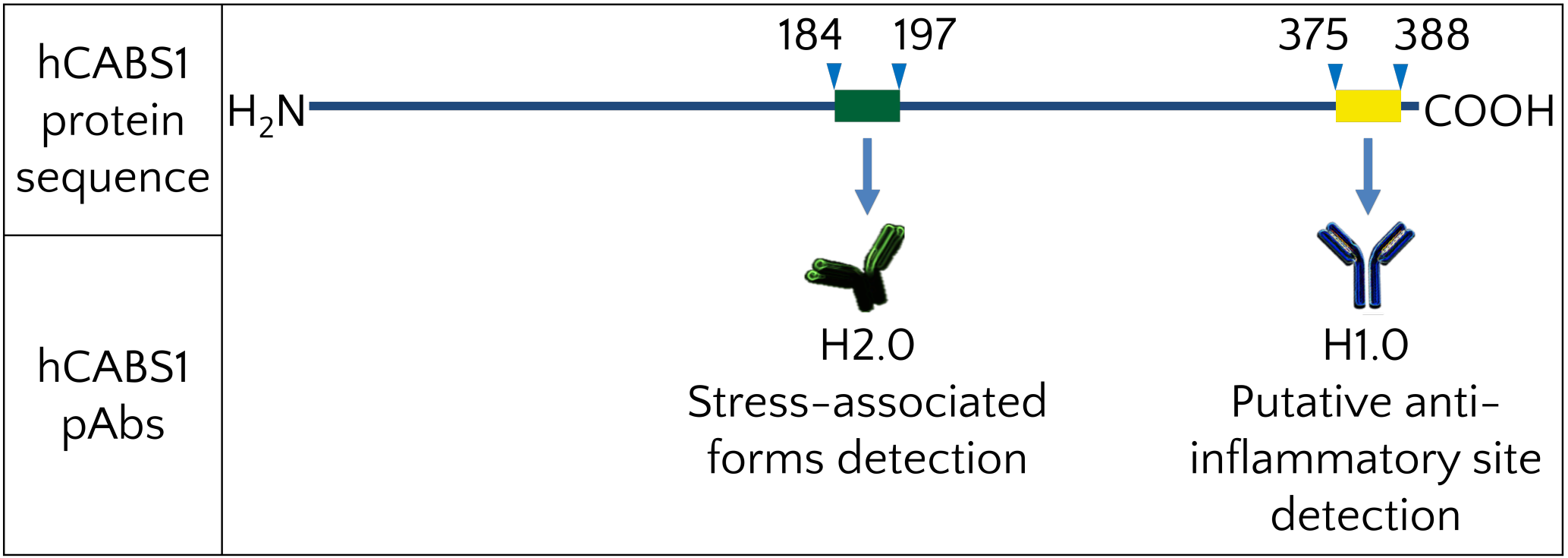


Fig. 1. We speculate that hCABS1 is proteolytically cleaved upon release in saliva. Generating two pAb to hCABS1 was important, as H1.0 and H2.0 could be detecting different-sized forms of hCABS1 that may be clinically relevant.

Using the 'Confusion Assessment Method (CAM) Tool to screen for delirium amongst hospitalized inpatients – a Quality Improvement Initiative

Mohammed Ashif Rahman, Frances Carr, Mina Pound, Caroyln Howel-Ridell, Laurie Nickerson

INTRODUCTION

Delirium is an acute, fluctuating confusional state that is treatable and potentially preventable when recognized early. The Confusion Assessment Method (CAM) is a standardized, validated screening tool to assist with the identification of delirium. Although AHS recognizes the value of the CAM tool both for screening and in diagnosing delirium, uptake of the CAM has been variable. Currently, on Unit 5G2 at the University of Alberta hospital, no standardized tool is being used to screen patients with delirium by nursing staff.

METHODS

The primary aim of this quality improvement initiative was to achieve 100% unit 5G2 patients (admitted to or residing on) screened for delirium by nursing staff using the CAM tool by the end of July. Seven 30 minute CAM training sessions were provided for nursing staff prior to CAM implementation, along with CAM educational materials. The CAM was implemented by nursing staff for delirium screening at admission, then twice daily at 7am and 7pm for all unit patients. Monitoring was conducted at weekly intervals for 8 weeks.

RESULTS

139 patients were enrolled over three months (May to July 2018). There were 23 cases of delirium. While 91% of patients were screened with the CAM at admission consistently during the study duration, overall usage of the CAM as per recommendations decreased to 66.7%. However, the incidence of falls and restraint use decreased.

CONCLUSIONS

While the CAM was consistently used by nursing staff at admission, its use as per recommendations fell. This was attributed to high usage of untrained float staff and poor study communication. However, nursing staff found the CAM easy to use and helped the screening process, and felt the amount of training received sufficient. Given its ease of use and positive clinical impact, incorporation of the CAM into the delirium screening process should be encouraged.

Supervisor: Dr. Darryl Rolfson

Age-Associated Immune Alterations in Patients with Ischemic Stroke

Gina Sykes, Glen C. Jickling

INTRODUCTION
The immune system changes with age with an increase in inflammation (inflammaging) and development of immunosenescence. The role of an aging immune system in patients with ischemic stroke remains unclear. Advancing age is associated with stroke outcome, and an aging immune system may contribute. This study evaluated the change in leukocyte gene expression with age in patients with ischemic stroke.

METHODS
Peripheral blood RNA was measured by whole genome Affymetrix HTA 2.0 microarray. Ischemic stroke (n=95) and controls (n=48) were analyzed by ANCOVA to identify genes associated with advancing age (FDR-corrected $p<0.05$, partial correlation coefficient +/- 0.3); adjusted for sex and vascular risk factors. Functional analysis identified pathways associated with age.

RESULTS
There were 270 genes associated with age in patients with ischemic stroke. Seventy-three increased with age including EPS8, H2BFM, and SPON2. One hundred ninety-seven decreased with age including CR2, CCR6 and CCR7. Functional analysis revealed pathways involved in activation of the humoral immune system, antibody production and B cell proliferation. Eighty-three genes overlapped with a previous meta-analysis on aging gene expression in non-stroke patients, 33 with a role in B cells.

CONCLUSIONS
A relationship between advancing age and leukocyte gene expression in patients with stroke was identified. Changes involved a shift humoral immune response including a change in B cell-related expression with age. The impact of these age related changes of the immune system on cerebral injury and stroke patient outcome requires further study.

Supervisor: Dr. Glen Jickling

Changing the Paradigm: A National Prospective Multi-Centered Study to Validate a Novel Algorithm for Cystic Fibrosis (CF)-related Diabetes (CFRD) Screening

Grace Y. Lam, Shelby Sissons, Jan Dayton, Maeve P. Smith, Neil E. Brown, Winnie M. Leung, and Mathew P. Estey

INTRODUCTION

CFRD is one of the most common complications in patients with CF and is associated with worsening pulmonary function and overall mortality. The current gold standard for the diagnosis of CFRD is the 2-hour 75 g oral glucose tolerance test (OGTT), with annual testing recommended by practice guidelines. Due its cumbersome nature, patients often choose to forgo screening. Consequently, a simpler screening alternative is urgently needed. Pilot data published by our group demonstrated the utility of fructosamine as a viable screening test for CFRD and impaired glucose tolerance (100% sensitivity and 67% specificity). While HbA1c has historically been unreliable in the CF population, we recently demonstrated that newer assays, which have improved precision, can identify CFRD with 95% sensitivity and 45% specificity. Therefore, we hypothesize that the combination of HbA1c and fructosamine may further enhance CFRD screening performance.

METHODS

Since 2017, patients at the Adult CF clinics in Edmonton, Calgary, Vancouver and Toronto undergoing OGTT screening for CFRD were recruited to perform the fructosamine test alongside their routine blood work. Fructosamine was measured using the Siemens fructosaminase-based method at DynaLIFE Medical Labs. HbA1c and OGTT results were obtained from each participating site and interim analysis of the 65 patients recruited to date was performed.

RESULTS

Fructosamine correlated with 2-hour OGTT glucose results ($r=0.3638$, $p=0.0029$). The optimal CFRD screening cutoff was >6.38 ?mol/g, which exhibited 100% sensitivity and 50% specificity. HbA1c also correlated well with 2-hour OGTT glucose results ($r=0.4144$, $p=0.0012$). The optimal CFRD screening cutoff was >5.8%, which had 100% sensitivity and 74% specificity. Strikingly, combining the fructosamine and HbA1c cutoffs led to further improvements in screening performance as specificity for CFRD increased to 81%, while maintaining 100% sensitivity.

CONCLUSIONS

Combining fructosamine with HbA1c would successfully eliminate the need for a confirmatory OGTT in 76% of patients with CF.

Supervisor: Dr. Winnie Leung

Comparison of cellular immune responses to human betaretrovirus versus autoimmune responses to mitochondrial antigens in patients with primary biliary cholangitis

Hiatem Abofayed - Bruna Dutra

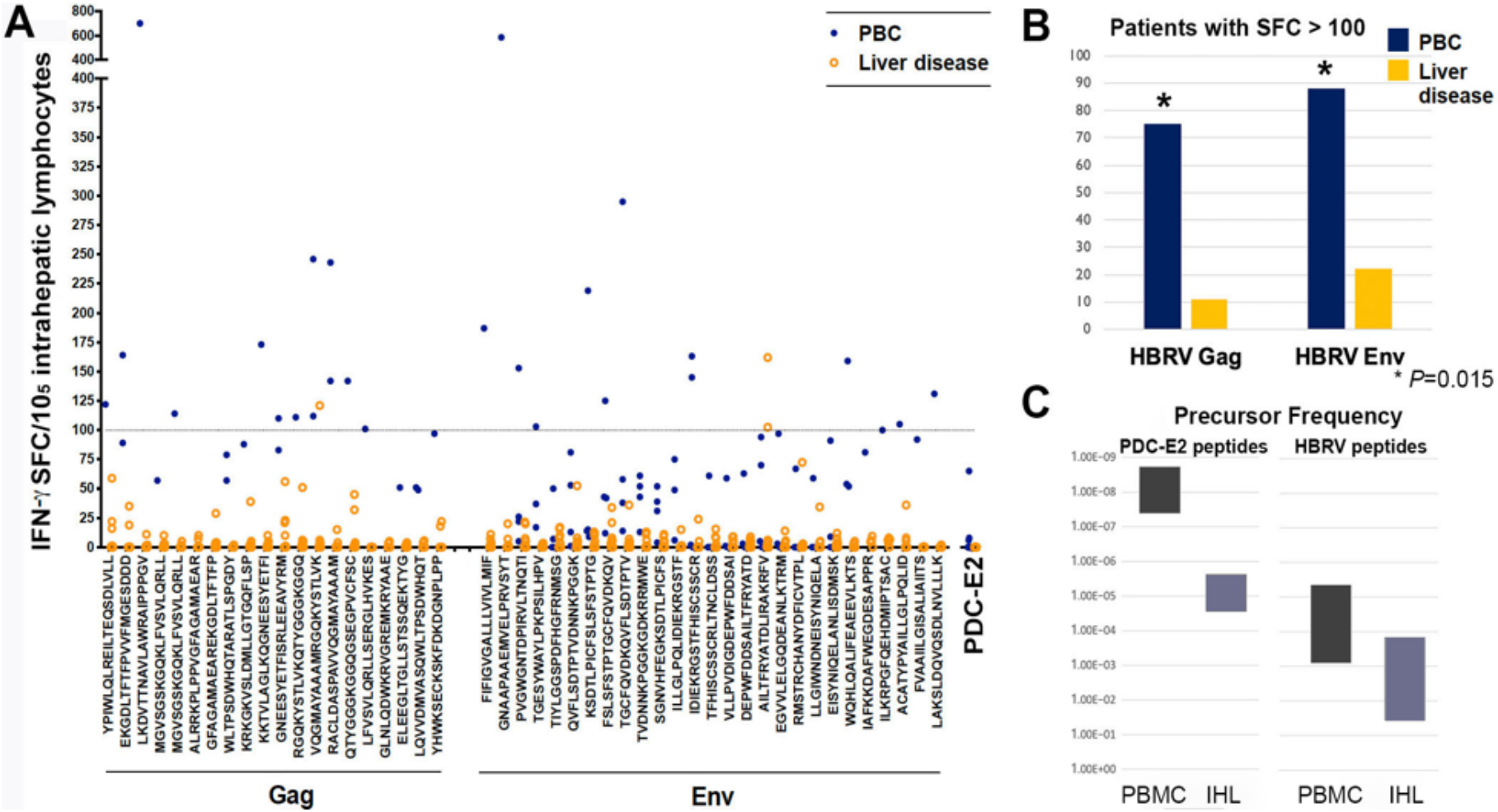
INTRODUCTION
A human betaretrovirus (HBRV) infection has been characterized in primary biliary cholangitis (PBC) patients. Our lab has documented HBRV proviral integrations in bile ducts of PBC patients. However, serological diagnostics cannot detect HBRV infection in the majority of PBC patients, limiting further confirmation of viral infection. In studies using pooled 17-20 aa peptides derived from the HBRV Gag (n=58) and Env (n=85) proteins, 40% of PBC patients were found to make proinflammatory cellular immune responses to HBRV. Then, to characterize immunodominant HBRV epitopes, we screened intra-hepatic lymphocytes (IHL) from PBC patients and control subjects for evidence of IFN- production.

METHODS
IHL isolated from liver transplant recipients with PBC (n=8) and other hepatic disorders (n=9) were individually stimulated with 18-mer peptides from HBRV Gag or Env proteins (n=143) or the characterized CD8+ reactive epitope to pyruvate dehydrogenase-E2 (PDC-E2). ELISpot was used to measure spot forming colonies (SFC) producing IFN-.

RESULTS
10 HBRV Gag and 12 HBRV Env peptides were found to stimulate IHL. The mean number of SFC producing IFN- was higher in PBC patients versus control subjects (75 vs. 10, $P<0.015$ for HBRV Gag peptides; and 88 vs.22, $P<0.015$ for HBRV Env peptides). Using a background cutoff level of 1:100 SFC, the individual HBRV Gag and Env peptides provided a high specificity and sensitivity for detecting HBRV infection in PBC patients IHL. Notably, only one PBC patient had detectable IFN-producing IHL following stimulation with the characterized CD8+ reactive mitochondrial autoantigen PDC-E2 peptide.

CONCLUSIONS
These are the first data to demonstrate that the intrahepatic proinflammatory cellular immune responses to HBRV greatly exceed the autoimmune response, suggesting that HBRV infection plays an important role in mediating PBC. The identified HBRV Gag and Env peptides can be evaluated to measure the IFN- release in peripheral blood mononuclear cells and construct a “Quantiferon” assay.

Supervisor: Dr. Andrew Mason


A
IFN-γ SFC/10⁵ intrahepatic lymphocytes
PBC
Liver disease
Gag
Env
PDC-E2
B
Patients with SFC > 100
PBC
Liver disease
HBRV Gag
HBRV Env
* P=0.015
C
Precursor Frequency
PDC-E2 peptides
HBRV peptides
PBMC
IHL
PBMC
IHL

Investigating TCR-VB repertoire expression profiles in Primary Biliary Cholangitis patients for evidence of Human Betaretrovirus Superantigen Activity

Hussain Syed, Leigh MacConnel, David Shapiro, Mary Erickson, Richard Pencheck, Andrew L. Mason

INTRODUCTION

Our laboratory characterized Human Betatretrovirus (HBRV) in Primary Biliary Cholangitis (PBC) patients and reported improvement in biochemical and histological cholangitis with combination antiretroviral therapy. HBRV shares 98% homology to mouse mammary tumor virus (MMTV), which is associated with PBC in mice and has well recorded superantigen (SAg) activity. SAg binding is T-Cell Receptor Variable-Beta region (TCR-VB) specific and involves massive non-specific activation of T-cells leading to increased cytokine release. T-cell subsets undergo depletion in later stages. To better understand PBC progression, we assess RNA-seq data from 128 PBC patients and evaluate alterations in TCR-VB subsets indicative of SAg activity. We hypothesize systematic expansion in TCR-VB profiles in selective subsets identifying major targets of SAg activity.

METHODS

Whole-blood RNA from 128 PBC patients and 15 healthy controls was cloned into TruSeq Libraries and processed by Illumina HiSeq to generate 5GB of data per library. Percentage transcripts per million (TPM) within 50 TCR-VB subsets were analyzed. A criterion of 3 Stdev +/- mean expression in healthy was used to characterize normal TCR-VB range to highlight deviations.

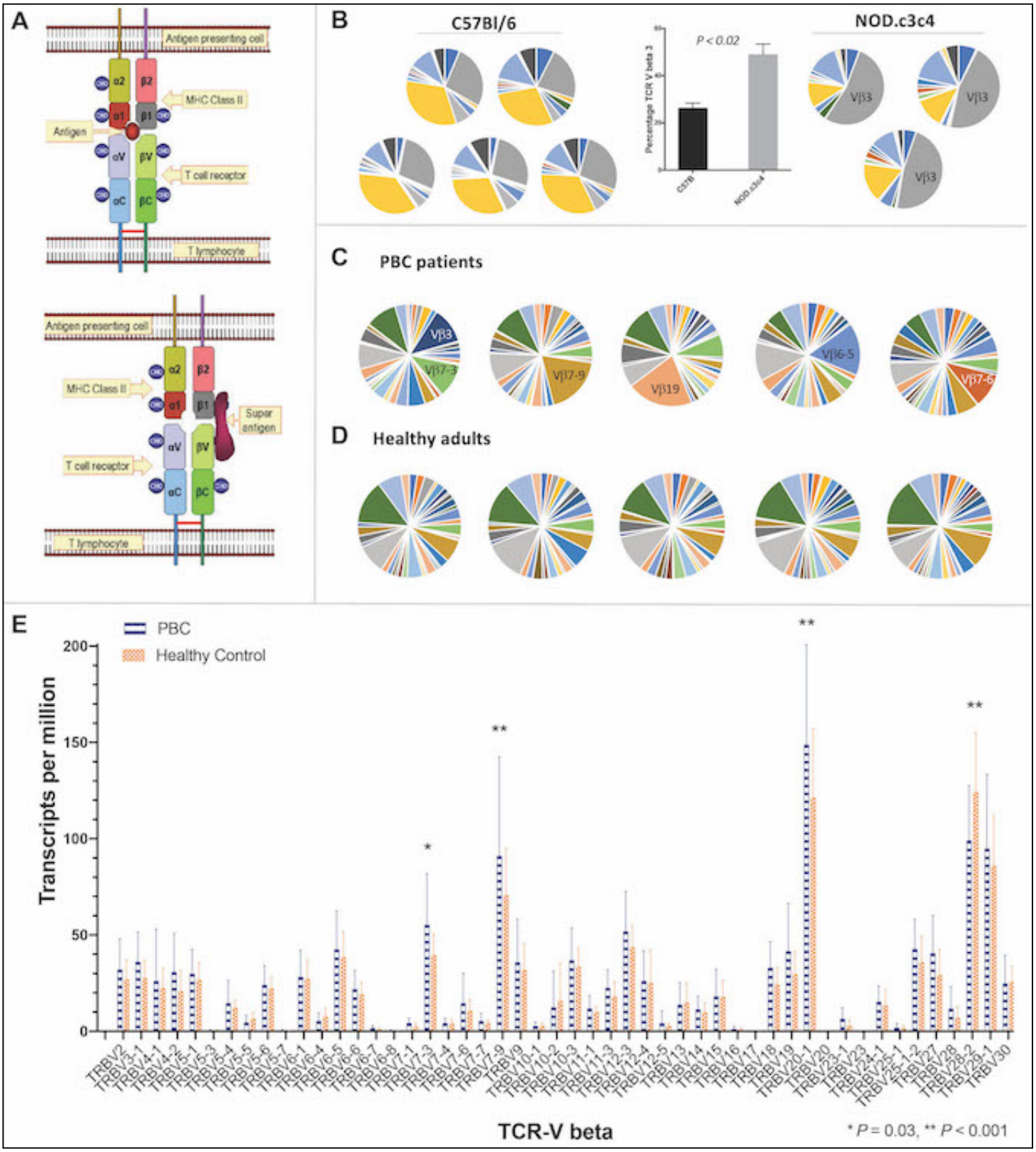
RESULTS

TCRVB7-3, VB7-9 and VB20-1 were significantly expanded ($p<0.001$) in mean PBC against control. 77% of PBC patients had VB expansion while 17% had depletions. VB7-3 was the most commonly expanded VB in PBC patients (20%), followed by VB5-7 (14%) and VB4-2 (13%). VB10-1 (9%) and VB30 (9%) were most commonly depleted. VB7-3 was most commonly clustered with VB12-5.

CONCLUSIONS

TCR-VB repertoire alteration consistent with SAg activity was observed in PBC patients. This allowed identification of TCR-VB subgroups targeted in PBC, of which VB7-3 appears to be most promising. VB7 has been highlighted in PBC patients in an independent study. Future directions involve the cloning of SAg sequences from patients with specific TCR-VB alteration to confirm specific SAg activity. This would allow improved therapeutic modalities targeting superantigen.

Supervisor: Dr. Andrew Mason


A
Antigen presenting cell
MHC Class II
Antigen
T cell receptor
T lymphocyte
Super antigen
B
C57Bl/6
NOD.c3c4
P < 0.02
Percentage TCR V beta 3
Vβ3
C
PBC patients
Vβ3
Vβ7-3
Vβ7-9
Vβ19
Vβ6-5
Vβ7-6
D
Healthy adults
E
PBC
Healthy Control
Transcripts per million
TCR-V beta
* P = 0.03, ** P < 0.001

Cost analysis of end of life care in idiopathic pulmonary fibrosis.

Kalluri M, Lu-Song J, Abdel-Basit A, Bakal JA, Sanjibad MN, Ohinmaa A, Nguyen T, Younus S, Richman-Eisenstat J

INTRODUCTION
Idiopathic pulmonary fibrosis (IPF) is a terminal disease, but palliative care is infrequently offered. This perpetuates high symptom burden and unmet care needs, triggering high healthcare resource utilization and associated costs. The cost of dying in Canada for IPF patients ranges from $2,000-$30,000. It is crucial to develop ambulatory care delivery systems that can integrate a palliative approach early in the disease trajectory to address these needs. In 2012 we implemented a Multidisciplinary Collaborative (MDC) care model by creating and linking clinic and community multidisciplinary teams. We adopted an early-integrated palliative approach, focusing on early symptom management and advanced care planning (ACP) from the first visit, with an aim to reduce acute care use and improve quality of care at end of life.

METHODS
Using AHS administrative data, we identified all patients in Alberta who presented to hospital with an IPF diagnosis between Jan 1, 2012 and Dec 31, 2016 and died within this timeframe. We compared the outcomes between 3 groups of patients: those who received 1. MDC care (our clinic patients), 2. specialist care (respirologist care), and 3. non-specialist care (no contact with respiratory clinic). The primary outcomes were healthcare resource utilization and costs in the period before death.

RESULTS
Of the 2838 patients across the three groups, MDC patients were more likely to die at home or in a palliative care facility (55% vs 33%) and 17% more likely to have palliative care at all. Total costs for MDC patients were ~27% lower than those receiving other types of care.

CONCLUSIONS
End of life costs in IPF associated with 3 different care models in Alberta between 2012 and 2016 were compared. A Multidisciplinary Collaborative care model with an early-integrated palliative approach was associated with reduced end of life costs, ICU time, and hospitalizations in our study.

Supervisor: Dr. Meena Kalluri

Acute Upper Gastrointestinal Bleeding: Evaluating Physician Practices in the Emergency Department

J. Stach, S. Sandha, M. Bullard, B. Halloran, H. Blain, G. Sandha, D. Grigat, E. Lang, S. Veldhuyzen Van Zanten

INTRODUCTION

Guidelines for blood transfusion in upper gastrointestinal bleeding (UGIB) recommend a hemoglobin (Hb) level of 70 g/L as a transfusion target. This study aims to determine the appropriateness of blood transfusions in a tertiary care ED for UGIB patients on the basis of expert opinion, and compare this to current guideline recommendations.

METHODS

We retrospectively reviewed 400 patients presenting with UGIB to the University of Alberta Hospital ED in 2016. These patients were screened for blood transfusions, and only those who received a blood transfusion are reported here. Data were obtained from the patient records. Chart derived data were verified with records obtained from the blood bank. For each patient, the history, vitals, Glasgow Blatchford Score (GBS), relevant labs, and record of blood transfusions were collected and organized into a case summary. Each patient summary was presented individually to a panel of three expert clinicians (2 Gastroenterology, 1 Emergency Medicine), who then decided on the appropriateness of each blood transfusion by consensus.

RESULTS

Blood transfusions (data available 395/400) were given to 51.1% (202/395) of patients presenting with UGIB. Of these, 86.1% (174/202) were judged to be appropriate. Details of the transfusion data are shown in Table 1.

Of all transfusions received by patients with a Hb > 70 g/L, 63.2% (48/76) were considered appropriate.

CONCLUSIONS

The panel of expert clinicians judged 86% of the blood transfusions to be appropriate. All transfusions under the recommended guideline of 70 g/L were considered appropriate. In addition, the majority of transfusions above Hb 70 g/L were considered appropriate, but 37% were not. Further studies evaluating the feasibility of current guideline recommendations in an ED setting are required. Educational interventions should be created to reduce inappropriate blood transfusions above Hb 70 g/L.

Supervisor: Dr. Sander Veldhuyzen Van Zanten

Table 1: **Blood transfusions (total number and appropriate) organized by hemoglobin level at time of transfusion.**

Hemoglobin Level (g/L)	# Total N=395	# Transfused N=202	# Appropriate if Transfused N=174
< 70	135 (34%)	126 (93%)	126 (100%)
71-80	70 (18%)	52 (74%)	41 (79%)
81-90	50 (13%)	14 (28%)	5 (36%)
> 90	140 (35%)	10 (7%)	2 (20%)

EMERGING THERAPEUTIC TARGETS FOR INFLAMMATORY BOWEL DISEASE-COLORECTAL CANCER: Case Study Analysis

Jimmy Yimeng Guo, Mohamed Salla, Hitesh Dooky, Leo Dieleman, Shairaz Baksh

INTRODUCTION

Persistent inflammation can trigger altered epigenetic, inflammation and bioenergetics states. Inflammatory bowel disease (IBD) is heterogeneous disease with an abnormal inflammatory state and subsequent metabolic syndrome disorder with abnormal leptin and alterations in the metabolic kinase, AMP-activated protein kinase (AMPK). Altered inflammation in IBD has been well studied and > 90% of current IBD therapeutics are directed to inhibiting altered inflammatory elements that drive inflammation of the epithelial cells of the colonic crypt. We hypothesize that to completely resolve mucosal inflammation we must (i) Inhibit inflammatory mediators (of which RIPK2 is a key player) and (ii) resolve secondary effects of inflammation such a reset of metabolic dysfunction (of which AMPK is key player). If these are not resolved in a timely manner, predisposition to the malignant state will occur. The aims of this study are to explore correlations between key inflammation/metabolic markers, clinical severity of disease and malignant transformation in 4 case study IBD-CRC patients to uncover emerging new therapeutic players.

METHODS

AMPK and RIPK2 activity will be tracked with phosphospecific antibodies. Immunohistochemistry and immunoblotting carried out as described by Gordon et al., PLOSone 2013. All patients have been consented under our IBD ethics protocol (Pro00001523 and Pro00077868).

RESULTS

Using longitudinal tissue sections from IBD-CRC case study patients, we explored the expression/activation levels of markers of epigenetic change (RASSF1A), inflammation (the obligate NOD2 kinase, RIPK2) and metabolism (AMPK) in order to gain insight into molecular drivers of disease. We confirm that the loss in the activity of AMPK and gain of activity of RIPK2 drives the inflammatory phenotype of the gut leading into the cancer state. Interestingly, active RIPK2 remains elevated in patients that were undergoing IBD therapeutics

CONCLUSIONS

Results suggest that directed therapeutics to RIPK2 may be a useful combination therapy to eliminate a robust driver of inflammation and malignant transformation.

Supervisor: Dr. Levinus Dieliman

AN ALTERNATIVE PROPHYLAXIS FOR DEEP VEIN THROMBOSIS USING INTERMITTENT ELECTRICAL STIMULATION

Kahir A. Rahemtulla, Dirk G. Everaert, Michel JA Gauthier, Vivian K. Mushahwar

INTRODUCTION

Deep vein thrombosis (DVT) affects approximately 45,000 Canadians annually. Of specific concern are immobilized patients who cannot use anti-coagulants because of bleeding risks or compression devices due to discomfort. Intermittent electrical stimulation (IES) may present an alternative intervention for prophylaxis by activating the calf-muscle pump to increase venous return and prevent stasis. The objective of this study was to determine the required stimulation intensity to increase venous velocity in typical and mobility impaired subjects.

METHODS

The study included three groups. The first group consisted of typical subjects (n=12). Testing was performed on the right leg, stimulating the gastrocnemius and the tibialis anterior muscles sequentially. Gastrocnemius stimulation intensity was modulated to produce gradual increases in force. Doppler ultrasound was used to measure the baseline (before stimulation) and peak (during stimulation) popliteal venous velocities. Isometric ankle forces were measured using a custom-built apparatus. The second group consisted of typical subjects (n=10); femoral vein velocity was measured in addition to the popliteal velocity. The third group consisted of in-patients, post-stroke who were relatively immobile (n=7); testing was performed on the more affected leg. Lastly, a questionnaire determined each subject's comfort level after each stimula-tion.

RESULTS

In the first and second groups, an 8-fold increase in peak popliteal venous velocity and a 4-fold increase in femoral venous velocity, respectively, was achieved at 20% MVC. The third group's preliminary results showed a 4-fold increase of popliteal venous velocity at 20% of the maximum contraction evoked during stimulation. The level of discomfort of the stimulation was rated "very little" to "moderate" in all subjects.

CONCLUSIONS

An increase in popliteal [for typical and immobile subjects] and femoral venous velocities [for typical subjects] was achieved at comfortable levels. Further research is required in acute care settings to further de-termine the feasibility of IES as a prophylactic method for DVT.

Supervisor: Dr. Vivian Mushahwar

Automated histology lesion interpretation in kidney transplant biopsies shows that pathologists often deviate from Banff

KS Madill-Thomsen, J Reeve, G Bohmig, A Perkowska-Ptasi?nska, F Eskandary, M Myslak, G Gupta, PF Halloran, and the INTERCOMEX Study Group

INTRODUCTION

Histologic diagnosis of kidney transplant biopsies requires an expert pathologist using Banff guidelines to interpret features. Some problematic guidelines require experts to use professional judgment. To explore variation (”noise”) in guideline applications, we created an “AutoBanff” algorithm that strictly applies Banff guidelines to recorded lesions.

METHODS

We studied 1679 prospective indication kidney transplant biopsies with lesion scores and clinical data (Clinical trials.gov #NCT01299168). An algorithm was developed using Banff guidelines, checked by expert pathologists, and the automated diagnoses compared to recorded histology (ExpertBanff) and molecular diagnoses (MMDx). Assigned diagnoses were based on a six-class model (antibody-mediated rejection ‘ABMR’, possible ABMR ‘pABMR’, T cell-mediated rejection ‘TCMR’, possible TCMR ‘pTCMR’, Mixed rejection, or No rejection ‘NR’). “Clear” discrepancies were between distinct classes (e.g. ABMR-NR), “boundary” discrepancies reflected ambiguity around boundaries (e.g. pABMR-ABMR).

RESULTS

AutoBanff diagnoses compared to ExpertBanff (Figure 1A) disagreed in 439 biopsies (26%). Discrepancies were more frequent in molecularly abnormal biopsies; biopsies with v-lesions>0; and biopsies with negative or ambiguous DSA or positive BK virus status. Clear discrepancies represented 46% of discrepancies. In 53 clear discrepancies experts diagnosed NR, while AutoBanff diagnosed 30 ABMR and 23 other. In 75 experts diagnosed as ABMR, AutoBanff diagnosed 59 NR and 16 other. The commonest clear discrepancy was NR vs. ABMR (89/202); the commonest boundary discrepancy was NR vs. pTCMR (82/237). Discrepancies were not limited to any specific histology diagnoses (Figure 1B). Of interest, ExpertBanff agreed more with MMDx than did AutoBanff (p=0.002), confirming that pathologists’ judgment added value.

CONCLUSIONS

Histology lesions can be interpreted by a computerized algorithm. The 26% discrepancy between AutoBanff and ExpertBanff reflects the intrinsic noise in histology, which is concentrated in certain scenarios - e.g. DSA negative ABMR, v-lesions, and BK nephropathy - that suggest areas for special focus in refining Banff guidelines.

Supervisor: Dr. Philip Halloran

A.

Table 1. 6 class agreement between AutoBanff and ExpertBanff in N=1679

		ExpertBanff diagnoses						
		ABMR	Mixed	NR	pABMR	pTCMR	TCMR	TOTAL
AutoBanff diagnoses	**ABMR**	213	4	25	10	2	2	**256**
	Mixed	6	23	3	0	0	5	**37**
	NR	33	2	767	32	5	1	**840**
	pABMR	71	2	49	36	19	9	**186**
	pTCMR	5	2	75	5	100	12	**199**
	TCMR	5	23	20	1	2	110	**161**
	TOTAL	**333**	**56**	**939**	**84**	**128**	**139**	**1679**

B.

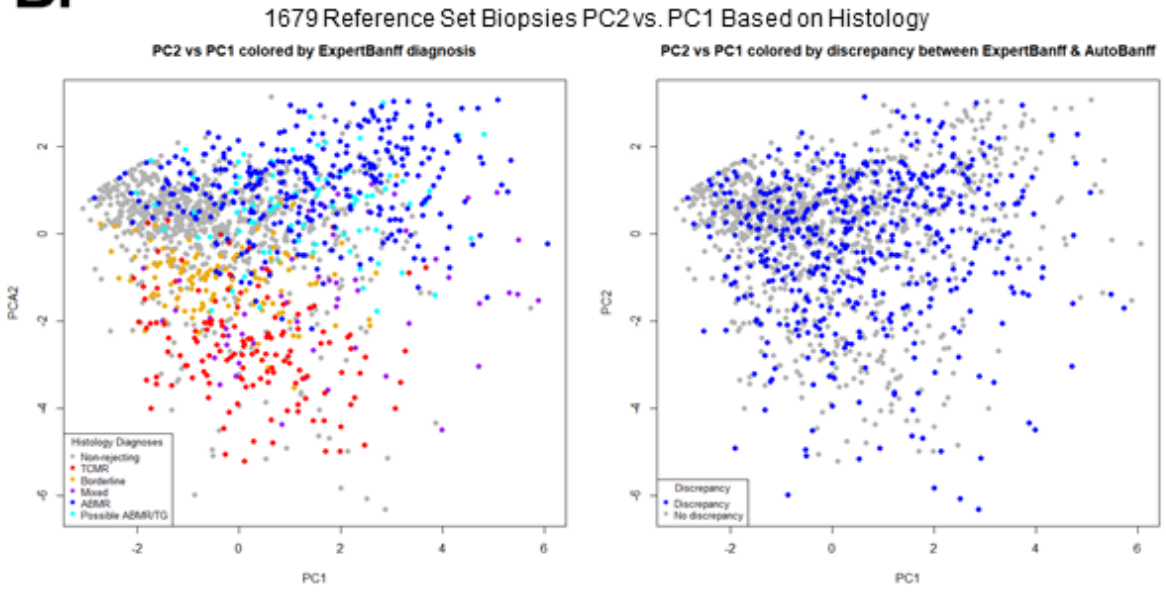


Figure 1. A) Agreement in 6 classes between AutoBanff and ExpertBanff in 1679 biopsies. Highlighted cells show the highest number in each row. B) Principal component analysis (PCA) based on histologic data showing 1679 biopsies colored by their ExpertBanff diagnosis (left), and colored by the presence (blue) or absence (grey) of a discrepancy (right).

Patient-Centered Decision-Making Algorithm for Deep Brain Stimulation Surgery in Parkinson's Disease

Kevin Yen, MD, Janis Miyasaki, MD, MEd, FRCPC, FAAN, Fang Ba, MD, PHD, FRCPC

INTRODUCTION

Deep brain stimulation (DBS) is an effective treatment for several cardinal motor symptoms and motor complications in Parkinson's Disease (PD), but less effective for axial and non-motor symptoms (NMS). Clinicians usually focus on motor symptoms without incorporating patient perspectives and expectations when selecting DBS candidates. Therefore, we developed a patient-centered decision-making application that allows patients to incorporate their perspective into the decision-making process.

METHODS

We recruited 62 PD patients referred for DBS assessment. We introduced them to an app that allowed them to select individual PD symptoms and learn about the likelihood of target symptom improvement. A pre- and post-application questionnaire was used to assess their knowledge of DBS. Patients who proceeded with further assessment and completed DBS surgery are given a follow up questionnaire to assess their symptom improvement, patient satisfaction, goal attainment, and quality of life improvement.

RESULTS

Most bothersome motor symptoms were tremor (58%), dyskinesia (52%), stiffness (45%), and motor fluctuations (42%); and NMS were fatigue (47%), anxiety (44%), constipation (26%), and depression (23%). All patients found the application helpful as an educational tool. Patients had good knowledge of motor symptoms that respond to DBS prior to the application and had improved understanding of symptoms that don't respond to DBS after the application [figure 1A]. Assessment of patient 6 months post DBS showed that there was good goal attainment and patient satisfaction [figure 1B] and still found the application to be helpful [figure 1C].

CONCLUSIONS

To our knowledge, this is the first patient-centered decision-making tool for PD patients going through DBS assessment. Our results showed that patients using the application had improved knowledge and expectations of DBS outcomes. This application acts as an educational tool for all PD patients and allows them to incorporate their perspective into medical decision making to assist with goal attainment.

Supervisor: Dr. Fang Ba

Figure 1A: Direction of improvement in understanding of symptoms response to DBS

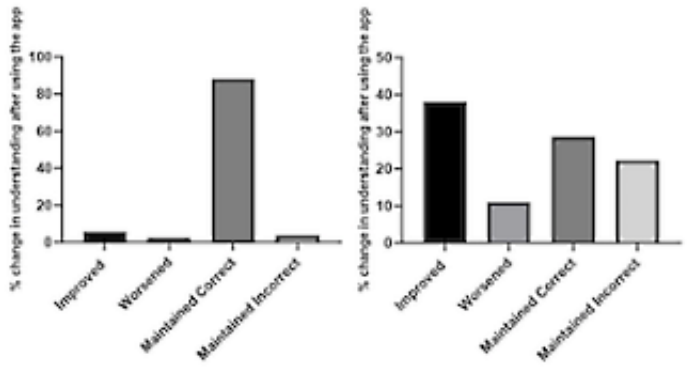
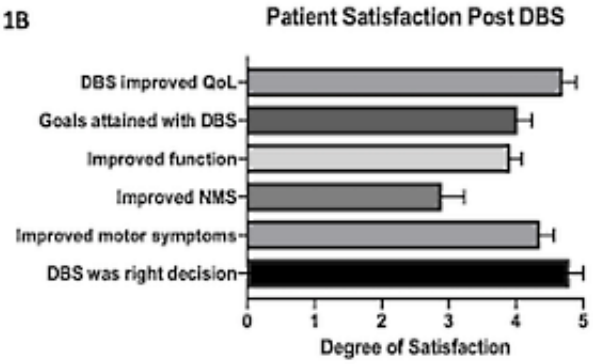
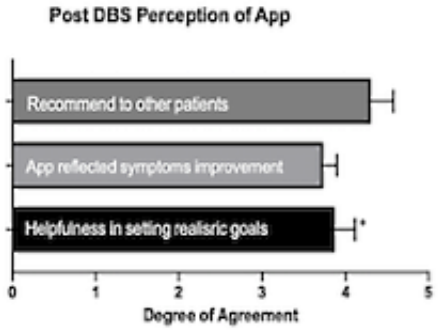


Figure 1B/C: Assessment of patient report 6 months post DBS surgery

1B



1C



German Cockroach Extract Proteolytic Activity Down-regulates Interleukin-13 Dependent Eotaxin-3 (CCL26) Expression in Airway Epithelial Cells

Khadija Alzahrani, Vivek Gandhi, Cheryl Laratta, and Harissios Vliagoftis

INTRODUCTION

Airway epithelium is the first barrier between the host and inhaled allergens. Airway epithelium recognize and interact with inhaled allergens, which result in activation of innate and adaptive immunity. IL-13 is a Th2 cytokine that among other functions in asthma it also promotes the expression of Eotaxin-3 (CCL26), a potent eosinophil chemoattractant, from the airway epithelium. In our laboratory we are interested to better understand the pro-inflammatory effects of cockroach allergens, allergens associated with asthma severity in many studies. Since both cockroach allergens and IL-13 mediate some of their effects through activation of the airway epithelium we studied the interactions between these two triggers.

METHODS

A human bronchial epithelial cell line (BEAS-2B) and primary cultures of normal human bronchial epithelial cells (NHBE) were cultured in pre-coated multi-well plates and stimulated with IL-13, cockroach extract (CE) or both. CCL26 mRNA was measured by qRT-PCR and the release of CCL26 protein by ELISA. To test the role of CE proteases in the described affect, heat inactivated CE (HICE), boiled CE or CE pre-incubated with protease inhibitors were used. Western blotting used to assess STAT-6 phosphorylation and IL-13 protein degradation.

RESULTS

CE prevented IL-13-induced CCL26 mRNA and protein expression from
BEAS-2B and NHBE cells. HICE and CE pre-incubated with serine protease inhibitors, aprotinin and soy bean trypsin inhibitor (SBTI), did not inhibit IL-13 induced CCL26 mRNA expression. CE did not significantly inhibit IL-13 induced STAT-6 phosphorylation. Western blot detected early and progressive degradation of IL-13 protein by CE.

CONCLUSIONS

CE inhibited IL-13 induced CCL26 expression. This inhibitory effect is dependent on CE proteases, particularly proteases with trypsin like activity. Degradation of IL-13 by CE proteases and depletion of CCL26 expression could be a mechanism of CE allergens to attenuate or alter Th2 mediated inflammation in allergic asthma.

Supervisor: Dr. Harissios Vliagoftis

A Multidimensional Dyspnea Scale To Characterize Episodic Breathlessness In Interstitial Lung Disease.

Laura van den Bosch, Janice Richman-Eisenstat, Meena Kalluri

INTRODUCTION

Breathlessness in interstitial lung disease (ILD) impairs quality of life and is frequently under-recognized and under-treated. Episodic breathlessness (EB) was recently defined as a “time-limited, severe worsening of intensity or unpleasantness of breathlessness in the patient’s perception” which is predictable or unpredictable (Simon et al., 2014). EB prevalence has not been described in ILD. No published clinical scales characterize EB. Multidimensional dyspnea scale (MDDS) is a rest- and activity-based scale for breathlessness profiling in ILD and used as a clinical decision tool for dyspnea management. Previous work showed it facilitates early recognition and treatment of dyspnea, demonstrating clinical utility. We describe EB in ILD using MDDS.

METHODS

This is a retrospective study of deceased ILD patients from our multidisciplinary ILD clinic 2012-2018. Baseline MDDS (linear scale: 0 = no dyspnea and 10 = worst dyspnea) plus other variables (age, gender, diagnosis, comorbidities, pulmonary function tests, 6-minute walk distance (6MWD) and baseline MRC grade) were extracted and analyzed. EB was defined as MDDS >=7/10 with any activity.

RESULTS

Forty-one patients were identified. Median age was 75 years; 61% male; 27 with idiopathic pulmonary fibrosis (IPF); 14 with other ILD. Reported comorbidities included: COPD 17%; Pulmonary Hypertension 25%; Cardiac Disease 39%; Anxiety 5% & Depression 20%. Median 6MWD was 229 meters (n=27); median FVC % predicted was 64% (n=32) and median % predicted DLCO Adj Hb was 42% (n=21). Median MRC was 4; median MDDS score was 1 with rest, 4 with low intensity activity and 7 with higher intensity activity. EB triggered by one or more activities was reported by 26 patients (63%); 5 (12%) reported unpredictable EB.

CONCLUSIONS

EB is prevalent in ILD and should be included in routine dyspnea assessment. MDDS helps identify EB and characterize dyspnea severity. MDDS may improve ILD symptom control by guiding management strategies (eg. rapid-acting opioids).

Supervisor: Dr. Meena Kalluri

Rapid leaflet expansion is the main adaptive change to maintain tricuspid valve (TV) competency from detrimental remodeling: a three-dimensional echocardiography (3DE) study in a novel chronic right ventricular (RV) pressure and volume loaded piglet model

Lily Lin, Sanaz Hatami, Darren Freed, James Yashu Coe, Timothy Colen, Consolato Sergi, Richard Thompson, Elena Di Martino, Walter Herzog, Ziad Abu Sara, Nee Scze Khoo

INTRODUCTION

Tricuspid valve (TV) regurgitation develops in 25-35% of children with hypoplastic left heart syndrome (HLHS), a risk factor for morbidity and mortality. We developed a novel piglet model simulating infant HLHS RV physiology to study TV adaptation to chronic increased preload and afterload. We hypothesize that TV competency is maintained by adaptive rapid leaflet expansion despite annular dilation.

METHODS

Sixteen piglets at 4-5weeks of age (maturity equivalent to infants) underwent left thoracotomy. Intervention piglets (IP, n=8) had their pulmonary valve torn to produce moderate to severe pulmonary regurgitation (volume loading) and pulmonary artery band placed to increase RV pressure. Control piglets (CP, n=8), age and gender matched, had sham surgery. Following a 4-week recovery, all piglets underwent hemodynamic assessment and 3DE of TV. We assessed TV annulus and leaflet geometry in mid-systole using a custom 3DE software (MATLAB). Ex-vivo TV total leaflet area was measured. Comparisons between IP and CP were made using Student t-test with significance at $p<0.05$. Values were expressed as mean (standard deviation).

RESULTS

IP had significant pulmonary regurgitation (mean PR reverse/forward VTI ratio 0.68) and mean RV systolic pressure 77.9% of systemic pressure, reflected in thicker RV free wall and anterior papillary muscle, consistent with an effective model. IP and CP are similar in weight and TR grade. IP TV annulus were larger ($p=0.02$), more circular ($p=0.03$) and leaflets more tethered ($p=0.02$) with 43% larger total leaflet area ($p=0.01$) [Table]. 3DE TV total leaflet area correlated with ex-vivo TV pathologic specimen area ($r=0.63$, $p=0.02$).

CONCLUSIONS

Following chronic exposure to increased RV preload and afterload, there is TV annular dilation and likely unchanged sub-valve apparatus, resulting in leaflet tethering. In-vivo 3DE identified rapid leaflet expansion as the main adaptive change to maintain competency from detrimental remodeling. Further research into modulation of TV leaflet growth may be important for understanding TV failure in HLHS.

Supervisor: Dr. Nee Khoo, Dr. Darren Freed, Dr. Evangelos Michelakis

Table: Comparisons of hemodynamic and echocardiographic parameters between intervention and control piglet groups. Values expressed as mean (standard deviation). Student t-test p-values reported. NS denotes non-significance.

Parameter	Control Piglets (n=8)	Intervention Piglets (n=8)	P-value
Weight (kg)	31.2 (5.8)	31.4 (6.1)	NS
RV systolic pressure/arterial systolic pressure (%)	30.3 (3.8)	77.9 (36.4)	0.003
Pulmonary regurgitation grade (0-4)	1.0 (0.5)	3.6 (0.4)	<0.0001
Tricuspid regurgitation grade (0-4)	1.9 (0.4)	2.4 (0.9)	NS
RV wall thickness (mm)	4.5 (0.9)	9.4 (1.2)	<0.0001
Anterior Papillary Muscle Cross-sectional Area (cm2)	0.4 (0.08)	1.0 (0.3)	0.0003
TV Annulus Width/Anteroposterior dimension ratio	0.8 (0.09)	1.0 (0.2)	0.03
TV Annulus Total Area (cm2)	6.2 (1.3)	8.3 (1.7)	0.02
TV leaflet area (cm2) measured on pathology in relaxed state	11.0 (2.2)	12.1 (2.9)	NS
TV Leaflet Total Area (cm2) at mid systole	7.0 (1.5)	10.1 (2.4)	0.01
TV Leaflet Area Posterior Leaflet (cm2)	1.8 (0.6)	3.3 (1.2)	0.009
TV Total Tethering volume (ml)	1.1 (0.5)	2.6 (1.4)	0.02
TV Posterior Leaflet Tethering volume (ml)	0.2 (0.1)	0.8 (0.5)	0.01

Serial fecal microbiota transplant plus fidaxomicin in treating severe or fulminant Clostridioides difficile infection

Lindsey Russell, Karen Wong, Christine Lee, Thomas Louie, Haili Wang, Lynora Saxinger, Wendy Sligl, Ryan Snelgrove, Tanya Monaghan, Gane Wong, Jens Walter, Julian Marchesi, and Dina Kao

INTRODUCTION
Current treatment for severe or fulminant CDI (SFCDI) consists of metronidazole plus vancomycin. Surgery is required in cases refractory to medical therapy. Despite these interventions, morbidity and mortality rates remain high. Sequential fecal microbiota transplantation (FMT) by colonoscopy combined with vancomycin has a high success rate of resolving SFCDI. However, colonoscopy is an invasive procedure, and vancomycin is not an FMT preserving antibiotic. Although fidaxomicin is a C diff specific antibiotic, it has not been used in SFCDI. In this prospective, open-label study, we aim to determine the efficacy and safety of using serial FMTs by enema plus fidaxomicin to treat SFCDI patients refractory to maximal medical therapy.

METHODS
Eligible SFCDI patients received treatment cycles, each consisting of 3 consecutive days of FMT by enema, with concurrent fidaxomicin for 7-10 days until resolution of diarrhea and/or normalization of inflammatory markers. Longitudinal blood and stool samples were collected before and after each treatment cycle. The primary outcome was CDI resolution 2 weeks after final FMT. Secondary outcomes were 1)sustained CDI resolution, defined as lack of recurrence 8 weeks after the last FMT, 2)frequency of serious adverse events including colonic perforation, recurrent hospitalization, infection related to FMT, and mortality, and 3)colectomy rate. Exploratory outcomes included stool metabolomics, stool microbial composition, and host immunophenotypic profiling.

RESULTS
Following 3 treatment cycles, one participant reached primary outcome. A second participant, despite 2 treatment cycles, developed CDI recurrence 12 days post final FMT requiring additional 4 FMTs outside the study protocol. No serious adverse events were observed. Colectomy rate was 0. Results from mechanistic studies are pending. Participant recruitment is ongoing.

CONCLUSIONS
Preliminary clinical results suggest intensive FMT combined with fidaxomicin may be safe and effective in treating severe or fulminant CDI refractory to standard medical therapy, and may be a better alternative to surgery.

Supervisor: Dr. Dina Kao

A Novel 3-Dimentional technique in Measuring pericoronary epicardial adipose tissue radiodensity

Lingyu Xu; Stanislau Hrybouski; Yuancheng Xu; Richard Coulden, Emer Sonnex , Ian Paterson, Craig Butler

INTRODUCTION

Pericoronary epicardial adipose tissue radiodensity (PCATrd) is of emerging interest as a risk factor for coronary artery disease (CAD), but can be difficult to measure. This study aims to investigate a novel semi automated three-dimensional quantification of PCATrd.

METHODS

Fifty-five patients with suspected CAD were retrospectively identified. PCATrd was measured in contrast CT dataset using image analysis software (ITK-SNAP, Version 3.6.0). We applied a thresholding map, using in-house MatLab code with range of (-190,-3) Hounsfield unit derived from previous work, to the contrast CT dataset. The cursor was probed in the center of the short axis of the coronary arteries in the coronal, sagittal and axial images simultaneously. Then the 3D round brush segmented the epicardial adipose tissue with the orthogonal distance from the coronary vessel wall equal to the coronary radius and, the segmentation followed the path of 4 major coronary arteries from proximal to the distal terminal (Figure 1 A & B). The PCATrd of each coronary artery was automatically computed. We compared this 3-D segmenting method (3D_PCATrd) with a 7-segment segmentation method (7S_PCATrd) published by the Society of Cardiovascular Computed Tomography. We further compared both PCATrd estimates with coronary artery disease severity (non-obstructive, obstructive and extensive obstructive) by using ordered logistic regression.

RESULTS

The 3D_PCATrd was substantially different from the 7S_PCATrd in the general_PCATrd, LM, LAD and RCA, but similar in LCX (Table 1 & Figure 1C). Standard deviations around 3D_PCATrd estimates were significantly smaller than estimates from 7S_PCATrd. The 3D_PCATrd, but not 7S_PCATrd, was independently associated with severity of coronary lesions (multivariable odds ratio 0.86 for per 1 HU increase, p=0.017).

CONCLUSIONS

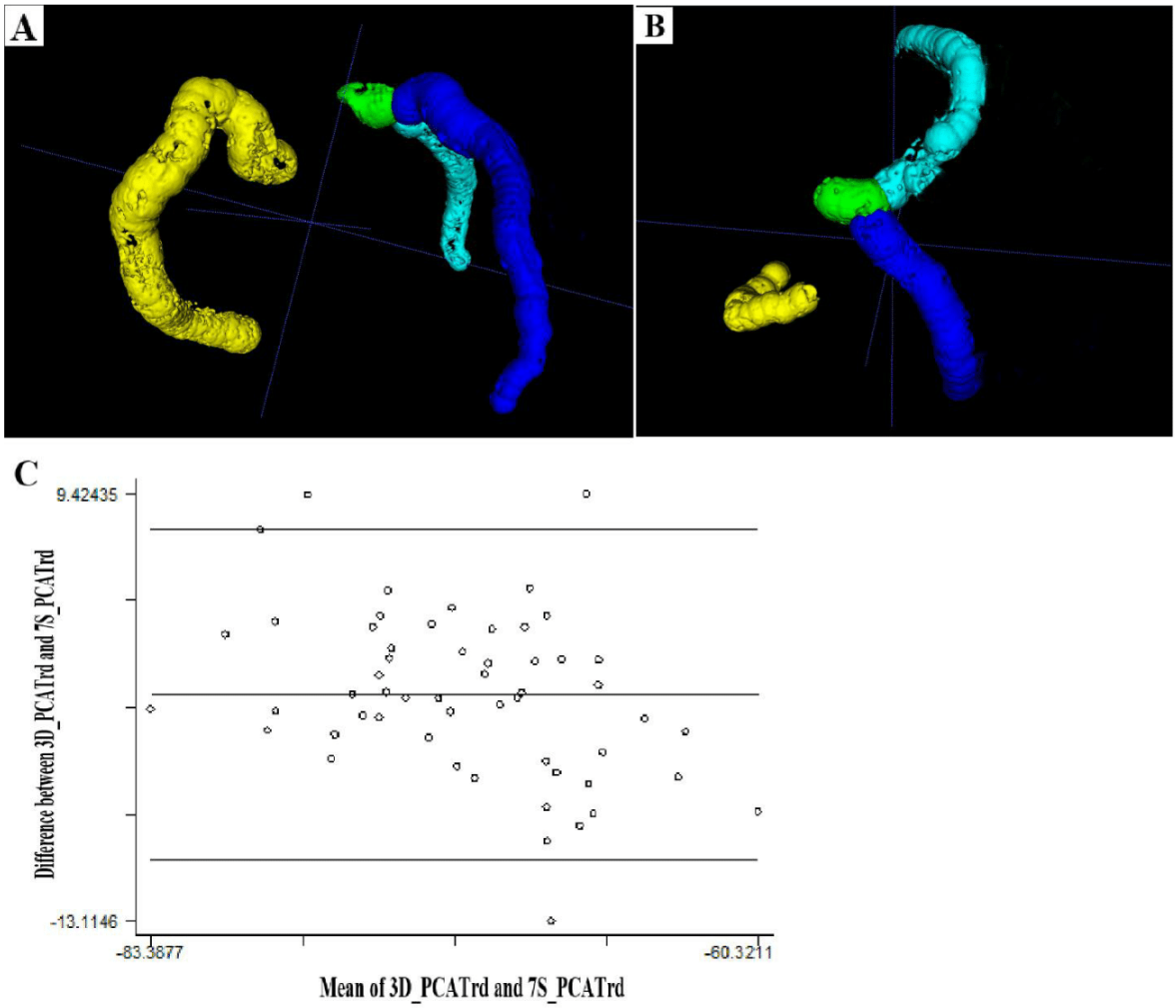
Our novel 3-dimension quantified PCATrd technique produced estimates that were significantly different than estimates derived from the SCCT published technique, was more precise than the 7-segment quantified PCATrd and was better associated with coronary artery disease severity.

Supervisor: Dr. Ian Paterson

Table 1. Comparison of 7 segments-derived pericoronary EAT radiodensity vs. 3-D EAT radiodensity

	7S_PCATrd (n=55)	3D_PCATrd (n=55)	p-value	Correlation: 7S_PCATrd vs.3D_PCATrd
LM	-68.8±10.2	-64.5±9.1	0.0002	R^2=0.43,P<0.001
LAD	-72.4±8.3	-74.5±5.6	0.0126	R^2=0.45,P<0.001
RCA	-74.2±7.2	-72.7±5.0	0.0397	R^2=0.43,P<0.001
LCX	-68.1±8.7	-66.5±5.5	0.1149	R^2=0.27,P<0.001
General	-70.8±5.9	-72.0±4.5	0.0595	R^2=0.45,P<0.001

Figure 1 A & B: Three-dimensional measurement of pericoronary epicardial adipose tissue radiodensity (3D_PCATrd) of the four major coronary arteries (LM: Green; LAD: Blue; LCX: light blue; RCA: yellow);



Cardiac remodeling predicts outcome for patients with stable heart failure: a serial cardiac magnetic resonance imaging study

Xu L; Ezekowitz J; Oudit, G; Dyck J; Haykowsky, M; Pagano J; Anderson T; White J A; Thompson R; Chow K; Paterson I; Alberta HEART Investigators.

INTRODUCTION

Cardiac remodeling is an alteration in geometry and/or function and is a predictor of clinical outcomes for patients with cardiovascular disease. To date no studies have performed serial cardiac measures in patients with stable heart failure (HF). We hypothesized that: 1) patterns of remodeling differ according to HF subgroups and 2) cardiac remodeling predicts clinical outcomes in patients with stable HF.

METHODS

Ambulatory patients from a prospective cohort of patients with stable HF underwent a clinical assessment and cardiac MRI at baseline and 1 year. Ventricular function, volume, mass, left atrial volume, global longitudinal and circumferential strain (GLS, GCS), and myocardial scar were derived. Clinical outcomes were obtained from electronic chart review. The primary outcome was a composite of death, cardiovascular admission or emergency room visit up to 4 years from the 1-year scan.

RESULTS

Data was available for 262 patients (median age 68 years, 57.3% males) including 96 at risk for HF, 97 with HF and preserved ejection fraction (HFpEF, LVEF≥50%) and 69 with HF and reduced EF (HFrEF, LVEF<50%). At 1 year, patients with HFpEF had worsening GLS and marginally increased LVmassi, but stable myocardial scar compared to baseline. Comparatively, patients with HFrEF had improved ventricular function, but increased myocardial scar (Table 1). After 4-year follow-up, 86 events occurred. Kaplan-Meier analysis showed patients with reverse remodeling (%ΔLVmassi >-14%) had better outcomes than patients with adverse remodeling (%ΔLVmassi >+14%) and patients without remodeling (Figure 1). Cox proportional hazard regression showed that a change in LVmassi, GLS and myocardial scar mass were independently associated with outcome after adjustment for clinical risk factors.

CONCLUSIONS

Patients with HFpEF experience interval adverse changes in cardiac structure and function while patients with HFrEF have improvement in both parameters. Cardiac remodeling measured as a change in indexed LV mass strongly predicts long-term outcomes in patients with compensated HF.

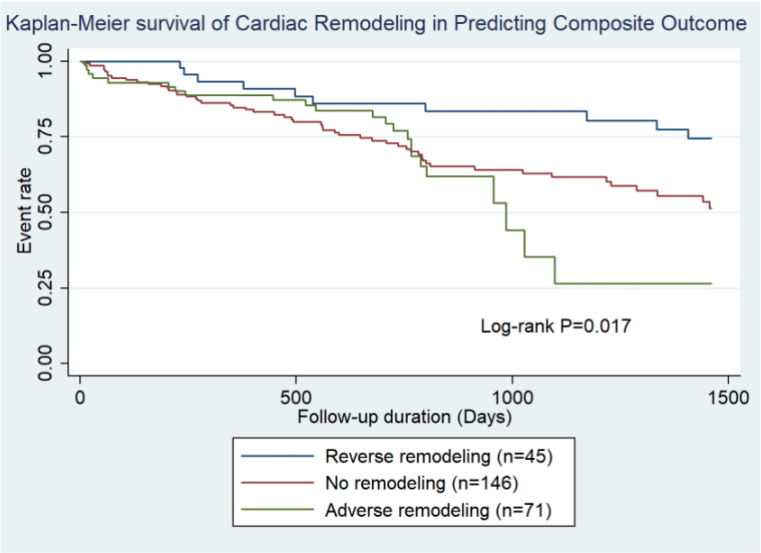
Supervisor: Dr. Ian Paterson

Table 1. Comparison of baseline and 1-year cardiac MRI measurements in 3 groups of patients

Variable	At risk (Baseline)	At risk (1 year)	P-value (At risk)	HFpEF (Baseline)	HFpEF (1 year)	P-value (HFpEF)	HFrEF (Baseline)	HFrEF (1 year)	P-value (HFrEF)
LVEF,%	64(59,70)	65(60,70)	0.080	61(55,65)	62(55,67)	0.43	42(35,45)	46(39,51)	<0.001*
LVEDVi, ml/m^2	65(58,78)	68(56,77)	0.27	66(58,77)	67(56,77)	0.37	98(79,116)	87(72,111)	0.069
LVESVi, ml/m^2	24(18,31)	23(18,29)	0.059	26(20,32)	25(19,32)	0.11	55(44,72)	45(38,63)	<0.001*
LVMassi, g/m^2	54(45,69)	56(48,64)	0.32	56(48,67)	58(50,70)	0.051	73(61,82)	70(57,82)	0.092
RVEF	60(55,66)	60(54,66)	0.76	57(51,62)	57(50,65)	0.29	52(45,57)	53(45,57)	0.72
RVEDVi, ml/m^2	69(55,76)	62(53,71)	<0.001*	64(53,77)	62(50,75)	0.009*	73(64,92)	72(54,84)	0.005*
RVESVi, ml/m^2	26(20,33)	25(19,31)	0.002*	28(22,35)	26(20,35)	0.012*	33(27,43)	33(25,40)	0.12
LAVi, ml/m^2	37(29,48)	40(28,48)	0.99	51(36,71)	51(38,66)	0.35	53(43,63)	52(49,62)	0.44
GLS,%	20.5±3.7	20.4±3.1	0.61	19.6±3.9	18.8±4.0	0.037*	12.3±3.3	13.9±4.0	<0.001*
GCS,%	30.0±5.6	29.6±5.7	0.50	28.7±5.6	28.1±6.5	0.33	16.2±4.8	17.7±5.3	0.012*
Scar mass,g	0(0,0)	0(0,0)	0.65	0(0,5.8)	0(0,6.1)	0.44	7.0(0,24.2)	8.8(0,25)	0.002*
Scar, %	0(0,0)	0(0,0)	0.36	0(0,5.3)	0(0,5.6)	0.89	6(0,16.2)	6.8(0,16)	0.012*

Continuous variables are expressed as mean±SD or median (interquartile range), as appropriate. P-values derived using paired t-test (or Wilcoxon signed-rank test), as appropriate. * $p < 0.05$ for comparison of baseline and 1 year measurements.

Figure 1. Kaplan-Meier analysis of cardiac remodeling in predicting outcome



Reverse remodeling = %ΔLVmassi >-14%, Adverse remodeling= %ΔLVmassi >+14%, No remodeling = %ΔLVmassi ≤ ±14%.
Outcome: death, cardiovascular admission or emergency room visit up to 4 years from the 1-year scan.

Combination of siRNA and Chemotherapeutic Agents in Acute Leukemic Cells

Mahsa Mohseni, Cezary Kucharski, Remant Bahadur KC, Hasan Uludag, Joseph Brandwein

INTRODUCTION

The combination of small interfering RNA (siRNA) therapy and the most common chemotherapeutics used for acute lymphoblastic leukemia (ALL) could improve treatment outcomes of current therapies by targeting oncogenic mechanisms1, 2, 3. Transcription factors including Signal Transducer and Activator of Transcription (STAT)- protein family members are key molecular targets for ALL, since they can activate expression of oncogenes leading to aberrant proliferation of cancer cells1. In hematological malignancies, downregulation of STAT5 can decrease proliferation of leukemia cells1, 2, 4. However, an effective siRNA therapy requires efficient delivery systems since polynucleotides are highly unstable in serum, and their anionic nature prevents them from traversing cellular membranes4. In this study, we evaluated therapeutic role of STAT5 inhibition by polymeric siRNA delivery systems in combination with drugs in ALL cell lines.

METHODS

Acute lymphocytic RS4; 11 and SUP-B15 leukemia cells were used. Lipid-modified low molecular weight polyethyleneimine (PEI) polymers were used as siRNA carriers. Doxorubicine, dexamethasone and vincristine were used as chemotherapeutics. Cell proliferation was assessed by MTT assay, Cellular uptake by Flow Cytometry and STAT5 knockdown at mRNA level by RT-qPCR.

RESULTS

Specific lipid substituted 0.6 and 1.2 kDa PEI (0.6PEI and 1.2PEI) displayed excellent complexation properties with siRNAs to form nanoparticles and gave high siRNA uptake in cells with negligible toxicity. STAT5 gene expression was downregulated (32%) in RS4; 11 cells using 1.2PEI-lipid polymer. In addition, siRNA complexes in combination with vincristine (10 nM) resulted in a significant growth inhibition in RS4;11 cells.

CONCLUSIONS

We demonstrated effective delivery of STAT5 siRNA by polymeric nanoparticles into leukemia cells, accompanied by marked inhibition of STAT5 gene. Cell growth was reduced significantly by combinational strategies involving drug-siRNA combinations. Further experiments will be directed at evaluating STAT5 protein silencing by siRNA therapy and exploring the effect of STAT5 downregulation on leukemic patient samples.

Supervisor: Dr. Joseph Brandwein

Understanding neuroendocrine tumour patient treatment preferences using discrete choice experiments

Anaka, M., Chan, D., Pattison, S., Thawer, A., Segelov, E., Singh, S.

INTRODUCTION
Neuroendocrine tumours (NETs) are a diverse group of rare malignancies, with significant heterogeneity in terms of prognosis, symptom burden, and impact on quality of life. There is little published information on NET patient preferences and priorities in regards to medical management. As patient-centered care increasingly becomes a focus in oncology, it is important to understand the perspectives and values of the NET patient population.

METHODS
We designed three discrete choice experiments using the 1000minds platform, which model clinical scenarios where NET patients have several treatment options. Data from the randomized clinical trials that support the use of different medical treatments for NETs was used to generate the DCE content. The DCEs were trialled in a pilot study as a test for technical issues and face validity.

RESULTS
Five NET patients completed the pilot study, which included all three DCEs in sequence. Based on semi-structured interviews, the DCEs achieved face validity, as they included treatment attributes identified as important by the participants. Participants expressed concern with the length of the DCEs, and on apparent redundancy of the choices between the clinical scenarios. The participant-level partial worth utility data revealed variable willingness to trade off factors like progression free survival (PFS) for side effects rates and method of treatment administration.

CONCLUSIONS
We developed and piloted a series of DCEs that model preferences for NET treatment. Preliminary results indicate that patients place variable importance on factors like PFS, adverse event profiles, and method of treatment administration. The DCEs are currently being refined based on feedback from the pilot study.

Supervisor: Dr Simron Singh (University of Toronto)

Goals of care designation associated with improved survival and indicators of quality end-of-life care in pancreatic cancer (PC) patients (pts) undergoing palliative chemotherapy

Anaka, M; Lee, M; Ghosh, S; Cheung, W; Spratlin, J

INTRODUCTION
Discussion of goals of care (GoC) is a key part of quality care for pts with palliative cancer. Numerous studies have shown that documentation of GoC in this population remains low. Here we describe changes in GoC documentation and other indicators of quality end-of-life care in PC pts undergoing palliative chemotherapy during a health-system wide initiative to improve advanced care planning (ACP).

METHODS
This is a retrospective cohort analysis of 106 pts with locally advanced or metastatic PC treated with palliative chemotherapy from 2012-2015 in Northern Alberta (Canada). In 2014, an initiative was launched to provide pts with hard copies of their GoC designation intended to be available at all health-system interactions. Data were obtained from outpatient medical oncology (MO) and palliative care (PAL) notes and the provincial cancer registry. Survival analysis used a multivariate Cox-regression. All other tests were Chi-squared.

RESULTS
50% (53/106) of pts had a documented GoC discussion, with 45% (48/106) receiving a specific GoC designation. In 2012, 31% (6/19) of pts had a GoC designation, which increased to 61% (20/33) in 2015. Of 84 individual GoC discussions documented, 34% (29/84) were by MO, 62% (52/84) were by PAL, and at least 8% (7/84) referenced prior discussions with a family physician or discussion while admitted to hospital. Pts with a GoC designation had increased median overall survival (287 vs 216 days; HR=0.62; p=0.041), and were less likely to receive chemotherapy in the last two weeks of life (p=0.016).

CONCLUSIONS
Rates of GoC discussions for PC pts undergoing palliative chemotherapy increased during a health-system wide ACP initiative. Having a GoC designation was associated with greater overall survival and indicators of higher quality end-of-life care.

Supervisor: Dr Jennifer Spratlin

The role of growth factor deprivation in PAR-2 regulation and autophagy induction in the airway epithelium

Nadia Daniel, Vivek Gandhi and Harissios Vliagoftis

INTRODUCTION

Asthma is an inflammatory disease of the airways that affects over 3 million Canadians. Autophagy is a key cellular response to nutrient withdrawal. Information on the role of autophagy in asthma is confusing with evidence both for a protective and a detrimental role. Proteinase-activated-receptor-2 (PAR-2) is a pro-inflammatory receptor implicated in asthma pathogenesis and has been associated with reducing the harmful effects of autophagy in the epithelium. However, we know little regarding the role of autophagy in airway epithelial cell (AEC) biology. Our preliminary data indicate that PAR-2 expression in AECs was upregulated when the cells were deprived of certain growth factors. We hypothesize that growth factor deprivation-induced PAR-2 upregulation, is a mechanism to limit the effects of autophagy that develops under the same conditions.

METHODS

Primary human AECs and the human AEC line BEAS-2B were cultured in serum free media with or without media supplements. As a positive control for autophagy induction, AECs were treated with Rapamycin. The autophagosomal marker LC3-II was detected by western blot to monitor autophagy activity. PAR-2 mRNA expression was studied by real time PCR.

RESULTS

Supplement deprivation induced autophagy in AECs within 24 hours but did not affect cell survival (there was no induction or apoptosis or cell death). Supplement deprivation also upregulated PAR-2 mRNA expression with similar time course.

CONCLUSIONS

Lack of growth factors induced both PAR-2 expression and autophagy in AECs, but we do not understand what the link between these two effects is. We will study the signalling pathways leading to PAR-2 upregulation and autophagy induction to understand whether they are functionally related. We will also activate PAR-2 in cells after autophagy induction to study whether PAR-2 activation can limit the effects of autophagy. This work will improve our understanding of the role of autophagy in asthma.

Supervisor: Dr. Harissios Vliagoftis

External validation of the H2F-PEF model in diagnosing patients with heart failure and preserved ejection fraction

Nariman Sepehrvand, Wendimagegn Alemayehu, Garrison J. B. Dyck, Jason R. B. Dyck, Todd Anderson, Jonathan Howlett, Ian Paterson, Finlay A. McAlister, Justin A. Ezekowitz, on behalf of the Alberta HEART Investigators

INTRODUCTION

Patients with heart failure (HF) and preserved ejection fraction (EF) (HFpEF) are at risk of misdiagnosis due to the lack of a single clear defining feature, leading to additional testing and clinical uncertainty. The aim of this study was to investigate the performance of a recent diagnostic model (H2FPEF) in identifying patients with HFpEF using Alberta HEART cohort.

METHODS

Patients with an adjudicated diagnosis of HFpEF in Alberta HEART cohort were defined as HFpEF and other groups including asymptomatic patients at-risk for HF, symptomatic patients at-risk for HF, HF with reduced EF, and healthy controls were pooled as “not-HFpEF”. The discriminatory performance of H2FPEF model in diagnosing HFpEF was evaluated using sensitivity, specificity, positive and negative likelihood ratios as well as c-statistic.

RESULTS

Age >=60 years, body mass index > 30 Kg/m2, atrial fibrillation, and hypertension were reported respectively in 83%, 53%, 49%, and 94% of patients with HFpEF, whilst 38% and 43% of patients had an E/e’ >9 and right ventricular systolic pressure > 35 mmHg. The frequency of HFpEF diagnosis increased with increasing H2PEF score, from 2.6% in patients with a H2PEF score of 0 to ~50% in patients with a score of 6 or higher. The H2FPEF score identified 30% and 25.7% as unlikely (H2FPEF<2) and highly likely (H2FPEF>=6) to be HFpEF. A H2FPEF score of > 2 had a sensitivity of 89% to detect HFpEF and a H2FPEF score < 6 had a specificity of 82% to rule out HFpEF in the Alberta HEART population (Table).

CONCLUSIONS

The H2FPEF had acceptable discriminative performance in identifying HFpEF patients in the Alberta HEART cohort. Further validation and refinement of the H2FPEF model and testing in different patient populations with different prevalences of HFpEF is likely needed before incorporating this model into clinical practice.

Supervisor: Dr. Justin A. Ezekowitz

Table. H_2FPEF model's performance in identifying HFpEF patients in the Alberta HEART cohort

	Alberta HEART cohort (n=621)		**Patients with dyspnea (n=272)**		**Baseline LVEF ≥50% (n=424)**		**LVEF ≥50%* (n=376)**	
	HFpEF	No HFpEF	HFpEF	No HFpEF	HFpEF	No HFpEF	HFpEF	No HFpEF
HFpEF (Score ≥6), n	83	77	52	46	68	29	57	23
No HFpEF (Score <6), n	108	353	71	103	79	248	62	234
NT-proBNP, pg/mL	614 (200-1466)	134 (52-659)	780 (241-1673)	548 (179-1554)	565 (161-1446)	67 (33-157)	600 (199-1446)	63 (30-129)
AUC	0.72 (0.68-0.76)		0.58 (0.51-0.65)		0.80 (0.75-0.84)		0.82 (0.78-0.87)	
Sensitivity based on cut-off of ≥6 vs <6	43.6% (36.4-50.5%)		42.3% (33.6-51.0%)		46.3% (38.2-54.3%)		47.9% (38.9-56.9%)	
Sensitivity based on cut-off of >2 vs ≤ 2	89.5% (85.2-93.9%)		89.4% (84-94.9%)		89.1% (84.1-94.2%)		90.8% (85.6-95.9%)	
Specificity based on cut-off of ≥6 vs <6	82.1% (78.5-85.7%)		69.1% (61.7-76.6%)		89.5% (85.9-93.1%)		91.1% (87.6-94.5%)	
LR+	2.43		1.37		4.41		5.38	
LR-	0.69		0.84		0.6		0.57	

AUC: area under the receiver operating curve; Dx: diagnosis; HFpEF: heart failure with preserved ejection fraction; LR: likelihood ratio; LVEF: left ventricular ejection fraction; AUC, sensitivity and specificity were presented as point estimate (95% confidence interval). Except for sensitivity which is reported based on two cutpoints (2 and 6), the other indices are reported based on the cut-off of ≥6 vs <6. *excludes patients with any history of a reduced LVEF.

CAN PREBIOTICS AND/OR DIETARY CHANGES REDUCE LEAKY GUT IN HEALTHY FIRST-DEGREE RELATIVES OF CROHN'S PATIENTS?

Authors: Premraj, N., R. Valcheva, O. Kovic, D. Gibson, K. Madsen and L.A. Dieleman

INTRODUCTION

Background: Crohn's disease (CD) affects approximately 130,000 Canadians and prevalence is projected to increase by nearly 50% by 2030. This incurable disease is characterized by discontinuous, transmural inflammation of the gastrointestinal tract, with symptoms including severe diarrhea, abdominal pain, fatigue and malnutrition. Etiology is complex and unknown; It is hypothesized that pathogenesis is mediated by commensal gut microbes and environmental factors in a genetically susceptible host. CD heritability is relatively low as 12% of patients have familial history of inflammatory bowel diseases (IBD). We found that approximately 20% of healthy first-degree relatives (FDRs) of CD patients have increased small intestinal permeability (SIP), a risk factor for CD. Reducing SIP attenuates experimental colitis. Western diet significantly increases SIP. β-fructans (indigestible but fermentable carbohydrates) and n-3 polyunsaturated fatty acids (PUFAs) reduce inflammation in IBD. We recently found that protective effects of β-fructans is modulated by n-6/n-3 PUFA intake in experimental colitis.

Hypothesis: β-Fructans alone or combined with high n-3/low n-6 PUFA diet (i.e. Mediterranean diet) can reduce abnormal SIP and prevent chronic intestinal inflammation in FDRs of CD patients.

Aims: To evaluate the effects of oral administration of β-fructans and/or dietary changes on SIP as well as possible effects on fecal microbiota composition and activity.

METHODS

Methods: Randomized placebo-controlled clinical pilot study that will include 32 healthy FDRs of CD patients with confirmed leaky gut (lactulose:mannitol $\geq$0.025). Subjects will be assigned to following treatment arms: 1. β-fructans and control diet (Canada's food guide); 2. β-fructans and Mediterranean diet (low n-6/high n-3); 3. placebo (maltodextrin) and control diet; 4. placebo and Mediterranean diet. Duration 12 weeks, with urine, blood and fecal samples collected every 6 weeks.

Primary outcome: Assess change in intestinal permeability (lactulose:mannitol ratio) between week 0 to 12 and associated protective mechanisms.

Secondary outcome: Assess changes to fecal microbiome composition and function.

RESULTS

N/A

CONCLUSIONS

N/A

Supervisor: Dr. Levinus Dieleman

Aging is associated with increased von Willebrand factor expression

Parnian Alavi, Radya Yousef Abdualla, Stephane Bourque, Jayan Nagendran, Nadia Jahroudi

INTRODUCTION

Von Willebrand factor (VWF) is an endothelial-specific pro-coagulant protein with a major role in thrombosis. We have demonstrated that external stimuli including irradiation and hypoxia upregulate VWF expression. Additionally, increased circulating VWF levels were reported with aging, therefore we hypothesized the aging provides stimuli that upregulate VWF expression and thus contribute to an age-associated increase in thrombogenicity.

METHODS

Circulating plasma levels of VWF were explored in young (3 months) and aged (18-27 months) mice. Cellular mRNA and protein levels as well as vascular pattern of VWF were determined in various organs. Correlation of platelet aggregates formation with VWF expression, and in response to aspirin treatment were determined in distinct vascular beds. In addition, in an in vitro model of aging, VWF expression were determined in prolonged culture of endothelial cells

RESULTS

Increased plasma levels of VWF were observed in aged mice. VWF mRNA and protein levels were significantly increased in the brains, lungs, and livers, but not in kidneys and hearts of aged mice. Immunofluorescence staining demonstrated that while VWF expression was primarily restricted to larger vessels in young mice, a significant proportion of microvessels also exhibited VWF expression in aged mice. Increased platelets aggregate formation was observed in vessels of aged organs that demonstrated increased VWF expression. Aspirin treatment significantly reduced platelets aggregates formation in the brain vasculature of aged mice. Prolonged culture of endothelial cells exhibited a significant increase in VWF mRNA level, which were associated with increased senescence. Senescence markers were also detected in aged brain microvascular endothelial cells that exhibited increased VWF expression.

CONCLUSIONS

Aging increases VWF expression patterns and levels in an organ-specific manner potentially through cell senesces mechanism. The increased VWF levels are concomitant with enhanced platelets aggregate formation. Aspirin treatment significantly reduces age associated enhanced platelets aggregate formation in the brain.

Supervisor: Dr. Nadia Jahroudi, Dr. Jayan Nagendran

Left Ventricular Thrombus Detection by Echocardiography After Acute Myocardial Infarction and the Incidence of Stroke

Peter(Yuan) Zhang, Michelle Graham, Harald Becher, Thomas Jeerathakil, Miriam Shanks

INTRODUCTION

Left ventricular (LV) thrombus may form after ST-elevation myocardial infarction (STEMI), increasing stroke risk. Echocardiography remains the primary diagnostic modality for LV thrombus detection. Strong data is lacking for optimal timing of initial echocardiogram post-STEMI. Most LV thrombi form within the first 2 days post-MI, but up to 39% are detected on repeat echocardiograms performed ?5 days post-admission. This study examines ischemic stroke incidence in the first year post-acute STEMI and its association with initial echocardiogram timing and LV contrast use.

METHODS

This retrospective observational study identified 416 patients without atrial fibrillation who had STEMI between 2010-2017. Patients underwent an echocardiogram 2.0±3.9 days post-STEMI, with 274(65.7%) echocardiograms being contrast enhanced.

RESULTS

LV thrombus was identified in 7(2.6%) patients with contrast and 6(4.2%) with non-contrast echocardiography. Eleven patients (2.6%) had a stroke within 12 months post-STEMI. Six strokes occurred during index admission, 5 strokes occurred 85.6±89.3 days post-STEMI, with one having LV thrombus on index echocardiogram. There was no difference in incidence of stroke (1(0.7%) vs. 10(3.6%); p=0.08) or timing of initial echocardiogram (1.9±3.5 vs. 2.1±3.8 days; p=0.59) between non-contrast and contrast echocardiography cases. Stroke patients trended towards having echocardiograms on days 1-2 compared to patients without stroke (Table 1). They were older, more likely to have prior stroke, less likely to undergo coronary angiogram, had more apical akinesis and trended towards lower LVEF (Table 2), suggesting greater myocardial injury. This, plus early timing of stroke post-STEMI, favored thromboembolism.

CONCLUSIONS

Detecting LV thrombus early (1-2 days) post-STEMI reduced thromboembolism risk with anticoagulation initiation. However, most patients with stroke within 3 months of STEMI did not have LV thrombus on initial echocardiogram. Many LV thrombi develop >2 days post-STEMI, therefore a repeat echocardiogram (e.g. prior to discharge) may be necessary in high-risk patients whose initial early echocardiogram is negative. Validation in prospective studies is warranted.

Supervisor: Dr. Miriam Shanks

Table 1. Proportion of echocardiograms performed on days 1-2 vs. days ≥3 after acute STEMI in patients with and without stroke			
Timing of Echocardiogram	Stroke n=11	No stroke n=405	p value
Days 1-2	81.8%	60.5%	0.15
Days ≥3	18.2%	39.5%	0.15

Table 2. Demographic and echocardiography data on the patients with and without stroke			
	Stroke n=11	No stroke n=405	p value
Age (years)	70±10.4	59.4±12.2	0.007
Risk factors			
Hypertension	5 (45.5%)	194 (47.9%)	0.88
Diabetes Mellitus	2 (18.2%)	95 (23.5%)	0.68
Dyslipidemia	2 (18.2%)	175 (43.2%)	0.10
Previous myocardial infarction	0	25 (6.2%)	0.39
Previous stroke/TIA	2 (18.2%)	14 (3.5%)	0.01
Intervention Strategy			
Thrombolysis only	0	13 (3.2%)	0.55
Pharmocoinvasive	0	59 (14.6%)	0.17
Rescue PCI	3 (27.3%)	55 (13.6%)	0.20
Primary PCI	4 (36.4%)	224 (55.3%)	0.21
CABG	0	31 (7.7%)	0.34
No revascularization	4 (36.4%)	23 (5.7%)	<0.0001
Echocardiography			
LV contrast	10 (90.1%)	264 (65.2%)	0.086
LVEF (%)	39.7±8.1	44.9±10.9	0.062
Apical akinesis	10 (90.1%)	234 (57.8%)	0.032
Timing of echo (days)	1.7±1.5	2.0 ±3.7	0.55
LV clot on initial echo	1 (9.1%)	12 (3.0%)	0.25

Characterization of Exosomes-derived from Cholesterol Accumulated Astrocytes and its Significance in Alzheimer's Disease Pathology

Wu Q, Cortez, L, Kamali-Jamil R, Sim V, Wille H and Kar S

INTRODUCTION

Intracellular accumulation of cholesterol within neurons can increase the level/production of beta-amyloid (A?) peptide which plays an important role in the development of Alzheimer's disease (AD). A number of recent studies have shown that exosomes, which are small vesicles (40-100 nm diameter) of endocytic origin secreted by most cells including neurons and glial cells, represent a novel form of intercellular communication in various physiological and pathological settings. Neuronal exosomes containing Aβ peptides have been shown to influence not only the function/vulnerability of neurons but also in "prion-like" propagation of AD pathology. Unlike neurons, the significance of glial exosomes, particularly those derived from astrocytes, remain unclear. Recently we reported that cholesterol accumulation within cultured astrocytes triggered by U18666A treatment can increase the level/secretion of A?-related peptides. Thus, as a follow up, we are now establishing the significance of exosomes derived from cholesterol accumulated astrocytes in the development of AD pathology.

METHODS

Exosomes were purified from control and U18666A-treated astrocytes culture supernatant by using differential centrifugation polyethylene glycol precipitation. While secreted exosomes were characterized by electron microscopy, dynamic light scattering and DiI labeling, the content of various proteins related to AD pathology was defined by dot blotting, Western blotting and ELISA.

RESULTS

We observed that cholesterol accumulation following U18666A treatment significantly decreased the release of exosomes compared to control cultured astrocytes as revealed by electron microscopy, dynamic light scattering and DiI labeling. However, exosomes derived from U18886A-treated astrocytes, as detected by dot blotting and Western blotting, contain higher levels of amyloid precursor protein (APP) and APP-cleaved products (i.e., α-CTF and β-CTF) in contrast to control exosomes. The levels of Aβ1-40 peptide, as measured using ELISA, also found to be increased in exosomes of U18666A-treated astrocytes compared to control astrocytes.

CONCLUSIONS

Cholesterol accumulation in cultured astrocytes can decrease the secretion of exosomes but enhance the levels of APP and Aβ-related peptides in secreted exosomes.

Supervisor: Dr. Satyabrata Kar

Kidney Function, Albuminuria, and the Risk Of Hemorrhage and Thrombosis After Kidney Transplantation

Rachel Jeong, MD, Robert R. Quinn, MD, PhD, Pietro Ravani, MD, PhD, Manish M. Sood, MD, MSc, Marcello Tonelli, MD, SM, Feng Ye, MSc, Brenda R. Hemmelgarn, MD, PhD, David Massicotte-Azarniouch, MD, Ngan N. Lam, MD, MSc

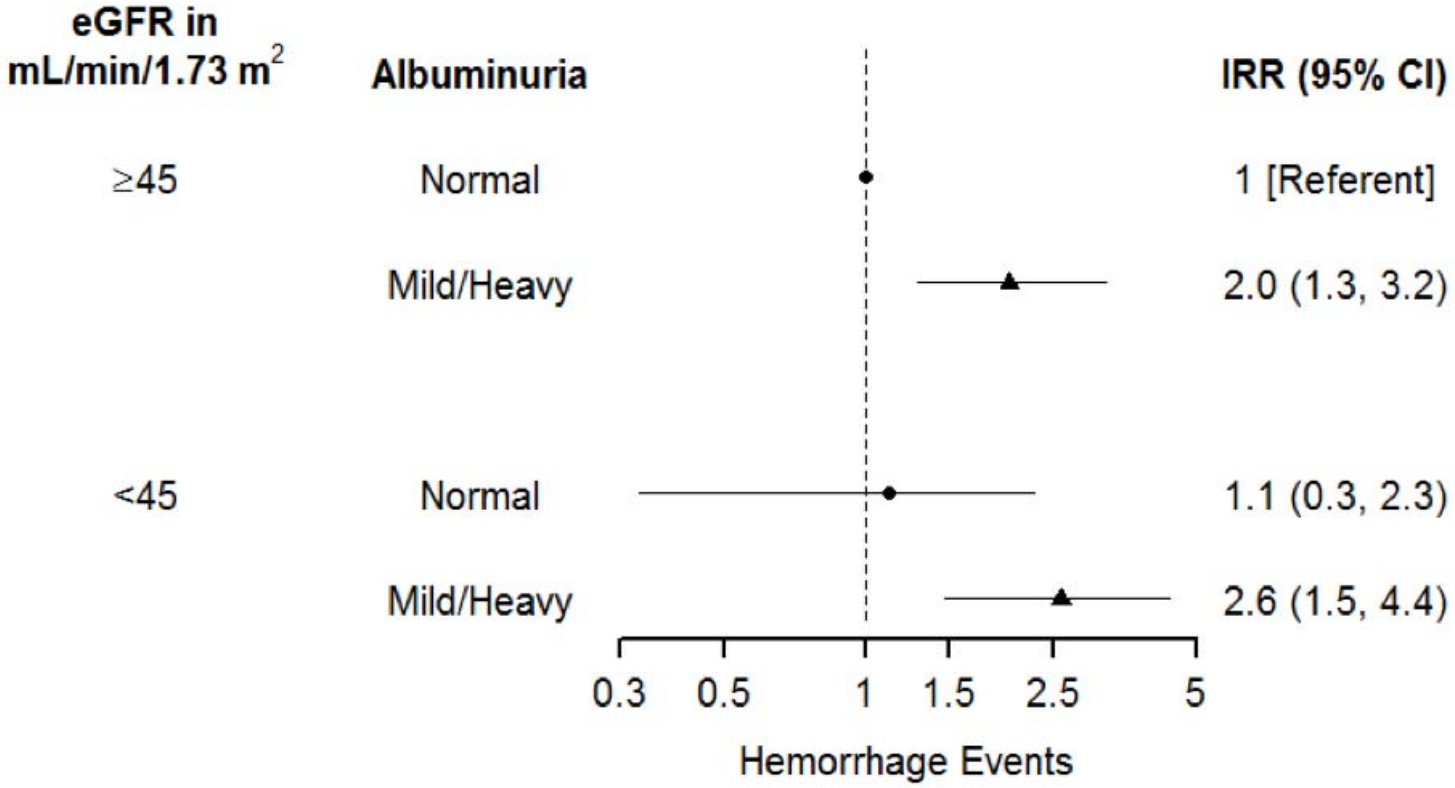
INTRODUCTION
Compared to the general population, kidney transplant recipients are at increased risk of hemorrhage and thrombosis. Whether this risk is affected by kidney function and albuminuria is currently unknown.

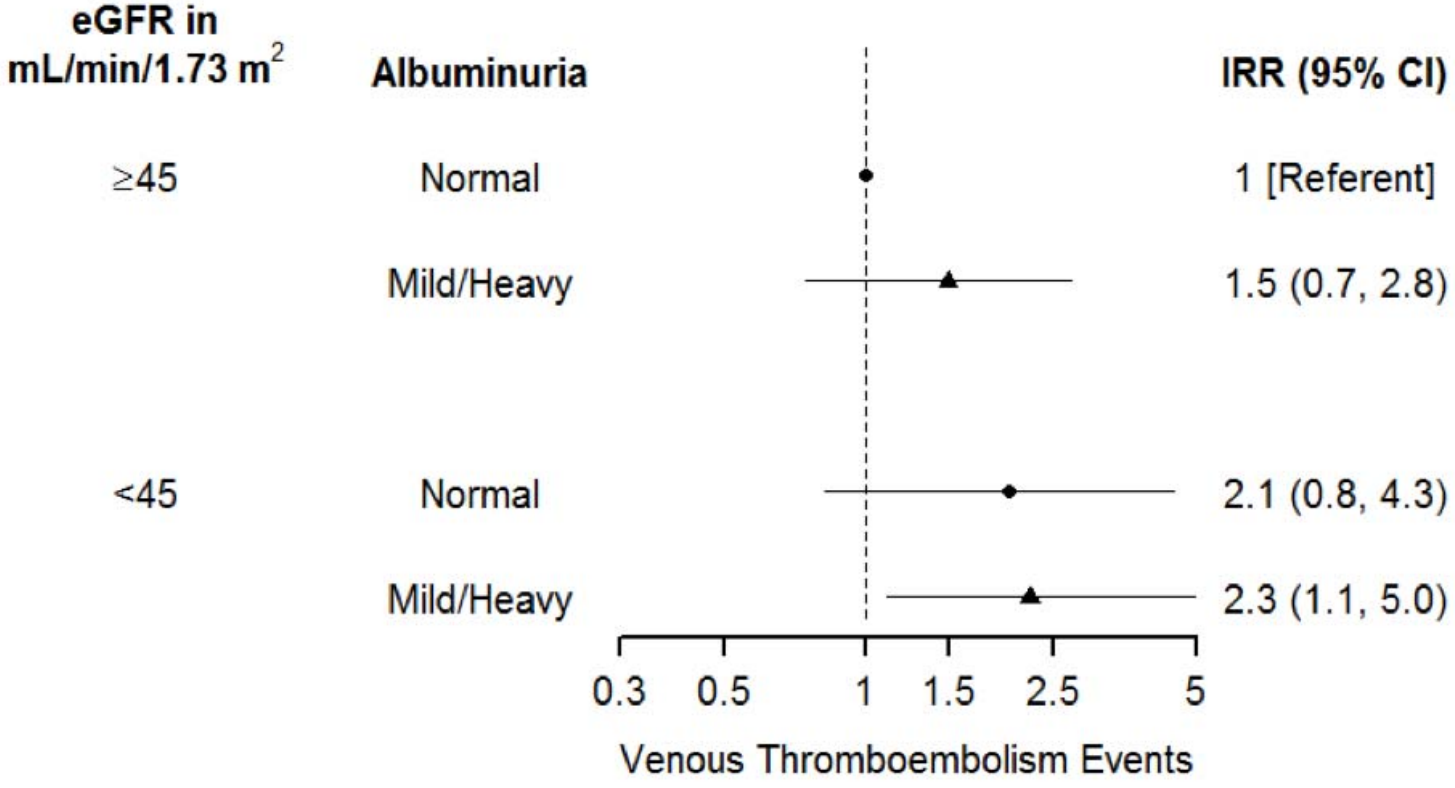
METHODS
We conducted a retrospective cohort study using linked healthcare databases to identify adult kidney transplant recipients from 2002-2015 in Alberta, Canada. Estimated glomerular filtration rate (eGFR) and albuminuria measurements at 1-year post-transplant were used to categorize recipients (eGFR: >=45 vs. <45 mL/min/1.73 m2; albuminuria: normal vs. mild-heavy). We determined the association between categories of eGFR and albuminuria and posttransplant hemorrhage and venous thrombosis based on diagnostic and procedural codes.

RESULTS
Of 1,284 kidney transplant recipients, 21% had an eGFR <45 mL/min/1.73 m2 and 40% had mild-heavy albuminuria at 1-year post-transplant. The mean age of the cohort was 53 years [interquartile range, IQR, 41-62]. Previous VTE was higher in recipients with lower eGFR, but previous hemorrhage was similar across all groups. Over a median follow-up of 6 years, the age- and sex-adjusted rate of hemorrhage and thrombosis was over 2-fold higher in recipients with lower eGFR and mild-heavy albuminuria compared to recipients with higher eGFR and normal albuminuria (hemorrhage: incidence rate ratio, IRR, 2.6, 95% confidence interval, CI, 1.5-4.4, p=0.001; thrombosis: IRR 2.3, 95% CI 1.1-5.0, p=0.046).

CONCLUSIONS
Among kidney transplant recipients, the risk of hemorrhage and venous thrombosis is higher with lower eGFR and mild-heavy albuminuria at 1-year post-transplant. Thus, eGFR and degree of albuminuria may help prognosticate kidney transplant recipients long-term.

Supervisor: Dr. Ngan Lam


eGFR in mL/min/1.73 m2
Albuminuria
IRR (95% CI)
≥45
Normal
1 [Referent]
Mild/Heavy
2.0 (1.3, 3.2)
<45
Normal
1.1 (0.3, 2.3)
Mild/Heavy
2.6 (1.5, 4.4)
0.3
0.5
1
1.5
2.5
5
Hemorrhage Events


eGFR in mL/min/1.73 m2
Albuminuria
IRR (95% CI)
≥45
Normal
1 [Referent]
Mild/Heavy
1.5 (0.7, 2.8)
<45
Normal
2.1 (0.8, 4.3)
Mild/Heavy
2.3 (1.1, 5.0)
0.3
0.5
1
1.5
2.5
5
Venous Thromboembolism Events

WAIT TIMES FOR IBD SURGERY IN EDMONTON: 50% ARE WAITING TOO LONG

Ravi Homenauth, Valentin Moncau, Ryan Snelgrove, Haili Wang, Karen Kroeker

INTRODUCTION

Approximately 75% of patients with Crohn's disease (CD) and a third of ulcerative colitis (UC) patients require surgery in their lifetime. In the absence of accepted standards for appropriate wait times for IBD surgery, we rely on expert opinion. In Alberta, the Adult Coding Access Targets for Surgery (ACATS) project has defined optimal waiting times (WT) surgery, including IBD-related surgery. Delayed surgery is believed to lead to poor outcomes and increased risk of postoperative complications. It is unknown whether IBD patients in Edmonton are receiving elective surgery (ES) within the defined WT.

METHODS

This is a 5-year, retrospective, quality assurance study of adult patients in Edmonton who underwent elective IBD surgery (January 1, 2013 to Dec 31, 2017). Data was extracted from the Edmonton Elective OR Database using relevant procedure codes. Surgical wait time was defined as the time between the decision to perform surgery and the date of the procedure for each type of surgery. Descriptive statistics were calculated to determine the proportion of patients who had surgery outside the accepted WT; and how long after the accepted time they waited. Of note, patients who had emergency surgery were excluded from this analysis.

RESULTS

Overall, 385 surgeries were included.

Half (50.9%) occurred outside predefined WT. For surgeries outside the window, 141 (71.9%) were done 50% beyond predefined WT with 111 (56.6%) occurring more than 100% beyond.

CONCLUSIONS

The average wait time for elective IBD surgery in Edmonton is longer than the provincially accepted wait times. Half of patients undergoing elective IBD surgery are waiting too long.

Supervisor: Dr Karen Kroeker

Table 1. Number of surgeries, average wait time and proportion waiting longer than the accepted by type of IBD surgery.

Surgery (5yr)	Accepted WT (days)	#Surgeries	AVERAGE WT (days±SE)	% out of window
FISTULA IN ANO CROHN'S	28	33	48±0.7	57.6%(19)
BOWEL INFLAMMATORY CROHN'S OR COLITIS NO OBSTRUCTION	84	75	89±13.5	30.7%(23)
BOWEL OBSTRUCTION INCOMPLETE INFLAMMATORY	21	70	40±7.7	52.9%(37)
BOWEL OBSTRUCTION STRICTURE	42	168	89±7.1	58.3%(98)
BOWEL FISTULA	42	39	55±14.8	46.2%(18)

A Ten-Year Retrospective Review of Temporal Artery Biopsy Lengths in Alberta

Raymond Chu, Caylea Foster, Mohsin Ali, Todd Chaba, Jason Soo, Alison Clifford, Jan Willem Cohen Tervaert, Elaine Yacyshyn

INTRODUCTION
Giant cell arteritis (GCA) is a large vessel vasculitis that involves extracranial arteries as well as extra-cranial large artery involvement. The historical gold standard for diagnosis is a temporal artery biopsy (TAB) recommended to be at least one centimetre in length. The purpose of this study is to review all biopsy lengths performed in the province of Alberta to assess whether an adequate sampling is being done and to identify predictors of a positive diagnosis of GCA.

METHODS
A retrospective chart review was performed on patients who had undergone a TAB procedure in 22 sites in Alberta between January 1st, 2008 to January 1st, 2018. Data extracted included patient's age, sex, levels of inflammatory markers (ESR and CRP), the side of biopsy, post-fixation length and final pathological diagnoses. Predictors of positive pathology were modelled using logistic regression. All statistical tests were two-sided, and a p-value of < 0.05 was considered statistically significant.

RESULTS
A total of 1203 biopsies were identified over the decade. Median age was 73 years, with 806 (67%) female patients. A total of 235 (20%) biopsies were diagnosed as GCA, with median biopsy length of 1.3 cm. Biopsy lengths between sites ranged between 0.8 cm to 2.2 cm. Univariate analysis noted increased age, ESR, CRP and biopsy lengths were associated with positive GCA diagnosis. In multivariate analysis, only age and CRP remained statistically significant. We noted increasing OR for a positive TAB for every increase of 0.5 cm with maximum yield between 2.0 – 2.49 cm

CONCLUSIONS
Our study indicates that the length of TABs performed in Alberta tends to vary and some sites acquire lengths that are less than recommended. We have noted that age, ESR, CRP and length of biopsies were significant independent predictors of pathological diagnosis. Maximal diagnostic yield for a TAB is between 2.0 - 2.49 cm.

Supervisor: Dr. Elaine Yacyshyn

ADHERENCE TO GUIDELINES AND BEST PRACTICES FOR IBD FLARE MANAGEMENT AND CORTICOSTEROID ADMINISTRATION: A RETROSPECTIVE CHART REVIEW

Reed T. Sutton, Ellina Lytvyak, David Pincock, Daniel C. Baumgart, Daniel C. Sadowski, Richard N. Fedorak, Karen I. Kroeker

INTRODUCTION

Induction and maintenance of remission is a major treatment goal for inflammatory bowel disease (IBD). Active disease is often treated with corticosteroids (CS). CS are effective but have significant side effects. They are not recommended for long term or frequent use, especially when safer medications are now available. Nonetheless, literature suggests that cumulative exposure to CS in IBD patients has not changed. In this study, we assessed adherence of practitioners to guidelines for corticosteroid use and treatment of disease flares.

METHODS

A retrospective, single-center study using data collected from outpatients of the University of Alberta IBD Clinic, receiving >1 dispensation of CS from an IBD expert clinician between March 2014-2016. Data for CS dispensations for 18 months following the initial dispensation were extracted from provincial databases. Other data was manually extracted from the region-specific electronic medical record (EMR).

RESULTS

Of 345 charts identified, 244 met inclusion. The majority, 157(64.3%), had Crohn's disease (CD). Median age was 40(IQR: 28-50) years. Maintenance IBD medications: 72 (29.5%) on none, 75 (30.7%) 5-ASA only, 34 (13.9%) immunomodulators, and 63 (25.8%) biologic therapy. CS were prescribed in clinic for 125 (51.2%), endoscopy for 54 (22.1%), hospital for 29 (11.9%), and by telephone for 36 (14.8%). The majority of CS were prednisone (176, 72.1%), the remainder budesonide.

Figure 1 shows adherence to flare and CS guideline indicators. On analysis of outcomes, visit type and steroid type were not associated with increased steroid use within 12 months. In regression models for predicting clinical remission at 12 months following dispensation, the most significant predictor was <2 additional CS prescriptions (OR, 6.86; p=0.016).

CONCLUSIONS

Additional steroid prescriptions beyond an initial flare do not appear to be associated with better outcomes. There are significant gaps between professional guideline recommendations and clinical practice for some aspects of IBD patient care, particularly documentation and fecal calprotectin.

Supervisor: Dr. Karen Kroeker

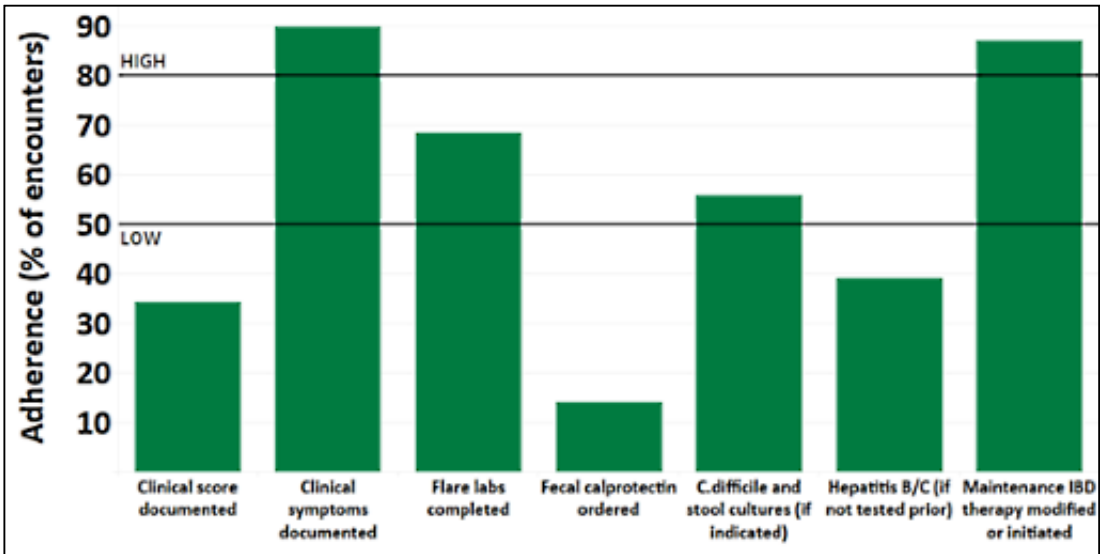


FIGURE 1A. Adherence to guidelines for IBD flare management by practitioners at the University of Alberta, displayed as percent of encounters, N = 244

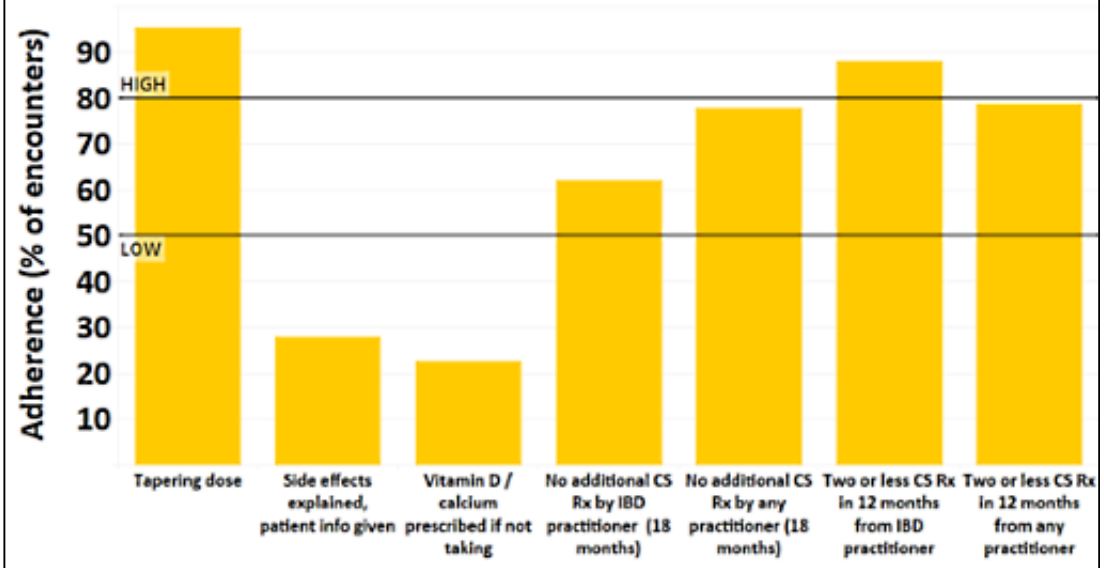


FIGURE 1B. Adherence to guidelines for corticosteroid prescribing by IBD practitioners at University of Alberta, displayed as percent of encounters, N=244.

Management of Inflammatory Bowel Disease Patients with Clinical Care Pathways Reduces Emergency Department Utilization

Reed T. Sutton, Ellina Lytvyak, Levinus A. Dieleman, Farhad Peerani, Richard N. Fedorak, Karen I. Kroeker

INTRODUCTION
Standardizing quality care through clinical care pathways (CCP) has been effective in reducing Emergency Department (ED) utilization among patients with various diseases. The aim of this study was to evaluate the impact of CCPs for inflammatory bowel disease (IBD) on reduction in ED utilization.

METHODS
IBD patients with at least one IBD clinic appointment at the University of Alberta during April 2014–September 2016 were retrospectively stratified into two groups; those managed by IBD CCPs, and those not managed. Stratification was based on receiving care from IBD clinic specialists in the 18 months preceding the study period (during which time the CCPs were implemented). Patient data were extracted from local medical record (EMR), and ED data from the National Ambulatory Care Reporting System. Negative binomial regression predicted the annual number of ED visits ($p<0.10$ purposeful selection, 95% confidence).

RESULTS
There was a difference of 30.7 ED visits/100 patients between managed and non-managed at 12 months ($p<0.001$). In multivariate analysis, the incidence rate ratio (IRR) of total ED visits occurring annually was 0.750 (95% CI: 0.603-0.928, $p=0.008$) for managed vs. non-managed patients. Protective factors that decreased ED rates included male sex, residence within Greater Edmonton and Azathioprine use. Crohn's disease, previous IBD surgery, anti-TNF and corticosteroid use, micronutrient deficiencies, and assigned family physician contributed to increased ED visit rates.

CONCLUSIONS
Management with IBD CCPs has significant impact on ED utilization with a sustained reduction in total ED visit rates 12 months later. Future studies will determine whether the IBD CCPs in their current form are cost-effective, and the efficacy of EMR integration.

Supervisor: Dr. Karen Kroeker

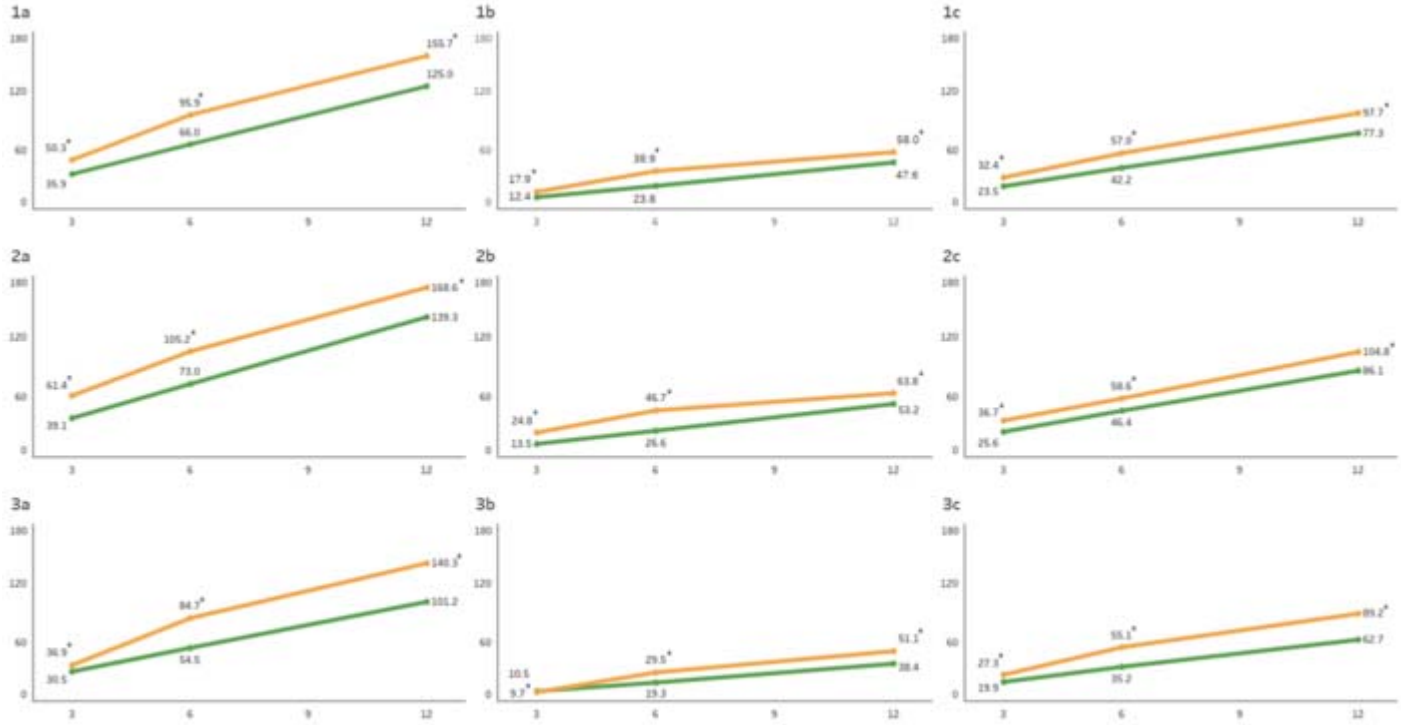


Figure 1. Temporal trends in ED visits per 100 patients over 12 months for: (1) All IBD patients; (2) Crohn's disease; (3) Ulcerative colitis; (a) Total ED visits; (b) IBD-related ED visits; (c) non-IBD-related ED visits. The green line represents the ED rate for IBD patients managed using IBD CCP. The orange line represents the ED rate for IBD patients not managed using IBD CCP. * – difference significant at $p<0.001$.

CONSUMPTION OF REFINED SUGAR RAPIDLY DECREASES MICROBIAL DIVERSITY AND ENHANCES SYSTEMIC RESPONSE TO MICROBIAL STIMULI

Sabitha Rajaruban, Robert Fedorak, Aiden Zalasky, Naomi Hotte, Michael Laffin, Jenny Hyun, Wei Jen Ma, Karen Madsen

INTRODUCTION

We have previously shown that short-term exposure to a high sugar diet in mice increases susceptibility to dextran-sodium sulfate (DSS) colitis and attenuates wound healing. This study aims to examine the effects of a short-term exposure to high sucrose on gut microbiota and monocyte function.

METHODS

Adult wild-type 129/SvEv mice were placed on chow (CH) or high sugar diet (HS) (50% sucrose: AIN76A). Stool samples were collected on day 0 (prior to diet) and on day 3 for 16S rRNA microbial analysis. As an assessment of gut barrier defense, ileal homogenates were analyzed for iNOS expression by qPCR. Bone-marrow derived monocytes (BMDM) were obtained from femurs of mice on day 3 and cultured for basal cytokine secretion and secretion in response to lipopolysaccharide (LPS). Blood was obtained from mice on day 3 and incubated with green fluorescent protein (GFP)-expressing Escherichia coli. Aliquots were plated at 30-minute intervals to assess bacteria killing ability.

RESULTS

Principal coordinate analysis (PCoA) based on Bray-Curtis dissimilarities showed stool microbial profiles differ between CH and HS fed mice. Verrucomicrobia was elevated in HS fed mice ($p<0.01$, FDR<0.01) while Lachnospiraceae was decreased ($p<0.01$, FDR <0.03). HS fed mice also demonstrated a loss of alpha-diversity. iNOS expression was significantly down-regulated in ileum in HS fed mice. BMDMs derived from HS fed mice exhibited enhanced basal secretion of TNF-alpha and IL-12p70 ($p<0.05$). When treated with LPS, BMDM from HS fed mice showed a dramatic increase in TNF-alpha and IL-10 secretion ($p<0.01$). Whole blood from HS fed mice exhibited enhanced bacterial killing ability.

CONCLUSIONS

Short term consumption of a high sucrose diet resulted in a loss of ileal defense, significant microbial changes and enhanced responses to microbial stimuli in blood and bone-marrow derived monocytes. These may act together to increase susceptibility to colitis and failure of tissue regeneration seen in sucrose-fed mice.

Supervisor: Dr. Karen Madsen

Using community based participatory approach in clinical trials involving older adults – Lessons from SHAPES

Rajabali S, Gartner S, Hunter K, Juby A, Dafoe W, Wagg A

INTRODUCTION
Older adults face complex health and social problems that are different from those faced by their younger counterparts. Older adults are often under-represented in clinical trials and participatory research. Community Based Participatory Research (CBPR) offers a means to address the needs of older adults and include their perspectives in research. We share the lessons learned by employing a CBPR approach in a mixed methods quantitative dominant, stepped-wedge cluster randomized trial, SHAPES, that aims to assess the impact of trained peer health coaches on healthy aging behaviours in community dwelling older adults.

METHODS
Using a CBPR approach, SHAPES trial engaged seniors' activity centres from the onset. The topics and format of the health education modules were identified by the seniors. Health coaches were recruited from seniors' centres to deliver the education modules. Based on health coaches' feedback, the modules were modified. Periodic meetings were held with health coaches to seek their feedback. Health coaches also participated in peer fidelity monitoring.

RESULTS
Using a CBPR approach resulted in increased recruitment and retention of the study participants. Recruitment was completed earlier than anticipated and had a wait-list. Using a participatory approach posed some practical constraints and methodological challenges. The trial design had to be modified and timelines had to be adjusted to align with the schedule of the seniors' centres. Flexibility had to be allowed to work with the seasonal variation in attendance at the seniors' centres as well as the availability of the health coaches.

CONCLUSIONS
It is possible to employ CBPR approaches in robust clinical trials, however, there are certain limitations and challenges of which researchers should be aware and take measures to overcome. By maintaining a strong sense of collaboration and partnership with older adults and by adhering to the principles of participatory research, any challenges that CBPR brings, can be overcome.

Supervisor: Dr. Adrian Wagg

Comparison of MRC breathlessness scale to a novel multidimensional dyspnea scale (MDDS) for clinical use

Kalluri, M, Bakal JA, Wang T, Younus S.

INTRODUCTION
MRC breathlessness grade is used to assess, but does not quantify, dyspnea. It measures perceived disability in a 5 point grading (none to almost complete incapacity). MRC lacks dimensions to capture day-to-day patient experience of dyspnea/associated severity. We developed the Multidimensional Dyspnea Scale (MDDS) to measure dyspnea across 7 activities of daily living, exercise and rest using a numeric scale (no breathlessness to worst possible breathlessness) for each component.

METHODS
Reviewed ILD clinic database to identify IPF patients with both MRC and MDDS data available at first visit (2012-2018). We compared MRC grade with MDDS, measured correlations and compared scales to pulmonary function test data and 6-minute walk distance (6MWD), a common clinical measure of physical capacity.

RESULTS
105 IPF patients; mean age 73 years (SD=10); 66% males. 75% were in MRC 3-5 grade, 95% reported mean dyspnea MDDS scores of 1/10 at rest, 3/10 with ADL and 6/10 with exercise. Statistical analysis showed ~40% variability in MRC score could be explained by “walking” ($r^2 = 0.40$) and “stairs” ($r^2 = 0.37$). Other MDDS dimensions showed poor correlations. MRC showed poor correlation with FVC/DLCO, and moderate correlation with 6MWD ($r^2 = 0.46$; $p < 0.05$). MDDS components activities of daily living (dressing, showering, talking, stairs, and exercise) were poorly correlated with FVC/DLCO, 6MWD.

CONCLUSIONS
MRC and MDDS are poorly correlated except for two components. MDDS captures dimensions not examined by MRC. MDDS does not correlate well with measures of lung function and physical capacity; it may provide complementary data for detecting clinically relevant impairment due to dyspnea. MRC 5 represents the most disabled patients, including those with dyspnea with resting/eating. Patients in MRC 3 and 4 grades also reported such type of dyspnea with MDDS. This may be relevant for targeted treatment advice. Our previous work shows the use of MDDS facilitates early identification and treatment of dyspnea in clinic.

Supervisor: Dr. Meena Kalluri

Perceptions of Frailty Amongst Older Adults

Selynne Guo, Dr. Heather Hansen, Dr. Sheny Khera, Dr. Darryl Rolfson

INTRODUCTION

Frailty is a state of decreased physiological reserve and increased vulnerability resulting from the accumulation of deficits in multiple systems. It manifests as a heterogeneous, multidimensional syndrome and is emerging as a clinical entity to enhance risk prediction and inform care planning. However, several studies have shown that older adults associate many negative aging stereotypes with the term frailty. This study aims to describe the acceptability and usefulness of the term frailty is as viewed by a mixed group of older adults.

METHODS

In this qualitative study, we aim to complete approximately 24 interviews with participants aged 65 or older, representing the spectrum from fitness to frailty. The semi-structured interviews are designed to explore participants' perceptions of the meaning of the term frailty and its individual components, as well as the perceived utility of the concept of frailty. The Edmonton Frail Scale (EFS) is used to assess the frailty status of each participant. We employ interpretive description methodology to qualitatively analyze the interview data. Data analysis consists of multiple reads of the transcripts, followed by line-by-line coding, then the identification of broad themes and patterns in the data based on respondent groups (i.e. frail vs non-frail), and finally a consensus summary.

RESULTS

To date, 14 participants, primarily non-frail, have been interviewed, and are being analyzed. Participants with more frailty will be interviewed subsequently. Preliminary results of broad themes identified in the non-frail group will be available for the Department of Medicine Research Day.

CONCLUSIONS

Frailty is an important concept in the care of older adults, however the term may be associated with negative stereotypes of aging for the target population receiving care. This study will describe the relative acceptability and perceived utility of the term and concept of frailty amongst older adults.

Supervisor: Dr. Darryl Rolfson

Resident mental models and experiences of the initial implementation of Competence By Design (CBD)

Shivani Upadhyaya, Marghalara Rashid, Andrea Davila Cervantes, Anna Oswald

INTRODUCTION

CBD is a hybrid competency-based model that focuses on residents' abilities in relation to the competencies needed for success in practice. This model is based on five components: a framework of competencies, sequenced progression, tailored experiences, competency-focused instruction, and programmatic assessment. There has been a limited exploration of residents' experiences of implementation of CBD thus far. We explored residents' mental models in relation to the core components and their general experiences to identify if CBD implementation in the first 8 disciplines is occurring as it was conceptualized.

METHODS

A descriptive qualitative design was used to explore and better understand the resident experiences. All residents who had exposure to CBD implementation were invited to participate. We conducted face-to-face or telephone semi-structured interviews. Interviews were digitally recorded and transcribed verbatim. Thematic analysis was used to create data-driven codes and identify themes and subthemes. We used an iterative consensus-building process to reach saturation. Research Ethics Board approval was obtained.

RESULTS

A total of 20/50 (40%) residents representing 6 different disciplines from the first(n=4) and second (n=16) cohorts of CBD implementation were interviewed. Five main themes emerged: i) value of feedback; ii) strategies for successful Entrustable Professional Activity (EPA) completion; iii) challenges encountered in CBD; iv) general perceptions regarding CBD, and v) recommendations to improve on existing challenges.

CONCLUSIONS

Exploring residents' mental models of CBD core components and understanding their experiences on the implementation will help identify/disseminate successes, challenges and future directions from the residents' perspective to assist programs at different stages of CBD implementation.

Supervisor: Dr. Anna Oswald

Investigating an infectious etiology for altered metabolism in biliary epithelial cells of patients with primary biliary cholangitis.

Steven Willows, Filip Wysokinski, Shawn Wasilenko, Andrew Mason

INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease associated with cholangitis and destruction of interlobular bile ducts. The major autoantigen in PBC is pyruvate dehydrogenase E2 protein (PDH-E2), a member of the mitochondrial pyruvate dehydrogenase complex. PBC patient derived biliary epithelial cells (BEC), the primary targets of immune destruction, have been found to bind AMAs on the plasma membrane, suggesting an aberrant localization of PDH-E2 to the cell surface. Previous work in our lab has identified and characterized a retrovirus in PBC patients called human betaretrovirus due to its close similarity to the mouse mammary tumor virus (MMTV). Proteomic studies in our laboratory identified several glycolytic enzymes aberrantly expressed in PBC BEC, leading us to investigate how PBC BEC metabolism differs from controls, and whether an infectious agent could be responsible for this change.

METHODS

Western blot was used to investigate levels of several glycolytic enzymes in PBC BEC while isotropic glucose tracing and an Oxygen Biosensor were used to probe changes to glycolysis and oxygen consumption respectively. Changes to mitochondria number were assessed by qPCR towards mitochondrial DNA. BEC cells were also exposed to two sources of viral infection, PBC lymph nodes and isolated MMTV, and changes to metabolism were assessed.

RESULTS

PBC BEC showed increased levels of enolase, and higher levels of both lactate production and oxygen consumption. Additionally, PBC BEC had increased levels of mitochondrial DNA. Treatment of BEC with PBC lymph nodes showed increased PDH-E2 and enolase, while treatment with MMTV caused increased levels of PDH-E2 and mitochondrial DNA.

CONCLUSIONS

Overall, our studies provide evidence that PBC BEC exhibit altered metabolism and mitochondrial biology, which may play a causative role in autoimmunity. Furthermore, our studies suggest these changes may be caused by an infectious agent.

Supervisor: Dr. Andrew Mason

EXPERIMENTAL CHRONIC KIDNEY DISEASE REDUCES STRENGTH OF TGF-SYNCHRONIZATION AND IMPAIRS AUTOREGULATION

Tayyaba Zehra, Heather More, Shereen Hamza, Will Cupples and Branko Braam

INTRODUCTION

Nephrons use tubuloglomerular feedback (TGF) to autoregulate blood flow and prevent transmission of high blood pressure to glomeruli. We have previously shown that TGF is not isolated to individual nephrons but instead, nephrons synchronize in a network. This ensures each nephron receives appropriate perfusion to match the energy-intensive reabsorption of Na+. We have shown that loss of synchronization impairs autoregulation which could cause chronic kidney disease (CKD). We hypothesized that structural damage to the nephron-network would impair TGF-synchronization.

METHODS

Male Lewis rats underwent uni-nephrectomy followed by partial nephrectomy to induce CKD (n=5) or underwent sham-operations (n=3). Six weeks later, the rats were anesthetized and mean arterial pressure (MAP), renal blood flow (RBF), and glomerular filtration rate (GFR) were assessed. Renal cortical perfusion was recorded with laser speckle perfusion imaging (LSPI; Moor Instruments)). After Fourier transformation of flow frequencies, we applied phase coupling and graph analysis to provide information about TGF synchronization between nephrons.

RESULTS

Within the CKD group, MAP (92.8+/-6.4 to 82.5+/-5.3mmHg) and RBF (7.5+/-1.1 to 6.6+/-1.3mL/min) were decreased compared to shams (113.0+/-7.8 to 94.6+/-6.3mmHg), (9.9+/-1.5 to 9.1+/-1.6mL/min), and GFR (1.35+/-0.3 to 0.58+/-0.20mL/min) was increased compared to shams (0.67+/-0.24 to 0.24 +/-0.074mL/min). Because of the low number of animals, this did not reach significance. Strength of TGF-synchronization between nephrons is indicated by higher values for phase coherence (PC). PC values were decreased for CKD rats compared to sham controls which indicates weaker synchronization for that group (Fig1). PC varied inversely with edge length, which represents the distance between two connecting nodes, for both groups.

CONCLUSIONS

CKD causes structural disruption in the kidney, leading to an impaired ability of nephrons to synchronize TGF as a network to match blood flow to demand and prevent hypertensive injury. Impaired autoregulation results from dysregulated synchronization and serves as a driving force of renal injury.

Supervisor: Dr. Branko Braam

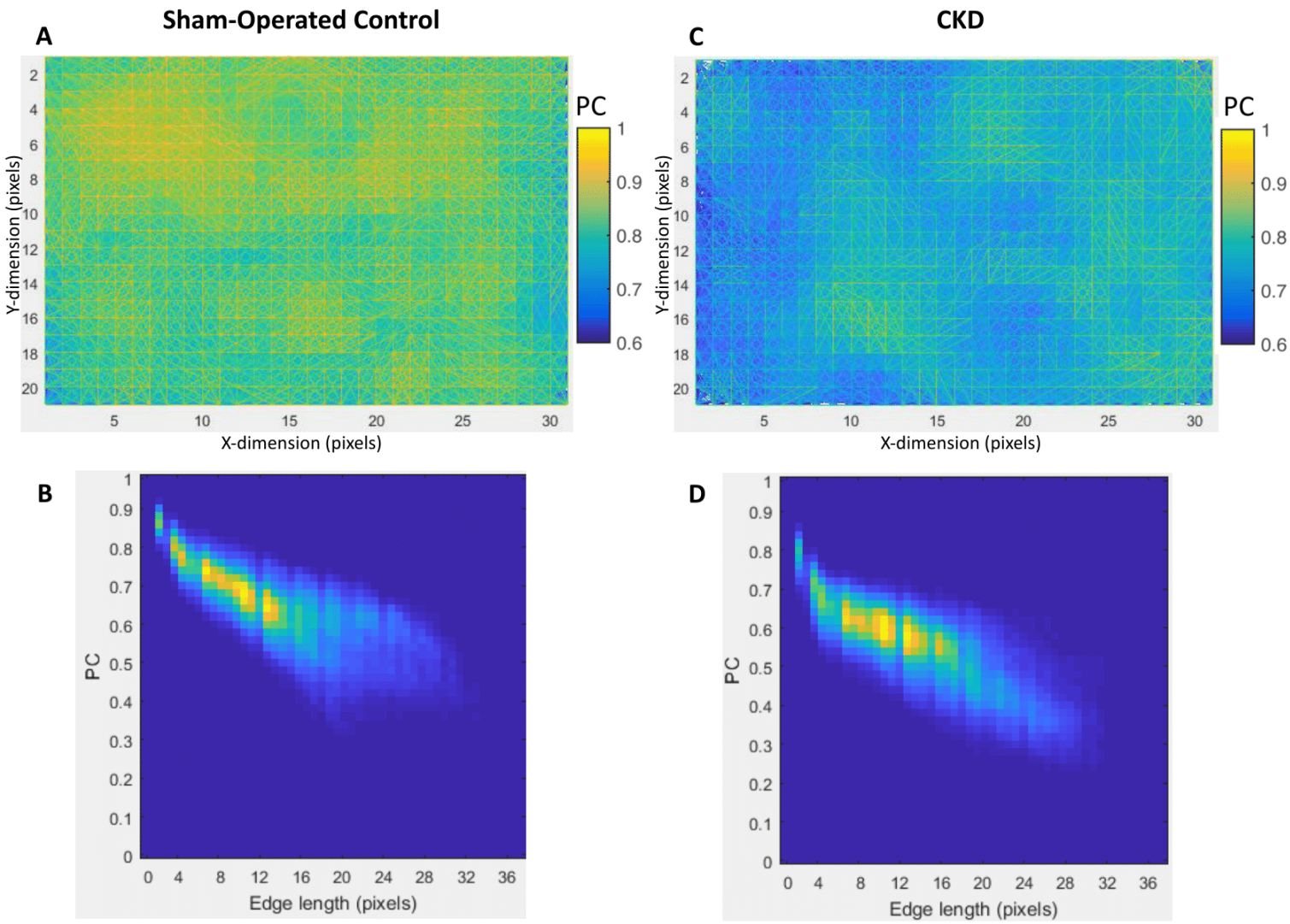


Figure 1: Graph analysis of TGF synchronization. Each pixel is treated as a node (orange dots), and PC between nodes form connections (edges). Higher PC values mean stronger synchronization. A: Strong synchronization of TGF is present in the control animal over long distances, as confirmed in B, which shows PC inversely varying with length of connections. C: After inducing CKD, TGF-synchronization is decreased as indicated by lower PC values but D: length of connections is maintained.

Multi-view Three-Dimensional Fusion Echocardiography System in Patients with Cardiac Resynchronization Therapy Devices

Victoria Sarban, Pierre Boulanger, Michelle Noga, Kumar Punithakumar, Miriam Shanks, Soori Sivakumaran, Harald Becher

INTRODUCTION

Comprehensive visual and quantitative evaluation of heart function is essential in heart failure patients with Cardiac Resynchronization Therapy (CRT) devices. According to the American Society of Echocardiography, the Three-Dimensional (3D) Echocardiography is the method of choice for quantification of left ventricular systolic function, however its use is limited due to signal dropouts and narrow Volume Of View (VOV). To overcome those limitations, a Multi-view Three-Dimensional Fusion Echocardiography (M3DFE) prototype has been developed. We hypothesize that M3DFE prototype can be applied successfully in a clinical echo lab setting in addition to the standard echo protocol.

METHODS

In a prospective, single center pilot study the M3DFE protocol has been applied in CRT patients after their standard Two-Dimensional Contrast Echocardiography (2DCE) visit. Siemens SC2000 echocardiography system was used for single 3D ultrasound datasets acquisition from different transducer positions on the chest. The position of the transducer, corresponding sound field and patients' movements were tracked by a customized optical tracking-based fusion system. Single 3D ultrasound datasets were pre-aligned using optical tracker information and a customized fusion software program. Pre-aligned output was uploaded into a modified 3D Slicer software for registration and wavelet transformation based image fusion. The M3DFE end product will be presented.

RESULTS

Seven participants are enrolled so far. Enrollment target of 30 participants is expected to be reached before end of June 2019. In 6 out of 7 participants the M3DFE recording could be processed with the prototype software.

CONCLUSIONS

This is the first application of M3DFE in patients. Further analysis will be performed to assess the accuracy of this method.

Supervisor: Dr. Miriam Shanks

Pharmacist Prescribing and Care Improves Cardiovascular Risk, But What Do Patients Think? A sub-study of the RxEACH study.

Al Hamarneh YN, Lamb S, Donald M, King-Shier K, Jones CA, Hemmelgarn BR, Mitchell C, Tsuyuki RT.

INTRODUCTION

The Alberta Vascular Risk Reduction Community Pharmacy Project: RxEACH, was a randomized trial which demonstrated that a community pharmacy-based case finding and intervention program (including prescribing, laboratory testing, and follow-up) reduced the risk for cardiovascular (CV) events by 21% when compared to usual care.

Objective

To evaluate patient perceptions regarding pharmacist prescribing and care in patients at high risk for CV events.

METHODS

All participants who took part in RxEACH received an invitation letter. Those who took part in the interviews provided verbal consent.

Participants were asked to provide their opinions about:

- The care they received from pharmacists
- Communication between patients, pharmacists and family physicians
- Suggestions for sustainability

Interviews were recorded and transcribed verbatim. Three reviewers (including one patient who did not participate in RxEACH) analyzed and coded the data independently.

RESULTS

Data saturation was achieved after interviewing 14 participants. Half of whom were male and approximately two-thirds were older than 60.

The following themes were identified:

(i) Patient-pharmacist relationship: Participants highlighted the importance of having a strong relationship with the pharmacist, indicating that could enhance their level of comfort with the pharmacist. They also felt that pharmacists truly cared about them as people.

(ii) Healthcare system characteristics: The majority of the participants supported expanded scope of practice and identified it as an opportunity to fill healthcare gaps highlighting easy accessibility, high quality and timeliness of pharmacist services.

(iii) Patient reaction: Participants were extremely satisfied with the care they received and reported that they felt empowered when pharmacists encouraged them to take responsibility for their own health.

CONCLUSIONS

Patients are highly supportive of an advanced scope of pharmacy practice which includes prescribing, follow-up, and remunerated care. Our inclusion of a patient in the analyses provided a unique perspective.

Supervisor: Dr. Ross Tsuyuki

Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the RxEACH study

Al Hamarneh YN, Johnston K, Marra C, Tsuyuki RT.

INTRODUCTION

The RxEACH randomized trial demonstrated that community pharmacist prescribing and care reduced the risk for cardiovascular (CV) events by 21%, compared to usual care.

Objective

To evaluate the economic impact of pharmacist prescribing and care for CV risk reduction in a Canadian setting.

METHODS

A Markov cost-effectiveness model was developed to extrapolate potential differences in long-term CV outcomes, using different risk assessment equations. The mean change in CV risk for the two groups of RxEACH was extrapolated over 30 years, with costs and health outcomes discounted at 1.5% per year. The model incorporated health outcomes, costs and quality of life to estimate overall cost-effectiveness. It was assumed that the intervention would be 50% effective after ten years. Individual-level results were scaled up to population level based on published statistics (29.2% of Canadian adults are at high risk for CV events). Costs considered included direct medical costs as well as the costs associated with implementing the pharmacist intervention. Uncertainty was explored via probabilistic sensitivity analysis.

RESULTS

It is estimated that the Canadian healthcare system will save more than $4.4billion over 30 years, if the pharmacist intervention was delivered to 15% of the eligible population. Pharmacist care would be associated with a gain of 576,689 Quality Adjusted Life Years and avoid more than 8.9 million CV events.

The intervention is economically dominant, i.e. it is both more effective and reduces costs when compared to usual care.

CONCLUSIONS

Across a range of one-way and probabilistic sensitivity analyses of key parameters and assumptions, pharmacist prescribing and care is both more effective and cost-saving compared to usual care. Canadians need, and deserve such care.

Supervisor: Dr. Ross Tsuyuki

A novel cardiac fibroblast-cardiomyocyte paracrine mechanism in the hypertrophied right ventricle in pulmonary hypertension

Yongneng Zhang, Vikram Gurtu, Rodrigo Siqueira, Alois Haromy, Gopinath Sutendra, and Evangelos Michelakis

INTRODUCTION
The biology and embryology of the right ventricle (RV) is very different than the left ventricle and mechanisms of RV failure cannot be extrapolated from the left ventricle, remaining largely unknown. Despite being the most common cell type in the heart, the role of cardiac fibroblasts (CF) in RV hypertrophy (RVH) in pulmonary hypertension (PHT) remains unknown. We hypothesized that RV-CF play a central role in the early stages of RVH in PHT.

METHODS
We studied normal RV versus RVH in monocrotaline-induced PHT, a standard PHT rat model; and measured RV contractility in an ex-vivo model (a modified working heart model where the pressure transducer is placed in the RV) and an in-vitro model of freshly isolated RV cardiomyocytes (RV-CM). We also studied mitochondrial function in isolated RV-CF and RV-CM.

RESULTS
In the isolated heart model, RVH had (as expected) significantly increased contractility, compared to normal RV. But isolated RVH RV-CM had the same contractility to isolated normal RV-CM, suggesting that the increased contractility mechanism is not intrinsic to the RV-CM, despite its hypertrophy and metabolic remodeling. Isolated RV-CM and RV-CF from RVH both showed evidence of mitochondrial remodeling (mitochondrial hyperpolarization, decreased mitochondrial reactive oxygen species) compared to those from normal RV. RVH RV-CF supernatant had increased levels of the mitochondrial diffusible metabolite succinate, compared to normal RV-CF. The succinate receptor SUCNR1 was expressed in RV-CM but not in RV-CF and its levels were higher in RVH than normal RV-CM. Exogenous succinate (0.1-0.5mM; similar to serum levels), increased contractility in isolated RVH RV-CM more than in normal RV-CM.

CONCLUSIONS
We propose a novel mechanism where RV-CF-derived succinate enhances RVH RV-CM contractility. The known increase in contractility in RVH may not be a result of the RV-CM hypertrophy and metabolic remodeling (as currently thought) but rather, due to RV-CF succinate, with important therapeutic implications.

Supervisor: Dr. Evangelos Michelakis

Differential immune activation in patients with acute ischemic stroke and admission blood pressure greater than 185/110 mm Hg

Yusra Batool, Gina Sykes, Bradley P Ander, Boryana Stamova, Frank R Sharp, Glen C Jickling

INTRODUCTION
A blood pressure > 185/110 mm Hg is associated with increased risk of tPA related hemorrhagic transformation (HT). Stroke guidelines recommend blood pressure >185/110 mm Hg be lowered before tPA treatment. How high blood pressure increases blood-brain barrier disruption and risk of hemorrhagic transformation remains poorly understood. We evaluated peripheral leukocyte activation in stroke patients in relation to elevated blood pressure and their potential contribution to blood-brain barrier disruption.

METHODS
Blood samples from acute ischemic stroke patients were collected within 3 hours of stroke onset, prior to treatment with thrombolytic. Patients were grouped by BP >185/110 mm Hg (n=19) and BP <185/110 mm Hg (n=46). Total blood RNA was assessed by whole genome microarray and differential gene expression analyzed by ANCOVA. Functional analysis of identified genes was performed. Correlation analysis was conducted to identify genes correlated with systolic blood pressure.

RESULTS
Strokes with admission BP >185/110 mm Hg had 231 genes differentially expressed compared to strokes with BP <185/110 mm Hg ($p < 0.05$, fold change $\geq |1.2|$). Key genes and pathways associated with BP>185/110 mm Hg included downregulation of caveolin-1 and upregulation of matrix metalloproteinases (MMPs). Several of these genes, including MMP-21, linearly correlated with increasing systolic blood pressure ($r=0.25$, $p = 0.02$).

CONCLUSIONS
A blood pressure >185/110 mm Hg is associated with differential immune activation in patients with acute ischemic stroke, including caveolin-1 and matrix metalloproteinases. These differences may contribute to blood-brain barrier disruption and risk of hemorrhagic transformation in acute stroke patients with blood pressure >185/110 mm Hg. Whether modulating immune activation could reduce blood-brain barrier disruption and risk of HT requires further study.

Supervisor: Dr. Glen Jickling