

# Research DAY

Department of Medicine 2015

GRADUATE STUDENTS | RESIDENTS | POSTDOCTORAL FELLOWS



**THURSDAY, MAY 14, 2015**

**ORAL PRESENTATIONS**

**CLASSROOM D**

**2F1.04 WALTER MACKENZIE CENTRE**

**POSTER PRESENTATIONS**

**LOWER LEVEL**

**JOHN W SCOTT HEALTH SCIENCES LIBRARY**



# Research DAY

Department of Medicine 2015

In 2014 the Department of Medicine contributed 718 original, peer-reviewed research papers to the literature, plus many scholarly reviews, book chapters, books and abstracts. The work spans the spectrum from molecule to patient, and from patients to health systems. In 2014 there was a paper in the *Journal Cell* from one of our Professors, one in *PNAS* from a new Assistant Professor, several in the *NEJM*, *JAMA* and *BMJ* among many others in prominent journals. Research is central to what we do – it is the life-blood of academic 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 66 graduate students and 28 postdoctoral fellows, and 185 residents are training in our core and subspecialty programs. Almost all of the 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:

Mark Zeidel, M.D. is Chair of the Department of Medicine at the Beth Israel Deaconess Medical Center, Harvard Medical School. He is a clinician-scientist with substantial contributions in the area of discovery research, but he also has a significant interest in the scholarship of quality improvement.

David Eisenstat, M.D., Professor of Pediatrics and Division Director of iHOPE (Immunology, Hematology, Oncology and Palliative Care). Dr. Eisenstat is also a clinician scientist with a specific interest in pediatric central nervous system tumors.

## **Barbara J. Ballermann, MD**

## **Evangelos D. Michelakis, MD, Associate Chair (Research)**

*For the students presenting their first abstract today:*

### **The First Step**

The young poet Evmenis  
complained one day to Theocritus:  
"I've been writing for two years now  
and I've composed only one idyll.  
It's my single completed work.  
I see, sadly, that the ladder  
of Poetry is tall, extremely tall;  
and from this first step I'm standing on now  
I'll never climb any higher."  
Theocritus retorted: "Words like that  
are improper, blasphemous.  
Just to be on the first step  
should make you happy and proud.  
To have reached this point is no small achievement:  
what you've done already is a wonderful thing.  
Even this first step  
is a long way above the ordinary world.  
To stand on this step  
you must be in your own right  
a member of the city of ideas.  
And it's a hard, unusual thing  
to be enrolled as a citizen of that city.  
Its councils are full of Legislators  
no charlatan can fool.  
To have reached this point is no small achievement:  
what you've done already is a wonderful thing."

***Constantine P. Cavafy (1904)***

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## Research Day Guest Oral Adjudicator

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Mark L. Zeidel, M.D., is Herrman L. Blumgart Professor of Medicine at Harvard Medical School and Chair of the Department of Medicine at Beth Israel Deaconess Medical Center in Boston. He is known as a productive and highly original scientist, an innovative educator, a leader in improving the quality of healthcare, and an effective chair of medicine. In his field, he has made multiple seminal observations: defining the role of atrial peptides in renal salt excretion, characterizing the biophysical function of water channels and barrier membranes, and advancing urothelial cell biology. His innovations in physiology teaching include an animated textbook, highly novel and nationally prominent week-long courses at the Mount Desert Island Biology Laboratories, and an upcoming series of review articles in his field's major clinical journal. He has pioneered the provision of highly reliable, cost-effective care, both at the U Pitt and Beth Israel Deaconess Medical Center (BIDMC), and helped make quality care a major priority of Alliance for Academic Internal Medicine. He is responsible for BIDMC's achievement of outstanding clinical outcomes, recognized by the American Hospital Association, Society for Critical Care Medicine, the Leapfrog Group, and HHS. He has led the BIDMC medicine department to develop a highly innovative curriculum in quality improvement for its residents and fellows; this serves as a template for all the training programs in the hospital, and a national model for helping residents achieve the competency in practice based learning and improvement and system based practice.

A *summa cum laude* graduate of Yale College, he received his medical degree from Columbia University College of Physicians and Surgeons, where he was elected to the national honor medical society, *alpha omega alpha*. He then served as an intern and resident in Medicine at Brigham and Women's Hospital in Boston, followed by a renal fellowship at the same institution. He came to Beth Israel Deaconess Medical Center in July 2005 from the University of Pittsburgh School of Medicine where his tenure spanned 12 years, first serving as Chief of the Renal and Electrolyte Division of the Department of Medicine, and then, starting in 1999, as the Jack D. Myers Professor and Chair of the Department of Medicine. He has served on many regional and national committees and is recognized by his peers for his numerous accomplishments, including elected membership to the American Society of Clinical Investigation and the Association of American Physicians.

# Research Day Guest Oral Adjudicator

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Dr. David Eisenstat is a Professor in the Department of Pediatrics and holds cross-appointments in the Departments of Medical Genetics and Oncology at the University of Alberta. David is the Division Director, Pediatric Immunology, Hematology/Oncology, Palliative Care and Environmental Health (iHOPE) and is the inaugural Muriel and Ada Hole Kids with Cancer Society Chair in Pediatric Oncology. He is also serving as the Interim Co-Director of the Cancer Research Institute of Northern Alberta (CRINA).



His laboratory is interested in the interface between nervous system cell fate, cancer and development, especially childhood brain tumours and retinoblastoma.

Dr. Eisenstat obtained his MD from the University of Toronto in 1985. David completed his Pediatrics residency at the Hospital for Sick Children (HSC) in 1990. After a Clinical Fellowship in Pediatric Hematology-Oncology at HSC, David joined the Laboratory of Molecular Neuro-Oncology in the Brain Tumor Research Center at the University of California, San Francisco (UCSF). In 1993, funded by the Medical Research Council of Canada, David worked with Dr. John Rubenstein in the Laboratory of Developmental Neurobiology and was awarded a Master's degree in Neuroscience from UCSF in 1997. In 1998, David was a Clinical Fellow in Pediatric and Adult Neuro-Oncology at the University of Texas M.D. Anderson Cancer Center.

David began his first faculty appointment at the University of Manitoba, Winnipeg, Canada, in 1999. Dr. Eisenstat was Director of the Advanced Degrees in Medicine at the University of Manitoba from 2007-2011 overseeing the MD/PhD and B.Sc. (Medicine) programs, and Senior Investigator in the Manitoba Institute of Cell Biology as well as Director of Neuro-Oncology for CancerCare Manitoba, from 1999 to 2011. He established the Canadian National Medical Student Research Symposium in 2009; this event continues to be held in Winnipeg on an annual basis.

Dr. Eisenstat is especially proud to have been awarded the Aubie Angel Young Investigator Award in Clinical Research in 2004, the Health Sciences Graduate Students Association Distinction in Mentorship Award in 2006, both from the University of Manitoba, and the Pediatric Chairs of Canada Pediatric Academic Leadership – Clinical Educator Award in 2010.

# Meeting at a Glance

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<b>8:00-8:15</b>	Welcome Address (Dr. E. Michelakis and Dr. B. Ballermann)
<b>8:15-8:30</b>	<b>Dr. Mark Zeidel Presentation</b>
<b>8:45-10:00</b>	Oral Presentations (Session Chair, Dr. S. McMurtry)
<b>10:00-10:15</b>	<b>Break</b>
<b>10:15-11:15</b>	Oral Presentations
<b>11:15-1:00</b>	Poster Presentations and <b>Lunch</b>
<b>1:00-1:15</b>	Translational Fellowship Award
<b>1:15-2:15</b>	Oral Presentations (Session Chair, Dr. D. Rolfson)
<b>2:15-2:30</b>	<b>Break</b>
<b>2:30-3:30</b>	Oral Presentations
<b>3:30</b>	<b>Break</b>
<b>4:15</b>	<b>Award Ceremony</b>





# Morning Oral Presentations

## Classroom D, 2F1.04 WMC

Time	Name	Title	Page
8:45	<b>Jenelle Pederson</b> Supervisor: Finlay McAlister	GS Depression Is A Negative Prognostic Factor For 30-Day Readmission Or Mortality In Patients Discharged From General Internal Medical Wards: A Multi-Site Prospective Cohort Study	22
9:00	<b>Braden Millan</b> Supervisor: Dina Kao	GS Effects of Fecal Microbial Transplantation on the Gut Resistome in Patients with Recurrent Clostridium difficile infection	23
9:15	<b>Sotirios Zervopoulos</b> Supervisor: Evangelos Michelakis	GS Microtubules Mediate Nuclear-Mitochondrial Communication Through $\alpha$ -tubulin Acetylation	24
9:30	<b>Mandana Rahbari</b> Supervisor: Andrew Mason	GS Immunological Profiling of Patients with PBC Against HBRV	25
9:45	<b>Vivek Gandhi</b> Supervisor: Harissios Vliagoftis	GS Growth Factors Regulate Proteinase-Activated Receptor-2 (Par-2) Expression On Airway Epithelium	26

**10:00 Break**





# Morning Oral Presentations

## Classroom D, 2F1.04 WMC

Time	Name	Title	Page
10:15	<b>Adam Kinnaird</b> Supervisor: Evangelos Michelakis	GS Myocyte Enhancer Factor 2A (Mef2A) is a Novel Biomarker and Therapeutic Target in Human Renal Cell Carcinoma	27
10:30	<b>Mahtab Tavasoli</b> Supervisor: Barbara J. Ballermann	GS Hypertension-Induced Pak1 Activation in Renal Glomeruli requires CLIC5A	28
10:45	<b>Roxane Paulin</b> Supervisor: Evangelos Michelakis	PDF Prohibitin: A Potential Circulating Mitokine That May Be Involved in Pulmonary Arterial Hypertension.	29
11:00	<b>Eugene Asahchop</b> Supervisor: <b>Christopher Power</b>	PDF Plasma MicroRNA Profiling Predicts HIV-Associated Neurocognitive Disorder	30

**11:15 Poster Sessions**



# Afternoon Oral Presentations

## Classroom D, 2F1.04 WMC

Time	Name	Title	Page
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1:30	<b>Laura Gioia</b> Supervisor: Kenneth Butcher	PDF Cerebral Blood Flow Within The Ischemic Penumbra Is Unrelated To Prehospital Blood Pressure	32
1:45	<b>Anand Krishnan</b> Supervisor: Douglas Zochodne	PDF Nuclear functions of BRCA1 Modify Regenerative Growth Response in Peripheral Neurons	33
2:00	<b>Vivian Huang</b> Supervisor: Richard Fedorak	PDF Fecal Calprotectin: A Biomarker and Predictor of Disease Activity During Pregnancy in Women with Inflammatory Bowel Disease	35
<b>2:15</b>	<b>Break</b>		



# Afternoon Oral Presentations

Classroom D, 2F1.04 WMC

<b>Time</b>	<b>Name</b>	<b>Title</b>	<b>Page</b>
2:30	<b>Christopher Ma</b> Supervisor: Richard Fedorak	CIM Early Initiation of Anti-Tnf Therapy Reduces The Risk of Loss of Response and Surgical Resection In Patients With Inflammatory Bowel Disease	37
2:45	<b>Zainab Alabdurubalnabi</b> Supervisor: Cynthia Wu	CIM Appropriateness of Thrombophilia Testing in Tertiary Care Centers in Edmonton	39
3:00	<b>ThucNhi Dang</b> Supervisor: Richard Fedorak	CIM Phenotypic Effects of Celiac Disease with Coexistent Inflammatory Bowel Disease	41
3:15	<b>Michael Ney</b> Supervisors: Puneeta Tandon	CIM Lifestyle Interventions in Patients with Cirrhosis – An Assessment of the Current Status and Patient Perceived Barriers to Intervention	43
3:30	<b>Sana Vahidy</b> Supervisor: Raj Padwal	CIM A Comparison of Casual In-Clinic Blood Pressure Measurements to Standardized Measurements in Severely Obese Individuals	44
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2	<b>Belga, Sara</b> Supervisor: Finlay McAlister	CIM Comparing the Predictive Impact of 3 Different Measures of Frailty On Short-Term Rates of Death or Readmission In Medical Inpatients: Multicenter Prospective Cohort Study	48
3	<b>Brar, Sandeep</b> Supervisor: Neesh Pannu	CIM Medication Use and Survival After Acute Kidney Injury	49
4	<b>Choi, Woo Young</b> Supervisor: Jason Barton	CIM Dynamics of Target and Distractor Spatial Averaging in The Global Effect of Saccades	50
5	<b>Cusnir, Ina</b> Supervisor: Anthony Russell	CIM Antimalarial Drugs Alone May Still Have a Role in Rheumatoid Arthritis	51
6	<b>Dissanayake, Tharindri</b> Supervisor: Steven Katz	CIM Natural Health Product Use in Patients with Rheumatological Conditions Based On Gender, Age, Education Level and Work Status	53
7	<b>Dissanayake, Tharindri</b> Supervisor: Steven Katz	CIM Natural Health Product Use in Patients with Rheumatological Conditions	54
8	<b>Fong, Shannon</b> Supervisor: Anna Oswald	CIM What Role Do Patient Educators Play in Medical Students' Development as Medical Professionals?	55



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10	<b>Lau, Darren</b> Supervisor: Finlay McAlister	CIM	Patient-Reported Discharge Readiness and 30-Day Risk of Readmission or Death: A Prospective Cohort Study	57
11	<b>Ma, Christopher</b> Supervisor: Richard Fedorak	CIM	IBD Patients are Frequently Non-Adherent with Scheduled Induction and Maintenance Infliximab	58
12	<b>Madsen, Norman</b> Supervisor: Elaine Yacyshyn	CIM	A Survey Of Safety Device Use in Joint Injection Amongst Canadian Rheumatologists	60
13	<b>Martow, Evan</b> Supervisor: Liam Rourke	CIM	Learning to Interpret ECGs: A Meta-Analysis	61
14	<b>Mazurek, Matthew</b> Supervisor: Maria Ho	CIM	Comparison of Adverse Events During Capecitabine Versus 5-Fluorouracil/Oxaliplatin Adjuvant Chemotherapy for Stage II/III Colon Cancer: A population based analysis	62
15	<b>McFarlane, Alexandra</b> Supervisor: Lynora Saxinger	CIM	Hospitalized Influenza Patients During 2013-2014; a Comparison of ICU and Ward Treated Patients Including Antimicrobial Therapy, Adverse Events, and Outcomes	64
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19	<b>Qamar, Hina</b> Supervisor: Cynthia Wu	CIM	A Unique Case of Superficial Vein Thrombosis and Disseminated Intravascular Coagulation	68
20	<b>Refaei, Mohammad</b> Supervisor: Cynthia Wu	CIM	Incidence of Catheter-related Venous Thromboembolism Event in Acute Leukemia patients; a retrospective study of the safety of Peripherally-Inserted Central Catheter	69
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# Scoring Criteria

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## Oral & Poster Presentations (1=Poor, 5= Excellent)

Clarity and Justification of the Research Questions/Hypothesis	1 2 3 4 5
Appropriateness of the Methods Used to Answer the Questions/Hypothesis	1 2 3 4 5
Validity and Relevance of the Results to the Questions/Hypothesis	1 2 3 4 5
Quality of the Discussion and Conclusion	1 2 3 4 5
Visual Layout and Visual Impact	1 2 3 4 5
Oral Response to Adjudicator's Question	1 2 3 4 5
<b>TOTAL SCORE</b>	<hr/> <b>35</b>



# **DEPRESSED PATIENTS HAVE A HIGHER FREQUENCY OF 30-DAY READMISSION OR MORTALITY AFTER DISCHARGE FROM GENERAL INTERNAL MEDICAL WARDS: A MULTI-SITE PROSPECTIVE COHORT STUDY**

Jenelle L. Pederson BA, Sumit R. Majumdar MD MPH, Raj S. Padwal MD MSc, Sharry Kahlon MD MHA, Sara Belga MD, Darren Lau MD PhD, Miriam Fradette BScPharm, Debbie Boyko RN, Mary Forhan MHSc PhD, Jeffrey A. Johnson PhD, Finlay A. McAlister MD MSc  
Supervisor: Dr. Finlay McAlister

## **INTRODUCTION**

Although unplanned readmissions and early death after discharge are frequent and serious events, predicting who is at risk is imperfect. Our aim was to investigate whether in-hospital depressive symptoms impacts 30-day readmission or death in patients discharged from General Internal Medicine (GIM) wards.

## **METHODS**

We assessed depressive symptoms before discharge in a prospective cohort of adults from 7 GIM wards at 2 teaching hospitals between 2013 and 2014 in Edmonton. Moderate-to-severe depressive symptoms (hereafter “depression”) were defined as score  $\geq 11$  on the previously validated 27-point Patient Health Questionnaire (PHQ-9). Primary outcome was the composite endpoint of 30-day readmission or death.

## **RESULTS**

Overall, 495 adults were enrolled with a median age of 64 years; 51% were women; 32% had diabetes; and 23% had history of comorbid depression. Most common reasons for admission were heart failure (10%), pneumonia (10%), and chronic lung disease (8%). In-hospital, 127 (26%) patients were classified as being depressed and only 46% of these had known comorbid depression. Depressed patients were more likely to be readmitted or die within 30-days of discharge: 27 (21.3%) versus 58 (15.8%) non-depressed patients ( $p=0.20$ ). In multivariable logistic regression analysis adjusted for age, sex, length of stay, prior emergency room visits, and comorbidities, depression was not independently associated with an increased risk of death or readmission (adjusted odds ratio 1.56 (95%CI 0.91-2.66),  $p=0.09$ ). Among those depressed in-hospital, 40% still had depression 30-days after discharge.

## **CONCLUSIONS**

Moderate-to-severe depressive symptoms were present in one-quarter of patients at time of hospital discharge, and at 30-days symptoms persisted in 40% of patients. Depression at discharge was associated with a higher frequency of readmission/death at 30 days, but this was not maintained on multivariate analysis. Further research is needed to determine whether mental health may be a modifiable risk factor for preventing post-discharge adverse events.



# Effects of Fecal Microbial Transplantation on the Gut Resistome in Patients with Recurrent Clostridium difficile infection

Braden Millan<sup>1</sup>, Naomi Hotte<sup>1</sup>, Olivier Mathieu<sup>2</sup>, Pierre Burguiere<sup>2</sup>, Thomas A. Tompkins<sup>2</sup>, Dina Kao<sup>1</sup>, Karen Madsen<sup>1</sup>  
Supervisor: Dina Kao

## INTRODUCTION

The emergence of drug-resistant pathogens has occurred as a direct result of increased usage of antibiotics and the gut microbiome harbors an enormous reservoir of microbes. Recurrent Clostridium difficile infection (RCDI) is associated with repeated antibiotic use and enhanced growth of antibiotic-resistant microbes. Treatment of RCDI with fecal microbial transplantation (FMT) is known to be efficacious, however its effect on the antibiotic resistant profile (resistome) of the recipient is unknown. The aim of this study was to determine if FMT alters the resistome in the gut microbiome of patients with RCDI and if changes are maintained over time.

## METHODS

Patients with RCDI (n=23) received FMT from 1 of 3 donors via colonoscopy. Fifteen patients were cured of RCDI following one infusion while eight required a second infusion from a different donor. Stool samples were collected from donors and patients prior to and at 2-52 weeks post FMT. DNA was extracted and analyzed on a custom oligonucleotide-based DNA microarray containing a total of 1,110 probes targeting 354 antibiotic resistance genes. Median signal intensities of three replicate spots per probe were used for analysis. The change in the gut resistome of the patient was compared over time to the donor and baseline samples.

## RESULTS

Prior to FMT, RCDI patients and individual donors exhibited large inter-individual variability in resistome profiles. Following FMT, the resistome of 19 of 23 patients showed dramatic changes to resemble the resistome profile of the specific donor; 4 patients did not show similarity to the donor and 12 of 16 with greater than 3 month follow-up maintained this change.

## CONCLUSIONS

In patients with RCDI, FMT alters the antibiotic resistant profile of most recipients to resemble the donor and is maintained over time. Selecting and screening donors based upon their resistome may be important to prevent transmission of potentially harmful antibiotic resistance genes.

Supervisor: Dr. Dina Kao

# **Microtubules mediate nuclear-mitochondrial communication through $\alpha$ -tubulin acetylation**

Zervopoulos S, Kinnaird A, Gurtu V, Boukouris AE and Michelakis ED  
Supervisor: Dr. Evangelos Michelakis

## **INTRODUCTION**

Mitochondria span the cytoplasm and form a dynamic network. Like the mitochondria, vesicles, endosomes and chaperones move between organelles using motor proteins that anchor on microtubules (cellular “highways”). The stability of microtubules ( $\alpha$ - and  $\beta$ -tubulin heterodimers) is regulated by acetylation by  $\alpha$ -tubulin acetyltransferase 1 ( $\alpha$ TAT1) versus de-acetylation by histone deacetylase 6. We recently showed (Cell; 2014) that the mitochondrial enzyme pyruvate dehydrogenase complex (PDC), which produces acetyl-CoA for the Krebs cycle, can be found in the nucleus as well, where it produces acetyl-CoA for histone acetylation and cell cycle progression. The precise mechanism for the PDC translocation remained unclear, although it involved the chaperone Hsp70. We hypothesized that microtubule acetylation is involved in this translocation, facilitating either mitochondrial translocation around the nucleus (where they can directly “donate PDC”) or by facilitating the trafficking of vesicles/endosomes containing PDC toward the nucleus.

## **METHODS**

We used human foreskin fibroblasts and A549 non-small cell lung cancer cells. We studied the effects of different proliferative signals (hypoxia and serum stimulation) and tubacin (a specific inhibitor of histone deacetylase 6) on mitochondrial localization and microtubule acetylation levels. We measured nuclear PDC levels by immunoblot and confocal imaging and distribution of stained mitochondria.

## **RESULTS**

Hypoxia (1% oxygen), and serum stimulation resulted in increased tubulin acetylation, increased perinuclear clustering of mitochondria and increased levels of PDC in the nucleus. Tubacin increased tubulin acetylation and also increased levels of nuclear PDC but had no effect on mitochondrial perinuclear clustering.

## **CONCLUSIONS**

These preliminary data suggest that tubulin acetylation regulates the translocation of PDC from the mitochondria to the nucleus either by promoting direct mitochondria-to-nucleus contact or by facilitating intracellular trafficking of chaperone-associated vesicles or endosomes. This work may have applications to the biology of mitochondria-to-nucleus communication and may be relevant to diseases affecting nuclear histone acetylation and cell cycle progression.

Supervisor: Dr. Evangelos Michelakis

# Immunological profiling of patients with PBC against HBRV

Mandana Rahbari<sup>1</sup>, David Sharon<sup>1</sup>, Amir Landi<sup>2</sup>, Michael Houghton<sup>2</sup> and Andrew Mason<sup>1</sup>

Supervisor: Dr. Andrew Mason

## INTRODUCTION

Primary biliary cirrhosis (PBC) is known as a cholestatic liver disease of autoimmune origin. PBC is a disease of unknown etiology. Both genetic and environmental factors impact on the development of PBC. Our laboratory has characterized a human betaretrovirus (HBRV) in PBC patients which is highly homologous to the mouse mammary tumor virus (MMTV). Our objective is to characterize the relationship of HBRV infection with PBC. We hypothesize that patients with PBC make cellular immune responses to HBRV.

## METHODS

Peripheral blood mononuclear cells (PBMCs) were purified from whole blood of 29 patients with PBC and 34 controls. T-cell responses in PBMC were assessed for reactivity to HBRV peptides. PBMCs were stimulated for 6 hours with pools of overlapping 20-mer peptides from HBRV Envelope and Gag as well as human cytomegalovirus peptides and PHA-Ionomycin mitogens, which were used as a positive control. The magnitude of ex vivo responses to stimulation were evaluated by measuring the number of T-cells secreting IL-6, IL-4, IL-10, TNF- $\alpha$  and IFN- $\gamma$ ; assessed by flow cytometry.

## RESULTS

38% of patients with PBC showed memory CD8<sup>+</sup> T-cell responses to HBRV Gag peptides, whereas significantly lower number (13%) of control samples showed reactivity to HBRV Gag peptides,  $p < 0.04$ .

Out of 28 patients with PBC, 7% of patients showed memory CD8<sup>+</sup> T-cell response to HBRV Env pool of peptides, whereas 4% of controls showed response to the stimulation with pool of HBRV Env peptides.

Despite CD8<sup>+</sup> T-cells, memory CD4<sup>+</sup> T-cells did not show the same level of reactivity following HBRV Gag or HBRV Env stimulation in PBC and control samples.

## CONCLUSIONS

In our assay 38% of patients with PBC showed reactivity to HBRV Gag pool of peptides.

Higher population of PBC patients with a CD8<sup>+</sup> memory T-cell response to the HBRV Gag compared to the controls suggests a link between the virus and the disease.

Supervisor: Dr. Andrew Mason

# **GROWTH FACTORS REGULATE PROTEINASE-ACTIVATED RECEPTOR-2 (PAR-2) EXPRESSION ON AIRWAY EPITHELIUM**

Vivek Gandhi, Drew Nahirney and Harissios Vliagoftis  
Supervisor: Dr. Harissios Vliagoftis

## **INTRODUCTION**

We have previously shown that activation of PAR-2, a pro-inflammatory receptor for aeroallergens and endogenous serine proteinases, mediates allergic sensitization and allergic airway inflammation in animal models of asthma. PAR-2 expression is increased on the airway epithelium of asthmatics, but the mechanisms and factors responsible for increased expression as well as the consequences of increased PAR-2 expression are unknown. Since asthmatic airways are under various types of physiological stress, we hypothesize that cellular stress upregulates PAR-2 expression on airway epithelium and this upregulation leads to increased PAR-2-mediated airway inflammation.

## **METHODS**

Normal human bronchial epithelial cells (NHBE) and asthmatic human bronchial epithelial cells (AHBE) were cultured with or without growth factors (growth factor deprivation) and PAR-2 mRNA levels were studied by qRT-PCR. PAR-2 function was assessed by measuring PAR-2-mediated calcium release, from intracellular stores into the cytoplasm, and inflammatory mediator IL-8 release in supernatants.

## **RESULTS**

Growth factor deprivation upregulates PAR-2 mRNA in NHBE (2.3 $\pm$ 0.1 fold, n=13) and AHBE cells (2.4 $\pm$ 0.1 fold, n=6, 3 different asthmatic individuals). This upregulation was reversible, in both the cell types, upon growth factor addition. We then cultured NHBE cells in the absence of individual growth factor. Among them only the absence of insulin caused PAR-2 mRNA upregulation (1.6 $\pm$ 0.1 fold, n=5) and the upregulation was reversible upon insulin addition. Growth factor-deprived cells and only insulin-deprived cells, compared to cells with growth factors, released more calcium. Moreover, growth factor-deprived cells, compared to cells with growth factors showed higher IL-8 response upon PAR-2 activation (NHBE 1.7 $\pm$ 0.1 fold; n=6, AHBE 2.6 $\pm$ 0.4 fold; n=3).

## **CONCLUSIONS**

Relative growth factor deficiency in a background of tissue edema and inflammation may be the reason for PAR-2 upregulation in the asthmatic airway epithelium. Insulin may be an important factor for PAR-2 regulation. Since PAR-2 is pro-inflammatory, understanding its regulation could allow development of new anti-inflammatory treatments.

Supervisor: Dr. Harissios Vliagoftis

# **Myocyte enhancer factor 2A (Mef2A) is a novel biomarker and therapeutic target in human Renal Cell Carcinoma**

Adam Kinnaird, Bruno Saleme, Vikram Gurtu, Kristalee Watson, Trevor Stenson, Peter Dromparis and Evangelos Michelakis  
Supervisor: Dr. Evangelos Michelakis

## **INTRODUCTION**

Mef2A is a master transcription factor involved in cellular metabolism, proliferation and apoptosis. While nearly exclusively expressed in heart and skeletal muscle, it has recently been identified in leukemia, breast and hepatocellular carcinomas. Mef2A regulates the expression of several genes involved in mitochondrial suppression - a hallmark of renal cell carcinoma (RCC), a highly glycolytic cancer. We hypothesized that Mef2A is up-regulated in RCC, leading to mitochondrial suppression and therefore facilitating tumorigenesis.

## **METHODS**

Fluorescent immunohistochemistry was performed on normal kidney and RCC tissues collected from patients undergoing partial or radical nephrectomy. Stable knockdown of Mef2A with a plasmid encoding shRNA to Mef2A (Origene) was induced in human RCC cells, which were then used in a xenotransplant model of nude mice. Tumor sizes were measured weekly for 4-5 weeks.

## **RESULTS**

Human RCC tissues express significantly higher levels of Mef2A compared to normal kidney tissues taken from the same patients,  $n=23$  ( $p<0.01$ ). Knockdown of Mef2A depolarized the mitochondrial membrane potential (TMRM) and increased production of mitochondrial reactive oxygen species (Mitoxox);  $p<0.05$  for both. This was associated with an increase in apoptosis (TUNEL;  $p<0.05$ ) and reduction in proliferation (ki67;  $p<0.01$ ). shMef2A tumor xenografts were significantly smaller compared to the shScr (scrambled shRNA) control tumors (167mm<sup>3</sup> vs. 440mm<sup>3</sup>, respectively;  $n=7$  and 12 mice, respectively,  $p<0.01$ )

## **CONCLUSIONS**

Mef2A is up-regulated in human RCC compared to normal kidney from the same patients, representing a novel biomarker for this disease. Inhibition of Mef2A increases mitochondrial activity and reduces tumor size, opening the potential of a new therapeutic approach to RCC, a tumor that remains fatal.

Supervisor: Dr. Evangelos Michelakis

# Hypertension-Induced Pak1 Activation in Renal Glomeruli requires CLIC5A.

Mahtab Tavasoli\*, Laiji Li, Lin-fu Zhu, Abass Al-Momany, Benjamin Alexander Adam, Zhixiang Wang and Barbara J. Ballermann  
Supervisor: Dr. Barbara J. Ballermann

## INTRODUCTION

Hypertension is a significant risk factor for chronic kidney disease progression, and glomerular capillary hypertension plays a major role in the development of diabetic nephropathy. CLIC5A is a glomerulus-predominant protein that triggers PI[4,5]P2-dependent ERM protein ezrin phosphorylation, in turn organizing the structure of glomerular podocytes. Since PI[4,5]P2 generation by PI[4]P5 kinase is Rac1 dependent, and glomerular hypertension activates Rac1, we determined whether CLIC5A interacts functionally with Rac1 and whether hypertension-induced Rac1 activation in glomeruli is CLIC5A-dependent

## METHODS

COS7 cells were co-transfected with GFP-CLIC5A or GFP and the PI[4,5]P2 reporter RFP-PH-PLC followed by live cell imaging. Uninephrectomized CLIC5 deficient (CLIC5<sup>-/-</sup>) and wild-type (CLIC5<sup>+/+</sup>) mice were treated with deoxycorticosterone and 1% saline drinking water (DOCA/Salt) for 20 days. COS7 cell and glomerular lysates were evaluated for activated Rac1-GTP, and for the Rac1 effector phospho-Pak1 (pPak1) and pERM.

## RESULTS

In COS-7 cells, GFP-CLIC5A, but not GFP, increased the level of active GTP-Rac1, enhanced apical PI[4,5]P2 cluster formation, and activated phosphorylation of the known Rac1 effector Pak as well as ezrin. GFP-CLIC5A-dependent PI[4,5]P2 cluster formation, Pak and ezrin phosphorylation were all blocked by the Rac1 inhibitor NSC23766 and by dominant negative Rac1 N17. Based on WB and immunofluorescence microscopy, pPak1 and pERM were significantly reduced in podocytes of CLIC5<sup>-/-</sup> relative to CLIC5<sup>+/+</sup> mice. In CLIC5<sup>+/+</sup> mice glomerular Pak expression and phosphorylation were strongly induced by hypertension. By contrast, while Pak1 expression was also induced in hypertensive CLIC5<sup>-/-</sup> mice, Pak1 remained un-phosphorylated. The degree of systemic hypertension was similar in CLIC5<sup>-/-</sup> and CLIC5<sup>+/+</sup> mice, but albuminuria and morphological injury were much greater in CLIC5<sup>-/-</sup> mice.

## CONCLUSIONS

Rac1 activation and downstream Pak phosphorylation are components of the podocyte response to DOCA/Salt hypertension, and depend critically on CLIC5A. The findings also suggest that protection from hypertension-induced glomerular injury requires CLIC5/Rac1/Pak1/ezrin dependent podocyte remodeling.

Supervisor: Dr. Barbara J. Ballermann

# **Prohibitin: a potential circulating mitokine that may be involved in Pulmonary Arterial Hypertension.**

Roxane Paulin, Adam Kinnaird, Aristeidis Boukouris, Vikram Gurtu and Evangelos D. Michelakis

Supervisor: Evangelos D. Michelakis

## **INTRODUCTION**

Pulmonary hypertension (PHT) is characterized by remodeled pulmonary arteries with suppressed apoptosis and mitochondrial suppression. In patients with PAH, extrapulmonary organs (heart, skeletal muscle, immune cells) have a similar suppression of mitochondria, raising the intriguing probability of a circulating mitochondrial inhibitor. In worms, there is recent evidence that (yet unidentified) “mitokines” can be secreted by tissues undergoing metabolic stress in order to “condition” remote organs. Prohibitin (PHB) is increased in both the tumor and the serum of cancer patients and may act as a “sensor” of metabolic signals. We hypothesized that PHB may be a mitokine candidate that may be involved in PAH. We speculated that a tumor-derived PHB (human breast cancer growing in the flank of xenotransplanted rats) may induce PAH.

## **METHODS**

We used CRL-2335 breast cancer cells and human healthy pulmonary artery smooth muscle cells (hhPASMCs) in culture as well as a rat xenotransplant model in vivo.

## **RESULTS**

Rats with tumor (n=18) developed a mild degree of pulmonary hypertension (closed chest catheterization, mPAP=12±1mmHg vs 20±2mmHg), which correlated with tumor size. Pulmonary embolism was excluded and muscularization remodeling of pulmonary arteries was increased (histology). PHB1 levels were increased in the serum of rats with tumor compared to controls and in the culture media of CRL2335 compared to normal cells. PASMCs exposed to Recombinant (Rec)PHB1 displayed mitochondrial suppression showing inhibition of pyruvate dehydrogenase, increased mitochondrial membrane potential (TMRM live cell imaging 37±0.5AFU vs 53±1.2AFU) and decreased respiration (Seahorse analyser). Preliminary data suggested that RecPHB1 activates the plasma membrane receptor ErbB2, which is translocated into the mitochondria (immunoblot on isolated mitochondria and immunostaining) where it acts as a negative regulator of mitochondrial function.

## **CONCLUSIONS**

We identified PHB1 as a potential mitokine that may explain the global metabolic changes in PAH and perhaps other conditions, including cancer cachexia.

Supervisor: Dr. Evangelos D. Michelakis



# Plasma MicroRNA profiling predicts HIV-Associated Neurocognitive Disorder

Eugene L. Asahchop<sup>1</sup>, William G. Branton<sup>1</sup>, Segun M. Akinwumi<sup>4</sup>, Noshin Koenig<sup>5</sup>, Esther Fujiwara<sup>3</sup>, John Gill<sup>5,6</sup>, Christopher Power<sup>1,2,3</sup>  
Supervisor: Dr Chris Power

## INTRODUCTION

The development of HIV-associated neurocognitive disorder (HAND) is influenced by multiple factors including altered host and viral gene expression. Host-encoded microRNAs (miRNAs) could contribute to the pathogenesis of HAND and thus, might serve as biomarkers of diagnosis and prognosis. Herein, we investigated plasma microRNA profiles among HIV/AIDS patients with and without HAND.

## METHODS

Plasma microRNAs was measured in HAND (n=22) or nonHAND (n=25) patients with HIV/AIDS (Cohort 1) by array hybridization (Affymetrix 3.0 miRNA genechip). Two software packages (Affymetrix Expression Console and Gene Spring) enabled normalization of data and determination of differentially-expressed miRNAs in the HAND versus nonHAND groups. A second cohort (Cohort 2), consisting of prospectively recruited HAND (n=12) and nonHAND (n=12) patients, was used to validate the miRNA profile in Cohort 1.

## RESULTS

Analyses of comparative expression identified 13 miRNAs in Cohort 1 that were up-regulated (fold change  $\geq 2$ ) in the HAND group compared to the nonHAND group ( $p < 0.05$ ). Analysis of Cohort 2 confirmed up-regulation of 3 miRNAs also identified in Cohort 1 and were verified subsequently by RT-PCR ( $p < 0.05$ ). The 3 microRNAs targeted host genes implicated in inflammation, cell survival and neuronal growth. In a univariate logistic regression analysis, education, CD4 and nadir CD4 T cell levels as well as these three miRNAs predicted HAND status. Prediction of HAND status by the individual miRNAs was more robust than either CD4 nadir or CD4 T cell levels. ROC curves showed that area under the curve (AUC) ranged from 0.78 to 0.86 depending on the individual miRNA.

## CONCLUSIONS

Our findings revealed differential expression of three cell plasma-derived miRNAs in HAND versus nonHAND patients in two cohorts that were predictive of diagnosis of HAND. These results imply that plasma miRNAs might be used as biomarkers for HAND but also provide insights into the underlying disease mechanisms.

Supervisor: Dr Chris Power

# **BLOOD PRESSURE REDUCTION WITH LABETALOL/GLYERINE TRINITRATE DOES NOT AFFECT CEREBRAL BLOOD FLOW IN ACUTE ISCHEMIC STROKE.**

Mahesh Kate<sup>1</sup> MBBS, MD, DM, Negar Asdaghi<sup>2</sup> MD, Laura Gioia<sup>1</sup> MD, Brian Buck<sup>1</sup> MD, MSc, Thomas Jeerakathil<sup>1</sup> MD, MSc, Ashfaq Shuaib<sup>1</sup> MD, Kenneth Butcher<sup>1</sup> MD, PhD

Supervisor: Dr Kenneth Butcher

## **INTRODUCTION**

Blood pressure (BP) reduction in acute ischemic stroke has been postulated to be harmful via reduced cerebral blood flow (CBF). We tested this hypothesis with stratified BP reduction in a 3-group non-randomized prospective study of serial CBF measurements.

## **METHODS**

Fifty-two patients underwent perfusion-weighted MRI (PWI) pre and 15 minutes following antihypertensive therapy. Treatment was stratified by mean arterial pressure (MAP); >120mmHg (n=14 patients): intravenous labetalol (5-20mg) and sublingual (SL) glyceryl trinitrate (0.3mg); MAP 100-120 mmHg (n=19): SL glyceryl trinitrate(0.3mg); MAP<100 mmHg(n=19): no antihypertensive drugs.

## **RESULTS**

Baseline perfusion weighted-MRI was performed at a mean±SD 23.4±15h from symptom onset. Baseline mean relative CBF (rCBF) in hypoperfused tissue was 0.84±0.17 in the MAP >120 group, 0.7±0.2 in the MAP 100-120 group and 0.84±0.17 in MAP<100 group (p=0.07). Median (IQR) hypoperfused tissue volume (CBF<18 ml/min/100g): MAP>120:6(17.3) ml; MAP100-120: 8.9(70) ml, and MAP<100: 32(41.4)(p=0.05). The time between pre and post-treatment PWI was 26.3±9.8min. Median post-treatment MAP reduction was 12.5(12.9) mmHg in the MAP>120 group, 6(16.4) mmHg in MAP100-120 group and 0.3(10) mmHg in the MAP<100 group (p=0.04). The mean post-treatment change in rCBF was similar in all 3 groups (MAP >120: 0.03±0.12, MAP 100-120: -0.06±0.19, and MAP<100: 0.01±0.11, p=0.5). Similarly, there was no difference in hypoperfused tissue volume after MAP reduction, between groups (MAP>120: -0.2±13.8ml, MAP 100-120: -2±17ml, and MAP<100: -1.9±16.5ml, p=0.5).

## **CONCLUSIONS**

Acute BP reduction in ischemic stroke does not exacerbate acute hypoperfusion severity or volume. The stability of CBF following antihypertensive therapy suggests these drugs may be safer acutely than has been assumed.

ClinicalTrials.gov Identifier:NCT02327793

Supervisor: Dr Kenneth Butcher

# **Cerebral Blood Flow Within The Ischemic Penumbra Is Unrelated To Prehospital Blood Pressure**

Laura C Gioia, Mahesh P Kate, Ken Butcher  
Supervisor: Dr. Ken Butcher

## **INTRODUCTION**

Resistance to treating elevated prehospital blood pressure (BP) in acute ischemic stroke is based on the fear of exacerbating decreases in cerebral blood flow (CBF) within the penumbra, despite an absence of available data. We tested the hypotheses that prehospital SBP is correlated to the severity and volume of cerebral hypoperfusion.

## **METHODS**

We conducted a retrospective analysis of acute ischemic stroke patients who underwent CT perfusion (CTP) at hospital admission and prior to antihypertensive or thrombolytic therapy. Ischemic penumbra was defined as cerebral tissue with a relative delay time (rDT) >2 seconds, and ischemic core was defined as rDT >2 seconds and relative CBF (rCBF) <30%. Pre-hospital SBP was obtained from EMS electronic records.

## **RESULTS**

A total of ninety-four patients with a mean  $\pm$  SD age of  $64.2 \pm 17.0$  years and a median (IQR) NIHSS of 12 (11) were included. The mean prehospital SBP was  $149.7 \pm 27$  mmHg. The median time from symptom onset to CTP was 4.8 (7.4) hours. Median penumbral volume was 32.9(46) mL with a mean rCBF of  $0.83 \pm 0.18$ . Median ischemic core volume was 21.3(31.9) mL, with a mean rCBF of  $0.34 \pm 0.18$ . Prehospital SBP was not correlated with penumbral rCBF ( $r=-0.65$ ,  $p=0.63$ ) or ischemic core rCBF ( $r=-0.03$ ,  $p=0.8$ ). Prehospital SBP was inversely correlated with penumbral tissue volume ( $r=-0.29$ ,  $p=0.008$ ). However, the correlation was no longer present after adjustment for the presence of large vessel occlusion ( $r^2=0.19$ ,  $p=0.48$ ). Prehospital SBP was not correlated with ischemic core volumes ( $r=-0.19$ ,  $p=0.1$ ).

## **CONCLUSIONS**

We found no relationship between prehospital SBP and penumbral or core CBF in untreated acute ischemic stroke patients. Although acute penumbral perfusion values and volumes are variable, this is likely related to other factors, including large vessel occlusion, and cannot be explained by prehospital SBP.

Supervisor: Dr. Ken Butcher

# **Nuclear functions of BRCA1 modify regenerative growth response in peripheral neurons**

Anand Krishnan, Jose A. Martinez, Kaylynn Purdy, Ambika Chandrasekhar, Arul Duraikannu & Douglas W. Zochodne  
Supervisor: Dr. Douglas Zochodne

## **INTRODUCTION**

Injuries to peripheral nerves, and associated disruption of neural signaling, result in loss of movement and sensation. Sustaining the regenerative growth response in neurons until the regrowing axons reach their targets is the key strategy for improving peripheral nerve regeneration. Intrinsic neuronal reprogramming that immediately follows a nerve injury favors regenerative growth responses in neurons. We have identified that tumor suppressor molecules modify intrinsic neuronal reprogramming, and thereby regulate the regenerative growth response. In this work, we investigated the role of BRCA1 (breast cancer susceptibility gene 1), a well-known tumor suppressor, transcriptional regulator and DNA repair protein, on the regenerative growth response in peripheral neurons.

## **METHODS**

Adult sensory neuron cultures were established from DRG (dorsal root ganglia) neurons isolated from adult SD rats. BRCA1 expression in neurons was modified using non-viral mediated siRNA transfection. Total neurite outgrowth was measured using metaexpress software. Inhibition of nuclear translocation of BRCA1 was achieved using a novel peptide synthesized in-house. In vivo axon regeneration and functional recovery studies were done using sciatic nerve transection and crush injury models respectively.

## **RESULTS**

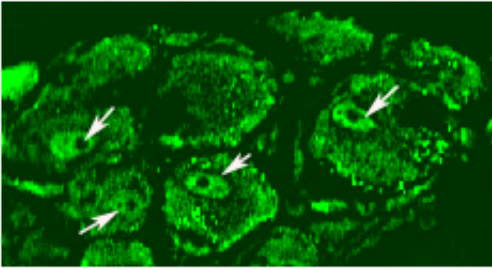
We identified increased nuclear expression of BRCA1 in injured neurons. Transient knockdown of BRCA1 resulted in reduced neuronal outgrowth. We noted that cultured neurons with higher sprouting capacity exhibit increased nuclear expression of BRCA1. Blocking of nuclear entry of BRCA1 limited neuronal sprouting in vitro. In vivo knockdown of BRCA1 impaired peripheral nerve regeneration and functional recovery. PCR-array in BRCA1 knocked-down conditions suggested the presence of possible growth promoting networks of BRCA1 in peripheral neurons and their associated Schwann cells. Interestingly, we also found that regenerating neurons accumulate mild DNA damage foci, which subsequently disappear but that are correlated with the nuclear presence of BRCA1.

## **CONCLUSIONS**

Our results indicate that the DNA repair functions of BRCA1 may preserve the integrity of regenerating neurons and thereby facilitate peripheral nerve regeneration.

[Supported by CIHR, AIHS]

Supervisor: Dr. Douglas Zochodne



**Nuclear expression of BRCA1  
in injured sensory neurons**

# **Fecal Calprotectin: a biomarker and predictor of disease activity during pregnancy in women with inflammatory bowel disease**

Huang V, Bal J, Ambrosio L, Foshaug R, Kroeker K, Madsen K, Dieleman L, Halloran B, Fedorak R  
Supervisor: Dr. Richard Fedorak

## **INTRODUCTION**

Active inflammatory bowel disease (IBD) during pregnancy is associated with adverse maternal and fetal outcomes, and requires early optimization of therapy. Women with IBD often have symptoms during pregnancy, and it is difficult to differentiate between pregnancy-related symptoms from active IBD. Fecal calprotectin (FCP) is a non-invasive biomarker of intestinal inflammation. It is unclear if it can be used as a biomarker in women with IBD during pregnancy. The objectives of this study were to determine if FCP is elevated with active IBD, and if FCP can predict active IBD within 3 months, during pregnancy in women with IBD.

## **METHODS**

Women with IBD are seen pre-conception (PC) and at each trimester of pregnancy (T[n]) in the Pregnancy in IBD clinic. Women complete the modified HBI (mHBI) for Crohn's disease (CD) or the partial Mayo (pMayo) for ulcerative colitis (UC). Women with mHBI > 5 or pMayo > 2 are classified as having active disease. FCP is measured from the stool samples from the women at each clinic visit. For this study, we compared FCP of women with active vs inactive disease at each visit. We compared FCP of women who had active vs no active disease within 3 months.

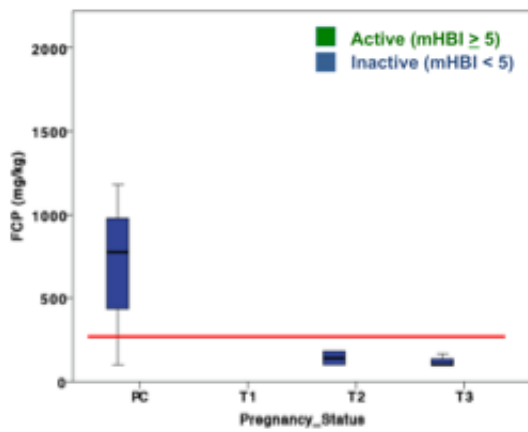
## **RESULTS**

We had 8 women with CD and 10 women with UC who provided stool samples. FCP was elevated in women with active disease compared to women with inactive disease at each clinic visit (Figure 1). FCP was also elevated in women who had active disease within 3 months (Figure 2). These findings were mainly seen among women with UC.

## **CONCLUSIONS**

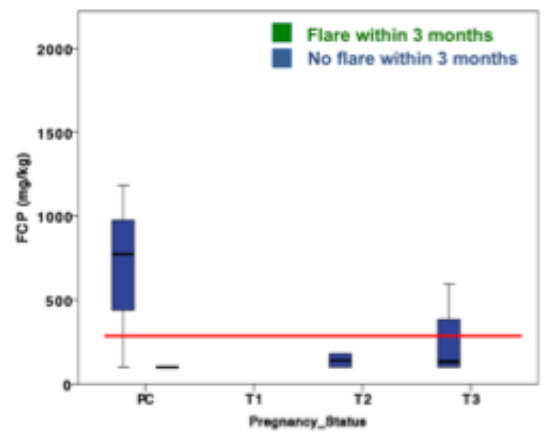
Fecal calprotectin is elevated in pregnancy in women with active IBD or who will have active IBD within 3 months. FCP has a potential to be used as a non-invasive biomarker for assessing disease activity in pregnancy in women with IBD.

Supervisor: Dr. Richard Fedorak

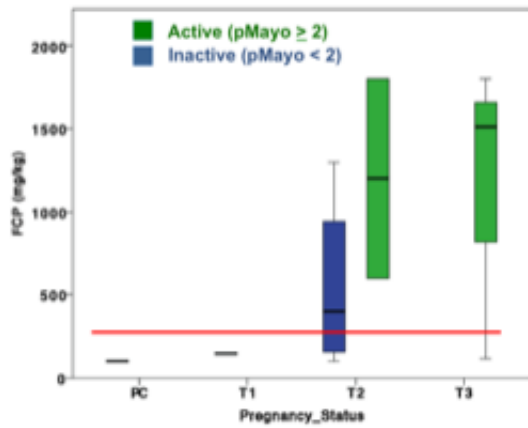


**A) Crohn's disease**  
n = 8 pts, 10 visits

FCP cut off 250 mg/kg  
for active disease

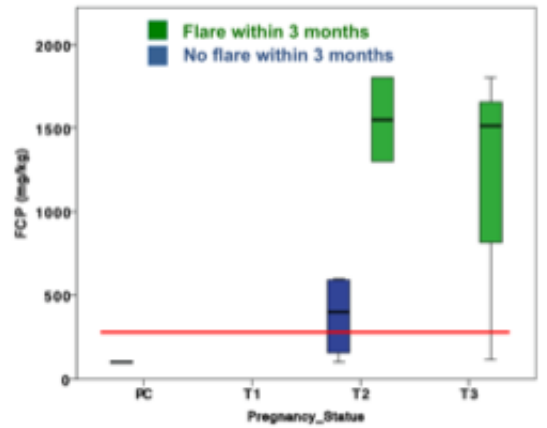


**A) Crohn's disease**  
n = 8 pts, 8 visits



**B) Ulcerative colitis**  
n = 10 pts, 12 visits

FCP cut off 250 mg/kg  
for active disease



**B) Ulcerative colitis**  
n = 9 pts, 10 visits

**Figure 1. Fecal calprotectin is elevated in women with IBD who have clinically active disease during pregnancy.**

**Figure 2. Fecal calprotectin is elevated in women with IBD who will flare by their next visit during pregnancy.**



# **EARLY INITIATION OF ANTI-TNF THERAPY REDUCES THE RISK OF LOSS OF RESPONSE AND SURGICAL RESECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE**

Christopher Ma, Vivian Huang, Darryl K. Fedorak, Karen I. Kroeker, Levinus A. Dieleman, Brendan P. Halloran, and Richard N. Fedorak  
Supervisor: Dr. Richard Fedorak

## **INTRODUCTION**

Biologic agents targeting tumor necrosis factor (TNF), including infliximab (IFX) and adalimumab (ADA), are effective in treatment of inflammatory bowel disease and may alter the natural history of Crohn's disease (CD) and ulcerative colitis (UC). We aim to determine if early initiation of anti-TNF therapy reduces the risk of surgical bowel resection and secondary loss of response.

## **METHODS**

A retrospective cohort study evaluating IBD outpatients on a maintenance schedule with ADA or IFX from 2004-2014 was conducted. Date of diagnosis was confirmed by histopathology, endoscopy, or history. Patients were stratified by time to initiation of anti-TNF therapy after diagnosis; early treatment was defined as starting anti-TNF induction within 156 weeks of diagnosis. The composite primary outcome was occurrence of surgical bowel resection or secondary loss of response. Loss of response was defined by a Harvey Bradshaw Index (HBI) score >5 (for CD) or increase in partial Mayo score >2 (for UC) requiring dose escalation of anti-TNF therapy. Kaplan-Meier analysis was used to assess time to the composite primary outcome.

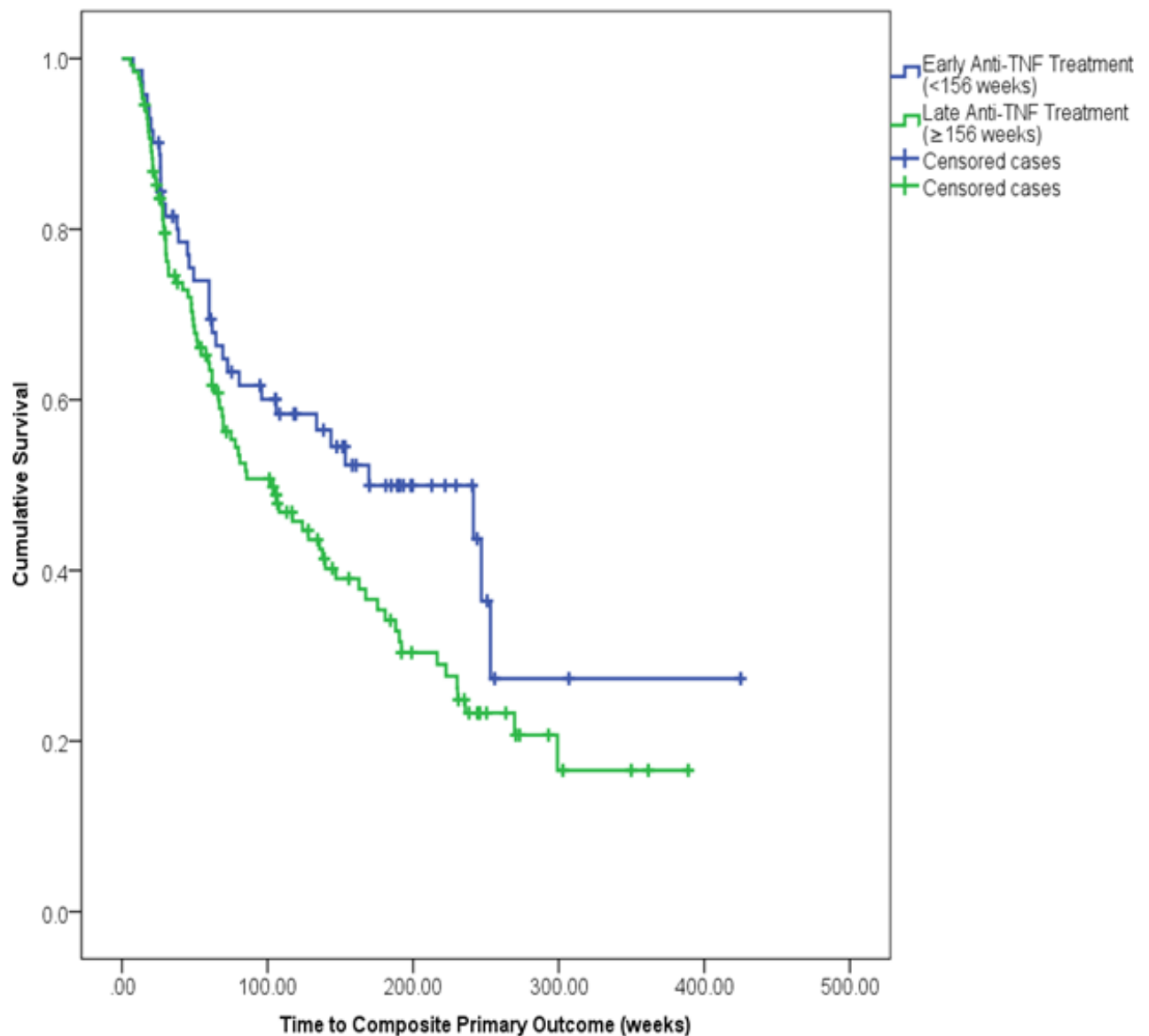
## **RESULTS**

200 patients (100 CD, 100 UC, 55% male) met inclusion criteria. 114 patients (57.0%) were treated with IFX; 86 patients (43.0%) were treated with ADA. 71 patients (35.5%) initiated anti-TNF therapy within 156 weeks of diagnosis. 31/71 (43.7%) patients treated with early anti-TNF therapy had a loss of response compared to 77/129 (59.7%) patients initiating anti-TNF therapy after 156 weeks post-diagnosis ( $p=0.03$ ). In Cox regression analysis, early initiation of anti-TNF therapy was protective against the composite primary outcome (HR 0.68 [95%CI:0.46-1.00]) and was associated with longer time to surgery or loss of response in Kaplan-Meier analysis (Figure 1)( $p=0.05$ ).

## **CONCLUSIONS**

Early initiation of anti-TNF therapy in IBD patients within the first three years of diagnosis affects the natural history of the disease, reducing the risk of surgical bowel resection and secondary clinical loss of response.

Supervisor: Dr. Richard Fedorak



**Figure 1** – Kaplan-Meier survival curve of time to composite primary outcome (surgical bowel resection or secondary clinical loss of response) during maintenance therapy in patients treated with early anti-TNF therapy within 156 weeks of diagnosis (blue) vs. late anti-TNF therapy (green). Hashed lines indicate censored cases (did not meet primary outcome to last follow-up).  $p = 0.05$ .

# Appropriateness of Thrombophilia Testing in Tertiary Care Centers in Edmonton

Zainab Alabdurubalnabi  
Supervisor: Cynthia Wu

## INTRODUCTION

Thrombophilia is associated with an increased risk of venous thromboembolism (VTE). Despite this link, determining the presence or absence of such conditions has no role in VTE management including determining the choice or duration of anticoagulant therapy. Testing can be potentially harmful when results are misinterpreted or impact patient anxiety and insurance eligibility.

## METHODS

We performed a retrospective chart review of adult patients presenting to the emergency department(ED) or were admitted to three tertiary care centers in Edmonton and underwent any number of thrombophilia tests (including factor V Leiden[FVL], prothrombin gene mutation[PT20210], protein C[PC], protein S[PS], antithrombin[AT] and antiphospholipid antibody testing). To assess for appropriateness of testing, categories of data were collected including presence of other strong risk factors obviating the need to look for other causes, indicators for higher yield (age of patient, presence of family history of VTE, idiopathic nature of VTE), presence of factors that confound testing (such as therapeutic anticoagulation) and relevant follow up (appropriate repeat testing when necessary). We also collected patient demographics, VTE details and ordering physician/service details to evaluate under what circumstances testing may be ordered more frequently.

## RESULTS

134 charts of patients tested for thrombophilia between 2007-2013 were reviewed. 91(67.9%) were over 40 years old, 82(61.2%)patients were tested within 3 months of VTE and 38(28.3%) due to arterial thrombosis. 965 thrombophilia tests were done (table 1). 13.4% of the testing was ordered by hematologists, 23.1% by neurologists and 52.2% by internists. Overall, all patients had tests performed inappropriately, lacked appropriate follow up or had uninterpretable results and none had documented counseling prior to testing.

## CONCLUSIONS

Thrombophilia testing is frequently ordered inappropriately and not adequately followed up. Strategies to educate physicians on indications and limitations of testing are warranted. These strategies can help decrease over/under/misinterpretation of thrombophilia testing as well as result in significant savings to the health care system if testing can be reduced.

Supervisor: Dr. Cynthia Wu

<b>Demographics</b>			
Sample Size	Males	Females	Total
	74 (55.22%)	60 (44.78%)	134 (100%)
Age at time of Testing (Yrs)	Range		19-88
	Average		48.7
<b>Patients' Test Results</b>			
Test		Times Performed	Abnormal Results
APCR		134 (100%)	32 (23.8%)
FVL genetic test		58 (43%)	21 (39%)
PT20210		105 (77%)	4 (3.8%)
Protein C		100 (74.1%)	8 (8%)
Protein S		99 (73.3%)	16 (16.2%)
AT levels		99(73.3%)	19 (19.2%)
Anticardiolipin Ab		117 (86.7%)	4 (3.4%)
Lupus Anticoagulant		109(81.3%)	10 (10.2%)
<b>Provoking Factors</b>			
Patients with One or More Provoking Factors	Major	10	7.4%
	Moderate	74	56%
	Minor	29	21.8%
No Provoking Factors		49	36.8%
History of VTE in a First Degree Relative		12	8.9%
<b>Protein C and Protein S Testing</b>			
Done During Acute VTE		64	64%
Patient was on Warfarin		25	25.0%
Number of Abnormal Test Results		24	16%
Number of Repeated Abnormal Tests		0	0%
<b>AT Testing</b>			
Total Tests Performed		99	73.3%
Done During Acute VTE		62	63%
Patient was on Therap. Heparin or LMWH		62	62.6%
Number of Abnormal Test Results		19	19.2%
Number of Repeated Abnormal Tests		7	37%
Repeat Tests Showing Normal Results		3	57%
<b>APA Testing</b>			
Tests were repeated after 12 weeks for confirmation			11%

# Phenotypic Effects of Celiac Disease with Coexistent Inflammatory Bowel Disease

Dang, TNT., Lu, C., Kroeker, Kl., Halloran, BP., Dielman, LA., Fedorak, RN.  
Supervisor: Dr. Richard Fedorak

## INTRODUCTION

Inflammatory bowel disease (IBD) and celiac disease (CeD) are the two most common autoimmune gastrointestinal diseases. The genetic loci PTPN2, IL18RAP, TAGAP, and PUS10, have been identified in both IBD and CeD. Recent studies have suggested that patients with IBD and CeD (IBD-CeD) may have a worse disease phenotype, though genetics for these patients has never been studied simultaneously. Our study aims to elucidate whether patients with both IBD and CeD shared a genetic risk factor which predisposes them to more aggressive disease.

## METHODS

This study was a retrospective, cross-sectional study including patients from a database of IBD (ulcerative colitis (UC) and Crohn's Disease (CD)) patients in Edmonton. Chart reviews for cases (IBD-CeD) and controls (IBD-only) were performed to assess disease phenotype and natural history. The genetic loci (PTPN2, IL18RAP, TAGAP, and PUS10) was sequenced and assessed from blood samples.

## RESULTS

Twelve IBD patients (6 CD, 6 UC) with CeD were identified from our search of 780 database patients giving a prevalence of IBD-CeD of 1.54%. In CD-CeD patients, there was more isolated ileal disease than those with CD-only ( $p=0.001$ ). UC-CeD patients had more pancolonic disease ( $p=0.02$ ) than UC-only. Patients with IBD-only were more likely to have had surgery than patients with IBD-CeD ( $p=0.003$ ). All patients 6/6 with UC-CeD were diagnosed with IBD prior to CeD. In contrast, 5 of the 6 patients with CD-CeD were diagnosed with CeD prior to CD. Genetic analysis showed that only TAGAP was significantly more prevalent in UC-CeD ( $p=0.03$ ) than UC-only.

## CONCLUSIONS

CeD appears to be a predisposing condition to the development of CD but not UC. CD-CeD patients had more isolated ileal disease than CD-only but this did not influence the natural history of CD. UC-CeD had extensive colitis compared to UC-only and only genetic loci TAGAP was associated with UC-CeD.

Supervisor: Dr. Richard Fedorak

**Table 1. Characteristics of IBD Patients with and without Celiac Disease**

Characteristic	IBD with Celiac Disease, n=10*	IBD without Celiac Disease, n=389*	P value
Current Mean age in years (SD)	48.1 (18.0)	46.1 (14.8)	0.035
Number of Males (%)	5 (50)	163 (42)	0.66
Number of Crohn's Disease Patients (%)	6 (60)	220 (56.6)	0.83
Number of Ulcerative Colitis Patients (%)	4 (40)	160 (41.1)	0.93
Number of Indeterminate Colitis Patients (%)	0	9 (2.3)	0.63
Age at IBD Diagnosis in years (SD)	35.4 (19.2)	29.7 (13.4)	0.37
Duration of IBD in years (SD)	12.7 (13.2)	15.8 (10.4)	0.35
Age of Celiac Disease Diagnosis in years (SD)	41.8 (17.6)	----	
Crohn's Disease Location (%)			
Terminal Ileum	4 (66.7)	85 (38.6)	L1 <b>0.002</b>
Colon	0	75 (34.1)	L2 0.31
Ileocolonic	2 (33.3)	60 (27.3)	L3 0.08
Ulcerative Colitis Location (%)			
Proctitis	0	29 (18.1)	E1: 0.59
Left Sided	1 (25)	31 (19.4)	E2: 0.17
Pancolitis	3 (75)	100 (62.5)	E3: <b>0.02</b>
IBD-related surgery (%)	2 (20)	160 (41.1)	<b>0.003</b>
Corticosteroids for IBD (%)	7 (70)	279 (71.7)	0.93
Anti-TNF agent (%)	3 (30)	187 (48)	0.26

IBD: Inflammatory Bowel Disease, SD: Standard Deviation, TNF: tumor necrosis factor

# **Lifestyle interventions in patients with cirrhosis - an assessment of the current status and patient perceived barriers to intervention**

M. Ney, J. Chaulk, N. Mansoor, J. Ramamurthy, R.J. Bailey, L. Gramlich, M. Ma, P. Tandon.

Supervisor: Dr. Puneeta Tandon

## **INTRODUCTION**

Physical frailty is an independent predictor of mortality in cirrhosis. The mainstays of treatment are exercise and nutrition. Success of these non-pharmacological therapies relies heavily on patient buy-in and active participation. We sought to a) describe nutritional intake, b) identify barriers to nutritional intake, c) characterize physical activity practices, d) describe the perceived benefits and barriers to physical activity.

## **METHODS**

This prospective study was conducted from August 2012 - February 2015 on adult patients with cirrhosis recruited from two tertiary care hospitals. Patients were excluded if they had hepatocellular carcinoma exceeding transplant criteria, other active malignancies, COPD on home oxygen, CHF or CKD. Surveys were administered to collect study data. Statistical comparisons were made using t-test or Chi-squared tests.

## **RESULTS**

A total of 127 patients had a mean age of  $60 \pm 9$ , were 58% male and 48% had Child Pugh (CP) B/C disease. Common disease etiologies were alcohol (35.4%) and hepatitis C (26.8%). Patients reported a mean of  $2.7 \pm 0.9$  meals per day and  $2.1 \pm 1.3$  snacks per day. Poor appetite ( $p=0.04$ ), poor consumption ( $p=0.001$ ), inability to maintain weight ( $p<0.001$ ), dysgeusia ( $p=0.02$ ) and difficulty buying/preparing meals ( $p=0.006$ ) were more common in CP-B/C patients. Frequency of physical activity was not significantly different between groups. Patients reported  $0.53 \pm 1.44$  and  $1.35 \pm 2.30$  days/week of vigorous and moderate physical activity respectively. CP-B/C patients were more likely to endorse fatigability ( $p=0.002$ ), but overall Exercise Benefits/Barriers Scale (EBBS) scores were similar between groups.

## **CONCLUSIONS**

CP-B/C patients are more likely than CP-A patients to experience dysgeusia, poor appetite and difficulty buying/preparing food. Although the study reported comparable EBBS scores to healthy controls, this translated into negligible weekly physical activity. Future trials should address modifiable barriers to improve nutritional intake and physical activity levels in cirrhosis.

Supervisor: Dr. Puneeta Tandon



# **A Comparison of Casual In-Clinic Blood Pressure Measurements to Standardized Measurements in Severely Obese Individuals**

Vahidy S, Majumdar SR, Padwal RS  
Supervisor: Dr. Raj Padwal

## **INTRODUCTION**

Severely obese patients are at risk for having spuriously elevated blood pressure readings in typical clinic settings. This could lead to overdiagnosis and overtreatment. The objective of this study was to compare casual BP measurements taken in a bariatric clinic to standardized guideline-concordant measurements.

## **METHODS**

A cross-sectional analysis was performed using baseline data from a randomized controlled weight management trial. Patients were recruited from a population-representative Canadian bariatric care program. Standardized BP measurements were performed using a Watch BP Office oscillometric device (three readings, first discarded, and latter two averaged). Casual in-clinic BP (single readings), taken using a Welch Allyn oscillometric device, were chart abstracted. Paired t-tests, Bland-Altman plots and Pearson's correlations were used to compare measurements.

## **RESULTS**

Data from 134 patients were analyzed. Mean age was  $41.5 \pm 8.9$  y, mean BMI  $46.8 \pm 6.5$  kg/m<sup>2</sup>, 101 (75%) were female and 40 (30%) had prior hypertension. Mean casual in-clinic BP was  $128.8 \pm 14.1/81.6 \pm 9.9$  mmHg and mean standardized BP was  $133.2 \pm 15.0/82.0 \pm 10.3$  mmHg (difference of  $-4.3 \pm 12.0$  for systolic [ $p < 0.0001$ ] and  $0.4 \pm 10.0$  mmHg for diastolic [ $p = 0.6$ ]). As BP increased above  $\approx 144$  mmHg, casual in clinic measurements were consistently lower than the standardized measurements. Pearson's coefficients were 0.66 ( $p < 0.0001$ ) for SBP and 0.50 ( $p < 0.0001$ ) for DBP. 28.4% of casual vs 26.9% of standardized measurements were  $\geq 140/90$  mmHg ( $p < 0.0001$ ).

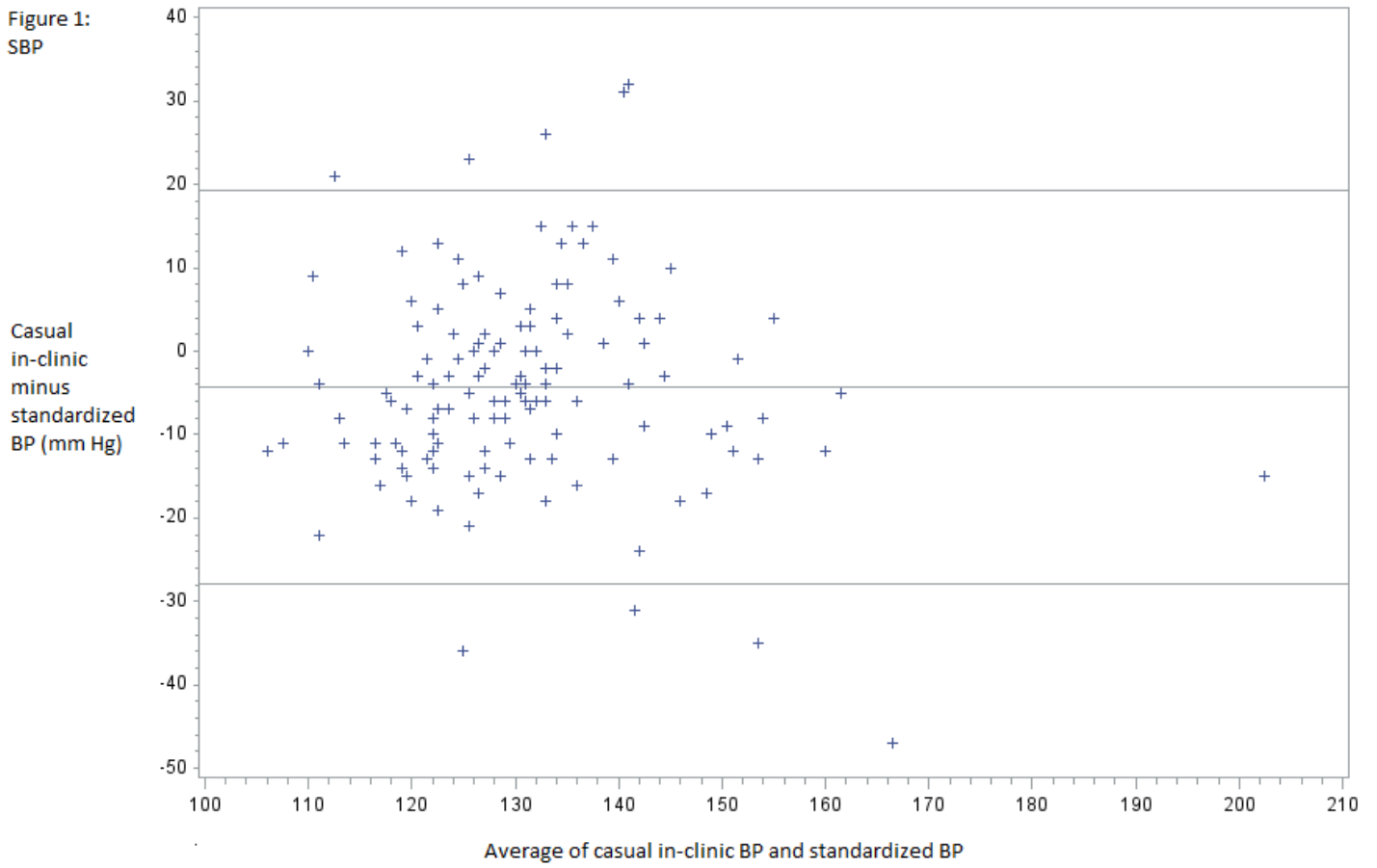
## **CONCLUSIONS**

In this bariatric clinic, single, mean casual BP was unexpectedly lower than standardized BP, with similar proportions of patients exhibiting BP levels  $\geq 140$  mmHg. We did not find spuriously elevated BP readings or a risk for systematic hypertension overdiagnosis and overtreatment.

Supervisor: Dr. Raj Padwal

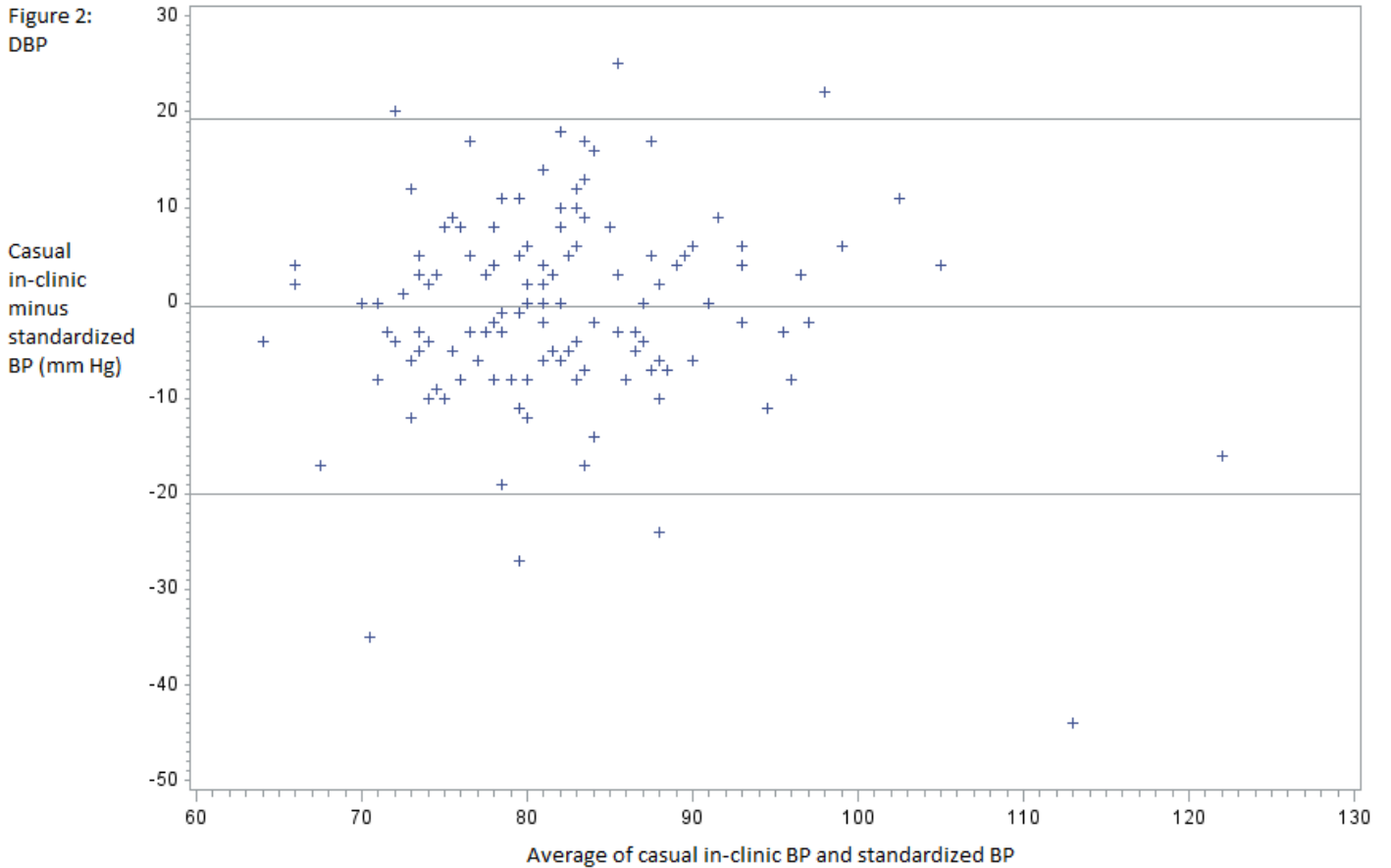
**Figure 1: Bland Altman for Systolic Blood Pressure**

Figure 1:  
SBP



**Figure 2: Bland Altman for Diastolic Blood Pressure**

Figure 2:  
DBP



# **Impact of Inadequate Handover on the Perceived Quality of On-Call Shifts by Residents.**

Dr. Aditi Amin, Dr. Liam Rourke (Department of General Internal Medicine, Educational Scholarship Director), Dr. Curtiss Boyington (Department of Infectious Disease, Associate Clinical Professor)  
Supervisor: Dr. Liam Rourke

## **INTRODUCTION**

Reduced resident duty hours and resulting increased transfers of patient care has led to growing interest in the quality of patient handovers. The literature suggests: “multiple handovers create an opportunity for communication breakdown that may lead to increased medical errors...[and] longer hospital stay[s]” [1].

Studies exploring resident perspectives on handover indicate residents find handover “haphazard” [2] and with important patient data being omitted. This made residents feel “[in]adequately prepared” [3] and that “inefficient and suboptimal care” [4] occurred.

Given the evidence described above, and concern regarding the quality of handover amongst Internal Medicine residents, this quality improvement initiative was designed to collect baseline data on handover quality at the University of Alberta Hospital.

## **METHODS**

Using the “Plan-Do-Study-Act” model of quality improvement as a framework, baseline data is being collected by: a) directly questioning residents coming off of overnight call; and b) directly observing morning report using a standardized template. Categorical data is being summarized using simple descriptive statistics (i.e., frequencies and percentages). Observational data is being summarized in a run charts (i.e., charts representing data in time ordered sequence).

## **RESULTS**

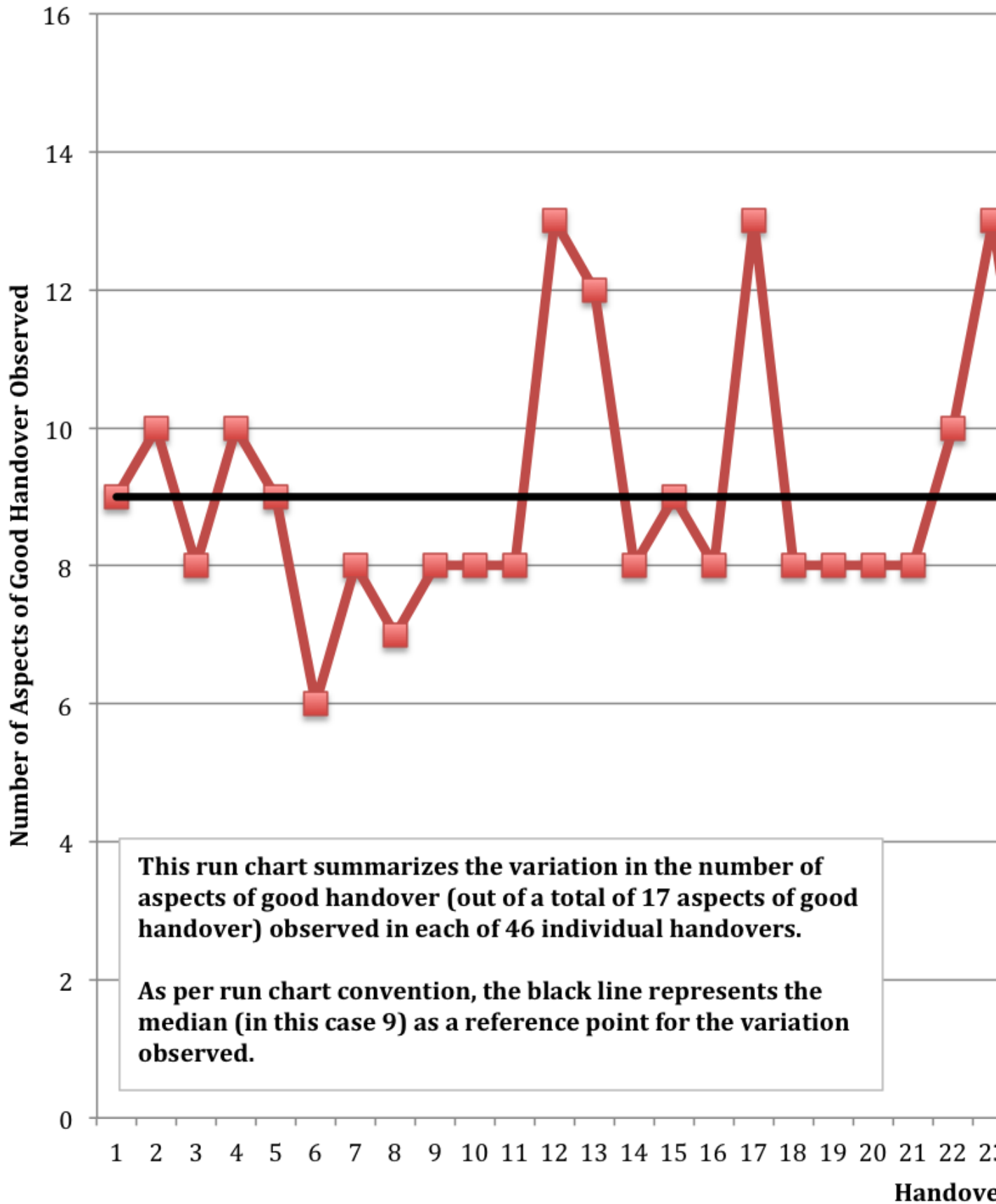
Residents reported 40% of the time that things happened on call for which handover did not adequately prepare them. Handover inadequacies most commonly included the following omissions: 1) rationale (30%); 2) patients’ clinical condition (20%); 3) outstanding tasks (20%); and 4) a plan (20%). The most frequently reported impacts of inadequate handover were: 1) increased workload (40%); 2) increased anxiety (25%); and impaired ability to care for patients (25%). Figure 1.0 summarizes the number of aspects of good handover (out of 17 total aspects) observed over 46 handovers.

## **CONCLUSIONS**

This baseline data will help inform the development, implementation and evaluation of interventions to improve handover quality amongst Internal Medicine residents in addition to potentially developing, implementing, and evaluating standardized handover practices.

Supervisor: Dr. Liam Rourke

**Figure 1.0: Number of Aspects of Good Handover (Handover) Observed Over 46 Handovers**



# **COMPARING THE PREDICTIVE IMPACT OF 3 DIFFERENT MEASURES OF FRAILITY ON SHORT-TERM RATES OF DEATH OR READMISSION IN MEDICAL INPATIENTS: MULTICENTER PROSPECTIVE COHORT STUDY**

Sara Belga (1), Sumit R. Majumdar (1,2), Sharry Kahlon (1), Jenelle Pederson (1), Darren Lau (1), Jeffrey A. Bakal (2), Raj S. Padwal (1,2), Finlay A. McAlister (1,2)  
Supervisor: Dr. Finlay McAlister

## **INTRODUCTION**

Frailty is a state of increased vulnerability associated with adverse health outcomes, and multiple tools for assessing frailty have been proposed. Whether phenotypic models (using standardized objective measurements) or cumulative deficit frailty models (using routinely collected data and clinical impression) are superior in predicting post-discharge events is uncertain.

Objectives: To compare frailty assessments using a cumulative deficits tool (Clinical Frailty Scale, CFS) vs phenotypic tools (Fried score, gait speed alone).

## **METHODS**

Prospective cohort study of adults being discharged from 7 medicine wards between October 2013 and November 2014 in Edmonton, Alberta. Patients were classified as frail if they scored > 5 on the CFS and/or > 3 on the Fried score and/or had slow gait speed (> 20 seconds on the Timed-Up and Go Test).

## **RESULTS**

Of 1147 potentially eligible patients, 495 were enrolled: 33% patients were deemed frail using the CFS, of which only 17% also met either of the phenotype frailty definitions using the Fried score or gait speed. Overall, 43% patients were frail according to at least one tool, only 9% met all 3 frailty definitions, and 17.1% died or were re-admitted by 30 days. While patients classified as frail on the CFS exhibited significantly higher 30-day readmission/death rates (24.1% vs 13.8% for not frail,  $p=0.005$ ) even after adjusting for age and sex (aOR 2.02, 95%CI 1.19-3.41), patients meeting either of the phenotypic definitions for frailty but not the CFS definition were not at higher risk (aOR 0.87, 95%CI 0.34-2.19). The group at highest risk for 30-day readmission/death were those meeting both the CFS and phenotypic definitions of frailty (25.6% vs 13.8% for those not frail, aOR 2.15, 95%CI 1.10-4.19).

## **CONCLUSIONS**

Frailty has a significant impact on post-discharge outcomes and the CFS is the most useful of the available frailty tools for predicting poor outcomes after discharge.

Supervisor: Dr. Finlay McAlister

# Medication Use and Survival After Acute Kidney Injury

Sandeep Brar MD, Neesh Pannu MD SM FRCP  
Supervisor: Dr. Neesh Pannu

## INTRODUCTION

The incidence of acute kidney injury (AKI) in hospitalized patients is rising, and there is a lack of effective therapies for treatment. Recent studies suggest that nephrology follow-up may reduce long term mortality after AKI; however, the processes of care that underlie this finding remain unknown. The objective of this study was to determine if medications of known benefit in chronic kidney disease (CKD) are also associated with improved mortality in survivors of AKI with CKD.

## METHODS

Retrospective cohort study of adults greater than 65 years of age, residing in Alberta, who were admitted to hospital between 2002 and 2008, developed AKI during the index hospitalization and progressed to CKD within 90 days after discharge (n= 16,017 mean age 78.6 years).

## RESULTS

Within 120 days of discharge, 60.5% of the participants received an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II-receptor blocker (ARB), 37.2% received a beta-blocker, and 29.4% received a statin. Over a subsequent 2 year follow up period, the adjusted hazard ratios (HR) (95% confidence interval [95% CI]) for mortality associated with use of these medications were 0.90 (0.84, 0.96) for ACEi/ARB, 0.91 (95% CI, 0.84, 0.98) for beta-blockers and 0.75 (95% CI, 0.69, 0.82) for statins. Participants who received ACEi/ARB or beta-blockers had higher risks of all cause re-hospitalization (adjusted HR, 1.16; [95% CI, 1.10, 1.22] and 1.07; [95% CI, 1.02, 1.12], respectively. Patients who received statins had lower risks of all cause re-hospitalization (adjusted HR, 0.89; 95% CI, 0.85, 0.94) and end-stage renal disease (ESRD) (adjusted HR, 0.78; 95% CI, 0.66, 0.93). There was no significant difference in the rate of re-hospitalization for renal causes associated with use of any of the medications.

## CONCLUSIONS

Among AKI survivors with CKD, ACEi/ARB, beta-blocker and statin use are associated with decreased mortality. However, ACEi/ARB and beta-blocker use are associated with higher risk of all re-hospitalizations.

Supervisor: Dr. Neesh Pannu

# **Dynamics of target and distractor spatial averaging in the global effect of saccades**

Woo Young Choi (1,2), Jayalakshmi Viswanathan (2), Jason Barton (2)  
Supervisor: Dr. Jason Barton

## **INTRODUCTION**

In the global effect, saccades are displaced towards a distractor that is near in location to the target, an effect that is thought to reflect neural averaging in the superior colliculus. The temporal profile of this averaging process has not yet been investigated, however. We studied how the global effect varied with the degree of temporal dissociation between target and distractor appearance.

## **METHODS**

In the first study, the target was flashed for 10ms at 8° horizontal eccentricity, followed after an interval varying between 0ms and 100ms, by a 10ms distractor at either 4° or 12° horizontal eccentricity. In the second study, the distractor appeared first, either as a 100ms flash or with sustained presence, at the same locations, and followed after an interval varying between 0ms to 800ms by the target. We analyzed saccade amplitude data from 12 subjects in terms of offsets, latencies and integration time.

## **RESULTS**

In the first experiment, the offset between the target and distractor did not influence the global effect. The global effect occurred only in saccades with latencies between 140 and 340ms, or with integration times between 90 and 310ms. In the second experiment, the global effect decreased significantly with 100ms of offset between the distractor and target, but was still evident. The global effect was stronger when the distractor was continuously present throughout the trial. Similar to the first experiment, the global effect occurred only in saccades with latencies between 150 and 350ms.

## **CONCLUSIONS**

Our results demonstrate that the global effect can occur despite separation of the distractor and target in time, suggesting that there is substantial persistence of distractor-related activity that is available for spatial averaging in a putative neural structure such as the superior colliculus.

Supervisor: Dr. Jason Barton



# **Antimalarial drugs alone may still have a role in Rheumatoid Arthritis**

Ina Cusnir, Selina Dobing, Niall Jones, Anthony Russell  
Supervisor: Dr. Anthony Russell

## **INTRODUCTION**

Antimalarials have been used for the treatment of Rheumatoid Arthritis for several decades. Current guidelines do not include the use of these drugs alone for rheumatoid arthritis patients.

The purpose of the study is to review rheumatoid arthritis patients, to find those who have done well on antimalarials alone, and see if there are common features that predict good treatment outcome with these drugs.

## **METHODS**

This is a retrospective chart review of patients who have been successfully treated with antimalarials alone. Patients who were attending routine follow up and were seemingly in remission defined by no swollen or tender joints were selected over a 6 month period. Those who had been doing well, but were now or had been on other agents are not included. The background data was reviewed to see if there were any common initial characteristics

## **RESULTS**

Thirty three patients were seen who had been started on antimalarials alone and where initial data was available. Patients remain in clinical remission. Based on clinical observation, inflammatory markers and X-ray reports, in the follow up visits, they remain with no signs of inflammation and no new erosions on X-ray. Initial bone erosions on 2 patients remain stable over the years.

## **CONCLUSIONS**

There are some patients with confirmed RA who without doubt respond well to antimalarials alone. It is hard to objectively measure, whether mild disease activity, early treatment initiation, lack of smoking or other factors are contributing to a good treatment response

Supervisor: Dr. Anthony Russell

Gender	Mean age at Dx/ range	RF positivity	Anti-CCP positivity	ANA positivity	Smoker
Males-11	57.2 (39-80yo)	8	7	3	1
Fem-22	48 (26-83yo)	16	18	10	3
		Neg-9	Neg-8	Neg-13	Neg-18
Total-33				Not done-7	Unknown-11

# **Natural health product use in patients with rheumatological conditions based on gender, age, education level and work status**

Tharindri Dissanayake, Karen Hagen, Steven Katz, Jill Hall  
Supervisor: Dr. Steven Katz

## **INTRODUCTION**

Previous literature has shown that Natural Health Product (NHP) use is higher in patients with rheumatological conditions compared to the general population and that NHP users are more likely to be female, middle aged, college educated, and relatively wealthy. We aimed to describe the prevalence of NHP use in patients with rheumatological conditions and determine whether there is an association with various patient specific factors.

## **METHODS**

We conducted an observational cross-sectional survey of patients attending the 2 largest rheumatology clinics in Edmonton, Alberta over a two-month period in 2013. The survey collected self-reported NHP use, medical conditions and medications, as well as demographic data. In this study we analyzed NHP use based on age, gender, education level, work status, and visit type using descriptive statistics and included an inflammatory arthritis (IA) subgroup.

## **RESULTS**

Of the 1063 patients who participated in this study (36% response rate), 557 self-identified as having inflammatory arthritis. Female patients utilized more NHP products ( $p < 0.05$ ) and NHPs more often compared to male patients ( $p < 0.01$ ). Patients aged 45 -74 most frequently used NHPs ( $< 0.05$ ) compared to other age groups. Work status also demonstrated variability in NHP use, with lack of statistically significant findings. Patients with a post secondary education used NHP products more often than those without ( $p < 0.05$ ). The entire cohort and the IA subgroup had no significant differences for the above patient specific factors. However, return patients in the entire cohort consumed more NHP products compared to patients on a first visit ( $p = 0.04$ ).

## **CONCLUSIONS**

This study confirmed that NHP use is more prevalent in females, college educated and middle-aged patients and demonstrated that patients who are female or are on a follow-up visit used more NHP products. Obtaining an improved understanding of NHP use patterns may prompt health care practitioners to regularly seek and provide information during patient visits.

Supervisor: Dr. Steven Katz

# Natural health product use in patients with rheumatological conditions

Tharindri Dissanayake, Karen Hagen, Steven Katz, Jill Hall  
Supervisor: Dr. Steven Katz

## INTRODUCTION

Natural health products (NHPs) are naturally occurring substances available without a prescription, frequently used to restore or maintain good health. Previous literature has shown that the prevalence of NHP use is higher in rheumatological populations compared to the general population. However, NHP use is frequently under-reported. Thus, the aim of this study was to describe the population-based rates and patterns of NHP use in patients with rheumatologic conditions.

## METHODS

We conducted an observational cross-sectional survey of patients with rheumatologic conditions in Edmonton, Alberta. Patients attending the 2 largest rheumatology clinics over an 8-week period were invited to participate. Response items included self-reported NHP use, medical conditions, and medications, as well as demographic data. Data were analyzed using descriptive statistics and included an inflammatory arthritis (IA) subgroup.

## RESULTS

1063 patients completed the survey (response rate, 36%). 60% reported using one or more NHPs (mean 2.9 products). When excluding vitamins and minerals, the prevalence decreased to 40% and mean number of NHPs to 1.8. Female patients utilized more NHP products ( $p < 0.05$ ) and NHPs more often compared to male patients ( $p < 0.01$ ). Patients aged 45 -74 and patients with a post secondary education most frequently used NHPs ( $p < 0.05$ ). There were no differences between the entire cohort and the IA subgroup. A variety of NHPs were reported, with joint health being the most common indication. 65% of NHP users informed their physicians of NHP use, however, only 20% informed their pharmacist and even fewer informed other health care professionals. A minority of patients noted benefit or adverse effects from therapy.

## CONCLUSIONS

In the largest North American study to date, our study confirms the frequent use, but under-reporting, of NHPs by patients with rheumatologic conditions. Obtaining an improved understanding of NHP use patterns may prompt health care practitioners to regularly seek and provide information during patient visits.

Supervisor: Dr. Steven Katz

# **What role do patient educators play in medical students' development as medical professionals?**

Amy Tan, Joanna Czupryn, Anna Oswald  
Supervisor: Dr. Anna Oswald

## **INTRODUCTION**

Patient educators are one of many teaching modalities used to foster principles of patient-centred care in medical students. In addition to serving as effective teachers of clinical skills, patient educators have been shown to aid in development of patient-centredness by sharing their unique knowledge and personal stories around their illness experiences. In our published 2014 study of pre-clerkship students' perspectives of patient educators, five themes were identified.

## **METHODS**

In this longitudinal follow-up study using the phenomenology approach, five focus groups were conducted with fourth-year medical students and first-year residents who wrote reflections for the original study. We explored how perspectives on patient educators may have changed, and determined which themes identified during pre-clerkship remained relevant to clinical trainees. Learners were asked to give their impressions of patient educators and to react to the themes from the original study. The transcripts were then analyzed thematically.

## **RESULTS**

This study identified two new themes: "value of early clinical experience" and "development of professional identity". Themes from the pre-clerkship study that increased in relevance for clinical trainees included: "seeing condition within context of patients' lives", "recognizing patients' needs" and "recognizing complexity of practicing medicine". "Patients supporting students' learning" was equally relevant and "seeing the patient as a capable part of the team" received mixed responses.

## **CONCLUSIONS**

While insights from pre-clerkship experiences with patient educators carry over into early clinical training, we identified shifts in emphasis and new perspectives. Further exploration of how patient educators help develop trainees' professional identity and patient-centredness is warranted.

Supervisor: Dr. Anna Oswald

# **Evaluating the Effect of Combination Therapy with Uricosuric Agents and Xanthine Oxidase Inhibitors versus Xanthine Oxidase Inhibitor Monotherapy on Serum Urate Levels: A Systematic Review**

Heyland, JD, Keeling, SO  
Supervisor: Dr. Stephanie Keeling

## **INTRODUCTION**

Gout is a crystalline arthropathy caused by an immune response to monosodium urate crystals within the synovium. Patients with refractory gout or intolerance to therapeutic doses of hypouricemic agents may benefit from a combination of a xanthine oxidase inhibitor and a uricosuric agent. Given the limited information on combination therapy, a systematic review was performed to evaluate the effect of uricosuric agents used in combination with xanthine oxidase inhibitors in comparison with xanthine oxidase inhibitor monotherapy in treatment of patients with hyperuricemia and/or gout.

## **METHODS**

EMBASE, MEDLINE, Scopus, Web of Science, ProQuest Theses and Dissertations, and the International Pharmaceutical Abstracts were searched for randomized controlled trials and observational trials that included patients with gout and/or hyperuricemia treated with combination therapy with uricosuric agents and xanthine oxidase inhibitors compared with xanthine oxidase inhibitor monotherapy. The primary outcome was change in serum urate and secondary outcomes included impact on gouty flares, resolution of tophi, and adverse effects.

## **RESULTS**

After removing duplicates, 2377 papers were identified. After the abstract/full paper screen, nineteen papers met criteria and were included in the review, including three randomized controlled trials and sixteen cohort studies. On average, combination therapy was able to decrease serum urate by an additional 19% (CI 14-19%) in comparison with xanthine oxidase inhibitor monotherapy. Seventeen studies including a total of 697 patients favored combination therapy over xanthine oxidase inhibitor monotherapy for reduction of serum urate. Two studies including 142 patients favored xanthine oxidase inhibitor monotherapy. Gouty flares and other clinical outcomes were not consistently reported.

## **CONCLUSIONS**

Combination therapy of uricosuric agents and xanthine oxidase inhibitors appeared to be more favorable than monotherapy for lowering serum urate. There is however a limited amount of high quality research in this area.

Supervisor: Dr. Stephanie Keeling

# **Patient-Reported Discharge Readiness and 30-Day Risk of Readmission or Death: A Prospective Cohort Study**

Lau D, Padwal RS, Majumdar SR, Pederson JL, Belga S, Kahlon S, Fradette M, Boyko D, McAlister FA  
Supervisor: Dr. Finlay McAlister

## **INTRODUCTION**

Post-discharge hospital readmissions are common and clinicians cannot accurately predict their occurrence. We examined whether patients who feel unready at the time of discharge have increase readmissions or death within 30 days.

## **METHODS**

Prospective cohort study of adult patients discharged home from 7 general internal medicine wards in Edmonton, Alberta, Canada, from October 1, 2013 to November 3, 2014. Patient-reported discharge readiness was measured with an 11-point Likert response scale, with scores < 7 indicating subjective unreadiness. The primary outcome was readmission or death. Logistic regression models were adjusted for age, sex, and a validated risk prediction score for post-discharge events (LACE index).

## **RESULTS**

Of 495 patients (mean age 62 years, 51% female, 32% with 3 or more comorbidities), 112 (23%) reported being unready for discharge. Risk factors for being unready at discharge were intellectual impairment (mild vs none), low satisfaction with health care services, lower education, depression, and persistent symptoms or disability. At 30-days, 96 patients (19%) had been readmitted or died, with no significant difference between patients who felt unready or ready (19% vs 20%, adjusted odds ratio = 1.02, 95% CI 0.58-1.80, p = 0.94).

## **CONCLUSIONS**

Although nearly one quarter of hospitalized medical patients report being unready at the time of discharge, they do not experience any higher risk of readmission or death in the first 30 days post-discharge, compared with patients who report being ready for discharge.

Supervisor: Dr. Finlay McAlister

# **IBD PATIENTS ARE FREQUENTLY NON-ADHERENT WITH SCHEDULED INDUCTION AND MAINTENANCE INFlixIMAB**

Christopher Ma, Chad J. Evaschesen, Grenvil Gracias, Vivian Huang, Darryl K. Fedorak, Karen I. Kroeker, Levinus A. Dieleman, Brendan P. Halloran, and Richard N. Fedorak  
Supervisor: Dr. Richard Fedorak

## **INTRODUCTION**

Although infliximab has efficacy in inducing and maintaining clinical response in IBD patients, adherence to scheduled dosing is required to maintain therapeutic trough drug levels and prevent anti-infliximab antibody formation. Previous administrative database studies have not been powered to evaluate adherence to the infliximab induction or maintenance administration schedule. We aim to characterize the adherence to regularly scheduled infliximab induction and maintenance in patients with IBD and to assess predictors of non-adherence.

## **METHODS**

A retrospective cohort study was conducted evaluating adult (>17 years) outpatients with Crohn's disease (CD) or ulcerative colitis (UC) on scheduled infliximab from 2008-2010. Official infliximab infusion records were reviewed and non-adherence was defined by a discrepancy of >72 hours between the scheduled date of infliximab infusion and the date of administration. Patients were deemed non-adherent if they received <80% of their infliximab doses per schedule. Multivariate logistic regression was performed to evaluate predictors of non-adherence.

## **RESULTS**

215 patients (173 CD, 42 UC) met inclusion criteria. Patients received a median of 12.0 (IQR7.0-13.0) infliximab infusions during the study period. 412 induction and 1837 maintenance infliximab doses were administered. 109/140 patients (77.9%) were adherent to infliximab induction; 68/215 patients (31.6%) were adherent to their maintenance regimen. Mean variance from an individual infliximab induction and maintenance infusions was 1.1 days ( $\pm$  1.6) and 4.0 days ( $\pm$  4.6), respectively. 92.1% of patients received at least one delayed maintenance infusion and 10.1% of patients received maintenance infusions on average more than one week late. In multivariate logistic regression analysis, only male gender (OR 1.77 [95% CI 1.01-3.11]) was predictive of non-adherence.

## **CONCLUSIONS**

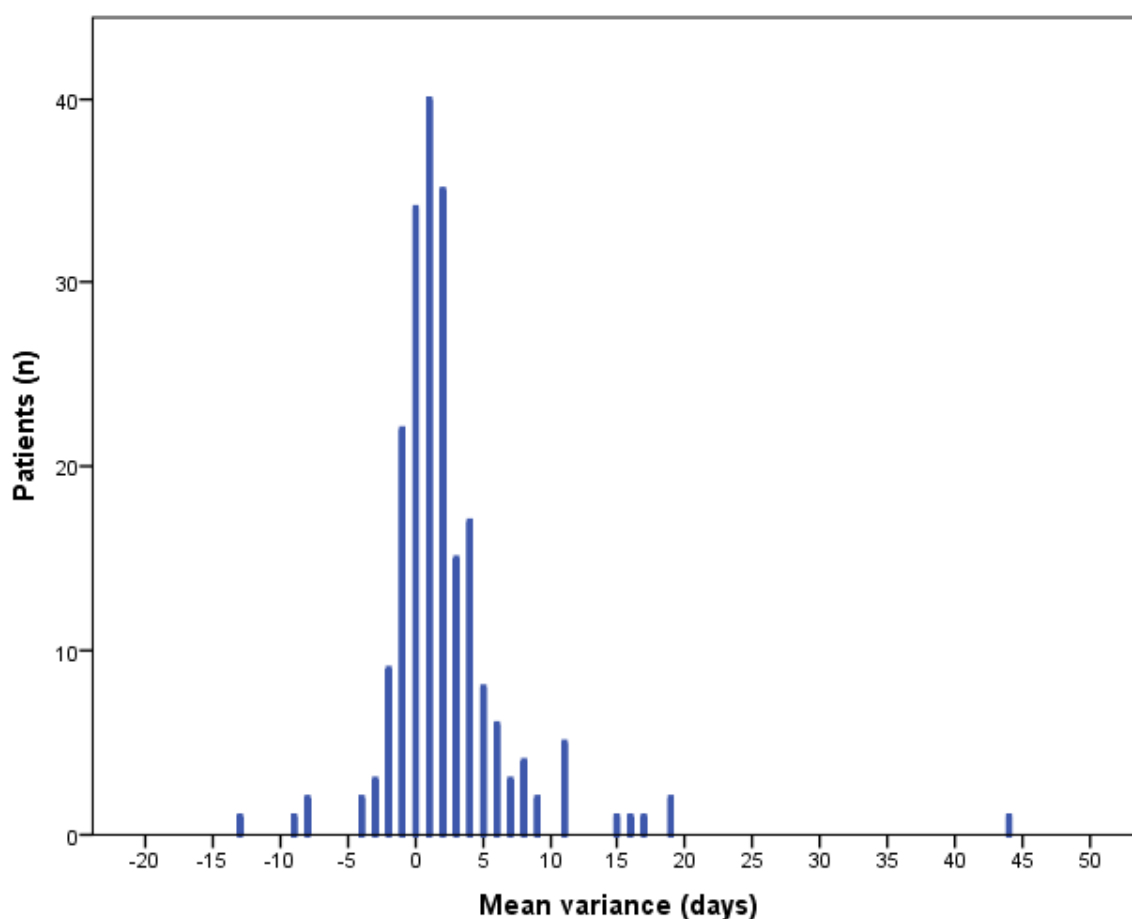
While three quarters of patients are adherent with infliximab induction therapy, less than one third remain closely adherent to their maintenance infliximab schedule.

Supervisor: Dr. Richard Fedorak



**Table 1:** Baseline Patient Demographics and Adherence to Infliximab Therapy

	<b>n</b>
Patients receiving induction IFX	140
Patients receiving maintenance IFX	215
Mean age at infliximab induction (years, $\pm$ SD)	40.8 $\pm$ 13.7
Median lifetime infliximab infusions (n, IQR)	12.0 (7.0–19.5)
Median study follow-up (weeks, IQR)	80.1 (38.7–100.9)
Patients adherent to IFX induction	109 / 140 (77.9)
Patients adherent to IFX maintenance	68 / 215 (31.6)
Mean delayed induction infusions per patient ( $\pm$ SD)	0.5 $\pm$ 0.6
Mean delayed maintenance infusions per patient ( $\pm$ SD)	3.5 $\pm$ 2.5



**Figure 1** – Mean variance (in days) from scheduled maintenance infliximab infusions

# **A Survey Of Safety Device Use in Joint Injection Amongst Canadian Rheumatologists**

Norman Madsen, Eugene Waclawski and Elaine Yacyshyn  
Supervisor: Dr. Elaine Yacyshyn

## **INTRODUCTION**

Needle safety devices are mechanical modifications to needles and/or syringes in order to reduce the risk of inadvertent needle stick injury (NSI). Following research showing reduction in NSI, these devices have been introduced to many hospital systems. To date, no research has been performed on the effects of these devices on reducing needle stick injuries amongst Canadian Rheumatologists performing joint injection and aspiration procedures. However, due to hospital policies, these devices are often the only available needles available for procedures. No data currently exists regarding the preference of Rheumatologists for safety needles versus standard needles or the effect of these devices on NSI during joint injection and aspiration.

## **METHODS**

An online survey was distributed via SurveyMonkey to actively practicing Canadian Rheumatologists who are currently performing joint aspiration or injection procedures. The survey assessed the use of safety devices by Rheumatologists and their perceptions regarding the usefulness and safety of such devices.

## **RESULTS**

A total of 138 Rheumatologists responded to the online survey. The survey showed the majority of Rheumatologists polled (65.9%) use standard needles over needles with safety devices. Rheumatologists were open to the use of safety devices (57.7%). 17.2% of responding Rheumatologists have suffered at least one NSI during joint injection or aspiration post fellowship. At present, only one responding Rheumatologist is actively using ultrasound guidance for joint aspiration or injection.

## **CONCLUSIONS**

Despite safety data on the use of needle safety devices in other healthcare settings, there is minimal data on the safety and effectiveness of safety needles in the setting of joint injection and aspiration by Rheumatologists. Rheumatologists in Canada have a preference for standard needles over needles with safety devices. Design changes to safety needles to improve ease of use during joint injection and aspiration could improve safety while also increasing compliance.

Supervisor: Dr. Elaine Yacyshyn

# Learning to Interpret ECGs: A Meta-analysis

Liam Rourke, Evan Martow, Jessica Leong  
Supervisor: Dr. Liam Rourke

## INTRODUCTION

Interpretation of ECGs is integral to medical practice. Considering the importance of ECG reading and interpretation, having an effective, evidence-based approach to training is clearly important to medical educators. The purpose of this systematic review is to determine the scope and effectiveness of existing educational strategies for ECG teaching.

## METHODS

A comprehensive search of the literature on ECG training was undertaken, with 1,596 studies identified (85 meeting inclusion criteria). Information regarding trainee population, educational intervention, evaluation method, and study quality was extracted. This was synthesized through meta-analysis using a random effects model. Effect size was calculated by dividing the differences between pre intervention and post intervention means by the pooled standard deviation.

## RESULTS

A variety of teaching methods have been used to teach ECG competency, including didactic lectures, small-group seminars, one-on-one tutorials, computer-based tutorials, self-directed learning, and multi-component interventions. The most effective methods emphasized active learning with individual practice and feedback. Of the 85 studies meeting our inclusion criteria, the aggregated effect on participants' abilities was large, with posttest scores approximately 1 SD above pretest scores. Effect sizes varied categorically between educational practices.

## CONCLUSIONS

There are a variety of educational approaches utilized in the medical community to improve participants' abilities to interpret ECGs with variable effectiveness. The most effective approaches engage participants in coordinated activities for an extended period, providing learners with the requisite depth of knowledge, as well as practical application opportunities, serving to favourably alter the mechanisms underlying performance.

Supervisor: Dr. Liam Rourke

# **Comparison of Adverse Events During Capecitabine Versus 5-Fluorouracil/Oxaliplatin Adjuvant Chemotherapy for Stage II/III Colon Cancer: A population based analysis**

Matthew Mazurek, Aliyah Pabani, Maria Ho, Jennifer Spratlin, Julie Price-Hiller, Leah Standeven, Karen Mulder, Sunita Ghosh, Winson Cheung

Supervisor: Dr. Maria Ho

## **INTRODUCTION**

5-fluorouracil (5FU)/oxaliplatin adjuvant chemotherapy following curative-intent surgery was shown to improve survival for patients who have stage III colon cancer with acceptable toxicity. In addition, data from randomized trials and meta-analyses indicate that 5FU-based chemotherapy may offer benefit in patients with resected high risk stage II disease. Little is known about the rates of oxaliplatin induced toxicities in the real-world population. The objectives of the present study are 1) to examine whether oxaliplatin-containing regimens result in measurable differences in toxicity versus capecitabine, and 2) to determine if the toxicity profiles differ in patients  $\geq 75$  years versus those  $< 75$  years

## **METHODS**

Patients with stage II and III first primary adenocarcinoma of the colon who received 5FU/oxaliplatin or capecitabine adjuvant chemotherapy at the Cross Cancer Institute between 2004 and 2007 were identified from the Alberta Cancer Registry. Hospitalizations, emergency room (ER) visits, and outpatient adverse events (AEs) were captured by chart review from 30 days to 9 months post resection. We conducted multivariate logistic regression analyses to determine the factors for binary outcome variable (5FU/oxaliplatin vs capecitabine).

## **RESULTS**

280 patients with complete medical records were identified. 51% (n=143) were male; median age was 72 (26-92) years. Patients  $< 75$  years were more likely to receive 5FU/oxaliplatin compared to those  $\geq 75$  years (OR 11.99;  $P < 0.0001$ ). Hospitalizations, ER visits and AEs were the same in patients who received 5FU/oxaliplatin versus those who received capecitabine alone. In addition, adverse outcomes were not increased by oxaliplatin for patients  $\geq 75$  years versus those  $< 75$  years.

## **CONCLUSIONS**

Adjuvant chemotherapy with 5FU/oxaliplatin did not result in incremental harms compared to capecitabine alone in patients with stage II and III colon cancer. There were no additional adverse outcomes observed in patient  $\geq 75$  years.

Supervisor: Dr. Maria Ho

**Table. Proportion of hospitalizations, ER visits, and outpatient adverse events (AEs) were not significantly different in patients with stage II and III colon cancer receiving adjuvant chemotherapy with 5FU/oxaliplatin (FOLFOX) compared with capecitabine alone.**

	<b>Hospitalizations</b>	<b>ER Visits</b>	<b>Outpatient AEs</b>
<b>FOLFOX</b>			
<b>No. eligible</b>	105	105	105
<b>No. affected (%)</b>	20 (22%)	34 (37%)	4 (4.4%)
<b>Capecitabine</b>			
<b>No. eligible</b>	175	175	175
<b>No. affected (%)</b>	38 (23%)	55 (33%)	13 (7.7%)
	(p=0.91)	(p=0.45)	(p=0.30)

# **Hospitalized Influenza Patients during 2013-2014; a Comparison of ICU and Ward Treated Patients including Antimicrobial Therapy, Adverse Events, and Outcomes**

Alexandra McFarlane, Stephanie Smith, Wendy Sligl, Lynora Saxinger  
Supervisor: Lynora Saxinger

## **INTRODUCTION**

To describe the epidemiology of hospitalized patients with laboratory confirmed influenza infection during the 2013-2014 season; to compare ICU and non-ICU patients; and to specifically describe antimicrobial therapy, outcomes and adverse events in the ICU cohort.

## **METHODS**

Laboratory and epidemiologic data were collected at the University of Alberta Hospital through the Serious Outcomes Surveillance Network (SOS). Additional detailed diagnostic, clinical and outcome data were collected by retrospective chart review of the ICU cohort and stratified by diagnostic features association with bacterial infections.

## **RESULTS**

Of 96 hospitalized influenza patients, 39 (41%) required ICU care, 4 (4%) required extracorporeal support, and 6 (6%) patients died. H1N1 was the predominant strain in both ICU (79%) and ward (69%) patients. ICU patients were less likely to be vaccinated (2; 5% vs. 14; 25%); however vaccination status was unknown in a large number (49; 51%) of patients. ICU patients were younger, with a higher BMI and comorbidity burden, had longer hospital stays, and higher rates of anti-bacterial use. Fourteen (36%) ICU patients had bacterial infection on presentation. Twenty-one suspected or proven nosocomial infections were treated, including 9 presumed hospital/ventilator-acquired pneumonia, 3 central venous catheter infections, 4 episodes of *C. difficile* infection and 3 cases of clinical sepsis with unknown source. In ICU patients the mean oseltamivir therapy duration was 8.8 days (range 0-19), and initial antibiotic course was 9.2 days (range 0-18), with those classified as low likelihood of bacterial infection receiving 6.8 days (range 0-17).

## **CONCLUSIONS**

Patients admitted to the ICU with influenza infection were younger, had higher BMI and comorbidity burden, and lower vaccination rates. Regardless of risk for bacterial infection, anti-biotic use was high in the ICU, with adverse outcomes such as *C. difficile* infection. Risk stratification for bacterial co-infection on admission may identify patients unlikely to benefit from antimicrobials thus minimizing unnecessary use.

Supervisor: Dr. Lynora Saxinger

# Improving the Prediction of Colon Cancer After Curative Resection

Aliyah Pabani, Winson Cheung, Matthew Mazurek, Jennifer Spratlin, Julie Price-Hiller, Leah Standeven, Karen Mulder, Sunita Ghosh, Maria Ho  
Supervisor: Dr. Maria Ho

## INTRODUCTION

Cancer staging systems convey valuable prognostic information to both clinicians and patients. Currently, colon cancer is staged according to the American Joint Committee on Cancer (AJCC) TNM classification system. However, survival estimates for patients with the same stage of colon cancer may vary considerably due to other factors including age, sex, grade, and number of lymph nodes sampled. The objectives of this study are to 1) assess the accuracy of the seventh edition of the TNM classification system in predicting survival of patients with primary colon cancer after curative-intent surgery, and 2) evaluate the utility of incorporating additional demographic and tumor variables in improving prognostic accuracy.

## METHODS

Patients with curative-intent resection of a first primary adenocarcinoma of the colon at the time of referral to the Cross Cancer Institute between 2004 and 2007 were identified from the Alberta Cancer Registry. We constructed three multivariate Cox's proportional hazard models to explore the effect of supplementing TNM staging with additional demographic and tumor variables in predicting overall survival (OS).

## RESULTS

559 consecutive patients were identified. 52 % (n=290) were male; median age was 74. In the first model based only on T and N elements, N2 disease was correlated with increased mortality. (hazard ratio (HR), 2.546;  $p < 0.0001$ ) When the number of lymph nodes examined (HR, 0.980;  $p = 0.034$ ) and number of metastatic lymph nodes detected (HR, 1.094;  $p < 0.0001$ ) were substituted for the N-staging element, both variables correlated positively and negatively with outcome, respectively. Finally, when tumor grade, sex and age were incorporated into the model, number of examined lymph nodes (HR, 0.980;  $p = 0.029$ ) and those containing tumor (HR, 1.093;  $p < 0.0001$ ) remained independent predictors of OS.

## CONCLUSIONS

Incorporating readily available demographic and tumor variables, such as age, sex and number of lymph nodes examined, can enhance the current TNM staging system and improve prognostication in early stage colon cancer.

Supervisor: Dr. Maria Ho

# **Venous Thromboembolism in Hospitalized Patients with Cancer: An Audit of Current Practice**

Gina Polley, Julia Tien  
Supervisor: Dr. Cynthia Wu

## **INTRODUCTION**

Venous thromboembolism (VTE) is common diagnosis in patients with malignancy. One of the strongest predictors of VTE is hospitalization. DVT prophylaxis in hospital has been shown to reduce VTE incidence by approximately 50%. The aim of our project was to assess the prophylaxis rate at our cancer centre and to identify patient characteristics that may influence non-compliance with prophylaxis guidelines.

## **METHODS**

Inpatient charts from the Cross Cancer Institute were retrospectively reviewed from Jan - June 2010. Data extracted included: patient demographics, malignancy type, VTE prophylaxis use, type of prophylaxis, contraindications to thromboprophylaxis, VTE risk factors, VTE diagnosis, risk factors for bleeding, clinically relevant bleeding events, and death during hospitalization.

## **RESULTS**

There were 493 patient charts reviewed. Forty were excluded as the patient was on anticoagulation prior to admission. The overall rate of prophylaxis was 24.3%. Only 31 (6.8%) patients had a contraindication to prophylaxis, and 316 (70%) patients had risk factors for thrombosis in addition to cancer and current hospitalization. The incidence of VTE was 2.4% (11 events). Four VTE events occurred in 110 patients that received prophylaxis (3.6%). Of those that had a VTE event, 100% had at least one additional VTE risk factor. There were 14 bleeding events, of which only 2 (14.3%) were on anticoagulation, and 5 (35.7%) had an identifiable risk factor for bleeding. There were 5 (1.1%) major bleeding events, with only 1 of these patients on anticoagulation.

## **CONCLUSIONS**

Our study demonstrated a VTE prophylaxis rate that does not meet the national standard, despite the presence of multiple risk factors for thrombosis in this patient population. There appears to be a slightly higher than expected rate of breakthrough thrombosis despite prophylaxis. Major bleeding rates were low with and without prophylaxis. Further studies are required to determine the optimal thromboprophylaxis strategies in cancer.

Supervisor: Dr. Cynthia Wu



# Case report: Tapazole associated cutaneous vasculitis

Nathan Puhl, Carrie Ye, and Elaine Yacyshyn  
Supervisor: Elaine Yacyshyn

## INTRODUCTION

Agranulocytosis and p-ANCA-associated vasculitis are rare complications of anti-thyroid therapy, and generally do not occur together simultaneously. Among those with anti-thyroid medication-induced vasculitis, reactions may resemble more lupus-like disease or idiopathic systemic vasculitis. Reported cases describe a leukocytoclastic infiltrates on skin biopsy.

## METHODS

We report a case of a woman with Grave's hyperthyroidism treated with methimazole who presented with necrotic skin lesions of the lower extremities inconsistent with the typical leukocytoclastic vasculitis and a coinciding agranulocytosis.

## RESULTS

The rash began as two erythematous lesions on the left leg which became ulcerated with eschar. Lesions appeared on the right leg five days later. There was no palpable purpura, arthritis, or pruritis. Medical history includes asthma and acne treated with oral contraceptive. Family history includes maternal hyperthyroidism and gestational diabetes and a sister with hypothyroidism. The patient denied drug use, is sexually active with no prior STIs, and has piercings and a tattoo. Investigations revealed aseptic, mixed dermal inflammation on biopsy and possible fibrin in the dermal vessels suggestive of a thrombotic vasculopathy. There was an absence of neutrophilic infiltrate. The patient had an isolated, severe neutropenia with an unremarkable peripheral smear. ENA, RF, ANA, anti-dsDNA, anti-tTGtg, cryoglobulins, and anti-centromere B were negative; however anti-MPO and anti-intrinsic antibodies were positive. Complement levels and renal function were normal. HBV, HCV, HIV, EBV, and CMV serology were negative. Two days after discontinuation of methimazole, G-CSF treatment was given with neutrophil normalization after four days. The patient's rash began to heal after ceasing methimazole but was present at discharge 12 days later.

## CONCLUSIONS

To our knowledge, this is the first case to report a mixed inflammatory appearance as opposed to a leukocytoclastic vasculitis associated with methimazole use. This may suggest a novel adverse reaction to methimazole or an interaction between pathways responsible for vasculitis with those of agranulocytosis.

Supervisor: Dr. Elaine Yacyshyn

# **A UNIQUE CASE OF SUPERFICIAL VEIN THROMBOSIS AND DISSEMINATED INTRAVASCULAR COAGULATION.**

Hina Qamar  
Supervisor: Dr Cynthia Wu

## **INTRODUCTION**

We present a case of a young male patient with Klippel Treneunay Weber Syndrome (KTWS) characterized by recurrent superficial vein thrombosis complicated by an episode of disseminated intravascular coagulation (DIC) who was ultimately maintained on prophylactic rivaroxaban to prevent recurrent thrombotic events.

## **METHODS**

An 18 yr old man with KTWS presenting as a large vascular malformation over his left chest and arm developed acute worsening superficial vein thrombosis (SVT) post tetradecyl injection. On exam, the venous malformation and left arm were extremely tender with significant bruising. Presenting labs: Hg 24, WBC 21.4, plt 98, bilirubin 588 (conjugated 376), LDH 1597, PTT 32, INR 1.9, Fg 1.1, Ddimer >20. He was treated with aggressive supportive care for DIC and routine DVT prophylaxis with LMWH. Symptoms improved after anticoagulation was started. Ultrasound of his left arm revealed old SVT with recanalization within the venous malformation.

## **RESULTS**

He subsequently developed recurrent painful crises in his arm secondary to recurrent SVT. We eventually elected to commence indefinite duration anticoagulation with rivaroxaban 10mg daily, with one recurrence when he stopped rivaroxaban for dental procedure.

## **CONCLUSIONS**

KTWS is a congenital malformation syndrome involving blood and lymph vessels and disturbed bone and soft tissue growth. The tortuosity of vessels results in trapping and subsequent destruction of platelets which leads to the activation of coagulation cascade and localized intravascular coagulopathy, rarely progressing to DIC. Prophylactic rivaroxaban (10mg daily) is effective as DVT prophylaxis post major orthopedic surgery. Prophylactic low-molecular-weight heparin and fondaparinux have been shown to be effective in the treatment of SVT. To our knowledge, this is the first case report to describe successful off-label use of prophylactic rivaroxaban to prevent further thrombotic events in a patient with KTWS.

Supervisor: Dr Cynthia Wu

# **Incidence of Catheter-related Venous Thromboembolism Event in Acute Leukemia patients; a retrospective study of the safety of Peripherally-Inserted Central Catheter.**

Mohammad Refaei, M.Sc. M.D.<sup>1</sup> Bruna Fernandes, B.Sc.<sup>2</sup> Joseph Brandwein M.D.<sup>3</sup>  
Cynthia Wu. M.D.<sup>3</sup>

Supervisor: Dr. Cynthia Wu

## **INTRODUCTION**

Central venous catheters (CVCs) are a leading cause of upper extremity deep vein thrombosis (UE DVT). There is little data on patients with acute leukemia (AL). Long term CVCs are required for chemotherapy in AL. Concomitant severe thrombocytopenia makes anticoagulation for CVC related thrombosis a challenge. Incidence of UE DVT has been reported to be increased in those with peripherally inserted central venous catheters (PICC lines) vs those with centrally inserted lines.

## **METHODS**

We reviewed 161 charts for AL inpatients requiring a PICC line admitted to Hematology at the University of Alberta Hospital between 2003-2013. Baseline patient characteristics were recorded. All venous thromboembolic events were objectively confirmed on imaging studies. Incidence of catheter associated thrombosis was calculated.

## **RESULTS**

311 patients were identified. We present the preliminary results of the first 161 reviewed charts. Of these, 126 met our inclusion criteria and 119 had at least one PICC line insertion. 107 (90%) had AML, 50 (42%) were smokers, 76 (64%) had cardiovascular risk factor, and only 9 (8%) had previous DVT. Overall, there were 236 PICC line insertions, with the 5FR dual lumen being the most commonly used PICC line (80%). Out of the 236 insertions, there were 28 (12%) new ipsilateral upper extremity DVTs, 22 (79%) of which developed acutely (<1month), and 19 (68%) in thrombocytopenic patients (platelet<50). Four (1.7%) other concurrent VTEs were recorded. There was an incidence of 1.85 DVT per 1000 catheter days.

## **CONCLUSIONS**

The incidence rate of DVT in our AL patients is higher than predicted for a general cancer patient population. This data will be compared to a similar cohort of AL inpatients who received a centrally inserted (Broviac/Hickman) CVC. Determining factors that are associated with a lower risk of DVT in this high bleeding risk population will be important to optimize patient care

Supervisor: Dr. Cynthia Wu

# **Isolated Aortitis with Acute Aortic Dissection: Atypical GCA or typical Fulminant Variety of Isolated Aortitis?**

M Refaei<sup>1</sup>; B Chiu<sup>2</sup>; C Ye<sup>3</sup>; J Homik<sup>3</sup>  
Supervisor: Dr. Joanne Homik

## **INTRODUCTION**

Aortitis is a chronic, progressive inflammatory condition of the aorta, most commonly associated with giant cell arteritis (GCA) or Takayasu arteritis (TA). Isolated aortitis refers to the clinical presentation of aortitis not meeting criteria for GCA or TA, and with no evidence of infectious or other autoimmune etiologies. The histopathological findings are often indistinguishable between GCA, TA, and isolated aortitis. A new entity of the latter, termed fulminant variant of isolated aortitis which often presents with acute, severe aortic dissection, has been inadequately described in the literature.

## **METHODS**

N/A

## **RESULTS**

Case Description: 56-year-old female smoker, previously healthy, presented with a one-day history of bilateral leg numbness and weakness, and sudden-onset chest pain confirmed to be type A aortic dissection on imaging. The dissection was extensive, extending from the ascending aorta to bilateral iliac arteries resulting in paraplegia, bilateral leg ischemia and compartment syndrome, and bilateral renal ischemia requiring dialysis. She underwent repair for her type A aortic dissection, axillary to right femoral artery bypass, and bilateral lower limb fasciotomies. Histopathological analysis of the resected aorta is in keeping with GCA. She was started on prednisone 50mg daily, along with acetylsalicylic acid and denosumab for stroke and osteoporosis risk reduction, respectively.

## **CONCLUSIONS**

The patient does not meet criteria for either GCA or TA, and neither typically present acutely with aortic dissection. There are case reports in the literature of first-presentation aortic dissection in the setting of large vessel vasculitis (LVV). Our patient represents a fulminant and rare subset of those cases, which has been termed fulminant variant of isolated aortitis. We will review cases of aortitis presenting with aortic dissection, in both patients who meet and do not meet criteria for GCA or TA. We hope to better delineate distinguishing characteristics of isolated aortitis from aortitis occurring in established LVV.

Supervisor: Dr. Joanne Homik

# **Mycophenolate Mofetil as a Steroid Sparing Agent in Polymyositis and Dermatomyositis: A Systematic Review of the Literature**

Janet Roberts, MD; Stephanie Keeling, MD FRCPC  
Supervisor: Dr. Stephanie Keeling

## **INTRODUCTION**

Idiopathic inflammatory myopathies (IM's) including polymyositis (PM) and dermatomyositis (DM) are rare autoimmune diseases associated with significant morbidity and mortality. Mycophenolate mofetil (MMF), an immunosuppressive agent, may be beneficial in the treatment of IM's with a relatively favorable side effect profile. This systematic review evaluated the benefits of MMF in the treatment of polymyositis and dermatomyositis.

## **METHODS**

A systematic review of four databases (Embase, Pubmed, Web of Science and Scopus) using keywords pertaining to IM's, DM, PM, immunosuppression and MMF was conducted. Two reviewers independently reviewed the title screen and data was extracted using a standardized form. Primary outcomes included changes in corticosteroid dose, muscle enzymes, strength, skin manifestations, and interstitial lung disease outcomes (ILD) (computed tomography (CT) scan and pulmonary function tests (PFTs)).

## **RESULTS**

One hundred and ninety (190) full articles were reviewed after the title screen of 458 articles. Sixteen articles met inclusion criteria, and a total of 102 patients (PM 14; DM 39) were treated with MMF. Ninety two percent of patients were on concomitant corticosteroids, with 95% (n=89) decreasing their steroid dose after initiation of MMF. Of those with baseline elevation in muscle enzymes, 95% (n=39) showed a decrease post treatment and 91% (n=29) showed improved skin manifestations. In the 48% (n=49) of ILD patients, improvements were noted in PFTs, perceived dyspnea and CT scan findings, including improvement in ground glass opacities and pneumonitis. Side effects (reported in 24% of patients) were generally mild, most common being gastrointestinal upset. Only 15% (n=21) required cessation of treatment.

## **CONCLUSIONS**

MMF is a potential alternative first line steroid-sparing agent in those with IM's. High quality trials are needed to further evaluate the efficacy and safety of MMF in this patient population.

Supervisor: Dr. Stephanie Keeling

# **IgA Cutaneous Purpura Post-Renal Transplantation in a Patient with Long Standing IgA Nephropathy: Case Report and Literature Review**

Janet Roberts, MD; Bahman Satoodian, MD; Nausherwan Mahmood, MD FRCPC;  
Elaine Yacyshyn, MD FRCPC  
Supervisor: Dr. Elaine Yacyshyn

## **INTRODUCTION**

IgA vasculitis (IgAV/ Henoch-Schönlein purpura (HSP)) is a small vessel vasculitis mainly affecting the pediatric population. IgA nephropathy is due to deposition of IgA antibodies in renal mesangium. IgA nephropathy and IgAV have long been considered related conditions, however the development of IgA vasculitis is unusual in renal transplant patients with IgA nephropathy. The objectives of this case report are; (1) To describe the case of a patient with renal biopsy proven IgA nephropathy, who developed IgA cutaneous vasculitis for the first time two years post renal transplant while on immunosuppression. (2) To perform a literature review of cases of IgA vasculitis after renal transplant due to isolated IgA nephropathy.

## **METHODS**

Chart review of one patient. Embase and Medline search was completed using the keywords: "IgA Vasculitis", "HSP vasculitis", "IgA nephropathy", "renal transplant", "prednisone".

## **RESULTS**

Case description: 56 year-old patient with renal transplant secondary to IgA nephropathy treated with prednisone, mycophenolate mofetil and tacrolimus. Two years post-transplant developed an acute onset of abdominal pain, a palpable purpuric rash over the lower extremities and multiple swollen painful joints, following a gradual reduction in his prednisone dose. Skin biopsy revealed IgA vasculitis and subsequent renal biopsy revealed recurrent IgA nephropathy. Literature review revealed the presence of only two similar cases.

## **CONCLUSIONS**

This is the third documented case of cutaneous IgAV after renal transplant due to isolated IgA nephropathy. While cutaneous vasculitis post renal-transplant is generally due to infections or drug reactions, it is important to recognize that it may herald the recurrence of underlying renal disease. The proper timeline for gradual tapering of prednisone or continuous use of the medication to prevent recurrence of IgA nephropathy or establishment of IgAV needs to be further evaluated.

Supervisor: Dr. Elaine Yacyshyn

# **Rituximab Monotherapy as Initial Treatment for Post-Transplant Lymphoproliferative Disorder (PTLD)**

Peters AC, Vahidy H, Akinwumi SM, Owen CJ, Mabiligan C, Doucette K, Preiksaitis JK  
Supervisor: Dr. Anthea Peters

## **INTRODUCTION**

PTLDs are a consequence of immune suppression in solid organ transplant (SOT) recipients. Treatment of PTLD is not standardized due to a paucity of high-quality evidence. The role of PET-CT in assessing response to therapy has not been adequately studied. We describe 54 patients treated with reduction of immunosuppression (RIS) and rituximab; chemotherapy was reserved for inadequate rituximab response. The prognostic value of PET scan after initial rituximab in a subset of patients was analyzed.

## **METHODS**

A database of PTLD cases diagnosed from 1999 to 2013 was queried for those initially treated with RIS and rituximab (n=68). Patients were excluded if they received concurrent rituximab and chemotherapy (n=12) or had primary CNS lymphoma (n=2). Patient and disease characteristics, treatment details and outcome were retrospectively reviewed. Survival was analyzed by Kaplan-Meier and prognostic factors by Cox regression (SPSS).

## **RESULTS**

28 (52%) achieved complete remission (CR) or partial remission (PR), and 26 (48%) patients had no response (NR) or progressive disease (PD). 22 patients had PET scan after initial rituximab; 8 (36%) achieved CR, 8 (36%) PR, 1 (5%) NR and 5 (23%) PD. Of the 28 responders, 26 received no further treatment; 7/26 (27%) relapsed and 19/26 (73%) maintained remission. Fifteen (15/54, 28%) received chemotherapy after rituximab; 8 achieved remission, 2 died prior to imaging and 5 progressed. 5-year overall survival (OS) was 52.6%, and 5-year time to progression (TTP) was 52.4%. Several factors were predictive of OS and TTP (Table 1). Poor response to rituximab on PET was predictive of poor OS (HR 6.3, p=0.013) and TTP (HR 8.74, p=0.004).

## **CONCLUSIONS**

One-third of patients treated for PTLD with RIS and rituximab monotherapy achieved and maintained remission without chemotherapy. PET scan after initial rituximab was predictive of TTP and OS.

Supervisor: Dr. Anthea Peters

Table 1. Factors Predictive of Adverse Overall Survival (OS) and Time to Progression (TTP)

Variable	OS	Variable	TTP
age > 60 at transplant	HR 4.2	age >60 at transplant	HR 3.0
age > 60 at PTLT	HR 3.1	age > 60 at PTLT	HR 3.5
IPI >2	HR 2.7	IPI > 2	HR 2.9
no maintained response to rituximab	HR 3.3	no maintained response to rituximab	HR 7.0
lymphopenia	HR 3.6	EBER-negative	HR 3.9
		male gender	HR 5.1
		ECOG >1	HR 2.8
		more than 1 extranodal site	HR 2.4
		late PTLT (>7 years post-transplant)	HR 3.2
		chemo post-rituximab	HR 2.4



# Observing Resident Handover Practices in Internal Medicine

Ashley Whidden

Supervisor: Liam Rourke

## INTRODUCTION

The National Steering Committee on Resident Duty Hours encourages the development of handover skills as a key component of medical education. A systematic process of curriculum development for effective handover begins with an assessment of learners' needs. The purpose of this study was to determine the needs of our Internal Medicine residents to engage in effective handover.

## METHODS

In order to do the needs assessment, we conducted a prospective descriptive study. Our participants were the 28 residents engaged in inpatient rotations at one of our teaching hospitals. In this setting, handover occurs each weekday morning, in an assigned room, between post-call residents and daytime residents. For twelve weeks we distributed daily surveys to post-call residents which prompted them to describe and rate the handover they had received, report any patient care situations for which handover did not prepare them, and make suggestions for handover improvement.

## RESULTS

Twenty-five residents completed surveys. 42% indicated that something happened while they were on call for which they had not been prepared. 42% reported that they were not given information that would have been helpful, and of these 23% stated that the situation could have been anticipated and should have been discussed during handover. The mean rating for handover quality, on a scale of 10, was 7.

## CONCLUSIONS

A comparison of these handovers to the ideal practice suggests that a training program for Internal Medicine residents should include an introduction to the importance of effective handovers and a tool to structure communication.

Supervisor: Dr. Liam Rourke

# **Extreme inhibition of mitochondrial function is compatible with cellular survival and promotes the expression of key stem cell factors**

Aristeidis Boukouris, Roxane Paulin, Sotirios Zervopoulos, Adam Kinnaird, Vikram Gurtu and Evangelos Michelakis

Supervisor: Dr. Evangelos Michelakis

## **INTRODUCTION**

While mitochondria generate ATP (the “molecule of life”) they also regulate cell death (apoptosis) and produce large amounts of toxic reactive oxygen species (ROS). Although it was initially thought to represent a paradox, it is now accepted that cancer cells exhibit significant mitochondrial suppression offering them apoptosis-resistance. Instead of using the carbon sources for oxidation in mitochondria, cancer cells shift them toward biomass synthesis. Suppressed mitochondrial function is also described in stem cells, in which the decrease in ROS is critical for avoidance of DNA damage. As mitochondria are previous bacterial endo-symbionts, mammalian cellular life may be possible without them. We hypothesized that near complete mitochondrial inhibition is compatible with life and confers a survival advantage.

## **METHODS**

We generated cancer cells (A549) with extremely reduced mitochondrial respiration by depleting mitochondrial DNA (mtDNA). A549 cells were cultured for 14 days in medium containing 50 ng/ml Ethidium Bromide (EtBr), supplemented with 1 mM pyruvate and 50 µg/ml uridine. EtBr is a DNA intercalator dye, which at low doses preferentially inhibits mtDNA replication. Mitochondrial respiration was measured with the XFe24 Seahorse Analyzer.

## **RESULTS**

EtBr resulted in a >95% mtDNA depletion and reduced respiration by 87%. Metabolic shift to glycolysis was confirmed by an increased (55%) proton production. Cells remained fully viable throughout the culture in EtBr, maintaining protein synthesis, as shown by uptake of BrdU. Interestingly, EtBr-treated cells showed increased expression of the stem cell markers and critical “stemness” transcription factors OCT3/4, KLF4 and NANOG.

## **CONCLUSIONS**

Extreme reduction of mitochondrial function is compatible with cell survival. The over-expression of key stem cell factors is in keeping with the recent observations that suppressed mitochondrial function characterizes stem cells. These data suggest that the mitochondrial suppression may not be a result of “stemness” but rather, that mitochondrial inhibition may be an intrinsic signal facilitating “stemness”.

Supervisor: Dr. Evangelos Michelakis

# **FGD5 regulates SDF-dependent angiogenesis in vitro**

Maikel Farhan, Allan G Murray  
Supervisor: Allan Murray

## **INTRODUCTION**

Although targeting tumors with anti-angiogenic therapy demonstrated efficacy, the development of tumor resistance, by secreting alternative pro-angiogenic factors to bypass the blockade, limited the overall survival benefits of this approach. Stromal derived factor (SDF) is one of the candidate alternative proangiogenic factors. Facio-genital dysplasia 5 (FGD5) is endothelial specific, and is essential for angiogenesis. However, its role in SDF-induced angiogenesis is poorly defined. We sought to investigate the involvement of FGD5 in SDF signaling pathway.

## **METHODS**

We used RNA interference and pharmacological inhibitors to isolate function of FGD5 and its downstream effector Cdc42. Angiogenic sprouting and endothelial cells' (EC) migratory movement were evaluated in a three dimensional in vitro model and scratch wound healing assay, respectively. We correlated these with candidate regulatory signaling events.

## **RESULTS**

In primary human EC, SDF potentiates the EC angiogenic and migratory response to the conventional proangiogenic factor, vascular endothelial growth factor (VEGF). Interestingly, FGD5 loss decreased the dual stimulatory effect of SDF and VEGF on angiogenesis. These functional defects were attributed to dramatic reduction in SDF-mediated Akt activity after FGD5 loss or Cdc42 inhibition. In contrast, the expression of the SDF specific receptor (CXCR4) and the mitogen-activated protein kinase (MAPK) pathway were normal.

## **CONCLUSIONS**

In conclusion, FGD5 regulates SDF derived angiogenesis by regulation of EC migration, Cdc42 and Akt activity. Thus, FGD5 can represent a potential target for avoiding tumor resistance to anti-angiogenic drugs.

Supervisor: Dr. Allan Murray

# **Ex Vivo Lung Perfusion as a Novel Method To Assess Vasoreactivity and Lung Health in Explanted Pig and Human Lungs with PAH**

Vikram Gurtu, Nader Aboelnazar, Christopher White, Adam Kinnaird, Darren Freed, Jayan Nagendran, and Evangelos Michelakis

Supervisor: Dr. Evangelos Michelakis

## **INTRODUCTION**

Ex vivo lung perfusion (EVLP) is used to “resuscitate” borderline quality donor lungs for transplantation. Its potential to study diseased (recipient) human lungs has not been explored. EVLP can offer invaluable information on the direct effects of therapies on pulmonary vascular resistance (PVR), lung metabolism and lung-specific biomarkers, otherwise impossible to study in vivo. We hypothesized that human pulmonary arterial hypertension (PAH) lungs can be studied with EVLP, but first studied normal pig lungs.

## **METHODS**

We used a custom-made EVLP system in 8 pig lungs. A ventilator was connected to the main bronchus and a pump-driven perfusion system (flow, pressure and temperature sensors connected to a computer) was connected to the main pulmonary artery, with the venous efflux re-circulated. The perfusate consisted of STEEN solution™ mixed with blood.

## **RESULTS**

The pig lungs exhibited normal oxygenation and blood pH for at least 12 hours. At 4 hours they demonstrated intact hypoxic pulmonary vasoconstriction (HPV; an important sign of lung vasculature health), with an increase in PVR of  $442 \pm 27$  dyn\*s/cm<sup>5</sup>. We then studied lungs from 2 transplant PAH recipients. HPV was absent, despite normal oxygenation on room air. Intravenous treprostinil caused a 30% decrease in PVR, at a level of flow corresponding to the patients’ cardiac output. One-hour perfusion with 5mM Dichloroacetate (DCA), with biopsies taken before and after, increased pyruvate dehydrogenase activity (the drug’s target enzyme), and mitochondrial respiration by 61%, confirming the preclinical data that DCA enhances mitochondrial function.

## **CONCLUSIONS**

This was the first time that human PAH lungs were studied with EVLP. HPV and acute vasodilators can be studied in pig and human lungs. The DCA-induced improvement in mitochondrial function is an invaluable addition to our recent clinical trial with DCA in PAH, which improved hemodynamics, but lacked evidence for the DCA effects on PDH and lung metabolism.

Supervisor: Dr. Evangelos Michelakis

# **Ulcerative colitis patients with and without subclinical inflammation can be differentiated from healthy controls through metabolomic profiling**

Ammar Hassanzadeh Keshteli, Floris van den Brand, Rosica Valcheva, David Wishart, Rupasri Mandal, Karen Kroeker, Richard N Fedorak, Karen Madsen, Levinus A Dieleman  
Supervisor: Dr. Karen Madsen

## **INTRODUCTION**

The exact mechanisms involved in the pathophysiology of inflammatory bowel disease (IBD) still remain unknown. In addition, most currently available tools for diagnosis and assessment of IBD are invasive, time-consuming and costly. Using a system-based approach to characterize specific metabolites associated with IBD phenotypes could help both in the discovery of specific biomarkers of disease and in the detection of underlying mechanisms. In this study, we aimed to use metabolomic profiling to identify metabolites that could discriminate between ulcerative colitis (UC) and healthy controls. In addition, we investigated if metabolomic profiles of UC patients differ between patients with and without subclinical inflammation.

## **METHODS**

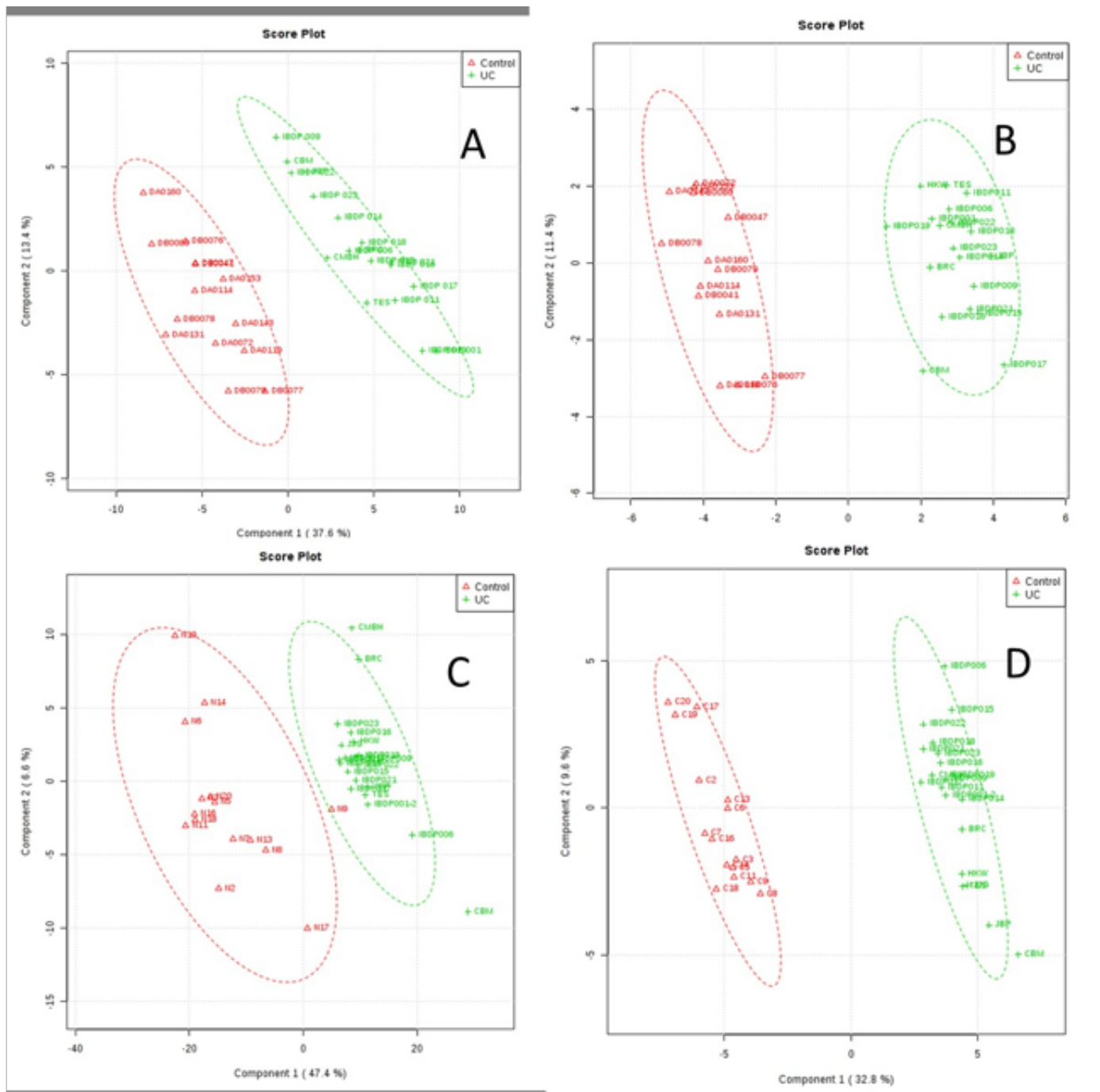
Serum and urine samples were obtained from UC patients (n=20) in clinical remission (partial Mayo score < 2) and non-IBD controls (n=15). Metabolomic profiling on samples was done using nuclear magnetic resonance (NMR) and direct infusion mass spectrometry (DIMS). Fecal calprotectin (FC) was measured in stool samples of UC patients in order to classify them into individuals with no colonic inflammation (FC < 150 µg/g) and patients with colonic inflammation (FC ≥ 150 µg/g).

## **RESULTS**

Using NMR and DIMS 138 and 166 metabolites could be identified and quantified in serum and urine samples, respectively. UC patients could be differentiated from non-IBD controls (Figure 1). Amino acids (e.g. glutamine, isoleucine, ornithine, tyrosine), gut microbial-related metabolites (e.g. formate, trimethylamine), phosphatidylcholines (e.g. PC aa C30:2, PC aa 38:3), sphingomyelins (e.g. SM C22:3) were found to be primarily responsible for discrimination. In addition, two phenotypes of UC patients could be discriminated from each other. Some metabolites including acetamide, carnosine, 3-hydroxybutyrate and serotonin were identified to be responsible for this discrimination.

## **CONCLUSIONS**

Metabolomic profiling can be used to distinguish UC patients from non-IBD individuals. Also, metabolomic profiling was found to differentiate UC patients with or without subclinical colonic inflammation. In addition to their potential role as diagnostic biomarkers, the identified metabolites could provide more insight in the pathophysiological mechanisms of UC.



Partial least squares discriminant analysis plots showing significant discrimination of ulcerative colitis (UC) patients from non-UC controls. A: direct infusion mass spectrometry (DIMS) on serum samples; B: nuclear magnetic resonance (NMR) on serum samples; C: DIMS on urine samples; D: NMR on urine samples

# **Detection of Ophthalmic Acid in Serum from Acetaminophen-induced Acute Liver Failure Patients is more frequent in Non-Survivors**

Gurnit Kaur, Elaine M. Leslie, Holly Battenhouse, William M. Lee, Diane P. Swanlund, and Constantine J. Karvellas

## **INTRODUCTION**

Acetaminophen (APAP) hepatotoxicity is related to the formation of N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified through conjugation with reduced glutathione (GSH). Ophthalmic acid (OA) is an analogue of GSH in which cysteine is replaced with 2-aminobutyrate. Metabolomics studies of mice with APAP-induced acute liver failure (APAP-ALF) identified OA as a marker of oxidative stress and hepatic GSH consumption. The aim of the current study was to determine whether OA is detectable in APAP-ALF human and whether OA levels were associated with in-hospital survival in the absence of liver transplant.

## **METHODS**

A case-control study of a total of 130 APAP-ALF patients enrolled by the US ALFSG was performed. Serum samples collected on day 2 (early) or day 4 (late) from these patients (82 survivors, 48 non-survivors) were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

## **RESULTS**

Survivors had significantly lower admission bilirubin (4.2 vs. 5.7 mg/dl) and lactate levels (3.3 vs. 6.5  $\mu\text{mol/l}$ ,  $p < 0.05$  for all). During the first 7 days of the study, survivors were less likely to require mechanical ventilation (55% vs. 88%), vasopressor support (9.8% vs. 67%) or renal replacement therapy (26% vs. 63%,  $p < 0.001$  for all). Non-survivors were more likely to have detectable OA levels early (31% vs. 15%,  $p = 0.034$ ) and late (27% vs. 11%,  $p = 0.02$ ). However there were no significant differences in mean OA levels between non-survivors and survivors (early 0.48 vs. 0.36, late 0.43 vs. 0.37,  $P > 0.5$  for all).

## **CONCLUSIONS**

OA was detectable more frequently in APAP-ALF non-survivors but mean OA levels were not associated with survival. The routine clinical administration of N-acetyl cysteine could shut off OA production. However, depletion/repletion of glutathione alone does not appear to predict outcome in APAP-ALF.

Supervisor: Dr. Elaine Leslie

# **Pyruvate Dehydrogenase Kinase is a novel therapeutic target for Renal Cell Carcinoma**

Adam Kinnaird, Peter Dromparis, Roxane Paulin, Vikram Gurtu, Bruno Saleme, Kristalee Watson, Trevor Stenson, Katia Simmon, Desmond Pink, John Lewis and Evangelos D. Michelakis

Supervisor: Dr. Evangelos Michelakis

## **INTRODUCTION**

Clear Cell Renal Cell Carcinoma (ccRCC) uses glycolysis due to suppression of the mitochondrial glucose oxidation (GO). This metabolic remodeling offers growth advantages (suppressed apoptosis, increased proliferation and angiogenesis). Most ccRCC have constitutively active Hypoxia Inducible Factor (HIF), which upregulates Pyruvate Dehydrogenase kinase (PDK) and thus inhibits Pyruvate Dehydrogenase (PDH), the gating keeping enzyme in GO. The constitutive activation of HIF (due to von Hippel-Lindau mutations) and the upregulation of its target VEGF are difficult to reverse pharmacologically, leading to many clinical failures of VEGF inhibitors. We hypothesized that an alternate way to inhibit the HIF axis is by PDK inhibition (by the small molecule Dichloroacetate), reactivation of GO, increasing  $\alpha$ -ketoglutarate ( $\alpha$ KG) levels that would inhibit Factor inhibiting HIF (FIH). This would suppress HIF activity and HIF-driven angiogenesis even though the HIF levels will remain unchanged.

## **METHODS**

The 786-O ccRCC line was used in vitro, in ovo (chicken), and in vivo (xenotransplant) in Nu/Nu mice, following prevention and reversal protocols at doses similar to those achieved in the serum of DCA-treated patients.

## **RESULTS**

In a cohort of human RCC the levels of PDK isoenzymes were much higher than in the neighboring non-cancer tissue from the same patient. DCA inhibited PDK and increased PDH activity, increased GO,  $\alpha$ -KG levels and HIF activity. DCA increased apoptosis, decreased proliferation and inhibited VEGF levels and angiogenesis. siRNA inhibition of FIH prevented most of the DCA-induced decrease in HIF activity in an  $\alpha$ KG-dependent manner. DCA prevented and reversed tumor growth in ovo (mean tumor weight 74mg control, 18mg DCA) and in vivo (271mm<sup>3</sup> control, 136mm<sup>3</sup> DCA).

## **CONCLUSIONS**

The DCA-induced PDK inhibition reverses ccRCC tumor growth and angiogenesis even though HIF is constitutively expressed. This strategy may be superior to VEGF inhibitors since it suppresses the HIF axis proximal to VEGF.

Supervisor: Dr. Evangelos Michelakis



# **Improving Healthcare Transition for Young Adults with Inflammatory Bowel Disease: A Literature Review**

Natalie R. Klostermann, Karen I. Kroeker  
Supervisor: Dr. Karen Kroeker

## **INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic illness, characterized by abdominal pain and diarrhea. Approximately 25% of patients are diagnosed in childhood and must be transitioned to adult gastroenterologists prior to their 18th birthday. Healthcare transition has generated significant interest, given the adverse health outcomes that can arise.

Transition patients can experience deficits in medication adherence, self-advocacy, self-management and knowledge of their disease, which can be ameliorated through patient education during the transition process. However, there is a lack of information about how patients would like to receive information. The emerging adult generation is disproportionately technologically active; they may have unique expectations or ideas about how to receive health information and improve the transition process.

## **METHODS**

A literature review was done to identify any studies addressing the health behavior, knowledge deficits and needs of pediatric transition patients with chronic illnesses.

## **RESULTS**

Several studies highlighted transition patient issues with health behaviours and knowledge. Others have developed interventions or educational tools to implement with this patient population. A few researchers have used focus groups or interviews to gain patient perspectives on aspects of disease management, and opinions on the transition process. There is no study informing health practitioners of the communication/education strategy that IBD transition patients would find most helpful during the process.

## **CONCLUSIONS**

While it is a burgeoning field of interest, there is still a paucity of literature addressing the educational needs and preferences of IBD transition patients. It is evident that deficits are experienced by this group of patients, which can lead to adverse health outcomes, and thus, structured interventions have been called for.

We have created a qualitative semi-structured interview guide to uncover IBD patients' experience of pediatric transition, to use along with validated assessments to uncover deficits, and most importantly to discover from patients how they prefer to learn health information.

Supervisor: Dr. Karen Kroeker

# Baseline Hematoma Volume Predicts Corticospinal Tract Disruption in Acute Intracerebral Hemorrhage

Rebecca McCourt, Laura Gioia, Mahesh Kate, Sarah Treit, Christian Beaulieu, Kenneth Butcher.

Supervisor: Dr Ken Butcher

## INTRODUCTION

White matter disruption after intracerebral hemorrhage (ICH) is associated with functional deficits. Fractional anisotropy (FA), a Diffusion Tensor Imaging (DTI) parameter, is used to evaluate tract integrity. We tested the hypotheses that 1) larger hematoma volumes are associated with lower FA in the corticospinal tract (CST), and 2) decreased FA is associated with worse day 7 motor outcome.

## METHODS

ICH patients were imaged within 2 weeks of onset. Relative FA (rFA) was measured in the entire CST (Figure 1). Hematoma volume was measured on acute and 48h CT scans. Day 7 motor function was assessed using a composite of the National Institute of Health Stroke Scale (NIHSS) upper and lower extremity subscales (0=normal, 8=hemiplegia).

## RESULTS

Thirty-seven ICH patients (mean age  $67 \pm 12$ ) were imaged with DTI at a median (IQR) of 42.1 (27.9)h and 7.6 (3.6) days. Hematoma volume was 7.2 (20.0)ml measured at the 2.1 (3.5)h CT and 8.2ml (25.1)ml at the 26.0 (24.2)h CT. NIHSS motor score was 5 (12) at baseline and 5 (9) at day 7.

Mean 48h FA was lower in the CST ipsilateral to the hematoma ( $0.42 \pm 0.09$ ) compared to the contralateral CST ( $0.48 \pm 0.04$ ,  $p=0.014$ ). Day 7 FA was also lower in the ipsilateral ( $0.43 \pm 0.04$ ) vs. contralateral CST ( $0.48 \pm 0.03$ ,  $p<0.0001$ ).

Acute hematoma volume predicted rFA at 48h ( $\beta=-0.415$ ,  $p=0.035$ ), but not day 7 ( $\beta=0.171$ ,  $p=0.446$ ). rFA at 48h ( $r=-0.58$ ,  $p=0.025$ ) and day 7 ( $r=-0.56$ ,  $p=0.013$ ) correlated with day 7 motor function. Patients with hematomas overlapping the CST had lower rFA than those with hematomas separate from the CST, at both 48h (adjacent:  $0.85 \pm 0.22$  vs. separate:  $1.0 \pm 0.13$ ,  $p=0.049$ ) and day 7 (adjacent:  $0.87 \pm 0.08$  vs. separate:  $1.0 \pm 0.07$ ,  $p=0.004$ ).

## CONCLUSIONS

Acute hematoma volume predicted decreased rFA at 48h, which was associated with worse day 7 motor outcomes. Direct proximity to the hematoma was associated with reduced CST integrity.

Supervisor: Dr Ken Butcher

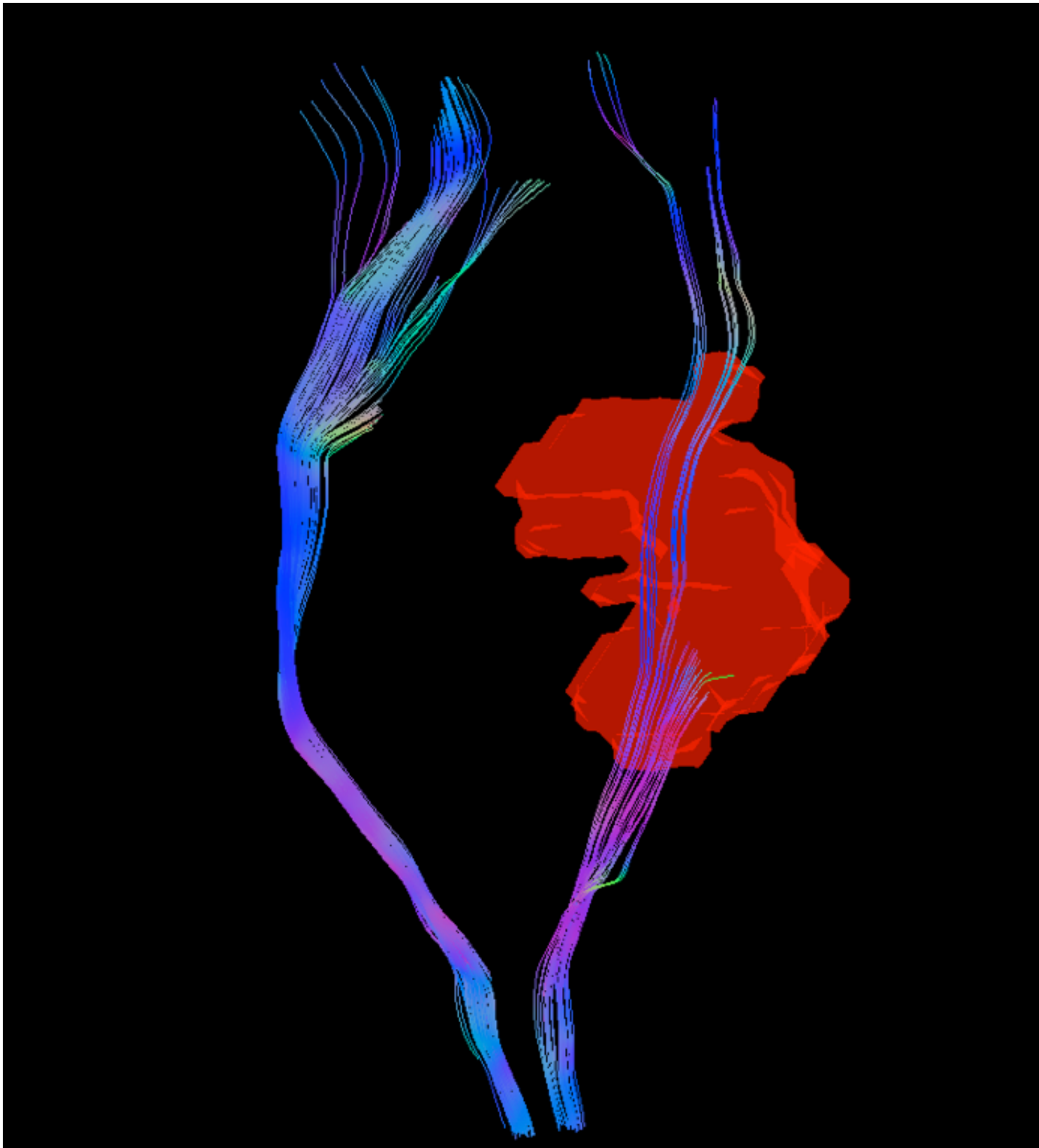


Figure 1. Example of disrupted integrity of the ipsilateral corticospinal tract (right), compared to the contralateral (left), in a patient with a 7.8ml parenchymal hemorrhage (in red). Ipsilateral FA=0.44; contralateral FA=0.47.

# **A Novel Insertion Mutation in the prion protein gene (Prnp) Causes Gerstmann-Sträussler-Scheinker Disease in transgenic mice.**

Robert C.C. Mercer, Charles E. Mays, Hristina Gapeshina, Lyudmyla Dorosh, Serene L. Wohlgemuth, Nathalie Daude, Jing Yang, Kerry Ko, Holger Wille, Neil R. Cashman, Michael B. Coulthart, Maria Stepanova, David Westaway

## **INTRODUCTION**

Gerstmann-Sträussler-Scheinker Disease is a progressive neurodegenerative disorder. Clinically, the disease primarily presents as ataxia before progressing to dementia at later stages. Recently, the Canadian CJD Surveillance System discovered a novel 24 base pair insertion mutation of PRNP in a GSS patient (Hinnell et al. Neurology, 2011). This mutation is predicted to extend the length of the hydrophobic domain (HD) by 8 residues which is of great interest in PrPC biology because: i) the HD is the most highly conserved segment, ii) it has been implicated in many of the proposed functions of PrPC and iii) it is thought to be involved in the early structural rearrangements during the transition between PrPC and the disease associated PrP<sup>Sc</sup>.

## **METHODS**

transgenic mice, biochemical and histopathological analysis, molecular dynamics simulations.

## **RESULTS**

We created transgenic mice expressing this mutated allele within the context of murine PrP and determined that these animals develop a spontaneous neurologic syndrome at ages >300 days. The onset of disease in these mice can be accelerated through intracranial inoculation with brain homogenate from clinically ill animals, demonstrating transmissibility. Histopathological analysis of these mice shows vacuolation and prominent gliosis. Biochemical profiling reveals a 7 kDa PrP fragment following exposure to proteinase K or removal of carbohydrates, a characteristic of GSS prions. Molecular dynamics simulations indicate an increase in the proportion of  $\beta$ -sheet content, which may prove useful in deciphering the early structural changes during the process of prion conversion.

## **CONCLUSIONS**

These mice recapitulate many of the features of GSS and can be used as a model system for the study of this genetic prion disease.

Supervisor: Dr. David Westaway

# **De novo expression of Von Willebrand Factor (VWF), an endothelial specific gene, in some cancer cell lines and patients' tumor samples**

Anahita Mojiri, Konstantin Stoletov, Katia Carmine Simmen, Paul Jurasz, David Eisenstat, John Lewis, Nadia Jahroudi.

Supervisor: Dr. Nadia Jahroudi

## **INTRODUCTION**

Introduction: VWF is an adhesive procoagulant protein that is exclusively expressed in endothelial cells (EC) and megakaryocytes. Increased plasma levels of VWF and alterations in coagulation system in cancer patients with metastasis and cancer progression are reported. We hypothesised that a subpopulation of some cancer cells of non-endothelial origin may acquire VWF expression and as a result develop enhanced metastatic potential.

## **METHODS**

Method: For VWF expression RT-PCR, western blot and immunofluorescence (IF) analyses were used. For transcription factor binding and epigenetic modifications Chromatin Immunoprecipitation (ChIP) was used. Functional analysis included cell-adhesion and Chick Chorioallantoic Membrane (CAM) assays.

## **RESULTS**

Results: RT-PCR, western blot and immunofluorescence (IF) analyses showed significant levels of VWF expression in an osteosarcoma (Saos2) and glioma (U251, M016, M049) cell lines. ChIP assays demonstrated similar pattern of transcription factors binding to the VWF promoter in EC and cancer cells. The epigenetic modification analysis showed that histone modifications of the VWF promoter in glioma (U251, M016, M049) and Saos2 are consistent with transcriptionally active VWF promoter. In vitro analyses showed that cancer cell lines expressing VWF, exhibit increased affinity for adhesion to the platelets and EC monolayer under shear stress. IF and immunohistochemistry analyses of human glioma and osteosarcoma tumor samples from patients demonstrated VWF expression in some cells of non-endothelial origin. Furthermore, CAM assay showed significant extravasation indicative of metastatic ability of glioma and osteosarcoma cells. Knock down of VWF through siRNA treatment reduced extravasation by  $98 \pm 2\%$ . We are now using a mouse metastatic model for investigating the effect of VWF protein expression by cancer cells.

## **CONCLUSIONS**

Conclusion: Our results demonstrated that cancer cells, which acquire de novo expression of VWF have increased platelet and endothelial adhesion as well as increased extravasation capability. These results strongly suggest a potential role for VWF in cancer metastasis.

Supervisor: Dr. Nadia Jahroudi

# **Adaptation of prion-infected brain organotypic cultures to other brain regions to probe cell death pathways.**

Grant Norman, Jody L. Campeau, and Valerie L. Sim  
Supervisor: Dr. Valerie Sim

## **INTRODUCTION**

The development of the prion organotypic cerebellar slice culture assay (POSCA) has generated a powerful tool for the study of prion disease pathogenesis, as the model itself undergoes aspects of prion pathology, including neuronal loss and a reduction in Purkinje cell spine density. We have now adapted this technique to non-cerebellar brain regions which we can infect with different prion strains. By comparing time courses of infection in cerebellar and cerebral cultures, we are determining how specific prion strains preferentially target particular brain regions and what autophagic pathways they induce.

## **METHODS**

Ten to twelve day old tga20 mouse pups were sacrificed for the experiments. Tga20 mice are on a C57Bl6 background and overexpress mouse PrPC by six times. Cerebellar slice cultures were prepared as described previously. For coronal sections, whole brains were fixed in low melting point agarose and cut into 250  $\mu$ m sections using a vibratome. Slices were then plated on a 30 mm diameter Millicell insert with 0.4  $\mu$ m pore size and infected with rodent-adapted scrapie (10  $\mu$ g/mL). Infection was confirmed by Western blotting for Proteinase K-resistant PrP using SAF83 (rodent-adapted scrapie). Changes in autophagy were determined by looking at the relative changes in the levels of LC3I and LC3II.

## **RESULTS**

PK-resistant PrP is detectable at day 42 in coronal slices infected with rodent-adapted scrapie. LC3I bands are stronger than LC3II bands in the control (uninfected) samples. In prion infected samples, LC3II bands are stronger when compared to the LC3II bands of the control samples.

## **CONCLUSIONS**

Our results show that an adapted version of the POSCA technique can be used to study other brain regions to investigate the susceptibility of different brain regions to prion infection. With this adaptation we can now analyze the changes in various autophagic markers across many different structures without being limited to solely to the cerebellum.

Supervisor: Dr. Valerie Sim

# **The Effect of A $\beta$ 42 Oligomers on APP Processing Enzymes and A $\beta$ 40 Expression in Cultured U373 Astrocytes**

Dimitar Ourdev<sup>1,2</sup>, Bahram V. Foroutanpay<sup>1,2</sup>, Yanlin Wang<sup>1,2</sup>, Satyabrata Kar<sup>1,2,3</sup>

Supervisor: Dr. Satyabrata Kar

## **INTRODUCTION**

Amyloid- $\beta$  (A $\beta$ ) peptides are a family of proteins that are considered to be a principal aspect of Alzheimer's disease (AD), the most common cause of senile dementia. These peptides result from the proteolytic processing of Amyloid Precursor Protein (APP) by the sequential cleavage of enzymes known as secretases. Although much work has been focused on the various interactions between A $\beta$  and neurons, the relationship between soluble A $\beta$  peptides and astrocytes has received relatively little attention. To address this issue, we incubated human astrocytes with oligomeric A $\beta$ 42 and assessed the effect of this treatment on APP processing and A $\beta$  production.

## **METHODS**

Using the human astrocytoma cell line U373, we investigated the effects induced by A $\beta$ 42 treatment on the cellular expression of APP and its proteolytically generated products,  $\alpha$ CTF,  $\beta$ CTF, and A $\beta$ 40 via Western Blot and ELISA. In conjunction with these experiments, we examined the relative cellular levels and activity of secretase enzymes, as well as the localization of the various components involved in the cellular processing of APP via immunostaining.

## **RESULTS**

Western Blot and ELISA data show that A $\beta$ 42 treatment increased the expression of APP and cleaved products within astrocytes in a time-dependent manner. This treatment additionally increased  $\gamma$ -secretase activity in order to yield greater amounts of A $\beta$ 40 in both cell lysates and cell media.

## **CONCLUSIONS**

Exposure to A $\beta$ 42 potentiates further production of A $\beta$  peptides in astrocytes. This can potentially form an important positive feedback loop that further exacerbates amyloid pathology observed in diseases such as AD.

Supervisor: Dr. Satyabrata Kar

# **Acute changes in ambient air pressure modulate vasodilatation of resistance arteries independently of endothelial mechanisms**

Anmol Shahid, Sean Michael McMurtry  
Supervisor: Dr. Sean McMurtry

## **INTRODUCTION**

Epidemiological studies have found populations living at higher elevations are at lower risk for acute myocardial infarction (MI) than those at lower elevation. Reduced compressive force on arteries due to elevation-related reductions in atmospheric pressure might alter arterial function, and could be a potential mechanism. We hypothesized that acute exposure to lower air pressure will dilate conduit arteries and increase arterial vasodilation.

## **METHODS**

Second order mesenteric arteries (n=7) were isolated from C57-WT male mice (n=7, age  $3.2 \pm 0.9$ ) and perfused with  $\text{Ca}^{2+}$ -free saline solution to assess passive properties of the vessels in a pressure myograph. This system was placed in a barometric chamber and arterial function was studied ex-vivo at acute exposure to three barometric pressure steps: 754 mmHg (p0), 714 mmHg (p1) and 674 mmHg (p2). Active vessel responses in the presence of L-NAME and Meclofenamate were assessed with mechanical manipulation of perfusion pressure (4-140 mmHg) or flow rate (0-70  $\mu\text{L}/\text{min}$ ). Lumen diameter was measured using a micrometer, with manometers for measurement of pressure drop across the vessel.

## **RESULTS**

Under static conditions, vessel diameters at p1 and p2 increased by  $20.9 \pm 9.3\%$  and  $28.2 \pm 8.6\%$  compared to baseline diameter at p0 ( $p < 0.01$  vs. p0 for p1 and p2). Flow-mediated vasodilation contributed little additional dilation. At a fixed flow rate of  $70 \mu\text{L}/\text{min}$ , vessels reached maximum diameters of  $108.6 \pm 13.6 \mu\text{m}$  at p1 and  $120.5 \pm 13.0$  at p2 versus  $106.0 \pm 4.0 \mu\text{m}$  for p0. This observed vasodilation was not diminished in the presence of L-NAME and Meclofenamate. Vascular resistance was statistically significantly reduced at p2 compared to p0 ( $2.14 \pm 0.60 \text{ mmHg} \cdot \text{min}/\mu\text{L}$  vs.  $3.21 \pm 0.49 \text{ mmHg} \cdot \text{min}/\mu\text{L}$ ,  $p < 0.05$ ).

## **CONCLUSIONS**

We conclude that acute exposure to reduced barometric pressure increases artery diameter ex-vivo in an endothelium-independent manner.

Supervisor: Dr. Sean McMurtry



# **Mouse mammary tumor virus (MMTV) is implicated in severity of colitis and associated pro-inflammatory response in interleukin-10 deficient mice**

H Thaker, A Thiesen, N Hotte, M Rahbari, D Sharon, K Madsen, A Mason  
Supervisor: Dr. Andrew Mason

## **INTRODUCTION**

Inflammatory bowel disease (IBD) is thought to occur in genetically predisposed individuals who are exposed to microbial, dietary, and environmental triggers, but the role of viruses in either the initiation or perpetuation of inflammation in IBD remains to be determined. We have previously shown that IL-10<sup>-/-</sup> mice have increased levels of Mouse Mammary Tumor Virus (MMTV) in colon and liver as compared with wild type (WT) mice. The aim of this study was to address the hypothesis that MMTV infection was a contributing factor to the spontaneous inflammation observed in the IL-10<sup>-/-</sup> mouse and treatment of MMTV with antiretroviral therapy (ART) would improve colitis.

## **METHODS**

IL-10<sup>-/-</sup> and WT mice were treated with combination HIV reverse transcriptase inhibitors, tenofovir/emtricitabine (Truvada) and HIV protease inhibitors, lopinavir/ritonavir (Kaletra) versus placebo in drinking water for 10 weeks (n=57). Mice were sacrificed at 18 weeks of age. MMTV RNA were measured using the QuantiGene reagent system. Colon samples were stained with H&E for histological scoring. Immune function was assessed in tissue homogenates using the MesoScale Discovery platform.

## **RESULTS**

IL-10<sup>-/-</sup> mice had higher levels of MMTV virus compared with WT mice (p<0.0001). IL-10<sup>-/-</sup> mice treated with antiretroviral therapy had a reduction in viral load which correlated with a decrease in overall histological score (p<0.007) compared with IL-10<sup>-/-</sup> on placebo. Pro-inflammatory cytokines (TNF $\alpha$ , KC GRO, IL-6) were increased in small intestine and colon of IL-10<sup>-/-</sup> mice relative to WT (p<0.005) and ART decreased levels (p<0.02).

## **CONCLUSIONS**

MMTV levels in IL-10<sup>-/-</sup> mice exhibiting colitis were higher than in WT mice. Viral load was reduced by ART and this correlated with a reduction in intestinal inflammation. Antiretroviral therapy also resulted in the down-regulation of several pro-inflammatory cytokines in IL-10<sup>-/-</sup> mice which could impact disease progression. These data suggest that MMTV may contribute to the IBD phenotype observed in IL-10 deficient mice.

Supervisor: Dr. Andrew Mason

# **Exercise in the dialysis unit: a randomized factorial mixed-method pilot study to improve health-related quality of life and physical function in hemodialysis patients (DIALY-SIZE!)**

Thompson S, Klarenbach S, Haykowsky M, Molzahn A, Lloyd A, Tonelli C  
Supervisor: Dr. Scott Klarenbach

## **INTRODUCTION**

Exercise improves quality of life (QoL) and dialysis adequacy in hemodialysis patients. However, uptake of exercise programs into practice is limited by knowledge gaps, such as what type of exercise should be prescribed. Prior to a definitive trial comparing the efficacy of aerobic and resistance exercise, a pilot is needed to evaluate feasibility and refine the study design.

## **METHODS**

In this single center, randomized, factorial (2 x 2), mixed-method study of adult, chronic, hemodialysis patients, participants were randomized to one of four intradialytic exercise (IDE) groups: cycling, resistance, cycling and resistance, or stretching (an attention control). Exercise was semi-supervised by a kinesiologist. Outcomes focused on a priori feasibility criteria: recruitment, fidelity to the protocol, and participant response to the intervention. To better understand feasibility, we conducted interviews with users and stakeholders. As a secondary outcome, we evaluated the main effect of cycling and weights each compared with control on QoL and physical function between baseline and 12-weeks.

## **RESULTS**

We exceeded the target accrual of 28 subjects over 12 weeks, demonstrating the feasibility of recruitment. Of 100 patients screened, 31 were enrolled (36 did not meet inclusion criteria, and 33 declined participation); 16% dropped out after randomization. Fidelity to the intervention was high: of 1,039 training sessions offered, 87% were delivered. Participant response to the intervention was favorable: 92% of participants reported they would continue exercising after the trial. Dialysis staff were not consistently available to assist with implementation, and so study staff were necessary to deliver IDE. Secondary outcomes were not statistically significant.

## **CONCLUSIONS**

Our study design is feasible and the intervention was acceptable to patients, reflected by high adherence. However, IDE will not be feasible in the long term unless dialysis staff assist with implementation. This will need to be addressed before executing a definitive trial.

Supervisor: Dr. Scott Klarenbach

# **Relationship of Betaretroviral Infection with Differential Expression of Metabolic Enzymes in Primary Biliary Cirrhosis**

Filip Wysokinski, Shawn Wasilenko, Weiwei Wang, Bo Meng, Stan Indik, David Sharon, Guangzhi Zhang, Andrew Mason  
Supervisor: Dr. Andrew Mason

## **INTRODUCTION**

Primary Biliary Cirrhosis (PBC) is a cholestatic autoimmune disease of unknown aetiology and is characterized by the destruction of intrahepatic biliary epithelial cells (BEC). In PBC anti-mitochondrial antibodies (AMA) are produced that target a subunit of the pyruvate dehydrogenase complex, which links glycolysis and oxidative phosphorylation. Human betaretrovirus (HBRV), a retrovirus closely related to MMTV, infection has been linked with PBC pathogenesis. Since AMA targets cellular respiration enzymes, we aim to characterize how energy production is altered in PBC BEC and whether HBRV infection can induce similar changes.

## **METHODS**

1. Oxidative phosphorylation was assessed by measuring oxygen consumption in PBC and non-PBC BEC in vitro using a 96-well oxygen biosensor assay.
2. Glycolysis was assessed by quantifying lactate in BEC supernatant using a commercial colorimetric lactate assay kit.
3. Differential gene expression was measured using RNA from cultured BEC on an Affymetrix Plus 2.0 microarray chip.
4. Proteomic differences between BEC were measured using LC-MS/MS.
5. MMTV-infected HEK293 and uninfected lysates were run on western blot looking at glycolytic protein expression.

## **RESULTS**

PBC BEC have increased levels of oxygen consumption and lactate production relative to controls in vitro, suggesting PBC BEC have altered energy consumption. Screening for differentially expressed genes in PBC BEC in vitro through microarray and proteomics revealed several enzymes in the glycolytic pathway (ENO2, GAPDH, HK1, ALDOA, LDHA) that are differentially expressed in PBC. Preliminary in vitro studies of these glycolytic enzymes using western blot revealed that ENO2 expression is also increased with MMTV infection.

## **CONCLUSIONS**

Altered energy consumption was shown in PBC BEC, which may be involved in pathogenesis. Preliminary data shows that MMTV infection may be inducing similar glycolytic changes to those seen in PBC; however, further experimentation must be done to show a causative link between HBRV infection and altered respiration.

Supervisor: Dr. Andrew Mason

# **Recombinant expression of the cardiac troponin I fragment, cTnI[135-209], that controls cardiac contraction**

Somaya Zahran, Jonathan S. Pan, and Peter M. Hwang  
Supervisor: Dr. Pater Hwang

## **INTRODUCTION**

The cardiac troponin-tropomyosin complex controls muscle contraction with every heartbeat. The C-terminal tail of cardiac troponin I, cTnI[135-209], anchors the complex to a myosin-blocking position on actin to shut off contraction. Contraction is initiated when troponin C binds to cTnI[148-158] in a calcium-dependent manner, releasing cTnI[135-209] from actin. >35 mutations in cTnI[135-209] have been associated with hypertrophic or restrictive cardiomyopathy.

## **METHODS**

On its own, cTnI[135-209] is an intrinsically disordered region (IDR) – a protein segment that lacks a fixed structure under physiologic conditions. IDRs are solvent exposed and susceptible to post-translational modifications, making them highly important in regulatory processes. They are also susceptible to proteolytic degradation, making them challenging to produce. We have expressed recombinant cTnI[135-209] in *E. coli* by fusing it to the bacterial membrane protein, PagP, causing it to accumulate in dense insoluble aggregates known as inclusion bodies. This is an improvement on a strategy that has been widely used since the 1970s to produce clinically important peptides like insulin.

## **RESULTS**

Harvested inclusion bodies contained almost pure cTnI[135-209]-PagP fusion protein. These were solubilized in guanidine denaturant and further purified using nickel affinity chromatography. We used nickel-catalyzed hydrolysis of a linker sequence, SRHW, to remove the PagP fusion partner. We found no evidence of chemical modification in cTnI[135-209] using MALDI-TOF mass spectrometry and NMR spectroscopy. We confirmed the biological activity of cTnI[135-209], showing that it binds to actin-DNase I monomer by NMR spectroscopy.

## **CONCLUSIONS**

Our PagP fusion protein system was an effective way to produce large quantities of cTnI[135-209] suitable for multinuclear multidimensional NMR. We are now poised to determine the three-dimensional structure of this important protein segment to explain how mutations in it cause heritable cardiomyopathies.

Supervisor: Dr. Pater Hwang

# Prehospital Systolic Blood Pressure Is Higher in Acute Stroke Compared to Stroke Mimics

Laura C Gioia, Rahel T Zewude, Mahesh Kate, Kim Liss, Brian Rowe, Ken Butcher  
Supervisor: Dr. Ken Butcher

## INTRODUCTION

Elevated admission systolic blood pressure (SBP) is common in acute stroke and is associated with poor outcomes. The natural history of prehospital BP in suspected stroke patients remains unknown. We tested the hypothesis that prehospital SBP is higher in acute stroke patients, relative to stroke mimics.

## METHODS

We conducted a retrospective observational analysis of a prospectively-maintained Emergency Medical Services (EMS) centralized database of electronic patient health care reports (including serial BP measurements) of all patients transported by EMS to the Emergency Department (ED) of the University of Alberta Hospital. All patients with an EMS dispatch code for suspected stroke during an 18-month period were included. Hospital charts and neuroimaging review were utilized to determine final diagnosis of ischemic stroke, transient ischemic attack (TIA), intracerebral hemorrhage (ICH) or stroke mimic.

## RESULTS

A total of 950 patients were transported by EMS to the ED with suspected stroke. Acute stroke was diagnosed in 543 (57.1%) patients (38.5% ischemic stroke, 12.3% TIA, 5.4% ICH), and 407 (42.8%) were considered stroke mimics. Mean  $\pm$  SD prehospital SBP was higher in acute stroke patients ( $156.6 \pm 27.1$  mmHg) compared to stroke mimics ( $145.3 \pm 25.1$  mmHg),  $p < 0.001$ ). Mean prehospital SBP was higher in ICH ( $172.3 \pm 31.7$  mmHg,  $p = 0.001$ ) than both ischemic stroke ( $155.1 \pm 26.7$  mmHg) and TIA ( $154.0 \pm 23.5$  mmHg). Median (IQR) SBP drop from first prehospital BP to ED BP was  $-4$  ( $-6$ - $17$ ) mmHg) in acute stroke patients. Mean prehospital SBP was correlated to SBP upon ED arrival ( $r^2 = 0.73$ ,  $p < 0.001$ ).

## CONCLUSIONS

Prehospital SBP is higher in acute stroke relative to stroke mimics. Prehospital SBP is highest in ICH. Given the strong correlation between prehospital SBP and ED SBP, elevated SBP in the prehospital setting may represent an acute prehospital treatment target in patients with acute stroke.

Supervisor: Dr. Ken Butcher

# **Penumbra Imaging-Based Thrombolysis with Tenecteplase is Feasible Up to 24 Hours After Symptom Onset**

Mahesh P Kate DM, Parnian Riaz BSc, Laura C Gioia MD, Brian Buck MD, MSc, Thomas Jeerakathil MD, MSc, Penelope Smyth MD, Ashfaq Shuaib MD, Kenneth Butcher MD, PhD.

Supervisor: Dr Kenneth Butcher

## **INTRODUCTION**

There is no approved therapy for ischemic stroke patients presenting >4.5 h after onset. We assessed the feasibility of tenecteplase (TNK-tPA) treatment in patients with evidence of an ischemic penumbra 4.5-24 h after onset.

## **METHODS**

Fifty-three patients were screened with pretreatment perfusion CT/MRI. Patients with NCCT/DWI ASPECTS score  $\geq 7$  and mismatch score  $> 2$  (defined as  $\geq 3$  ASPECTS regions with visible delay on Mean-Transit-Time maps) were eligible for treatment with TNK-tPA (0.25mg/kg). Screened patients with mismatch patterns enrolled in non-endovascular/thrombolysis trials and those without mismatch patterns were used as comparators.

## **RESULTS**

The median (IQR) baseline NIHSS in TNK-tPA treated patients (n=12) was 13.5(8.3). In the untreated mismatch (n=18) and non-mismatch (n=23) groups, the baseline NIHSS was 12(6.5) and 16(12, p=0.06) respectively. Median time-to-TNK-tPA treatment was 10h 41min (Range: 5-18 h). There was one symptomatic hemorrhage in the TNK-tPA group (ECASS grade Parenchymal Hemorrhage (PH) Type 1). One non-mismatch patient also developed a symptomatic hemorrhage (PH Type 2). TNK-tPA treated patients had more penumbral salvage (35 (31.7) ml) compared to the untreated mismatch (17.4 (48.1) ml) and non-mismatch (-90.8(186.7) ml, p<0.0001) patients. Good functional outcome (modified Rankin Score= 2) at day 90 were more common in TNK-tPA treated patients (8/12,66.7%) than untreated mismatch (4/18,22.2%) and non-mismatch (1/23,4.3%, p<0.0001) patients.

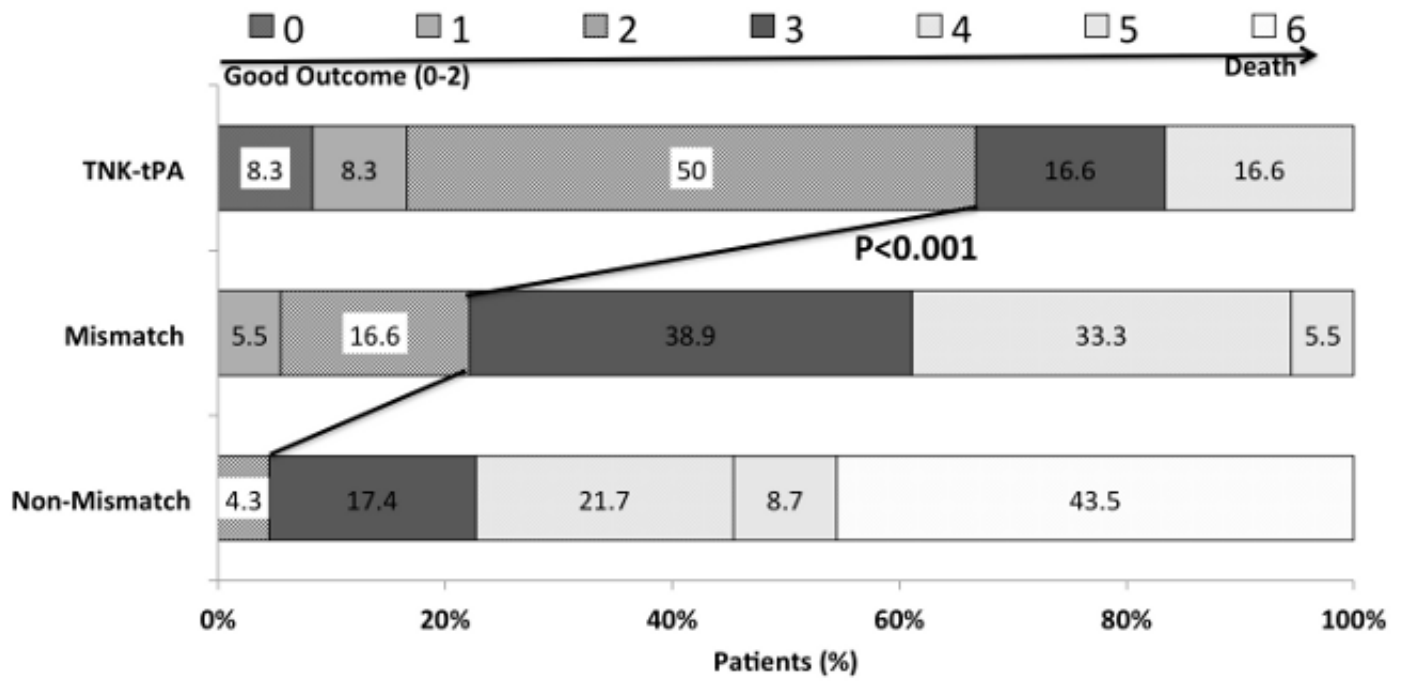
## **CONCLUSIONS**

Thrombolysis with TNK-tPA in patients selected on the basis of a penumbral signature is feasible up to 24 h after symptom onset. Randomized studies of penumbral imaging based selection of TNK candidates in an extended therapeutic window are warranted.

ClinicalTrials.gov Identifier: NCT02101606

Supervisor: Dr Kenneth Butcher

### Modified Rankin Scale Score



# **BLOOD PRESSURE LOWERING WITH TRANSDERMAL GLYCERYL TRINITRATE IS NOT ASSOCIATED WITH IMPROVEMENT IN CEREBRAL PERFUSION.**

Mahesh Kate<sup>1</sup> MBBS, MD, DM, Negar Asdaghi<sup>2</sup> MD, Laura Gioia<sup>1</sup> MD, Brian Buck<sup>1</sup> MD, MSc, Thomas Jeerakathil<sup>1</sup> MD, MSc, Ashfaq Shuaib<sup>1</sup> MD, Kenneth Butcher<sup>1</sup> MD, PhD

Supervisor: Dr Kenneth Butcher

## **INTRODUCTION**

Hyper-acute treatment with the vasodilator glyceryl trinitrate (GTN) has been hypothesized to be beneficial in acute ischemic stroke, potentially via an increase in cerebral blood flow. We tested this hypothesis with serial perfusion-weighted MRI (PWI) in acute stroke patients.

## **METHODS**

Thirty-five patients underwent PWI immediately before and 72h after BP management. Patients with mean baseline arterial blood pressure (MAP) >100mmHg (n=20) were treated with transdermal glyceryl trinitrate (GTN) (0.2mg/h) for 72hours without a nitrate-free interval. Patients with MAP≤100mmHg (n=15) were not treated. The primary endpoint was the mean relative delay time (rDT) within the hypoperfused region.

## **RESULTS**

Mean±SD baseline MAP was 112.5±12mmHg and 92±7.5mmHg in the GTN-treated and untreated groups (p<0.0001). Baseline PWI was performed 22.9±15h after symptom onset. The mean baseline rDT was similar in the GTN-treated (3.9±1.7 s) and untreated (4.3±1 s, p=0.4) groups. The median(IQR) baseline infarct volume was 7.2(49) ml in the GTN-treated group and 32.6(49.5) ml in untreated patients (p=0.2). MAP in GTN-treated patients decreased by 11.4±12.2 and 15.8±23mmHg at 2h and 72h respectively. Repeat PWI was performed at 72±18h. Mean rDT was unchanged in the GTN-treated (0±1.2sec) and untreated patients (0.2±1.8sec) and did not differ between groups (p=0.9). Infarct growth was similar in both groups (3(13.9) ml vs. 15.5(45) ml, p=0.1).

## **CONCLUSIONS**

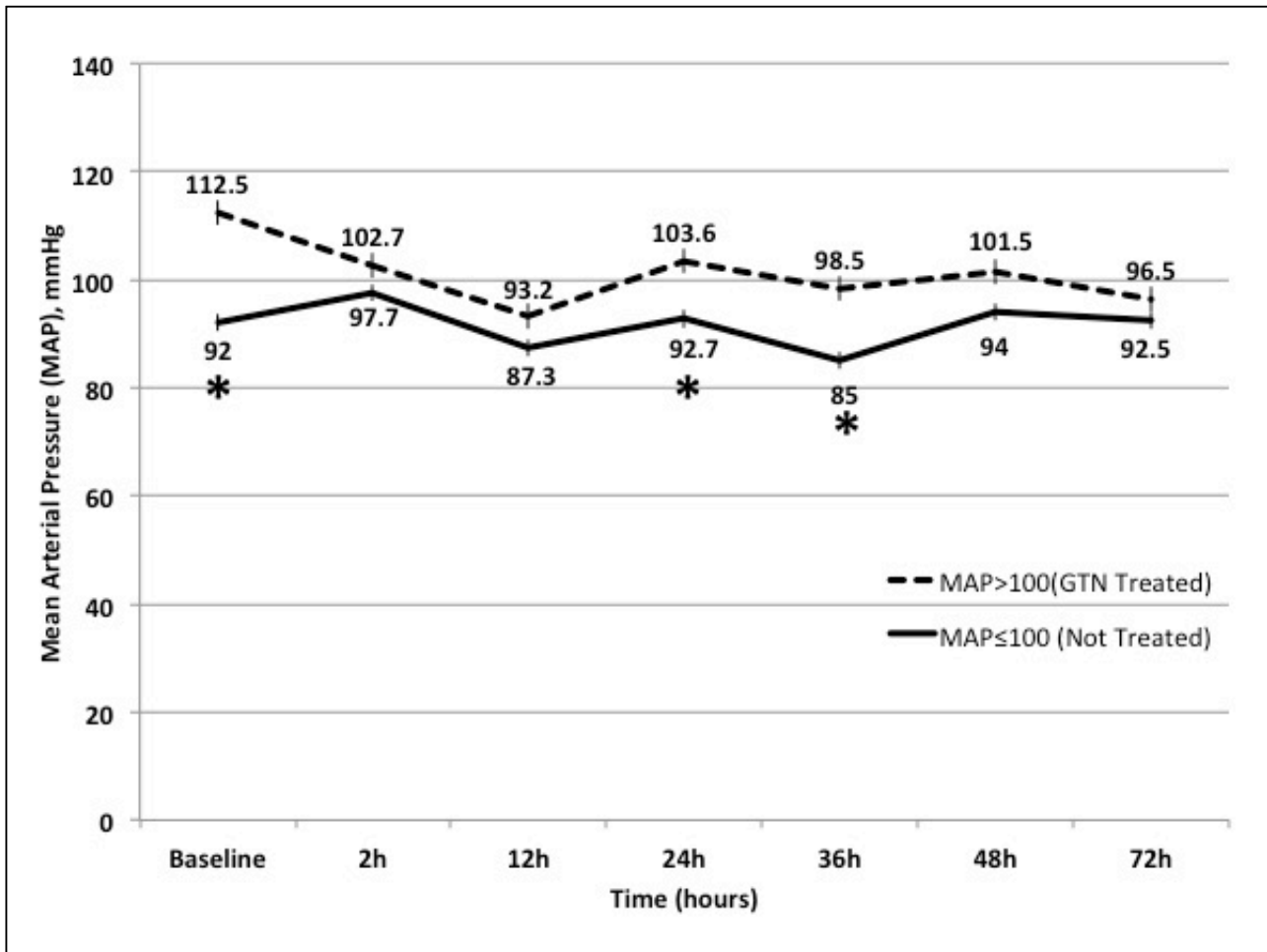
GTN is associated with a fall in BP in acute ischemic stroke patients, but there is no improvement in cerebral perfusion.

ClinicalTrials.gov Identifier:NCT02327793

Figure1: Temporal profile of mean arterial blood pressure (MAP) in glyceryl trinitrate (GTN) treated and untreated patients. \*p<0.05

Supervisor: Dr Kenneth Butcher





# **New molecular targets and the mechanisms underlying diabetic sensory neuron degeneration**

Masaki Kobayashi 1, Chu Cheng 2, Cristiane de la Hoz 2 , Douglas W. Zochodne 1,2  
Supervisor: Dr. Douglas W. Zochodne

## **INTRODUCTION**

Sensory polyneuropathy is a common complication of diabetes mellitus that may target neuron gene expression. Cajal bodies (CBs), nucleoli and nuclear speckles are unique nuclear bodies known to be altered along with the changes of mRNA metabolism in stress conditions. CBs colocalize with SMN (survival motor neuron protein) and functions in the assembly of small nuclear ribonucleoprotein particles (snRNPs) which form spliceosomes and catalyze pre-mRNA splicing. Nuclear speckles colocalize with CWC22, which is a spliceosomal protein. However, the dynamics of these nuclear bodies in diabetic sensory neurons remains unclear.

## **METHODS**

L4 and L5 dorsal root ganglion sensory neurons in a 16 week model of type 1 (STZ) diabetes in C57BL/6 mice with experimental neuropathy: DRG gene expression microarray, qRT-PCR, behavior, electrophysiology, immunohistochemistry near nerve injection of siRNA.

## **RESULTS**

Diabetic mice with sensory neuron atrophy and conduction slowing had up-regulation of CWC22. The nuclei in diabetic sensory neurons had a rise in the number of CBs per neuron, whereas CWC22 and nucleoli were preserved. Some CBs colocalized with SMN foci and the number of SMN-positive CBs per neuron was reduced. snRNPs were dispersed throughout the nucleoplasm and colocalized with CBs in controls, while snRNPs formed multiple foci that lost their colocalization with CBs in the diabetic nuclei. CWC22 siRNA in vivo unilaterally improved sensory conduction slowing and thermal sensitivity.

## **CONCLUSIONS**

Rises in CWC22 and CB expression might reflect an aberrant mRNA splicing demand in experimental diabetic neuropathy whereas loss of SMN and snRNPs colocalized with CBs may cause misregulation of pre-mRNA splicing leading to sensory neuron degeneration akin to motor neuron loss in SMA. Taken together, our findings identify novel degenerative mechanisms that include two new molecular targets relevant to diabetic neuropathy. [Supported by the Denyse-Lake fellowship, Hotchkiss Brain Institute, University of Calgary, University Hospital Foundation, CDA and CIHR]

Supervisor: Dr. Douglas W. Zochodne

# Structure-based peptide design to modulate amyloid beta aggregation and reduce cytotoxicity

Jitendra Kumar, Risa Namsechi and Valerie Sim  
Supervisor: Dr. Valerie Sim

## INTRODUCTION

The deposition of A $\beta$  peptide in the brain is the key event in Alzheimer disease progression. Therefore, the prevention of A $\beta$  self assembly into disease-associated oligomers is a logical strategy for treatment. Pi stacking is known to provide structural stability to many amyloids; two phenylalanine residues within the A $\beta$  14-23 self recognition elements are in such an arrangement in many solved structures.

## METHODS

The peptides were synthesized by using standard Fmoc-based solid phase synthesis on a Liberty-1 microwave peptide synthesizer (CEM). Aggregation reactions were carried out in 10 mM sodium phosphate, 50 mM sodium chloride, pH 7.4 at 37°C and monitored by Thioflavin T (ThT) fluorescence at 482 nm. Mouse primary cortical neurons were prepared from 18 day-old embryos of timed pregnant BALB/c mice and used for cytotoxicity experiments. Aggregation of the peptides was examined by electron microscopy. Dynamic light scattering (DLS) experiments were performed with Malvern Zetasizer-Nano S using a 633 nm wavelength laser and detected back-scattered light at a fixed angle of 173°.

## RESULTS

we targeted pi-pi structural stacking by substituting these two phenylalanine residues with their D-enantiomers. The resulting peptides were able to modulate A $\beta$  aggregation in vitro and reduce A $\beta$  cytotoxicity in primary neuronal cultures. Using kinetic analysis of fibril formation, dynamic light scattering and electron microscopy, we demonstrate that these peptides shift the equilibrium of A $\beta$  oligomerization towards either larger amorphous aggregates or fibrils with altered structural characteristics

## CONCLUSIONS

Our result demonstrates how minimal changes to the amyloid core sequence of A $\beta$  1-42 can generate a peptide that both influences toxic aggregation and is incorporated into A $\beta$  1-42 assemblies. This latter point will be of interest to those looking for peptides amenable to <sup>19</sup>F labelling for diagnostic studies.

Supervisor: Dr. Valerie Sim

# **Asymmetrical flow field-flow fractionation of chronic wasting disease affected brain**

Jitendra Kumar, Valerie Sim  
Supervisor: Dr. Valerie Sim

## **INTRODUCTION**

The separation of the macromolecules in prion infected biological samples (such brain tissues) is a challenging task. The size exclusion chromatography (SEC) is not suitable due to the irreversible adsorption on the solid supports of the column packing materials. Asymmetrical flow field-flow fractionation (AF-FFF) is a method of choice, which yields size fractionation similar to SEC and avoids adsorption during separation. The technique allows separating particles ranging in size from a few nanometers to several microns. The sizes of prion protein oligomers are considered to drive the toxicity within the brain of infect animals.

## **METHODS**

An AF-FFF with a channel thickness of 350  $\mu\text{m}$  was used. The system was connected to a UV-Vis spectrophotometric detector, a refractive index (RI) detector, a multi-angle light scattering (MALS) and a dynamic light scattering (DLS) detector connected to the 140° angle of the MALS detector. The UV, MALS and DLS signals were simultaneously recorded as plots of detector signal versus time.

## **RESULTS**

After flow equilibration, the chronic wasting disease (CWD) affected elk brain (2% w/v) was injected. After 20 minutes of focusing, cross-flow rate was decreased linearly from 3.0 mL/min to 0 mL/min within 20 min for elution. The detector flow rate was constant 0.6 mL/min. Fraction collected were analyzed for prion protein using dot blot and corresponding particle size was calculated from cumulant analysis of scattered light intensities.

## **CONCLUSIONS**

Given the complexity of particles present in the brain homogenates, still can be fractionated by AF-FFF and suggest that the technique is applicable to profile the oligomeric distribution of prion protein oligomers in brain. Moreover, the combination of electron microscopy analyses with AF-FFF separation may be a powerful approach to characterize the oligomers of prion protein in affected brains.

Supervisor: Dr. Valerie Sim

# **HIV-1 VPR INDUCES NLRP3 INFLAMMASOME ACTIVATION: REGULATION BY A CASPASE-1 INHIBITOR**

M. K. Mamik, W. Branton, B.A. McKenzie and C. Power  
Supervisor: Dr. Christopher Power

## **INTRODUCTION**

Human immunodeficiency virus type 1 (HIV-1) infects the brain during seroconversion and leads to neuroinflammation and neurodegeneration in susceptible individuals. Inflammasomes are cytosolic protein complexes that serve as platforms for caspase-1 activation and ensuing cleavage and release of interleukin (IL)-1 $\beta$  and IL-18. Our group recently showed that HIV-1 infection of human microglia induces the NLRP3 inflammasome. The viral protein R (Vpr) is an accessory protein encoded by HIV-1, essential for macrophage infection.

## **METHODS**

We used human monocytic cell line THP-1 and primary human microglia to study inflammasome activation in vitro. Vpr and IL-1 $\beta$  levels were measured by ELISA. HIV-YU2 and HIV-SF162 strains were used for infection. Real-time PCR, immunohistochemistry and cytotoxicity assays were performed to analyze inflammasome activation. Vpr transgenic mice were used for in-vivo analysis.

## **RESULTS**

We detected Vpr in cerebrospinal fluid of HIV-1 infected patients and in supernatants of HIV-1 infected microglia. Extracellular Vpr exposure to differentiated THP-1 and primary human microglia caused caspase-1 activation and reduced cell viability ( $p < 0.01$ ). Infection of THP-1s and microglia with Vpr-deficient HIV-1 showed significantly reduced caspase-1 activation and IL-1 $\beta$  production ( $p < 0.01$ ), compared to cells infected with Vpr-encoding HIV-1. Intracellular Vpr expression in THP-1 cells, transfected with vpr, led to enhanced caspase-1 activation and reduced cellular viability ( $p < 0.001$ ) but without significant IL-1 $\beta$  release. We extended these observations in vivo by showing increased NLRP3, caspase-1 and IL-1 $\beta$  in vpr transgenic mice, following Complete Freund's Adjuvant (CFA) subcutaneous injection. Treatment with the caspase-1 inhibitor, VX-765, suppressed inflammasome activation in CFA-stimulated vpr transgenic mice. Open field behavioral testing of CFA-stimulated vpr transgenic mice showed reduced anxiety levels in VX-765 treated animals.

## **CONCLUSIONS**

Vpr-induced NLRP3 inflammasome activation likely contributes to HIV-1 associated neuroinflammation and can be abrogated by caspase-1 inhibition. Our findings provide evidence that caspase-1 inhibition might provide therapeutic interventions in controlling HIV-1 associated neuroinflammation.

Supervisor: Dr. Christopher Power

# **Leptomeningeal collaterals may predict stroke related to vasospasm in patients with subarachnoidal bleeding due to ruptured aneurysm**

H.A. Manosalva Alzate, N. Sharafaddinzadeh, C. Dekerson, K. Khan, A. Shuaib, M. Chow, O'Kelly and M. Saqqur  
Supervisor: Dr. Maher Saqqur

## **INTRODUCTION**

Around 30% of patients with subarachnoid bleeding (SAB) due to ruptured aneurysm develop angiographic vasospasm (AVS). Half of these patients present with delayed neurological symptoms, and only one third end up with a stroke. The reason why not all patients with vasospasm are symptomatic, and why not all develop stroke is still unknown. Poor collateral blood flow is a well known marker for stroke outcome. The study of these collaterals in patients with AVS, and the prediction of stroke as a primary outcome has not been studied sufficiently.

## **METHODS**

Consecutive patients with SAB were studied from 2005 to 2013 at the University of Alberta. Angiograms were performed for the assessment of vasospasm. Collaterals were classified accordingly to the Christoforidis, Higashida and modified Tan classification, and the new developed MALEJ Score. The new scale evaluated the presence of leptomeningeal blood flow in the arterial territory affected by vasospasm. CT head and/or brain MRI was done in all patients.

## **RESULTS**

From 196 patients with SAB, 66 (33%) developed angiographic vasospasm. From these last patients only 32 (48%) had delayed neurological deficits due to symptomatic vasospasm, and 19 (28%) finally developed an ischemic stroke confirmed by neuroimaging.

Status of collaterals did not predict the presence of delayed neurological symptoms, but predicted the occurrence of ischemic stroke (Pearson Chi-Square correlation 5.49, positive likelihood ratio of 7.05,  $p = 0.029$ ). Poor leptomeningeal collateral blood flow in the MALEJ score was associated with twice the risk for development of an ischemic stroke (odd ratio 2.8 CI 90% 1.01 - 8.21). Regression analysis using stroke as a primary outcome showed a trend for this association.

## **CONCLUSIONS**

Assessment of leptomeningeal blood flow in patients with AVS might predict the occurrence of stroke. Future and larger studies are necessary to confirm these findings

Supervisor: Dr. Maher Saqqur

# **Generation and Characterization of Human Endothelial-Derived Induced Pluripotent Stem Cells and Further Differentiation to Endothelial Cells as a Tool to Study Von Willebrand Factor Gene Regulation**

Maryam Nakhaei-Nejad, Maikel Farhan, Allan G. Murray, and Nadia Jahroudi  
Supervisor: Dr. Nadia Jahroudi

## **INTRODUCTION**

Damage to endothelial cells (EC) of blood vessels is the core of various vascular diseases. To determine the consequences of injuries to EC an understanding of the mechanism that establishes EC phenotype, as represented by EC specific gene regulation in general is needed. We aimed to study endothelial gene regulation by generating induced pluripotent stem cells (iPS) from human umbilical vein EC (HUVECs) and differentiating the resulting iPS back into EC. This model provides a system with a homogenous genetic background to explore how EC phenotype is revoked (HUVEC to iPS), and reestablished (iPS to EC).

## **METHODS**

iPS colonies were generated using originally reported transcription factors. Quantitative RT-PCR, microarray analysis, and immunofluorescence were used to characterize iPS and cell lineages derived from iPS. Pluripotency of the iPS were demonstrated by generation of the three germ layer markers, direct differentiation of iPS to functional neurons and glial cells, beating cardiomyocytes, as well as functional EC.

## **RESULTS**

We explored the mechanism of activation and repression of a highly EC-specific gene, von Willebrand factor (VWF), in HUVEC, iPS, and iPS that was differentiated into EC (EC-diff). EC-diff expressed endothelial markers (including VWF) to similar levels as HUVEC and formed tube-like structures, assessed by an in vitro angiogenesis assay. We explored whether the expression pattern of transcription factors that regulate VWF are associated with establishment of EC phenotype. Our results indicate that expression of transacting factors that activate VWF promoter correlated with VWF expression, however the expression of transacting factors that repress VWF did not correlate with VWF expression.

## **CONCLUSIONS**

The results demonstrate that the establishment of VWF transcription in EC is directly dependent on expression of transacting factors that function as activators, and not diminished levels of repressors. This system provides an opportunity for understanding endothelial gene regulation.

Supervisor: Dr. Nadia Jahroudi

# 5 year renal outcomes after Islet Transplantation in 111 subjects with and without CKD/DN

Oram R, Olateju T, Ling Y, C Hoekstra, S Imes, A Malcolm, Shapiro J, Senior P  
Supervisor: Dr Peter Senior

## INTRODUCTION

Renal impairment has often been viewed as a contraindication to islet transplantation (ITx). We examined long term impact of ITx on renal function in recipients with baseline eGFR > 30 ml/min treated at a single centre.

## METHODS

We assessed renal function from 111 type 1 diabetic patients (mean age  $46 \pm$  SD 10 years, HbA1c  $8.1 \pm 1.3\%$ ) with at least 5 years follow up. Subjects received up to 4 islet infusions (1 (n=14), 2 (n=70), 3 (n=23) or 4 (n=4)). Maintenance immunosuppression (IS) was tacrolimus combined with either sirolimus or mycophenolate mofetil. eGFR was calculated using MDRD pre transplant and 5 years post transplant. An albumin creatinine ratio (A:Cr) > 2.5 mg/mmol was defined as abnormal.

## RESULTS

Prior to transplant, mean eGFR was  $76 \pm 21$  ml/min (range: 37 - 137) ml/min and 29% had albuminuria. During 5 year post transplant follow up subjects had a mean fasting C-peptide  $0.59 \pm 0.24$  nmol/L, HbA1c  $6.4 \pm 0.7\%$ , blood pressure  $124 \pm 11 / 69 \pm 7$  mmHg and tacrolimus level  $6.9 \pm 2.0$   $\mu$ g/L. 5 years post ITx, eGFR fell to  $59 \pm 21$  ml/min ( $p < 0.0001$ ), which is equivalent to an annual decline of  $3.3 \pm 3.5$  ml/min. There was no change in A:Cr (median 0.91 IQR 0.49-0.36 v 1.02, 0.50-3.25,  $p = ns$ ), although patients experiencing greater decline in GFR were more likely to have albuminuria (chi-square,  $p = 0.04$ ). Two subjects developed end-stage renal disease.

## CONCLUSIONS

Across a range of renal function, ITx recipients with good control of blood pressure and glycaemia experience a decline in eGFR but no increase in albuminuria. Subjects with albuminuria are at greater risk for decline in eGFR. The decline in eGFR, despite good glycaemia control, may be due to nephrotoxicity of IS in at risk kidneys. The benefits of ITx must be weighed particularly in those with limited renal reserve.

Supervisor: Dr Peter Senior



# **Fecal microbial transplant modulates host-microbial interactions differentially in ascending and descending colon in IBD patients**

Park HK, Hotte N, Kao D, & Madsen K  
Supervisor: Dr. Dina Kao

## **INTRODUCTION**

Fecal microbial transplantation (FMT) has shown dramatic success in treating patients with recurrent *Clostridium difficile* infection (RCDI) but has inconsistent results in patients with inflammatory bowel disease (IBD).

## **METHODS**

This study was to examine host-microbial interactions in RCDI (n=4) and IBD (Crohn's:n=2; UC:n=2) patients and determine effects of FMT on the gut microbiome and mucosal immune profiles in IBD patients using stool samples and biopsies from ascending (AC) and descending colon (DC).

## **RESULTS**

Prior to FMT fecal microbial profiles from IBD and RCDI patients clustered together and appeared very different from donors; after FMT microbial profiles of patients were similar to donors. IBD patients had increased expression of pro-inflammatory cytokines (PIC: IFN $\gamma$ , IL1 $\beta$ , IL8, IL12,IL13) compared with RCDI and healthy control (HC) in both AC and DC. RCDI patients had increased IFN $\gamma$ , IL8, and IL10 compared to HC in AC only ( $p < 0.05$ ). Correlation analysis showed that HC and RCDI had +ve correlations between pro-inflammatory cytokines (IL1 $\beta$ , IL8, IL13) and Enterobacteriaceae and *Clostridium* Cluster XI in both AC and DC while IBD patients showed the opposite with -ve correlations. However, IBD patients had +ve correlations between pro-inflammatory cytokines and *Clostridium* Cluster\_XI (non-pathogenic commensal). IBD patients responded to FMT with a decrease in CRP and FC, but also had increased mucosal expression of IL1 $\beta$ , IL8, and IL13 in the AC, but not DC.

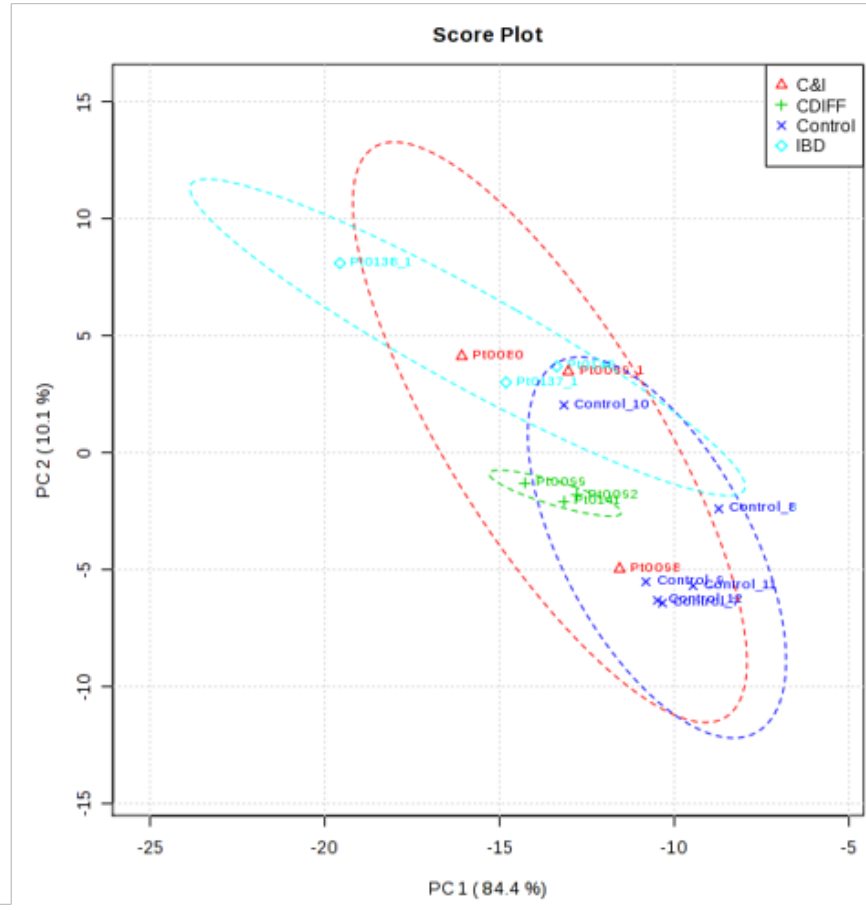
## **CONCLUSIONS**

IBD patients exhibit dysregulated cytokine-microbial interactions with decreased cytokine expression linked with pathogenic microbes and increased expression with commensals. FMT elicits differential responses in AC and DC, with a stimulation of cytokine expression in the AC but a normalization of host-microbial interactions in DC. This dissimilar response could be a result of either regional microbial differences and/or immune compartmentalization in the colon and has significant implications in using FMT to treat IBD patients.

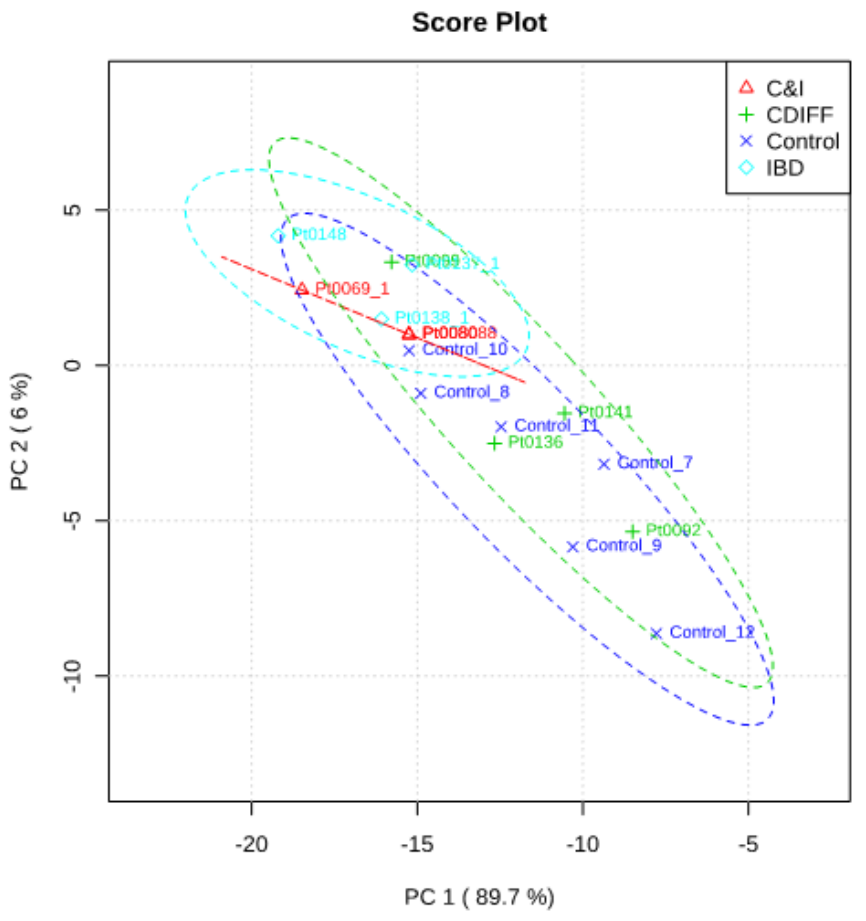
Supervisor: Dr. Dina Kao

# Before

Ascending



Descending



# **A novel role for the mitochondrial deacetylase Sirtuin 3 (SIRT3) in the pathogenesis of Idiopathic Pulmonary Fibrosis**

Roxane Paulin, Hengjia Zang, Vikram Gurtu, Aristeidis Boukouris, Alois Haromy, Evangelos D. Michelakis  
Supervisor: Evangelos D. Michelakis

## **INTRODUCTION**

Idiopathic pulmonary fibrosis (IPF) is a chronic disease with extremely poor prognosis and no available therapies. Fibroblast and myofibroblast proliferation and reduced apoptosis are key in IPF pathogenesis. Loss of mitochondrial function has been associated with proliferation and resistance to apoptosis in several diseases like pulmonary hypertension and cancer, but its role in IPF is unknown. SIRT3 is a mitochondrial deacetylase that activates mitochondrial proteins. Sirt3 loss causes a global suppression of mitochondrial function, cell proliferation and resistance to apoptosis. We hypothesized that SIRT3 downregulation is implicated in IPF pathogenesis by promoting fibroblast proliferation, differentiation and collagen production.

## **METHODS**

We used human lung sections from healthy (unused transplant) donors and recipients with IPF. Sirt3 wild type (Sirt3WT) and knockout (Sirt3KO) mice we used in vivo and to isolate pulmonary fibroblasts. IPF was induced by intra-tracheal delivery of aerosolized bleomycin (BLEO) treatments both in vivo and in vitro (a standard IPF model).

## **RESULTS**

SIRT3 expression was decreased in human IPF lungs and in Sirt3WT+BLEO lungs and fibroblasts compared to healthy lungs and Sirt3WT. Sirt3KO fibroblasts, like Sirt3WT+BLEO, had decreased mitochondrial function assessed by decreased PDHE1a activity, decreased respiration (Seahorse Assay) and increased mitochondrial membrane potential (TMRM dye in live cell imaging). Sirt3KO and Sirt3WT+BLEO fibroblasts had increased collagen production and smooth muscle actin expression (immunoblot). In vivo, Sirt3KO mice treated with BLEO developed worse IPF than Sirt3WT+BLEO (dynamic resistance  $2 \pm 0.5$  vs  $1.4 \pm 0.2$  cmH<sub>2</sub>O.s/mL, dynamic elastance  $20 \pm 3$  vs  $38 \pm 10$  cmH<sub>2</sub>O/mL). Intra-tracheal delivery of an adenovirus overexpressing SIRT3 improved both Sirt3KO+BLEO and Sirt3WT+BLEO compared to GFP-only adenovirus.

## **CONCLUSIONS**

Sirt3 downregulation plays an important role in the development of IPF. While the exact mechanisms by which Sirt3 is downregulated remains to be established, this work opens new perspectives for the treatment of IPF and suggests a previously unrecognized role of mitochondria in its pathogenesis.

Supervisor: Dr. Evangelos D. Michelakis

# **DEVELOPMENT OF BRAIN PENETRANT AMYLIN RECEPTOR BASED PEPTIDES: NOVEL THERAPEUTICS FOR ALZHEIMER'S DISEASE**

Rania Soudy<sup>1,2</sup>, Wen Fu<sup>1</sup>, David MacTavish<sup>1</sup>, Kamaljit Kaur<sup>2</sup>, Jack Jhamandas<sup>1</sup>  
Supervisor: Dr.Jack Jhamandas

## **INTRODUCTION**

Brain deposition of aggregated  $\beta$ -amyloid (A $\beta$ ) peptides plays a pivotal role in Alzheimer's disease (AD). We have identified the amylin receptor as a putative target for the deleterious effects of A $\beta$  in the brain. AC253, an amylin receptor peptide antagonist, restores memory and learning in in vitro and in vivo experimental paradigms of memory and AD. However, peptides suffer from poor enzymatic stability and inability to penetrate blood-brain barrier (BBB). Here we describe AC253\*, a novel, brain penetrant, and amylin receptor subtype3 (AMY3) selective antagonist.

## **METHODS**

Cy5.5labelled peptides were synthesized, purification, and serum stability were performed using reversed-phase HPLC and MALDI-TOF mass spectrometry. In vitro cell uptake was evaluated in transfected HEK-293 AMY3-expressing cells using flow cytometry and fluorescence microscopy. In vivo, and ex-vivo brain uptake studies were done using near infrared imaging in Kodak imager.

## **RESULTS**

AC253\* blocked human amylin responses in HEK293-AMY3 cells with twice the potency as AC253, and was seven times more stable in human serum. In vitro cell uptake studies demonstrated that AC253\* has selective and significantly higher specific binding to HEK293 cells than AC253. In vivo brain imaging of AC253\* in wild type mice revealed that the peptide can cross the BBB, and can be detected in the brain for up to 24 hours. Ex vivo brain imaging further confirmed the brain uptake, and that the peptide was mainly distributed in the hippocampal and cortical regions, which coincides with the amylin receptor localization in the brain. Using models of genetically engineered mice with either down- or up-regulated amylin receptors, we demonstrated that AC253\* peptide is tightly correlated with the quantity of CNS amylin receptors in the brain.

## **CONCLUSIONS**

These data support the notion that amylin receptor is a viable therapeutic target in AD and that AC253\* is a promising candidate for future pre-clinical and clinical studies in AD.

Supervisor: Dr.Jack Jhamandas

# Hereditary Spastic Paraplegia: Characterization of an Albertan Cohort

Anil Venkitachalam 1, Erica McKenzie 1, Setareh Ashtiani 2, Cathleen Huculak 3, Linda McLaren 3, Oksana Suchowersky<sup>1, 2, 4</sup>  
Supervisor: Oksana Suchowersky

## INTRODUCTION

Hereditary spastic paraplegias (HSP) are rare neurological disorders with onset from early childhood to late adulthood, inherited as autosomal dominant (AD), autosomal recessive (AR) or X-linked (XR) traits with over 50 identified genes. HSP is classified as uncomplicated or complicated. Prevalence is estimated at 5 per 100,000, but epidemiological data is scarce and misdiagnosis common. The main objective is to identify families with HSP, create a clinical registry and genomic DNA bank to screen for known and novel mutations.

## METHODS

Participants were recruited through Neurogenetic and Neuromuscular clinics in Alberta, and assessed yearly by Spastic Paraplegia Rating Scale and SPATAX-EUROSPA disability score. DNA will be sent for exome sequencing to McGill University (Dr. G.Rouleau), as part of a Canadian consortium.

## RESULTS

49 families with 64 patients (36 men and 28 women) have been identified. Thirty one patients (48%) have a positive family history, with AD inheritance in 18 families (37%), AR (9 families) and XR (4 families). Eighteen families (37%) had sporadic HSP. Mean age of onset for AD was 36 years, sporadic 32 years, AR 11 years and XR 1.5 years. Complicated HSP was seen in 27 patients (46%). Abnormalities among complicated patients include dysarthria (n=19), sensory deficits (n=17), oculomotor abnormalities (n=14), ataxia (n=17), amyotrophy (n=12), dysphagia (n=9), cognitive deficits (n=11) and peripheral neuropathy (n=8). Neuroimaging was abnormal in 9 patients. Thirty four patients (53%) had SPATAX-EUROSPA disability stage of 3 or more (moderate to severe functional handicap). Results of genetic testing are pending.

## CONCLUSIONS

This is the first comprehensive population based study looking at all forms of HSP. Prevalence is 2 per 100000. This lower than expected rate could be due to either incomplete ascertainment or lower prevalence in this population. The most common mode of inheritance was AD with almost 50% having the complicated form.

Supervisor: Dr. Oksana Suchowersky

# **C9orf 72 repeat expansions in a Canadian provincial cohort**

Anil Venkitachalam 1, Stacey Hume 2, Setareh Ashtiani 2, Susan Christian 2, Oksana Suchowersky 1, 2  
Supervisor: Oksana Suchowersky

## **INTRODUCTION**

The Chromosome 9 open reading frame 72 (C9orf72) gene, located on chromosome 9p21 contains a hexanucleotide GGGGCC repeat located in a non-coding region. Normal range is 2 to 23 repeats, with repeats greater than 30 considered pathogenic. These are inherited in an autosomal dominant fashion. Repeats between 23 to 30 are of intermediate significance. Research has demonstrated this repeat expansion as the most common cause of familial Amyotrophic Lateral Sclerosis (ALS) and Fronto- Temporal Dementia (FTD) with a worldwide incidence of 34% and 25% respectively. Clinical testing for this expansion became available in Alberta in January 2013. All testing for C9orf72 mutations in Alberta is performed in one laboratory at the University of Alberta in Edmonton. The main objective is to determine the referral indication, family history and clinical test sensitivity of C9orf72.

## **METHODS**

Using the Molecular Diagnostic laboratory database, we identified all requests for C9orf72 testing and reviewed patient data.

## **RESULTS**

To date, 59 patients (35 men, 24 women) have been tested, 35 for ALS, 13 FTD, 4 Atypical Parkinsonism and 4 Late onset ataxia (LOA). Family history was positive in 27 patients (14 ALS, 7 FTD, 3 Atypical Parkinsonism and 3 LOA). C9orf72 abnormalities were detected in 10 patients (7 ALS, 3 FTD); all had a positive family history. In the FTD phenotype, 1 pathogenic expansion, 1 homozygous expansion and 1 intermediate expansion were detected. In the ALS phenotype, 1 deletion and 6 pathogenic expansions were detected. No mutations were detected in the Atypical Parkinsonism, LOA phenotypes and sporadic cases.

## **CONCLUSIONS**

C9orf72 abnormalities were detected in 17% of total cases, with 23% positive in ALS and 20% positive in FTD, similar to rates seen in Western European populations. Lack of family history significantly decreases the possibility of a positive result.

Supervisor: Dr. Oksana Suchowersky

# **Disease Modifying Anti-Rheumatic Drug Efficacy and Safety in Chronic Kidney Disease and Dialysis: A Literature Review**

Carpenter, Thirza, Hall, Jill, Katz, Steven  
Supervisor: Dr Steven Katz

## **INTRODUCTION**

Recommendations regarding the use of DMARDs in both chronic kidney disease and renal replacement therapy are limited in guiding clinicians in the choice of a DMARD. In order to find the best current evidence to assist clinicians in prescribing safe and effective therapy for their patients with inflammatory arthritis and co-existing chronic kidney disease, we performed a literature review regarding the safety and efficacy of disease modifying agents (DMARDs) in this patient population.

## **METHODS**

The Medline and EMBASE databases were searched. Studies eligible for inclusion evaluated the safety and efficacy of DMARDs in patients with chronic kidney disease or requiring renal replacement therapy and were published in English. Studies examining the serum concentrations and other pharmacokinetic properties of DMARDs in hemodialysis or peritoneal dialysis were also included. Additionally, relevant studies cited within the search criteria were also included.

## **RESULTS**

There were 93 relevant studies examining DMARDs in chronic kidney disease or renal replacement therapy. The vast majority of studies were case reports or case series. While limited, the current literature suggests that antimalarials, azathioprine and TNF- $\alpha$  inhibitors can be used safely in patients with chronic kidney disease with appropriate dosing adjustments. In renal replacement therapy, antimalarials, leflunomide, TNF- $\alpha$  inhibitors, and non-TNF biologics appear to be safe. Azathioprine may be safe but require post-dialysis administration, while sulfasalazine requires more clinical and pharmacokinetic studies before a recommendation can be made. Data suggest methotrexate and gold are unsafe.

## **CONCLUSIONS**

This literature review suggests that many DMARDs are likely safe to use in patients with inflammatory arthritis and co-existing chronic kidney disease. However, more prospective studies are needed to support these results and to guide the creation of clinical practice guidelines for this population.

Supervisor: Dr Steven Katz

# **Retrospective review of gonococcal and chlamydial cases of epididymitis, Edmonton STI Clinic, 2004-2014**

Chen JZ, Gratrix J, Brandley J, Smyczek P, Parker P, Read R, Singh AE  
Supervisor: Dr. Ameeta Singh

## **INTRODUCTION**

Two-thirds of epididymitis cases are related to sexually transmitted infections (STI). No Canadian data exists on the characteristics, treatment and outcomes of gonococcal and chlamydial epididymitis. Our study examined this in Edmonton STI Clinic attendees.

## **METHODS**

Gonococcal and chlamydial cases of epididymitis reported by the Edmonton STI Clinic from January 1, 2004 to September 30, 2014 were reviewed. The diagnosis of epididymitis was based on the presence of epididymal swelling and tenderness and/or testicular tenderness. Improved disposition was defined as no worsening of symptoms at the follow-up visit. Treatment failure was defined as those with persistent symptoms requiring additional treatment and no sexual contact between the start of treatment and follow-up. Descriptive analysis was completed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). Ethics approval was obtained from the University of Alberta's Health Research Ethics Board.

## **RESULTS**

Forty-three cases of epididymitis were reviewed. The median age of cases was 26 years (IQR 21-31). The majority of cases were among Caucasians (67.4%, n=29), and heterosexuals (74.4%; n=32). A total of 81.4% (n=35) of cases were diagnosed with Chlamydia alone, 4.6% (n=2) with Gonorrhoea alone and 13.9% (n=6) were infected with both. Three (6.5%) cases were HIV positive. The majority of cases were treated with ceftriaxone and doxycycline. Three quarters (76.7%; n=33) of cases returned for follow-up, of which 11 cases (33.3%) had not improved; four of these cases were re-exposed to a sexual partner. The remaining 7 cases did not respond to their first line treatment; 4 of these cases were not treated according to Alberta STI guidelines (Table 1).

## **CONCLUSIONS**

Epididymitis was an infrequent presenting complication of gonorrhoea and chlamydia over a 10 year period at the Edmonton STI clinic. Of those who returned for follow up, the majority treated as per current guidelines responded to treatment.

Supervisor: Dr. Ameeta Singh



Table 1. Description of epididymitis cases that did not improve upon follow-up visit (n=7).

Case	Age	Disease	Year of Diagnosis	Day	Treatment	Treated per AB STI guidelines
1	54	Gonorrhea	2006	0	Ciprofloxacin 500mg x 1 dose Doxycycline 100mg BID x 14 days	Y (as per 2003 guidelines)
				31	Ciprofloxacin 500mg daily x 14 days	
2	31	Chlamydia	2012	0	Doxycycline 100mg BID x 7 days	N
				20	Ciprofloxacin 500mg daily x 14 days	
3	31	Chlamydia	2012	0	Cefixime 400mg x 7 days Doxycycline 100mg BID x 10 days	N
				17	Ceftriaxone 250 mg x 1 dose Doxycycline 100mg BID x 14 days	
4	22	Chlamydia	2013	0	Ceftriaxone 250 mg x 1 dose Doxycycline 100mg BID x 14 days	Y
				2	Ofloxacin 300mg BID x 14 days	
5	37	Gonorrhea	2013	0	Ceftriaxone 250 mg x 1 dose Azithromycin 1g x 1 dose	N
				9	Ceftriaxone 250 mg x 1 dose Doxycycline 100mg BID x 14 days	
6	37	Chlamydia	2014	0	Ceftriaxone 250 mg x 1 dose Doxycycline 100mg BID x 14 days	Y
				42	Ofloxacin 300mg BID x 14 days	
7	49	Chlamydia	2014	0	Cefixime 800mg x 1 dose Azithromycin 1g x 1 dose	N
				28	Doxycycline 100mg BID x 14 days	

# **Retrospective review of gonococcal and chlamydial cases of PID, Edmonton STI Clinic, 2004-2014**

Chen JZ, Gratrix J, Brandley J, Smyczek P, Parker P, Read R, Singh AE  
Supervisor: Dr. Ameeta Singh

## **INTRODUCTION**

Pelvic inflammatory disease (PID) commonly affects women of reproductive age. No Canadian data exists on the characteristics, treatment and outcomes of gonococcal and chlamydial infections complicated by PID. Our study sought to examine this in Edmonton STI clinic attendees.

## **METHODS**

Gonococcal and chlamydial cases of PID cases reported by the Edmonton STI Clinic from January 1, 2004 to September 30, 2014 were reviewed. Clinical criteria for PID diagnosis were cervical motion tenderness with or without adnexal tenderness. Improved disposition was defined as no worsening of symptoms at the follow-up visit. Treatment failures were defined as persistent symptoms requiring additional treatment and no sexual contact between the start of treatment and follow-up visit. Descriptive analysis was completed using IBM SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). Ethics approval was obtained from the University of Alberta's Health Research Ethics Board.

## **RESULTS**

Eighty-four PID cases were reviewed. The median age of cases was 20 years (IQR 18-26). The majority of cases were among Caucasians (54.8%, n=46), and 6 (7.1%) cases were pregnant. Seventy-six (90.4%) cases were diagnosed with Chlamydia alone, 1 (1.1%) case with Gonorrhoea alone and 7 (8.3%) were co-infected with both. Co-infections with bacterial vaginosis (n=25) and trichomoniasis (n=3) also occurred. No cases were co-infected with HIV. Nearly three-quarters (71.4%; n=60) of cases were treated with ceftriaxone and doxycycline +/- metronidazole, and 17.8% (n=15) cases were treated with ofloxacin +/- metronidazole. Two-thirds (61.9%; n=52) of cases returned for follow-up. Of those who returned for follow-up, 10 cases (11.9%) had not improved; 3 of these cases were non-responsive to their first line treatment (Table 1).

## **CONCLUSIONS**

The majority of PID cases treated with recommended treatment regimens improved with only 3 cases (3.6%) not responding to treatment; all non-responders were treated with alternate treatment regimens for PID.

Supervisor: Dr. Ameeta Singh

Table 1. Description of pelvic inflammatory disease cases that did not improve upon follow-up visit (n=3)

Case	Age	Disease	Year of Diagnosis	Day	Treatment	Treated as per AB STI guidelines
1	19	Chlamydia & bacterial vaginosis	2005	0	Ofloxacin 400mg BID x 14 days Metronidazole unknown dose	Y
				8	In-patient: Clindamycin 900g IV q8h Gentamicin 140mg IV loading dose, then 70mg IV q8h Azithromycin 1g x 1 dose	
				15	At discharge: Clindamycin 300mg QID x 7 additional days Ofloxacin 400mg BID x 7 additional days	
2	24	Chlamydia	2007	0	Ofloxacin 400mg BID x 14 days	Y
				7	Ceftriaxone 250mg IM x 1 dose Metronidazole 500mg BID x 14 days Doxycycline 100mg BID x 7 days	
3	18	Chlamydia	2010	0	Ofloxacin 400mg BID x 14 days	Y
				64	Ofloxacin 400mg BID x 14 days Metronidazole 500mg BID x 14 days	

# **Quality of Life (QOL) in Diabetics with Multi-Vessel Coronary Artery Disease: Real-World Experience Comparing Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG)**

Brent M. McGrath, MD, MSc, PhD; Colleen M. Norris, MN, PhD, FAHA & Kevin Bainey, MD, MSc, FRCPC  
Supervisor: Dr. Kevin Bainey

## **INTRODUCTION**

Recent studies demonstrate mortality benefit supporting coronary artery bypass graft (CABG) surgery over percutaneous coronary intervention (PCI) in diabetics with multi-vessel coronary artery disease (CAD). However, differences in health status are largely unknown. Accordingly, our aim is to compare the effects of each revascularization technique on quality of life (QOL) in diabetics with multi-vessel CAD.

## **METHODS**

Using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), an outcomes registry capturing all patients undergoing cardiac revascularization in Alberta, Canada, we identified 1319 diabetic patients with multi-vessel CAD requiring revascularization from January 2009 to December 2012 who reported health status outcomes using the Seattle Angina Questionnaire at baseline, 1 and 5 years (599 CABG; 720 PCI). Adjusted analysis was performed using a propensity score-matching technique.

## **RESULTS**

At baseline, adjusted mean scores were lower with CABG compared to PCI: exertional capacity (64.5 vs 74.4,  $p < 0.001$ ), angina stability (62.6 vs 75.6,  $p < 0.001$ ) angina frequency (75.7 vs 85.2,  $p = 0.001$ ), treatment satisfaction (85.5 vs 89.5,  $p = 0.018$ ), quality of life (59.6 vs 70.0,  $p < 0.001$ ). However, at 1-year improved adjusted mean scores were noted in favor of CABG: exertional capacity (80.5 vs 79.5,  $p = 0.54$ ), angina stability (81.7 vs 77.1,  $p = 0.001$ ) angina frequency (92.7 vs 90.5,  $p = 0.06$ ), treatment satisfaction (93.2 vs 90.1,  $p = 0.004$ ), quality of life (81.7 vs 77.1,  $p < 0.002$ ). At 5-years, results were attenuated: exertional capacity (77.6 vs 78.7,  $p = 0.60$ ), angina stability (77.8 vs 74.8,  $p = 0.19$ ) angina frequency (94.0 vs 91.7,  $p = 0.08$ ), treatment satisfaction (94.1 vs 92.8,  $p = 0.22$ ), quality of life (84.2 vs 82.2,  $p < 0.21$ ).

## **CONCLUSIONS**

Despite worse baseline status, CABG compared to PCI in diabetics with multi-vessel CAD improves 1-year health-related quality of life. However, these outcomes are not sustained at 5-years. Our findings should be taken into consideration when contemplating a revascularization strategy in diabetics with multi-vessel CAD.

Supervisor: Dr. Kevin Bainey

# **The proportion of nondiagnostic computed tomographic pulmonary angiography and ventilation/perfusion lung scans in pregnant women with suspected pulmonary embolism: a systematic review.**

Arabesque Parker, Ghazi Alotaibi, Cynthia Wu, Sarah Takach Lapner  
Supervisor: Dr. Sarah Takach Lapner

## **INTRODUCTION**

Both computed tomographic pulmonary angiography (CTPA) and ventilation/perfusion (VQ) lung scanning are used to investigate patients with suspected pulmonary embolism (PE); however, controversy exists over which is better to use in pregnant women. The chance of obtaining a nondiagnostic result is important when choosing an imaging test in patients with suspected PE. While CTPA has a lower proportion of nondiagnostic scans compared to VQ in the non-pregnant population, the proportion of nondiagnostic scans in pregnant women is unknown for either modality. We conducted a systematic review to determine the proportion of nondiagnostic CTPA and VQ scans in pregnant women with suspected PE.

## **METHODS**

We searched the MEDLINE, EMBASE, and Cochrane databases for relevant studies. We included retrospective or prospective studies (including abstracts) that enrolled pregnant or postpartum women who underwent CTPA or VQ lung scanning for suspected PE and reported the number of nondiagnostic scans for either test. Pooled proportions of nondiagnostic scans were calculated using a random effects model for CTPA and for VQ. Predefined subgroup analysis included antepartum vs. postpartum, dose of CT contrast agent and dose of perfusion tracer.

## **RESULTS**

22 studies including 2391 scans were eligible for inclusion. 16 studies described 1226 CTPA, and 13 studies described 1165 VQ lung scans. The pooled proportion of nondiagnostic scans using CTPA was 12.5% (95% CI 7.5% - 18.4%, I<sup>2</sup> = 86%), and using VQ was 11.5% (95% CI 5.3% - 19.6%, I<sup>2</sup> = 93%). Heterogeneity was not explained by any of the predefined subgroups.

## **CONCLUSIONS**

The proportion of nondiagnostic scans is low in women undergoing either CTPA or VQ, and should not be a factor in determining which imaging modality is chosen to investigate PE in the pregnant population.

Supervisor: Dr. Sarah Takach Lapner

# **Quantum Blue® Calprotectin High Range Kit Field Tested in an IBD Clinical Setting - Does It Measure Up?**

Rowan Lumb, Rae Foshaug, Brian Reuter, Karen Kroeker, Richard Fedorak  
Supervisor: Richard Fedorak

## **INTRODUCTION**

Faecal Calprotectin (FCP) calcium/zinc-binding protein excreted into the intestinal lumen during inflammation. ALPCO-Immunoassays developed the Quantum Blue® (QB) Calprotectin High Range test, a quantitative lateral flow assay to provide rapid point-of-care device to measure FCP levels in stool and not yet clinically approved. FCP is stable at 2-8°C for up to 6 days and measured between 100-1800µg/g, where active intestinal inflammation is >200µg/g.

1. Evaluate consistency of stool processing using ALPCO Extraction devices.
2. To measure consistency of FCP readings over time under multiple storage conditions.
3. To determine if QB cartridges can be pre-loaded and produce consistent results to decrease assay time.

## **METHODS**

Samples were collected from the Zeidler IBD Clinic. (1) 3 samples were processed using pre-weighed extraction device caps to determine sample weight. (2) 8 samples were pre-loaded onto 5 cartridges and remained on the benchtop for 15 minutes. (3) Raw aliquots of 3 samples were stored at room temperature and 4°C to be run daily for 1 week. All samples were processed as per the ALPCO manual and loaded onto the test cartridge for FCP levels to be calculated after 15 minutes.

## **RESULTS**

(1) Stool sample weight loaded into each device ranged from 0.0764g - 0.0884g. (2) Percent differences between the 4°C and room temperature storage condition results ranged from 0% - 37% with an average of 3.98% over the 8 day testing. (3) Percent differences between the normal load FCP result and the preload FCP result range from <1% - 72% with an average percent difference of 4.16% between all results.

## **CONCLUSIONS**

Based on results obtained thus far, stool processing values recorded are consistent, Quantum Blue High Range cartridges can be preloaded to save time and FCP levels were inconsistent at different storage conditions. A larger cohort of samples will be needed in order to investigate further.

Supervisor: Dr. Richard Fedorak

# **THE INTRODUCTION OF ANTI-TNF THERAPY TO TREAT CROHN'S DISEASE HAS CHANGED THE CHARACTERISTICS OF PATIENTS UNDERGOING INTESTINAL RESECTION**

Alexandra E. Dittrich, Richard N. Fedorak, Haili Wang, Karen I. Kroeker  
Supervisor: Dr. Karen Kroeker

## **INTRODUCTION**

Crohn's Disease (CD) is a chronic inflammatory bowel disease that can occur anywhere from mouth to anus. The behaviour of CD is characterized into three classes: inflammatory, stricturing, and penetrating. Anti-TNF agents entered the Alberta therapeutic armamentarium for CD in 1998. Recent evidence has shown that early treatment of CD with biologic agents will reduce the need for intestinal surgery.

## **METHODS**

Through a population-based retrospective study, the Data Integration, Measurement, and Reporting (DIMR) Database was used to identify patient eligibility: (1) male or female CD patients >18yrs and (2) have undergone intestinal surgery for CD in one of the four Edmonton-area hospitals between January 1, 1996 and December 31, 2013. The characteristics of patients undergoing surgery before and after 1998 were compared. Statistical analysis was completed using SPSS.

## **RESULTS**

Demographic data is shown in Table 1. To date, the charts of 250/1650 patients undergoing intestinal surgery have been reviewed. There is a trend toward, patients having surgery after 1998 being older ( $41.9 \pm 15.0$  v.  $38.4 \pm 12.4$  years,  $p=0.087$ ) and having longer disease duration (Table 1). Analysis of gender showed an increase in surgeries performed on women after 1998 (Table 1). There was a trend for more patients to undergo laparoscopic rather than open surgery after 1998 ( $18.1\%$  v.  $9.7\%$ ,  $p=0.10$ ). Medication use prior to surgery showed an increase in anti-TNF ( $0\%$  v.  $11.2\%$ ,  $p=0.003$ ) and immunosuppressive use ( $15.3\%$  v.  $28.1\%$ ,  $p=0.033$ ) after 1998. While 5-ASA use was lower after 1998 ( $41.7\%$  v.  $19.7\%$ ,  $p<0.001$ ) and steroid use remained similar ( $56.9\%$  v.  $56.2\%$ ,  $p=0.912$ ).

## **CONCLUSIONS**

After the introduction of anti-TNF therapy for Crohn's disease in 1998, we can see a trend toward older age and longer disease duration at the time of surgery. There was both an increase in anti-TNF and immunosuppressive use, while 5-ASA use declined. The proportion of women undergoing intestinal resection after 1998 increased.

Supervisor: Dr. Karen Kroeker

Table 1. Demographic characteristics of patients.

	Surgery Before 1998	Surgery After 1998	p-value
<b>Characteristics</b>	n = 72	n = 178	
Age (mean ± SD)	38.4 ± 12.4	41.9 ± 15.0	p = 0.087
Gender %, (n) F	26.4% (19)	45.4% (81)	p = 0.005
Disease Duration (mean ± SD)	9.4±7.8	11.8±10.9	p = 0.051



