2012-13

LEADERS IN MEDICINE

UNIVERSITY OF CALGARY
FACULTY OF MEDICINE

ANNUAL REPORT

LIM SYMPOSIUM 2012

This is a report of accomplishments and highlights of the University of Calgary's Leaders in Medicine (LIM) program for the period of June 2012 to May 2013.

Prepared for the Dean of Medicine, Faculty of Medicine
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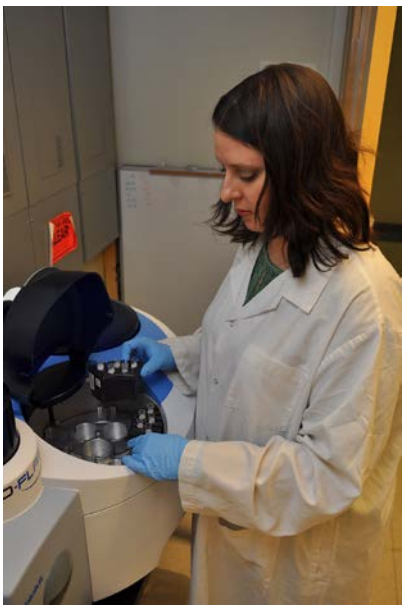
INTRODUCTION

Since 1996 when we had our first student, Leaders the Leaders in Medicine LIM) program has grown to an enrolment of more than 65. The three-year old Affiliate program (medical students interested in research) has a current enrolment of 30.

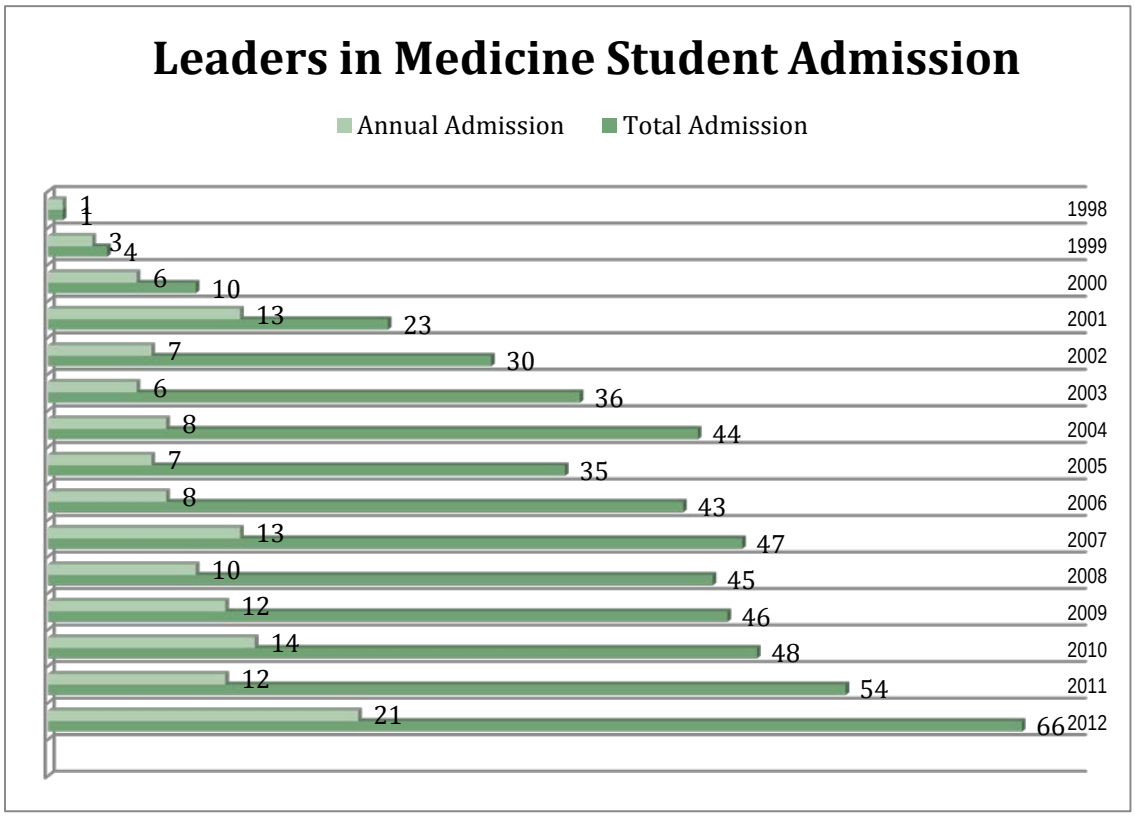
Our mentorship program, which includes clinician-scientists, MDs and scientists who are actively involved in dual careers, is a success. The program strives to help students meet the changing needs in health care, where MDs are not only physicians, but top researchers, educators, administrators, politicians, business leaders and innovators in many areas.

The LIM program is still unique in Canada. It is a program that includes and trains all dual degree (MD and other graduate degree) students. The majority of students are from the Faculty of Medicine Graduate Programs and are pursuing MD/PhD or MD/MSc combined degrees. However it is available for other University of Calgary graduate programs and it has included a MD/MBA and others.



JOANNA MOSER MD/PHD 2014
(*see comment below)

The funding we received from our anonymous donors and from the CIHR grants allows the program to offer travel awards, tuition awards and monthly stipends. There is an annual AiMs award for up to two of our MD/PhD students. A MD/PhD student in his/her final year of Medical School is eligible for the AiMs award. All of this funding helps our students maintain focus on their career objective and takes pressure of the need rush through school to earn a living. AIHS now funds joint degree students through MD/PhD awards, adding another area for students to get educational funding.
We work to keep the LIM program flexible, allowing and encouraging students from graduate and medical programs to design an individual course of study. Currently there is no limit to the number of students admitted into the program and we maintain an average admittance between 1 to 6 students per year usually, this year we had 21 new admissions in the joint degree program.



Student Comment

*** "The Leaders in Medicine program has a remarkable reputation for fostering the development of successful clinician scientists.**

The key feature of the program that encouraged me to apply was the flexibility and support to maintain a research project while training to be a physician. I research GW/P Body (GWB) components and their relationship to primary cilia in brain cancer cells with the goal to develop personalized cancer therapy. Although I was highly specialized in a specific research area, I didn't realize how much my PhD skills equipped and enhanced my critical thinking, teaching and leadership skills, which benefited me during my clinical training. Medicine and research really are inextricably linked." Joanna Moser, PhD/MD, Leaders in Medicine

Overview

The Leaders in Medicine joint degree program works to maintain its flexibility. The requirements that stay consistent are that it is necessary for a student to be accepted into both the University of Calgary's medical school and one of the graduate programs. A few improvements to the application process have been implemented, based on input from the graduate program supervisors and the Associate Dean of Graduate Science Education, Dr. van der Hoorn with the agreement of the Associate Dean of Undergraduate Medical Education (UME) and the LIM program directors. The medical school application now includes a supplemental form "UME Applicants Currently Enrolled in a Graduate Degree Program" which asks when the student plans to complete the graduate degree and if they plan to defer medical school or the graduate program. Designed to help UME count the number of openings needed to hold, it is given to the graduate student's supervisor to alert him/her of any students planning to enter medical school either before or after completing the graduate program. It affords the opportunity to the student and his/her supervisory committee to make plans to complete graduate program prior to entering medical school, or to defer that graduate program to enter medical school.

An additional step to enhance the program application process, includes a meeting between all new students and the LIM program advisor. The meeting usually occurs when applications are submitted and it is designed to discuss expectations, commitments and funding. Funding can depend on the student activities within the program so that is discussed and the Letter of Commitment, which is part of the application is reviewed. That letter when signed by the program director and the student and becomes part of the student's file.

Program Administration

The Graduate Science Education department supports the program in many ways, one of which is providing one-third to one-half of the program advisors time for administration of the LIM program. The program advisor processes all applications, does budgeting and other daily administration of the program and works with students to answer questions or concerns and to help them manage their way through the program.

The rest of the program is student run by an executive committee chosen each year by the LIM members and by volunteers who help at events. This year students successfully organized the 4th Annual Research Symposium, monthly Research in Progress (RIP) meetings, monthly translational Journal Club and a Visiting Speaker series.

LEADERS IN MEDICINE STUDENT COMMITTEE

2012-2013 LIM EXECUTIVE:

Chair	Andrea **Mosher** MD/PhD
Committees:	
Communications	Lorie **Kwong** MD/MSc; Jason **Bau** MD/PhD
Visiting Speaker Series	Christina **Thornton** MD/PhD
LIM Research Seminar	Nathan **Bracey** MD/PhD and Kyla **Huebner** MD/PhD
Research in Progress	Dustin **Anderson** MD/PhD and Judy **Luu** MD/PhD
Journal Club	Anna **Schmidt** MD/PhD and Aman **Wadhwani** MD/MSc
Social Committee	Ian **Hons** MD/PhD, Megan **Blades** MD/MSc and Anna **Schmidt** MD/PhD

EXECUTIVE COMMITTEE CHAIR REPORT

The 2012-2013 academic year was another successful one for the Leaders in Medicine (LIM) Program. The program continues to grow, both in terms of full members and affiliate members. One of the highlights of the past year was the excellent selection of visiting speakers, organized by Chair of the Visiting Speaker Committee, Christina Thornton [see Visiting Speaker Series information under Educational Events]. We hosted many prominent speakers, both locally (Dr. Michael Parkins, Dr. Suzanne Tough) and from other institutions (Dr. Lori West from the University of Alberta and Dr. Hugh Scully from the University of Toronto). The goal of the visiting speaker series is for the guest speakers to share their research as well as their experience as a clinician-scientist.

We spearheaded an 'Introduction to Clerkship' question & answer session where senior LIM students shared their experiences and advice for clerkship. We also introduced 'TED talk' style presentations at the Research in Progress seminars, which allowed students to discuss a topic of interest in research or medicine.

The LIM Program is a strong learning environment and great networking opportunity. Over the past year, I began the MD portion of my training and my involvement with LIM has helped me stay connected to the research community.

PROGRAM DIRECTOR'S REPORT

It was another outstanding year for the LIM Program! From the staff perspective we added Dr Bryan Yipp an acting associate director who will directly oversee the Translational Journal Club, Visitors Speaker Series and Research in Progress. Enrollment in the program continues to expand with students joining as both full LIM members and as Affiliate members. LIM students continue to show many accomplishments. LIM students attended numerous national and international conferences where they presented their research and won numerous awards. There was excellent attendance of LIM students at the annual CITAC meeting in Toronto and CNMRS conference in Winnipeg. These are specifically designed to bring clinician scientist trainees together to present their work and interact with colleagues and faculty. LIM students have published 44 papers with an additional 26 submitted and 4 published book chapters. There were four students that were awarded the MD/PhD awards from AI-HS and 43 other students won major awards. Our full-time LIM students did incredibly well on their residency matches with 13 of the 14 students receiving their first choice. The Translation Journal Club, Research in Progress and Visiting Speaker Series was extremely well attended and was effective at engaging students and staff. The fourth annual LIM Research Symposium was an outstanding success with over 60 abstracts submitted and presented either in oral or poster format. The guest speaker, who also acted as a judge was Dr. Hugh Scully from University of Toronto. The event each day was attended by over 30 staff and over 100 students

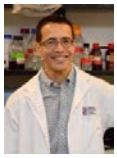
.

Our program continues to grow and diversify adding more interesting events for students, increasing interactions among students and staff, as well as supporting students through both their medical school and graduate school endeavors. The program excels in its student body executive that facilitate all of the LIM events. Ms. Michelle Selman. Program Administrator has provided outstanding support for both students and staff. We believe that the LIM continues to strive and be a highlight of both the University of Calgary's Medical School and the Faculty of Graduate Studies by providing an excellent environment for the development the leaders in medicine of the future.

Program Director, Dr. Paul Beck

Dr. Paul Beck, was awarded the 2012 AGA Institute Council Immunology, Microbiology & IBS Section Research Mentor Award

Dr. Morley Hollenberg, co-director, Leaders in Medicine program is the 2012 recipient of the Henry Friesen Award, as chosen jointly by the Canadian Society for Clinical Investigation (CSCI) and the Royal College of Physicians and Surgeons of Canada. This is the second time in three years that a member of the University of Calgary's Faculty of Medicine has received the award.



Dr. Bryan Yipp MD/MSc, Leader in Medicine alumni, appointed as Acting Associate Director for Leaders in Medicine Program.

MENTORSHIP

Mentorship within the Leadership in Medicine program remains a key part of our structure. The director (Dr. Beck), co-director (Dr. Hollenberg) and acting assistant director (Dr. Yipp) believe that mentorship is critical to a successful program. Students in the graduate part of the program are encouraged to have a clinician on their thesis committee. The LIM program works to maintain a "mentorship flow" where mentorship is available while a student transitions from non-clinical activities to clinical activities which a critical to best support and guide the student. Ideally we provide mentorship during non-clinical training, clinical/medical training, into residency, fellowship and to further research training and a junior faculty position. Students are encouraged to explore mentors on their own and if they have a question about where to look or who might be best, they can contact the LIM Directors or Co-Director. The Directors can provide mentorship and/or put the student into touch with an appropriate mentor here and at another institution. LIM graduates and senior students are encouraged to act as junior mentors to our current LIM students. This is an exciting new initiative that has been very successful.

LIM GRADUATE MENTORS

As part of our ongoing effort to provide a continuum of mentorship, as students begin to transition through graduate research, undergraduate medical education, and beyond, the program began a new initiative designed to connect current students with LIM program graduates nationwide. The expanding size of the program and increased number of graduates enrolled in a variety of residency and fellowship programs across the country provides an important resource for current LIM students. Recent LIM graduates provide a unique perspective and first-hand insight about information that is important to LIM students. Over the past year, a number of our students have been informally in touch with LIM graduates across the country in order to facilitate discussions about the transition from medical school into residency, get information about residency programs, the CaRMs application process, and opportunities for research. For example, students interested in doing electives or residency at the University of Toronto have been given the contact information of a 2010 LIM graduate who is currently an R1 in neurology at that institution.

We have received positive feedback from students as well as LIM graduates who are enthusiastic about keeping these lines of communication open. Undoubtedly, these relationships will serve our goal of "mentorship flow", as students are able to form mentorship bonds with graduates who may become their senior residents and can provide guidance into residency. Over the next year, we hope to formalize this mentorship initiative by creating a comprehensive database on our website of participating LIM graduates and their residency training program information. In this way, current students will have access to the experience and insight from those who have recently navigated the transition from research and medical education to residency training programs and beyond.

EDUCATIONAL EVENTS

Program Educational Events are intended to enrich the student research experience. LIM students and Affiliates are expected to commit to a minimum of 2 to 4 hours per month to the program and to attend up to an average of 60% of the monthly seminars. There are many opportunities to present research through seminars, the journal club, national conferences and the yearly LIM Research Symposium.

The program sponsors attendance at two main national symposiums. An average of 16 LIM students present research abstracts to the Clinician Investigator Trainee Association of Canada (CITAC), held in Ottawa each year in September. Five to 8 students are accepted to present at the annual Canadian National Medical Student Research Symposium (CNMSRS) held in Winnipeg in June.

Our students consistently win poster and/or oral research presentation awards at these events (see more information on specific events below). Students use their Leaders in Medicine CIHR or AI-HS MD/PhD research allowances and the program uses our anonymous donor funds to reimburse student expenses for these trips.

ANNUAL LEADERS IN MEDICINE SYMPOSIUM

Each year the Leaders in Medicine students organize and run the annual Leaders in Medicine research symposium. Held in early November, 4th Annual Symposiums is well organized and well attended. Several categories of student research were either presented through a talk or a poster and were judged by Faculty, Alumni and other students. See below and **Appendix A** for details on each year.

Summary Poster of the 2012 LIM Research Symposium

RESEARCH IN PROGRESS (RIP) – STUDENT SPEAKER SERIES

Leaders in Medicine, affiliate, interested medical and graduate students are encouraged to attend Research in Progress (RIP) meetings held once a month. Meetings are coordinated by one or two student representatives. RIP presentations are typically short (5-10 minutes) allowing students to share a specific research passion. The sessions foster discussion, new ideas, and often collaboration. Three to five students do a presentation on their research at each monthly meeting, focusing on how the research ties to exciting work in their field.

List of Speakers:-

2012/13	Speaker(s)	# attending
June	General discussion regarding research interests	23
September	Megan Blades, Ryan Lewinson, Mike Keough	45
October	Jason Bau, B. Sullivan, Sarah Tulk	41
November	General discussion regarding research interests	43
December	Wiber, Elliot Sampson, Christine Thornton	38
January	General discussion regarding research interests	23
February	B. Yipp – ARDS	30
March	General discussion regarding research interests	19
May	Mike Keough, Joanna Mosher and K. Kosior	29

JOURNAL CLUB – SEMINAR SERIES

The LIM Journal Club is focused on new translational research that holds a broad medical interest. designed to provide opportunities to learn about important research that may be outside the student's field of study. Various students present research papers, followed by a general discussion. Meetings are moderated by experts from the Faculty of Medicine. Journal Club presentation are from 45 to-55 minutes and delve fairly deep into the subject matter. Presenters are welcome to talk about whatever is of interest to them, so long as the topic is translational. Average attendance is 42 per meeting.

VISITING SPEAKER SERIES

Throughout the year, there are a variety of visiting Medical Educators, some jointly sponsored and others fully sponsored by LIM who visit the University of Calgary, Faculty of Medicine campus. This student organized program is to bring educators here to give presentations and to meet students for an informal question and answer period, usually over lunch.

2012/13	Speaker(s)
May	Dr. Lori West, University of Alberta
August	Dr. Holly Mewhort, University of Calgary
September	Dr. Michael Parkins, University of Calgary
October	Dr. Bryan Yipp, University of Calgary
November	Dr. Joaquin Madrenas, McGill University
November	Dr. Hugh Scully, University of Toronto – LIM Research Symposium
February	Dr. Suzanne Tough, University of Calgary
March	Dr. Stephanie Wilson, University of Calgary
April	Several LIM Students (Braedon McDonald, Chris Sibley, Saara Rawn and Rithesh Ram) in Clerkship for a "Panel" Discussion, University of Calgary

CANADIAN NATIONAL MEDICAL STUDENT RESEARCH SYMPOSIUM

An annual conference hosted by the University of Manitoba's Faculty of Medicine, the CNMSRS invites MD and MD-plus students from other Canadian universities to present research. Held in conjunction with the CIHR Canadian Student Health Research Forum, students are invited to attend a number of interesting presentations and symposia. This is a unique educational opportunity or trainees. Attendees at the 2012 CNMSRS included: Ian Hons, Alby Richards, Chris Skappak, Christina Thornton, Sarah Tulk, Craig Beers and Aman Wadhwani. Dr. Morley Hollenberg attended as faculty.

CITAC/CSCI Young Investigators Forum

Each year, in conjunction with the annual general meeting, the Canadian Society for Clinical Investigators (CSCI) and Clinician-Investigator Trainee Association of Canada (CITAC, national MD-Plus student organization) host a young investigator forum. The meeting includes presentation of oral and poster presentations from a minimum of 12 LiM students along with other students from around Canada.

Leaders in Medicine Social Events

To allow a more balanced work-life experience our students attend a number of social events each year. A welcome (to new and returning students) is held each autumn, for example. A graduation dinner and end of year dinner is held in spring and there are occasional luncheons sponsored during the year.

Leaders in Medicine Students

Current Students

Students in the LIM program are from the following graduate programs:

MDBC – Biochemistry & Molecular Biology
MDCH – Community Health Sciences
MDIM – Immunology
MDMI – Microbiology & Infectious Diseases
MDBT – Biomedical Technology
BMEN- Biomedical Engineering
ENG – English
MDCV – Cardiovascular/Respiratory
MDGI – Gastrointestinal Science
MDSC – Medical Sciences
MDNS – Neuroscience
KNES – Kinesiology
BISI – Biological Sciences
SOC – Sociology

This year there are currently there are 31 PhD, 33 Masters and 2 MA student for a total of 66.

STUDENT ACCOMPLISHMENTS

Leaders in Medicine trainees are high achievers in both in their personal and scholastic pursuits. These are a few of the special achievements.

Diamond Jubilee Medal, 2012-13: Zaheed **Damani**, a student enrolled in the Leaders in Medicine (MD/PhD) program and is currently completing his PhD in Health Services Research in the Department of Community Health Sciences, has received the Jubilee Medal for his dedication, commitment and initiatives to represent youth and the youth voice at the local, national and international level.

Braedon **McDonald** (MD/PhD), MD Class of 2013 was awarded the Chancellor's Graduate Medal for excellence in academic achievement at the graduate studies level.

Megan **Blades** (MSc/MD) raised $3395 for the Canadian Cancer Society by dying her hair purple and shaving it off. Congratulations.

2012-13 ACCOMPLISHMENTS:

A list of some general accomplishments

Rithesh **Ram, MD/PhD** received the 2013 CMA Award for Young Leaders

Christopher **Skappak, Affiliate** received TD Insurance Meloche Monnex outstanding student service award (UofA)

Nabeela **Nathoo MD/PhD** award Multiple Sclerosis Society Doctoral Scholarship

Aman **Wadhwani MD/MSc** attended and presented at CAR 76th Annual Scientific Meeting

Waleed **Rahmani MD/PhD** received a CIHR graduate studies training program studentship

Zaheed **Damani MD/PhD** won QEII Diamond Jubilee Medal.

Nathan **Bracey;** Brandon **Hisey;** Taryn **Ludwig** and Nabeela **Nathoo** awarded AIHS MD/PhD funding (more below)

Christopher **Skappak** won prestigious ASTech Foundation Award

Braedon **McDonald** won Governor General's Gold Medal

Braedon **McDonald and** Chris **Sibley -** 2012 Leaders in Medicine AIMS award winners

Joanna **Moser and** Saara **Rawn -** 2012 LIM Outstanding Achievement award winners

Kristine **Woodward's** abstract accepted for Canadian League Against Epilepsy and is invited to present in San Diego

Nabeela **Nathoo** has manuscript accepted in Multiple Sclerosis Journal

Ryan **Lewinson** received the APEGGA Education Foundation Graduate Scholarship

Amrita **Roy and** Craig **Beers** - both received the recent AIHS MD-PhD Studentship Competition.

Michael **Chiu** Attended the Canadian Society for Chemistry conference here in Calgary at the end of May.

LIM Students Award MD-PhD Studentship from Alberta Innovates Health Solutions

AWARDEE	SUPERVISOR *(Institution, Department)*	PROJECT TITLE
Bracey, Nathan	**Duff, Henry J.** *University of Calgary, Physiology & Pharmacology*	*Cytosolic Pattern Recognition Receptors in Cardiovascular Disease*
Hisey, Brandon	**Herzog, Walter** *University of Calgary, Biomedical Engineering*	*Mechanics of Active and Passive Failure in Amphibian Skeletal Muscle*
Ludwig, Taryn	**Schmidt, Tannin A.** *University of Calgary, Biomedical Engineering*	*The Role of Proteoglycan 4 in Boundary Lubricating and Biophysical Properties of Osteoarthritic Human Synovial Fluid*
Nathoo, Nabeela	**Dunn, Jeffery F.** *University of Calgary, Medicine*	*Characterizing Susceptibility Weighted MRI in the Experimental Autoimmune Encephalomyelitis Mouse Model of Multiple Sclerosis*

2012-13 RESIDENCY RESULTS

The program continues to show its success through the number of students that match their desired residency program. Since this is a critical point in all medical students' career, it is an indication of the quality of our students and the usefulness of the program when most of our students receive their residency, either first or second choice, in their desired Institution and Speciality. This matching means that a student can follow his/her desired career rather than change direction and perhaps end up in a field that is not a passion.

Matches:

LIM Student Name		CARMS	1st choice	Not 1st Choice
Chiu	Michael	Internal Medicine/Calgary	X	
Jalal	Hamza	Neurology/Toronto	X	
Kapur	Puneet	Emergency/Saskatoon	X	
Lawson	Keith	Urology/Toronto	X	
Lee	Kovid	Obgyn/Calgary	X	
Leung	Kare	Family Med/Edmonton	X	
McDonald	Braedon	Internal Medicine/Vancouver	X	
Nguyen	Kimchi	Family Medicine/Vancouver	X	
Ram	Rithesh	Family Medicine/Calgary	X	
Rawn	Saara	Internal Medicine/N.Ontario	X	
Seamone	Mark	Othalmology/Halifax	X	
Sibley	Christopher	Dermatology/Ottawa	X	
Solverson	Kevin	Internal Medicine/Calgary	X	
Tsang	Allison	Family Medicine/Kingston		X

ALUMNI

The Leaders in Medicine program is set up to help train successful clinicians, medical practioners and researchers. The program boasts of several highly successful alumni. This year an alumni, Dr. Bryan Yipp, a LIM graduate, joined the program as acting Associate Director. There are more plans being discussed to involve alumni in the program.

AWARDS/SCHOLARSHIPS

TYPES OF AWARDS (as listed in Student's 2012-13 Annual Reports)

1. Dr. T Chen Fong Doctoral Scholarship in Neuroscience $30,000
2. Achievers in Medical Science Research Excellence Award $3500
3. Achievers in Medical Science $25,000
4. Achievers in Medical Science Award, LIM $40,000
5. Alberta Innovates Health Solutions Studentship $30,000
6. Dr. Gary MacPherson Leadership Scholarship $2000
7. Queen Elizabeth II Graduate Award MSc $10,800
8. Queen Elizabeth II Graduate Award PhD $15,000
9. Leaders in Medicine Outstanding Achievement Award $1000
10. Medical Science Academic Productivity Scholarship $500
11. Leaders in Medicine's CIHR Stipend Scholarship $21,000
12. Lydia Sikora Award for Research Excellence $10,000
13. University of Calgary Eyes High Doctoral Research Excellence Award $5000
14. 15th Anniversary Prize, Department of Biomedical Engineering $3000
15. The Dr. Benno Nigg Distinguished Faculty Graduate Achievement Award $1000
16. Graduate Award, Association of Professional Engineers & Geoscientists of Alberta $5000
17. NSERC CREATE Doctoral Award $21,000

18. Canadian Graduate Students Masters Scholarship $17,500
19. Alberta Graduate Student FGS Fee Scholarship $3000
20. University of Calgary Faculty of Medicine International Elective Studentship $1500
21. GRS Graduate Student Scholarship $2000
22. Frederick Banteng and Charles Best Canada Graduate Scholarship Doctoral Award $35,000
23. Dr. Gary McPherson Leadership Scholarship $2000
24. Nat Christie Foundation medical Entrance Award $5,000
25. BME Graduate Program Director's Prize for Leadership $2500
26. Alberta Graduate Citizenship Award $2000
27. AITF PhD Scholarship $26,000
28. Alberta Cancer Foundation Graduate Studentship Award $40,000
29. Outstanding Achievement Award $500
30. Dawson Jarock Research Award in Pediatric Nephrology and Rheumatology $2500
31. Louise McKinney Award $2500
32. Professional Development Grant, University of Calgary $470
33. Biochemistry & Molecular Biology publication award $100
34. Cystic Fibrosis Canada Studentship $19,000
35. Persons Case Scholarship, Government of Alberta $2000
36. Geral Weber Cosmopolitan International Club of Calgary Graduate Scholarship $21,000
37. American Society of Nephrology Student Scholar Grant $7000
38. Alberta Heritage Graduate Student Scholarship Award $3000
39. Scobey Hartley Doctoral Award from Alberta Centre for Child, Family and Community research $32,000
40. Izaak Walton Killam memorial Scholarship $36,000
41. IODE Canada War memorial Scholarship $15,000
42. Medical Science Academic Productivity Scholarship $500

2012/13 PUBLICATIONS

PUBLISHED – Total Reported 44

Engbers, J.D.T.*, **Anderson, D.***, Tadayonnejad, R.*, Mehaffey, W.H., Molineux, M.L., and Turner, R.W. (2011) Distinct roles for IT and IH in controlling the frequency and timing of rebound spike responses. *J. Physiol* (*Lond.*) 589 (Pt 22): 5391-5413. * Shared first author.
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Blades, ML, Grekova, E, Wobma, H, Chen, K, Chan, W, Cramb, D. Three-colour fluorescence cross-correlation spectroscopy for analyzing comples nanoparticle mixtures. *Analytical Chemistry* 2012; 84 (21): 9623-9631.

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Chiu MH, Wan CP, Weers PM and Prenner EJ. Apolipophorin III interaction with model membranes composed of phosphatidylcholine and sphingomyelin using differential scanning calorimetry, *Biochim. Biophys. Acta.*1788 (2009) 2160-2168.

Damani Z, Conner-Spady B, Noseworthy T. Waiting less for hip and knee replacement: Canadian orthopaedic surgeons' acceptability of single-entry models as a means of managing patients (Abstract). Clin Invest Med. 2012;35(6S):E1 - E34.

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Grinwis, ME., Sibley CD., Parkins, MD., **Eshaghurshan, CS.,** Rabin, HR., and MG Surette. 2010. Macrolide and clindamycin resistance in *Streptococcus milleri* group isolates from the airways of cystic fibrosis patients. Antimicrob Agents Chemother. **54:** 2823-2839.
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APPENDIX A: 4TH ANNUAL LEADERS IN MEDICINE RESEARCH SYMPOSIUM

4th Annual

University of Calgary
Leaders in Medicine Research Symposium

November 2nd, 2012

Distinguished Guest and Speaker:

Dr. Hugh Scully MD

Professor of Surgery and Health Policy

University of Toronto

4th Annual
University of Calgary
Leaders in Medicine Research Symposium

November 2nd, 2012
2:00-7:00 p.m.
Health Sciences Centre, Faculty of Medicine

Program

1:00 – 2:00 pm: **Registration and Poster Set-Up**

2:00 – 2:15 pm: **Welcome and Introduction of Keynote Speaker**

2:15 – 3:15 pm: **Keynote Address – Dr. Hugh Scully MD**

3:15 – 3:30 pm: **Refreshments**

3:30 – 4:30 pm: **Oral Presentations**

4:30 – 4:45 pm: **Reception (Food & Drinks)**

4:45 – 6:15 pm: **Poster Presentations**

6:15 – 6:45 pm: **Awards and Closing Remarks**

Keynote Speaker

Dr. Hugh Scully MD

Professor of Surgery and Health Policy (University of Toronto)

This year we are delighted to have Dr. Scully as our honorable guest and keynote speaker. Dr. Scully is an honorary consultant surgeon at University Health Network - Toronto General Hospital and a professor of surgery and of health policy management at the University of Toronto. Having earned his MD at Queen's University, Dr. Scully continued his medical training in cardiac surgery at hospitals affiliated with Harvard University and University of Toronto. Throughout his career, Dr. Scully has held notable positions including deputy surgeon-in-chief, deputy head of cardiac surgery, chief of staff at the Toronto General Hospital, chair of medical and surgical education, founding member of the Cardiac Care Network of Ontario, and member of board of trustees on various medical and government groups. Furthermore, with over 300 peer-reviewed articles, book chapters, and invited presentations on cardiac surgery, Dr. Scully has made a significant impact on the scientific community.

In addition to his academic roles, Dr. Scully has been a key player in the world of motorsports. He is a founding member of the FIA (World) Institute of Motor Sport Safety, and of the Ontario Race Physicians (serving as their President). In 2000, he was elected in the Canadian Motorsport Hall of Fame.

Dr. Scully's tremendous contributions to the medical, scientific, and sports communities have been recognized by numerous awards including the W. Anderson Award for Excellence in Education Administration (1986), the John F. Bassett Award for his commitment to the promotion of Canadian motorsports (1990), the John Reid Trophy for outstanding contribution to motorsport (1991), Medal of Merit from International Society of Heart Research (2001), the Commerative Medal for the Queen's Golden Jubilee, and the Canadian Medical Association Medal of Service (2010).

We are truly honoured to have Dr. Scully as our keynote speaker for the 4th Annual LIM symposium.

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4:00 — 4:10	Misha Bawa	PI3Kγ deficiency increases cancer development by increasing susceptibility to inflammation and early activation of tumorigenic pathways	4
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ORAL PRESENTATIONS

Presenter's Name: Christina Thornton

Program and Year: MD/PhD, Year 4

Category: Basic/Translational Project

The *Streptococcus* Antibiotic Resistome of Adult Cystic Fibrosis Patients Results from Mutation and Horizontal Gene Transfer

Christina S. Thornton[1,3], Margot E. Grinwis[1], Christopher D. Sibley[1,3], Harvey R. Rabin[1,2] and Michael G. Surette[1,4]

[1]Department of Microbiology, Immunology and Infectious Diseases, [2]Adult Cystic Fibrosis Clinic, [3]Leaders in Medicine Program, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada. [4]Departments of Medicine and Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada.

Introduction/Objectives: Cystic fibrosis (CF) is the most common lethal genetic disease among Caucasians. 90% of CF patients succumb to pulmonary failure from chronic respiratory infections. Traditionally, research has focused on a narrow spectrum of microorganisms thought to be principal pathogens such as *Pseudomonas aeruginosa.* However, emerging species, such as the *Streptococcus* genus, have been shown to be overlooked pathogens. Within the streptococci, there is the potential for an antibiotic resistome due to constant pressure from several prescribed antibiotics as well as the naturally competent nature of the bacteria. Earlier studies done on the microbiome within CF has shown the presence of multiple isolates from several novel species of streptococci, which may play a role in CF exacerbation. As such, the objectives were to determine rates of resistance among common antibiotics in CF and to elucidate molecular mechanisms of resistance.

Methods: In this study, 459 streptococcal isolates from 68 adult CF patients comprising of 16 novel and typed species underwent susceptibility testing for nine antibiotics. Molecular mechanisms of resistance for the macrolides were determined by a PCR-based screen or DNA sequencing.

Results: Resistance rates were the greatest for macrolide antibiotics at 51.6% for erythromycin and 56.4% for azithromycin, but with novel isolates closer to 80%. As such, macrolide resistance was looked at in closer detail. The two most common mechanisms of macrolide resistance within the streptococci acquired by horizontal gene transfer, the *mef* (efflux pump) and *erm* (target site methylation) accounted for only 53% of resistant isolates. Interestingly, the rarely described mechanism of 23S ribosomal point mutations, the target site of macrolides, accounted for 47% of resistant isolates.

Conclusions: The prevalence, species distribution and influence of therapy on resistance profiles suggest complex ecological interactions among the streptococci in the airways of CF patients with mutation, rather than solely horizontal gene transfer, being a significant mechanism of acquired antibiotic resistance in some species within this community. This is in contrast to similar studies done within CF demonstrating resistance solely by acquisition of virulence determinants. This study also illuminates the potential roles for the *Streptococcus* genus in CF disease progression.

Presenter's Name: Kevin McLeod

Program and Year: MD/MSc, Class of 2015

Category: Clinical Project

Resting State fMRI in ADHD and Developmental Coordination Disorder (DCD)

McLeod, K[3], Langevin L M[1,3], Goodyear, B[4,5], Dewey D[1,2,3].

Departments of Paediatrics[1] and Community Health Sciences[2], Alberta Children's Hospital Research Institute[3] (ACHRI), Departments of Radiology[4] and Clinical Neurosciences[5]

Introduction: Attention Deficit/Hyperactivity Disorder (ADHD) and Developmental Coordination Disorder (DCD) are prevalent childhood disorders that frequently co-occur. Neuroimaging, genetic and behavioral studies suggest that disruption in neural motor circuitry may be associated with both DCD and ADHD and could account for the high rate of co-occurrence. Resting state functional Magnetic Resonance Imaging (rs-fMRI) is a neuroimaging technique that measures the communication or synchrony of brain networks during rest. Using the primary motor cortex as a seed region, we hypothesized that neural communication would be disrupted in the primary motor networks of children with ADHD, DCD and co-occurring ADHD/DCD.

Methods: rs-fMRI using the primary motor cortex as a seed region was performed on 21 children with ADHD, 7 with DCD, 18 with ADHD/DCD and 23 typically developing controls. Resting-state maps of children with disorders were contrasted with those of healthy controls. Age, sex and handedness were considered as covariates.

Results: Children with ADHD, DCD and ADHD/DCD had altered communication between the primary motor cortex and numerous brain structures, specifically those involving inhibition, motor regulation and sensorimotor integration. Additionally, the groups displayed different patterns of communication with age. Specifically, the children with ADHD, DCD and ADHD/DCD demonstrated a lack of improved communication between the primary motor cortex and the contralateral motor cortex with age, whereas the typically developing children exhibited improved communication with age.

Conclusions: Children with ADHD, DCD and ADHD/DCD have altered communication in the motor network compared to typically developing controls. By understanding the contribution of these structures to movement, targeted therapies could be created for children with ADHD, DCD and ADHD/DCD that could result in improved motor function.

Presenter's Name: Mark Seamone

Program and Year: MD/MSc, Class of 2013

Category: Clinical Project

A direct comparison of spectral domain optical coherence tomography (SD-OCT) and multifocal electroretinography (mfERG) findings in hydroxychloroquine retinopathy

Mark E. Seamone[1], Katherine Milton[2], Micheline Deschênes[2], Amin Kherani[2,3], Michael Fielden[1] and R. Geoff Williams[2,3],

[1]Department of Medicine, [2]Calgary Retina Consultants, [3]Department of Surgery, University of Calgary, Calgary Alberta Canada

Background: Multifocal electroretinogram (mfERG) is considered the gold standard for detecting early-stage hydroxychloroquine-induced retinal pathology. However, mfERG access is limited and discrepancies in mfERG recordings are encountered upon serial examination of individual patients. Spectral domain ocular coherence tomography (SD-OCT), a newly described method of ocular imaging, allows for high-speed analysis of retinal pathology. We compared the ability of mfERG and SD-OCT to detect hydroxychloroquine-induced retinal injury.

Methods: Patients receiving hydroxychloroquine for a minimum of 5 years were selected retrospectively on the basis of mfERG findings (N=15). Individual eyes were then assigned an mfERG grade (mfERG grade 1-3) reflecting the observed degree of retinal pathology (N=30). Two retinal experts familiar with SD-OCT analysis compared SD-OCT abnormalities with mfERG findings for each grade.

Results: SD-OCT abnormalities were not observed in individuals with grade 1 and 2 mfERG findings. However, SD-OCT was capable of detecting retinal injury in eyes with grade 3 mfERG abnormalities. Commonly observed irregularities indicative of hydroxychloroquine toxicity included focal and generalized macular thinning, degradation of the IS/OS photoreceptor junction and thinning of the outer nuclear layer. When eyes with grade 3 mfERG abnormalities were sub-divided into groups of moderate and end-stage hydroxychloroquine toxicity, thinning of the outer nuclear layer consistently preceded injury to the IS/OS junction. In support of these observations, outer nuclear layer thickness was decreased in individuals with moderate and end stage toxicity upon quantitative analysis.

Conclusions: These results suggest that mfERG can detect hydroxychloroquine toxicity prior to SD-OCT. Nonetheless, thinning of the outer nuclear layer upon SD-OCT analysis should raise clinical suspicion of hydroxychloroquine-induced retinal injury. We suggest that SD-OCT should be used in conjunction with mfERG for the early detection of hydroxychloroquine retinopathy.

Presenter's Name: Misha Bawa

Program and Year: MD/PhD, Year 5

Category: Basic/Translational Project

PI3Kγ deficiency increases cancer development by increasing susceptibility to inflammation and early activation of tumorigenic pathways

Misha Bawa, Vadim Iablokov, Jacob Charette, Bjoern Petri, Wallace McNaughton, DM McCafferty
Department of Physiology and Pharmacology, University of Calgary

The class I phosphatidylinositol 3-kinases (PI3K) are lipid kinases that regulate several cell responses, including cell cycle progression and differentiation. p110γ (class I_B) subunits are expressed at higher levels in hematopoietic cells and regulate the immune response. The role of mice PI3Kγ in inflammation and cancer remains controversial in literature. Published work has shown that mice lacking PI3Kγ spontaneously develop colorectal carcinomas and the loss of PI3Kγ is protective in the acute phase, but detrimental in the resolution phase of hapten-induced colitis. Whereas other studies have shown that PI3Kγ is necessary for the development of chronic inflammatory diseases and tumor growth. The aim of this work was to establish the role of PI3Kγ in the azoxymethane and dextran sodium sulfate (AOM/DSS) model of colitis associated cancer. We hypothesized that PI3Kγ deficiency ($PI3K\gamma^{-/-}$) would decrease colon cancer development in the AOM/DSS model. Treated mice were given 10mg/Kg of intraperitoneal injection of AOM. One week later mice were given 2.5% DSS in drinking water for 7 days. Mice were sacrificed at 6 weeks after the end of DSS. Interestingly, PI3Kγ deficiency significantly increased cancer development, including polyps and dysplasia scores. Treated $PI3K\gamma^{-/-}$ mice lost more weight and suffered higher mortality than their wild type counterparts, indicating and increased inflammatory insult. To evaluate the inflammatory injury we repeated the experiment, but sacrificed the mice at 4 days post DSS. This earlier time point showed significantly increased macroscopic and histological inflammation scores in the PI3Kγ deficient mice. PI3Kγ deficient mice also had increased levels of cox-2 protein as determined via western blot and immuhistochemistry as well as increased prostaglandin E2 and D2 levels demonstrating an earlier activation of tumorigenic pathways. Our data show that PI3Kγ deficiency leads to increased cancer development in the AOM/DSS model by exacerbating the inflammatory injury and activating neoplastic pathways.

Presenter's Name: Trevor Cook

Program and Year: MD/MSc, Class of 2014

Category: Clinical Project

Low social support as a risk factor for a major depressive episode among Canadian community dwelling seniors

Cook, TM (1), Wang, JL (2)

(1) MD/MSc. student, Department of Community Health Sciences
(2) Associate Professor, Departments of Community Health Sciences and Psychiatry

Background: Major depression represents one of the leading causes of disease burden worldwide. Further, the proportion of Canadian citizens aged 65 years of age and older is rapidly growing. Despite this, there is a lack of longitudinal data on risk factors for a major depressive episode in seniors. While current literature has established social support as an important factor in the development and prevention of a major depressive episode, comprehensive measures of social support are rarely employed. A longitudinal approach to examining the relationship between depression and comprehensive social support tools has yet to be conducted in Canada.

Methods: This study utilized 8-years of population-based longitudinal data from the National Population Health Survey, collected by Statistics Canada. Sample was restricted to individuals 65 years of age and older at baseline, free of a current or previous depressive episode. Sample demographics, measures of 2- and 8-year depression incidence were prepared using bootstrap weighted chi-square statistics. Multi and univariate cross-sectional and longitudinal logistic regression models were used to identify risk factors for a major depressive episode.

Results: The majority of participants were female, married and living with partner. Roughly 80% of participants reported a chronic condition, though only 25% reported a pain problem and a third restriction to activity. Chronic pain, chronic conditions, and restriction to activity were each associated with higher incidence of major depression. Of five types of social support examined, lack of positive social interaction (OR 1.52, CI: 1.07-2.17), tangible (OR 3.06, CI: 1.49-6.29), affection (OR 2.08, CI: 1.34-3.25) and emotional (OR 1.483, CI: 1.04-2.09) social support, were significantly associated with risk of MDE. Female gender (OR 2.28, CI 1.49-3.50), having a chronic condition (OR 2.60, CI 1.50-4.40), and a restriction to activity (OR 3.00, CI: 2.00-4.35) were independent risk factors for depression in longitudinal models.

Conclusion: Some but not all types of social support are significant risk factors for a major depressive episode in longitudinal analysis. Chronic conditions, pain and activity limitations are important risk factors for depression.

POSTER PRESENTATIONS

Presenter's Name: Aditi Amin

Program and Year: MD/MPH (UBC), Class of 2014

Category: Clinical Project

Patient and Family Satisfaction of Care (P/FSoC) and Health-Related Quality of Life (H-RQoL) in Children and Youth with Diabetes Living in British Columbia (BC) – A Pilot Study.

Aditi Amin[1,2] BSc(Hons), MPH; Kristen Favel[2,3] BASc; Catalin Taraboanta[2] MD, MSc; Shazhan Amed[2,3,4] MD, FRCPC, MSc.PH.

[1]U of C Faculty of Medicine, [2]Child & Family Research Institute – BC Children's Hospital, [3]UBC Faculty of Medicine, [4]UBC Department of Pediatrics

Introduction: Currently, a large number of BC's diabetic pediatric patients receive care outside their health service delivery area at a tertiary clinic (TC) at BC Children's Hospital (BCCH). The aim is to provide this care through a provincial "shared care" network (SCN). This pilot study will inform the design of a province-wide P/FSoC and H-RQoL study, a baseline determination necessary to inform the creation of a SCN and monitor changes and improvements in care of diabetic pediatric patients.

Objectives: 1) Assess the feasibility of P/FSoC and H-RQoL questionnaire administration; 2) Assess the willingness of parents/legal guardians to consent to providing their children's personal health numbers (PHNs) for data linkage; 3) To compare the effectiveness of web- versus paper-based questionnaires; and 4) Understand the facilitators and barriers to questionnaire completion.

Methods: Mixed-methods cross-sectional design with a prospective semi-structured qualitative interview component. 271 eligible patients from Abbotsford and the surrounding area attending a TC at BCCH (and their families) had the option of consenting to: 1) Completion of a web- or paper-based P/FSoC and H-RQoL questionnaires; 2) Allowing access to PHNs; and 3) Completion of a phone or e-mail interview on facilitators and barriers to questionnaire completion.

Results: 50 families (39%) consented to participate. Of those 50 families: 30 (59%) completed the questionnaires (responders); 48 (96%) consented to data linkage; 40 (85%) preferred web-based questionnaires; and 47 (94%) consented to take part in the interview. Additional findings include: teens had low compliance; responders reported web-based questionnaires were convenient; and non-responders indicated that other obligations prevented them from completing the questionnaires.

Conclusions: The results of this study will inform the design of a larger study to assess P/FSoC and H-RQoL of children and youth with diabetes across BC. Lessons learned include: data linkage and questionnaire administration is feasible; web-based questionnaires are preferred; web-based questionnaires are convenient and economical for province-wide administration; and questionnaire design and follow-up requires improvement to enhance compliance.

Presenter's Name: Aman Wadhwani

Program and Year: MD/MSc, Class of 2014

Category: Clinical Project

Contrast Enhanced US in Inflammatory Bowel Disease: Should it be an Occasional or an Essential Component of Every Exam?

Aman Wadhwani[1], Alexandra Medellin[1], Kerri L. Novak[2], Stephanie R. Wilson[1,2]

[1]Department of Diagnostic Imaging, [2]Division of Gastroenterology, Faculty of Medicine, University of Calgary, Calgary, AB

Background: A clinical challenge in managing Crohn disease (CD) is establishing reliable, non-invasive methods to assess disease activity. Increasingly, this is performed on traditional ultrasound (tUS) with greyscale assessment of bowel wall thickening, inflammatory fat and adenopathy. Color Doppler imaging (CDI) allows subjective assessment of blood flow, as a reflection of inflammation. Our purpose is to show the benefit to this assessment of the addition of the recently introduced technique of contrast enhanced ultrasound (CEUS) of the bowel. Where available, CEUS activity prediction is compared with gold standard colonoscopy.

Method: CDI, tUS and CEUS were performed on 100 CD patients. All scans were reviewed by 2-blinded readers to determine CD activity on the baseline scan with CDI. Then, disease activity was objectively assessed on CEUS to show its impact on the initial assessment, upgrading or downgrading disease activity from the initial predictions based on tUS with CDI.

Results: 60 patients showed **concordance** between tUS and CDI, 36/60 of which showed either moderate or severe inflammation and 24/60 showed quiscent or mild inflammation of the bowel wall. In the **indeterminate** group of 40 patients, CDI did not corroborate tUS findings, generally showing thick bowel wall without expected blood flow on CDI. Therefore, disease activity could not be confidently predicted in the indeterminate group on the baseline scan alone. The addition of CEUS upgraded disease activity (none/mild ☐moderate/sev
disease activity was upgraded in 22/40 of patients belonging to the indeterminate group. Downgrading with CEUS was infrequent in both groups. In the 36 patients with concordant result of baseline US and CDI suggesting moderate to severe disease, CEUS did not suggest significantly different disease activity. The overall confidence in predicting disease activity in the indeterminate group was low. However, using CEUS increased reader confidence level by 58-64% with an overwhelming majority in the indeterminate group. Limited numbers of analyzed colonoscopies show a clear trend in peak enhancement between milder and more severely inflamed bowel.

Conclusion: CEUS is optimally used to determine the disease activity in IBD patients on whom baseline prediction with CDI and tUS is indeterminate. Performing CEUS selectively on CD patients may better predict the disease activity in a non-invasive manner with optimal use of resources.

Presenter's Name: Amanda Eslinger

Program and Year: MD/MSc, Class of 2015

Category: Basic Science/Translational Project

The effect of combined sitagliptin and oligofructose therapy on glucagon-like peptide-1 secretion and gut microbiota in pre-pregnant diet-induced obese rats

Amanda J. Eslinger and Raylene A. Reimer

Objectives/Introduction: Maternal obesity and impaired glucose tolerance can program increased risk for obesity and type 2 diabetes in offspring. Consequently the pre-pregnant period offers a unique opportunity for preemptive treatment of obesity in females of reproductive age and for prevention of obesity in future generations. The gut hormone glucagon-like peptide-1 (GLP-1) increases insulin secretion, slows gastric emptying and enhances satiety. Products that enhance GLP-1, like the prebiotic fiber oligofructose (OFS), or prolong the action of endogenous GLP-1, such as the dipeptidyl peptidase-IV inhibitor Sitagliptin, may be useful in improving satiety and glucose metabolism in obese females of reproductive age. The purpose of this study was to examine the effects of OFS+Sitagliptin therapy on circulating GLP-1 and weight loss in pre-pregnant obese rats. Offspring health was examined separately.

Methods: Female diet-induced obese Sprague-Dawley rats (n=52) were randomized to 1 of 4 treatments for 8wk: 1) AIN-93M(lean control); 2) OFS+Sitagliptin; 3) OFS; 4) AIN-93M+Sitagliptin. The primary outcomes were body weight, blood glucose and gut microbiota measured in fecal matter using qPCR. High fat high sucrose (HFHS), AIN-93M and weight-matched rats (via caloric restriction, CR) served as reference groups.

Results: Rats fed HFHS gained the most weight ($p=0.045$) while AIN-93M ($p=0.045$) and Sitagliptin ($p=0.054$) resulted in greater post treatment weight than the lean control, CR and OFS+Sitagliptin. OFS and OFS+Sitagliptin were bifidogenic ($p<0.0001$) and exhibited decreased %Firmicutes ($p=0.031$) compared to all other groups. C.leptum was increased in HFHS rats ($p=0.016$) compared to OFS and OFS+Sitagliptin. Total bacteria present in HFHS rats was decreased compared to all other groups ($p=0.04$).

Conclusions: Combining a targeted dietary treatment with a pharmacological treatment enhanced weight loss. Both OFS and OFS+Sitagliptin exhibited microbial profiles associated with a lean phenotype. It is anticipated that the benefits of these pre-pregnant treatments will act protectively and reduce detrimental programming in offspring.

Presenter's Name: Andrea Mosher

Program and Year: MD/PhD, Class of 2015

Category: Basic Science/Translational Project

The development of an *in vitro* cell culture model to study the pregnant human uterus

Andrea A. Mosher[1], Seunghwa S. Bolstad[1], Kelly J. Rainey[1], Stephen Wood[2], Donna M. Slater[1,2]

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Introduction: The development of *in vitro* cell culture models has greatly facilitated our ability to study human systems. However, there are concerns about the lifespan of cultured cells and whether they remain representative of the tissue of origin. The myometrium is the contractile machinery of the uterus, which is composed of smooth muscle cells and undergoes significant growth and remodelling throughout pregnancy. The objective of this study was to establish and validate primary cultured human myometrial cells that could be used to study the cellular mechanisms involved in labour.

Methods: Myometrial biopsies were obtained from women undergoing Caesarean section at term, prior to labour onset (38-40 weeks gestation). Paired biopsies were taken from both the upper and lower segments of the uterus. Myometrial cells were isolated from the biopsies and cultured to confluence. To assess the response to a cytokine known to be involved in labour, cells were stimulated with IL-1β (1 ng/ml). This treatment was repeated from passage 1 (p1) to p10. RT-PCR and immunocytochemistry were used to identify smooth muscle markers (a smooth muscle actin, calponin, caldesmon, tropomyosin) and fibroblast markers (vimentin and 1B10).

Results: We demonstrate that both upper and lower segment human myometrial cells stably express smooth muscle markers and fibroblast markers until at least p10, suggesting that these cells represent myofibroblasts. Both cell populations retain their ability to respond to IL-1β, demonstrated by a robust release of IL-8.

Conclusions: Primary human myometrial cells can be isolated from myometrial biopsies and cultured to study the human uterus. The cells retain their ability to respond to an inflammatory stimulus for at least ten passages and exhibit a myofibroblast phenotype, demonstrated by expression of both smooth muscle markers and fibroblast markers. This cell culture model will greatly enhance our ability to study critical mechanisms involved in the onset of labour.

Presenter's Name: Andrew Robb

Program and Year: MD, Class of 2015

Category: Basic Science/Translational Project

Concussion Diagnoses and Management Practices among Physicians in British Columbia

Andrew Robb, Geraldine van Gyn, Brad Curry

University of Victoria School of Exercise Science, Physical and Health Education

Objectives/Introduction: A consensus statement on the management of concussion in sport was released in 2009; however, the extent to which this is known and used by physicians is unknown. The aim of this study was to determine the assessment and management practices of physicians in British Columbia.

Methods: Thirteen physicians, recruited via the Victoria Medical Society and British Columbia Medical Association, participated in the study thus far. Participants completed an online survey, answering questions on: demographic information; background and definition of concussion; diagnosis; management; and barriers and patient information.

Results: We found significant variability in both diagnosis and management practices of physicians. The majority of physicians are still using mostly subjective measures, and despite 46% of physicians reporting awareness of the consensus statement, a significant number do not report following the outlined guidelines.

Conclusions: Future studies should investigate which tests are being administered within a clinical examination, and identify where the gaps in physician education are stemming from.

Presenter's Name: Angie Karlos

Program and Year: MD/MSc, Class of 2015

Category: Clinical Project

THE EFFECT OF THE 1P13.3 LDL-ASSOCIATED LOCUS IS SEX SPECIFIC IN A FIT, CANADIAN YOUNG ADULT POPULATION

Angie Karlos, BSc (Hons)[1]; Andrea Lutsch[1]; Kimberly Connors[1]; Elizabeth Gnatiuk MKin[1]; Chiatogu Onyewu MD PhD[2]; Gina Many, MS[2], Eric P Hoffman PhD[2]; Dustin Hittel, PhD[1]

[1] Faculty of Kinesiology, University of Calgary

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Introduction: The 1p13.3 LDL-associated locus is strongly associated with LDL-cholesterol (LDL-C) and subsequently, the risk of developing cardiovascular disease (CVD) and myocardial infarct. While the effect size of this locus has been small in older, symptomatic individuals, recent investigations have revealed large effect sizes in children and young healthy adults. As such, we sought to validate the previously observed association between the 1p13.3 LDL-C locus and to describe the prevalence of risk factors (RF) for CVD in a group of fit, healthy, Canadian young adults.

Methods: Healthy young adults (n=122, mean age=23.2) were recruited from the University of Calgary. Lipid measures and genomic DNA were collected from peripheral blood after an overnight fast. Additional RF's included blood pressure, family history, BMI, body fat (%BF), smoking behaviour, and low cardiovascular fitness. Associations between genotype and LDL-C were investigated using linear regression.

Results: No subjects were hypertensive, 2.5% reported smoking (n=3), and 5.7% (n=7) reported a family history of premature MI or CVD. Nearly half (42.9%) of the female and 21.7% of male subjects had %BF that was above a healthy range. Over a quarter of subjects had LDL-C values that were considered to be non-optimal. A significant association was observed between the rs12740374 locus (GG: 2.46±0.11 mmol/L versus TG/TT: 2.06±0.12 mmol/L, p=0.016) and the rs646776 locus (TT: 2.42±0.11 mmol/L versus CT/CC: 2.03±0.12 mmol/L, p=0.027), and LDL-C in male subjects with genotype explaining 3.0% of the variability in LDL-C.

Conclusion: A high prevalence of non-optimal LDL-C exists in this young Canadian population despite being otherwise fit and healthy. A significant association was found between LDL-C and the 1p13.3 variant in male subjects with an effect size larger than previously reported in older populations. This locus is a valuable target to identify individuals who would most benefit from early interventions to prevent CVD.

Presenter's Name: Anna Schmidt

Program and Year: MD/PhD, Class of 2015

Category: Clinical Project

T1 mapping for the assessment of diffuse myocardial fibrosis in type 2 diabetes

Schmidt, Anna[1,2], Chow, Kelvin[3], Lau, David[2], Friedrich, Matthias[1]

[1]Stephenson CMR Centre, [2]University of Calgary, [3] University of Alberta

Introduction: Type 2 diabetes (T2D) is an independent risk factor for adverse cardiac events. The underlying biochemical changes associated with diabetes have been shown to increase collagen deposition and cross-linking, with subsequent preclinical reductions in cardiac function. Non-invasive imaging methods are important for risk stratification of asymptomatic patients, and to better understand the pathophysiology of diabetic heart disease. T1 mapping is a Cardiovascular Magnetic Resonance Imaging (CMR) sequence for quantification of increased extracellular volume fraction, indicative of diffuse collagen replacement.

The objective of this research is to examine post-contrast T1 Mapping times in asymptomatic T2D patients.

Methods: Patients diagnosed with type 2 diabetes (Hb_{A1c} 7.5-9.9%; mean age 53±8; n=10), and healthy, non-diabetic age-matched controls (mean age 47±10; n=10) were assessed at the Stephenson CMR Centre using a clinical 1.5 T scanner. Medical history and ECG were reviewed to rule out ischemic heart disease. Qualified patients underwent a CMR scan including T1 mapping protocol pre- and 15 minutes post-Gadolinium contrast injection. Additionally, standard CMR protocols were used to assess function, and Late Gadolinium Enhancement (LGE).

Results: A significant difference in post-contrast T1 mapping values was observed in patients as compared to controls (580 ± 54 and 623 ± 31 ms; $p < 0.05$). No significant differences in functional parameters were found; both had normal systolic function (LV Ejection Fraction 57.9 ± 2.6 and 57.8 ± 2.9%, respectively), although T2D patients had a slightly reduced LV End Diastolic Volume Index. No regional areas of LGE were detected in either group.

Conclusion: The observed decrease in T1 mapping times reflect an increased extracellular volume fraction, and may reflect globally increased collagen deposition in diabetic myocardium. This finding compliment previous findings by this group of preclinical changes in microvascular function in diabetes. Further studies are required to assess the pathophysiologic context and prognostic impact.

Presenter's Name: Antoine Seguin & Justin Wong

Program and Year: MD

Category: Clinical Project

Proposal for Implementation: An Emergency Department Sunrise Clinical Manager Order Set to Aid in the Detection, Investigation, and Management of Delirium

Antoine Seguin and **Justin Wong**

PI: Dr. Eddy Lang, Dr. Jayna Holroyd-Leduc, University of Calgary/Alberta Health Services

Introduction: Delirium is an acute disturbance in patient cognition characterized by inattention, disorganized thinking, alterations in level of consciousness and disturbance of perception (Han, Wilson & Ely, 2010). It is associated with a high burden of illness, carrying significant costs to the health care system, increased morbidity and potentially increased mortality (Han et al., 2010). Delirium is a symptom of significant underlying disease and determining the precipitating medical event is important for appropriate patient management (Murphy, 2000). Early identification of delirium and appropriate management is essential to reduce the burden that it currently poses to the health care system.

Methods: A literature review of delirium and acute mental status change was completed using PubMed, limited to articles on delirium diagnosis and management in the emergency department. Using this literature review, we will develop an order set for the diagnosis and management of delirium in the emergency department. The components evaluated will be the overall use of the order set and specific diagnostic and management options selected by clinicians. The analysis of the order set will be conducted at three and six months after implementation to assess engagement.

Results: The results of the SCM order set are anticipated to be completed in 2013. With completion of the delirium order set, we aim to have clinician participation in the emergency department as measured through usage statistics. The primary limitation of the project is that the incidence of delirium and primary health outcomes will be unmeasured and the impact on diagnosis and management will be unknown.

Conclusions: Delirium is a common presentation of the elderly to the emergency department, but currently, there is no delirium order set. By implementing this program we hope to improve the detection, investigation and management of delirium in Calgary emergency departments.

Presenter's Name: Arfeen Malick

Program and Year: MD/MSc (Columbia), Class of 2014

Category: Clinical Project

Assessing Patient Health Literacy and Patient Satisfaction with Care in a Student Run Clinic Setting: Project Homeless Connect (PHC) Pilot Project.

Aditi Amin[1,2] BSc(Hons), MPH and **Arfeen Malick**[1,2] BSc(Hons), MSc; Michael Weldon[1,3]; Matthew Ward[1,3]; Aaron Wong HBSc, MSc[1,2]; Dr. Janette Hurley[1,2,3,4] MD, CCFP.

[1]U of C Faculty of Medicine, [2]U of C Student Run Clinic, [3]U of C Project Homeless Connect, [4]U of C Department of Family Medicine

Background: Project Homeless Connect (PHC) is a biannual free event where "those at risk of or experiencing homelessness in Calgary" can access services and resources. The student run clinic (SRC) at PHC was developed by two medical students at the University of Calgary under the mentorship of Dr. Janette Hurley. As a part of the evaluation of this SRC, and given the criticism that SRCs often receive for conferring more benefits to student learning at the expense of quality of patient care, this pilot study was launched.

Objectives: The objectives of this pilot study were fourfold: 1) assess the health literacy status of patients attending PHC; 2) determine if student clinicians at PHC were communicating health information at a level appropriate to the health literacy status of their patients; and 3) evaluate patient satisfaction with care delivered by student clinicians at PHC.

Methods: A mixed-method (qualitative/quantitative) questionnaire was developed and validated. Health literacy questions were adapted from the validated and field tested "Rapid Estimate of Adult Literacy in Medicine (REALM)" health literacy measurement tool. Patient satisfaction with care questions were adapted from RAND Health's validated "Patient Satisfaction Questionnaire". This questionnaire was administered to patients who received care at the student run clinic at PHC. Quantitative data analysis consisted of scoring questionnaire results and generating descriptive statistics. Qualitative analysis consisted of basic content analysis through reducing questionnaire responses into "patterns" and "themes".

Results: Approximately 50 questionnaires were completed at the first SRC at PHC that took place on April 21, 2012. Patient health literacy was variable (e.g., "low" to "high"). Areas for improvement in student clinician communication were also identified. Overall, patient satisfaction with care was consistently highly rated (e.g., "Good" or "Very Good") with numerous positive comments from patients regarding quality of care.

Conclusions: The SRC at PHC is a valuable service for the underserved homeless population of Calgary. Furthermore, the findings of this study indicate that SRC environments provide quality patient care in addition to unique learning opportunities for medical students.

Presenter's Name: Brad Sullivan

Program and Year: MD/MSc (McGill), Class of 2015

Category: Basic/Translational Project

A Murine Model of Early Onset Scoliosis

Michael B Sullivan (1,2,4), Ali Esmaeel (2,4) Marco Kneifel (4,5), Jean A. Ouellet (2,4), Neil Saran (2,4), Janet E. Henderson (2,3,4)

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Introduction: Scoliosis can be infantile or juvenile in onset; however, it is more frequently identified in older children, particularly girls as they enter puberty. Untreated scoliosis progresses with age and there are currently few non-operative therapies for severe scoliosis. Furthermore, current animal models inadequately represent human scoliosis: a characteristic necessary in pre-clinical research. We have noticed that FGFR3-/- mice develop progressive scoliosis until end of life and may be a viable model of scoliosis.

Methods: Forty-seven FGFR3-/- and 44 wildtype mice were serial radiographed with posterior-anterior and lateral views to measure kyphotic and scoliotic Cobb angles. Age and Gender matched mice were euthanized at ages ranging from 4 to 25 weeks and processed for histology and high resolution micro-computed tomography (micro-CT) to compare parameters such as vertebral and inter-vertebral disc (IVD) morphology, micro architecture, vertebral rotation, and cellular activity.

Results: FGFR3-/- mice developed scoliosis by 8 weeks ($p<0.05$) and scoliosis progressed until the end of study, reaching a maximum of $40.9^{o}\pm18.3$ (100% incidence) compared to wild-type counterpart of $5.1^{o}\pm4.2$. Micro-CT analysis revealed poorer FGFR3-/- vertebral body micro-architecture of the convex side and decreased IVD thickness on the concave side of the curve. Vertebral bodies were overgrown, with the convex side being comparatively greater. Histological analysis of bone mineralization and cartilage support micro-CT data, and indicates concave IVD compression and convex nucleus pulposus translation.

Conclusion: FGFR3-/- mice developed a high incidence of scoliosis with comparable severity to that seen in humans. Because the proposed model features spontaneously occurring scoliosis, we see it as more clinically relevant than surgically induced scoliosis. We propose the Fgfr3-/- mouse as an animal model that is inexpensive, easily available, non-invasive, and closely reproduces the disease. This model will be used to test novel biological therapies to serve as non-surgical alternatives in progressive early onset scoliosis.

Presenter's Name: Brandon Hisey

Program and Year: MD/PhD, Year 1

Category: Basic/Translational Project

Differences Between Active and Passive Muscle Failure

Brandon Hisey[1, 3] and Dr. Walter Herzog[2, 3]

1. Leaders in Medicine Program, University of Calgary 2. Faculty of Kinesiology, University of Calgary 3. Department of Biomedical Engineering, Schulich School of Engineering, University of Calgary

Introduction/Objectives: Lengthening contractions of skeletal muscle have been shown to cause damage. The majority of these studies examine either the deficit in isometric force following repetitive strain cycles or the complete failure of muscle, showing that active muscles require greater force-to-tear than passive counterparts and that strain-to-tear is not different. However, damage to muscle may precede tearing after a single insult. Leonard *et al.* (2010) showed that actively failed rabbit psoas myofibrils failed at higher stresses than passive counterparts, and that both groups failed at similar lengths beyond myofilament overlap. These results suggest that cross-bridge-dependent forces alter interactions/structures within the myofibril to produce high forces during stretch that persist beyond myofilament overlap. However, it is not known if this difference persists at higher tissue levels.

The purpose of this study is to examine mechanical properties of failure. Differences in stress and strain between actively stretched and passively stretched muscles will be considered.

Methods: The tibialis anterior (TA) of *Rana pipiens* was isolated from surrounding tissues. The frog's tibiofibula was fixed in a stereotaxic frame, and the TA was severed distally with a piece of tarsal bone and affixed to a force transducer that was mounted on a linear motor. The TA was activated by stimulation of the sciatic nerve via an impanted hook electrode. A force-length relationship was established for each muscle with a series of contractions over a range of lengths. The muscle was positioned at optimal length (L_0), and pulled to failure either actively or passively at a rate of 5% L_0/s.

Results: No significant differences in the force-to-failure or strain-to-failure were observed between the active and passive failure groups.

Conclusion: The result found by Leonard was not observed at the level of the whole muscle, indicating the onset of damage is not activation-dependent at this level in this muscle.

Presenter's Name: Craig Beers

Program and Year: MD/PhD, Year 4

Category: Clinical Project

The minimum number of discharges needed to detect BOLD signals using intracranial EEG-fMRI at 3T

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Introduction: Simultaneous scalp EEG-fMRI is a powerful tool that is quickly gaining popularity in both research and clinical settings. Combining intracranial EEG with fMRI (iEEG-fMRI) is of particular interest, as it would allow interictal discharges to be recorded during fMRI with unprecedented precision. In this study, we sought to determine the minimum number of epileptiform discharges required to generate consistent maps of fMRI activation during simultaneous iEEG-fMRI.

Methods: Three subjects were studied with iEEG-fMRI at 3T. fMRI activity was modelled by convolving the timing of epileptiform events with a hemodynamic response function. Statistical maps were generated for the fMRI activation every 10 discharges until all recorded epileptiform activity had been modelled (i.e. 10 discharges, 20 discharges, etc.). The fMRI maps generated by analysing all recorded discharges were then used to contrast each discharge interval for significant differences (e.g., 676 discharges vs. 10).

Results: A large number of discharges were recorded from each subject (478-820). Upon analysis of the stratified data, it was found that the locations of significant fMRI activation changed little after a certain threshold was reached for each subject (61-180 discharges). As the number of interictal discharges included in the model increased, the statistical power of the activation increased and became more localized.

Contrast analyses were performed between the fMRI signal seen with the maximal number of discharges versus fewer discharges. There were few statistically significant differences once 50-96 discharges were modelled.

Conclusions: Based on these data, a minimum of 50-100 interictal discharges need to be recorded during simultaneous iEEG-fMRI in order to produce reliable maps of fMRI activation. While as few as 10 discharges did result in localized fMRI activation, the activation was scattered and diffuse. Although EEG-fMRI may produce maps of fMRI activation in subjects with relatively few discharges, these maps may not be accurate.

Presenter's Name: David Nicholl

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Obstructive Sleep Apnea Enhances Blood Pressure Responsiveness to Angiotensin II in Humans

DDM Nicholl[1], PJ Hanly[1,2], GB Handley[2], BR Hemmelgarn[1,3], MJ Poulin[1], DY Sola[1], and SB Ahmed[1,3]

(1) Department of Medicine, University of Calgary (2) Sleep Centre, Foothills Medical Centre (3) Alberta Kidney Disease Network

Introduction: Obstructive sleep apnea (OSA) is strongly associated with vascular disease in humans. Though the mechanism remains unclear, limited studies suggest a prominent role for the renin-angiotensin system (RAS), activation of which is deleterious to cardiovascular and kidney function. By examining the hemodynamic response to angiotensin II (AngII) challenge, a well-accepted indirect measure of RAS activity, we sought to determine the effect of OSA status on the vascular RAS.

Methods: Twenty-three newly diagnosed OSA subjects who were otherwise well and 40 healthy subjects were studied in high salt balance, a state of maximal RAS suppression. OSA was diagnosed by a sleep study (respiratory disturbance index >15hr^{-1}). Blood pressure (BP), plasma renin activity (PRA), and aldosterone were measured at baseline and in response to a graded AngII infusion (3ng/kg/min x30min, 6ng/kg/min x30min). The primary outcome was the effect of OSA status on the BP response to AngII challenge, at 30 and 60 minutes. Secondary outcomes were the PRA and aldosterone responses to AngII.

Results: OSA subjects demonstrated greater baseline BP (SBP: 129±3 vs. 114±2, $p<0.001$; DBP: 76±2 vs. 67±1, $p<0.001$) compared to healthy controls. There were no differences in circulating PRA, AngII, and aldosterone levels between groups. Compared to healthy controls, OSA subjects had a significantly greater increase in SBP (3ng/kg/min, 22±4 vs. 10±2, p=0.021; 6ng/kg/min, 26±3 vs. 19±2, p=0.042) and aldosterone (3ng/kg/min, 169±20 vs. 99±16, p=0.009; 6ng/kg/min, 242±28 vs. 227±23, p=0.67) in response to AngII. Following adjustment for covariates the association between OSA status and SBP response remained significant (6ng/kg/min, β=15[95CI: 4, 26], p=0.007). There were no differences in the DBP or PRA responses to AngII between the groups.

Conclusions: OSA is associated with enhanced blood pressure and adrenal sensitivity to AngII, demonstrating that RAS activation has a role in the development of hypertension in OSA patients.

Presenter's Name: Devon Livingstone

Program and Year: MD, Class of 2013

Category: Clinical Project

Silver Nitrate Mimicking a Radiopaque Bony Foreign Body in the Paraphayngeal Space

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Silver nitrate is a form of chemical cautery commonly used for control of minor hemorrhage in the head and neck and in the management of hypergranulation tissue. Few case reports exist that describe its radiographic appearance, and its potential for imitation of a foreign body. We report a case where silver nitrate applied to halt bleeding from a peritonsillar incision was later mistaken for a chicken bone lodged in the parapharyngeal space on computed tomography (CT) imaging. We stress that knowledge of the radiographic appearance of silver nitrate can help prevent unnecessary surgical exploration, and can aid in the radiographic diagnosis of head and neck infections.

Presenter's Name: Dustin Anderson

Program and Year: MD/PhD, Class 2014

Category: Basic/Translational Project

A calcium sensitive ion channel complex maintains inhibitory charge transfer during fluctuations in extracellular calcium

Dustin Anderson, Jordan D.T. Engbers, Colin Heath, Theodore M. Bartoletti, W. Hamish Mehaffey, Gerald W. Zamponi and Ray W. Turner

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Objectives/Introduction: The concentration of extracellular calcium ($[Ca]_o$) is a critical determinant of synaptic transmission and neuronal excitability, yet repetitive synaptic input is known to decrease $[Ca]_o$ in numerous brain regions. The mechanisms that neurons use to maintain normal levels of excitability in the face of such a rapid change in the calcium gradient have remained an enigma. In the cerebellar molecular layer, synaptic input reduces $[Ca]_o$ by up to 0.4 mM in the vicinity of stellate cell interneurons that inhibit Purkinje cell dendrites. Here we show that a Cav3-Kv4 ion channel complex expressed in stellate cells acts as a calcium sensor that responds to a decrease in $[Ca]_o$ by dynamically adjusting stellate cell output to maintain inhibitory charge transfer to Purkinje cells.

Methods: A-type and T-type currents were recorded from stellate cells in P15-P20 rat cerebellar slices and from tsA-201 cells co-transfected with Kv4, Cav3, KChIP, and DPP10 cDNAs.

Results: Whole cell recordings of stellate cell A-type current revealed that Kv4 inactivation followed a sigmoidal relationship with changes in $[Ca]_o$. Similarly, in tsA-201 cells expressing Cav3-Kv4 complex members, Kv4 inactivation tracked $[Ca]_o$ in a sigmoidal fashion. When the calcium sensing subunit of Kv4 channels (KChIP3) was omitted from the transfection, this relationship was abolished. Previously, we demonstrated that internal perfusion of antibody directed at KChIP3 increased the gain of stellate firing by roughly two-fold. Using dynamic clamp, we extend those findings here and show that the gain of stellate firing is dynamically modulated by fluctuations in extracellular calcium.

Conclusion: Collectively, this data demonstrates that the Cav3-Kv4 complex acts as a calcium sensor to adaptively regulate inhibitory input in relation to local changes in the extracellular milieu that accompanies repetitive synaptic input.

Presenter's Name: Elizabeth Kelly

Program and Year: MD, Class 2013

Category: Clinical Project

Evaluating Foothills Medical Center's Healthcare Volunteer Programs

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Objectives/Introduction: Healthcare volunteers are vital members of the social support network for patients, and there is a growing interest in increasing volunteer involvement in care delivery. However, many healthcare organizations and hospitals report difficulty in recruiting and retaining volunteers. To address this issue, an understanding of the motivations and levels of satisfaction of healthcare volunteers is of key importance.

Methods: We conducted a cross-sectional study of 200 healthcare volunteers at the Foothills Medical Center (FMC). We used paper questionnaires guided by the Volunteer Functions Inventory (VFI), a validated instrument which creates summary scores for motivations (max 35) and outcomes (max 14) in the categories of Career, Social, Values, Understanding, Enhancement, and Protection.

Results: 106 surveys were returned (53%). 37% were male, and 63% female. The average age was 37. Locations included on the units (27%), Wayfinder (13%), the gift shop (14%), the emergency department (11%), and several others. All summary scores had good internal consistency (Crohnbach's alpha >0.7) except outcomes in understanding. The highest ranked motivations were in Values and Understanding (medians of 31.5 and 27) followed by Enhancement (22.5), Career (18), Social (17), and Protection (16.5). The highest ranked outcomes were in Values (median 12), then Social (11) and Enhancement (10) followed by Career (6) and Protection (5.5). The median satisfaction based on 5 questions was 32/35 with a mean self-reported satisfaction of 8.4/10 (95% CI [8.2-8.7]).

Conclusions: The results suggest that volunteers are motivated more by humanitarianism, a desire to grow, and learn more about the world, than they are by forwarding their careers or developing social connections. If this is so, effective volunteer retention efforts could include appreciation events, collecting and distributing patient stories about how volunteers made a difference to them, or altruistic prizes such as making charitable donations in a leading volunteer's name.

Presenter's Name: Elliot Sampson

Program and Year: MD/MSc, Class of 2015

Category: Clinical Project

Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis.

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Background: Differentiated thyroid cancer has a good prognosis and only rarely presents with distant metastasis at diagnosis. The clinical outcome of this presentation was assessed with respect to survival and factors that may determine prognosis.

Methods: A retrospective review was undertaken of patients with stage M1 differentiated thyroid cancer at presentation (n = 49), referred from 1980-2000 at a single institution.

Results: The median age was 68 (range, 17-90), with 69% females. The initial site(s) of metastasis were lung only, 45%, bone only, 39%, other single site, 4%, and multiple sites, 12%. Histology: papillary, 51%, follicular, 49%. Initial treatment(s) included: thyroidectomy, 82%, radioactive iodine (RAI), 88%, excision of metastasis, 29%, radiotherapy, 47%, and chemotherapy, 6%. With a median follow-up time of 3.5 years, 25 patients are alive (51%) and 24 died (49%), with 3-year and 5-year actuarial survivals of 69% and 50%, respectively. Only a minority of patients (4/25, 16%) had no clinical evidence of disease at last follow-up. Most deaths (17/24, 71%) were due to progressive cancer. Prognosis was associated with age, site of metastasis, histology, and iodine avidity of the metastasis. Patients aged </=45 (n = 8) had a 3-year survival of 100%, versus 62% for those age > 45 years (P = .001). The 3-year survival for lung only versus bone only metastasis was 77% versus 56% (P = .02); for papillary versus follicular carcinoma, 75% versus 62% (P = .006); for iodine-avid disease (n = 29) versus not avid (n = 14), 82% versus 57% (P = .02), respectively. In multivariate analysis after adjusting for age, only histology and iodine avidity remained significant for survival. The hazard ratio for follicular histology was 3.7 (95% confidence interval [CI], 1.1-12.1, P = .03), and for tumors not avid for iodine, 3.4 (95% CI, 1.2-9.2, P = .02).

Conclusions: The data support the aggressive management of patients presenting with stage M1 thyroid cancer, with thyroidectomy and RAI. Complete clinical eradication of disease was rarely seen, and 50% of patients survived for more than 5 years. Young patients with papillary tumors and/or iodine-avid disease have an even better prognosis.

Presenter's Name: Erik Nohr

Program and Year: MD, Class of 2013

Category: Basic/Translational Project

Validation of a Histopathologic Classification Scheme for ANCA-Associated Glomerulonephritis

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Objectives/Introduction: Anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides cause multiple organ system problems often including rapidly progressive glomerulonephritis. Such cases are associated with a high rate of renal failure and mortality; therefore accurate prognosis is valuable. Berden *et al.* (2010) proposed a new histopathologic classification scheme separating biopsies into four classes: focal, crescentic, mixed, and sclerotic. Here we present additional validation of the prognostic use of their classification scheme.

Methods: We included all patients who were diagnosed with ANCA-associated glomerulonephritis (microscopic polyangiitis, Wegener's granulomatosis, or Churg-Strauss syndrome) from a renal biopsy in the Calgary area between January 2005 and August 2010 with at least one year of followup and no concurrent glomerulonephritic disorder. Slides were scored independently by a renal pathologist and a medical student, and discrepancies were resolved at a double-headed microscope. Clinical data was retrieved from PARIS (Province of Alberta Renal Information System) and Netcare. The study tentatively includes 124 patients; the current analysis uses 47.

Results: Of the 47 biopsies, there were 10 focal, 17 crescentic, 15 mixed, and 5 sclerotic. At diagnosis, patients with focal biopsies had the highest eGFRs (p=4.97e-08; focal: 68±33, crescentic: 13±8, mixed: 19±19, sclerotic: 15±9). Focal biopsies were also associated with higher 1-year followup eGFRs (p=7.23e-04; focal: 72±34, crescentic: 33±14, mixed: 35±27, sclerotic: 13±8), and higher lowest eGFR values (p=8.37e-05; focal: 72±34, crescentic: 9±7, mixed: 13±12, sclerotic: 9±6). At 1-year followup, 2/5 patients with sclerotic biopsies were dead and another 2/5 were in ESRD; at 1-year no patients with a focal classification developed ESRD and only one died.

Conclusions: The focal class was associated with the best prognosis, while crescentic, mixed, and sclerotic classes had relatively poor prognoses. Though more data collection and analysis remains to be done in this project, so far results corroborate the prognostic utility of this new classification scheme.

Presenter's Name: Farah Ladak

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

SHOULD THE FIBROSCAN S2 PROBE BE USED FOR LIVER STIFFNESS MEASUREMENT INSTEAD OF THE M PROBE IN SMALL ADULTS WITH CHRONIC LIVER DISEASE?

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Objectives/Introduction: The success of liver stiffness measurement (LSM) by transient elastography (TE, FibroScan) is influenced by anthropometric factors. In smaller adults, the M probe may fail due to narrow intercostal spaces and rib interference. We aimed to compare LSM using the FibroScan S2 (pediatric) probe with the M probe in small adults with chronic liver disease.

Methods: In this prospective study, 41 liver disease patients and 18 controls with a thoracic perimeter <75 cm underwent LSM using the FibroScan M and S2 probes. TE failure was defined as no valid LSMs and unreliable examinations as <10 valid LSMs, an interquartile range (IQR)/LSM >30%, or success rate <60%.

Results: TE failure was not observed and reliability did not differ between the M and S2 probes (86% vs. 95%; P=0.20). Liver stiffness measured using the M and S2 probes was highly correlated (ρ=0.81; P<0.0005) and median liver stiffness did not differ between probes (4.5 vs. 4.4 kPa; P=0.10). However, in participants with a skin-capsular distance ≥15 mm, median liver stiffness was higher using the S2 probe (5.5 vs. 4.9 kPa; P=0.008). When compared with validated liver stiffness cut-offs, the S2 probe would have overestimated the stage of fibrosis compared with the M probe in 12% of patients.

Conclusions: The FibroScan S2 probe does not improve the feasibility of LSM in adults of smaller stature and may overestimate liver stiffness compared with the M probe. The FibroScan M probe should remain the preferred tool for LSM in small adults with chronic liver disease.

Presenter's Name: Francisco Lee

Program and Year: MD, Class of 2015

Category: Clinical Project

Perspectives on an inquiry-based learning strategy designed for a large-scale, pre-professional, second-year course in human anatomy at Queen's University.

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Introduction: Inquiry-based learning (IBL) has been identified as an effective strategy for active learning. The intention of this technique is to encourage students to be responsible for their learning by generating questions, performing research, and proposing solutions. Knowledge is said to develop actively through discovery rather than passively through transfer from a higher authority. While active-learning strategies have been utilized broadly for professional-level training, similar opportunities remain rare in large-scale, pre-professional anatomy education. This study describes the adoption of IBL in a large-scale second-year human anatomy course as a term-long, team-based research project, and reports perceptions of its learning utility from the vantage of students and project facilitators.

Methods: Students were organized into groups and required to propose, research, and resolve an anatomical question of their choosing, with guidance from an experienced facilitator. Students presented their work at a year-end symposium. Assessment surveys were administered at the conclusion of the project.

Results: Responses from students suggested that inquiry-based learning was most useful for developing teamwork skills and achieving personal goals; while facilitators implied that inquiry was most beneficial for deep and active learning. Although the perceived benefits of IBL differed between the two groups, the overall reaction was positive for all participants.

Conclusions: These observations offer a favourable view of IBL as presented here and support the integration of active-learning methods in large-scale, undergraduate anatomy courses to augment the student learning and to expose perspective instructors to active-learning strategies at the pre-professional level.

Presenter's Name: Graeme Matthewson

Program and Year: MD, Class of 2014

Category: Clinical Project

Treatment of a Multi-Ligament Injured Knee: A Case Report of Bicruciate Peel-Off Lesions

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Background: Multiple ligament injured knee's (MLIK's) are a rather rare but potentially fatal traumatic event, as well as a potential career ending injury in athletics. We report here, a case of a 35-year-old female soccer player who sustained a multi-ligamentous injury to her right knee during play.

Purpose: To investigate a case of MLIK with double primary repairs of the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) as this combination has yet to be reported in the literature.

Methods: The MLIK was arthroscopically repaired with a primary ACL repair to the tibial spine and a primary PLC repair to the femur, using the native ligaments in both. A Tibialis Anterior allograft was used for reconstruction augment of the posterolateral corner using the Larson technique secured with a suture button.

Results: At two weeks post procedure, on x-ray there was pull out of the suture button from the fibular head. At 3 months post procedure the patient had reduced range of motion, which was suspected to be due to arthrofibrosis of the knee. At 9 months an MRI was done which showed healed cruciate ligaments and posterolateral corner, however there was evidence of arthrofibrosis in the anterior interval and suprapatellar pouch. The patient was brought in for lysis of adhesions and debridement, which caused an immediate increase in ROM (range of motion) and she began her return to sport.

Conclusion: Primary repair of peel-off lesions through a single bone tunnel is a viable option for the treatment of double peel of lesions of the ACL and PCL, with proper healing to the anatomic footprint. However, this approach may not mitigate the risks regarding development of post-operative arthrofibrosis as other techniques that have been used for reconstruction. If employed in the future, it is suggested that some of the techniques used to decrease arthrofibrosis in reconstruction of the ligaments be used.

Presenter's Name: Jaclyn Strauss

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

Investigating a Role for *Fusobacterium nucleatum* in Inflammatory Bowel Disease

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The genus *Fusobacteria* comprises several species that are anaerobic, Gram negative members of the human microflora, including the Gastrointestinal tract. Several of these species are pathogenic, and in particular, *Fusobacterium nucleatum* (*Fn*) has a well-characterized role in periodontitis in the oral setting. *Fn* has only recently been found to be a frequent resident of the intestinal mucosa, and thus, little is known about the role of this species in the gut. Given its involvement in inflammatory disorders in the mouth, we sought to investigate a potential role for *Fn* in inflammatory bowel disease (IBD).

Using culture based methods and strict anaerobic conditions, *Fn* was isolated from human intestinal mucosal biopsies obtained during colonoscopy. Invasion into intestinal epithelial cells *in vitro* was examined using immunofluorescence microscopy and an antibiotic-dependant assay. The ability of *Fn* isolates to induce a pro-inflammatory response in host cells was assessed by quantitative real-time PCR and ELISA.

From an initial pilot study we determined that there is a positive correlation between recovery of *Fn* from intestinal biopsies and IBD status of the host; *Fn* was isolated from 50% of patients with IBD, versus 17.6% of healthy controls (p=0.02). *Fn* strains from IBD patients were more invasive *in vitro* than strains from healthy controls and demonstrated the ability to survive and proliferate inside host cells. Furthermore, while *Fn* strains from both IBD patients and healthy controls induced expression of the pro-inflammatory cytokine IL-8 *in vitro, Fn* strains from IBD patients resulted in decreased levels of IL-8 protein outside the host cells, suggesting that these strains may utilize sophisticated tactics to promote their survival. Thus, differences in virulence determinants among strains may be key to understanding a potential role for *Fn* in IBD. Characterization of virulence mechanisms utilized by *Fn* isolates from IBD patients could define a potentially important aspect of microbe/host interactions in this devastating disease, and indicate future therapeutic targets.

Presenter's Name: James Cotton

Program and Year: MD/PhD, Year 4

Category: Basic/Translational Project

A *Giardia* cathepsin B-like cysteine protease cleaves interleukin-8 and attenuates neutrophil chemotaxis

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Introduction. *Giardia duodenalis* (*G. intestinalis, G. lamblia*) is a non-invasive, protozoan parasite of the upper small intestine of many animals including humans. In the majority of *Giardia*-infected individuals, the intestinal mucosa is devoid of signs of overt inflammation and research now suggests that *Giardia*-infected hosts have attenuated inflammatory responses. The *Giardia* genome contains at least 20 cathepsin-like genes, most of which have no known function. We hypothesized that *Giardia* cathepsin-like proteases may be involved in attenuating acute inflammatory responses within the intestinal mucosa of *Giardia*-infected individuals.

Methods. *Ex vivo* human small intestinal mucosal biopsy tissues and *in vitro* colonic monolayers (Caco-2 and HCT-8) were co-incubated with *G. duodenalis* trophozoites (Assemblage A isolates NF, or WB, or Assemblage B isolate GS/M) for 2 hours and subsequently administered pro-inflammatory interleukin (IL)-1β (1.0 ng/mL: 4h), recombinant CXCL8 (rCXCL8) (1.0 ng/ml: 4h), or *Salmonella typhimurium* (MOI 100:1: 5h). Samples were processed for various activity assays, qPCR, Western blotting, and neutrophil (PMN) chemotaxis assays.

Results. Co-incubation of *ex vivo* human small intestinal mucosal biopsy tissues or *in vitro* monolayers with *Giardia* trophozoites resulted in attenuation of IL-1β- and *Salmonella*-induced CXCL8 secretion. *Giardia* trophozoites incubated in the presence or absence of Caco-2 monolayers significantly decreased levels of administered rCXCL8; these supernatants also attenuated PMN chemotaxis. Cysteine protease activity was detected in *Giardia* supernatants incubated in the presence or absence of *in vitro* monolayers and activity based probes of *Giardia* supernatants demonstrated the presence of at least three cysteine proteases. Inhibition of *Giardia* cysteine protease activity using a broad-spectrum cysteine protease inhibitor (E-64d) or a cathepsin-B specific inhibitor (Ca-074Me) prevented *Giardia*-mediated cleavage of CXCL8.

Conclusion. *Giardia* trophozoites secrete a cathepsin B-like cysteine protease that cleaves CXCL8 and attenuates neutrophil chemotaxis. This factor may participate in attenuating acute inflammatory responses in *Giardia*-infected individuals.

Presenter's Name: Jan Rudzinski

Program and Year: MD, Class of 2014

Category: Basic/Translational Project

Bacitracin-induced Platelet Angiostatin K1-3 Generation: Mechanism, Isolation, and Functionality

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Introduction: Angiogenesis is defined as growth of new capillaries from pre-existing blood vessels. Under normal physiological conditions, there is a balance between angiogenesis promoters and inhibitors. In diseases such as cancer, angiogenic switch in favor of angiogenesis promoters occurs, which stimulates tumor growth. Hence, during cancer it would be desirable to increase the level of endogenous angiogenesis inhibitors to counteract the angiogenic switch. The endogenous angiogenesis inhibitor angiostatin, derived from plasminogen and generated by platelets, has been shown to have potent anti-angiogenic activity. Our lab has discovered that bacitracin, a bacteria derived peptide antibiotic with reported protein disulfide isomerase (PDI) inhibitory activity has the ability to enhance platelet generation of angiostatin containing the first three kringle subunits (K1-3). Hence, we hypothesized that blocking platelet PDI activity enhances plasminogen susceptibility to protease-dependent cleavage into angiostatin.

Aim: To study the mechanism and the role of platelets in bacitracin-induced angiostatin K1-3 production.

Methods: Isolated human platelets or platelet membranes were incubated with plasminogen in an aggregometer. Angiostatin generation was detected by western blot. Centrifugal filtration was used to purify angiostatin K1-3. A Matrigel™ angiogenesis assay was used to assess angiostatin K1-3 activity.

Results: Bacitracin-induced rapid angiostatin K1-3 overproduction in the presence of platelets or their membranes. In their absence, bacitracin also caused angiostatin K1-3 production from plasminogen, albeit less rapidly. Unlike bacitracin, a PDI neutralizing antibody failed to induce angiostatin K1-3 generation. Angiostatin K1-3 isolation by centrifugal filtration proved to be a rapid and effective method of angiostatin purification. A single Matrigel™ angiogenesis assay suggested that bacitracin-generated angiostatin K1-3 was functional.

Conclusion: We have shown that bacitracin-induced angiostatin K1-3 generation proceeds through a PDI-independent mechanism. We speculate a bacterial proteolytic contaminate within bacitracin maybe responsible for enhancing platelet angiostatin K1-3 production. Future studies will focus on identifying this angiostatin K1-3 generating contaminate.

Presenter's Name: Jason Bau

Program and Year: MD/PhD, Year 5

Category: Basic/Translational Project

Salicylate inhibits human topoisomerase IIα by a novel Mg^{2+}-dependent mechanism.

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Introduction: Topoisomerase IIα (topo II) is a ubiquitous enzyme that is essential for cell survival through its role in regulating DNA topology, chromatid separation and DNA supercoiling. Topo II is also the intracellular target of a number of common chemotherapeutic agents (topo II poisons), treatment with which results in the accumulation of cytotoxic enzyme-linked DNA double-stranded breaks. In contrast, non-break inducing topo II catalytic inhibitors have also been described and have more limited use in clinical chemotherapy. Recently, we identified salicylate, the primary metabolite of aspirin, as a novel catalytic inhibitor of human topo II, independent of the salicylate-mediated inhibition of cyclooxygenases or NF-κB. We demonstrated that a brief pretreatment of human breast cancer cells with salicylate attenuates the cytotoxicity of the topo II poisons doxorubicin and etoposide.

Methods/Results: We have now extended these findings and identified a mechanism of topo II inhibition that has not previously been described. In contrast to mechanisms described for other catalytic inhibitors of topo II, we determined that salicylate is unable to intercalate DNA, does not prevent DNA binding and does not promote stabilization of topo II-DNA closed clamps. Interestingly, salicylate decreased topo II ATPase activity in a dose-dependent manner, but not to the extent of known competitive inhibitors of ATP binding. Further studies revealed that salicylate-mediated inhibition of topo II occurs through a magnesium (Mg2+)-dependent reaction, possibly through blockage of the catalytic core during the DNA strand passage mechanism.

Conclusions: Here, we describe a novel mechanism of topo II catalytic inhibition has not been previously identified. Salicylate appears to inhibit topo II activity through a (Mg2+)-dependent reaction in which more 'classical' catalytic inhibitors do not follow. This mechanism is reminiscent of that described for catalytic inhibitors of bacterial topoisomerases, but has not previously been described for inhibitors of human topo II.

Presenter's Name: Jennifer Au

Program and Year: MD, Class of 2014

Category: Clinical Project

Time-Driven Activity Based Costing (TD-ABC) analysis of an endoscopic sinus surgery for chronic rhinosinusitis

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Objectives/Introduction: Chronic rhinosinusitis (CRS) is an inflammatory condition of the nose and paranasal sinuses that can significantly reduce quality of life. When there is failure of best medical efforts, endoscopic sinus surgery (ESS) may be indicated to restore physiological sinus ventilation and drainage. As healthcare resources are limited, it is becoming increasingly important to evaluate health economics. Using the Time-Driven Activity Based Costing (TD-ABC) analysis model, the objectives of our study will be to (1) identify the total costs of a functional endoscopic sinus surgery based on data from a Canadian hospital and (2) to demonstrate the utility of TD-ABC to calculate healthcare associated costs.

Methods: Using the TD-ABC cost-analysis model we have gathered the unit cost and time per activity as a patient undergoes ESS at the Rockyview General Hospital, Calgary, Alberta. At each location through ESS (pre-operative holding area, operating room, sterilization room, post-anesthesia recovery unit (PACU), and day surgery ward), we collected the unit costs of staff, equipment, and space for the activities of admission, ESS procedure, instrument sterilization, post-anesthesia care, and day surgery ward care, respectively.

Results: The costs (and time in hours (h)) for using the pre-operative holding area (2 h), PACU (1 h), and day surgery (2 h) for one ESS case were $29.44, $14.72, and $30.01, respectively. Sterilization for ESS equipment sets (0.63 h) costs $139.01 per ESS case. The costs an ESS procedure (3.22 h), includes nurses and doctors' salary, anesthesia, surgical equipment and medications, and operative space to total $3576.46. The grand total cost for an ESS from a patient's day entry until discharge is $3789.63 CDN.

Conclusions: Detailed sensitivity analyses will be performed on this data. We are able to identify that TD-ABC is a feasible model to calculate healthcare expenditures and reveal the economic impact of ESS on the government payer perspective.

Presenter's Name: Jennifer Corrigan

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Motor, Behavioural and Pathological Deficits in a Rat Model of Cerebral Palsy

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Introduction Cerebral Palsy (CP) is a group of permanent disorders of movement and posture. Children with CP commonly exhibit co-morbidities including cognitive and behavioural impairments. Currently, there is no cure for CP, and present therapies are rescue in nature with limited efficacy. Epidemiological data has implicated prenatal ischemia in the development of CP. A reliable and clinically relevant animal model is required to better understand the underlying pathogenesis and test potential therapies.

Objectives 1. To determine if prenatal ischemia induced by bilateral uterine artery ligation results in motor, cognitive and behavioural impairments in the adult rat, consistent with the CP phenotype. 2. To determine if prenatal ischemia results in neuropathology consistent with CP in the adult rat.

Methods The study consisted of 2 groups; SHAM and Bilateral uterine artery ligation (BUAL). On gestational day 20, both uterine arteries were permanently ligated in BUAL dams. Beginning on PD 40, offspring underwent a series of motor, cognitive and behavioural testing including; single pellet, tapered beam, gait analysis, Morris water maze, open field, novel object and elevated plus maze. Subsequently, the rats were euthanized on P80 and brains were fresh frozen. Brains were stained with H+E, MBP, Olig-2, SMI-32 and APP.

Results BUAL rats were born growth restricted, compared to SHAMs. BUALs scored significantly worse on the single pellet evaluation, tapered beam and gait analysis indicating fine motor, hind-limb function and posture deficits, respectively. BUALs performances during novel object and elevated plus maze revealed problems with working memory and anxiety. Preliminary histological data revealed enlarged ventricles, consistent with loss of white matter (periventricular leukomalacia), the anatomical substrate for CP.

Conclusion Current motor, behavioural and neuropathologic data support prenatal ischemia induced by BUAL as a reliable animal model for CP. This model will be useful in the ongoing determination of specific therapeutic interventions.

Presenter's Name: Jodie Roberts

Program and Year: MD/MSc, Year 1

Category: Clinical Project

Neurologists' Knowledge and Attitudes Towards Epilepsy Surgery: A Canadian Survey

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Objectives/Introduction: Despite clinical practice guidelines recommending epilepsy surgery in patients with drug resistant epilepsy, surgery continues to be underutilized. On average, patients wait 10-20 years before undergoing surgery. We aimed to determine: 1) neurologists' knowledge and attitudes towards epilepsy surgery, and 2) perceptions of local barriers to surgical evaluation.

Methods: A brief questionnaire was developed following an extensive literature review. Face validity was achieved through pilot-testing a sample of ten neurologists. All 796 eligible neurologists listed in the Canadian Medical Directory received a mailed paper survey with a postage-paid return envelope. The initial mailing was followed by two additional reminders; the first being an emailed/faxed/telephoned reminder, and the final being a second mailed survey.

Results: A total of 425 neurologists participated in the study, of whom 327 followed epilepsy patients in their practice (response rate 53.4%). Non-responders did not significantly differ from responders according to gender, but were more likely to be based in Saskatchewan or Quebec, prefer communicating in French, and have graduated from medical school prior to 1985. Attitudes towards epilepsy surgery were reasonably positive. Only 18% of neurologists felt that surgery should be considered a last-resort treatment, and 69.3% had made a surgical referral in the past year. Areas for improvement included poor familiarity with epilepsy surgery clinical practice guidelines and the recent definition of drug-resistant epilepsy; 43% incorrectly believed that at least 3 antiepileptic drugs must fail in order for a patient to be considered drug-resistant. The median estimated waiting time for an epilepsy surgical evaluation was nine months; with some participants reporting wait times exceeding two years at their centre of referral.

Conclusions: Familiarity with epilepsy surgery clinical practice guidelines and relevant definitions could be improved. Resource limitations were identified as the largest nationwide barrier to surgical evaluation for epilepsy.

Presenter's Name: Jody Platt

Program and Year: MD, Class of 2014

Category: Clinical Project

What do Mothers think of Communication about their Child with Tracheoesophageal Fistula (TEF)?

I. Mitchell, J. Platt, M. Bailey, C. Bjornson, M. Brindle, M. Soles, L. Fairservice.

Parents of children born with congenital Tracheoesophageal Fistula (TEF) face multiple challenges of surgeries, long hospital stays, and a future of a chronic condition and complications in the first years of life. This challenging time can be highly stressful for the parents of a child with TEF (Spitz, 1993). Children born with TEF require numerous health care services to manage their complicated condition. Previously, it had been documented, that services required by children with TEF were not appropriately coordinated (Bjornson & Mitchell, 2000). The TEF Clinic at the Alberta Children's Hospital (ACH), which started in 2006, aims to coordinate the complex care of these children and their families, in order to provide more effective and quality care (Bjornson & Mitchell, 2006). In order to assess the impact of the clinic on the child's health, it is imperative to gain an understanding of the parents' perception of the care provided by and communications with the health care team. With greater coordination, and access to information, parents will be more able to focus on their ill child (Howells & Lopez, 2008). The purpose of this study is to gain a qualitative understanding of communication perceptions of 3-4 parents of children with TEF. Interviews will be conducted with the main primary caregiver only of that child in order to understand the perceptions of the parent who was most often present for new information and communication regarding the care of their child (Acrockiasamy et al., 2008). A previous study of the care of children with TEF at the ACH identified four key areas of improvement. Qualitative data obtained from these interviews will be analyzed to identify whether the TEF clinic has contributed to improvement in these areas of need and whether there remain areas for improvement.

Presenter's Name: Judy Luu

Program and Year: MD/PhD, Year 3

Category: Clinical Project

A Novel Approach to Detect Coronary Artery Disease using Non-Invasive Cardiovascular Magnetic Resonance Imaging

Judy Luu, MD/PhDc[1], Jacqueline Flewitt, M.Sc.[1], Matthias G. Friedrich, MD[2]

[1]Stephenson CMR Centre at the Libin Cardiovascular Institute of Alberta, [2]CMR Centre at the Montreal Heart Institute, Montreal, Quebec.

Introduction/Objectives: Oxygen-sensitive Cardiovascular Magnetic Resonance (OS-CMR) uses the signal generated by deoxyhemoglobin in the blood to detect ischemia in patients with coronary artery disease (CAD). We hypothesized that this new, non-invasive method would be equivalent to current tests such as coronary angiography, with the advantage of not exposing the patients to *radiation*, *contrast agents*, and *physical exertion*. Our aim was to evaluate the transmural differences in myocardial oxygenation using CMR images of patients with CAD, in comparison to the gold standard of coronary catheterization.

Methods: Symptomatic patients (n=18, mean age 61±10 years) scheduled for coronary angiography and healthy volunteers (n=11, mean age 29±4) were scanned using a clinical 1.5T MRI system. Oxygen-sensitive CMR was performed at rest and during adenosine-induced vasodilation (stress). The % change in signal intensity due to adenosine vasodilation was calculated for the subepicardial and subendocardial regions of the heart muscle. In patients, CMR images were compared to fractional flow reserve (FFR), a procedure performed in the cath lab to determine whether a coronary stenosis is limiting blood flow and oxygen delivery to the heart.

Results: CAD patients had an overall reduced response following adenosine stress across the whole myocardium when compared to healthy subjects. CAD patients had significantly different responses in the subepicardium versus the subendocardium, but there was no detectable transmural gradient on CMR images in the healthy subjects. There was unexpected evidence for subendocardial ischemia in the CAD patients, despite having normal FFR cath measurements.

Conclusion: Oxygen-sensitive CMR can identify reduced myocardial oxygenation present in CAD patients and not present in healthy subjects. Abnormal oxygenation seen in myocardium indicated as normal by angiography of symptomatic patients suggests underlying pathophysiology that warrants further investigations. This technique provides a non-invasive assessment of myocardial ischemia and may prove to be a valuable tool over the currently employed 'gold standard' procedures.

Presenter's Name: Justin Lui

Program and Year: MD, Class of 2014

Category: Basic/Translational Project

Pre-Operative Waste Reduction in Otolaryngology

Lui, J.T., Randall, D.R., Rudmik, L.R.

Objectives/Introduction: To determine what proportion of pre-operative and perioperative waste is recyclable and to project the amount of waste that can be diverted from landfills. Potential barriers to recycling in the OR are explored.

With an estimated 720,000 kg in waste generated by hospitals in Calgary and a continuous reduction in landfill space, hospitals are seeking new ways to reduce waste. With nearly 21% of hospital waste stemming from operating rooms, we have identified the setup of operating rooms as a viable option for waste reduction since pre-operative waste is free from biohazardous contaminants and can be sorted easily. Otolaryngology was selected for its high operating volume and variety.

Methods: Operative staff at the Alberta Children's Hospital (ACH) have separated and weighed recyclable waste from non-recyclable during OR setup in Otolaryngology procedures. Materials were deemed recyclable through verification with manufacturers. Additionally, pre- and post-investigation questionnaires were anonymously completed by operative staff to identify barriers to recycling.

Results: Approximately 96% of pre-operative waste is recyclable, which attributes to an 18% reduction in total waste. With an estimated 2507 procedures in Otolaryngology procedures completed annually at ACH, which projects to nearly 472 kg of landfill diversion.

Conclusions: Pre-operative waste is a viable option to divert from landfills since it is free from biohazardous contaminants and is nearly 96% recyclable. There is overall agreement among operative staff that OR waste needs to be addressed. The top three barriers to OR recycling identified were time, staff attitudes and lack of recycling facilities.

Presenter's Name: Karen Leung

Program and Year: MD/MSc, Year 3

Category: Clinical Project

The effect of using chlorhexidine vaginal and neonatal cleansing on neonatal sepsis and mortality: A systematic review and meta-analysis

Karen Leung, Christine Li, Neil Drummond

University of Calgary, Department of Family Medicine

Introduction: Nearly 3.5 million neonatal deaths occur annually in low and middle-income countries, with infections accounting for an estimated 40 percent of deaths in the first week of life. Although antibiotics significantly reduce neonatal sepsis and mortality, the lack of availability and equitable distribution hinder their widespread use in resource-poor settings. Cleansing the birth canal before delivery and the newborn with chlorhexidine, an affordable wide-spectrum microbicide with an established safety profile, has been proposed as an alternative strategy for reducing adverse neonatal outcomes. Therefore, the objective of this systematic review and meta-analysis was to examine whether chlorhexidine use would reduce neonatal admission to hospitals, sepsis, and mortality in low and middle-income countries.

Methods: Comprehensive database searches of MEDLINE, EMBASE, Ovid HealthStar, Global Health, PUBMED, and CENTRAL were conducted without language restrictions and supplemented with grey literature and manual reviews of bibliographies of retrieved articles. Clinical trials and randomized clinical trials comparing chlorhexidine cleansing to standard care were included.

Results: Nine studies were selected for meta-analysis, including from Africa (4), Asia (4), and South America (1). Findings were heterogeneous across outcomes. Results suggested that chlorhexidine significantly reduced hospital admissions (pooled relative risk [RR]: 0.92, 95% CI: 0.84–0.99, $p < 0.05$), neonatal mortality (RR: 0.83, 95% CI: 0.69–0.99, $p < 0.05$), but not early-onset sepsis (RR: 0.99, 95% CI: 0.84–1.18). However, when the results were stratified according to the use of randomization, these estimates of effects were no longer significant.

Conclusions: Findings suggest that cleansing with chlorhexidine does not significantly reduce adverse neonatal outcomes after accounting for the use of randomization in studies. These effect estimates further need to be interpreted with caution given the presence of heterogeneity, small sample sizes, and evidence of publication bias.

Presenter's Name: Kathleen Moncrieff

Program and Year: MD/PhD (Saint Mary's), Class of 2014

Category: Basic/Translational Project

The Purkinje Effect and Inter-Observer Variability in Visual Brightness Measurements of Red Stars

Kathleen E. Moncrieff (1), David G. Turner (2)

(1) Faculty of Medicine, University of Calgary; (2) Department of Astronomy and Physics, Saint Mary's University

The Purkinje effect is the tendency of the peak light sensitivity of the human retina to shift towards the blue end of the spectrum in low light levels. In ordinary light levels, vision is accomplished primarily by the color-sensitive cone cells in the retina, which have a combined light sensitivity that peaks closer to the red end of the spectrum. When light intensity becomes too low to activate the cones, the rods cells take over, and their light sensitivity peaks closer to the blue end of the spectrum. In observational astronomy, the fact that the rods are responsible for vision in low-light and are relatively insensitive to red light is taken advantage of with the use of red ambient lights in observatories, allowing observers to walk around safely without losing their dark adaptation. However, there is one area of observational astronomy in which the effect causes a problem - visual observations of red variable stars.

Visual brightness measurements of variable stars (stars whose brightness changes for a variety of reasons) are made by comparing the brightness of the variable star to nearby comparison stars of known and constant brightness. But most comparison stars are not red, which can cause the visual brightnesses of red variable stars to be systematically underestimated as they appear fainter than they are when compared to bluer stars. Additionally, in our work on supergiant red variable stars using databases of visual brightness measurements made by different observers, we have at times found significant inter-observer variability. Thus we are attempting to examine and quantify inter-observer variability in visual brightness measurements, investigate its causes, and develop a method to correct for it. Red supergiant variable stars have complex physical processes occurring inside them that cause both periodic changes in brightness as well as non-periodic changes as the stars evolve, and it is imperative to standardize the observations as much as possible so that a variation caused by differences in the retinal anatomy or technique of the observers is not mistaken for a physical process occurring in the stars' atmospheres.

Presenter's Name: Keith Lawson

Program and Year: MD/MSc, Year 4

Category: Basic/Translational Project

Sunitinib augments oncolytic virus mediated anti-tumor immunity in a preclinical renal cell carcinoma murine model

***Keith A. Lawson*[1]*, Zhong Q. Shi*[1]*, Jason Spurrell*[1]*, Wenqian Chen*[1]*, Jun Kawakami*[2]*, Don G. Morris*[1]

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Objective: In the current study, we investigated the ability of the oncolytic virus, reovirus (RV), to prime an adaptive anti-tumor immune responses against renal cell carcinoma (RCC). Moreover, based on clinical trials demonstrating sunitinib's ability to reverse RCC induced immunosuppression, we sought to determine the utility of combining this agent with reovirus for superior anti-tumor protective immunity.

Methods: *In vivo*, 8-9 week old Balb/c mice were inoculated with 2.5 x 10^6 RENCA cells subcutaneously to establish a syngeneic immunocompetent murine model of RCC and treated with RV (i.t), sunitinib (i.p) or a combination of these agents. Mice were followed for tumor size and overall survival. IFN-γ production from isolated anti-tumor CD8+ splenocytes was determined by ELISA assay. Gr-1^+/$CD11b^+$ splenic myeloid derived suppressor cells (MDSC) were quantified by flow cytometry. Adoptive transfer of splenocytes from mice treated with RV, sunitinib or a combination these agents into treatment naive mice followed by RENCA tumor challenge was utilized to assess protective immunity.

Results: Combination RV/sunitinib therapy decreased tumor burden and improved overall survival more significantly than either agent used as a monotherapy [132mm^2 (PBS) vs. 61mm^2 (RV) vs. 82mm^2 (S) vs. 21mm^2 (RV+S); $p < 0.05$]. This was associated with a downregulation of splenic MDSC and enhanced anti-tumor $CD8^+$ splenocyte IFNγ response [$p < 0.02$]. Decreased tumor burden was observed in treatment naive mice receiving splenocytes from RV/sunitinib treated mice versus RV or sunitinib alone following RENCA tumor challenge [80mm^2 (RV) vs. 74mm^2 (S) vs. 35 mm^2 (RV+S); $p < 0.05$].

Conclusions: Here, we demonstrate that reovirus has both direct oncolytic as well as immunotherapeutic activity against RCC. Moreover, we highlight that combination of this agent with sunitinib, a first line mRCC agent, leads to decreased tumor burden, increased overall survival and improved protective immunity.

Presenter's Name: Kevin Solverson

Program and Year: MD/MSc, Year 5

Category: Clinical Project

An assessment of the Calgary Health Region Medical Emergency Team 3 years after implementation

Kevin Solverson, Dr. Chip Doig, Dr. Tom Stelfox

Objective: To evaluate the reason for Medical Team Activation (MET), patient characteristics, the MET processes of care, and the patient outcomes from a regional adult critical care program over 3 years. Methods: A retrospective analysis of prospectively collected data after MET implementation across all 3 adult hospitals in the Calgary Health Region (CHR) was conducted. All adult hospitals in Calgary including a 700-bed academic/trauma center and two community hospitals with over 500 beds were included. All patients seen by the MET team between January 1, 2007 and December 31 2009 and were included in the analysis.

Results: During the study period there were 3494 MET activations. Across all three sites, respiratory (FMC, 63%; PLC, 45%, RGH, 42%) and neurological problems (FMC, 53%; PLC, 46%, RGH, 52%) were the most common reasons for MET activation. 72% to 75% of MET activations occurred during the week and 54% to 61% of the calls occurred between 1700 and 0800hr across the hospital sites. The most common interventions were oxygen, fluid bolus initiation and peripheral intravenous line initiation. Common aggressive interventions included endotracheal intubation, vasoactive medication infusion started and central venous lines. The rate of intensive care unit (ICU) admission within 2 hours of MET activation was 22% at both FMC and PLC and 12% at RGH. In hospital mortality was the highest at FMC (36%) followed closely by RGH (33%) and PLC (30%).

Conclusions: The data collected by the MET program in the CHR has shown the system is identifying patients who are critically ill, have high rates of ICU admission and high in-hospital mortality. Advanced lifesaving interventions are being given during the MET activations, justifying physicians being apart of the MET system. The high rate of calls and ICU admissions demonstrates METs are meeting a demand in the CHR.

Presenter's Name: Kimberly Williams & Lynn Peterson

Program and Year: MD, Class of 2014

Category: Basic/Translational Project

12 Stories. Narratives from New Canadians.

Williams, K.[1, 7], Peterson, L.[1], Wadhwani, A.[1], Lim, R.[1], Houwing, M.[1], Marani, F.[1], Tsang, L.[1], Chopra, D.[2], Li, K.[3], Sediqzadah, S.[3], Wang, C.[4], Delorme, T.[5] and Stokes, W.[6]

1. University of Calgary, 2. Queens University, 3.University of Toronto, 4. University of Alberta, 5. University of Northern Ontario, 6. Memorial University and 7. The Canadian Federation of Medical Students

Introduction: It is widely recognized that immigrants and refugees are among the most marginalized members of Canadian society and carry additional burdens as a result of their past and ongoing life experiences. Their health issues may be more complex for a variety of reasons, including longstanding prior lack of access to health care, physical and mental effects of war, displacement or torture, neglected chronic infections and disease, and adjustment issues. Immigrants and refugees require assistance beyond the initial resettlement period, as the challenges of adjusting to a new place can persist for many years. The Canadian Federation of Medical Students (CFMS) used qualitative research to create a tool and advocate for change.

Methods: Twelve interviews with refuges and immigrants to Canada were collected by medicals students. Interviewees were chosen using the purposeful sampling. Data was analyzed using thematic analysis by the primary investigators. Any discrepancies in findings were discussed with a third person. The main themes were then provided to the interviewers for feedback. Their feedback was then incorporated into the main findings.

Results: The main themes were: a lack of public understanding about immigrants and refugees and why they are integral to Canada's social and economic well-being, a lack of access to health care, such as language services, and a disconnect between the presence of services and the awareness of their existence by the people that need them. There is a deficiency of culturally safe care and an absence of research regarding the provision of appropriate health programs for this population.

Conclusions: Changes are needed to ensure optimal health for all Canadians. Analyzed interviews from new Canadians can act as a guide to making health system improvements and an effective advocacy tool for medical students.

Presenter's Name: Kristine Woodward

Program and Year: MD/MSc, Year 2

Category: Clinical Project

Motor reorganization in frontal lobe epilepsy

Woodward KE[2,3], Gaxiola I[2,3], Mainprize D[3], Grossi M[3], Goodyear BG[2,3], Federico P[1,3].

1. Clinical Neurosciences, University of Calgary, Calgary AB; 2. Hotchkiss Brain Institute, Calgary AB; 3. Seaman Family MR Center, Calgary AB

Introduction: Cortical reorganization has been demonstrated in temporal lobe epilepsy patients, but little research has investigated reorganization in frontal lobe epilepsy (FLE) patients. FLE may cause subtle changes in motor cortex organization, which could explain functional motor deficits experienced by these patients during day-to-day activities. Therefore, cortical motor organization in FLE patients was studied using functional magnetic resonance imaging (fMRI).

Method: Ten right FLE and ten control subjects were studied. fMRI was performed at 3T. Participants underwent two motor tasks; first, a finger-tapping task and second, a series of coordinated hand movements (hand held vertical, hand held horizontal, fist). Both were executed unimanually and bimanually while following visual stimuli. fMRI data was analyzed using standard methods, and first level analysis was entered into separate group analyses with group (right FLE, control) and task (right/left unimanual, bimanual) entered as variables. Maps were generated to determine brain regions exhibiting a significant difference in response magnitude between groups and tasks ($Z>2.3$, corrected cluster significance $p=0.05$).

Results: During the bimanual and left-handed tasks, patients had significantly decreased activation in the hemisphere ipsilateral to the seizure focus while finger-tapping, yet had significantly increased activation in the hemisphere contralateral to the seizure focus while performing the coordination task. No significant difference was found between patients and controls during the right-handed tasks.

Conclusions: These results demonstrate that motor cortical reorganization occurs due to FLE. The possibility that seizures induce brain reorganization has important implications for epilepsy surgery, and supports the notion that a combination of methods, including fMRI, should be used when brain mapping is required.

Presenter's Name: Lorie Kwong

Program and Year: MD/MSc, Class of 2014

Category: Basic/Translational Project

miR-125b: A Potential OncomiR in Cutaneous Squamous Cell Carcinomas

Lorie M. Kwong, Jennifer M. Tran, Habib Kurwa, P. Régine Mydlarski

Division of Dermatology, Department of Medicine, University of Calgary, Calgary, AB

Introduction: Non-melanoma skin cancer (NMSC) is the most common form of cancer worldwide. While ultraviolet radiation is the primary risk factor for developing NMSC, much remains unknown about the process of skin carcinogenesis. miRNAs are small, non-coding RNAs that regulate gene expression. Certain miRNAs function as oncogenes or tumour suppressors, yet their roles in the promotion and progression of cancer are not clearly established. Herein, we investigate the role of miRNAs in cutaneous squamous cell carcinomas (SCC).

Methods: To compare the miRNA profile of normal human keratinocytes (NHK) and cutaneous SCC cells, total miRNA was extracted from commercially available cell lines. Using µParaflo® Microfluidic Biochip technology and probe content based on the Sanger miRBase Version 12.0, a genome-wide miRNA microarray analysis was performed.

To examine the expression of miR-125b in SCC tumours, miRNA was isolated from patient-matched normal and SCC tissue pairs (n = 4) and miR-125b expression was quantified through qRT-PCR techniques.

miR-125b was exogenously upregulated in SCC cells using synthetic miRNA mimics. The effects of miR-125b deregulation on cellular proliferation, differentiation, apoptosis and invasion were examined.

Results: Of 856 miRNAs studied, 27 miRNAs displayed high signal intensities and were significantly up- or down-regulated in the SCC cell lines. While the majority of miRNAs in the genome remain uncharacterized, miR-125b, a highly down-regulated miRNA in SCC cells, has been implicated in the carcinogenesis of numerous cancers. miRNA analysis of matched normal skin and SCC tissues confirmed miR-125b suppression in all SCC tumours.

In vitro studies indicate miR-125b does not regulate cellular proliferation or apoptosis in SCCs. However, exogenous de-regulation of miR-125b in SCCs induces a loss of cellular differentiation that results in a more invasive phenotype.

Conclusions: The identification of unique miRNA profiles within NHKs and SCCs allows our dataset to serve as a roadmap for future studies of the microRNAome. By characterizing the role of miR-125b in SCCs, molecular insight will be gained into the process of skin cancer development.

Presenter's Name: Lorraine Lau

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

Chondroitin Sulfate Proteoglycans: Novel Inhibitors of Remyelination

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Objective: Multiple Sclerosis (MS) is a chronic demyelinating condition of the central nervous system (CNS). Remyelination, a critical repair process, occurs spontaneously in many MS patients. However, it is often incomplete and insufficient to restore function. This failure may be attributed to the presence of a glial scar. Components of the glial scar, including chondroitin sulfate proteoglycans (CSPGs), are deposited in MS lesions, but little is known about their role in remyelination. Hence, we examined the novel hypothesis that CSPGs impair remyelination in a mouse model of demyelination, and that targeting CSPGs may be therapeutic in promoting repair in MS.

Methods: A lysolecithin-induced demyelinating/remyelinating mouse model was used to characterize deposition and clearance of CSPGs in the lesion microenvironment. Expression of CSPG was investigated at the DNA and protein levels. Subsequently, we investigated the impact of CSPG substrate on isolated mouse and human oligodendrocytes. Lastly, we sought to disrupt CSPG biosynthesis or increase its proteolysis in an attempt to promote growth and repair in our *in vitro* and *in vivo* models, respectively.

Results: In our mouse model, the expression of CSPGs was increased during demyelination and decreased during remyelination. When exposed to CSPG substrates in culture, both mouse and human oligodendrocytes were significantly impaired. Specifically CSPGs inhibited the adhesion and the morphological differentiation of oligodendrocyte precursors. Furthermore, oligodendrocytes and their processes were selectively repelled by the CSPG stripes compared with control protein stripes. This effect was overcome by the addition of two proteases used to degrade CSPG. Lastly, when xyloside, a glycoside that targets the biosynthesis of CSPGs, was administered following a demyelinating injury in mice, remyelination was promoted.

Conclusion – Altogether, our results identify CSPGs as novel impediments to oligodendrocytes and suggest that future remyelinating therapies may seek to degrade CSPGs enzymatically or to target downstream signaling mechanisms.

Presenter's Name: Marcia Abbott

Program and Year: MD, Class of 2014

Category: Clinical Project

Family Medicine Curriculum: Introduction to laboratory test ordering, interpretation and resource utilization.

Marcia Abbott[1], Heidi Paulin[2], Davinder Sidhu[1], Christopher Naugler[1,3]
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Objectives/Introduction: Laboratory utilization has increased and a significant proportion of tests ordered are unnecessary. As most investigations begin with the primary care family physician, it is pertinent that physicians understand judicious usage of limited resources. In a search of all the Canadian Family Physician residency programs, none list mandatory laboratory training as part of their curriculums, nor list it as an optional elective. To fill this gap, a collaborative educational program at the University of Calgary was designed to introduce family medicine residents to the basics of the laboratory test ordering and interpretation.

Methods: The program was run as a series of identical four-hour small group sessions to facilitate discussion and laboratory tours. The curriculum centered around seven key topics: test utilization, errors, results, and costs and requisition completeness, quality assurance, local laboratory processes and quality assurance. Residents were taken to a specimen collection site for a tour and two hours of didactic sessions, ending with a tour of a diagnostic services facility. In addition, residents completed an anonymous survey before and after the session that asked them to self-assess their knowledge of the curriculum topics.

Results: This novel approach teaches residents how to be efficient in test ordering and encourages responisible medical resource stewardship amongst primary care physicians. The use of a small group format allowed for more tailored teaching based on concurrent feedback and questions with additional take-home resources. Pre and post survey results of 68/69 residents shows statistically significant ($P<0.001$) self-identified changes in levels of knowledge of laboratory utilization, sources of error and quality assurance programs.

Conclusions: The first cohort of PGY1 family residents completed this program in July 2012. Overall the program was very well received, with significant increases in the residents' knowledge self-assessment across all subject areas covered in the curriculum.

Presenter's Name: Marvin Braun

Program and Year: MD, Class of 2014

Category: Basic/Translational Project

Life without oxygen: neuronal survival strategies from the snail, Helix aspersa

Marvin H Braun and Christof Schwiening

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Introduction: Most neuronal tissue is exquisitely sensitive to a drop in oxygen levels (hypoxia) and will rapidly begin an irreversible calcium-mediated apoptotic cascade during hypoxia. However, there are animals which have evolved defenses not only to hypoxia but to anoxia (complete absence of oxygen). An example is the land snail, *Helix aspersa*, which is capable of surviving days to weeks in anoxia. Most of the mechanisms used by animals to survive anoxia revolve around decreasing the basal rate of energy consumption. This strategy prolongs their survival on the limited ATP amounts that can be produced via glycolysis. In neurons, this involves slowing the rate of ion pumping by (1.) spike arrest, whereby the rate of action potential firing decreases and (2.) channel arrest, where the movement of ions across the neuronal membrane is slowed.

Methods: Standard electrophysiological techniques of current and voltage-clamping were employed on both whole brains and individual neurons isolated from *Helix aspersa*.

Results and Conclusion: During anoxia, *Helix* neurons undergo spike arrest, as the rate of intrinsic action potential firing falls. However, the degree of this response is affected by the makeup of the saline solution bathing the neurons. If the saline does not contain any carbohydrate, the fall in action potential firing occurred earlier and is more severe, implying that the response is mediated via the snail's ability to maintain glycolysis. Simultaneous with the spike arrest, voltage clamped neurons showed that membrane impedance (resistance) increased during anoxia. This increase in the impedance implies that the neurons are decreasing the flux across the membranes, evidence of channel arrest. However, measurements of intracellular calcium transients indicate that, despite their energy-limited state, anoxic neurons actually increase the rate of calcium pumping, an indication of the importance of maintaining calcium homeostasis.

Presenter's Name: Megan Blades

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Developing and characterizing three-colour fluorescence cross-correlation spectroscopy

Megan Blades[a], Ekaterina Grekova[a], Holly Wobma[ab], Dylan McGuire[c], Kun Chen[d], Warren Chan[d], David Cramb[a]

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As the field of proteomics expands, so must the techniques used to study the biomolecular reactions involved in physiological activity. Currently, binding events at the picomolar (10^{-12}) level can be monitored with dual-colour fluorescence cross-correlation spectroscopy (FCCS). FCCS temporally correlates fluctuations in fluorescence intensities resulting from the diffusion of two molecules with spectrally distinct fluorescent labels through a small interrogation volume. Species that are physically bound to one another produce a cross-correlation, which provides information about the association. However, many biological reactions and pathways are complex, involving more than two interacting species. In this study, a novel FCCS technique was developed to track fluctuations in fluorescence intensities of three spectrally distinct fluorophores. A triple cross-correlation can be calculated if all three species are physically linked. Currently, three-colour quantum dot barcoded nanobeads, as well as oligonucleotide-linked quantum dots, are being used to develop and optimize the technique. This study is the first example of direct three- colour FCCS.

Presenter's Name: Mehrnoosh Aghaei

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Discordant effects of a vascular disrupting agent on MDA-MB-231 breast cancer cell line-induced osteolytic metastases versus subcutaneous tumors.

Mehrnoosh Aghaei, Frank Jirik.

Department of Biochemistry and Molecular Biology, and The McCaig Institute for Bone and Joint Health.

Objectives/Introduction: The ability to recruit and expand new blood vessels is an essential component of tumour growth. Hence, the main goal of this study was to determine whether it was possible to prevent the growth of bone metastases and subcutaneous tumors induced by the MDA-MB-231 breast cancer cell line using the vascular disrupting agent (VDA), DMXAA. DMXAA, an agent of the flavonoid class, has been shown to disrupt the tumor vasculature in a number of tumor models (mainly subcutaneous) by selectively inducing apoptosis of intra-tumoral vascular endothelial cells. We investigated whether MDA-MB-231 subcutaneous and metastatic tumors would be affected by DMXAA treatment.

Methods: Bone metastases were generated via intracardiac injection of the MDA-MB-231-EGFP-Luc2 human breast cancer line into 5 wk-old NIH-III athymic (nude/beige) mice. Subcutaneous tumors were generated via the injection of MDA-MB-231-EGFP-Luc2 cell into the flanks of 5 wk-old NIH-III mice. After tumors had developed, mice were treated with 25 mg/kg DMXAA (as a single dose given on day 21) to study the effects of this agent on tumour growth and vasculature. Bioluminescence imaging (BLI) following luciferin administration was then carried out to monitor the effects of the drug on bone metastases and subcutaneous tumors. Tissues were also examined histologically to determine the effects of DMXAA on tumor vasculature, apoptosis, and proliferation.

Results and Conclusions: While DMXAA, either alone or in combination with the phosphatidylinositol 3-kinase inhibitor, GDC-0941, failed to have a significant effect on bioluminescence of established metastases, bioluminescence from subcutaneous tumours was severely attenuated. We hypothesize that the more slowly developing and less necrotic bone metastases may be resistant to DMXAA owing to a greater degree of vessel stabilization. Our studies provide a possible explanation for the failure of DMXAA in human clinical trials.

Presenter's Name: Michael Chiu

Program and Year: MD/MSc, Class of 2013

Category: Basic/Translational Project

Novel Antimicrobial Mammalian Histone Peptide Interaction with Biomimetic Membrane and Monolayer Systems

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Histones have been implicated in the immune system conferring antimicrobial activity. In prior studies, novel mammalian histone derived antimicrobial peptides (AMPs) H2A1 and H3 were designed and showed high affinity and specificity to bacterial model membranes.

Differential scanning calorimetry (DSC) was employed to study the thermodynamic change of the membrane in the presence of an AMP through analysis of melting temperature (T_m), width ($T_{1/2}$) and enthalpy of the transition. Surface pressure vs time isotherms and Brewster Angle Microscopy were utilized to further characterize and visualize potential AMP-lipid interactions. Biomimetic membranes were composed of Phosphatidylcholine and cholesterol for mammalian systems and phosphatidylglycerol and phosphatidylethanolamine for bacterial.

DSC studies indicated peptides H2A1 and H3 had minimal interactions with mammalian model membranes. However with bacterial model membranes the peptides showed a marked perturbance to the lipid phase transition. Both peptides induced a decrease in the T_m and enthalpy of the phase transition as well as an increase in the $T_{1/2}$ indicating an interaction within the bilayer preventing the lipids from undergoing their normal transition. Furthermore in the mixed lipid systems the peptides preferentially interact with the anionic phosphatidylglycerol over the zwitterionic lipids indicating the role of charge in the interaction. Surface pressure monolayer studies showed an increase in surface pressure with peptides and bacterial lipid systems suggesting the peptide is inserting into the membrane. Imaging of the monolayers demonstrated a change in the lipid domains seen in bacterial model membranes, showing insertion and interaction with the lipid domains as the primary form of interaction.

These studies showed that H2A1 and H3 had a preferential interaction with the anionic lipids in the domain. This helps to further elucidate the interactions of these histone derived AMPs with the bacterial model membranes allowing for future improvements in design and therapeutics.

Presenter's Name: Michael Peplowski

Program and Year: MD/PhD, Year 6

Category: Basic/Translational Project

Mechanisms Involved in the Downregulation of Aquaporin 3 mRNA Expression by Tumour Necrosis Factor α and Interferon γ.

Michael A. Peplowski, Andrew J. Vegso & Wallace K. MacNaughton

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Introduction: Inflammatory bowel diseases (IBD) are characterized by altered water transport leading to the development of diarrhea. However, the status of Aquaporin (AQP) 3 expression, localization and its role in the barrier dysfunction that characterizes IBD remains unknown. *We hypothesized that AQP3 expression and localization were altered in IBD.*

Methods: C57Bl/6 mice were treated with 2.5% dextran sodium sulfate (DSS) in drinking water for up to 7 days to induce colonic inflammation. AQP3 expression was assessed using real-time RT-PCR and localization was assessed by immunofluorescence of colonic tissue. Furthermore, AQP3 expression was assessed in serum-starved HT29 colorectal adenocarcinoma cells exposed to human recombinant tumour necrosis factor (TNF) α and/or interferon (IFN) γ. Inhibitors of signaling pathways activated by TNFα and IFNγ were used in an attempt to reverse the downregulation of AQP3 mRNA expression.

Results: AQP3 mRNA expression in mucosal scrapings was unaltered at both 3 and 7 days following the start of treatment. However, immunofluorescence studies revealed overall downregulated expression of AQP3 in 3 day DSS-treated tissues, with diminished basolateral staining in cells lining colonic crypts. Time-course experiments in HT29 cells with a single treatment of TNFα (25ng/mL) or IFN γ (500U/mL) resulted in significantly reduced expression of AQP3 mRNA at 6 to 12 hr post-treatment. AQP3 mRNA downregulation induced by TNFα at the 12 hr timepoint could be reversed by an inhibitor of the nuclear factor κB signaling pathway (BAY11-7082, 30μM), but not by inhibitors of the ERK/MAPK and p38 MAPK signaling pathways (U0126, 10μM and SB203580, 10μM respectively). Furthermore, AQP3 mRNA downregulation induced by IFNγ at the 12 hr timepoint could be reversed by a broad-spectrum JAK inhibitor (JAK Inhibitor I, 10μM), but not by a JAK2 specific inhibitor (JAK2 Inhibitor II, 10μM).

Conclusions: Our data suggest that changes in AQP3 expression and localization represent early events that occur in colonic inflammation and that TNFα and IFNγ appear to be involved in the downregulation of AQP3 mRNA expression *in vitro*.

Presenter's Name: Minaa Amin

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

Upregulation of Epithelial Stromal Interation1 (EPSTI1) in Human Bronchial Epithelial Cells following Human Rhinovirus Infection

Minaa A. Amin, Cora Kooi, David Proud, Richard Leigh

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Objectives/Introduction: The majority of asthma exacerbations are induced by Human Rhinovirus (HRV) infections. Furthermore, HRV infections have been postulated to play a role in airway remodeling. We performed a microarray analysis of remodeling genes expressed in the airway epithelium following HRV infection and found that Epithelial Stromal Interation 1 (EPSTI1) mRNA was significantly upregulated following HRV infection of human bronchial epithelial (HBE) cells *in vitro*. Limited research on EPSTI1 indicates that it is an interferon (IFN) response gene, proposed to play a role in epithelial-mesenchymal transition (EMT) and tumor progression in breast carcinoma cells. We therefore sought to further characterize EPSTI1 expression following HRV infections of HBE cells and identify a potential function of EPSTI1 in the pathogenesis of airway remodeling.

Methods: Primary HBE cells or the BEAS-2B HBE cell line were cultured in growth medium until confluent, pre-treated with hydrocortisone-free medium and were subsequently stimulated with either medium control, purified HRV-16 (MOI: 0.3-1), or various stimuli. Cellular RNA was collected for mRNA analysis via real time RT-PCR and whole cell lysates were used for protein analysis via western blot.

Results: HRV-16 infection of HBE cells *in vitro* resulted in a time-dependent induction of EPSTI1 mRNA and protein with a peak mRNA expression observed at 36 hours post-infection and maximal protein expression observed at 48 hours post-infection. IFN β, α and λ stimulation of BEAS-2B cells results in a dose-dependent EPSTI1 protein expression, with a peak protein induction observed at an IFN concentration of 3ng/mL. Furthermore, IFN β (3ng/mL) results in a time-dependent induction of EPSTI, with a higher induction observed at 16h post-stimulation and a subsequent decrease in expression over time.

Conclusions: We provide the first demonstration that EPSTI1 is upregulated following HRV infection of HBE cells and speculate that EPSTI1 may play a role in HRV-induced airway remodeling.

Presenter's Name: Natalie Chan

Program and Year: MD, Class of 2015

Category: Clinical Project

HIV SCREENING IN DENTAL CLINICS – Pilot Project

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Does HIV Look Like Me? International Society

Vancouver Coastal Health

According to the Public Health Agency of Canada up to 26% of Canadians do not know they are infected with HIV. Timely diagnosis improves access to HIV treatment and lowers mortality and in turn, timely treatment of HIV-positive individuals improves their outcomes and has potential to prevent further transmission of the virus. However, given that many individuals do not have a family doctor, or do not see a physician regularly, dental practices present an opportunity to increase access to routine rapid HIV screening. Similarly, approximately 64 percent of Canadians aged 12 and over visited a dental office in 2005. This pilot project aimed to introduce routine provider-initiated screening for HIV infection as one of the potential elements in the well-known and standardized intra-oral and dental examination along with x-rays, charting for caries and periodontal disease, and head and neck exams. Using rapid HIV screening technology, the project aimed to expand HIV screening into dental clinics, decrease stigma in the dental community and increase accessibility and frequency of individuals being tested.

STOP HIV/AIDS, or "Seek and Treat for Optimal Prevention of HIV/AIDS" is a pilot project designed to increase and routinize HIV testing and expand access to HIV/AIDS medications, among hard-to-reach and vulnerable populations in Vancouver's Downtown East Side and Prince George, British Columbia. The HIV Screening in Dental Clinics Project is funded by Vancouver Coastal Health, under the "seek" arm of the STOP HIV/AIDS Project, and was conceptualized and managed by Does HIV Look Like Me? International.

Presenter's Name: Natasha Wright

Program and Year: MD, Class of 2013

Category: Clinical Project

Cognitive Impairment Screening in the Emergency Department

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Introduction: Unrecognized cognitive impairment in the Emergency Department (ED), namely in the form of delirium, is an area of "medical errors, missed diagnoses and a quality of care concern". It leads to poor patient outcomes, increased mortality and higher incidence of ED re-visits resulting in hospitalizations. This problem also directly effects an emergency physicians' ability to provide appropriate care, for elderly patients, as unrecognized cognitive impairment compromises patient safety through undiagnosed pathology, increased risk of falls, adverse drug reactions and inappropriate discharge from an often busy ED environment.

Recent literature has highlighted the need to improve the detection rate of delirium and other cognitive impairment syndromes in the emergency department. Studies have shown that the sensitivity of an emergency physicians' clinical assessment, to detect delirium or cognitive impairment, ranges only from 17-35%. Inadequate recognition of delirium and cognitive dysfunction can lead to suboptimal recognition of etiology, inappropriate management, and failed opportunities to intervene in patients at risk. The goal of this literature review was to identify which clinical screening tool provides the more accurate and efficient detection of cognitive impairment in the ED.

Methods: Systematic searches of Ovid Medline, EMBASE, PsycINFO, CINAHL and EBM Reviews were performed. Pubmed was hand searched and several articles were identified from scanning the references of relevant papers. Only English articles were included. Two individuals, to ensure no relevant studies were omitted, performed the search strategy independently.

Results: 685 Articles were identified from all databases, 7 of which were relevant for inclusion. Results were summarized in table format.

Conclusion: Review of literature revealed that it is reasonable to use tools such as the SBT, O3DY or the SIS to screen for cognitive impairment in the ED. These screening tools were able to display moderate sensitivity and specificity. They are also are brief, simple assessment tools suitable for any healthcare provider to administer in a fast paced environment. The CAM is the only ED-validated screening tool that detects and distinguishes delirium from other forms of cognitive impairment.

Presenter's Name: Neha Sarna

Program and Year: MD/MSc, Class of 2014

Category: Clinical Project

Hypertensive disorders in pregnancy and future risk of stroke

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Introduction: Stroke is the 4th leading cause of death in Canada, and is a major contributor to disability. Many risk factors are targeted in primary prevention, however hypertension in pregnancy, and its effect on future stroke risk has yet to be elucidated.

Currently women are monitored throughout pregnancy for changes in blood pressure, however no specific recommendations have been made regarding stroke related screening and primary prevention postpartum.

In order to address this gap, we are conducting a systematic review in order to assess whether or not there exists a relationship between hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, HELLP syndrome and eclampsia) and stroke.

Methods: A Medline search was conducted using the terms: hypertension, pregnancy-induced; pre-eclampsia; eclampsia; and HELLP with the modifier OR. Second, a search was conducted using the MeSH terms Stroke; stroke, lacunar. Both searches were auto-exploded to include all subheadings and were subsequently combined using the modifier AND.

Results: The search strategy generated 113 studies in total. Preliminary data analysis from cohort and case-control studies alone–which include three cohort studies and one case-control study–demonstrates an increased risk of stroke postpartum in women with gestational hypertension, with an even greater risk in pre-eclampsia and eclampsia. We are now analyzing the remaining papers for additional valid insights into this question.

Conclusions: Currently, little is known about the effect of hypertensive disorders in pregnancy on long-term health outcomes. This review will provide insight into the relationship between these disorders and future risk of stroke. We hope to conduct a more rigorous review of the literature before making definitive conclusions, however a strong relationship between these variables may provide a case for screening these patients and may change the standard of care.

Presenter's Name: Nick Bosma

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Targeting the PI3K and Ras Signal Transduction Pathways in a Murine Model of Osteolytic Breast Cancer Metastasis

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Introduction: Bone is considered the most common site of metastatic colonization in patients with advanced breast cancer. Osteolytic metastasis results primarily from the unchecked activity of bone resorbing osteoclasts. PI3K mutations, loss of the PTEN tumor suppressor, and increased Ras-MAPK pathway activity are frequently seen in high-grade metastatic breast cancers, making these attractive targets for therapeutic intervention. Furthermore, mounting evidence suggests the presence of sophisticated mechanisms for the perpetuation of cancer cell growth and survival, with signal crosstalk between the PI3K and Ras pathways being a prime example of this. Therefore dual pathway inhibition may be an ideal way to target bone-colonized breast cancer cells.

Methods: We employed the PI3K and MEK inhibitors, PX866 and AZD6244, respectively, in order to target bone metastases resulting from intracardiac injection of MDA-MB-231-Luc2 human breast cancer cells. Development and progression of bone metastases *in vivo* was assessed by bioluminescence imaging, and bone integrity was evaluated by μCT (micro-computed tomography).

Results: PI3K inhibition did not have an effect on the growth kinetics of bone metastases, but demonstrated a significant attenuation of bone osteolysis, whereas MEK inhibition resulted in a significant reduction in tumor growth, as well as tumor-induced osteolysis. Simultaneous inhibition of PI3K and MEK resulted in a reduction of tumor bioluminescence, similar to MEK inhibition alone, but interestingly demonstrated an exacerbation of bone damage.

Conclusion: Our findings suggest (a) that MEK inhibition alone may be a valuable treatment for osteolytic metastasis, and (b) that combined PI3K and MEK inhibition has the potential to actually enhance bone destruction and thus should be avoided.

Presenter's Name: Payam Pournazari

Program and Year: MD, Class of 2014

Category: Basic/Translational Project

B-Lymphoblastic Leukemia/ Lymphoma (B-ALL) With Favorable Cytogenetics: *Expression of PAX5 Defines a Subgroup With Poor overall survival.*

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Background: Recurrent genetic abnormalities define risk stratification among B-ALL (WHO- 2008). t(9;22), Hypodipolidy and MLL gene rearrangements are considered poor prognostic while, normal karyotype, hyperdiploidy and t(12;21) are believed to have favorable prognosis. Gene expression profile data has recently identified various genes to be associated with pathogenesis and prognosis, especially among patients with normal cytogenetics. PAX5 is a key player in B-cell differentiation and development. We have studies the expression of PAX5 protein by IHC in a homogenous population of B-ALL patients (pts) and correlated its expression with cytogenetic and clinical outcome data.

Design: Pts were diagnosed according to WHO 2008 criteria. Diagnostic BM biopsy samples (FFPE) were used (triplicate, 0.6 mm) to create TMAs. Standardized IHC staining protocol, utilizing automatic immunostainer (Ventana, Tucson, AZ) was used for PAX5 staining (1:10; clone G148-74, Pharmingen, San Diego, CA). Staining intensity was scored on 4-tier system without the knowledge of the clinical outcome. All pts received standardized chemotherapy +/- BMT. SPSS software was utilized for overall survival (OS) (Kaplan-Meier) and correlation (two tail fisher exact t test).

Results: 130 pts (1-82 yrs; median 11 yrs; mean 23.7 yrs; M:F 1.1:1) were included. Differential expression of PAX5; 0 (20/15%); 1(15/11%); 2(24/19%); 3 (40/ 31%); 4(31/24%) was noted. Strong correlation was noted between PAX5 expression and age <15 ($p<0.004$; r 0.318) compared to adult ALL (age >30 yrs; $p< 0.089$). Poor prognosis cytogenetic was noted among 58 (45%) while favorable cytogenetics was noted among 72 (55%) pts. Higher expression of PAX5 (3) correlated with shorter OS ($p=0.002$) (at 60 m f/u) among good prognostic group, vs. poor prognosis group ($p = 0.987$).

Conclusion: Our results show that there is a differential pattern of PAX5 protein expression in B-ALL. PAX5 protein positivity is mostly seen in pediatric age group. PAX5 is associated with shorter OS among patients with cytogenetic abnormalities associated with favorable prognostic.

Presenter's Name: Phillip Tran

Program and Year: MD, Class of 2014

Category: Clinical Project

Asymptomatic Scapholunate Tears in Wrist MRIs

P. TRAN, V. BOWEN (MB ChB, MD, FRCSC), G. DHALIWAL (MD, FRCSC)

Introduction: Asymptomatic lesions are commonly found when patients are investigated for musculoskeletal conditions. These incidental lesions have become particularly prevalent with the increasing use of magnetic resonance imaging (MRI) to investigate patients with wrist pain. MRI has high sensitivity and specificity for showing structural abnormalities, but is poor at differentiating relevant pathology. The purpose of this paper was (A) to review the literature on scapholunate tears, (B) to describe the different techniques used to evaluate scapholunate tears, and (C) to review methods for differentiating between a clinically relevant scapholunate tear and one that is an asymptomatic incidental finding.

Methods: The electronic databases Pubmed, Medline/Embase, and Web of Science were searched using a constellation of terms focused around 'scapholunate', 'asymptomatic', 'instability', 'ligament tear', and 'MRI'. The cited references from collected papers were then reviewed.

Results: The combination of search terms and abstract review yielded 35 papers, and the review of cited references yielded an additional 15 papers. Many papers were from a technical radiological perspective. Eight papers concluded that asymptomatic scapholunate ligament tears occur. One emphasized that complete intrinsic tears alone may not produce instability. Seven papers used comparison techniques to determine if tears were significant: comparisons to the other side, another imaging technique, or clinical evaluation. Two cadaveric studies did not reveal a method of distinguishing clinically relevant and asymptomatic tears, but suggested that a clinical correlation was important.

Conclusions: The increasing use of MRI in the diagnosis of patients with wrist pain has demonstrated that scapholunate ligament tears are common in patients who clearly have other causes for their symptoms. MRIs are highly sensitive and specific for distinguishing anatomical normality and abnormality but, due to the high number of asymptomatic 'wear and tear' abnormalities, the literature indicates that careful clinical evaluation and good judgment are essential when interpreting results.

Presenter's Name: Puneet Kapur

Program and Year: MD/MSc, Class of 2013

Category: Clinical Project

Comparison of hospitalization rates for Emergency Department Patients with Atrial Fibrillation in Canada and the United States

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Introduction: Atrial fibrillation is a common presenting complaint for emergency department (ED) patients in Canada and the United States (US). Despite recently published national guidelines, research shows that there remains considerable variation among various Canadian academic EDs in deciding how to manage patients with atrial fibrillation (rhythm or rate control / admit or discharge). However the larger question of Canada - US differences in atrial fibrillation treatment has not been fully examined. The choice of treatment strategy and in particular the decision to admit patients with atrial fibrillation to hospital versus outpatient treatment is of considerable interest since hospital admission accounts for 44-70% of the cost of treating this disease.

Methods: The design of this study is a retrospective cohort of ED visits extracted from nationwide information on ED visits in both the United States and Canada. Our population of interest is atrial fibrillation patients seen by ED physicians in the years 2006-2009 but our initial investigation will be limited to patients seen in 2008. The American data sources were the H-CUP family of databases. Canadian admission data was obtained from the Canadian Institutes for Health Research.

Results: Anticipated results are that there is a statistically significant difference in national rates of hospital admission for atrial fibrillation between the USA and Canada in favor of more American admissions and fewer Canadian admissions.

Conclusions: Our anticipated conclusion is that Americans admit a higher proportion of atrial fibrillation patients despite minimal differences in the respective patient populations. While we currently lack definitive date on the long term outcome of Canadian and American patients once they are released from hospital anecdotal evidence suggests that the outcomes are approximately equal. Consequently clearer admission guidelines for atrial fibrillation patients may represent an opportunity to reduce the financial and personal costs of this disease.

Presenter's Name: Ratika Srivastava

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

Effects of acute and chronic methamphetamine and cocaine on impulsive choice in rats as assessed by reward-delay discounting

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Objectives: Research shows a strong, positive relationship between addictive drug intake and impulsive choice. Impulsive choice can be defined as preference for a small immediate reward over a larger delayed reward and measured using a delay discounting task. As part of a larger study of addictive drug action on impulsivity, we tested rats under acute and chronic methamphetamine and cocaine exposure to assess effects on delay discounting.

Methods: 48 Sprague-Dawley rats were trained to lever-press between two choice reinforcements: one food pellet immediately or three food pellets after various delays. Based on baseline performance on the delay-discounting procedure, rats were categorized into "high-impulsive" and "low-impulsive" groups. Effective doses of methamphetamine (1 mg/kg, i.p.) and cocaine (15 mg/kg, i.p.) were determined and administered chronically to both groups for 30 consecutive days. Increases in delay discounting indicated an increase in impulsive choice.

Results: Across all delays, methamphetamine decreased delay discounting after both acute and chronic administration. Consistent with previous literature, chronic cocaine increased delay discounting in low-impulsive rats after 10 days of treatment. However, rats that had higher impulsive baselines showed a decrease in delay discounting after acute and chronic cocaine exposure.

Conclusions: Overall, data indicate that moderate-dose methamphetamine may increase the subjective value of delayed reward in rats, decreasing impulsive choice. Though cocaine typically increases impulsive choice, it may have variable effects in rats that are unable to tolerate longer delays. This suggests cocaine's actions on impulsive choice could possibly be related to baseline levels of impulsivity. Results of our study will contribute to the growing literature on cognitive and behavioral effects of psychostimulants, as well as help to understand relationships between impulsive choice and addiction.

This work was supported by NIDA/NIH.

Presenter's Name: Ryan Lewinson

Program and Year: MD/PhD, Year 3

Category: Basic/Translational Project

Altering knee abduction angular impulse as the mechanism of treatment for patellofemoral pain syndrome: a 6-week Phase I randomized control trial

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Objectives/Introduction: Patellofemoral pain syndrome (PFPS) is the most common running injury, and is often treated using medially wedged footwear; however, the reason why they reduce pain is unknown. In this Phase I randomized control trial, we compared laterally and medially wedged footwear to determine the relationship between change in internal knee abduction angular impulse (KAAI) and pain reduction in runners with PFPS.

Methods: Runners with PFPS were randomly assigned to either an experimental 3mm lateral wedge or control 6mm medial wedge footwear group. Subjects completed biomechanical gait analysis to quantify KAAIs with their assigned footwear, and with a neutral condition so that the influence of the wedge on KAAIs could be determined. Subjects were asked to use their assigned footwear for six-weeks during their regular runs. A weekly survey monitored co-intervention use, fluctuations in weekly running mileage, and new injury development. Usual pain during running was measured at baseline and at six-week follow-up using a 100pt visual analog scale. Statistical analyses were conducted on a per-protocol basis. A multiple linear regression (α=0.05) with baseline pain and %change in KAAI from neutral as predictor variables and %pain reduction as the outcome variable was the primary analysis. Differences between wedge conditions were compared using independent-samples t-tests (α=0.05).

Results: 370 runners were screened, 36 enrolled in the trial, and 27 were analyzed (14 lateral, 13 medial). Adjusting for baseline pain, a significant relationship between absolute %change in KAAI and %pain reduction was observed (R^2=0.21; p=0.030). Clinically meaningful reductions in pain (>33%) were measured for each footwear group, and no differences between wedge groups were found (p=0.697).

Conclusion: The greater the absolute change in KAAI during running, the greater the reduction in pain, regardless of wedge type. Laterally wedged footwear can be considered as an alternate treatment for PFPS.

Presenter's Name: Sarah MacEachern

Program and Year: MD/PhD

Category: Basic/Translational Project

Enteric glia mediate ion transport abnormalities in mouse colon during colitis

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Objectives/Introduction: Enteric glia are an important functional component of the enteric nervous system, and play a role in the cholinergic regulation of epithelial ion transport. However, their role in regulating ion transport during colitis is not well understood. Using a model of glial metabolic inhibition, we investigated the role of enteric glia in neurogenic regulation of ion transport in colitis.

Methods: Experiments were conducted in distal colon from wild-type CD1 mice. Colitis was induced using Dextran Sodium Sulfate (DSS; 5% w/v in drinking water). The net electrogenic movement of ions across the epithelium was recorded as short-circuit current (I_{SC}) in full-thickness colon mounted in Ussing chambers. Myenteric plexus preparations were utilized for electrochemical detection of real-time nitric oxide (NO) release. Tissues were treated with the glial metabolic poison fluoroacetate (FA; 5 mM; 60-120min) and stimulated with electrical field stimulation (EFS; 50V, 10Hz, 5s) in Ussing experiments or veratridine (10 μM) in electrochemical detection experiments.

Results: In control animals, EFS resulted in an increase in I_{SC} (ΔI_{SC}, 44±7μA/cm^2, n=12) that was unaffected by FA treatment (39±6μA/cm^2, n=14). Veratridine resulted in myenteric NO release (581±11pA, n=5), which was not altered following FA treatment (546±16pA, n=5). In animals with colitis, EFS did not elicit a secretory response (3±2μA/cm^2, n=14). FA treatment of inflamed colon restored the EFS response (27±5μA/cm^2, n=12; $P<0.05$). Veratridine stimulated a larger NO release during colitis (727±26pA, n=6; $P<0.001$), which was reduced by FA treatment (412±6pA, n=6; $P<0.001$).

Conclusions: Under physiological conditions, the activation of enteric neurons regulates ion transport in a glial-independent manner. During colitis, enteric glia inhibit ion transport through nitric oxide production, which is reversed through the metabolic inhibition of enteric glia. Our data show that enteric glia contribute to the dysregulation of ion transport during colitis.

Presenter's Name: Sarah Perry

Program and Year: MD/MSc, Class of 2014

Category: Clinical Project

THE EFFECT OF DIFFERENT INTERVENTIONS ON THE SENSORY AND AFFECTIVE DIMENSIONS OF DYSPNEA IN PATIENTS WITH COPD DURING EXERCISE

Perry, S., Koelwyn, G., Melzer, B., Rolf, D., and Eves, N.

Objectives/Introduction: Dyspnea is a complex sensation that has been recognized as a similar entity to the sensation of pain. Research has shown that dyspnea can be caused by a variety of diverse mechanisms and can be interpreted differently by each individual. Hyperoxia, heliox, and Bi-level positive airway pressure (BiPAP) are able to reduce dyspnea in patients with chronic obstructive pulmonary disease (COPD) but it is unknown how they specifically influence the affective (A1) and sensory (SI) dimensions of dyspnea during exercise. The aim of this study was to examine the extent to which hyperoxia, heliox and BiPAP alter A1 and SI scores and if changes in these dimensions of dyspnea are associated with improvements in exercise capacity.

Methods: 10 patients with moderate to severe COPD (post-bronchodilator FEV1/FVC <0.7, 30%< FEV1 < 80% pred, >10 pack year history of smoking) who were exacerbation-free for at least 6 weeks prior to the study performed constant-load cycling at 75% of maximal work rate breathing air, hyperoxia (40% O2, 60% N2), heliox (21% O2, 79% He), or BiPAP (pressure optimized for each individual).

Results: At an isotime during exercise, hyperoxia reduced the sensory intensity of dyspnea (p=0.033). The change in A1 and SI were also significantly reduced compared to air with both hyperoxia (p=0.033, p=0.025, respectively) and heliox (p=0.047, p=0.041, respectively) but not with BiPAP. The A1/SI ratio was unchanged with all interventions compared to air. There were no significant changes in the sensory qualities of dyspnea with any intervention, except for the sensation of breathing a lot (rapidly, deeply, or heavily), which was significantly reduced with heliox at isotime. There were no significant differences in dyspnea measures or ventilatory parameters at end exercise.

Conclusions: Hyperoxia and heliox altered the affective and sensory dimensions of dyspnea during exercise, leading to improvements in exercise time with hyperoxia. There were considerable individual differences in the reported quality of dyspnea scores, as well as exercise time. These findings suggest that phenotyping patients based on their specific type of dyspnea to a particular therapy before an exercise intervention may be warranted to enhance the known benefits of exercise for patients with COPD.

Presenter's Name: Sarah Tulk

Program and Year: MD/MSc, Class of 2015

Category: Basic/Translational Project

Vitamin D_3 induces release of IL-1β via the NLRP3 inflammasome: Implications for Crohn's disease

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Rationale: Recently the Crohn's disease (CD) pathogenesis has been proposed to involve hypoactive innate immune and inflammatory responses. Supporting this is the fact that the NLR NOD2, an innate immune receptor which activates inflammatory pathways, contains hypofunctional mutations in CD. Thus, an inability to initiate appropriate inflammatory responses may play a role in CD. Vitamin D_3 has recently been shown to induce NOD2. NLRP3, another NLR, has also been shown to have hypofunctional mutations in CD. Vitamin D_3 has been shown to induce production of the NLRP3 product precursor, pro-IL-1β. We therefore hypothesized that vitamin D_3 could activate the NLRP3 inflammasome, much like NOD2, to induce release of mature IL-1β from macrophages.

Methods: PMA-differentiated THP-1 cells were stimulated with $1,25(OH)_2D_3$ or $25(OH)D_3$ for up to 24 hours and IL-1β release was assessed via ELISA. CYP27 gene expression was assessed via PCR.

Results: $1,25(OH)_2D_3$ induced release of IL-1β from PMA-differentiated THP-1 cells after 24 hours of stimulation at concentrations above, but not below, 1 nM. This effect was blocked with the caspase-1 inhibitor yVAD and the NLRP3 inhibitor glyburide. Further, treatment with the $1,25(OH)_2D_3$ precursor, $25(OH)D_3$, also induced IL-1β release in a caspase-1 and NLRP3 dependent fashion.

Conclusions: We have shown that macrophages release IL-1β following stimulation with $1,25(OH)_2D_3$ or $25(OH)D_3$, and that this is dependent on caspase-1 and NLRP3. We believe that this holds important implications for CD, as vitamin D_3 could help 'boost' basal levels of the innate immune system to help compensate for the defective innate immunity seen in this disease.

Presenter's Name: Simon Sun

Program and Year: MD, Class of 2013

Category: Clinical Project

Learning curve analysis for cytoreductive surgery: a useful application of the cumulative sum (CUSUM) method.

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Objectives/Introduction: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancy is complex surgery associated with major morbidity rates of 29 – 54%. This morbidity rate appears to decline as surgeons undergo a "learning curve" (LC) for CRS+HIPEC. Cumulative sums (CUSUM) graphing plots the cumulative deviation of a process from an established target. LC-CUSUM analysis estimates the number of cases required to achieve a threshold limit, given pre-set values for Type I/II errors. We aim to use CUSUM and LC-CUSUM analysis techniques to quantitate the learning curve associated with CRS+HIPEC at a high-volume Canadian centre.

Methods: Using a prospective database maintained by the operating surgeons, sequential patients who underwent primary CS+HIPEC between January 2000 and December 2010 were included. Their clinicodemographic characteristics and perioperative morbidity (Dindo-Clavien Grade III/IV/V) were extracted. CUSUM graphing was conducted for target major morbidity rates of 0.20. 0.25. 0.30, 0.35, and 0.40. LC-CUSUM analysis was conducted for the same range of target major morbidity rates, with α=0.05 and β=0.20. Ethics review board approval was obtained (IRB#25871).

Results: A total of 213 patients were included, of which 36% experienced a major complication. The CUSUM graphing analysis demonstrated stabilization of the learning curve for target morbidity rates of 0.30-0.40. LC-CUSUM analysis signalled completion of the LC at 138 cases for a target morbidity of 0.30-0.40, and 78 cases for a target morbidty of 0.40-0.50.

Conclusions: Major morbidity following CRS+HIPEC is common. There is a substantial learning curve, estimated at 90-140 cases using LC-CUSUM analysis, associated with achieving a stable rate of 30-40% morbidity.

Presenter's Name: Stuart Wiber

Program and Year: MD, Class of 2015

Category: Basic/Translational Project

Tumour necrosis factor-α abrogates carbachol induced glucagon-like peptide-1 secretion in the mGLUTag L cell line

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Background/objectives: Glucagon-like peptide-1 (GLP-1) is an incretin hormone released from the L. Long-acting GLP-1 receptor agonists and GLP-1 degradation inhibitors are successful treatments for the management of patients with type 2 diabetes (T2D). GLP-1 secretion is impaired in rodents under conditions of insulin resistance and obesity, such that there is a specific reduction in vagally-mediated, nutrient-induced release of GLP-1. One common feature of both of these pathologies is enhanced levels of tumour necrosis factor alpha (TNF-α). The L cell is a direct target of other adipokines/cytokines, we therefore hypothesized that TNF-α exerts direct effects on the intestinal L cell, leading to reduced GLP-1 release.

Methods: mGLUTag L cells were pre-incubated for 24 hr ± TNF-α (50 ng/ml). Cells were then treated with media alone (control) or the muscarinic-agonist, carbachol (0.5 - 1 mM) for 2 hr. Expression of TNFR1 and TNFR2, receptor isoforms for TNF-α were determined(n=4). Treatment cytotoxicity was determined (n=4). Percent GLP-1 secretion relative to total cell content was measured (n=8-12). Finally, protein level of phos-pErk1/2 levels, a downstream kinase of GLP-1 secretion, was determined (n=8).

Results: Cells expressed TNFR1 and 2. Treatments were not cytotoxic. As previously demonstrated, carbachol treatment of control cells increased GLP-1 release by 131.7 ± 7.9 % of control ($P<0.001$). Pre-incubation of the cells with TNF-α markedly increased basal GLP-1 release, by 121.7 ± 5.6 % of control ($P<0.01$) and carbachol-induced GLP-1 secretion was completely abrogated. Phos-pErk1/2 protein levels were increased by 143 ± 18 % ($P<0.05$) with treatment of carbachol, and by 192 ± 27% ($P<0.05$) and 185 ± 18% ($P<0.01$) with pre-incubation of TNF-α. TNF-α abrogated carbachol's effect on phos-pErk1/2.

Conclusion: These findings demonstrate that TNF-α directly impairs both basal and carbachol-stimulated intestinal L cell function, and may therefore contribute to the decrease in vagally-induced GLP-1 secretion in T2D and obesity. This suggests a novel means by which systemic inflammation may dysregulate glucose homeostasis.

Presenter's Name: Taryn Ludwig

Program and Year: MD/PhD, Year 4

Category: Clinical Project

Effect of Acute Flare Reaction to Intra-Articular Injection on Cartilage Lubricating Ability of Human Synovial Fluid

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Objectives/Introduction: Proteoglycan 4 (PRG4) and hyaluronan (HA) are constituents of synovial fluid (SF) that synergistically contribute to the boundary lubrication of articular cartilage. *In vitro* studies have shown that decreased PRG4 and HA levels in SF can lead to compromised boundary lubrication, which can be restored by lubricant supplementation. Intra-articular (IA) HA and corticosteroid are common treatments for knee osteoarthritis (OA). A recent review discussed the small benefit of IA HA treatment and increased risk of flare reaction (hot, painful, swollen knee 24-72 hours after injection). The effects of flare on SF lubricant content and lubricating ability are unknown. The objectives of this study were to 1) quantify PRG4 and HA content in flare OA SF and 2) assess the cartilage boundary lubricating ability of PRG4-deficient flare SF and flare SF supplemented with PRG4±HA.

Methods: PRG4 and HA concentration in flare OA SF (≤11 days after injection, N = 14) was measured by sandwich enzyme linked immunosorbent assay. Lubricating ability of PRG4-deficient flare SF, flare SF supplemented with normal levels of PRG4±HA, and normal SF was tested in a normal human cartilage-on-cartilage friction test.

Results: Three IA HA flare SF samples deficient in PRG4 were selected for friction testing. HA concentration in the flare SF did not differ from normal (p=0.3). Lubricating ability in flare SF was not diminished, and no changes were observed with PRG4 or PRG4+HA supplementation (p=0.96-0.98).

Conclusions: Some flare SF exhibits altered lubricant composition, as has been previously observed in ACL injury and chronic OA, but retains normal boundary lubricating ability. Other characteristics of PRG4, including glycosylation and size distribution, remain to be compared between healthy and diseased SF and may affect lubricating ability. Evaluation of flare SF composition over a longer time course will provide further insight into effects of inflammation on joint lubrication.

Presenter's Name: Valerie Hurdle

Program and Year: MD, Class of 2013

Category: Clinical Project

Traumatic Aneurysm of Arterial Venous Malformation in Right Hand: Case Report

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Arteriovenous malformations (AVMs) account for 10-15% of all congenital vascular anomalies. Their varied clinical presentations, unpredictable clinical course, anatomical and hemodynamic complexities, and high recurrence rates make AVMs extremely challenging to treat. AVMs of the hand are one of the most demanding surgical problems encountered in the field of hand surgery. This case report outlines a surgical approach to an unusual vascular lesion in an anatomically complex location.

A 35-year-old male presented with a mass at the base of his fourth finger on his right hand, which had recently enlarged following trauma to the area. Findings of an angiogram were consistent with an AVM in the ulnar distribution of the patient's right hand, involving both the fourth and fifth digits, in addition to an aneurysm of the D4 common digital artery. Significant steal phenomenon was observed at the palmar arch, with blood flow being diverted away from the thumb, index and long digits. The vascular lesion was surgically resected and submitted for pathological assessment. Histopathology, in conjunction with clinical history, physical exam and angiography indentified the vascular lesion as a traumatic aneurysm of an arteriovenous malformation.

The operation consisted of removing the aneurismal portion of the AVM, however, the entire AVM was not resected as it involved several essential anatomical structures. The patient remains at risk for further expansion of the AVM and development of pseudoaneurysm, especially near the anastomosis site. If the patient becomes symptomatic in the future, it is possible that more extensive vascular reconstruction of the hand may be necessary, particularly if the digits of his right hand become hemodynamically compromised.

Presenter's Name: Veronique Ram

Program and Year: MD/PhD

Category: Arts & Humanities in Health Care Research

Every *Body* is a Story: Narrative Medicine in Canadian Context

Veronique Dorais Ram

Background/Purpose: Current international literature demonstrates that health care professionals with exposure to narrative theory improve their critical thinking skills and bring enhanced sensitivity and analysis to diagnostic reasoning. Medical programs, particularly in the United States, are incorporating "narrative medicine" into their curriculum to develop physicians with enhanced communication skills, stronger knowledge translation aptitudes, and astute and creative thinking tools. Existing studies illustrate that this thriving area of research can highlight the importance of biomedical narrative forms and promote the balance of treatment options between belief systems, patient history, and the technological possibilities offered by medical science.

Research Questions: 1) What are Canadian programs doing to keep up with the trend of "narrative medicine"? 2) Which studies clarify the principles of "narrative medicine" and how can we expand on the benefits, beyond better patient care, that this field of research holds for clinical practice?

Methods: Publications on "narrative medicine" from January 2002 to July 2012 were identified searching all EBM Reviews, Embase, Medline, MLA Bibliography, and Grey Literatures.

Results: 118 articles address "narrative medicine," 9 theses focus on "narrative medicine," from theory to implementation, and the grey literature search shows over 2,500 results. The vast majority of studies focus on narrative theory and experiential exercises, such as reflective writing, while only **one** examines clinical texts as narratives themselves. In Canada, there are **no** published studies on clinical texts, but there is a recent collaborative project between the Department of English and the Faculty of Medicine at McGill employing narrative theories to analyze clinical texts.

Despite the overwhelming qualitative support for the potential effect of "narrative medicine" training in medical education, the lack of long-term evidence based studies proving the benefits of "narrative medicine" remain an obstacle to curriculum changes in Canada.

Conclusion: The current trend of narrative medicine offers a complex and fascinating new avenue to examine physician practices beyond the overly broad rubric of "medical humanities." There are two significant opportunities for narrative medicine in a Canadian context: (1) practically, more clinically focused projects are needed on the benefits of narrative medicine to medical education. (2) Theoretically, physician documents, such as clinical charts, require analysis under a narrative medicine lens to demonstrate the benefits of narrative medicine beyond medical education. Reflective writing techniques may enhance physician health, and patient stories may build empathy, but only through the analysis of both sides of the story can narrative medicine actually prove beneficial to the patient-physician relationship.

Presenter's Name: Waleed Rahmani

Program and Year: MD/MSc

Category: Basic/Translational Project

In vivo lineage tracing of dermal stem cells during hair follicle regeneration and wound healing

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Dermal stem cells residing within the hair follicle mesenchyme have recently been identified and characterized as key multipotent cells that induce hair follicle growth and appear to play a role in dermal maintenance. Moreover, both dermal compartments (dermal sheath and dermal papilla) of the hair follicle have been shown to express the stem cell gene Sox2 as well as generate skin-derived precursors (SKPs) when cultured. However, the primary source, migration pattern, and fate of these dermal precursors remain a mystery. Here, we investigate whether αSMA+ cells within the dermal sheath represent a progenitor population that migrate into the dermal papilla during the course of hair regeneration as well as contribute to wound healing. To address this, we generated an inducible Cre-lox transgenic mouse αSMA-CreERT2:RosaYFP to perform *in vivo* genetic lineage tracing experiments. Tamoxifen treatment during the early days of anagen (hair follicle growth phase) exclusively labeled dermal sheath cells, but not dermal papilla, within hair follicles. We then documented the fate of these cells over time (1, 3, 7, 14, 28 days and 6 months post treatment) in both normal and wounded skin. In normal skin, we show that the dermal sheath continuously repopulates with YFP+ cells over the lifetime of the mouse while the dermal papilla shows a steady increase of YFP+ cells with the majority of the dermal papilla YFP+ at 6 months time. Most notably, we have been able to localize the label-retaining precursor responsible for continuously regenerating the dermal sheath to the junction between the dermal papilla and secondary germ. In wounded skin, preliminary results have shown YFP+ cells infiltrating the wound suggesting a role for dermal precursors in wound healing. This work provides definitive evidence for the functional role of dermal precursors within the skin and provides new insights into the lineage relationships within the mesenchymal compartment of the hair follicle.

Presenter's Name: Wesley Chan

Program and Year: MD/MSc (Montreal), Class of 2015

Category: Basic/Translational Project

Cyanocobalamin is a Superoxide Anion Scavenger and Neuroprotectant in Neuronal Cells

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Introduction: Damage to the optic nerve (optic neuropathy) can result in permanent vision loss or blindness through retinal ganglion cell (RGC) death. Our prior work identified a burst of superoxide anion as a critical molecular event in RGCs prior to injury-induced apoptosis. Recently, vitamin B_{12} has been shown to scavenge superoxide as effectively as superoxide dismutase (SOD). Vitamin B_{12} deficiency can lead to optic neuropathy through unknown mechanisms. We investigated the relationship between superoxide scavenging by cyanocobalamin, the most abundant vitamin B_{12} vitamer, and its neuroprotective properties in neuronal cells.

Methods: Superoxide anion reacts with hydroethidine to produce a fluorescent product, 2-hydroxyethidium. Superoxide scavenging by cyanocobalamin in a cell-free system was measured with a fluorescent microplate reader. Superoxide scavenging in RGC-5 neuronal cells was assessed *in vitro* by fluorescent microscopy. Neuroprotection against menadione was evaluated by calcein-AM/propidium iodide assay to identify living and dead cells. An optic nerve transection model in Long-Evans rats was used to study superoxide scavenging and neuroprotection *in vivo*, with visualization of superoxide within retrograde-labelled RGCs by confocal scanning laser ophthalmoscopy.

Results: Cyanocobalamin at concentrations of 10 μM and 100 μM reduced the rate of superoxide generation by 34% and 79% in cell free assays, respectively. In menadione-treated RGC-5 cells, cyanocobalamin concentrations above 10 nM scavenged superoxide anion similar to those treated with SOD. Cyanocobalamin at concentrations of 100 μM and 1 mM reduced RGC-5 cell death from menadione by 20% and 32%, respectively. In rats with optic nerve transection, a single intravitreal dose of 667 μM cyanocobalamin significantly reduced the number of 2-hydroxyethidium-positive RGCs. This dose also increased RGC survival compared to rats injected with saline.

Conclusions: These data suggest that vitamin B_{12} may be an important neuroprotectant, which could cause death of RGCs when depleted in nutritional deficiency. Vitamin B_{12} could also potentially be used as a therapy to slow progression of RGC death in patients with optic neuropathies characterized by overproduction of superoxide.

Presenter's Name: Zaheed Damani

Program and Year: MD/PhD, Year 2

Category: Basic/Translational Project

Single-entry models in health care: values and acceptability of a novel waiting time management strategy among patients awaiting hip and knee replacement in Canada

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Introduction / Objectives: *Single-entry* is a successful wait time management strategy (WTMS) in retail. Gaining prominence in healthcare, its suitability and acceptability is not fully known.

Study Objectives: 1) to provide comprehensive understanding of *single-entry models* (SEMs) -- defining their usage/determining their effectiveness in reducing wait times (WTs); 2) exploring their acceptability to patients and clinicians, and under what conditions.

Methods: A two-step approach was adopted: a systematic literature synthesis involving nine medical, selected non-medical and multidisciplinary electronic bibliographic databases and a patient questionnaire. To explore patient perspectives towards pooled lists and single-entry approaches, questionnaires were administered to 114 patients from major Canadian cities: Calgary, Winnipeg, Toronto and Halifax who were awaiting or had undergone hip and/or knee replacement. The questions asked patients about surgeon preference and their acceptability of being seen by the next available surgeon.

Results/Review: SEMs allow waiting lists to be pooled, services to be accessed through a single point-of-entry and for patients to see the first-available surgeon (FAS). Ten studies were considered, in general, found that by shortening WTs for patients awaiting surgery and increasing the number of patient referrals/patients seen, SEMs can improve access to and the efficiency of patient care in both surgical and outpatient settings. Surgeons are generally opposed to pooling whereas most GPs favour it.

Questionnaire: Patients consider trust, skill, reputation when selecting their surgeon – 81% valued choice. Patients were divided on seeing the FAS, even if it meant a reduction in waiting times. Patients would consider the FAS provided that he/she is equally qualified and that waiting times will decrease.

Conclusions: Findings suggest that SEMs are a promising WTMS and means of improving access. However, given that WTMSs are often used in combination, reduced WTs cannot solely be attributed to SEMs. While favoured by some, acceptability of SEMs isn't universal.

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