UBC MD PhD

UBC MD/PhD Program

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Newsletter – Summer 2009

http://www.med.ubc.ca/education/md_ugrad/mdphd/news.htm

David McVea — Inaugural Recipient of Canada's Highly Prestigious Vanier Canada Graduate Scholarship

David McVea

David McVea, Year II MD/PhD student, is an inaugural recipient of the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship -- one of the most prestigious scholarships available for doctoral studies at a Canadian university.

The Vanier Canada Graduate Scholarships (CGS) program is designed to attract and retain world-class doctoral students who demonstrate leadership skills and a high standard of scholarly achievement in doctoral studies. The program helps attract top doctoral students to Canadian universities by offering a significant financial award to assist successful candidates during their studies. Beginning in May 2009, David will receive $50,000 per year for up to three years to support his graduate studies at UBC.

David's PhD research supervisor is **Dr. Timothy Murphy** of the Department of Psychiatry. David's hosting department is the Graduate Program in Neuroscience. His PhD thesis title is "Using optical tools to test the role of muscle spindles in plasticity following brain injury".

Congratulations, David!

My project aims to help understand how neural circuits in the brain change during recovery from injury. I plan to use voltage-sensitive dyes and transgenic animals that express light sensitive channels to monitor the recovery of cortical function after stroke. I will compare the recovery of cortical function in normal mice and those missing muscle spindles to test the hypothesis that aberrant sensory feedback spurs and drives cortical reorganization. Along the way, I hope to gain some insights into the role of distributed cortical networks in complex stepping and reaching tasks.

David McVea

Recent publications (selected list):

McVea DA, Taylor AJ, Pearson KG. (*in press*) Long-lasting working memories of obstacles established by foreleg stepping in walking cats requires area 5 of the posterior parietal cortex. *Journal of Neuroscience.*

Donelan JM, **McVea DA**, Pearson KG. (2009) Force-regulation of ankle extensor muscle activity in freely walking cats. *Journal of Neurophysiology*, 101(1):360-371.

McVea DA, Pearson KG. (2009) Object avoidance during locomotion. *Advances in Experimental Medicine and Biology*, 629: 293-315.

Dr. Peter Leung

The UBC combined MD/PhD Program was highlighted in a presentation by **Dr. Peter Leung**, UBC Faculty of Medicine Associate Dean of Graduate and Postdoctoral Education, at the recent inaugural meeting of the Association of Faculties of Medicine of Canada (AFMC) Graduate Studies Section. This meeting was held at the University of Manitoba in Winnipeg (2-5 June 2009), in conjunction with the inaugural meeting of the Canadian Medical Student Research Forum, the Canadian Student Health Research Forum and the Canadian Institutes of Health Research (CIHR) Graduate Student Poster Awards Competition.

Dr. Leung described the program structure and enrolment statistics of the UBC combined MD/PhD Program over the past 10 years. Overall, the members of the AFMC Graduate Studies section (comprised of Associate Deans of Graduate Studies from all Faculties of Medicine across Canada) were highly impressed with the significant growth and achievements of the Program, particularly in the past few years under the leadership of its current Director (**Dr. Lynn Raymond**) and Associate Director (**Dr. Torsten Nielsen**). In view of the expected and continuous growth of this Program in the next 2-3 years, Dr. Leung also took the opportunity to pledge for additional MD/PhD awards to UBC from the CIHR Capacity and Development Branch whose representative was also invited to speak at this meeting. Thank you, Dr. Leung!

Alumni News — Dr. Stephen Yip (Class of 1999)

Dr. Stephen Yip obtained his combined MD/PhD degree in 1999. His PhD research supervisor was **Dr. Julia Levy**, in the Department of Microbiology and Immunology. After graduation, Stephen went on to receive his FRCPC in Neuropathology in 2006, and then undertook a research-intensive fellowship at Massachusetts General Hospital in Boston.

Dr. Stephen Yip

Stephen will be returning to Vancouver. He will start on 10 August 2009 at the BC Cancer Agency (BCCA) as a Pathologist in Cancer Genetics. He will be responsible for clinical neuropathology and clinical molecular diagnostics related to brain tumors at the BCCA -- as part of his 40% clinical duty. The other 60% will be devoted to research -- mainly translational with assisting the establishment of a collaborative brain tumor research initiative in BC. His research interest is in the genomic and epigenomic profiling of cancer, especially brain tumors, and their subsequent clinical validation and eventually the development of novel molecular diagnostic assays from these findings.

Stephen will be presenting at our annual Open House on Monday, 14 September 2009, 1-4 pm, at the Michael Smith Laboratories, UBC. He will talk about his success in the clinician-scientist career. All are welcome!

Recent Publications (selected list):

1. **Yip S**, Miao J, Cahill DP, Iafrate AJ, Aldape K, Nutt CL, Louis DN. (*in press*). MSH6 mutations arise in glioblastomas during temozolomide resistance. *Clinical Cancer Research*.
2. **Yip S**, Shah K. (2008) Stem-cell based therapies for brain tumors. *Current Opinion in Molecular Therapeutics*, 10(4): 334-42. Review.
3. **Yip S**, Iafrate JA, Louis DN. (2008) Molecular diagnostic testing in malignant gliomas: a practical update on predictive markers. *Journal of Neuropathology and Experimental Neurology*, 67(1): 1-15. Review.

Alumni News — Dr. Stephen Yip (con't)

Recent Meeting Abstracts (selected list):

1. **Yip S**, Miao J, Cahill DP, Iafrate AJ, Aldape K, Nutt CL, Louis DN.MSH6 somatic mutations in mediating temozolomide resistance in recurrent glioblastomas. American Association of Neuropathology and Experimental Neurology. June 2009.
2. Quant EC, Silver M, **Yip S**, Ryg P, Provencher K, McCormack K, Louis DN, Betensky R, Nutt C, Batchelor TT. Case-control study of long-term survivors of glioblastoma. American Society of Clinical Oncology. May 2009.
3. Gerstner ER, **Yip S**, Wang DL, Louis DN, Iafrate AJ, Batchelor TT. MGMT methylation status may predict survival in elderly patients with newly diagnosed glioblastoma (GBM). American Society of Clinical Oncology. May 2009.

Recent Awards (selected list):

1. Travel award. American Association of Neuropathology and Experimental Neurology, June 2009, meeting in San Antonio.

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Message from Dr. Stephen Yip

After completion of my two year research with Dr. David Louis at the MGH Molecular neuro-oncology laboratory (as part of my Clinician Investigator Training) I elected to stay in Boston for one more year to continue my research in the lab. Also, I joined the HMS Molecular Genetic Pathology training program as an "unofficial" fellow to further my training in this challenging field and to expose myself to various clinical molecular diagnostic tools -- such as arrayCGH, FISH, microsatellite analysis, etc.

I continued my research in the Louis lab as well and continued my work on treatment failure in glioblastoma, specifically the role of the mismatch repair protein *MSH6* on temozolomide resistance. In addition, we are currently performing extensive resequencing of matched pairs of pre- and post- treatment glioblastomas from MGH and have found novel mutations in *msh6* in post- treatment, recurrent tumors.

My affiliation with the MGH Translational Research Laboratory in the past year has introduced me to the potentials (as well as difficulties) of molecular diagnostics in clinical oncology. We instituted a multiplex mutation assays examining known mutations in oncogenes on incoming cancer patients which give clinicians a catalog of genetic changes which can alter therapeutic decision making.

I very much look forward to my return to the west coast and collaboration with new colleagues and old friends. I strongly believe that molecular diagnostics will transform pathology and medicine and hopefully will improve patient well-being. However, one thing that I have learned in the past year is tissue/cell histology still plays a significant role in the diagnostic pathway so it is important to appreciate both. I strongly believe in the power and potential of "translational research" and the important role that pathology plays in this endeavor.

I have also started numerous collaborative projects with my colleagues here in Boston in the past year which I plan to continue after my departure. I will miss Boston especially MGH where I had been based in the past three years, my mentors, David Louis and John Iafrate, and numerous work colleagues and friends who made life interesting in this great city.

PhD Oral Defense

Congratulations go to **Heather Heine** and **Inna Sekirov**, both Year VI MD/PhD students, for successfully defending their PhD theses. They made beautiful presentations and answered all questions well. We are very proud to share their research interests with everyone. Great work!!


Heather Heine


Inna Sekirov

Heather Heine, PhD research supervisor **Dr. Bruce McManus**, Department of Pathology and Laboratory Medicine, defended her thesis on 15 April 2009.

"Characterization and Use of a Controlled In Vivo Model for Angiogenesis"

ABSTRACT In this thesis, it was of major interest to better understand progenitor cells participating in neoangiogenesis. Due to the need for clarity regarding the identity of endothelial progenitor cells (EPCs), I sought to use multicolor flow cytometry to compare cells positive for some of the most commonly cited EPC surface proteins. Cells positive for 2-3 markers could not be reliably isolated due to limitations of techniques available. Furthermore, the absence of a convincing functional assay made the significance of positive results unclear. This led to use of a murine subcutaneous model of angiogenesis employing a custom-built chamber. I have combined this tool with the use of an automated high-resolution imaging system to established baseline parameters of growth in vivo. Chamber size, thickness, matrix and supplemented growth factor concentration have established a baseline understanding of cell types that infiltrate during angiogenesis, the rates of infiltration of each cell type, and high-resolution morphology of the complex capillary structures that form. With this model established, attempts to examine the outcome of three manipulations were undertaken. (1) Purified EPC populations were implanted within the chamber to test their potential to participate in neoangiogenesis. After an apparently successful pilot project implanting Sca-1+ cells within chambers and six additional studies, the activity of purified cells involved in neoangiogenesis was not confirmed. Alternate approaches to introduce sorted subsets of cells will be required to continue these studies. (2) Bone marrow (BM) transplants with green fluorescent protein (GFP)-labeled cells was undertaken in order to examine BM-derived cell contributions to neoangiogenesis. The majority of BM-derived cells within the chamber were F4/80+ white blood cells. In rare cases dual GFP+CD31+ cells were visible. (3) CD34 is an important cell surface sialomucin widely used for EPC isolation however its function remains unclear. Chambers implanted within CD34 null mice show differences in the rates of penetration and cell density in Hoechst 33342+, CD31+ and NG2+ cells, and endothelial tubule formation appears to be defective. Characterization of this model now provides a stepping-stone for studies of specific cells, growth factors, and environmental components best suited to support therapeutic efforts in neoangiogenesis.

Inna Sekirov, PhD research supervisor **Dr. Brett Finlay**, Department of Microbiology and Immunology, defended her thesis on 27 April 2009.

"The Role of the Intestinal Microbiota in Host Susceptibility to Salmonella enterica Serovar Typhimurium"

ABSTRACT Intestinal microbiota comprise microbial communities that reside in the gastrointestinal tract and are critical to normal host physiology. Understanding the microbiota's role in host response to invading pathogens will further expand our knowledge of host-microbe interactions, as well as foster advances in the design of novel therapeutic and prophylactic methods. In this dissertation I used clinically relevant doses of antibiotics to disturb the intestinal microbiota balance in a murine infection model. Pre-infection perturbations in the microbiota with two antibiotics resulted in increased mouse susceptibility to Salmonella enterica serovar Typhimurium intestinal colonization, greater post-infection alterations in the microbiota, and more severe intestinal pathology. This demonstrates the importance of a balanced microbiota community in host response to an enteric pathogen. This infection model also allowed further characterization of the host-pathogen-microbiota interactions during enteric salmonellosis. It was shown that in the presence of high numbers of indigenous microbes S. Typhimurium deficient in Salmonella pathogenicity island 2 (SPI2) is unable to trigger intestinal inflammation, while a SPI1 mutant strain promotes late typhlitis. Additionally, it was demonstrated that pathogen-induced intestinal inflammation does not always translate into extensive alterations to the host microbiota, as inflammation during a SPI1 mutant infection did not promote the same changes in host microbiota composition and numbers as inflammation induced by wild-type S. Typhimurium. Differential neutrophil recruitment by the three S. Typhimurium strains was implicated as one possible agent of microbiota perturbations. A thorough understanding of the tripartite host-microbiota-pathogen relationship in the progression of the enteric infections is needed to fully appreciate the disease process, as well as to suggest new avenues through which to interfere with the infection progression. These studies enhance our understanding of the microbiota's role in the progression of S. Typhimurium infection and the effects of inflammation upon the microbiota, thus broadening our knowledge of S. Typhimurium pathogenesis and associated host response.

Aaron Joe — APSA Best Poster Award

Congratulations to **Aaron Joe**, Year VI MD/PhD student, for winning one of the Best Poster Awards, US$1000, at the 5th American Physician Scientists Association Annual Meeting (APSA), Chicago, Illinois (23-26 April 2009). This award is in recognition of outstanding presentations from the Poster Session. Posters are judged on scientific merit and clarity of presentation. Aaron's PhD research supervisor is **Dr. Fabio Rossi**, Experimental Medicine Graduate Program. Aaron's APSA research abstract is entitled, "High fat diet selectively modulates proliferation of subcutaneous adipocyte progenitor cells". We are sharing his award-winning research abstract with everyone.

> White adipose tissue (fat) is the primary organ for energy storage and an excess or lack of fat tissue can result in significant human morbidity due to metabolic, reproductive or cardiovascular complications. It is becoming clear that the size of specific fat depots is associated with different medical risks. Fat is chiefly comprised of adipocytes (fat cells), which represent the smallest functional unit of fat tissue and must change in size and/or number to change fat tissue mass. Little is known about whether adipocyte progenitor (AP) cells contribute to an expanding fat mass under physiological conditions in adults, and whether depot-specific differences in APs may account for the functional differences between fat depots. Here we characterized APs that were prospectively purified from either subcutaneous (S-AP) and visceral (V-AP) fat depots of mice and show that S-APs, but not V-APs, contribute to adipocyte hyperplasia after high fat feeding in adult animals. Our analyses highlight the heterogeneity of fat progenitor cells, and we reveal distinct differences in the clonogenic and adipogenic ability of APs harvested from different depots. These results suggest that differences in depot-resident AP populations may be responsible for the physiological differences observed between different fat depots.
>
> The field of adipocyte hyperplasia is in its infancy as the identification of new adipocyte generation throughout life, and existence of fat-resident adipocyte progenitors, were only recently confirmed. Since large adipocytes are associated with insulin resistance and metabolic disease, whether fat mass expands by adipocyte hypertrophy (resulting in large adipocytes) or hyperplasia (resulting in small adipocytes) might ultimately determine a depot's behavior. Our findings provide the basis for future work to identify the factors controlling adipocyte hyperplasia, and their effects fat depot physiology.

Aaron Joe

Clara Westwell-Roper

Michael Copley

Congratulations!

Michael Copley and Clara Westwell-Roper — Graduate Award

Congratulations go to **Michael Copley** and **Clara Westwell-Roper**, both Year I MD/PhD students, for winning a Faculty of Medicine Graduate Award (Graduate Support Initiative) for the 2009 Summer Session. This graduate award is offered to outstanding incoming students to the MD/PhD Program. Michael's PhD research supervisor is **Dr. Connie Eaves**, Experimental Medicine Graduate Program. Clara's PhD research supervisor is **Dr. Bruce Verchere**, Department of Pathology and Laboratory Medicine.

PhD Comprehensive Exams

Arezoo Astanehe | Kate Potter

The intent of the comprehensive examination is to ensure that the student has adequately prepared for the proposed thesis research and can gain maximum benefit from this experience. The comprehensive examination format consists of two parts:

- a CIHR style research grant proposal in an area of the student's research
- an oral examination.

Two MD/PhD students have been admitted to candidacy.

Congratulations!

Kate Potter (Year 4) successfully passed her PhD comprehensive examination on 23 January 2009. Kate is completing her PhD research with **Dr. Bruce Verchere**, in the Department of Pathology and Laboratory Medicine. Her thesis topic is "Endoplasmic reticulum stress: role in islet transplant graft dysfunction". Her examination committee members are: Drs. Catherine Pallen (Chair), Jaki Chantler, Jim Johnson, Alice Mui, and Garth Warnock. Thanks everyone!

Arezoo Astanehe (Year 4) successfully passed her PhD comprehensive examination on 17 April 2009. Arezoo is completing her PhD research with **Dr. Sandra Dunn**, in the Experimental Medicine Graduate Program. Her thesis topic is "Role of YB-1 in breast cancer". Her examination committee members are: Drs. Laura Sly (Chair), Vincent Duronio, Michael Kobor, Torsten Nielsen, Steven Pelech and Calvin Roskelley. Thanks everyone!

Claire Heslop — Study of Heart Disease Patients

Claire Heslop

Claire Heslop, Year V MD/PhD student, used mapping data provided by the Human Early Learning Partnership at UBC to study 485 patients with heart disease across more than 13 years. Death rates from different types of diseases were compared to the patients' neighbourhood data based on education, median family income and unemployment. Claire found that patient death rates from chronic diseases - other than heart disease - were more than twice as high in the lowest socioeconomic area than in the highest. Surprisingly, no difference was found in deaths from heart disease across neighbourhoods. Claire's findings suggest disease interventions performed at centralized hospitals may equalize cardiac care, but patients may still suffer from disparities in overall health and health care related to their neighbourhood environment. Claire suggested that more research is needed to find out exactly what is causing the gap and how to fix it. Her study was published in the online journal Public Library of Science ONE (PLoS one), entitled, "Neighbourhood Socioeconomics Status Predicts Non-Cardiovascular Mortality in Cardiac Patients with Access to Universal Health Care". http://www.plosone.org. Claire's study was reported in the Vancouver Sun in January 2009. Claire is completing her PhD research in emerging cardiovascular disease risk markers with **Dr. John Hill**, Department of Pathology and Laboratory Medicine. Good job, Claire!!

Arezoo Astanehe — Graduate Student Committee

Arezoo Astanehe, Year IV MD/PhD student, is our representative on the UBC Faculty of Medicine Graduate Student Committee (2008-2009).

Aaron Joe — Research Council

Aaron Joe, Year VI MD/PhD students, is our representative on the UBC Faculty of Medicine Research Council. Aaron has been sitting on this committee since 2005.

Thank you! Keep up the good work!

MD/PhD "Building Bridges Seminar Series" — ALL ARE WELCOME

This well established seminar series is aimed at illustrating the relationship that exists between clinical practice and medical research. The meetings offer a casual and relaxed atmosphere in which to profile individuals who have successfully combined both clinical and research aspects into their medical careers. In addition to talking about their active research, the invited speakers also talk about their experiences, discuss their training background, share their advice for prospective clinician-scientists, and talk about their opinions on career development options for clinician-scientists.

Dr. Ken Bassett

All faculty, clinical investigator trainees and students in the Faculty of Medicine are invited. Presentations are video-conferenced and broadcast to the Island Medical Program and the Northern Medical Program. The event is being held at the Medical Student Alumni Centre, 12th Avenue & Heather Street, at 6:00 - 7:00 pm.

On 6 April 2009, **Dr. Ken Bassett**, Professor, Family Practice, Anaesthesiology, Pharmacology and Therapeutics, UBC, Chair, Drug Assessment Work Group, Therapeutics Initiative, UBC, and Director, BC Centre for Epidemiologic and International Ophthalmology, made a presentation about his research, training background and how he combines clinical work and research, and shared his advice for clinician-scientist trainees. Thank you, Dr. Bassett.

For information on upcoming seminars, please visit our webpage at
http://www.med.ubc.ca/education/md_ugrad/mdphd/seminars.htm

Rural and Underserved Community Practice

Heather Heine, Claire Heslop, Aaron Joe and **Inna Sekirov** will be participating in the Rural Family Practice Clerkship (4 week practicum in rural communities) in the summer of 2009. They will spend 4 weeks one on one with a rural physician. In June, Heather will be working with **Dr. Jack Bryson** in Sechelt, and Inna will be working with **Dr. Clarence Fernandes** in Maple Ridge. Claire will be going to Gibsons to work with **Dr. Edward Berinstein** in August. Aaron will also be working with **Dr. Paul Lanfear** in Nanaimo in August. Have fun! Thanks go out to **Mr. Mark Nash** in the Department of Family Practice for his hard work in organizing the rotations!

Research Conferences Attended/Presented by Current MD/PhD Students in January – June 2009 (selected list)

- **Clara Westwell-Roper**, Year I MD/PhD student, presented at the UBC Diabetes Forum (14 March 2009), organized by the UBC Centre for Human Islet Transplant and Beta-Cell Regeneration. This annual forum features the latest diabetes research advances at UBC. Her poster presentation was entitled, "The role of TLR4 in multiple low-dose streptozotocin-induced diabetes."

- **Suze Berkhout**, Year V MD/PhD student, presented at the National Conference for Physician-Scholars in the Social Sciences and Humanities Meeting (28-29 March) in Philadelphia, Pennsylvania. She presented a talk on "Wanton women: transgression, pathology, and the contours of agency in the negotiation of HIV care". She is completing her PhD research with **Dr. Mark Tyndall**, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital.

- **Heather Heine**, Year VI MD/PhD student, presented her paper entitled, "Defects in de novo neoangiogenesis in CD34KO mice revealed in a Matrigel chamber model" at the Experimental Biology meeting (18-22 April) in

New Orleans, Louisiana. Heather also presented at the "UBC Beyond the BSc Science Career Expo 2008-2009" (6 February) in her capacity as an MD/PhD student at UBC and co-owner of a coffee company, she spoke as a panelist in the context of her career and how her degree in Science has contributed to her development.

- Besides **Aaron Joe** (see page 5), two other MD/PhD students also presented at the 5th American Physician Scientists Associate Annual Meeting, in Chicago, Illinois (23-26 April).
  - **Arezoo Astanehe**, "Induction of *PIK3CA* by Y-box binding protein-1 (YB-1) increases invasion of tumor cells"
  - **Claire Heslop**, "Oxidative stress genotypes and phenotypes for prediction of cardiovascular mortality in patients with stable coronary artery disease"

- **Michael Kozoriz**, Year III MD/PhD student, presented at the 3rd Annual Canadian Neuroscience Meeting, Vancouver, BC (24-27 May 2009), organized by the Canadian Association for Neuroscience. This annual scientific meeting attracts approximately 1000 neuroscientists. Michael presented, "The C-terminal region of connexin43 protects neurons during stroke". Michael is completing his PhD research with **Dr. Christian Naus**, in the Department of Cellular and Physiological Sciences.

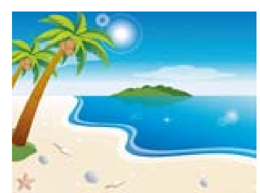
Michael Kozoriz

- On 29-30 May 2009, **Michael Kozoriz** also attended the 7th annual "Medical Students Mentoring Workshop: how to combine clinical and research careers in neurosciences" in Washington, DC. The event was put together by the Association of University Professors of Neurology, the American Neurological Association and the National Institute of Neurological Disorders and Stroke. Over 50 MD/PhD students were invited to attend this symposium where neuro MD/PhD students were encouraged to pursue clinical training and choose clinician-scientist careers. There were lectures and discussion on strategies for successfully melding clinical and research careers. Also, the satisfaction and power of a combined research and clinical career was emphasized. A session was devoted to discussing the sources and strategies for obtaining training and research support. The highlight of the forum was an opportunity for students to meet mentors who have successfully combined clinical and research careers in neuroscience.

Upcoming Events

❋CSCI/CIHR Joint Program: Young Investigators Forum, Ottawa, September 2009

UBC will be very well represented at this year's Canadian Society for Clinical Investigation (CSCI) Young Investigators Forum, 21-23 September 2009, in Ottawa. Seven MD/PhD students have been selected to present their outstanding research projects! They are: **Suze Berkhout, Brennan Eadie, Michael Kozoriz, David McVea, Kate Potter, Clara Westwell-Roper** and **Fiona Young**.



Have a great summer!

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Comments and Suggestions!

We welcome comments and suggestions to the UBC MD/PhD Program and to our newsletters.
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