



UBC MD PhD

UBC MD/PhD Program

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Newsletter – 2014 Summer Term

<http://mdprogram.med.ubc.ca/mdphd/news/>

Award Winners

The UBC MD/PhD students have been very successful in the 2014 external award competitions.

Philip Edgcumbe, Andrea Jones, Victor Li and Sandy Wright won prestigious Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarships. The Vanier Graduate Scholarship program is designed to attract and retain world-class doctoral students by offering them a significant financial award to assist them during their studies at Canadian universities. **Cynthia Min** won a CIHR Canada Graduate Scholarships Doctoral Award (CGS-D). **Parker Jobin, Hwan Lee and Eric Zhao** won a CIHR Canada Graduate Scholarships Master's Awards (CGS-M). The CIHR awards provide financial support to outstanding students pursuing master's or doctoral studies in health sciences. Congratulations to all the recipients and their supervisors for this year's outstanding results!



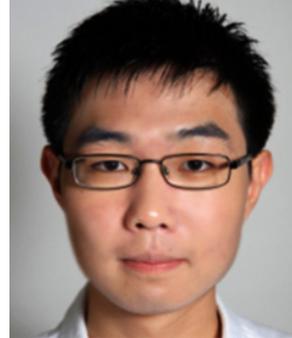
Philip Edgcumbe



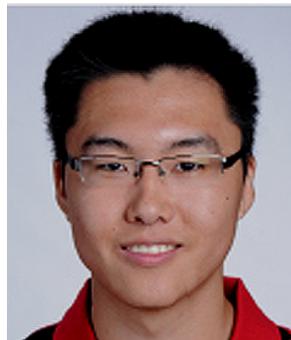
Parker Jobin



Andrea Jones



Hwan Lee



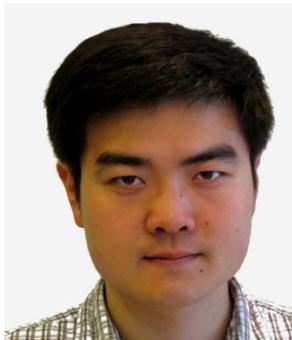
Victor Li



Cynthia Min



Sandy Wright



Eric Zhao

Class of 2014 – David McVea



Dr. Lynn Raymond (left) and **David McVea** (right)

Congratulations, David.

David McVea is our graduate in 2014.

David was an inaugural recipient of the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship in 2009. He also received a Michael Smith Foundation for Health Research Trainee Award and a UBC Four Year Doctoral Fellowship (4YF). His PhD research supervisor is **Dr. Timothy Murphy** in the Graduate Program in Neuroscience. His PhD dissertation title is “Spatial and temporal details of spontaneous cortical activity provide insights into functions in the adult and developing brain”.

Message from David:

I walked a lot as an MD/PhD student. We all do ... Hurriedly from our labs to a lunch-time seminar, frantically to see a sick patient in the middle of the night, sluggishly into a coffee shop after a long night on call or analyzing data in the lab. So I was well prepared for a few more steps across the stage to receive my combined MD/PhD degrees this year. And they were pretty memorable steps, too. Even though I had only known most of my graduating classmates for a few years, it was an honor to celebrate our accomplishments together in front of family, friends, and faculty.

It was also a great opportunity to reflect back on the program. Was it really seven years ago that I sat nervously in a conference room being interviewed by Drs. Raymond and Nielsen? I had to double check my calendar, but it was indeed. Seven pretty eventful years, too. In those years I learned how to build research equipment, deliver babies, sew up cuts and cast broken bones, give presentations to world experts in research, and comfort a family after breaking terrible medical news.

I also learned how much I have to learn. Every patient I met and every new student in the lab had something to teach me. I made lots of mistakes, but had great people to help me fix them. I especially appreciate all the help my supervisor, **Dr. Tim Murphy**, and **Dr. Lynn Raymond**, the MD/PhD Program Director, gave me. The many clinical teachers I've had over the four years have been superb, also. And my family, particularly my parents and my spouse, Jodie, have been constantly at my side through the ups and downs.

I get to keep learning, too. I'm very happy to be staying at UBC to begin my residency in Neurology, studying the most mysterious organ of the body (never mind what nephrologists might say). I am thrilled to have the chance to keep working with Dr. Raymond in a whole new capacity, as well as Dr. Murphy and all of the research contacts I have made during my PhD here.

So, a few more steps. Around the wards at night, down to the ER to see patients, to and from seminars, and even along the beaches and hiking paths on sunny post-call days. Good luck to all my colleagues in the program – the road is long but well worth the journey!

UBC Medicine Undergraduate Research Forum and Journal Release

The 10th Annual UBC Medicine Undergraduate Research Forum (MURF) and UBC Medical Journal Release events were held on Thursday, 20 February 2014, at the UBC Life Sciences Centre. These events were co-hosted by the UBC Medical Undergraduate Society, UBC Medical Journal and the UBC MD/PhD Program. Our Program Director, **Dr. Lynn Raymond**, delivered the opening remarks.

As in previous years, the research forum included a presentation from the UBC Medical Journal, a student-run academic journal with a goal to engage students in dialogue in medicine. The journal's scope ranges from original research and review articles to medical trends, clinical reports and commentaries in the principles and practice of medicine. Other activities included a panel discussion featuring clinician researchers and residents discussing the incorporation of research into residency and clinical practice, undergraduate student poster presentations, undergraduate student mini oral presentations and a research resource fair. We received over 40 submitted abstracts.



Farzad Jamshidi (left) and **Cynthia Min** (right).

This was a great opportunity to showcase the diverse range of projects being conducted by UBC students involved in biomedical health research. The event was video-conferenced to the Island Medical Program, the Northern Medical Program and the Southern Medical Program. Our sincere thanks to **Farzad Jamshidi** and **Cynthia Min** for their involvement in this annual event.

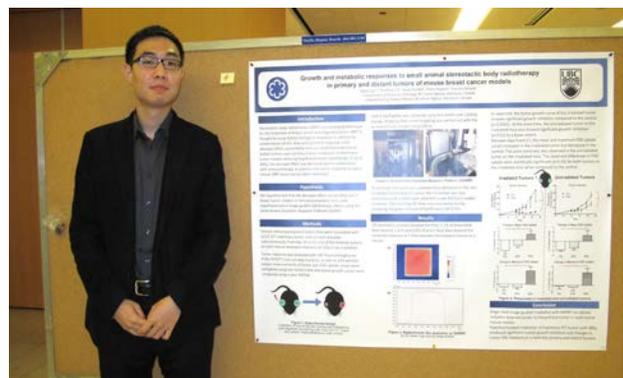
UBC Clinician Investigator Program Research Day

The annual UBC Clinician Investigator Program (CIP) Research Day was held on Monday, 2 June 2014, at the Paetzold Health Education Multi-Purpose Room, Vancouver General Hospital. Our Program Director, **Dr. Lynn Raymond**, was the keynote speaker. The MD/PhD students were invited to present at the CIP Research Day. We welcome this good opportunity for our trainees to mingle with other residents and clinician-scientists trainees.

Long Nguyen presented “Cell of origin affects the properties of De Novo generated primary human breast tumors”.

Julia Pon presented “MEF2B mutations recurrent in Non-Hodgkin Lymphoma decrease MEF2B transcriptional activity and dysregulate migration and proliferation”.

Hwan Lee presented “Growth and metabolic responses to small animal stereotactic body radiotherapy in primary and distant tumors of mouse breast cancer models” and won honorable mention in the poster competition.



Hwan Lee

The UBC CIP is available to residents enrolled in specialty or subspecialty residency programs accredited by the Royal College of Physicians and Surgeons of Canada (RCPSC) who have demonstrated an interest in and a potential for a career as clinician investigators. For more information on the CIP, visit their website at <http://www.cipubc.ca>

UBC MD/PhD PROGRAM

PhD Oral Defense - Long Nguyen



Long Nguyen

Congratulations to **Long Nguyen**, for successfully defending his PhD dissertation entitled, “Clonal heterogeneity of normal and transformed mammary stem cells” on 3 June 2014. Long made a superb presentation of his research work and answered all questions well. Long’s research work was highly recognized by the Examination Committee. The Chair of the Examination Committee commented that “Indeed, the oral examination largely took the form of a discussion between individual examiners and the candidate. As chair, I found it enjoyable to follow.” The External Examiner, **Dr. Jeff Rosen**, Baylor College of Medicine in Texas, commented that the thesis clearly meets and exceeds the criteria for a successful dissertation.

Long’s PhD research supervisor is **Dr. Connie Eaves**, Experimental Medicine Graduate program. We are very proud to share Long’s research interests with everyone. Great work, Long!!

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Clonal heterogeneity of normal and transformed mammary stem cells – **ABSTRACT**

The normal mammary gland contains “stem cells” with extensive *in vivo* growth and bi-lineage differentiation potential and a surface phenotype of basal cells (BCs). BCs also contain cells with more limited growth and differentiation activity *in vitro*. An analogous luminal-restricted progenitor (LPs) subset has surface characteristics of both basal and luminal cells. I hypothesized that the growth and differentiation activity displayed by *individual* mammary epithelial cells from both subsets would be highly diverse, and that the properties of tumours produced from these cells would be affected by their cell of origin. To address this hypothesis, I first developed a lentiviral-mediated barcoding strategy that involves transducing each cell with a unique 27-base pair non-coding DNA sequence so that the number of its clonal progeny can be inferred from high-throughput sequencing data obtained on the progeny of bulk-transduced populations. The use of “spiked-in” control cells carrying a known barcode provided an internal calibration for clone size calculations and allowed clones of ≥ 100 cells to be reliably detected. Application of this strategy to normal mouse and human mammary cells identified expected bi-lineage clones but an unanticipated predominance of lineage-restricted clones produced in primary transplants. These experiments also revealed that many clones apparent in secondary hosts were not detected in the primary hosts, indicating their origin from cells with very delayed growth activity. Application of the barcoding strategy to normal human BCs and LPs transduced with lentiviruses encoding $KRAS^{G12D} \pm PI3KCA^{H1047R} \pm TP53^{R273C}$ showed tumour formation in subsequently transplanted immunodeficient mice was rapid (within 8 weeks) and efficient from both cell types (8-12/18 donors, 1/200-1/4,000 transduced cells). However, tumours generated from LPs contained larger clones than tumours generated from BCs. Surprisingly, none of the LP-derived tumours were ER α^+ (typical of luminal-like breast cancers) whereas 60% of the BC-derived tumours were. Earlier analysis of xenografts of similarly transduced cells revealed changes in both the number and phenotype of the cells present. Taken together, these findings underscore the diverse regenerative activity of normal mammary cells and provide definitive evidence that the cell of origin can affect the properties of human breast tumours generated using identical oncogenes.

UBC MD/PhD PROGRAM

PhD Oral Defense - Clara Westwell-Roper

Congratulations to **Clara Westwell-Roper**, for successfully defending her PhD dissertation entitled, "Islet amyloid polypeptide aggregation is a local trigger for pancreatic islet inflammation" on 8 April 2014. Clara made an exceptional presentation of her research work and answered all questions well. The Examination Committee unanimously agreed that Clara's dissertation exceeded the standards expected of a doctoral candidate and is worthy of recognition with an appropriate award. The excellence of her dissertation was also noted by the External Examiner, **Dr. Marc Donath**, University Hospital Basel, Switzerland.

Clara's PhD research supervisor is **Dr. Bruce Verchere**, Department of Pathology & Laboratory Medicine. We would like to share Clara's research interests with everyone. A job well-done, Clara!!



Clara Westwell-Roper

* * *

Islet amyloid polypeptide aggregation is a local trigger for pancreatic islet inflammation – **ABSTRACT**

Patients with type 2 diabetes experience an inevitable deterioration of glycemic control leading to long-term complications and dependence on exogenous insulin. Amyloid deposition, macrophage infiltration, and upregulation of pro-inflammatory cytokines are common pathological features of both type 2 diabetic and transplanted islets. Islet amyloid is comprised primarily of aggregates of islet amyloid polypeptide (IAPP), a peptide that is co-secreted with insulin by beta cells. IAPP fibrils share a common cross- β -sheet structure with other amyloids of eukaryotic and microbial origin that activate innate immune cells via interaction with pattern recognition receptors. We therefore hypothesized that IAPP aggregation acts as a local trigger for islet inflammation.

We found that human IAPP, but not non-amyloidogenic rodent IAPP, induced a potent pro-inflammatory response in islets and macrophages that was amplified by autocrine/paracrine induction of interleukin-1 (IL-1). Pre-fibrillar IAPP activated the membrane-associated pattern recognition receptor Toll-like receptor 2 (TLR2) to induce expression of proIL-1 β . Secretion of mature IL-1 β required fibrillar IAPP and was attenuated by inhibitors of caspase-1 and the cytosolic NLRP3 inflammasome. Pancreatic islets from transgenic mice with beta cell expression of human IAPP expressed higher levels of pro-inflammatory cytokines than islets from wild-type littermates. Transgenic expression of human IAPP also altered the activation state of resident islet macrophages, the primary cell type responsible for IAPP-induced upregulation of IL-1 β . Clodronate liposome-mediated macrophage depletion improved islet function in human IAPP transgenic mice. Moreover, administration of IL-1 receptor antagonist improved human IAPP-induced glucose intolerance in mouse models of islet transplantation and type 2 diabetes. Inhibition of a local IAPP-induced pro-inflammatory response mediated by islet macrophages may therefore help to explain the islet-specific effects of anti-IL-1 therapies in patients with type 2 diabetes.

Collectively, these data suggest a novel – and potentially reversible – mechanism by which IAPP aggregation contributes to beta cell dysfunction and implicate the resident islet macrophage as a critical mediator of chronic islet inflammation in the setting of amyloid formation. Strategies to block TLR2 or NLRP3 activation, inhibit IL-1 signalling, or alter macrophage polarization may improve IAPP-induced islet dysfunction in type 2 diabetes and islet transplantation.

Meet our Incoming Students - May 2014

The MD/PhD Program admits applicants from three main routes: students completing a BSc (honours), a Master's program, or students who are in their Med I year. In 2013-2014, there was a particularly large amount of interest from the UBC Med I class. Three students, **Victoria Baronas**, **Adam Ramzy** and **Allen Zhang**, were



Victoria Baronas



Adam Ramzy



Allen Zhang

accepted into the combined MD/PhD Program in May 2014. They each come from different places, graduated from different programs, and are taking on projects in different fields. We welcome them into this first phase of training as future clinician-scientists!

Successful applicants who will be starting Med I in September 2014 will be profiled in the next issue of the newsletter.

Welcome to the Program!

Message from **Victoria Baronas**:

I am very excited to be joining the family of MD/PhD students at UBC! It will be a tough but rewarding and enlightening journey.

I was born and raised in Bogota, Colombia before making the big move to Vancouver 14 years ago with my family. At UBC I finished an honours degree in pharmacology where I was fortunate to experience a variety of research environments from clinical virology at Hoffmann La Roche to examining pacemaker channel regulation under the supervision of **Dr. Eric Accili** for my honours thesis. During my last year of the pharmacology program I was exposed to ion channel structure and function, and after a summer of working under **Dr. Harley Kurata** on voltage-gated potassium channels, I knew this was something I wanted to pursue and integrate into my medical education.

Adam Ramzy

To anyone who knows Adam, they know that his life is defined by near obsession for the few things in his life that he cares about. This has always included his family: his mother, father, and sister who live in his hometown of Calgary, Alberta. His family has recently grown to include his fiancée Jessica Pow; a graduate student in the Department of Psychology here at UBC. Otherwise, Adam has always been extremely devoted to athletics and has played several sports competitively including swimming, triathlon, and his current passion, powerlifting. He has competed at the local level since 2009 and joined the Canadian Powerlifting Union's (CPU) Team Canada in 2012. He has represented Canada at the International Powerlifting Federation's (IPF) Junior World Championships in 2012 and 2013, in Szczyrk, Poland and Killeen, Texas respectively. He is currently ranked as the #1 male powerlifter in Canada in his weight class and despite the major time constraints associated with his education, continues to be an active competitor. Adam holds 4 official and 3 unofficial Canadian records. He plans to continue bettering himself and competing on the international stage. His athletic dream is to reach the podium at the IPF World Championships in 2016 to qualify to represent Canada at the World Games in 2017.

My PhD research will be done under the co-supervision of **Dr. Harley Kurata** and **Dr. Filip van Petegem**. I will be investigating how ion channel regulation changes with repetitive stimulation, and how this alters generation and duration of action potentials. More specifically, I will be focusing on a voltage-gated potassium channel, Kv1.2, and identifying and characterizing a novel regulatory mechanism whereby repetitive stimulation causes an increase in potassium current, which may act to inhibit excessive neuronal excitation.

Outside of the lab and school I'm involved with a wonderful program called The Reading Bear which brings together kindergarten and high school students from different parts of the city through reading and education. I also love running outdoors and taking in the beautiful scenery Vancouver has to offer.

Academically, Adam began his training at the University of Calgary in 2008 where he completed his Bachelor of Health Science (BHSc) degree with honors in 2012. During this time, he was trained in both basic laboratory and animal study techniques, and developed a sincere passion for improving the clinical management of diabetes. Diabetes is a disease that has severe complications and despite incredible advancements in care – from the first patient injected with insulin in 1922, to the first islet cell transplants by 1990, patients continue to live shorter lives than their healthy counterparts and live with greater morbidity. Desiring to change this situation drove him to complete an honors thesis project on a surgical approach for treating diabetes and obesity. His honors thesis project was published in 2013.

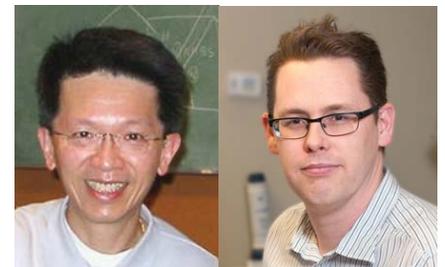
Adam joined the MD/PhD program in May 2014 as a MED I student. For his PhD, he will continue to research clinically relevant treatment strategies for diabetes. He will be working under the supervision of **Dr. Timothy Kieffer** and will be hosted by the Department of Cellular and Physiological Sciences, where he will be working on using a gene therapy based approach to combat the eventual loss of functional beta-cells observed in every diabetic patient. He hopes that the extensive training he will receive as an MD/PhD student will lead to a long career as a clinician-scientist involved in the evolving management of diabetes.

Allen Zhang

Allen Zhang's co-supervisors are **Dr. Wyeth Wasserman**, Department of Medical Genetics and **Dr. Sohrab Shah**, Department of Pathology & Laboratory Medicine, and his hosting department is the Bioinformatics Graduate Program. Allen's research harnesses computational techniques to evaluate changes in gene regulation in several types of cancers. Defective gene regulation can disrupt the cell cycle and coupled with protein alterations, induce uncontrolled cell division. Genome sequencing techniques have evolved rapidly over the past decade, but their predictive capacity in clinical scenarios has lagged behind. While protein-coding changes in cancer can be directly identified and characterized, reliable analysis tools for regulatory mutations are virtually nonexistent. Bridging cancer genomics with patient therapeutics will require a strong foundation in both computational and clinical work. Allen believes that a more complete understanding of defective regulation and signaling in cancers will lead to great improvements in targeted treatments for personalized medicine.

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

This well-established seminar series aims to illustrate the relationship that exists between clinical practice and medical research. The seminars are organized for budding clinician-scientists of the MD/PhD and Clinician Investigator Programs, which allow the trainees to hear about different career tracks and various ways to combine clinical and research work. In addition to speaking about their active research, the invited speakers discuss their experiences and training backgrounds, share their advice with prospective clinician-scientists, and give their opinions on career development options for clinician-scientists. All faculty, clinical investigator trainees, and students in the Faculty of Medicine are invited. Our usual venue is at the Medical Student Alumni Centre, 6:00-7:00 pm, video-conferenced to Victoria, Prince George and Kelowna.



Dr. David Li **Dr. David Scott**

Monday, 28 April 2014

Invited speaker: **Dr. David Li**, Professor, Department of Radiology, UBC

Monday, 16 June 2014

Invited speaker: **Dr. David Scott**, Clinician-scientist, Centre for Lymphoid Cancer, BC Cancer Agency

For information on upcoming seminars, please visit our webpage at <http://mdprogram.med.ubc.ca/mdphd/seminars/>

Science Translational Medicine Current Policy Collection
http://stm.sciencemag.org/site/misc/current_policy_collection.xhtml

Five MD/PhD students received Faculty of Medicine Graduate Awards in 2014 – **Amanda Dancsok, Parker Jobin, Andrea Jones, Frank Lee and Eric Zhao.** Congratulations!

Victor Li is our student representative on the Faculty of Medicine Research Council, 2014-2015.

Our sincere thanks to the **Child & Family Research Institute** for the continued support that we have received. The generous financial support has allowed the MD/PhD Program to develop stable funding for additional MD/PhD studentship slots in the coming years.



Comments and Suggestions

We welcome comments and suggestions to the UBC MD/PhD Program and to our newsletters. Please send comments to the MD/PhD Program office, 2N6 - 2818 Detwiller Pavilion, 2255 Wesbrook Mall, UBC, Vancouver, BC, Canada V6T 2A1. Phone: 1-604-822-7198 Fax: 1-604-822-7917
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Edited by Jane Lee, Program Coordinator, MD/PhD Program, UBC