



# UBC MD PhD

## UBC MD/PhD Program

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### Newsletter – 2019 Summer

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

### Dr. and Mrs. Anthony W. Chow MD/PhD Studentship



Dr. Anthony Chow

Our Founding Program Director and his wife have generously funded the new **Dr. and Mrs. Anthony W. Chow MD/PhD Studentship**. Awardees will be selected by our Program Directors, and the first studentship will be assigned in September 2019. Thanks to Dr. Chow, for his kindness and continued support for the program he founded in 1996.

**Dr. Anthony Chow** is Professor Emeritus and former Head of the Division of Infectious Diseases, Department of Medicine, University of British Columbia and Vancouver Hospital. He retired from clinical practice, teaching and administration in July 2006. His own research focused on the role of anaerobic bacteria in health and disease, structure/function of staphylococcal superantigens, and the molecular pathogenesis of staphylococcal toxic shock syndrome. Since

retirement, Dr. Chow has continued to be active in knowledge acquisition and translation in the field of infectious diseases nationally and internationally.

Dr. Chow was the keynote speaker at the Project Pulse Vancouver (PPV), on Saturday, 2 March 2019. PPV is a student organization targeting those undergraduate and postgraduate students interested in Medicine and the Health Sciences. Dr. Chow spoke on the topic of Translational Medicine and the Clinician-Scientist career track. Two of our students, **Andy An** and **Eric Zhao**, represented the program and participated at the event as student panelists. They shared their experience as a trainee in the UBC MD/PhD Program and answered questions about their research. Thank you.

**Thank you!**



Andy An (left) and Eric Zhao (right)  
at the Project Pulse Vancouver 2019

## Dr. Liam Brunham - New MD/PhD Associate Director

We are delighted that our own program alumnus, **Dr. Liam Brunham**, has agreed to take on the responsibility as Associate Director of the MD/PhD Program as of 1 July 2019.



**Dr. Liam Brunham**

**Dr. Liam Brunham** graduated from the UBC MD/PhD Program in 2008, winning the Governor General's Gold Medal for the top PhD thesis across the entire university that year. After completing residency in Internal Medicine, and fellowship in General Internal Medicine, he completed the Clinician-Investigator Program in Singapore before eventually being recruited by UBC. Liam is currently an Assistant Professor in the Department of Medicine at the University of British Columbia and a Principal Investigator at the UBC Centre for Heart and Lung Innovation. He is an attending physician at the Health Heart Program Prevention clinic at St. Paul's Hospital, one of the largest specialty lipid clinics in Canada. Liam is also a Canadian Institutes of Health Research (CIHR) New Investigator and a Michael Smith Foundation for Health Research Scholar. In 2017, he was recognized as one of Canada's Top 40 under 40. His research focuses on genetic aspects of cholesterol levels, cardiovascular disease, and pharmacogenomics, and he holds a Tier 2 Canada Research Chair in Precision Cardiovascular Disease Prevention.

As a role model for our students, Dr. Brunham has been actively involved with the MD/PhD Program as a member of the Admissions Committee. In his new role as Associate Director, he will no doubt bring a fresh and exciting perspective to our program. Welcome!

### Message from Dr. Liam Brunham:

"I am thrilled to take on the role of Associate Director of the UBC MD/PhD program. As a graduate of the program myself, I firmly believe that training in an MD/PhD program provides an incredible opportunity to advance the science of medicine and improve the lives of our patients. It is amazing to see how the UBC program has grown under the leadership of Drs. Raymond and Nielsen over the past 10 years, and I am excited to participate in continuing to grow and develop this excellent training program. I look forward to working with our students and supporting you on your pathways to becoming clinician-scientists."

--Liam Brunham

## Adam Ramzy - 3 Minute Thesis Winner!



**Adam Ramzy at the 3MT competition**

Over the past few months **Adam Ramzy**, MD/PhD student, has competed in the 3 Minute Thesis (3MT) competition. The 3MT is an international competition wherein graduate students are asked to summarize their thesis research in a 3-minute presentation for a general audience. This year, Adam competed against over 80 graduate students and won the [UBC 3MT](#) competition, which qualified him for the [Western Canadian](#) competition in Prince George on 17 April 2019. Adam then won the Western Canadian regional championship and represented UBC at the Canadian Association of Graduate Studies National competition. Congratulations!

Adam shares, "Competing in the 3MT competition was a great experience that I recommend to fellow graduate students. It offered not only the great experience of meeting diverse students from throughout UBC and learning about their research, but was also an extremely useful opportunity to practice scientific communication. After spending 4 years focused on writing papers and a 250-page thesis, it was a valuable exercise to reconsider how to communicate your research with a non-specialized audience in a pragmatic timeframe. It was a privilege to not only compete in the official 3MT competitions, but as a UBC finalist I was able to participate in three community outreach events that were great opportunities to refine the presentation and gain further insight into how best to engage with a lay audience. I would be happy to discuss my experiences with anyone interested."

See Adam's thesis abstract on page 7 in this newsletter.

# UBC MD/PhD PROGRAM

## Class of 2019

We had three graduates this spring – **Victor Li**, **Daniel Woodsworth** and **Sandy Wright**. The graduation ceremony was held on 23 May 2019 where they received congratulations from the Dean of Medicine **Dr. Dermot Kelleher**, UBC president **Dr. Santa Ono**, MD/PhD Program Directors **Dr. Torsten Nielsen** and **Dr. Lynn Raymond**, and their family and friends. Congratulations!

## Messages from Our Graduates (Class of 2019)

### Victor Li

The MD/PhD program has played an integral part of my life in the last 8 years. I've had the opportunity to pursue my passions in medicine and neuroscience in an academic environment full of the brightest and most supportive mentors, alongside many like-minded and inspirational colleagues. It has been a wonderful journey, and now at its end, I look forward to the many opportunities ahead. For this, I have **Lynn Raymond**, **Torsten Nielsen**, and **Jane Lee** to thank. Their passion and dedication to raising the next generation of clinician scientists is very clear, and I feel privileged and grateful to have been part of this community that they established at UBC.

I ended up exploring a few different directions in my research before finally settling on the study of NMDA receptor allosteric modulators and their role in neuropsychiatric disorders. My PhD co-supervisors **Yu Tian Wang** and **Tony Phillips** were great mentors and supports during my slightly tortuous studies, and always helped me find the opportunities in each adversity. They helped me mature from a wide-eyed dreamer into a rigorous and passionate scientist, and have taught me so much along the way. As I now start my residency at UBC in the Psychiatry Research Track, I thank them for their gift to me as I move confidently into the next chapter of my career.

Numerous other experiences have been highlights during my time here. I had a wonderful experience in clerkship, with a smooth transition back with support from the program and from classmates now ahead of me in training. I had the pleasure of working on the Alzheimer's disease XPrize Project with **Philip Edgcumbe**, who opened my eyes to the sorts of things that could be accomplished with exponential thinking, and how MD/PhD's might fulfill roles outside the perceived norms. And, I met and married my wife **Jennifer**, and have the program to thank for serving as our de facto matchmaking service.

Congratulations to **Dan Woodsworth** and **Sandy Wright**, who are graduating alongside me this year! For the rest of us not quite at the finish line, hang in there. It's an adventure very few people get to experience, and it opens a world of opportunities when you finish. I look forward to hopefully working with you in the future!

Thanks again to everyone for a very colorful and formative 8 years. It's been a blast!



**Victor Li** tied the knot with MD/PhD Year 4 student **Jennifer Ji** on 1 June 2019. This is the first time our MD/PhD Program has led to an engagement and a marriage!! Congratulations!



## Messages from Our Graduates (Class of 2019) con't

Daniel Woodsworth



Daniel Woodsworth

I am writing this from a small internet cafe in Ladakh in Northern India, which makes my time in the UBC MD/PhD program seem more remote than the 11 days it has been since I wrote my last exam. One year short of a decade is a long time by any measure. During this time I have learned much about biology, the process of research, and the practice of medicine, as well as much about myself. That acquisition took some doing, and so I would like to thank the many people who have helped me get here. First and foremost I would like to thank my family: my mum and dad and my sister. From when I was little through to deciding on my residency choices, they have provided love and support. It is hard for me to imagine a trajectory in which I arrived where I am today without my family, and I am incredibly grateful for them.

When I think of my time in the MD/PhD program, I imagine my PhD in the centre with medicine as bookends at either end. I would like to thank my supervisor **Dr. Robert Holt** for his enthusiasm for trying new things, and for supporting my entry into the world of wet lab biology-- I learned a lot from him and his nearly indecipherable whiteboard! Any PhD has long days and months, and mine were greatly brightened by **Scott Brown**, **Govinda Sharma**, and **Lisa Dreolini**. Finally I would also like to thank **Dr. Dan Coombs** for the many enjoyable hours we spent writing models on his chalkboard.

Looking back now, my discussions with **Dr. Lynn Raymond** and **Dr. Torsten Nielsen** regarding the UBC MD/PhD program seem remote, yet they are easily remembered. I would like to thank them for their support and guidance, but far more importantly, I think they have built one of the top MD/PhD programs in the country and they deserve a huge amount of credit and appreciation for that. Finally their efforts, along with **Jane Lee's**, in navigating the necessary bureaucracies of a dual degree program is greatly appreciated.

When I started this program I had no idea what type of medicine I wanted to practice. Looking to the future, I am now truly excited to be starting my Internal Medicine residency program here in Vancouver in July. So many faculty and residents have made an impact over the past 2 years, and I would like to thank them for their teaching, guidance and encouragement. With that, I would like to once again thank and acknowledge all the teachers, mentors and friends, many of whom I look forward to seeing at talks and on the wards over the coming years.



## Messages from Our Graduates (Class of 2019) con't

### Alexander (Sandy) Wright

It is with deep gratitude that I move forward from the MD/PhD Program at UBC. As I glance over the past and present MD/PhD students I still cannot believe I am lucky enough to be counted amongst you. In particular, a heartfelt thank you to **Philip Edgcumbe, Victor Li, Eric Zhao, Cynthia Min, Andrea Jones, Amanda Dancsok, Adam Ramzy, Farzad Jamshidi, and Gareth Mercer**; you continue to inspire and amaze me on a daily basis. I am indebted to **Drs. Lynn Raymond and Torsten Nielsen** for taking a chance on having a student complete the combined degree at a distributed medical site; it was an absolute privilege to complete my training in Kelowna at the Southern Medical Program (SMP). The highs and lows of training as a clinician scientist over the last 8 years have been transformative. From the moment we arrived in Kelowna as the inaugural SMP class, the entire community – from patients to physicians to nurses to techs to volunteers – embraced us with open arms. The excitement around having a new medical program in the Interior directly contributed to an unparalleled clinical experience as medical students.



Sandy Wright

My research background and interest in injury biomechanics combined with my history in athletics created a perfect opportunity to pursue a PhD under the supervision of **Dr. Paul van Donkelaar**. I cannot thank him enough for his trust, patience, and support in allowing me the freedom to shape my PhD, alongside his mentorship and insights from a highly successful academic career. The numerous talented, knowledgeable, inspiring researchers and clinician scientists across the globe I've had the pleasure to work with during my PhD have fuelled my drive to never stop exploring. Moreover, they have been instrumental in helping me move forward with confidence and humility.

The irony of suffering a devastating concussion in a hockey game while I was completing my doctoral thesis on sport-related concussions was not lost on me. Worse, it happened when my first daughter was 3 days old... my poor wife. The experience came with many silver linings however, especially since the forced 7 months away from my studies afforded irreplaceable bonding time as a new family. I owe much gratitude to the Physician's Health Program, and encourage all physicians in BC to become aware of exactly what this initiative provides. The long, complicated (and thankfully complete) concussion recovery process allowed me to peer over the curtain and gain meaningful insight into the patient experience of traumatic brain injury, as well as mental health struggles more broadly. Clinically, this helps ground me in a place of compassion. Academically, it provides context and personal meaning to my research.

Of course, the most influential piece of the last 8 years has been family. My wife, **Kari**, has been the anchor that allowed me to weather this whole experience. Our daughters, **Eleanor** and **Waverly**, bring a new perspective and lesson to my life every day; it is such a privilege to be the father of two talented, kind, thoughtful, and confident girls. My parents, in-laws, sister, and extended family have been astonishingly supportive of every need along the way, a debt which I can never repay. Thank you so much to all of you.

With incredible excitement we are off to Saskatoon for five years, as I've been fortunate to match into Ophthalmology at the University of Saskatchewan where I plan to broaden my expertise in neuroscience and concussion to focus on the eye-brain axis. Thank you to everyone at the MD/PhD Program, and good luck!

## Award Winners

The current group of UBC MD/PhD students have been very successful in 2019 external award competitions. **Wissam Nassrallah** won prestigious Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship. **Daniel Kwon** won a CIHR Doctoral Research Award. **Andy An** and **Katrina Besler** won a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Master's Award (CGS-M) in their first year of eligibility. Congratulations to all the recipients and their supervisors for this year's outstanding results!

**Wissam Nassrallah** (supervisor: **Dr. Lynn Raymond**)

Hosting department: Graduate Program in Neuroscience

- Neuroprotective effect of Sigma-1 receptor and Activin A on synaptic function and calcium handling in Huntington's disease

**Daniel Kwon** (supervisor: **Dr. François Bénard**)

Hosting department: Interdisciplinary Oncology Program

- Novel radiotracers targeting proteases overexpressed in invasive cancers

**Andy An** (supervisor: **Dr. Robert Hancock**)

Hosting department: Microbiology & Immunology Graduate Program

- Temporal epigenetic and transcriptomic changes in the innate and adaptive immune responses in sepsis

**Katrina Besler** (supervisor: **Dr. Gordon Francis**)

Hosting Department: Experimental Medicine Graduate Program

- Smooth muscle cell lysosomal acid lipase in atherosclerosis

**UBC MD/PhD Award Winners**

### Other Award Winners

**Rozlyn Boutin** – Keystone Symposium Travel Award: National Institute of Allergy and Infectious Diseases Scholarship

**Amanda Dancsok** – Duncan Hamilton Award

**Frank Lee** – Canadian Blood Services Graduate Fellowship

**Alvin Qiu** – Interdisciplinary Oncology Program Outstanding Student Award

**Mark Trinder** – Faculty of Medicine Graduate Student Initiative Fund (Research-Partnership Initiative)  
– Golden Helix Abstract Competition (First Place)

**Sandy Wright** – UBC Faculty of Medicine Publication Award

## Meet Incoming Student - Rohit Singla

**Rohit Singla** was admitted into the MD/PhD Program in May 2019, applying and entering during his Med I year. Rohit holds a BSc in Computer Engineering and a MSc in Biomedical Engineering, both at UBC. In his undergrad, he worked at a FORTUNE 500 company that is a global leader in geographic information



**Rohit Singla**

systems, and did a senior project with an industry leader in medical imaging. During his graduate studies, his research was at the intersection of ultrasound imaging, augmented reality, surgical robotics and kidney cancer surgery. Collaborating with industry and an international academic institute, Rohit built three ultrasound-based augmented reality guidance systems for use with the da Vinci surgical system in partial nephrectomies. This work resulted in two best paper awards. Prior to entering his MD, Rohit would spend a year as a research engineer leading projects in anesthesia, urology and maternal/fetal medicine. Rohit's MD/PhD will be under the joint supervision of **Dr. Robert Rohling** and **Dr. Christopher Ngan**, exploring how to improve ultrasound imaging and its role in clinical decision making. Outside of academia, Rohit is an avid football fan, film buff, and a brunch connoisseur. Welcome aboard!

## PhD Oral Defense

Five of our students (a new record for a single year in our program) successfully defended their PhD dissertations and returned to clinical rotations this spring. We are very proud to share their research abstracts with everyone.

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### Allen Zhang

Research supervisor: **Drs. Wyeth Wasserman and Sohrab Shah**

Hosting department: Bioinformatics

Defense date: 25 April 2019

Dissertation title: Evolutionary dynamics of ovarian cancer microenvironments and tumour cells



Allen Zhang

### ABSTRACT

High-grade serous ovarian cancer (HGSC) is the most common and lethal histotype of epithelial ovarian cancer. Often presenting as multi-site disease, HGSC exhibits extensive malignant clonal diversity with widespread but non-random patterns of disease dissemination. The proclivity of HGSC toward clonally heterogeneous disease is thought to underlie the prevalence of treatment-resistant disease. Yet, the factors that influence the spatial distribution of cancer clones in HGSC remain largely uncharacterized. Hypothesizing that distinct peritoneal niches formed by microenvironmental cell types shape the observed patterns of clonal dynamics in HGSC, the primary aim of this thesis was to understand how microenvironmental factors influence malignant cell evolutionary dynamics.

To establish the experimental substrate for this thesis, I led the construction of a cohort of 148 tumour samples from 41 HGSC cases (Chapter 2). In addition to coordinating clinical case identification, I oversaw and learned how to create patient-derived xenograft models and conduct single cell experiments from patient tumours. Leveraging this resource, I explored whether local immune microenvironment factors shape tumor progression properties at the interface of tumor-infiltrating lymphocytes and cancer cells (Chapter 3). Through multi-region study with whole-genome sequencing, immunohistochemistry, image analysis, gene expression profiling, and T- and B-cell receptor sequencing, I identified three immunologic subtypes across samples associated with patterns of malignant clonal diversity. These findings were consistent with immunological pruning of tumor clones as evidenced by neoantigen depletion, HLA loss-of-heterozygosity, and spatial tracking between T cell and tumor clones. Finally, in order to explore the non-lymphocytic components of the tumour microenvironment, I developed an automated approach to cell type identification from single cell RNA-seq data that eliminates the manual work involved in traditional workflows reliant on post-hoc expert annotation (Chapter 4). I demonstrated how this method performs superiorly to state-of-the-art workflows for cell type identification and applied the method to profile the HGSC microenvironment.

Collectively, this work highlights multiple interfaces of evolutionary interplay between malignant and non-malignant cells in the HGSC microenvironment, identifying novel mechanisms by which tumour cells escape from immune recognition. These results will inform the interpretation of results from immunotherapy clinical trials and set the stage for comprehensive microenvironment profiling in large HGSC cohorts and other cancers.

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### Adam Ramzy

Research supervisor: **Dr. Timothy Kieffer**

Hosting department: Cellular & Physiological Sciences

Defense date: 2 May 2019

Dissertation title: Removing, replacing, and processing proinsulin in Beta-cells



Adam Ramzy

### ABSTRACT

Diabetes affects over 425 million worldwide, costs billions, and causes morbidity and mortality for patients. Though insulin injections are lifesaving, insufficient  $\beta$ -cell mass and function leaves patients facing risks of chronic hyperglycemia and acute risks of hypoglycemia. Replacement of  $\beta$ -cells via transplantation of cadaveric islets is a functional cure but is limited by a paucity of donor tissue. If  $\beta$ -cell replacement or (re)generation therapies were abundantly available, they could be potential cures for diabetes. To this end, investigating  $\beta$ -cell development and function is worthwhile. In the current thesis, we first characterized the role of insulin on  $\beta$ -cell development and maturation by studying insulin knockout mice (Ins1-/-Ins2-/-). Though insulin was necessary for  $\beta$ -cell maturation, insulin replacement by islet transplantation but not insulin injection, supported maturation of endogenous

$\beta$ -cells. Second, we developed and characterized an adeno associated virus (AAV) carrying Cre recombinase regulated by an insulin promoter (AAV Ins1-Cre) for *in vivo* genetic manipulations. AAV Ins1-Cre produced efficient recombination in  $\beta$ -cells alongside off-target recombination, making it a useful tool when off-target effects are controlled for or deemed unimportant. Third, we assessed the viability of a gene therapy for the Ins1-/-Ins2-/- mouse model of monogenic diabetes. We delivered an insulin gene to  $\beta$ -cells (an Ins1 promoter driving human insulin (INS) or mouse insulin 1 (Ins1)) using AAV Ins1-INS or AAV Ins1-Ins1. Though the AAV delivered the insulin gene to  $\beta$ -cells, Ins1-/-Ins2-/-  $\beta$ -cells retained a processing defect leading to secretion of insulin's precursor proinsulin. We created adult insulin knockout mice using AAV Ins1-Cre and failed to prevent onset of diabetes with AAV Ins1-Ins1. Finally, in Chapter 5 we assessed the production of mature insulin in human  $\beta$ -cells. Despite consensus on the role of prohormone convertase 2 (PC2) in proinsulin processing, we provide evidence that unlike mouse  $\beta$ -cells, human  $\beta$ -cells produce mature insulin without PC2. This thesis provides insight into the developmental impact of "removing insulin" from  $\beta$ -cells, assesses the viability of a gene therapy "replacing insulin" in  $\beta$ -cells, and revises a longstanding theory on the "processing of proinsulin" in human  $\beta$ -cells. These findings may guide development of gene- and cell- based therapies for diabetes.

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## Cynthia Ye

Research supervisor: **Dr. Wyeth Wasserman**

Hosting department: Medical Genetics

Defense date: 6 May 2019

Dissertation title: Towards the identification of causal genes and contributing molecular processes underlying strabismus



Cynthia Ye

## ABSTRACT

Eye misalignment, or strabismus, has a frequency of up to 4% in a population, and is known to have both environmental and genetic causes. Genes associated with syndromic forms of strabismus (i.e. strabismus concurrent with multiple phenotypes) have emerged, but genes contributing to isolated strabismus remain to be discovered. Only one isolated strabismus locus, STBMS1 on chromosome 7, has been confirmed in more than one family, but the inheritance model of the locus is inconsistent between studied families and no specific causal variant has been reported. The large set of syndromes with strabismus suggests that within the visual system multiple perturbations of an underlying genetic network(s) can have the common output of disrupted eye alignment. Thus, I used a bioinformatic-driven approach to analyze curated genes associated with strabismus to provide insight into the biological mechanisms underlying strabismus, highlighting a link to the Ras-MAPK pathway. During the process, I noticed strabismus presenting within a large number of intellectual disability disorders. Therefore, I studied the co-occurrence of strabismus and other common phenotypes in a series of patients with intellectual disability, which confirmed a significant correlation between eye alignment and intellectual disability. Finally, I resumed efforts from my prior studies to identify the genetic cause in a seven-generation family with isolated strabismus inherited in an autosomal dominant manner. The top candidate gene disruption, altering a likely *is*-regulatory region of the *FOXC1* gene, was identified through the incorporation of linkage analysis, next generation sequencing, and in-depth bioinformatic analyses. This thesis identifies potential roles for genes participating in the Ras-MAPK pathway, emphasizes the role of the central nervous system, and reveals *FOXC1* as a causal gene candidate for isolated strabismus.

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## Parker Jobin

Research supervisor: **Dr. Christopher Overall**

Hosting department: Biochemistry & Molecular Biology

Defense date: 22 May 2019

Dissertation title: Moonlighting tRNA synthetases as extracellular targets of matrix metalloproteinases



Parker Jobin

## ABSTRACT

Protease activity is of particular interest because of its irreversible nature and hence commitment by living systems to post-translationally truncate or remove by degradation its substrates. Degradomics, a combination of approaches used to study proteases, their inhibitors, and their substrates, allows powerful analyses of proteolytic networks. Degradomics has allowed the identification of a vast number of novel protease substrates, leading to speculation of molecular partnerships previously unknown to biology.

For the matrix metalloproteinase (MMP) family of extracellular proteases, degradomic screens have led us to realize that many proteins with intracellular roles are secreted by non-canonical means to perform novel extracellular functions that may be modulated by MMPs. Where it was once thought MMPs only degraded extracellular matrix (ECM), they are now known to process diverse signaling substrates.



Interesting multifunctional targets of MMP processing are “moonlighting” proteins that have more than one unique activity and can shuttle between intracellular and extracellular compartments to exhibit different functions in each. Recently, intracellular tRNA synthetases have been identified as extracellular moonlighting proteins. Despite the lack of signal peptides, six tRNA synthetases have been found to be secreted and perform different functions in the extracellular environment, notably activation of the immune response.

I hypothesized that MMP processing of tryptophanyl-tRNA synthetase (WRS), a cytokine, and tyrosyl-tRNA synthetase (YRS), fragments of which are proinflammatory, would modify the inflammatory activities of these tRNA synthetases. First, WRS and YRS secretion from human cells was confirmed. I then expressed and purified full-length WRS and YRS to evaluate MMP processing of these proteins. MMP cleavage sites within WRS and YRS were determined, revealing that MMPs cut the N-terminus from WRS but cleave the C-terminus from YRS, generating stable proteoforms. Cell culture assays revealed that both WRS and YRS have proinflammatory functions, each activating Toll-like receptors (TLRs). While removal of the N-terminus of WRS by MMP processing attenuated these activities, conversely, MMP cleavage of YRS increased proinflammatory functions, suggesting that MMPs play differing roles depending on the substrate being processed. This research exposes the exciting biology that awaits in tapping a previously unknown well of moonlighting MMP substrates with diverse bioactive roles.

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**Amanda Dancsok**

Research supervisor: **Dr. Torsten Nielsen**

Hosting department: Pathology & Laboratory Medicine

Defense date: 6 June 2019

Dissertation title: The immune microenvironment of sarcomas: A comprehensive evaluation of infiltrating immune cells and checkpoint biomarkers in musculoskeletal tumors







**Amanda Dancsok**

## **ABSTRACT**

Sarcomas are aggressive cancers of the connective tissues, such as bone, muscle, cartilage, and fat. Despite their diverse origins, sarcomas are predominantly treated by surgery and radiation, as conventional chemotherapy has limited benefit for most subtypes. When sarcomas recur or metastasize, there are few options for systemic therapy, and prognosis is very poor. Despite advancements in our understanding of the molecular drivers of sarcomas, almost no new treatments have proven benefit for metastatic sarcomas. Immunotherapy has shown value for other cancers, such as melanoma and lung cancer; however, sarcomas lag behind the common cancers in our understanding of their immune microenvironment and potential for treatment with immunotherapeutics. Early trials using single-agent immune checkpoint inhibitors in sarcomas delivered mixed results, but these studies somewhat indiscriminately lumped together different sarcoma subtypes that might have critical immunological differences. My study employs tissue microarrays incorporating 1360 sarcoma specimens (spanning 23 subtypes) to characterize immune infiltrates and expression of targetable immune biomarkers, using immunohistochemistry. Genomically-complex sarcoma types – driven by mutations and/or copynumber alterations – are found to have much higher levels of lymphocytic and phagocytic immune infiltrates than translocation-associated sarcomas. Across nearly all subtypes, tumor-associated macrophages outnumber tumor-infiltrating lymphocytes, predominately M2 (antiinflammatory) macrophages. Expression of the target of first-generation immune checkpoint PD-(L)1 is uniformly low, but expression of LAG-3 and TIM-3 – emerging immune checkpoints – is significantly more common. Expression of anti-phagocytic immune checkpoint CD47 is yet more predominant, displaying all-or-nothing expression with 100% positivity seen in over half of positive cases. To further characterize the lymphocytic response, T-cell receptor (TCR) sequencing was performed on specimens from 25 sarcoma patients on a clinical trial of tremelimumab (anti-CTLA-4) with durvalumab (anti-PD-L1). We found that the TCR repertoire is richer and more diverse among the genomically-complex sarcomas relative to the translocation-associated sarcomas, and following immune checkpoint blockade, we observed an overall increase in the clonality of the peripheral TCR repertoire. My study demonstrates a tangible positive relationship between genomic complexity and immunogenicity, and highlights novel immune checkpoints of relevance to sarcomas. As such, this work provides the essential translational background to direct the use of immunotherapy in sarcoma management.

## PhD Comprehensive Exam

Congratulations! **Rozlyn Boutin**, **Michael Skinnider**, **Mark Trinder** and **Daniel Kwon** successfully passed their comprehensive examinations and have therefore been "admitted to candidacy." Our students follow the comprehensive examination guidelines in their hosting department for completion of exam and advancement to candidacy (with no additional or alternate regulations being imposed by the MD/PhD Program).

Name of student	Exam date	Research supervisor	Research topic
 <b>Rozlyn Boutin</b>	26 February 2019	<b>Dr. Brett Finlay</b>	Mechanistic elucidation of the asthma-protective and -predictive effects conferred by specific members of the gut microbiota in early life
 <b>Michael Skinnider</b>	8 March 2019	<b>Dr. Leonard Foster</b>	Understanding human biology and disease through tissue-specific protein-protein interaction networks
 <b>Mark Trinder</b>	30 April 2019	<b>Dr. Liam Brunham</b>	Cholesteryl ester transfer protein as a novel regulator, predictor, and therapeutic target of sepsis
 <b>Daniel Kwon</b>	17 June 2019	<b>Dr. François Bénard</b>	Development of novel theranostic agents targeting the tumour microenvironment

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

Our seminar series aims to illuminate the relationship that exists between clinical practice and medical research, allowing MD/PhD and other interested students 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 of all stripes, students in the Faculty of Medicine and prospective applicants to our program are invited. Our usual venue is at the Medical Student Alumni Centre, 6:00-7:00 pm, web linked at <https://meet.vc.ubc.ca/webapp>.

Thanks go to **Dr. Inna Sekirov** for sharing her clinical and research experiences with us on 10 June 2019. Title of talk: "[Career in Laboratory Medicine - from residency to faculty](#)". Dr. Sekirov is one of our alumna. She is now Clinical Assistant Professor, Department of Pathology & Laboratory Medicine, UBC; and Program Head, Mycobacteriology, Public Health Microbiology and Reference Laboratory, BC Centre for Disease Control.

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



**Dr. Inna Sekirov**

## Student Publications

Over the years, MD/PhD students have been very successful in publishing their outstanding papers in national and international journals. The list of publications is available on our [webpage](#). Congratulations, everyone.

## UBC Medicine Spring Gala

The 25<sup>th</sup> UBC Medicine Spring Gala took place on Saturday, 9 March 2019, 5:00-8:00 pm, at the UBC Chan Centre. The Spring Gala is a non-profit production, organized completely by the UBC medical and MD/PhD students. Any profit from ticket sales was donated to a local BC charity. This year, the students supported Covenant House Vancouver. From dazzling dance displays to moving vocal performances, the students put together an unforgettable and exciting night. Many of the M.D/PhD students performed at the event. Here are some memories to share with our readers.



Left: "Murmur & Trill" piano and flute duet, **Eric Zhao** and **Sabine Lague** (MD student)

Centre: Classical guitar & cello duet, **Dr. Liam Brunham** (our Associate Program Director and MD/PhD alumnus) and **Erin Sachs**

Bottom: UBC Med Choir, **Katrina Besler** was a tenor, and **Amanda Dancsok** was a soprano and also arranged the piece they sang, a medley of songs from Les Miserables.



Carotid Chop - Martial Arts Routine,  
**Wissam Nassrallah**





## UBC Medicine Spring Gala (cont')



Top left: FIFE girls acapella group,  
**Amanda Dancsok**

Top right: Medical Undergraduate Student  
Ensembles, **Paulina Piesik**

Centre: Boys2Med acapella group,  
**Frank Lee**

Bottom: Terpsichore, contemporary dance  
group, **Lianne Cho**

***Bravo!***



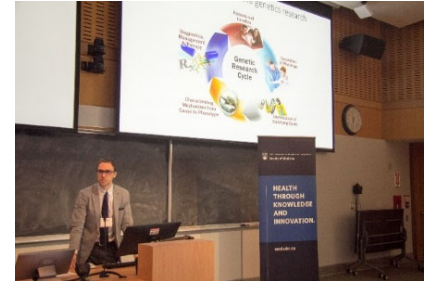
## Faculty of Medicine Research Trainee Day

The annual Faculty of Medicine Research Trainee Day was held on Friday, 3 May 2019, at the Paetzold Lecture Theatre and Atrium, Vancouver General Hospital. This annual event is designed to showcase the diverse and innovative research work of Faculty of Medicine research trainees and recent senior faculty prize awardees, as well as to provide a venue for the building of new connections and collaborations throughout the Faculty and at all levels. Three MD/PhD students presented their research work at the event.

**Katrina Besler** presented a poster on “The role of exogenous lysosomal acid lipase in enhancing cholesterol removal from arterial smooth muscle foam cells”. Katrina won a prize (runner-up) for her poster presentation. Congratulations!

**Daniel Kwon** presented a poster on “Synthesis and evaluation of <sup>68</sup>Ga-labelled marimastat for PET imaging of matrix metalloproteinase activity in ewing sarcomas”

**Mark Trinder** presented an oral presentation on “Elevated levels of genetically-determined high-density lipoprotein associate with sepsis survival and reduced risk of infectious disease”



**Mark Trinder at the  
FoM Research Trainee Day**

## Clinician Investigator Program (CIP) Research Fellows Day

The 19<sup>th</sup> CIP Annual Research Fellows Day was held on Friday, 7 June 2019 at the Medical Student & Alumni Centre, Vancouver General Hospital. Three MD/PhD students presented their research work at the event.

**Mark Trinder** presented “Genetically-determined levels of HDL cholesterol, influence risk of infectious disease”

**Daniel Kwon** presented “Evaluation of BL01 and BL02 as theranostic agents targeting C-X-C chemokine receptor 4”

**Adam Ramzy** presented “Revisiting proinsulin processing: Evidence that human B-cells lack prohormone convertase 2 and can produce mature insulin without its function”

## Canadian Student Health Research Forum (CSHRF)

The 32<sup>nd</sup> annual Canadian Student Health Research Forum (CSHRF) was held in Winnipeg, Manitoba, June 10-14, 2019. The aim of the CSHRF is to provide a venue for the networking, research exposure and recognition of Canada's most promising research trainees in the health sciences. **Daniel Kwon** and **Alvin Qiu** were nominated as top PhD students in health sciences at UBC and presented their posters at the forum.

**Alvin Qiu** presented “The SS18-SSX oncoprotein is directed by DNA methylation state to evict polycomb in primary synovial sarcomas”. He received the Canadian Student Health Research Forum Travel Award.

**Daniel Kwon** presented “Evaluation of BL01 and BL02 as theranostic agents targeting C-X-C Chemokine receptor 4”. His presentation was within the pool of the top 8, and was being nominated for participation at the next Nobel laureate meeting at Lindau in Physiology and Medicine!

Our students had the valuable opportunity to attend the career workshop, the networking dinner, the small group sessions, and the Gairdner Symposium. They found the experience very enlightening. We are very happy to have both of them represented the MD/PhD Program and UBC. Congratulations!

## Admissions 2019

From January to March 2019, members of the MD/PhD Program Advisory & Admissions Committee interviewed and adjudicated an impressive cadre of short-listed applicants for admission in 2019. Our students organized two dinners for our shortlisted applicants in February. The dinner serves as a great opportunity for the applicants to learn more about our program. Through the years, exceptional individuals from across the country have been recruited to the UBC MD/PhD Program. Details of our incoming students will be reported in the next newsletter...



Our students at the two applicant dinners on 4 & 8 February, 2019.  
Alvin Qiu (on the right) is our student representative.

UBC's MD/PhD Program is one of the nation's best and most competitive programs for training future clinician-scientists. Our program boasts an exceptional student publication record, guaranteed funding for all our students starting in the spring of the first year of the program, and outstanding success in external funding applications. We also offer reduced tuition and funding support to attend conferences. Our alumni go on to top-tier residency programs across North America in specialties such as radiology, neurosurgery and neuropathology, ophthalmology, internal medicine, psychiatry, pathology and emergency medicine, and later establish careers bridging clinical medicine with scientific research.

## Kudos

**Andrea Jones**, UBC MD/PhD student, worked on article with several MD/PhD students across Canada as part of their work with Clinician Investigator Trainee Association of Canada (CITAC). It includes considerations and recommendations for MDPhD training in Canada. Great work, Andrea.

Ng E, **Jones AA**, Sivapragasam M, Nath S, Mak LE, Rosenblum ND. The integration of clinical and research training: How and why MD-PhD Programs work. Acad Med. 2019 May;94(5):664-670. doi: 10.1097/ACM.0000000000002467. [[PMID: 30256250](#)]

## 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, 2894 Detwiller Pavilion, 2255 Wesbrook Mall, UBC, Vancouver, BC, Canada V6T 2A1. Phone: 1-604-822-7198 Fax: 1-604-822-7917 Email: [md.phd@ubc.ca](mailto:md.phd@ubc.ca) Website: <http://www.med.ubc.ca/mdphd>

Edited by Jane Lee, Program Coordinator, MD/PhD Program, UBC