



UBC MD PhD

2775 Laurel street, Gordon and Leslie Diamond health care Centre, Vancouver, BC V5Z1M9

Email: md.phd@ubc.ca Website: www.med.ubc.ca/mdphd



NEWSLETTER - 2022 SUMMER

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

We welcomed summer and all our program members with a bright and refreshing social at our program director's beautiful house. We want to thank everyone who came out and Dr. Nielsen and his family for hosting such a wonderful event to finally reconnect and recharge. Stay tuned for more fun photos to come later on in this newsletter but first let's see what has been happening in the program over the last few months.

CONGRATULATIONS!



MD/PhD Award Winners:



Dhiraj Mannar

Chloe Gao

Katherine Baillie

Lianne Cho

Li Qing Wang

Maggie Chopra

Saif Dababneh

Peipei Wang

Amy Wang

We are pleased that the current group of UBC MD/PhD students have been very successful in 2022 external and internal award competitions. Congratulations to all the recipients and their supervisors for this year's outstanding results! We take pride in the ongoing achievements of our outstanding students.

Dhiraj Mannar and **Chloe Gao** were winners of the prestigious Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship. The mandate of the Vanier awards program is to strengthen Canada's ability to attract and retain world-class doctoral students and establish Canada as a global centre of excellence in research and higher learning. Dhiraj's supervisor is Dr. Sriram Subramaniam and is hosted by the Biochemistry and Molecular Biology Graduate Program. The title of his research project is "Structure, Function, and Broad Neutralization of Emerging SARS-CoV-2 Variant Spikes". Chloe's supervisor is Dr. Skye Barbic and is hosted by the Experimental Medicine Graduate Program. The title of Chloe's research project is "Understanding the mental health and recovery needs of first- and second-generation Canadian East Asian immigrant youth aged 12-24: A strategy for patient-oriented research (SPOR) collaboration study".

Katherine Baillie won a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award (CGS-D). Her research project title is "Investigating protein trapping mutations to target the replication stress response in cancer". Katie was also an awardee for the Killam Doctoral Scholarships, provided annually from the Izaak Walton Killam Memorial Fund for Advanced Studies. These are the most prestigious graduate awards administered by UBC, and are awarded to the top doctoral candidates in the annual Tri-Agency Canada Graduate Scholarships - Doctoral and UBC Affiliated Fellowship competition.

Lianne Cho and **Li Qing Wang** were winners of the 2022 Canada Graduate Scholarship Doctoral Awards (CGS-D). Lianne's research project title is "Characterization of depression among homeless and precariously housed adults" and is hosted at the Graduate Program in Neuroscience; with her supervisor being Dr. William Honer. As for Li Qing, she is hosted by the Graduate Program in Reproductive and Developmental Sciences and is supervised by Drs. Wendy Robinson and Sarka Lisonkova. Li Qing's research project title is "Genetic and non-genetic factors of pre-eclampsia".

Maggie Chopra, **Saif Dababneh**, **Peipei Wang** and **Amy Wang** all were winners of the 2022 Canada Graduate Scholarship Master's Awards (CGS-M). Maggie is hosted by the Experimental Medicine Graduate Program and her supervisor is Dr. Kelly McNaghy. Saif's research project title is "Investigating Ca²⁺ release deficiency syndrome (CRDS) in human iPSC derived cardiomyocytes" and hosted by the Cell and Development Biology Graduate Program. His supervisors are Dr. Edwin Moore and Dr Glen F. Tibbits. Peipei's provisional hosting department is the Pathology Graduate Program and her research supervisor is Dr. Will Lockwood. Amy's research project title is "Targeting SS18-SSX biology in synovial sarcoma genesis" and her hosting department is the Interdisciplinary Oncology Program. She is co-supervised by our very own Dr. Torsten Nielsen and her main supervisor is Dr. Michael Underhill.



UBC MD/PhD program visits the Okanagan campus

Our program made a very successful daylong tour and presentation at UBC-O on May 6, 2022 to promote and spread awareness about our students, their projects, and the overall program and to update ourselves on the many exciting research opportunities at the Faculty of Health and Social Development.

Class of 2022

We had two graduates this spring - Rozlyn Boutin and Frank Lee. The MD/PhD Program Director attended and celebrated with our students at the graduation ceremony for the Class of 2022 on 26th May. Congratulations!



Class of 2022

MESSAGE FROM ROZLYN BOUTIN

It feels like just yesterday that I flew to Vancouver for my MD/PhD Program interview, yet the past seven years have been some of the most transformative of my life and career. It's hard to find the words to describe just how thankful I am to the mentors and colleagues who have believed in me and supported me along the way. I feel very lucky to have benefited from the opportunities provided to me through the UBC MD/PhD Program, which have prepared me well for my future career as a clinician-scientist in Medical Genetics. Torsten Nielsen, Lynn Raymond, and Liam Brunham have been the most supportive Program Directors I could have asked for, and I would have been lost in the weeds of registration and paperwork without the help of Jane Lee and Naureen Khan.

I always felt like a valued member of the program and never felt alone in this long journey. I owe a huge thank you to my classmates and especially my friend Jennifer Ji, who has always been there for me through the good times and the bad. Similarly, I would not be where I am today without the immense support of my lab-mates and especially my mentor and friend Charisse Petersen. My supervisor Dr. Brett Finlay and unofficial co-supervisor and mentor Dr. Stuart Turvey have taught me so much more than they know, and I will be forever grateful to them for their past and continued support. I'm looking forward to continuing my path towards a career as a clinician-scientist as a resident at UBC, and wish current and future MD/PhD students every success!



MESSAGE FROM FRANK LEE

What a journey! I still remember taking that leap of faith and moving from my home in Toronto to Western Canada. Spending nearly a decade exploring the sheer beauty of British Columbia and persevering through the rigor and joys of the MD/PhD program at UBC has been a great privilege. This most recent chapter in my life has been so memorable and I am so grateful for everyone who supported me through my training in medicine and basic science research. I would like to thank my MD and MD/PhD peers, the entire Pryzdial Lab at the UBC Centre for Blood Research, Dr. Lynn Raymond, Dr. Torsten Nielsen, and Dr. Liam Brunham for their ongoing encouragement. As I embark on the next chapter as an anesthesiology resident at UofT in Toronto, I hope to seek opportunities to utilize my skills and experience in clinical medicine and research to build upon the foundations of a clinician-scientist



CONGRATULATIONS
CLASS OF
2022!

PhD Oral Defense

Two of our students successfully defended their PhD dissertations this spring, all passing with flying colors! We are very proud to share their dissertation abstracts with everyone. Full theses are deposited at UBC cIRcle. These students returned to MD Year 3 Clinical Rotations in the summer of 2022.



Alvin Qiu

Research Supervisors: Dr. Martin Hirst and Dr. Torsten Nielsen

Hosting Department: Interdisciplinary Oncology Program

Defense date: May 26, 2022

Dissertation title: Epigenetic Dysregulation in Synovial Sarcoma

ABSTRACT

Synovial sarcoma is an aggressive soft tissue malignancy characterized by a pathognomonic chromosomal translocation leading to the production of SS18-SSX, a fusion oncoprotein which associates with BAF, a chromatin remodeling complex. BAF complexes exist in three main subtypes and recent research demonstrated that SS18-SSX drives the degradation of cBAF, leading to a relative increase in ncBAF and PBAF.

I analyzed 31 cases of primary human synovial sarcoma using ChIP-seq for histone modifications, RNA-seq for transcriptomes, and whole genome bisulfite sequencing for DNA methylomes. In addition, I analyzed chromatin accessibility in 14 cases using scATAC-seq.

Unsupervised hierarchical clustering of ChIP-seq density for active histone modifications (H3K27ac, H3K4me1, H3K4me3) reveals two major synovial sarcoma epigenetic subgroups: “Group 1” and “Group 2”. Enhancers from Group 1 tumors show lower levels of cBAF binding compared to enhancers from Group 2 tumors. Group 1 enhancers also show greater overlap with binding sites of oncogenic BAF complexes (from cell lines containing SS18-SSX) compared to non-oncogenic BAF complexes (from cell lines with SS18-SSX knockdown). Therefore, the differences in these subgroups could be driven by differences in SS18-SSX activity. This led to my hypothesis that synovial sarcomas can be sub grouped based on epigenomic state, and this relates to disease severity. In support, I demonstrate that Group 1 tumors are higher grade sarcomas and that treating synovial sarcoma cells with a histone deacetylase inhibitor or knockdown of SS18-SSX both cause proliferative arrest and increase the expression of Group 2 enhancer associated genes.

scATAC-seq analyses reveal a rare cluster of cells (6%) shared among all tumors. These cells express SS18-SSX yet differ from all other malignant cells in their expression of synovial sarcoma signature genes, as predicted by open chromatin. The chromatin state of these cells is more correlated with the lower grade subgroup (Group 2) compared to higher grade subgroup (Group 1). These cells may therefore represent an intermediate/early malignant cell state.

Overall, my analysis suggests that human synovial sarcomas can be classified by epigenomic state, which may reflect the activity of SS18-SSX. My findings are relevant for guiding emerging therapeutic strategies that target BAF complex imbalances.

**Wissam Nassrallah**

Research Supervisors: Dr. Lynn Raymond

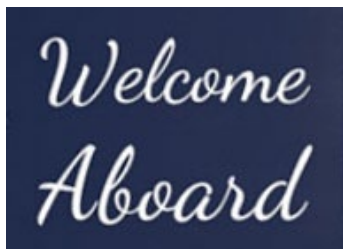
Hosting Department: Graduate Program in Neuroscience

Defense date: May 19, 2022

Dissertation title: Neuroprotective Effect of Sigma-1 Receptor and Activin A on Synaptic Function and Calcium Handling in Huntington Disease

ABSTRACT

Huntington disease (HD) is a monogenic disorder with autosomal dominant inheritance. In HD patients, neurons in the striatum and cortex degenerate, leading to motor and cognitive disorders. Dysregulation of synaptic function and calcium handling is common in many neurodegenerative diseases. N-methyl-D-aspartate (NMDA) receptor function is enhanced at extra synaptic sites, altering the balance of calcium-dependent neuronal survival vs. death signalling pathways. Another important level of calcium regulation is at the endoplasmic reticulum (ER), and this regulation is abnormal in HD. The ER is also suggested to be involved in nuclear calcium signalling, and I hypothesise that this signalling pathway is altered in HD. Sigma-1 receptors (S1Rs) – proteins located on the ER – play an important role in calcium regulation and thus gene transcription. Interestingly, activating S1Rs has been shown to normalize this ER calcium handling and restore synaptic function in HD mouse models. Furthermore, recent work has shown that overexpression of Activin A, a secreted protein whose transcription is nuclear-calcium-dependent, reduces toxic extra synaptic NMDA receptor signalling in the hippocampus. The goal of this project is to determine the link between S1Rs, calcium handling, Activin A, and synaptic function to better understand the pathophysiological mechanisms of HD and to find new potential treatments. Neuronal cultures, imaging techniques, behavioral assessment, and electrophysiology were used to investigate these processes in a mouse model of HD. Our data shows contributions of different calcium channels to nuclear calcium signalling. Calcium imaging also suggests impairments in nuclear calcium signalling in HD striatal medium-sized spiny neurons in co-culture with cortical neurons, which was not corrected by treatment with S1R agonists. Furthermore, our data show that Activin A is decreased in HD culture media, and its overexpression normalizes extra synaptic NMDA receptor expression. Moreover, early injection of an Activin A AAV virus into the striatum led to a significant improvement in a motor coordination task at an age when HD mice are known to show impairment. This project has brought to light the potential therapeutic benefits of Activin A in the treatment of HD; more research needs to be done in order to understand Activin A's mechanism of action, as well as further explore its potential benefits in other neurodegenerative diseases.



Class of 2029

From January to March 2022, members of the MD/PhD Program Advisory & Admissions Committee interviewed and adjudicated an impressive cadre of short-listed applicants for admission in 2022. We are fortunate to have recruited five incoming students to the MD/PhD Class of 2029. Details about our five incoming students will be reported in the next newsletter but for now please welcome:

Adam Sunavsky, Amardeep Sekhon, Monica Luo, Nikolay Alabi and Torin Halvorson.

Welcome to the MD/PhD Program! 😊



Speaking of welcoming, I know most of you have seen this smiling face in the office, at the socials, during our meetings (boy, she really is everywhere!) and mainly during the times you require any administrative support because this is our new Program Coordinator, Naureen Khan!

Naureen has a Bachelor's Degree in Business Administration and has been with UBC for 4 years now. She took over the MD/PhD Coordinator role from Jane Lee (who was the program administrator for 20 years), as of last November 2021.

She is fully aware of the gigantic shoes she has to fill-in for but with that smile and a "can do" attitude, Naureen is striving to do her best to catch up, learn and administer the program all at the same time. So please be patient as she gets her bearing in the program!

Message from Naureen:

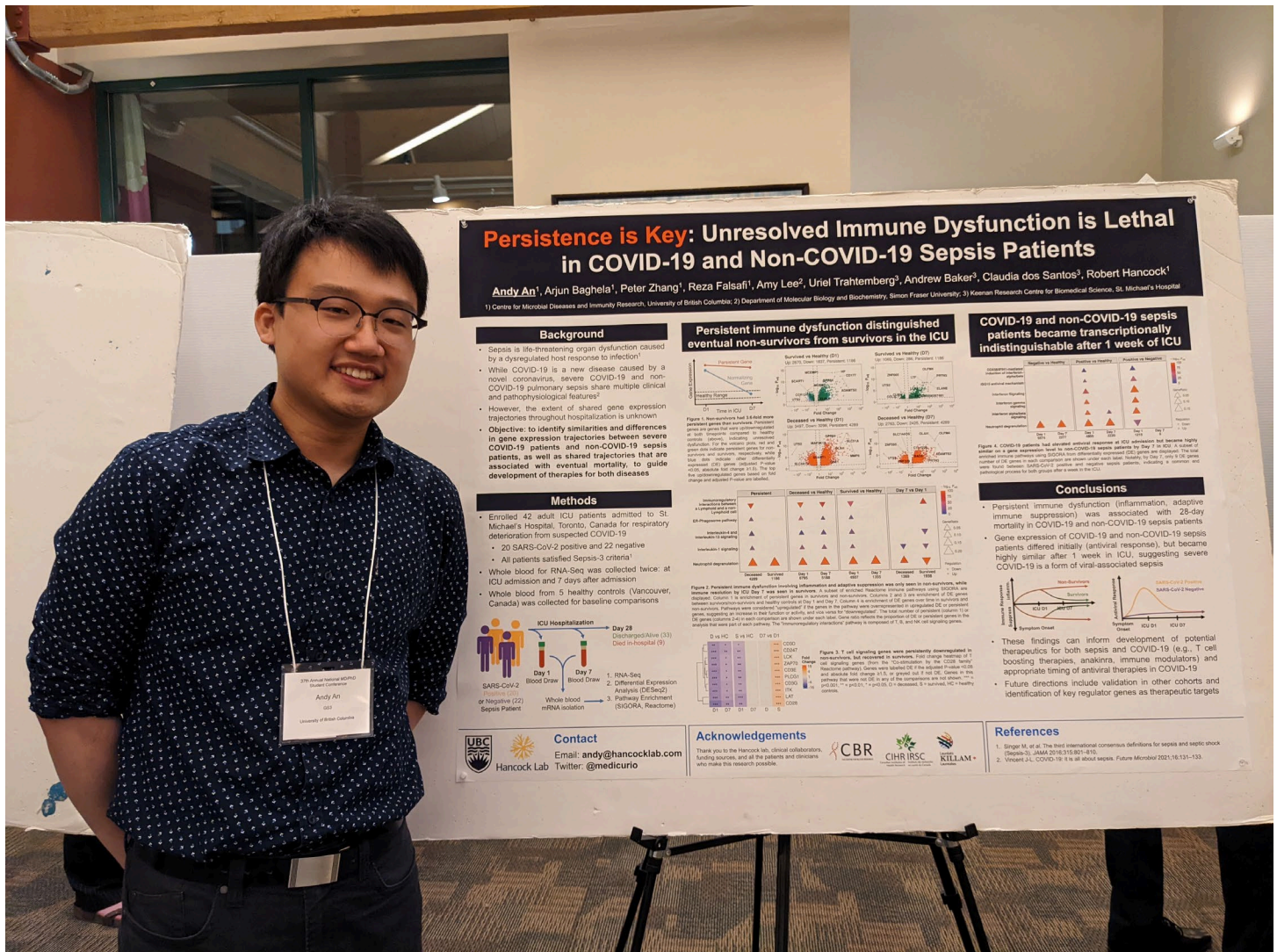
"My passion to provide reliable support and make everyone's life easier is the driving force for everything I do. So, with my strong work ethic and the pride and joy I take in continuous learning, I happily took on this challenging role...and I am ecstatic that I did, despite all the constant challenges, because I have never met such brilliant people before this. Our students, our leaders, my peers, and everyone around me have this infectious thirst to make a better tomorrow and that's exactly what will lead me to do my best. The MD/PhD program has already achieved so many great things but I cannot wait and I am so excited to see all the amazing things this wonderful program will produce in the near future!"



The MD/PhD program provides some funds* for their current students to attend two MD/PhD clinician-scientist meetings/conferences in Canada and or in the United States of America.

*please contact Naureen Khan at naureen.khan@ubc.ca for more information.

Here is a picture of our former Student Liaison, Andy An, at the 37th MD/PhD National Student Conference held at Copper Mountain in Colorado, this year July:



And finally, as mentioned earlier, here are some highlights from our summer social held on June 26, 2022:

Pictured in the upper left: the MD/PhD leadership team: Liam Brunham, Naureen Khan and Torsten Nielsen



Pictured in the lower right: the MD/PhD Student Liaisons: Maryam Vaseghi-Shanjani, Andy An and Shayda Swann

Comments and Suggestions

We welcome questions, comments and suggestions about our newsletters and our program. Please send comments to the MD/PhD Program office at: md.phd@ubc.ca

Edited by Naureen Khan, Program Coordinator, MD/PhD Program, UBC