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Newsletter – 2018 Summer

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

MD/PhD Program Director

Dr. Lynn Raymond stepped down from her role as UBC MD/PhD Program Director effective 1 July 2018. Dr. Raymond was appointed Program Co-Director in January 2002 and Program Director in July 2006. During her tenure, she provided leadership to the MD/PhD Program within the UBC Faculty of Medicine, and worked tirelessly to recruit excellent candidates to the program, while ensuring enhanced educational and funding support opportunities were available for our students. Dr. Raymond will take on the role of Program Associate Director from July 2018 to June 2019, in effect trading places with Dr. Nielsen during a one year leadership transition. The sincere thanks of The Faculty of Medicine and from all our alumni and current students go out to Dr. Raymond for her efforts to build and support the UBC MD/PhD Program. Her tenure has been an unqualified success, growing the program to its largest student body ever, with a large majority of our graduates going on not only to the first choice of research-intensive residencies, but also ultimately to achieve their career goals of becoming academic clinician-scientists.

Dr. Torsten Nielsen is our new Program Director, effective July 2018. Dr. Nielsen is a Professor in the UBC Department of Pathology & Laboratory Medicine. He was our Associate Program Director from July 2007 to June 2018. We look forward to Dr. Nielsen's leadership to the MD/PhD Program.



Dr. Torsten Nielsen

Message from Dr. Nielsen:

After a decade of service as the UBC MD/PhD program's Associate Director, many of you will know me, but for those of you who don't, here is a bit of my story. I grew up across the street from Cates Park in North Vancouver, and as a child I was inspired by Terry Fox to dedicate myself to becoming a cancer researcher. During my undergrad in biochemistry at UBC, I worked in several labs, and decided that if I wanted to do research that really impacts on cancer care, I should train rigorously in both medicine and in science. I spent most of the 1990s at McGill University as a student in their combined MD/PhD program, completing my PhD in DNA replication biology at the McGill Cancer Centre. I was fascinated with new molecular genomic technologies, but after some time on the oncology wards I realized that most of the action translating molecular biology into clinical care was poised to happen first

and most directly in diagnostics, before it would lead to new drugs and treatment. So I decided to do a residency in Pathology, which really turned out well for me given its clinical focus on cancer and the excellent opportunities to link cancer specimens and health care data from British Columbia to new genomics research findings from UBC and from my network of collaborators in the USA and Europe. I secured a faculty position with 75% protected research time in 2003, with UBC, VGH and BC Cancer as my employers, and since that time I have received competitive funding from many Canadian and US agencies for my research programs studying breast cancer and sarcomas – the very type of disease my hero Terry Fox had, which has even become my clinical specialty! Even while working as Associate Director, I have been able to translate basic science into clinical trials in sarcomas, and to develop new diagnostics in breast cancer to the point of FDA approval and clinical implementation around the world. More importantly, I have been able to work with Lynn Raymond to provide openings and mentorship for a new generation of bright young people to pursue their dreams of becoming clinician-scientists themselves, in any of the many areas of medical need and scientific opportunity available in this emerging age of big data that is affecting all fields. As Director, I hope to maintain the excellence of this flagship program at UBC, while working to grow it further – so that even more of Canada's best & brightest can bring their talents to harnessing the power of science and technology to improve the health of people not just in BC, but worldwide.

MD/PhD Program Newsletter Summer 2018

Kevin Fan

MD/PhD Award Winners

Congratulations to all the recipients and their supervisors for this year's outstanding results! **Jennifer Ji, Alvin Qiu** and **Mark Trinder** won prestigious Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarships – the top award available to Canadian graduate students.

Jennifer Ji (supervisor: Dr. David Huntsman), hosting department: Pathology & Laboratory Medicine

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- The proteomic and metabolomic characterization of clear cell ovarian carcinoma vin Qiu (supervisor: Drs. Martin Hirst and Torsten Nielsen) bosting department. Laterdi

Alvin Qiu (supervisor: Drs. Martin Hirst and Torsten Nielsen), hosting department: Interdisciplinary Oncology – Epigenomic dysregulation in synovial sarcoma

Mark Trinder (supervisor: Dr. Liam Brunham), hosting department: Experimental Medicine

- Cholesteryl ester transfer protein as a novel regulator, predictor, and therapeutic target of sepsis

But that's not all - our students have also won multiple other prizes! Congratulations to the following award winners!

Kevin Fan - UBC Faculty of Medicine Clinician Investigator Scholarship
Jennifer Ji - Canadian Conference on Ovarian Cancer Research Trainee Travel Award
Translational Cancer Genomic Travel Award
Daniel Kwon - Radiological Society of North America (RSNA) Research Medical Student Grant
Cynthia Min - Special UBC Graduate Scholarship
Michael Skinnider - William and Dorothy Gilbert Scholarships in Bio-Medical Sciences
UBC Department of Statistics Award in Data Science
Mark Trinder - Gwynne-Vaughan Memorial Award in Medicine

- Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology (CSATVB) Trainee Travel Subsidy Award

- Canadian Institutes of Health Research (CIHR) Travel Award (Institute Community Support)

Allen Zhang - UBC BIG Research Day Poster Presentation Award

- Canadian Conference on Ovarian Cancer Research Trainee Travel Award

In addition, one of our alumni, **Dr. Paul Yong**, now an Assistant Professor in the Department of Obstetrics & Gynaecology, UBC, won a prestigious and highly competitive Health Professional-Investigator Award from the Michael Smith Foundation for Health Research. "<u>Sexual pain in endometriosis: Role of somatic mutations</u>".

Meet Our Incoming Student* - Kevin Fan

Kevin Fan was admitted into the MD/PhD program in May 2018, applying and entering during his Med 1 year. His supervisor is **Dr. Steven Jones** in the Graduate Program in Bioinformatics.

Kevin's current research involves identifying biomarkers of response to checkpoint inhibitor immunotherapy. Checkpoint inhibitors block inhibitory immune checkpoints in order to restore immune function, allowing T cells to attack the tumour. Since 2011, checkpoint inhibitors have been approved by the FDA, and have resulted in a paradigm shift in the treatment of many advanced cancers. However, given the variability in patient response, there is an urgent need to identify robust biomarkers to guide the optimal use of these therapies. Kevin is analyzing whole genome and transcriptome sequencing data from the Personalized OncoGenomics (POG) program at the BC Cancer Agency to explore tumour genetic and immunological determinants of sensitivity and acquired resistance to checkpoint inhibitors. Outside of academics, Kevin is involved in the a cappella group Boys2Med, the UBC Medical Journal, medical mentorship groups, and intramural sports. Welcome to the Program!

* Four other students were also admitted from the 2017-2018 application cycle. They will be entering Med 1 in 2018, and will be profiled in our next newsletter!







Mark Trinder

Congratulations!

MD/PhD Recruitment

The UBC MD/PhD Program developed and published its first dedicated video this summer, featuring two of our current MD/PhD students – one who is in a relatively early stage and another in a later stage of the program, all to show what it is like to be a UBC MD/PhD student. The video provides information for applicants who would like to know about the UBC MD/PhD Program. We hope this video promotes the program well and attracts many outstanding applicants. Our sincere thanks to **Dr. Lynn Raymond, Dr. Connie Eaves, Dr. Liam Brunham, Dr. Torsten Nielsen, Paulina Piesik, Eric Zhao, Rozlyn Boutin** and **MedIT** for making this video possible.

The video is now available on our website: <u>http://mdprogram.med.ubc.ca/mdphd/video/</u>



Paulina Piesik presenting at the IMP on 8 March 2018

Our MD/PhD student representative, **Paulina Piesik**, visited the Island Medical Program (IMP) campus on 8 March to meet with prospective applicants and presented a talk on the MD/PhD Program. We welcome applicants seeking to work with health researchers based at any of the UBC Faculty of Medicine's distributed sites: Vancouver, Victoria, Kelowna and Prince George!

As the student representative, Paulina sits on the MD/PhD Program Advisory & Admissions Committee (2017-2018). She participated in the selection process this year and helped in interviewing and adjudicating an impressive cadre of short-listed applicants for admission in 2018. She also organized welcoming dinners for our selected applicants. Thank you, Paulina.

For 2018-2019, the student representative will be Alvin Qiu.

MD/PhD Seminars

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 they may be able 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 any stripe, 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 link at https://meet.vc.ubc.ca.

Invited speakers:

12 March 2018. **Dr. Fidel Vila-Rodriguez**, Department of Psychiatry, UBC 4 June 2018. **Dr. Scott Tyldesley**, Radiation Oncology, Department of Surgery, UBC Thanks go to the speakers for sharing their clinical and research experiences with us.

Student presentation:

30 April 2018. **Cynthia Ye** presented "Identifying the genetic mechanisms and corresponding phenotypic features of strabismus"

The seminar series will resume in October 2018. For information on upcoming seminars, please visit our webpage at http://mdprogram.med.ubc.ca/mdphd/seminars/

UBC MD/PhD PROGRAM

Allen Zhang



Allen Zhang

Allen Zhang is a Year 6 MD/PhD student in the UBC program. His paper recently published in the elite journal Cell, "Interfaces of Malignant and Immunologic Clonal Dynamics in Ovarian Cancer", dissects the nature of the evolutionary interplay between immune and cancer cells in high-grade serous ovarian cancer. The most common and lethal subtype of epithelial ovarian cancer, high-grade serous ovarian carcinoma, is characterized by poor survival (5-year survival < 50%) and frequently presents with metastatic disease, indicating a desperate need to identify effective therapeutic inventions for these patients. Immunotherapies - treatments that leverage the immune system to attack cancer cells - have demonstrated success in other cancer types and are one of the major areas of interest for therapeutic development for this type of ovarian cancer. However, trials of immunotherapies that have benefitted melanoma and lung cancer patients have been disappointing in high-grade serous ovarian cancer, highlighting the need to develop a better understanding of the nature of tumour-immune interaction in high-grade serous ovarian cancer.

Zhang AW et al Interfaces of Malignant and Immunologic Clonal Dynamics in Ovarian Cancer. Cell. 2018 May 7. pii: S0092-8674(18)30445-8. doi: 10.1016/j.cell.2018.03.073. PMID: <u>29754820</u>

Together with a team of researchers from BC Cancer (including members of the **Shah, Nelson, Holt, and Huntsman** labs) and international collaborators, Allen conducted a first-of-kind multimodal analysis of whole-genome sequences, gene expression, immune infiltration patterns, and cutting-edge immune receptor sequencing at scale to understand the nature of tumour-immune interplay. In doing so, he identified 3 immunologic patterns associated with distinct patterns of cancer cell evolution. Immunologically hot tumours contain the lowest levels of cancer cell diversity, whereas cold tumours appear to be permissive to cancer cell diversification. The cancer cell diversity observed in cold tumours poses a therapeutic challenge, as any treatment needs to eliminate all cancerous populations to be successful. In fact, Allen and team show that, even within immunologically hot tumours, cancer cells have evolved adaptations that appear to enable them to survive immune attack, spurring clinical trials to develop immunotherapies that can overcome these obstacles.

Allen entered the UBC MD/PhD Program in 2014, co-supervised by **Dr. Wyeth Wasserman** and **Dr. Sohrab Shah**. Allen's hosting department is the Graduate Program in Bioinformatics. His PhD research interests have been in exploring the role of the tumour microenvironment in influencing cancer evolution and progression. He has won a Vanier Canada Graduate Scholarship, the UBC Four Year Fellowship, a CGS-M Canadian Institutes of Health Research Graduate Scholarship, the Elwyn Gregg Memorial Fellowship, the Pacific Blue Cross Medical Entrance Scholarship, and Faculty of Science and Faculty of Medicine Graduate Scholarships. In addition, he has given oral presentations nationally and internationally at conferences such as Cancer and the Immune System (Barbados), the 2017 Canadian Cancer Research Conference, and the 2018 Canadian Conference on Ovarian Cancer Research, and co-authored publications in *Nature Genetics, PLoS Biology, Nucleic Acids Research,* and *Genome Biology*. In 2019 he plans to undertake an elective research rotation at Memorial Sloan-Kettering Cancer Center in New York, before re-entering Med Year 3.

Way to go, Allen!

UBC MD/PhD PROGRAM

Michael Skinnider



Michael Skinnider, Year 3 MD/PhD student, is actively engaging in a series of exciting research collaborations in the laboratory of **Dr. Leonard Foster**, in the Department of Biochemistry and Molecular Biology. The first of these began almost immediately after he started in our Program in fall 2015, and focused on the cellular networks of interactions between proteins that mediate higher-order biological processes. Conventional proteomic techniques have mapped a large network of protein-protein interactions (PPIs), but most of them rely on genetically manipulated cell lines or heterologous expression. As a result, it is unclear which interactions actually take place in physiological contexts, like specific tissues or cell types. Michael's research centred on the analysis of a large-scale proteomic dataset generated within the Foster lab, using a unique *in vivo* approach to identify PPIs in seven mouse tissues. He conducted an integrative computational analysis of this dataset, incorporating evolutionary, structural, functional, topological, and regulatory perspectives to

characterize the dynamics of the *in vivo* protein-protein interactome across healthy tissues. The group has identified widespread physiological rewiring of the PPI network, and speculates that this rewiring might be a key mediator of cellular and organismal phenotype.

A second set of collaborations, with **Dr. Brian Kwon, Dr. Chris West**, and fellow MD/PhD student **Jordan Squair**, has centred around applying multi-omic, high-throughput technologies to better understand the pathophysiology of spinal cord injury (SCI). Decades of small-scale studies have probed the molecular response to SCI, but have employed highly heterogeneous injury models and experimental designs. The Foster lab took an integrative approach to catalog the complete set of genes that had ever been implicated in SCI by small-scale studies, then overlaid these onto a genome-wide gene coexpression network from the human spinal cord. Remarkably, the analyses converged on a single, evolutionarily conserved module within the network, the expression of which scaled with injury severity and was reversed in treatments that promote functional recovery. The Foster Lab was able to validate their molecular network signature of SCI at the transcriptomic and the proteomic levels in our own prospective experiments. Future work will focus on identifying multi-omic biomarkers of SCI severity and recovery in human patients, and on understanding how patterns of alternative mRNA splicing might contribute to the pathophysiology of SCI.

Michael has already co-authored two published articles from the Foster Lab and there are three more submitted -- one as first author and one as senior author! In addition to publications from his primary research, he is first and co-author on four articles related to outcomes of MD/PhD Program graduates and lists six refereed journal articles on work that he completed before starting the MD/PhD Program. This is outstanding productivity for an MD/PhD student who is not even midway through the combined program.

Michael has been incredibly successful in obtaining funding, including a Wings for Life Individual Grant, William and Dorothy Gilbert Graduate Scholarship, UBC Department of Statistics Data Science Award, IODE War Memorial Scholarship, Dorothy May Ladner Memorial Fellowship, Donald M. Byers Memorial Prize, Izaak Walton Killam Memorial Pre-Doctoral Fellowship, Vanier Canada Graduate Scholarship, Dorothy Helmer Scholarship in Medicine, Mensa Canada Edgar Kerstan Memorial Scholarship, UBC Innovation Grant, CGS-M Canadian Institutes of Health Research Graduate Scholarship, UBC Four Year Doctoral Fellowship, and a UBC Faculty of Medicine Graduate Award

Outside the Foster lab, Michael also continues to be involved in his undergraduate research field of antibiotic discovery, through a company formed to commercialize a suite of algorithms he developed for genome-guided drug discovery from nature. The company completed a very successful financing round last year.

Well done, Michael!

PhD Oral Exam

Three of our students successfully defended their PhD dissertations, on diverse topics hosted by different departments. They have returned to clinical clerkships this summer. Congratulations!

Andrea Jones

Research supervisor: **Dr. William Hones** Hosting department: Neuroscience Defense date: 18 April 2018 Dissertation title: The clinical actionability and evolution of mutational processes in metastatic cancer

ABSTRACT

People living in marginal or inadequate housing experience increased risk for premature mortality and face accumulating health challenges associated with poverty, substance use, and physical and mental illness. In particular, psychotic disorders, such as schizophrenia or schizoaffective disorder, may be more common. Psychosis, or grossly impaired reality testing, is a key feature of these disorders, but remains poorly understood, due to the heterogeneous course, multifaceted etiology, and complex clinical presentation. As part of a five-year longitudinal study of adults living in urban marginalized housing in Vancouver, Canada, we sought to characterize the consequences, risk factors, and dynamics of psychosis over time. First, we demonstrated that psychotic disorders were a significant risk factor for premature mortality over the study period, beyond other potentially treatable illnesses. Second, through direct clinical interviews each month, we observed a high prevalence of psychosis and psychosis risk factors. Among those without schizophrenia or schizoaffective disorder, the number of days of methamphetamine, powder cocaine, cannabis, or alcohol use predicted dose-related increases in odds of psychosis, without evidence of interaction or reverse causation. Recent trauma, and histories of early-life trauma or brain injury, also had independent effects on psychosis. No relationships with risk factors were demonstrated in the schizophrenia/ schizoaffective group. Lastly, we examined how psychosis may evolve over time through the interplay between psychotic symptoms themselves. By assessing symptoms monthly and applying a multilevel dynamic network analytic approach, we disentangled the within-individual temporal dynamics of psychotic symptoms from the stable betweenindividual differences. Psychotic symptoms fluctuated and were positively reinforcing over time. Delusions had a central role in the symptom network, at both the between-individual and within-individual levels. Delusions were associated with more severe unusual thought content or suspiciousness, but not conceptual disorganization. In the dynamic symptom network, suspiciousness was upstream and hallucinations were downstream in the symptom activation cascade. Dynamic network connectivity was greatest in the group with schizophrenia or schizoaffective disorder. Overall, these studies identify multiple risk factors and psychopathological processes that contribute to the longitudinal characteristics of psychosis and suggest potential targets for intervention and prevention strategies among adults at risk for psychosis.



Andrea Jones – happily running to her friends after her exam

Selected Publications:

- Ramos-Miguel A, **Jones AA**, Sawada K, Barr AM, Bayer TA, Falkai P, Leurgans SE, Schneider JA, Bennett DA, Honer WG. Frontotemporal dysregulation of the SNARE protein interactome is associated with faster cognitive decline in old age. Neurobiol Dis. 2018 Jun;114:31-44. doi: 10.1016/j.nbd.2018.02.006. Epub 2018 Feb 26. PMID: <u>29496544</u>
- Jones AA, Jang K, Panenka WJ, Barr AM, MacEwan GW, Thornton AE, Honer WG. Rapid Change in Fentanyl Prevalence in a Community-Based, High-Risk Sample. JAMA Psychiatry. 2018 Mar 1;75(3):298-300. doi: 10.1001/jamapsychiatry.2017.4432. PMID: 29387869
- Jones AA, Vila-Rodriguez F, Leonova O, Langheimer V, Lang DJ, Barr AM, Procyshyn RM, Smith GN, Schultz K, Buchanan T, Krausz M, Montaner JS, MacEwan GW, Rauscher A, Panenka WJ, Thornton AE, Honer WG. Mortality from treatable illnesses in marginally housed adults: a prospective cohort study. BMJ Open. 2015 Aug 21;5(8):e008876. doi: 10.1136/bmjopen-2015-008876. PMID: 26297373

PhD Oral Exam (con't)

Eric Zhao

Research supervisor: **Dr. Steven Jones** Hosting department: Bioinformatics Defense date: 7 May 2018 Dissertation title: The clinical actionability and evolution of mutational processes in metastatic cancer

ABSTRACT

Cancers are characterized by somatic mutation arising from the interplay of mutagen exposure and deficient DNA repair. Whole genome sequencing of tumours reveals characteristic patterns of mutation, known as mutation signatures, which often correspond with specific processes such as cigarette smoke exposure or the loss of a DNA repair pathway. Quantifying DNA repair deficiency can have clinical implications. Cancer chemotherapies which induce DNA damage are known to be more effective against cancers with deficient DNA repair. However, it is not yet known whether mutation signatures can serve as reliable predictive biomarkers for response to these treatments. Furthermore, the current understanding of mutation signatures stems largely from studies of primary, untreated tumours, whereas metastasis underpins as much as 90% of cancer-related mortality. This thesis aims to (1) describe the association between mutation signatures and clinical response to DNA damaging chemotherapy, (2) enable accurate personalized assessment of mutation signatures and their evolution over time, and (3) characterize the evolution of mutational processes in metastatic cancers. To assess clinical actionability, we quantified signatures of single nucleotide variants, structural variants, copy number variants, and small deletions in 93 metastatic breast cancers, 33 of which received platinum-based chemotherapy. We found that patients with signatures of homologous recombination deficiency had improved responses and prolonged treatment durations on platinum-based chemotherapy. Next, we formulated a Bayesian model called SignIT, which improves the accuracy of individualized mutation signature analysis and infers signature evolution over tumour subpopulations. We demonstrated SignIT's superior accuracy on both simulated data and somatic mutations from The Cancer Genome Atlas, and validated temporal dissection using whole genomes from 24 multiplysequenced cancers. We highlighted a potential clinical application of mutation signature timing in a BRCA1-mutated pancreatic adenocarcinoma with low HRD signature but exceptional response to platinum-containing chemotherapy. Finally, we deciphered mutation signatures from nearly 500 metastatic cancer whole genomes, revealing evolution of mutational processes associated with late metastasis and exposure to cytotoxic chemotherapy. Taken together, our findings demonstrate the complex interplay of factors shaping the metastatic cancer genome. We highlight both clinical opportunities of studying genomic instability and the additional insights available from understanding their temporal evolution.



Eric Zhao – crossing a "PhD finish line" ribbon that his friends made

Selected Publications:

- Zhao EY, Shen Y, Pleasance E, Kasaian K, Leelakumari S, Jones M, Bose P, Ch'ng C, Reisle C, Eirew P, Corbett R, Mungall KL, Thiessen N, Ma Y, Schein JE, Mungall AJ, Zhao Y, Moore RA, Den Brok W, Wilson S, Villa D, Shenkier T, Lohrisch C, Chia S, Yip S, Gelmon K, Lim H, Renouf D, Sun S, Schrader KA, Young S, Bosdet I, Karsan A, Laskin J, Marra MA, Jones SJM. Homologous Recombination Deficiency and Platinum-Based Therapy Outcomes in Advanced Breast Cancer. Clin Cancer Res. 2017 Dec 15;23(24):7521-7530. doi: 10.1158/1078-0432.CCR-17-1941. PMID: <u>29246904</u>
- Thibodeau ML, Reisle C, **Zhao E**, Martin LA, Alwelaie Y, Mungall KL, Ch'ng C, Thomas R, Ng T, Yip S, Lim H, Sun S, Young SS, Karsan A, Zhao Y, Mungall AJ, Moore RA, Renouf D, Gelmon K, Ma YP, Hayes M, Laskin J, Marra MA, Schrader KA, Jones SJM. Genomic profiling of pelvic genital type leiomyosarcoma in a woman with a germline CHEK2:c.1100delC mutation and a concomitant diagnosis of metastatic invasive ductal breast carcinoma. Cold Spring Harb Mol Case Stud. 2017 Sep 1;3(5). pii: a001628. doi: 10.1101/mcs.a001628. Print 2017 Sep. PMID <u>28514723</u>
- Siu C, Wiseman S, Gakkhar S, Heravi-Moussavi A, Bilenky M, Carles A, Sierocinski T, Tam A, Zhao E, Kasaian K, Moore RA, Mungall AJ, Walker B, Thomson T, Marra MA, Hirst M, Jones SJM. Characterization of the human thyroid epigenome. J Endocrinol. 2017 Nov;235(2):153-165. doi: 10.1530/JOE-17-0145. Epub 2017 Aug 14. PMID <u>28808080</u>

PhD Oral Exam (con't)

Victoria Baronas

Research co-supervisors: **Dr. Harley Kurata & Dr. Filip van Petegem** Hosting department: Pharmacology and Therapeutics Defense date: 5 June 2018 Dissertation title: Moment-to-moment regulation of voltage-gated potassium channel function

ABSTRACT

Kv1.2 channels are prominently expressed in neurons where they help to set the threshold of action potential firing. While we have a good understanding of the mechanism of voltage sensing and gating, we have comparatively little information on the compendium of regulatory molecules that can impact Kv1.2 function and expression. Kv1.2 channels are subject to a unique mechanism of regulation whereby a train of brief, repetitive depolarizations elicit increasing amounts of current, a phenotype we term 'use-dependent activation'. In heterologous cells expressing Kv1.2 and primary hippocampal cultures from rats, there is remarkable diversity in this phenotype. While use-dependent activation is absent in all other Kv1 channels, it persists in heteromeric channels containing at least one Kv1.2 subunit. Exposing cells expressing Kv1.2 to reducing conditions causes a dramatic shift in use-dependent activation where there is very little or no current elicited by the first pulse, but over the course of the train there is a hundred-fold or more increase in current. Additionally, reducing conditions cause a depolarizing shift in the activation curve of Kv1.2 by +64 mV. Taken together, we postulate that use-dependence arises from an extrinsic, redoxsensitive inhibitory regulator that associates with Kv1.2 preferentially in the closed, reduced state.

We have identified a new regulator of Kv1.2 function, Slc7a5, an amino acid transporter. Co-expression of these two proteins decreases Kv1.2 expression and produces a hyperpolarization of the activation and inactivation curves. Together these effects result in Kv1.2 channels being caught in an 'inactivation trap'. These effects of Slc7a5 can be rescued by co-expressing a third protein, Slc3a2, which is known to heterodimerize with the Slc7a5 channel. Using bioluminescence resonance energy transfer we show that Slc7a5 and Kv1.2 are within 10 nm of each other. Other Kv1 channels we have tested (Kv1.1 and Kv1.5) are insensitive to the activation shift produced by Slc7a5, however Kv1.1 channels are exquisitely sensitive to current inhibition.

Overall, the work in this thesis expands our knowledge of how Kv1.2 channels are regulated and opens the door to examining how these interactions contribute to normal neuronal function.



Victoria Baronas – smiling to her friends prior to her oral exam

Selected Publications:

- Baronas VA, Yang RY, Kurata HT. Extracellular redox sensitivity of Kv1.2 potassium channels. Sci Rep. 2017 Aug 22;7(1):9142. doi: 10.1038/s41598-017-08718-z. PMID: 28831076
- Baronas VA, Yang R, Vilin YY, Kurata HT. Determinants of frequency-dependent regulation of Kv1.2-containing potassium channels. Channels (Austin). 2016;10(2):158-66. doi: 10.1080/19336950.2015.1120390. Epub 2015 Dec 8. PMID: <u>26646078</u>
- **Baronas VA**, McGuinness BR, Brigidi GS, Gomm Kolisko RN, Vilin YY, Kim RY, Lynn FC, Bamji SX, Yang R, Kurata HT. Use-dependent activation of neuronal Kv1.2 channel complexes. J Neurosci. 2015 Feb 25;35(8):3515-24. doi: 10.1523/JNEUROSCI.4518-13.2015. PMID: 25716850

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: <u>md.phd@ubc.ca</u> Website: <u>http://www.med.ubc.ca/mdphd</u>

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