UBC MD/PhD Program
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Newsletter – 2016 Summer Term

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

MD/PhD Student Funding

We are grateful to announce that we have received tremendous positive response from four UBC-affiliated research institutes which have committed to ongoing funding support for MD/PhD student stipends.

Our sincere thanks go to

- **BC Cancer Agency**
- **Child and Family Research Institute**
- **Providence Health Care Research Institute (St. Paul's Hospital)**
- **Vancouver Coastal Health Research Institute**

Thank you!

Each research institute has pledged funding for a period of 6 fiscal years (2016-2022) to support MD/PhD student stipends. The pooled resources from our research institutes will give us the opportunity to offer additional slots as needed, and provide a better match between the number of funded slots and qualified applicants. Importantly, the pooled research institute funding will allow us the opportunity to leverage funding from external organizations.

The UBC-based combined MD/PhD program is a rigorous 7-year training program offered jointly by the Faculty of Medicine and the Faculty of Graduate and Postdoctoral Studies, designed for high-achieving students who want to pursue a career as clinician-scientists. This program provides highly-qualified undergraduate, graduate and medical students with the opportunity to combine medical school experience with intensive scientific training. Over the past 20 years UBC has built a premier program for training clinician-scientists. With further improvements in funding we hope to increase the number of students in the program, and to further expand and build on the excellence of the program.

Our students have historically been distributed among the sites including St. Paul's Hospital, VGH/BCCA, Children's and Women's Hospital, and UBC. Our students conduct their research across the full spectrum of medical fields. These range from molecular biology, mechanisms of brain function, cancer and microbiology, to population health research involving a large cardiovascular disease patient cohort or the homeless living in the Downtown Eastside, to studies that address improving health services and care delivery. The program has doubled in size since 2006, from an average of 12 students up to 27 today.

Award Winners

The UBC MD/PhD students have been very successful in the 2016 external award competitions.

Victoria Baronas and **Allen Zhang** 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 Ye won a Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarship – Doctoral Award (CGS-D). **Rozlyn Boutin** and **Michael Skinnider** won Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarships – Master's Award (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!

Research project titles:

Victoria Baronas – Molecular mechanism of use-dependent activation of Kv1.2 channel complexes and its impact on regulation of neuronal electrical excitability

Allen Zhang – Deciphering the mechanisms of platinum resistance in high-grade serous ovarian cancer

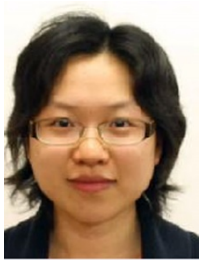
Cynthia Ye – Intersecting genealogic and genetic approaches to identify a mutation causing autosomal dominant, non-syndromic strabismus and its general application to precision medicine

Rozlyn Boutin – Mechanistic determination of the protective effects of four constituents of the early life gut microbiota against childhood asthma

Michael Skinnider – A network medicine analysis of the tissue-specific interactome

Victoria Baronas

Allen Zhang



Cynthia Ye

Rozlyn Boutin

Michael Skinnider

Congratulations!

Dr. Torsten Nielsen – Day on the Hill

Our Associate Director, **Dr. Torsten Nielsen**, spent a day on Parliament Hill on 7 March 2016. His trip there was on behalf of the University of British Columbia as the Faculty of Medicine's chosen representative researcher for UBC's annual "Day on the Hill." The purpose of the delegation, which included interim president **Martha Piper**, Dean **Dermot Kelleher**, and Associate Vice President of Research **Helen Burt**, was to introduce the new federal government to UBC, to raise awareness of UBC's significant research and innovation prowess, to highlight the specific areas of expertise at UBC and why they matter to Canadians, to speak to UBC's impact and partnerships with the broader community (industry, non-profits, governments), and to demonstrate how UBC is and can be a critical partner in achieving the federal government's goals. Dr. Nielsen and the Faculty of Medicine delegation met with high ranking members of the ministries of Science; Health; Finance; and Innovation, Science and Economic Development; as well as CIHR and Genome Canada. This was followed by the UBC100 centenary celebration event for Ottawa alumni, where Dr. Nielsen was one of six faculty members chosen to present as part of the Centennial Speaker Series. After taking questions about his talk on cancer research at UBC, he was given a tour of Parliament by the Honourable **Yonah Martin**, UBC alumnus and Deputy Leader of the Opposition in the Senate.

From Left: **Kirsty Duncan**, Minster of Science, **Dr. Torsten Nielsen**, and **Dr. Martha Piper**, UBC (interim) President

Dr. Nielsen has been the Associate Director of the UBC MD/PhD program since 2007. A graduate of McGill's MD/PhD program, he completed a residency in pathology at UBC and holds a faculty position as a clinician-scientist. At VGH and BCCA, he works as a musculoskeletal pathologist. His active research encompasses two major areas. As director of the Genetic Pathology Evaluation Centre at Vancouver Hospital he leads several active tissue microarray and genomic profiling projects. A common theme of his work is to make clinical sense out of results from breast cancer and sarcoma basic science investigations, and their translation into diagnostic and predictive tests. As an independent principal investigator, Dr. Nielsen directs his lab in research programs to develop much-needed systemic treatments for sarcomas, particularly synovial sarcoma and myxoid liposarcoma, neoplasms most commonly occurring in the limbs of young adults, and to develop practical clinical tests for the intrinsic subtyping of breast cancer and for the identification of cancers that might be susceptible to new immunotherapies.

Dr. Nielsen presented at the MD/PhD Seminar Series on 25 January 2016, on the topic of "Bench to bedside development of the Prosigna test for breast cancer molecular risk".

Class of 2016 – Clara Westwell-Roper

Dr. Bruce Verchere and **Clara Westwell-Roper**

Congratulations, Clara.
Clara Westwell-Roper is one of our graduates in 2016.

Clara's PhD research supervisor is **Dr. Bruce Verchere** in the Department of Pathology & Laboratory Medicine. Her PhD dissertation title is "Islet amyloid polypeptide aggregation is a local trigger for pancreatic islet inflammation".

Message from Clara:

There are only a few occasions when the most important people in one's life – from both academic and personal realms – come together under one roof. I have had the good fortune to experience several during the past eight years of MD/PhD training: my wedding, my PhD defense, and – most recently – graduation! What an honour to join my colleague and friend **Long Nguyen** on stage, in the presence of my husband, my parents, my PhD supervisor **Bruce Verchere**, and MD/PhD program director **Lynn Raymond**.

I am grateful to have made it to this time of transition from MD/PhD student to resident. I am also saddened to leave some of the communities that have helped me along the way. It has been a privilege to be part of this program, and to enjoy the wonderful support provided by Lynn, Torsten, and Jane – thank you! At various times I have also found a home in the Department of Pathology and Laboratory Medicine, the Child & Family Research Institute, the Department of Surgery, the BCCH Division of Pediatric Rheumatology, and the MD Undergraduate Program. I hope one day to be a mentor who is as supportive, curious, energetic, and compassionate as Bruce has been.

My time in the MD/PhD program has been defined by opportunities for integration: of clinical training with work at the lab bench, of immunology with endocrinology and metabolism, of research with teaching and travel and advocacy. I have learned a great deal from clinicians and scientists at UBC and around the world, as well as more junior trainees whom I have had the pleasure of teaching. It is easy to feel pulled in many directions, but I think this has helped to broaden my perspective and fuel my motivation to work at the interfaces between discovery science and clinical medicine.

My thesis work identifies a previously unappreciated role of pancreatic islet amyloid as a potent pro-inflammatory stimulus and points to several potential therapeutic targets to improve beta cell function in type 2 diabetes. In just a few days I will start my residency in the Psychiatry Research Track at UBC, shifting my focus from the pancreas to the brain while maintaining an interest in innate immunity. I hope to pursue a career in child and adolescent psychiatry and am particularly interested in neuroinflammation and its consequences in the setting of childhood chronic diseases, including rheumatologic and metabolic conditions. Let me know if you're interested in collaborating!

Thank you again for the opportunity to be part of the UBC MD/PhD community, and I hope we will stay in touch.

Awards (selected list):

- Hamber Medal - Head of the Graduating Class in Medicine, MD degree, best cumulative record in all years of study.
- Y.S. Hsieh Prize - Awarded to the graduating student in the MD program who achieves the highest standing in Obstetrics and Gynecology.
- Harold Krivel Prize in Paediatrics - Awarded to a student who excels in paediatrics.
- Premier Undergraduate Scholarship (HSBC Emerging Leader Award) - UBC's most prestigious designations, given to senior students with outstanding academic performance, leadership, and involvement in student and community activities.
- CFRI Award for Outstanding Achievement by a Doctoral Student (2014) - Recognizes the outstanding achievement of a Doctoral student based at BCCH and/or BCWH, whose demonstrated originality, research ability and capacity for critical thinking identify the individual as being likely to become a contributing member in the scientific community.

Class of 2016 – Long Nguyen

Long Nguyen

Congratulations, Long.
Long Nguyen is one of our graduates in 2016.

Long was a recipient of the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship, and he also received a UBC Four Year Doctoral Fellowship (4YF). His PhD research supervisor is **Dr. Connie Eaves** in the Experimental Medicine Graduate Program. His PhD dissertation title is "Clonal heterogeneity of normal and transformed mammary stem cells".

Message from Long:

Reflecting on my time in the MD/PhD program at UBC, I am amazed at how quickly 7 years seems to pass. It has been a truly incredible experience. For this opportunity, I will forever be grateful to the program directors, **Dr. Lynn Raymond**, and **Dr. Torsten Nielsen**. They are the twin pillars of excellence and steadfastness to which we trainees turn to as our mentors in this ever transformative journey. Also an integral part of this program is our coordinator, **Jane Lee**, who provides a tremendous amount of support to us, and is always so kind when we come see her for help. Thank you for all that you do, Lynn, Torsten, and Jane.

I would also like to thank my colleagues in the MD/PhD program, past and present, for their camaraderie and support along the way. A special thanks to **Dr. Clara Westwell-Roper**, my fellow MD/PhD graduate with whom I completed the last two years of the program. Thanks for reaching the finish line with me, Clara!

I conducted the research for my thesis project under the guidance and support of **Dr. Connie Eaves**. She is an incredible woman, world-class scientist and the best "scientific mother" I could ever have hoped for. She challenged me to discover new insights fundamental to our understanding of stem cell biology and cancer. She taught me to critically examine the validity of results and conclusions, finely dissect all the caveats of a method, and to never back down when your findings are based on solid and reproducible evidence. She has made me into the confident and competent scientist I am today, and it is with great honour that I continue my research career having trained under such a remarkable scientist. Thank you, Connie, for inspiring me.

My last thanks must go to my parents, who had the courage to escape a war-torn country to seek a world of opportunity for me. I hope I have made you proud as I continue with my career. The next chapter of my journey as a budding clinician-scientist brings me to Toronto, where I am excited for my residency in Internal Medicine.

A few last words to my fellow trainees in the MD/PhD program – you are different from your MD peers, sometimes over-looked, and at other times undeservedly praised. Embrace this difference, for it is what will allow you, with your unique training and experience, to make a significant impact in the field of medicine, with the potential to help thousands of patients. I look forward to working with you in our future careers!

Publications (selected list):

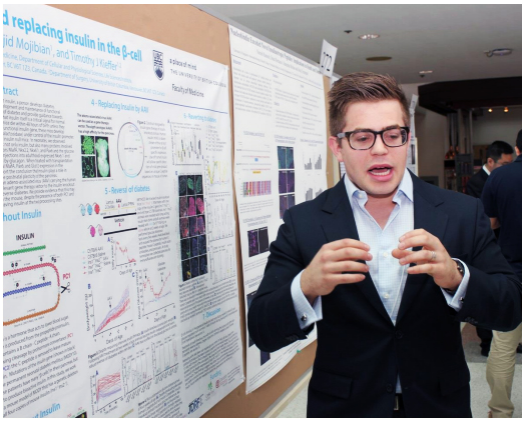
- **Nguyen LV**, Pellacani D, Lefort S, Kannan N, Osako T, Makarem M, Cox CL, Kennedy W, Beer P, Carles A, Moksa M, Bilenky M, Balani S, Babovic S, Sun I, Rosin M, Aparicio S, Hirst M, Eaves CJ. Barcoding reveals complex clonal dynamics of de novo transformed human mammary cells. Nature 528(7581):267-71. 2015. [PMID 26633636]
- **Nguyen LV**, Cox CL, Eirew P, Knapp DJ, Pellacani D, Kannan N, Carles A, Moksa M, Balani S, Shah S, Hirst M, Aparicio S, Eaves CJ. DNA barcoding reveals diverse growth kinetics of human breast tumour subclones in serially passaged xenografts. Nat Commun. 2014 Dec 23;5:5871. doi: 10.1038/ncomms6871. [PMID 25532760]
- **Nguyen LV**, Makarem M, Carles A, Moksa M, Kannan N, Pandoh P, Eirew P, Osako T, Kardel M, Cheung AMS, Kennedy W, Tse K, Zeng T, Zhao Y, Humphries RK, Aparicio S, Eaves CJ, Hirst M. Clonal analysis via barcoding reveals diverse growth and differentiation of transplanted mouse and human mammary stem cells. Cell Stem Cell 14(2):253-63. 2014. [PMID 24440600]
- **Nguyen LV**, Vanner R, Dirks P, Eaves CJ. Cancer stem cells: an evolving concept. Nat Review Cancer 12(2):133-43. 2012. [full text]

MD/PhD Student – Adam Ramzy

Adam Ramzy was nominated by the MD/PhD Program as being within the top 5% of doctoral students, for participation in the Canadian Institutes of Health Research (CIHR) Research Poster Presentation, 8 June 2016, within the Canadian Student Health Research Forum, in Winnipeg, Manitoba.

'β-cells' without insulin: characterizing pancreas from insulin knockout mice

When pancreatic β-cells fail to secrete sufficient insulin, a patient develops diabetes. Understanding what factors are critical to the development and maintenance of functional β-cells may provide insight into the pathogenesis of diabetes and provide guidance towards effective therapeutic strategies. We hypothesize that insulin itself is a critical signal for normal β-cell maturation and function. Insulin knockout mice die within 48 hours of birth unless they receive insulin therapy. Despite the absence of a functional insulin gene, these mice develop 'β-cells' as observed by expression of a tracer (β-galactosidase) under control of the insulin promoter. We aimed to characterize the 'β-cells' found in these mice with no insulin gene. In neonates, we observed increased β-cell area. Importantly, these cells lack not only insulin, but also many proteins involved in β-cell function including the transcription factors MafA, Nkx2.2, Nkx6.1, and Pax6 and the glucose transporter Glut-2. Animals treated with insulin injections into adulthood expressed Nkx6.1 and Nkx2.2 and an increase in α-cell area marked by glucagon. When treated with transplantation of normal healthy islets, we also observed normal MafA, Pax6, and Glut-2 expression in the endogenous pancreatic 'β-cells'. These data support the conclusion that insulin plays a role in β-cell maturation and function and highlights the postnatal plasticity of the pancreas. Additionally, islet transplant can better support endogenous β-cells which may occur through superior glycemic control, native insulin production, and/or production of other endocrine hormones, though more work is required to understand these intriguing findings. In complimentary work, we have generated an adeno-associated virus (AAV) carrying the human insulin gene. We have delivered this clinically relevant gene therapy vector to the insulin knockout mice and are in the process of evaluating the efficacy of this therapy.



Adam Ramzy, winner of an Honourable Mention in the 2016 CIHR National Poster Presentation, presents his research to the judges.

Adam Ramzy won three main non-academic awards since 2015, all are lifting awards. We are so proud of his achievements.

Best Male Lifter – Canadian Powerlifting Union National Championships 2015
St John's, NL, 10 April 2015

Best Male Lifter – Commonwealth Powerlifting Championships 2015
Richmond, BC, 4 December 2015

Best Male Lifter – Canadian Powerlifting Union National Championships 2016
Regina, SK, 19 February 2016

MD/PhD Student – Sandy Wright

Sandy Wright

We are excited that **Sandy Wright** was the Winner 1st Prize of the Young Investigator Award at the 16th International Symposium on Intracranial Pressure and Neuromonitoring, in conjunction with the 6th Annual Meeting of the Cerebral Autoregulation Research Network, 28 June – 2 July 2016, Cambridge, MA, USA.

The conference attracted contributions from 28 countries across six continents. Ten finalists for the Young Investigator Award were selected from 81 eligible trainee contributors. The panel of judges consisted of world experts in neurocritical care, neurosurgery, electrical and biomedical engineering, and cerebrovascular autoregulation. The judges were very impressed by the quality of Sandy's work.

Sandy is a student in the Southern Medical Program. He is working closely with **Drs. Paul van Donkelaar** and **Philip Ainslie** at UBC Okanagan's School of Health and Exercise Sciences, **Dr. Alexander Rauscher** at the UBC MRI Research Centre in Vancouver, and **Dr. Bradley Monteleone**, a Kelowna-based sport medicine physician.

Systolic and diastolic regulation of the cerebral pressure-flow relationship differentially affected by acute sport-related concussion

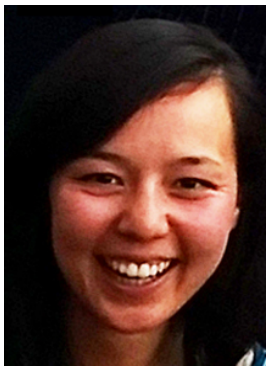
Objective: Cerebral autoregulation impairments have been proposed as a contributing mechanism underlying concussion. Recently, we reported that the relationship between oscillations in mean blood pressure and mean cerebral blood velocity at 0.10 Hz is transiently disrupted for at least 2 weeks post-concussion, with recovery by one month. Whether concussions differentially affect regulatory properties during systole versus diastole is unknown. This study aimed to prospectively evaluate the acute effects of concussion on phase and gain metrics for the systolic and diastolic components of the cardiac cycle.

Methods: Pre-season testing (T0) of 132 elite contact-sport athletes was completed; concussed athletes (n=14) were re-tested at 72-hours (T1), 2-weeks (T2), and 1-month (T3) postinjury. Transcranial Doppler was used to index middle cerebral artery velocity. Squat-stand manoeuvres at both 0.05 and 0.10 Hz were used to assess cerebral pressure-flow dynamics separately for systolic and diastolic cardiac cycles, using transfer function analysis. Coherence (correlation metric), phase (timing offset), and gain (amplitude modulation) between blood pressure and cerebral blood velocity waveforms were subjected to a 4 (time) x 2 (cardiac cycle) repeated-measures ANOVA at each frequency, adjusting for multiple comparisons using Bonferonni correction. Significance was set *a priori* as $p<0.05$.

Results: Significant main effects were observed for cardiac cycle across all outcome metrics at both driven frequencies ($p\leq0.003$). A significant main effect of concussion was observed for 0.10 Hz phase ($p=0.015$); systolic and diastolic phase metrics were reduced at T1 (21.8 ± 5.2%) and T2 (22.7 ± 7.1%) compared to T0, but returned to pre-season values by T3. Concussion also had a significant effect on diastolic, but not systolic, normalized gain, whereby 0.10 Hz diastolic gain was increased (27.2 ± 7.7%) at T2, returning towards baseline by T3.

Conclusions: The previously reported impairment of the cerebrovasculature's buffering capacity for a transient period following sport-related concussion appears to be differentially affected across the cardiac cycle. Similar patterns were observed for systolic and diastolic phase; interestingly, normalized gain changes were significant only in diastole. These findings may suggest that the cerebrovasculature maintains its ability to protect against surges in blood pressure, as compared to reductions in blood pressure, even after concussion.

MD/PhD Student – Andrea Jones



Andrea Jones

On behalf of the UBC Faculty of Medicine and the UBC MD/PhD Program, **Andrea Jones** attended the Consensus Conference on Clinician Scientist Training in Canada in London, ON, 21-23 February 2016. Education leaders from across the country met to determine strategies to support the sustainability and effectiveness of clinician scientist training in Canada. Opening lectures described an inadequate training pathway that loses aspiring clinician scientists (a "leaky pipeline"). Key deficiencies in the training pathway included:
(1) quality and quantity of mentorship, (2) structural flexibility to personalize training, (3) sustainability of funding for the entire pathway, and (4) a lack of supported and well-structured job prospects upon training completion. In addition, the value and identity of clinician scientists is not well understood by medical and research colleagues and the general public.

Attendees heard from international representatives to learn about training models from around the world. The Clinician Investigator Trainee Association of Canada (CITAC/ACCFC) also presented data from a 2015 survey of trainees and program directors, led by Andrea and a team of Canadian MD/PhD students. This data informed the group of the diverse program and funding structures and mentorship needs across the country. Future studies of trainee needs and outcomes will be critical to inform funding and training strategies. Unfortunately, the Canadian Institutes of Health Research (CIHR) representation at the conference did not indicate future reinstatement of MD/PhD studentship funding. In small groups, attendees identified goals and challenges for training at all stages of the clinician scientist life cycle. Based on these discussions, a series of draft recommendations for training were prepared by all attendees and will be finalized in a forthcoming white paper.

It was particularly important to have a student voice at the conference, and it was wonderful for Andrea to represent the UBC MD/PhD Program and connect with leaders from around the world and witness their passion and commitment to supporting clinician scientist training.

Canadian Resident Marching Service (CaRMS) Debrief – 3 March 2016

After hearing about their exciting CaRMS match results, **Long Nguyen** and **Clara Westwell-Roper** met with other MD/PhD students for drinks and snacks as an informal get together to share their experience with the whole CaRMS process.

From left: **Alexis Crabtree, Clara Westwell-Roper, Cynthia Ye, Jordan Squair, David Twa, Victoria Baronas, Cynthia Min** and **Long Nguyen**

Match Day 2016

They both got their first choice.
Long – U of Toronto (Internal Medicine)
Clara – UBC (Psychiatry Research Track)

PhD Comprehensive Exam

Victoria Baronas

Congratulations to **Victoria Baronas** and **Parker Jobin.** They passed their comprehensive examinations and had been admitted to candidacy.

The MD/PhD Comprehensive Examination format consists of two parts:

- a CIHR style research grant proposal in an area of research
- an oral examination.

Parker Jobin

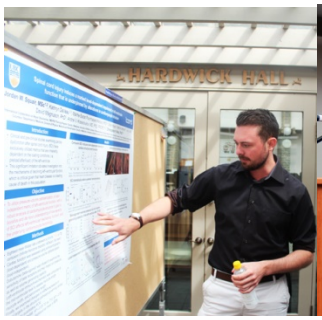
Victoria's research co-supervisors are **Drs. Harley Kurata** and **Filip van Petegem**, in the Department of Anesthesiology, Pharmacology & Therapeutics. Parker's research supervisor is **Dr. Christopher Overall**, in the Department of Biochemistry & Molecular Biology.

MD/PhD Social

The MD/PhD group and their families had a wonderful time in the afternoon of 23 May 2016. After a get-together for Frisbee Golf at Eastview Park, our Associate Director, **Dr. Torsten Nielsen**, kindly offered to host our annual summer social at his beautiful home in North Vancouver. We had a catered party with great food and a chance to swim in his warm pool. This annual event is to celebrate our graduates and also serves as a great opportunity for our significant others to join us for fun. The group picture turned out really well!

UBC Clinician Investigator Program Research Day

The annual UBC Clinician Investigator Program (CIP) Research Day was held on Friday, 3 June 2016, at the UBC Medical Student & Alumni Centre. The MD/PhD students were invited to present at the CIP Research Day. This is a great opportunity for our trainees to mingle with residents and clinician-scientists trainees pursuing other stages of training.



Jordan Squair

David Twa

Jordan Squair presented "Spinal cord injury induces level-dependent impairment in left-ventricular function that is underpinned by alternations in cardiomyocyte structure". Jordan won best overall in the poster competition. Congratulations!

David Twa presented "Targeted high-throughput sequencing and characterization of programmed death ligand structural rearrangements in non-Hodgkin lymphoma".

2016 UBC Students in Health Annual Research Conference (SHARC)

Parker Jobin and **Amanda Dancsok**

The 2016 UBC Students in Health Annual Research Conference (SHARC) is a yearly event that showcases biomedical and health-inspired research projects undertaken by UBC undergraduate, MD, and DMD students. This year's event took place on Saturday, 19 March 2016, 10 am to 3 pm, at the Life Sciences Centre on the Point Grey main campus.

An amazing diversity of research projects highlighted spanning basic sciences, clinical sciences, health systems & services, medical education, and population health. Day of the event activities included keynote speaker, discussion panel, 1-minute lightning talks, and poster presentations.

Parker Jobin and **Amanda Dancsok** represented the MD/PhD Program and helped organize the event. Our alumnus **Dr. Liam Brunham** participated at the audience-driven discussion panel. Residents and faculty from the UBC Faculty of Medicine discussed their training, current research and how they incorporate research into their practice alongside clinical responsibilities. The event was a great success! Thanks to Parker and Amanda for their great work.

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 Website: http://www.med.ubc.ca/mdphd

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