



UBC MD PhD

UBC MD/PhD Program

2894 DETWILLER PAVILION, 2255 WEBBROOK MALL, VANCOUVER BC V6T 2A1
Tel: 604-822-7198 Fax: 604-822-7917 Email: md.phd@ubc.ca Website: www.med.ubc.ca/mdphd

Newsletter – 2015 Summer Term

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

Award Winners

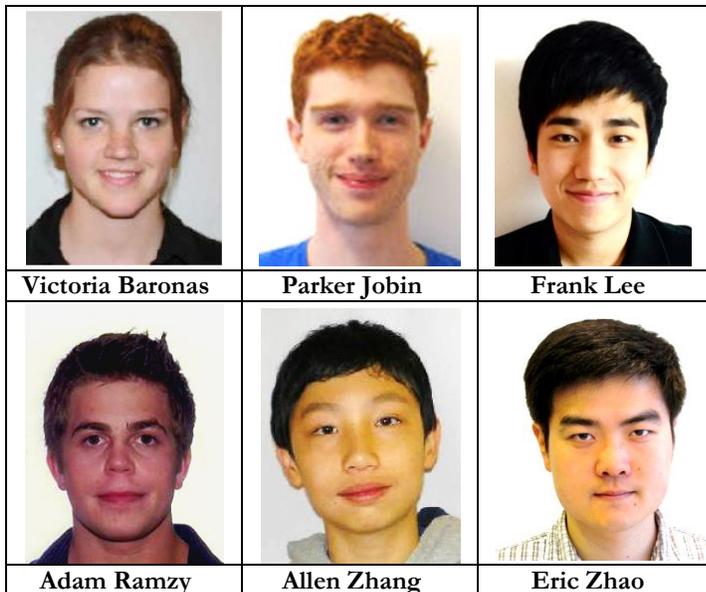
The UBC MD/PhD students have been very successful in the 2015 external award competitions.

Parker Jobin, Frank Lee, Adam Ramzy and Eric Zhao 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.

Adam Ramzy's Vanier application was ranked #1 nationwide in 2015!

Victoria Baronas and Allen Zhang won CIHR Canada Graduate Scholarships Master's Awards (CGS-M). The CIHR awards provide financial support to outstanding students pursuing master's or doctoral studies in health sciences.

Congratulations to all the recipients and their supervisors for this year's outstanding results!



Research project titles:

Victoria Baronas – Use-dependent activation of a neuronal voltage-gated potassium channel

Parker Jobin – tRNA synthetases as extracellular targets of matrix metalloproteinases

Frank Lee – Dissecting the mechanism of a novel clot dissolving agent: Amino acid-tethered clotting factor Xa

Adam Ramzy – An adeno-associated virus based gene therapy treatment for diabetes: Using transcription factors to guide the expansion of insulin producing beta-cell mass in the pancreas

Allen Zhang – The role of cis-regulatory element rearrangements in high-grade serous ovarian cancer platinum resistance

Eric Zhao – Networks, signatures, and personalized medicine: a whole genome approach to cancer therapy

Congratulations!

Class of 2015 – Michael Copley



Congratulations, Mike.
Michael Copley is our graduate in 2015.

Michael 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 “Regulation of Developmental Changes in Hematopoietic Stem Cell Self-Renewal”.

Message from Mike:

This year I was the only MD/PhD graduate and thus the only one wearing a floppy hat and royal blue and maroon gown in a sea of sensible black gowns. A fitting finale to such an unforgettable experience! To my fellow MD/PhD students, it has truly been a privilege to work amongst such talented individuals and I wish you all the best for the future. While it may seem hard sometimes, try to enjoy each and every moment as it really does fly by. To Lynn, Torsten and Jane, thank you for your tireless efforts and advocacy. I am so very proud to be a graduate of the world-class program you have been so integral in creating and nurturing.

My research project was focused on understanding how and why blood stem cells change their properties during development. This work followed on the findings of **Dr. Michelle Bowie**, a previous PhD student in our lab, who discovered that mouse blood stem cells change a series of key properties during early development. My work revealed that one of these properties, termed self-renewal, is determined by the differential activity of a highly-conserved molecular pathway (Lin28b-let-7-Hmga2). I am hopeful that this work may inform methods to expand blood stem cell numbers for research and therapeutic use and also help us understand why different types of blood cell cancers afflict children and adults. While I felt well over my head for most of this journey, my dedicated and incredibly supportive supervisor, **Dr. Connie Eaves**, was there whenever I needed her. Connie, you have taught me not only the nuts and bolts of being a world-class scientist, but perhaps more importantly, have shown me that this can be accomplished through collaboration, collegiality and integrity. You are truly an inspiration and I look forward to remaining your colleague and friend for years to come.

Returning to clinical work after being away is a challenging aspect of any MD/PhD program. I was fortunate that this transition was made easier because of the incredible teachers and equally astounding group of classmates I encountered in Victoria at the Island Medical Program (IMP). To my fellow IMPers, thank you so much for welcoming me into your family, it has truly been a pleasure. Furthermore, a special thank you to the inspirational **Dr. Patrick Kenny**, for introducing me to the fascinating field of Dermatology.

To my parents, Brian and Pam, thank you for encouraging me to always do my best and supporting me in all my crazy endeavours. To my sisters, Anna and Alex, you are both amazing sisters and aunts. To Grandpa Doug and Grandpa Paul, thank you for believing in me. To my boys, Jack and Leo, thank you for always bringing a smile to my face and to Jenn, my wife, I love you and could not have done any of this without you.

Now onto the next chapter, a residency in Dermatology at UBC. I couldn't be happier about joining such a fantastic program with such wonderful mentors and colleagues. Take care of yourselves and keep in touch (mcopley@alumni.ubc.ca)!

All the best. – Mike, UBC MD/PhD 2015

UBC MD/PhD PROGRAM

PhD Oral Defense - Farzad Jamshidi



Farzad Jamshidi

Congratulations to **Farzad Jamshidi**, for successfully defending his PhD dissertation entitled, “Characterization of Epithelioid Sarcoma Using Massively Parallel DNA and RNA Sequencing and *In Vitro* Models” on 8 June 2015. Farzad made a superb presentation of his research work and answered all questions well. His research work was highly recognized by the Examination Committee. The External Examiner, **Dr. Jason Hornick**, Brigham and Women’s Hospital at Harvard Medical School, commented that the dissertation presents a comprehensive body of work that represents significant contributions to the field of sarcoma biology.

Farzad’s PhD research supervisor is **Dr. Torsten Nielsen** and his thesis was under the auspices of the Interdisciplinary Oncology Program. We are very proud to share Farzad’s research interests with everyone. Great work, Farzad!!

* * *

Characterization of Epithelioid Sarcoma Using Massively Parallel DNA and RNA Sequencing and *In Vitro* Models

ABSTRACT

Epithelioid sarcoma is a soft tissue tumor with an unusual predilection for the distal extremities in young adults. Despite wide-margin resections the 10-year survival is in the range of 50%. The biology of epithelioid sarcoma remains incompletely understood, but one key feature is the loss of SMARCB1. We use whole genome sequencing of four cases of epithelioid sarcoma matched to normal germline DNA, looking for mutations other than SMARCB1. These index cases are supplemented with three additional tumors and three cell lines that undergo whole transcriptome sequencing and are analyzed for somatic point mutations, copy number changes, translocations, and expression patterns. Unlike the situation in other SMARCB1 inactivated tumors, we find a complex genome with a relatively high mutational burden. However, aberrations of SMARCB1 remain the only consistent mutation. Some cases do not show biallelic DNA-level inactivation of this gene which leads us to examine other possible second-hit silencing mechanisms. HSES cells are identified as an *in vitro* model of epithelioid sarcoma containing an intact yet unexpressed allele which is not silenced by DNA methylation nor by the microRNAs recently suggested in the literature. Lastly, SMARCB1 inducible cell lines are generated and used *for in vitro* studies. Following up on these, EZH1/2 inhibitors are tested and shown to be effective *in vitro*. Additionally, observing the existence of a residual SWI/SNF complex, we show synthetic lethality with SMARCA4 inhibition in epithelioid sarcoma which indicates another possible therapeutic approach.

Publications (selected)

Jamshidi F, Nielsen TO, Huntsman DG. Cancer genomics: why rare is valuable. *J Mol Med (Berl)* 93(4):369-81. 2015. [[PMID 25676695](#)]

Jamshidi F, Pleasance E, Li Y, Shen Y, Kasaian K, Corbett R, Eirew P, Lum A, Pandoh P, Zhao Y, Schein JE, Moore RA, Rassekh R, Huntsman DG, Knowling M, Lim H, Renouf DJ, Jones SJ, Marra MA, Nielsen TO, Laskin J, Yip S. Diagnostic value of next-generation sequencing in an unusual sphenoid tumor. *Oncologist* 19(6):623-30. 2014. [[PMID 24807916](#)]

UBC MD/PhD PROGRAM

PhD Oral Defense - Matthew Mayer

Congratulations to **Matthew Mayer**, for successfully defended his PhD dissertation, entitled "Identification and Therapeutic Targeting of Innate Immune Networks in Human Inflammatory Diseases" on 31 July 2015. Matt did a great job presenting his research and answering questions in front of his examiners and audience. His research work was greatly recognized by the Examination Committee. The External Examiner, **Dr. Peter Ghazal**, Division of Pathway Medicine, University of Edinburgh Medical School, highly rated the thesis, describing it well written and exciting to read providing a coherent scientific investigation of innate defence pathways anchored around hypothesis generation from microarray gene expression data and subsequent experimental testing.

Matt's PhD research supervisor is **Dr. Robert Hancock**, Microbiology & Immunology Graduate Program. We are very proud to share Matt's research interest with everyone. A job well-done, Matt.



Matthew Mayer

* * *

Identification and Therapeutic Targeting of Innate Immune Networks in Human Inflammatory Diseases

ABSTRACT

Innate defence regulator (IDR) peptides are novel immunotherapeutics under investigation as anti-infectives. IDRs enhance recruitment of innate immune cells to infection sites while simultaneously suppressing microbially-induced inflammation. Dysfunctional innate immune responses to microorganisms drive chronic inflammation in other diseases, including Crohn's disease, ulcerative colitis, and cystic fibrosis (CF). The aim of this work was to investigate the effect of anti-inflammatory peptide IDR-1018 in disease models of IBD and CF inflammation.

In the dextran sodium sulphate mouse colitis model, IDR-1018 was found to significantly attenuate both clinical and histological signs of intestinal inflammation. In colitic mice, peptide-treatment led to enhanced intestinal leukocyte-recruiting chemokines and neutrophil recruitment *in vivo*. Mechanistic studies revealed that IDR-1018 polarized neutrophils to a phenotype associated with the resolution of inflammation without inhibiting their antibacterial functions, suggesting that these cells were mediating the protective effect *in vivo*.

Given a lack of pathway-level insights into the origins of CF-associated inflammation, transcriptomics and computational analysis using systems biology and network analysis approaches were utilized to investigate the mechanisms of IDR-1018 in relevant models. Network analysis was able to identify dysfunctional inflammatory networks in pediatric lung diseases, and successfully predicted the immunomodulatory effects of IDR-1018 in primary monocytes treated with innate immune-stimulating bacterial ligands. In CF, network analysis predicted that abnormal calcium fluxes caused CF airway cells to secrete exaggerated inflammatory cytokines when treated with bacterial 3-oxo-C12 homoserine lactone. Subsequent experimental testing confirmed this hypothesis, thereby establishing the feasibility of using network analysis to study inflammation associated with lung diseases, including CF.

IDR-1018 attenuated inflammatory responses in CF airway cell lines and CF patient peripheral blood mononuclear cells stimulated with different bacterial ligands. Using network analysis, the anti-inflammatory effect of IDR-1018 was predicted to involve the modulation of autophagy. Biochemical studies validated this hypothesis, and established autophagy as a therapeutic target for treating CF-associated inflammation.

These findings suggest that immunomodulatory IDR peptides may show therapeutic potential in non-infectious, inflammatory diseases. In addition, this work demonstrates the utility of network analysis for studying the actions of immunotherapeutics in human disease by identifying the dysfunctional inflammatory networks that they target.

Publications (selected)

Mayer ML, Blohmke CJ, Falsafi R, Fjell CD, Madera L, Turvey SE, Hancock RE. Rescue of dysfunctional autophagy attenuates hyperinflammatory responses from cystic fibrosis cells. *J Immunol* 190(3):1227-38. 2013. [[PMID 23264659](https://pubmed.ncbi.nlm.nih.gov/23264659/)].

UBC MD/PhD PROGRAM

PhD Oral Defense - Gareth Mercer

Congratulations to **Gareth Mercer**, for successfully defending his PhD dissertation entitled, “Do fathers care? Measuring mother’s and father’s perceptions of father’s involvement in caring for young children in South Africa” on 19 June 2015. Gareth made an exceptional presentation of his research work and answered all questions well. The Examination Committee unanimously agreed that Gareth’s dissertation well deserved to pass. The excellence of his dissertation was also noted by the External Examiner, **Dr. Victoria Hosegood**, University of Southampton, who commented that “innovative aspects of the thesis stand out as providing new insights and approaches in family studies and practice in South Africa”.



Gareth Mercer

Gareth’s PhD research supervisor is **Dr. Julie Bettinger**, in the School of Population and Public Health, and he represents the first MD/PhD graduate from this School, highlighting the broad areas of research covered by our program. Well done, Gareth!!

* * *

Do fathers care? Measuring mother’s and father’s perceptions of father’s involvement in caring for young children in South Africa

ABSTRACT

Positively involved fathers are an important source of support for children. However, in South Africa, many children do not reside with their biological father and little is known about fathers’ involvement in children’s care. A questionnaire that reliably measures fathers’ involvement and is adaptable to varied residential arrangements would facilitate future population-level research. In this study we explored whether children who reside with their biological father have better health than children whose fathers live elsewhere. We also assessed whether a questionnaire adapted from surveys in the United States would give reliable measurements of South African fathers’ involvement in caring for children. The questionnaire was designed to measure involvement in five hypothetically distinct modes of care.

With data from the 1998 Demographic and Health Survey, we used multilevel logistic regression to estimate associations between father-child coresidence status and four child health outcomes: breastfeeding for at least six months; being completely immunized; and having had a recent acute respiratory infection or episode of diarrhoea. We found that children who do not reside with their father were not at higher risk of any of these health outcomes.

In a separate study conducted in the Western Cape, we had a sample of mothers complete questionnaires about their infants’ fathers’ care involvement when infants were 2 weeks, 16 weeks and 6 months old. Using Item Response Theory models we estimated the distribution of the fathers’ levels of involvement in five modes of care. We used total information functions to assess the precision of the estimates of involvement. For the majority of fathers, the questionnaire gave reasonably precise estimates of involvement for three modes of care: Accessibility, Direct Caregiving, and Practical Support for Mother. In contrast, items measuring father’s Material Provisioning and Responsibility gave imprecise estimates for the majority of fathers in the sample.

Our findings reinforce existing evidence that co-residence status is an inadequate proxy for care involvement. Future population-level research into fathers’ influences on children’s health should directly measure fathers’ care practices. With further validation, the questionnaire assessed in this study could be used to measure the more direct modes of infant care.

Publications (selected)

van den Berg W, Brittain K, **Mercer G**, Peacock D, Stinson K, Janson H, Dubula V. Improving Men’s Participation in Preventing Mother-to-Child Transmission of HIV as a Maternal, Neonatal, and Child Health Priority in South Africa. PLoS Med 12(5):e1001836. 2015. [[PMID 25961291](https://pubmed.ncbi.nlm.nih.gov/25961291/)]

UBC MD/PhD PROGRAM

PhD Oral Defense - Julia Pon

Congratulations to **Julia Pon**, for successfully defending her PhD dissertation, entitled “The MEF2B Regulatory Network” on 23 June 2015. She did a great job in the oral defense, earning lots of compliments from the audience and the examining committee. The committee was highly impressed by the difficulty level of the project she took on and the excellent dialogue with the candidate on both scientific and clinical questions. Julia was strongly supported for graduating doctoral awards. The external examiner, **Dr. James Davie**, Manitoba Institute of Child Health, commented that Julia’s research provides important information about the genomic location and function of the transcription factor myocyte enhancer factor 2B (MEF2B). MEF2B is a transcriptional activator that is mutated in diffuse large B cell lymphomas and in follicular lymphomas, but her work has significant implications for other cancers and cell biology in general.



Julia Pon

Julia’s PhD research supervisor is **Dr. Marco Marra** in the Genome Sciences & Technology Program. We would like to share Julia’s research work with everyone. Great work, Julia!

* * *

The MEF2B Regulatory Network

ABSTRACT

Myocyte enhancer factor 2B (MEF2B) is a transcription factor with somatic mutation hotspots at K4, Y69 and D83 in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. The recurrence of these mutations indicates that they may drive lymphoma development. However, inferring the mechanisms by which they may drive lymphoma development was complicated by our limited understanding of MEF2B’s normal functions. To expand our understanding of the cellular activities of wildtype and mutant MEF2B, I developed and addressed two hypotheses: (1) identifying genes regulated by wildtype MEF2B will allow identification of cellular phenotypes affected by MEF2B activity and (2) contrasting the DNA binding sites, effects on gene expression and effects on cellular phenotypes of mutant and wildtype MEF2B will indicate mechanisms through which *MEF2B* mutations may contribute to lymphoma development.

To address these hypotheses, I first identified genome-wide MEF2B binding sites and transcriptome-wide gene expression changes mediated by MEF2B. Using these data I identified and validated novel MEF2B target genes. I found that target genes of MEF2B included the cancer genes *MYC*, *TGFB1*, *CARD11*, *NDRG1*, *RHOB*, *BCL2* and *JUN*. The identification of target genes led to findings that MEF2B promotes expression of mesenchymal markers, promotes HEK293A cell migration, and inhibits DLBCL cell chemotaxis.

I then investigated how K4E, Y69H and D83V mutations change MEF2B’s activity. I found that K4E, Y69H and D83V mutations decreased MEF2B’s capacity to promote gene expression in both HEK293A and DLBCL cells. These mutations also reduced MEF2B’s capacity to alter HEK293A and DLBCL cell movement. Overall, these data support the concept that *MEF2B* mutations may promote lymphoma development by reducing expression of MEF2B target genes that would otherwise function to help confine germinal centre B-cells to germinal centres.

My research demonstrates how observations from genome-scale data can aid in the functional characterization of candidate driver mutations. Moreover, my work provides a unique resource for exploring the role of MEF2B in cell biology. I map for the first time the MEF2B regulome, demonstrating connections between a relatively understudied transcription factor and genes significant to oncogenesis.

Publications (selected)

Pon JR, Marra MA. Driver and passenger mutations in cancer. *Annu Rev Pathol* 10:25-50. 2015. [[PMID 25340638](https://pubmed.ncbi.nlm.nih.gov/25340638/)]

Meet our Incoming Students - Cynthia Ye

Welcome to the Program!



Cynthia Ye

Cynthia Ye was admitted into the MD/PhD program in May 2015, applying and entering during her Med 1 year. She is co-supervised by **Dr. Wyeth Wasserman** and **Dr. Millan Patel** in the Department of Medical Genetics. Her research focuses on the genetic causes of non-syndromic strabismus. Strabismus is commonly known as crossed-eyes or squint, and this eye misalignment condition is one of the earliest recorded genetic disorders. More than 2400 years ago, Hippocrates observed 'Children of parents having distorted eyes squint also for the most part'. The prevalence of strabismus is up to 4% in the general population, but very little is known, especially for the non-syndromic form. Cynthia is working with a large kindred showing an autosomal dominant inheritance pattern of non-syndromic strabismus, and the research project seeks to identify the genetic cause, utilizing modern next-generation sequencing, linkage analysis, high-resolution magnetic resonance imaging (MRI) and functional MRI.

The variant of interest will be studied through a model organism, and the frequency of the variants in strabismus cohorts will be examined. The research findings will improve our understanding of strabismus genetics and may suggest genetic testing for early diagnosis and preventive therapy.

Cynthia applied to the UBC MD/PhD Program out of Med 1, having been admitted to medicine in 2014, and will enter Med 2 during 2015. This is one of three main paths taken by most of our successful applicants, the others being application during or after the last year of an honours Bachelor's degree program or the graduating year of a Master's program. Five other new MD/PhD students were admitted in 2015 using these routes and will enter Med 1 in August 2015, and will be profiled future issues of this newsletter.

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

Our seminar series aims to illustrate 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, and students in the Faculty of Medicine are invited. Our usual venue is at the Medical Student Alumni Centre, 6:00-7:00 pm, video-conferenced to Victoria, Prince George and Kelowna.

Monday, 27 April 2015. Invited speaker: **Dr. Nadia Khan**, Cardiology, Department of Medicine, UBC

Monday, 22 June 2015. Invited speaker: **Dr. Liam Brunham**, Internal Medicine, Department of Medicine, UBC



Dr. Nadia Khan



Dr. Liam Brunham

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

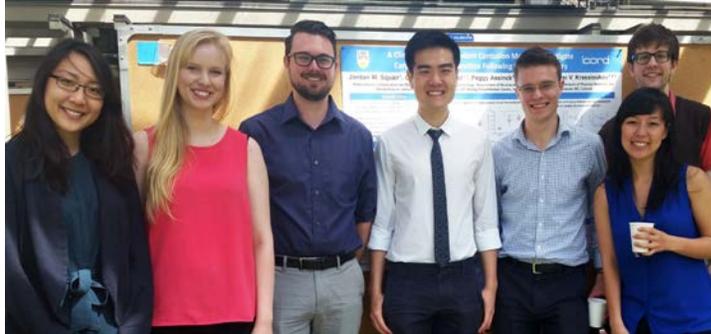
Our Southern Medical Program MD/PhD student, **Sandy Wright**, presented his research project on 23 March 2015. His peer group had a great gathering after the seminar judging from their happy faces!!

Left to right: Cynthia Min, Victoria Baronas, Parker Jobin, Adam Ramzy, Sonja Babovic, Sandy Wright, Amanda Dancsok, Victor Li and Eric Zhao



UBC Clinician Investigator Program Research Day

The annual UBC Clinician Investigator Program (CIP) Research Day was held on Friday, 5 June 2015, 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.



Left to right: Jennifer Ji, Amanda Dancsok, Jordon Squair, Eric Zhao, Philip Edgcumbe, Andrea Jones and David Twa

Philip Edgcumbe presented “Pico Lantern; Surface Reconstruction and Augmented Reality in Laparoscopic Surgery Using a Pick-Up Laser Projector”.

Andrea Jones presented “Potentially treatable illnesses increase mortality in marginally housed adults in Vancouver, Canada: A prospective cohort study”.

Jordan Squair presented “A Clinically Relevant Rodent Contusion Model to Investigate Cardiovascular Dysfunction Following Spinal Cord Injury”.

David Twa presented “Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell Lymphoma”.

Eric Zhao presented “Searching for Targetable Mutation Signatures in a Mixed Cancer Cohort”.

Jordan Squair’s poster won an “honorable mention”.
Congratulations!

Good job, everyone!



The UBC CIP is open to residents enrolled in specialty or subspecialty residency programs accredited by the Royal College of Physicians and Surgeons of Canada who have demonstrated an interest in and a potential for a career as clinician investigators. For more information on the CIP, visit their website at <http://www.cipubc.ca>. This represents an alternative route for medical trainees to gain serious research experience and credentials.

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>

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