University of British Columbia M.D./Ph.D. Program

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Newsletter – Summer 2003

MD/PhD News

					
Cheng-han Lee (Year 7)	Jimmy Lee (Year 7)	Ryan Hung (Year 6)	Michael Rauh (Year 5)	Claire Sheldon (Year 5)	Paul Yong (Year 5)
					
Clara Tan (Year 4)	Liam Brunham (Year 3)	Bryan Coburn (Year 3)	Amy Weber (Year 2)	Heather Heine (Year 1)	Aaron Joe (Year 1)

This is our distinguished group of MD/PhD students at the University of British Columbia. MD/PhD students do their PhD research and complete clinical training in various departments and units with the UBC Faculty of Medicine and affiliated teaching hospitals. Every year, our students present at provincial, national and international research conferences and win great research awards. We would like to take this opportunity to congratulate our students on their outstanding achievement.

MD/PhD News (con't)

Eight MD/PhD students presented at the Western Student Medical Research Forum in Carmel, California (28 January 2003 – 1 February 2003). They were Jimmy Lee, Paul Yong, Michael Rauh, Claire Sheldon, Clara Tan, Liam Brunham, Bryan Coburn and Amy Weber. **Paul Yong** won the **Subspecialty Award in Morphogenesis and Dysmorphology** . **Clara Tan** won the best **Oral Presentation Award**. **Liam Brunham** won the **Lowell Glasgow Student Research Award and the Meade Johnson Travel Award.** The Lowell Glasgow Student Research Award is given to the student submitting the most outstanding abstract to the Western Society for Pediatric Research meeting based on ranking by all subspecialty reviewers. Liam's abstract was chosen by the WSPR President for oral presentation at the Joint Plenary Session of the Western American Federation for Medical Research, Western Society for Clinical Investigation, Western Association of Physicians, and Western Society for Pediatric Research.

Liam's award-winning abstract:

FUNCTIONAL ANALYSIS OF MUTATIONS IN THE *ABCA1* GENE

Liam Brunham[1,3], Roshni Singaraja[1], Henk Visscher[1], Erick James[2] and Michael Hayden[1].
1) Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, B.C.
2) Xenon Genetics Inc. Burnaby, B.C., 3) UBC MD/PhD Program, Vancouver, B.C.

Introduction: Our laboratory and others have identified more than 50 disease-causing mutations in the *ABCA1* gene, the genetic cause of Tangier's Disease (TD) and Familial HDL-deficiency (FHA). Patients with these mutations present with varying degrees of lipid abnormalities and coronary artery disease. To elucidate the mechanisms underlying the observed disease phenotypes we have performed an *in vitro* functional analysis of several of these mutations. **Methods**: We create polyclonal stable cell lines expressing cDNA clones of the various *ABCA1* alleles by transfecting Human Embryonic Kidney 293 Flipin cells with cDNA-bearing plasmids. We have established five assays to characterize each cell line. These are: efflux of phosphocholine (PC), efflux of cholesterol, binding of ApoA1, ATP cross-linking, and subcellular localization. **Results and discussion**: We have created 10 polyclonal stable cell lines expressing ABCA1 mutants and have developed assays to characterize these cell lines. These analyses reveal a broad spectrum of functional defects associated with mutations throughout the gene. For instance, several mutations have abnormal sub-cellular localization and accumulate in the endoplasmic reticulum. As might be expected these mutants also display defective ApoA1 binding and PC efflux. Of mutants that localize normally, those defective in ApoA1 binding are uniformly defective in PC efflux, indicating that efflux is dependent on the presence of an ApoA1 acceptor molecule. By combining structure-function observations with patient data we can gain insight into the function of this key cholesterol transporter and understanding of how mutations in this gene result in disease.

MD/PhD News (con't)

MD/PhD Students won Michael Smith Foundation for Health Research (MSFHR) Doctoral Trainee Incentive Awards

The following MD/PhD students were successful in the MSFHR Doctoral Trainee Incentive Award competition over the past several years. These awards provide top-up for our students who also hold concurrent CIHR MD/PhD Studentship Awards.

2003

Liam Brunham – Medical Genetics (supervisor: Dr. Michael Hayden)
The contribution of hepatic ABCA1 to HDL levels and composition, and suceptibility to atherosclerosis

Claire Sheldon – Physiology (supervisor: Dr. John Church)
Anoxia and the regulation of intracellular ion concentrations in hippocampal neurons

Paul Yong – Experimental Medicine (supervisor: Dr. Wendy Robinson)
Pathogenesis of confined placental mosaicism (CMP) during pregnancy

2002

Jimmy Lee – Pathology and Laboratory Medicine (supervisor: Dr. Neil Reiner)
Role of PI3-kinase family in phagocytosis and phagosome maturation

2001

Michael Rauh – Experimental Medicine (supervisor: Dr. Gerald Krystal)
The role of SHIP in normal and aberrant macrophage and osteoclast development and function

Amy Weber – Health Care & Epidemiology (supervisor: Dr. Mark Tyndall)
Barriers to reproductive health care among marginalized women in Vancouver, British Columbia

Incoming Students (2003)

Heather Heine and **Aaron Joe** will be joining the MD/PhD Program in August 2003. They completed an Honours BSc degree at the University of British Columbia in April 2003. Both Heather and Aaron are among our top candidates for the Program. They are to be congratulated for succeeding in this first step towards an exciting career as a clinician-scientist. They have been awarded a Graduate Entrance Scholarship (GES) for the first year of their MD/PhD studies. Welcome aboard!

MD/PhD News – Cheng-han Lee

Cheng-han Lee is one of our senior students in the MD/PhD Program. Cheng-han joined the Program in 1997. His PhD research supervisor is Dr. Casey van Breemen in the Department of Pharmacology and Therapeutics. During academic year 2001-2002, Cheng-han served as the MD/PhD student representative on the MD/PhD Advisory Committee. Cheng-han successfully defended his PhD thesis in April 2002 for his research on calcium oscillations in vascular smooth muscle. Last summer, Cheng-han had a great experience in his rural practice rotation in Gibson, B.C. Cheng-han will be entering his final year in the Program before receiving his MD/PhD dual degree in the Spring of 2004. Cheng-han has always been an excellent role model for the junior students in the MD/PhD Program. We are delighted to share Cheng-han's research interest and rural practice experience with everyone.

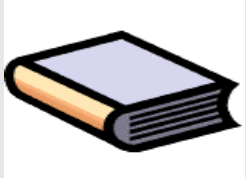
Cheng-han Lee – PhD thesis abstract

The function and the mechanism of agonist-induced asynchronous wave-like $[Ca^{2+}]_i$ oscillations in the in situ smooth muscle cells of the rabbit inferior vena

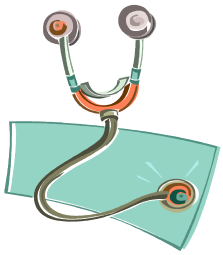
The rabbit inferior vena cava (IVC) is a large capacitance vessel that displays typical contractile dose-response curves for phenylephrine (PE). We observed that PE initially elicited Ca^{2+} waves in individual *in situ* vascular smooth muscle cells (VSMC) of the IVC. The $[Ca^{2+}]_i$ in cells challenged with PE exhibited repetitive asynchronous Ca^{2+} waves. The lack of synchronicity of the wave-like $[Ca^{2+}]_i$ oscillations between VSMCs can explain the observed tonic contraction at the whole-tissue level. Various properties of these Ca^{2+} waves such as the amplitude and the frequency were further characterized and correlated to the force generation. We found that increasing concentrations of PE resulted in increasing cell recruitment over the lower concentration range and increasing frequency of the $[Ca^{2+}]_i$ oscillations at the higher concentration range. It thus appears that PE stimulates vessel contractility through differential recruitment of VSMCs and enhancement of the frequency of asynchronous wave-like $[Ca^{2+}]_i$ oscillations once the cells are recruited.

Mechanistically, we found that the generation of the recurrent Ca^{2+} waves is the result of repetitive cycles of sarcoplasmic reticulum (SR) Ca^{2+} release via IP_3R-channels followed by adequate SR Ca^{2+} refilling via sacroplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA). Our findings suggest that a putative store-operated non-selective cationic channel (NSCC) is activated as a result of IP_3R-mediated SR Ca^{2+} release or store depletion. Na^+ entry through a putative store-operated NSCC then accumulates in a diffusionally-restricted junctional space beneath the plasma membrane (PM) which is formed by the close apposition between the superficial SR and the PM membranes. The elevated $[Na^+]$ in this PM-SR junctional space facilitates Ca^{2+} entry through the PM Na^+-Ca^{2+} exchanger operating in the reverse-mode. This mode of Ca^{2+} entry is critical for the refilling of the SR Ca^{2+} store and the maintenance of PE-induced $[Ca^{2+}]_i$ oscillations. In addition, some Ca^{2+} entry through the L-type voltage-gated Ca^{2+} channel (VGCC) serves to modulate the frequency of the oscillations and the magnitude of force development.

In the recent years, asynchronous recurring Ca^{2+} waves has emerged as an universal mode of Ca^{2+} signaling involved for contractile regulation in VSM. The complete elucidation of its mechanism of generation is thus important both from a physiological and a therapeutic point of view. The findings presented in this thesis should provide valuable insights to the understanding of this phenomenon.



Cheng-han Lee – Rural Practice Highlights



It was near the end of my 5th year in the MD/PhD program when I went through the one-month rural practice rotation. For myself, it marks the first time in three years (since the family practice course in year two) that I have interacted with patients in a real clinical setting. My objective was therefore to take this opportunity before the clerkship year to expand my clinical knowledge base and to refresh as well as to refine my clinical skills. On top of that, given that the rural practice rotation takes place in the summer time, I was hoping to enjoy the local sceneries wherever that I ended up going. I was fortunate enough to be at Gibson on the Sunshine Coast for my rotation and spend a month living in a house with a gorgeous ocean-front view. More importantly, I had a wonderful preceptor – Dr. Edward F. Berinstein. I spent about one-third of the time at his family practice clinic with him and the other two-thirds of the time at St. Mary's hospital (a mid-sized community hospital). While in the hospital, the majority of my time was divided between the OR and the ER. I also got to spend some half-days with the internist, the GP anaesthesiologist, the radiologist and the ophthalmologist. For me, there were always plenty of options to pursue during the day and the choice is oftentimes up to me. All the physicians and surgeons that I followed around were happy to have a student with them and were delighted to teach. Overall, this rotation was a great learning opportunity and I was able to customize the experience to address my areas of interest and deficiency (depending on the location you choose, you may not have as much flexibility as I did). I also have couple pieces of advices for the MD/PhD students who are entering rural practice soon. Firstly, you have to make sure at the beginning at the year that the rural practice office knows that you are going to enrol in the rotation in the upcoming summer. This will ensure that your name is in the lottery and hopefully enables you to have more places to choose from. Secondly, you may want to bring some of the recommended internal medicine and surgery textbooks along for some case-centered reading. This may help you to get ready for the two core clinical clerkship rotations in the upcoming year. Lastly and most importantly, you must have fun and relax. Go hiking, kayaking, swimming, or mountain-biking, and do indulge yourself on those big juicy BC cherries. Keep in mind that you will not have many moments like that for the entire upcoming clerkship year (especially if you also plan to keep some research going on the side).

Cheng-Han Lee, Year 6
UBC MD/PhD Program
May 2003

MD/PhD News – Cheng-han Lee (con't)

Cheng-han Lee – Publications (selected list):

Szado T, Kuo KH, Bernard-Helary K, Poburko D, **Lee CH**, Seow C, Ruegg UT, van Breemen C. Agonist-induced mitochondrial Ca2+ transients in smooth muscle. FASEB J 2003;17:28-37.

Crowley CM, **Lee CH**, Gin SA, Keep AM, Cook RC, van Breemen C. The mechanism of excitation-contraction coupling in phenylephrine-stimulated human saphenous vein. Am J Physiol Heart Circ Physiol 2002;283:H1271-81.

Lee CH, Rahimian R, Szado T, Sandhu J, Behara T, van Breemen C. Requirement for the opening of IP_3-sensitive Ca^{2+} channels and SOC in α_1-adrenoceptor mediated constriction of the rabbit inferior vena cava. Am J Physiol Heart Circ Physiol 2002;282:H1768-77.

Lee CH, Poburko D, Kuo KH, Seow CY, van Breemen C. Ca^{2+} oscillations, gradients and homeostasis in vascular smooth muscle. Am J Physiol Heart Circ Physiol 2002;282:H1571-83.

Lee CH, Poburko D, Kuo KH, Seow CY, van Breemen C. Relationship between the sarcoplasmic reticulum and the plasma membrane. Novartis Foundation Symposium 2002; 246:26-41; discussion 41-7:48-51.

Lee CH, Poburko D, Sahota P, Sandhu J, Ruehlmann DO, van Breemen C. The mechanism of phenylephrine-mediated $[Ca^{2+}]i$ oscillations underlying tonic contraction in the rabbit inferior vena cava. J of Physiol 2001;534:641–50.

Ruehlmann DO, **Lee CH**, Poburko D, van Breemen C. Asynchronous Ca^{2+} waves in intact venous smooth muscle. Circulation Research 2000;86:E72-9.

Wright JM, **Lee CH**, Chambers GK. Real-world effectiveness of anti-hypertensive drugs. (Letter to the editor) CMAJ 2000;162:190-1.

Wright JM, **Lee CH**, Chambers GK. Systematic review of anti-hypertensive therapies: does the evidence assist in choosing a first-line drug? CMAJ 1999; 161:25-32.

Wright JM, **Lee CH**, Chambers GK. Choosing a first-line anti-hypertensive. (Letter to the editor) CMAJ 1999;161:1101.

Cheng-han Lee – Oral Presentations (selected list):

Lee CH, Crowley CM, van Breemen C. Calcium signaling in venous smooth muscle. 8th International Symposium on Mechanism of Vasodilation. May 31-June 3, 2001. Boston, Massachusetts.

van Breemen C, **Lee CH**, Poburko D, Sandhu J, Sahota P. Mechanism and function of asynchronous Ca^{2+} waves in vascular smooth muscle. The 45th Biophysical Society Annual Meeting. February 17-21, 2001. Boston, Massachusetts.

Lee CH, Sandhu J, Poburko D, Sahota P, van Breemen C. Asynchronous Ca^{2+} waves regulate vessel contractility. 29th Western Student Medical Research Forum, Cardiovascular I. February 7-10, 2001. Carmel, California.

Lee CH, Poburko D, Ruehlmann DO, Sahota P, Sandhu J, van Breemen C. Asynchronous Ca^{2+} waves regulate vascular contractility. Joint program for clinical scientist in training and MD-PhD students. Canadian Institutes of Health Research & Canadian Society for Clinical Investigation. September 21, 2000. Edmonton, Alberta.

Lee CH, Poburko D, Ruehlmann DO, van Breemen C. From Ca^{2+} waves to tonic contraction in blood vessels. 28th Annual Western Student Medical Research Forum, Cardiovascular I. February 9-12, 2000. Carmel, California.

Dr. Anthony W. Chow Launched A New Training Program

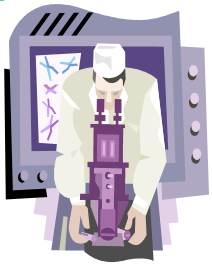
*** * * CIHR-UBC Strategic Training Program for Translational Research in Infectious Diseases * * ***
(TRID)
Website: http://cmdr.ubc.ca/trainingprogram/

Dr. Anthony Chow, Director of the MD/PhD Program, has launched a new training program. A 6-year award totally $1.8 million ($300,000 per year) has been granted to Dr. Anthony W. Chow and his associates to launch a CIHR Training Program for Translational Research in Infectious Diseases (TRID) at the University of British Columbia. The Training Program is funded by the Institute of Infection and Immunity of the Canadian Institutes of Health Research (CIHR), as part of a federal strategic training initiative to build capacity within Canada.

Translational research in Infectious Diseases defines two processes: 1) the translation of knowledge gained from basic research into new or improved methods for the diagnosis, treatment and prevention of infectious diseases in patients; and 2) the translation of clinical insights into hypotheses that can be validated in the laboratory.

The specific aims of this CIHR Strategic Training Program are: 1) to promote and strengthen the national capacity for translational research in infectious diseases through an integrative Training Program, 2) to raise the national standards in the training of health researchers, and 3) to cultivate and facilitate transdisciplinary and translational research in infectious diseases.

The funding received will provide support for five categories of research trainees in Infectious Diseases, including: a) Undergraduate medicine and science students undertaking summer research, and co-op students selected from UBC, University of Victoria and Simon Fraser University; b) MD/PhD students; c) PhD doctoral students; d) MD and PhD postdoctoral research fellows; and e) Clinician Investigator Program (CIP) trainees.



The goal is to provide a longitudinal experience for trainees that facilitates "tracking" into future career options. It is anticipated that maximum synergistic interactions will take place among these trainees within the Training Program, and that the more advanced trainees will also serve as mentors for new recruits. This approach is particularly important for the nurturing of future physician-scientists because for the first time ever, there is a funding mechanism for tracking candidates right from the undergraduate level through either MD/PhD or MD paths to the CIP level.

Upcoming Events

Six MD/PhD students will be presenting at the Canadian Society for Clinical Investigation (CSCI) Young Investigator's Forum, 11 September 2003, Halifax, Nova Scotia.

- **Ryan Hung** (Year 6), Experimental Medicine (Dr. Anthony Chow)
  - Mitochondrial Involvement During Apoptosis Triggered by the G31R Mutant of Toxic Shock Syndrome Toxin-1
- **Michael Rauh** (Year 5), Experimental Medicine (Dr. Gerry Krystal)
  - The Role of SHIP in Macrophage Activation
- **Clara Tan** (Year 4), Biochemistry & Molecular Biology (Dr. Shoukat Dedhar)
  - Integrin-Linked Kinase as a Diagnostic Tool: Tissue Microarray Technology
- **Liam Brunham** (Year 3), Medical Genetics (Dr. Michael Hayden)
  - Contribution of Hepatic ABCA1 to HDL-C Levels and Atherosclerosis in vivo
- **Bryan Coburn** (Year 3), Microbiology & Immunology (Dr. Brett Finlay)
  - Pathogenomics of Salmonella Infection *in vivo*
- **Amy Weber** (Year 2), Health Care & Epidemiology (Dr. Mark Tyndall)
  - Predictors of Initiation into Prostitution among Female Street Youth

* * *

The annual MD/PhD Students Research Forum and Open House will be held on 8 September 2003. Participation in the annual Open House by the public is encouraged. This annual function provides a valuable opportunity for the MD/PhD students to showcase their research. It also serves as an occasion to promote the training of clinician-scientists to the University community and the public. MD/PhD students have the opportunity to talk to various graduate advisors, supervisors, students, and potential applicants. MD/PhD students also provide valuable information and serve as a resource for potential applicants to the MD/PhD Program.

For more information, please call 604-875-5063 or visit our website at http://www.med.ubc.ca/mdphd.

Comments and Suggestions!

We welcome comments and suggestions to the UBC MD/PhD Program and to this Newsletter.
Please send comments to the MD/PhD Program office, D452 - Heather Pavilion East, 2733 Heather Street, VHHSC, Vancouver, BC Canada V5Z 3J5. Phone: 1 604-875-5063. Fax: 1 604-875-4013.
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Have a nice summer!

Edited by Jane Lee, Program Co-ordinator, MD/PhD Program, UBC.