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Newsletter – Summer 2004

Paul Yong - PhD Trainee Research Award

Congratulations!! Paul Yong, Year 6 MD/PhD student, was the recipient of the BC Research Institute for Children's and Women's Health 2004 PhD Trainee Research Award. This award recognizes the outstanding achievement of a PhD student (Paul Yong) based at the Children's & Women's Health Centre of British Columbia site whose originality of thought, research skills and analytical capacity clearly demonstrate the individual's potential to make an original contribution to the scientific community. Paul's research project title is "Clinical aspects and pathogenesis of confined placental mosaicism during pregnancy". Paul, together with other award recipients, was honoured at an Award Ceremony held on 9 March 2004, at the Chan Centre for Family Health Education, Children's & Women's Health Centre of British Columbia.



Above: Paul Yong (right) at the Award Ceremony. Dr. Dan Rurak (left), Associate Director, BC Research Institute for Children's and Women's Health.

Paul Yong is currently completing his PhD research with Dr. Wendy Robinson, in the Experimental Medicine Graduate Program. Dr. Robinson nominated Paul for the C&W PhD Trainee Research Award. Dr. Robinson proudly cited that Paul began his PhD research on placental mosaicism in the summer of 2000. In this short time Paul has made 10 presentations and published 4 manuscripts with several others in preparation. Paul has won 6 presentation awards and various studentship and research awards. His statistical analysis of data from a large number of pregnancies affected by trisomy 16 mosaicism is useful for predictive outcome and also provides insight into the underlying biological mechanisms leading to poor pregnancy outcome in these pregnancies. Paul has collected further important data on long-term outcomes of these newborns and association of trisomy mosaicism with birth weight and pre-eclampsia. To complement the clinical research, Paul has also been using in vitro cultures and immunoassays and gene expression assays to investigate the behaviour of chromosomally normal versus abnormal trophoblast and stromal cells. This is the first step towards identifying potential treatments to reduce complications in mosaic pregnancies."



*Many thanks go out to the
BC Research Institute for Children's and Women's Health
and the Vancouver Hospital & Health Sciences Centre
for their kind contribution of \$5000 per year
towards the UBC MD/PhD Program.*



Abstract of Paul Yong's talk at the BC Research Institute for Children's and Women's Health 2004 Award Ceremony (9 March 2004)

Protein Kinase Profiling in Trisomic and Euploid Miscarriages

Paul J. Yong¹, Deborah E. McFadden², Colin D. MacCalman³, Wendy P. Robinson⁴

¹MD/PhD and Experimental Medicine Programs, ²Department of Pathology and Laboratory Medicine, ³Department of Obstetrics and Gynaecology, ⁴Department of Medical Genetics and British Columbia Research Institute for Children's and Women's Health.

Approximately 15% of clinically recognized miscarriages end in miscarriage, of which about one-quarter are associated with trisomy (an extra chromosome). Altered placental structure and function likely play a role in the pathogenesis of miscarriage in trisomic pregnancies. Presumably this involves a perturbation of gene expression at both the RNA and protein levels due to the presence of the extra chromosome.

Extravillous trophoblast and villus fibroblasts were cultured from placentas ascertained from euploid and trisomic miscarriages for the profiling of protein expression. However, extravillous trophoblast outgrowth was relatively poor (especially in trisomy 16 miscarriages, $p = 0.04$), and so protein expression was profiled only in the cultured villus fibroblasts. Profiling was done using Kinetworks™ KPKS-2.0 analysis (Kinexus Bioinformatics), which involves the simultaneous screening of 75 protein kinases (including isoforms, >90 proteins in all).

The trisomy 16 group ($n = 3$) and trisomy 15 group ($n = 3$) each exhibited an increase in inter-individual variability in expression (quantified as 'scaled noise' = variance/mean²) across all 75 kinases compared to the euploid group ($n = 4$) ($p < 0.005$). Five kinases (CDK1, CDK7, PKC-epsilon, S6K p70, IKK) were significantly ($p < 0.05$) underexpressed in the trisomy 16 group compared to the euploid group, while one (PKG1) was overexpressed. Six kinases (CK1-epsilon, DNAPK, MKK4, S6K p70, Oncogene SRC, IKK) were significantly underexpressed in the trisomy 15 group compared to the euploid group, while two (CK2 (35), ERK1 (41)) were overexpressed. Assuming a null hypothesis that the direction of expression change (under- or overexpression) in the trisomic groups should be random, there is a (borderline) significant trend towards non-random underexpression in the trisomic groups ($p = 0.057$). Notably, of the three kinases (CK2, PKC-beta, ERK1) with genes on chromosome 16 and the three kinases (CSK, ERK3, MKK1) with genes on chromosome 15, only one (ERK1) showed a (borderline) significant increase in expression in its trisomic group (trisomy 16) ($p = 0.063$).

In conclusion, the perturbation in gene expression caused by an extra chromosome may manifest as an increase in noise and global underexpression at the protein kinase level.

Inna Sekirov - CIHR-UBC Strategic Training Program for Translational Research in Infectious Diseases (TRID) MD/PhD Studentship Award

Inna Sekirov, Year 2 MD/PhD student, who joined the MD/PhD Program in May 2004, is currently completing her PhD research with Dr. Brett Finlay in the Department of Microbiology & Immunology. Inna is awarded the CIHR-UBC Strategic Training Program for Translational Research in Infectious Diseases (TRID) MD/PhD Studentship Award. She is the first recipient of the TRID MD/PhD Studentship Award since the Program's inception. The award offers a stipend of \$20,000 per year for a period of six years.



Inna presented her research work, entitled "NleA: a non-LEE encoded type III translocated virulence factor of EHEC 0157:H7" at the First TRID Annual Research Day on 7 June 2004 and she won the Best Poster Presentation prize. Inna also received the UBC Graduate Entrance Scholarship (GES) for 2003-2004.

***UBC MD/PhD Students won Michael Smith Foundation for Health Research (MSFHR) Doctoral Trainee Incentive Awards
- Bryan Coburn and Heather Heine***

Bryan Coburn and Heather Heine were successful in the MSFHR Doctoral Trainee Incentive Award 2004 competition. These awards provide top-up for our students who also hold concurrent CIHR MD/PhD Studentship Awards.



Bryan Coburn – Year 4 MD/PhD student
Supervisor: Dr. Brett Finlay
Department of Microbiology & Immunology
Research title: Host resistance and Salmonella typhimurium gastroenteritis



Heather Heine – Year 2 MD/PhD student
Co-Supervisors: Drs. Bruce McManus & Thomas Podor
Department of Pathology & Laboratory Medicine
Research title: Myocardial regeneration with hematopoietic stem cells

Our Winner - Dr. Anthony Chow

The primary mission of the UBC MD/PhD Program is to train and nurture future clinician-scientists who excel both in clinical medicine and basic sciences. The program aims to be Canada's leader in preparing the future generation of clinician-scientists.

In April 2004, our Program Director, Dr. Anthony Chow was honoured with the Janssen-Ortho Canadian Infectious Diseases Society (CIDS) Distinguished Service Award. This award recognizes Dr. Chow's longstanding commitments and contributions to the Society as a Council member and Chair of the Grants and Awards Committee, and for mentorship to young investigators. Dr. Chow has recently been offered membership of the UBC Quarter Century Club which honours faculty members with 25 or more years of service at UBC.

Dr. Cheng-han Lee

Cheng-han Lee, our first MD/PhD graduate, received his MD/PhD dual degree in June 2004. Cheng-han started in the MD/PhD Program in September 1997, his PhD research supervisor is Dr. Casey Van Breeman in the Department of Pharmacology & Therapeutics. Cheng-han's PhD research thesis title is "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".

Cheng-han has been offered a position in the UBC Pathology & Laboratory Medicine Residency Training Program, for five years (2004-2009), under the supervision of Dr. Blake Gilks. Cheng-han's area of study is Anatomical Pathology.



Congratulations, Cheng-han.

Clara Tan

Clara Tan, Year 5 MD/PhD student, is currently completing her PhD research with Dr. Shoukat Dedhar, in the Department of Biochemistry and Molecular Biology. Earlier this year, the Dedhar lab discovered the way to halt cancer's spread. The new discovery showed that integrin-linked kinase (ILK) stimulates the expression of vascular endothelial growth factor (VEGF) by stimulating HIF-1 α protein expression in a PKB/Akt- and mTOR/FRAP-dependent manner.

The team's work was featured on the cover of journal *Cancer Cell* in January 2004. The work was also reported in television news (CTV, City TV & Global TV) and the cover page of local newspaper Vancouver Sun on 20 January.

Congratulations Dr. Dedhar and Clara!!



Recent Publications by Current MD/PhD Students (partial list)

Brunham L, MacDonald M, **Coburn B**. Genetic discoveries identify novel treatments for achondroplasia and Alzheimer's disease and molecular basis of ethylmalonic encephalopathy. *Clin Genet* 65(6): 458-62. 2004.

Lee JSI, Hmama Z, Mui A, Reiner NE. Stable gene silencing in human monocytic cell lines using lentiviral-delivered siRNA: silencing of the p110 α isoform of phosphoinositide 3-kinase reveals differential regulation of adherence induced by 1 α , 25-dihydroxycholecalciferol and bacterial lipopolysaccharide. *J Biol Chem* 279: 9379-88. 2004.

Gruenheid S, **Sekirov I**, Thomas NA, Deng W, O'Donnell P, Goode D, Li Y, Frey EA, Brown NF, Metainikov P, Pawson T, Ashman K, Finlay BB. Identification and characterization of N1eA, a non-LEE-encoded type III translocated virulence factor of enterohaemorrhagic *Escherichia coli* O157:H7. *Mol Microbio* 51(5): 1233-49. 2004.

Tan C, Cruet-Hennequart S, Troussard A, Fazli L, Costello P, Sutton K, Wheeler J, Gleave M, Sanghera J, Dedhar S. Regulation of tumor angiogenesis by integrin-linked kinase (ILK). *Cancer Cell* 5:79-90. 2004.

MDPhD (Clinical Medicine + Basic Sciences)

The UBC MD/PhD Program is receiving application for September 2005.

Who can apply?

- ◆ Students who have a BSc degree with first class standing.
- ◆ Students who are registered in the first year of a PhD Program.
- ◆ Students who are registered in Medicine Year 1 in September 2004.

Deadline: 1 October 2004

<http://www.med.ubc.ca/mdphd/apply.htm>

Questions?

Email: ubcmdphd@interchange.ubc.ca

Thank you to Ryan Hung, Year 7 MD/PhD student, for designing the new UBC MD/PhD logo (on right). Ryan has also designed our annual Open House announcement poster and pamphlet. Ryan also generously helped out at the early phase of the current MD/PhD web page.

The new UBC MD/PhD logo and the new MD/PhD web page (in progress) will be on-line in the coming months.



Ryan Hung - PhD Defense



Ryan Hung, Year 7 MD/PhD student, successfully defended his PhD thesis on 17 May 2004. Ryan is one of our senior students, he has always been an excellent role model for the junior students in the Program. Ryan was one of those rare child prodigies whose intellectual abilities far exceed those of others in his age group. He was the youngest student ever to enter UBC (age 13), and the youngest to graduate from University (age 17), with combined honours in Physics & Chemistry. Ryan obtained first class standings throughout his university years. Ryan joined the MD/PhD Program in 1998. His PhD research supervisor is Dr. Anthony Chow, in the Department of Medicine (Infectious Diseases). During academic years 1998 -2000, Ryan served as the MD/PhD student representative on the MD/PhD Advisory Committee. Ryan will be entering his final year in the Program before receiving his MD/PhD dual degree in the spring of 2005. We are delighted to share Ryan's research interest with everyone.

Ryan Hung - PhD Thesis The Regulation of Apoptosis by Toxic Shock Syndrome Toxin-1 and Associated Mutants

Toxic shock syndrome toxin-1 (TSST-1) is an exotoxin produced by *Staphylococcus aureus* and a member of the superantigen family of T cell mitogens. Activation-induced cell death (AICD) of superantigen-reactive T cells is thought to play a role in modulating the hyperactive immune response, permitting host survival. While this form of apoptotic cell death occurs with the related staphylococcal enterotoxins (SE) A and B, conflicting reports exist for TSST-1. Therefore, our objective was to investigate the regulation of apoptosis by TSST-1 and site-directed mutants.

TSST-1 was found to exert dose-dependent effects on apoptosis, resolving some past contradictory reports. At commonly assessed concentrations (<1 μ M), TSST-1 was less potent at inducing apoptosis than SEB, displaying evidence for early induction of anti-apoptotic pathways in reactive T cells. However, high doses of TSST-1 (>1 μ M) potently and rapidly elicited apoptosis with broad specificity. The glycine 31-to-arginine site-directed mutant of TSST-1 (G31R) displayed the same pro-apoptotic effect with as little as 10nM, affecting T cells, monocytes and T lymphoma-derived cell lines.

The mechanism behind this novel form of apoptosis was examined. When ligated, classical death receptors like Fas primarily activate the extrinsic pathway. In contrast, conditions unfavourable to cell survival such as growth factor withdrawal, ionizing radiation, and other cell damage, converge at the mitochondrial level to trigger death through the intrinsic pathway. G31R-induced apoptosis was dependent upon the intrinsic, but not significantly on the extrinsic, pathway.

Because TSST-1 is not known to possess direct enzymatic effects that could account for this cytotoxicity, the most likely site of action for the induction of apoptosis by G31R and high-dose TSST-1 was considered to be a non-classical death receptor coupled to the intrinsic apoptotic pathway. However, with upstream pathways still unclear, other possibilities include direct cell membrane disruption or production of reactive oxygen species.

Taken together, this previously unknown apoptotic effect of TSST-1 may translate to pathogenesis by causing local immunosuppression at infection sites through deletion of nearby lymphocytes and monocytes. Regardless of the apical mechanism for apoptosis in this system, possibilities exist for the therapeutic use of G31R or derivatives in the treatment of tumours and autoimmune diseases.

MD/PhD Students - Rural Practice

Five MD/PhD students are conducting rural practice in the summer of 2004: Jimmy Lee, Michael Rauh, Claire Sheldon, Clara Tan and Paul Yong. This is the largest crop of MD/PhD students doing rural practice in one summer. The rural practice experience is to give students an understanding of the total health care of individuals and their community, including an understanding of the philosophy of medical care that looks after patients from birth to death and from home to hospital.

Below are the five MD/PhD students and the city where they conduct rural practice. The students spend four weeks in a rural community working with a family physician and are exposed to many aspects of health care.



Jimmy Lee
Maple Ridge, BC



Michael Rauh
Delta, BC



Claire Sheldon
Nanaimo, BC



Clara Tan
Maple Ridge, BC



Paul Yong
Prince George, BC



Our sincere thanks go to Valerie Berry, Program Assistant, Undergraduate Program, Department of Family Practice, for her unfailing effort in scheduling rural practice sessions for the MD/PhD students.



Message from Aaron Joe - Year 2 MD/PhD Student

Assistant VP Academic Affairs, UBC Medical Undergraduate Society

Who says that MD/PhD students are simply bookworms and lab rats? Entering into the first year class this past September, I quickly learned how much the 'MuD-PhuDs' do here at UBC Medicine. I was amazed that though we comprised less than 2.5% of the entire UBC Medical Student population, our students were actively involved in organizing conferences, advocating for student and physician rights, participating in student government, representing students on various faculty committees, and even performing at the Spring Gala - all while keeping up with school work, outside-school work, and bench work! Simply meeting these people was motivation enough for me to become involved in student government.



This past year, I played my part working on the Medical Undergraduate Society (MUS) as the 1st year Class President, and I will continue working on the MUS through 2004-05 as it's Assistant VP Academic Affairs. I plan to advocate towards academic continuity and fairness in light of the continuing medical school expansion. I also have a vested interest to ensure high standards of teaching, especially for MD/PhD students who must spread their MD education over 7 years and are members of at least 4 different graduating MD classes. Please feel free to speak to me about any of your concerns.

Email: bunj@brc.ubc.ca

Incoming Students (2004)



Susan Berkhout

Susan Berkhout and **Claire Heslop** will be joining the MD/PhD Program in August 2004. Both Susan and Claire completed an Honours BMedSc degree at the University of Western Ontario in April 2004. They 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. The two of them have been awarded a Graduate Entrance Scholarship (GES) for the first year of their MD/PhD studies.

Welcome aboard!



Claire Heslop



~~ Building Bridges in Medicine ~~

The MD/PhD students successfully raised \$450 from the UBC Medical Undergraduate Society (MUS) Education Initiative Fund, for five seminars in the upcoming MD/PhD seminar series "Building Bridges in Medicine" (September 2004 to April 2005). The MD/PhD students meet monthly to discuss important issues with the Program Director. Top-notch clinician-scientists are invited to deliver talks at the meetings. The goal of these seminar series is to celebrate, increase enthusiasm and promote basic and translational research interests among the students. For more information on the upcoming seminars, please check out the MD/PhD web page at <http://www.med.ubc.ca/mdphd>. All MD/PhD and MD students are welcome!



An exciting event happened on 4 March 2004 when Dr. Timothy Rowe, Department of Obstetrics & Gynaecology, gave an awesome presentation and discussion on "Hormone Replacement Therapy". Dr. Rowe's talk was well received by the MD/PhD and MD students who came for this event. Thank you Dr. Rowe!

MD/PhD Guitarist - Liam Brunham

For the third year, Liam Brunham, Year 4 MD/PhD student, performed in the UBC Medicine Undergraduate Society Spring Gala. Liam played Leyende by Issac Albeniz for solo guitar. Liam blew the crowd away with his guitar and singing performances. Next year will hopefully mark the debut of the MD/PhD band at Gala.

Liam has won various awards for his phenomenal classical guitar music. In addition to his musical talent, Liam has also won championships in Taekwondo competitions, and, not surprisingly, he is likewise a magician. Is there any natural connection between these qualities?

Liam is currently completing his PhD research with Dr. Michael Hayden, in the Department of Medical Genetics at the Centre for Molecular Medicine and Therapeutics.



Liam in the Spring Gala 2004

Upcoming Events - Student Conferences

Four MD/PhD students (Liam Brunham, Bryan Coburn, Heather Heine, Aaron Joe) will be presenting at the 19th Annual National MD/PhD Student Conference (NSC), 9 -11 July 2004, Keystone, Colorado, USA. The students have applied for and successfully received some funding (in the amount of \$160) from the Medical Undergraduate Society (MUS) to supplement travel expenses for attending this conference.

The MD/PhD students are grateful to the Faculty of Medicine for their continued funding support (in terms of travel awards) for them to attend and present at national and international research conferences (such as the CSCI, NSC & WSMRF).

The conferences are rewarding for all concerned.

Five MD/PhD students will be presenting at the Canadian Society for Clinical Investigation (CSCI) Young Investigator's Forum, 30 September 2004, Ottawa.

- ◆ **Michael Rauh** (Year 6), Experimental Medicine (Dr. Gerry Krystal)
- ◆ **Liam Brunham** (Year 4), Medical Genetics (Dr. Michael Hayden)
- ◆ **Bryan Coburn** (Year 4), Microbiology & Immunology (Dr. Brett Finlay)
- ◆ **Heather Heine** (Year 2), Pathology & Laboratory Medicine (Drs. Bruce McManus & Thomas Podor)
- ◆ **Aaron Joe** (Year 2), Experimental Medicine (Dr. Fabio Rossi)

Upcoming Events - MD/PhD Students Research Forum & Open House

The upcoming annual MD/PhD Students Research Forum and Open House will be held on 13 September 2004. 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. Details to follow. For more information, please call 604-875-5063 or visit our web page 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, D25 Heather Pavilion East, 2733 Heather Street, VHHSC, Vancouver, BC Canada V5Z 3J5
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Previous issues of the UBC MD/PhD Newsletters are available at our website: <http://www.med.ubc.ca/mdphd/news.htm>



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