



University of Manitoba
Faculty of Medicine



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University of Manitoba
Faculty of Medicine

Translational Research Symposium

Tuesday, September 28, 2010

9:00 a.m. - 5:30 p.m.

Frederic Gaspard Theatre (A), Basic Medical Sciences Building



One-day Symposium including the inaugural

Dr. Patrick Choy Distinguished Seminar in

Translational Research in Medicine

Programme

Welcome

to

A One-Day Symposium on Translational Research in Medicine

and

The Inaugural

**Dr. Patrick Choy Distinguished Seminar in Translational
Research**

The seed for this event was planted after many discussions by the Basic Science Department Heads on how to enhance communication and collaboration between Basic Science and Clinical Medicine Departments. One strategy is to organize an annual Faculty of Medicine symposium on current topics relevant to biomedical health research that bridges the proverbial gap between basic and clinical research. This symposium will be the hub for a new annual series of seminars in translational research in Medicine to be given by distinguished leaders in this field. The objective of the 2010 symposium is to platform “local” success stories that weave a tale of a translational continuum as the cornerstone of health research. In light of an outstanding research career with “translational” overtures, it is appropriate that Dr. Patrick Choy serves as mascot for this new distinguished seminar series. We hope that you enjoy this event and that you come away with the realization that translational research is an on-going reality within the Faculty of Medicine at the University of Manitoba.

- The Organizing Committee

Message from Dean Postl, Faculty of Medicine



Dear Colleagues

It gives me great pleasure to welcome all of you to the first annual University of Manitoba Translational Research symposium. This is a critical Faculty of Medicine event which will encourage and foster outstanding translational research.

Over the course of the day a wide range of topics will be addressed by leaders in Translational Research at the University of Manitoba, as well as by up-and-coming colleagues. This event reflects both the excellence of our faculty researchers and the vital interaction between Clinical and Basic Science investigators who address major national and international health care issues. I am delighted that the Heads of Basic Science Departments in the Faculty of Medicine have initiated and now realized the Dr. Patrick Choy Distinguished Seminar in Translational Research in Medicine. Dr. Choy is a most worthy recipient of this honor having promoted close interactions between the clinical and basic science disciplines during his past tenure as Associate Dean (Research). I am delighted that Dr. D. Lorne Tyrrell is the inaugural Distinguished Seminar speaker. Dr. Tyrrell is the ideal role model for many of us in Medicine, having successfully bridged the gap between these two aspects of research.

It is wonderful to have this distinguished group of scientists gathered together to pursue a significant goal. I wish you a pleasant and successful day and encourage you all to use this event as a means to foster stronger and productive research collaborations, linking the bedside to the lab bench, and resulting in better public health outcomes.

Yours truly,

Brian Postl, MD, FRCPP
Dean, Faculty of Medicine

The Inaugural Dr. Patrick Choy Distinguished Seminar In Translational Research



PATRICK C. CHOY, PhD, MD (Hon.), FAHA, FIACS

Professor Emeritus, Associate Dean of Development

Dr. Patrick Choy joined the University of Manitoba in 1979 as a researcher and professor in the Department of Biochemistry and Medical Genetics within the Faculty of Medicine. A successful trajectory as a basic scientist was predicted by his ability to secure a New Investigator Scholarship Award from the Heart and Stroke Foundation of Canada and, on its heels, a Scientist Award from the Medical Research Council of Canada. Dr. Choy, an international leader in the study of cardiovascular phospholipids and lipoproteins, was the first to demonstrate that phospholipids were synthesized *in situ* in the heart; this work was cited by almost every study on cardiac phospholipids in the 1980s and 1990s. He further hypothesized that lysophosphatidylcholine was a key factor in the regulation of cardiac phospholipids and was able to uncover previously unsuspected synthetic pathways. Importantly, Dr. Choy was the first to establish novel connections between lipid metabolism, cardiac arrhythmias and atherosclerosis. His keen interest in natural health products led him to serve as a founding member of the Expert Advisory Committee on Natural Health Products in Health Canada for six years.

Dr. Choy's research was supported by the Canadian Institutes of Health Research for an uninterrupted 30 years and the fruits of his labor have appeared in over 120 full-length papers and 20 book chapters. In 1999, Dr. Choy established the Centre for Research and Treatment of Atherosclerosis with a million dollar award from the Federated Insurance Companies of Canada and other sources. He supervised the research of 20 students and over a dozen postdoctoral fellows and many of these trainees now occupy key academic and industrial positions in Canada and abroad. Consequently, the impact of Dr. Choy's scientific insights continues to ripple through the research that these trainees have spawned worldwide.

Dr. Choy also carried exemplary service and administrative responsibilities. He was the President of the Canadian Biochemical Society, Vice-President of the Heart and Stroke Foundation of Manitoba, Chair of the AHFMR Senior Scholarship Review Committee, Chair of the CIHR New Investigator Review Committee and currently serves on the CIHR Team Grant Review Panel. Dr. Choy is the Secretary/Treasurer of the Canadian Society for Clinical Investigation and also serves on the editorial boards of four international journals. He assumed very important administrative roles, first as Head of the Department of Biochemistry, then as Associate Dean of Research in the Faculty of Medicine. He also served as the Acting Head of the Department of Immunology. Dr. Choy was promoted to Professor Emeritus upon his retirement in 2010. He currently serves as Associate Dean of Development for the Faculty of Medicine.

Keynote speaker:

The Inaugural Dr. Patrick Choy Distinguished Seminar In Translational Research



D. LORNE TYRRELL, OC, AOE, MD, PhD, FRCP, FRSC

Professor and CIHR/GSK Chair in Virology
Director, Li Ka Shing Institute of Virology
University of Alberta

Dr. Lorne Tyrrell holds the CIHR/GSK Chair in Virology in the Department of Medical Microbiology and Immunology at the University of Alberta. He has focused his research since 1986 on viral hepatitis. His work on the development of antiviral therapy was supported by CIHR and Glaxo Canada and resulted in the licensing of the first oral antiviral agent to treat chronic hepatitis B infection – lamivudine – in 1998. Today, lamivudine is licensed in over 200 countries worldwide for the treatment of HBV.

Dr. Tyrrell was the Dean of the Faculty of Medicine and Dentistry from 1994-2004. Since leaving the Deanship in 2004, Dr. Tyrrell has been appointed to a number of important new positions. These include the Chair of the Boards of the Institute of Health Economics and the Health Quality Council of Alberta. He served seven years on the Medical Advisory Board of the Canada Gairdner International Awards and is currently the Chair of the Board of Directors. Most recently, Dr. Tyrrell has been appointed as the Founding Scientific Director of the newly-created Li Ka Shing Institute of Virology at the University of Alberta.

For his studies on viral hepatitis, Dr. Tyrrell has received numerous prestigious awards including the Gold Medal of the Canadian Liver Foundation (2000), the Alberta Order of Excellence (2000), Officer of the Order of Canada (2002), Fellow of the Royal Society (2004), FNG Starr Award of the Canadian Medical Association (2004), and the Principal Award of the Manning Foundation (2005).

Viral Hepatitis: Animal Models and the Development of Improved Therapy

Viral hepatitis remains a major medical problem affecting approximately 600 million [200 million – hepatitis C virus (HCV) and 400 million – hepatitis B virus (HBV)]. My work originally focused on the development of antiviral therapy for HBV and the duck model of viral hepatitis played a key role in the development of the first oral antiviral agent for HBV, lamivudine, licensed in 1998. Based on the value of the model, we developed the first non-primate model for HCV infection and replication. The animal model is playing a critical role in understanding viral and host cell genetics in the outcomes of pegylated interferon and ribavirin therapy. It is also proving to be very useful in gaining a better understanding of the mechanism of HCV pathogenesis. The model has been used extensively to study novel antivirals for the treatment of HCV. The results from studies in the animal model have been highly predictive of the success of antiviral agents in clinical trials. Recent modifications have also led to a more reliable production of immunocompromised mice with successful human hepatocytes engraftment which is increasing the availability and utility of the model.

A One-Day Symposium on Translational Research in Medicine

9:00 – 17:30h
Tuesday, September 28th, 2010

Frederic Gaspard Theatre (Theatre A), Basic Medical Sciences Building
Faculty of Medicine, University of Manitoba
730 William Avenue, Winnipeg, Manitoba R3E 0W3

Program

09:00 **Welcome**

The Faculty of Medicine

09:15 **Moderator:**
Redwan Moqbel, Phd, FRCPath, Professor and Head, Immunology

Charles Bernstein, MD, FRCPC
Director, IBD Clinical and Research Centre
Head, Section of Gastroenterology
Department of Internal Medicine

Searching for a Cause of IBD

09:45 **Davinder Jassal, MD, FACC, FRCPC**
Section of Cardiology, Department of Internal Medicine
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre

The Art of Healing Broken Hearts in Breast Cancer: Translation Research From a Cardiologist's Perspective

10:15 **Estelle Simons, BSc, MD, FRCPC, FAAP, FACAAI, FAAAAI**
Section of Allergy and Clinical Immunology
Department of Pediatrics and Child Health

Anaphylaxis: New Frontiers in the 21st Century

10:45 **Coffee break**
Joe Doupe Concourse, 2nd floor, Basic Medical Sciences Bldg

11:00 **Peter Jones, PhD**
Director, Richardson Centre for Functional Foods and Nutrition
Professor, Departments of Food Science and Human Nutritional Sciences
Canada Research Chair I in Nutrition and Functional Foods

Plant Sterols in Foods: From Research Bench to the Corner Store

11:30 **Leigh Murphy, BSc (Hons), PhD**
Department of Biochemistry and Medical Genetics
Chair, Breast Cancer Research Group
Senior Scientist, Manitoba Institute for Cell Biology

***A Phosphorylation Code for Estrogen Receptor Alpha:
A Better Biomarker for Prediction of Prognosis in Human Breast Cancer***

12:00 **Lunch**
Joe Doupe Concourse, 2nd floor, Basic Medical Sciences Bldg

Introductions:

Louise Simard, BSc, PhD, Professor and Head, Biochemistry and Medical Genetics, and
Redwan Moqbel, PhD, FRCPath, Professor and Head, Immunology

13:00 **The Inaugural Dr. Patrick Choy Distinguished Seminar in Translational Research**

D. Lorne Tyrrell, OC, AOE, MD, PhD, FRCP, FRSC
Professor and CIHR/GSK Chair in Virology
Director, Li Ka Shing Institute of Virology
University of Alberta

Viral Hepatitis: Animal Models and the Development of Improved Therapy

14:00 **Moderator:**
Kelly Kaita, MD, Director, Viral Hepatitis Investigative Unit (VHIU), Health Sciences
Centre

Alex Silaghi, BSc, MSc
MD Program, Undergraduate Medicine
Phd Program, Medical Microbiology

***Influenza Evades Type I Interferon Responses Through an ERK1/2-Dependent
Pathway***

14:30 **Allan Becker, MD, FRCPC**
Head, Section of Allergy and Clinical Immunology
Department of Pediatrics and Child Health

Allergy Prevention: Are We Creating More Allergy as a Result?

15:00 **Maneesh Sud, BSc (Hons)**
MD Program, Undergraduate Medicine

Gene Expression Characterization of EVI1+ Acute Myeloid Leukemia

15:30 **Coffee break**
Joe Doupe Concourse, 2nd floor, Basic Medical Sciences Bldg

15:45 **Paul Fernyhough, BSc, PhD**
Pharmacology & Therapeutics
St Boniface Hospital Research Centre

Can Fishing Expeditions Bring Home the Translational Bacon?

16:15 **Barbara Triggs-Raine, BSc, PhD**
Department of Biochemistry and Medical Genetics
Scientist, Manitoba Institute of Child Health

Bowen Conradi Syndrome: From Gene Discovery to a Diagnostic Chip

16:45 **Discussion panel with Dr. D. Lorne Tyrrell and guest speakers**

How Does Biomedical Research Impact Human Disease?

Chair: Dr. Spencer Gibson, BSc, PhD, Provincial Director, Research, CancerCare
Manitoba & Director of Translational Research, Manitoba Institute of Cell Biology

Concluding remarks and closing

Guest Speakers:

A One Day Symposium on Translational Research in Medicine



CHARLES BERNSTEIN, MD, FRCPC

Director, IBD Clinical and Research Centre

Head, Section of Gastroenterology

Department of Internal Medicine

Dr. Charles N. Bernstein graduated from the University of Manitoba School of Medicine in 1985, and completed a residency in internal medicine at the University of Manitoba in 1989 and a fellowship in gastroenterology at UCLA in 1991. He was an Assistant professor of Medicine at UCLA until 1993 when he returned to the University of Manitoba. In 1994 he established the University of Manitoba IBD Clinical and Research Centre, of which is the director. He became Head, Section of Gastroenterology in 2001, a post he continues to hold. From 2003-2008 he was also program Director, University of Manitoba Gastroenterology Fellowship Training Program. Since 2001, he has been Professor of Medicine, Head. In 2008 he was elected into the Canadian Academy of Health Sciences and he became the inaugural holder of the Bingham Chair in Gastroenterology at the University of Manitoba. He was one of the inaugural recipients of the Crohn's and Colitis Foundation of Canada Research Scientist Awards in 2001 and it was renewed in 2006 for a second 5 year term. He is a previous holder of a CIHR Investigator Award. In 1998 he was elected into the International Organization for the Study of IBD (IOIBD) and in 2007 he became that organization's Scientific Secretary of the IOIBD. In 2007 he was voted by his peers into *Best Doctors Canada*. In 2010 he was awarded for outstanding contribution to Research by his peers in Doctors Manitoba. He has been continuously funded from CIHR (or forerunning organizations, NHRDP and MRC) since 1995. Dr. Bernstein has authored or coauthored 225 peer reviewed articles and 19 book chapters. He is the Editor of the annual Yearbook of IBD (Remedica publishers) now in its 7th volume. He has previously been on the editorial boards of Gastroenterology, the American Journal of Gastroenterology, the Canadian Journal of Gastroenterology. He currently sits on the editorial board of Clinical Gastroenterology and Hepatology and is an Associate Editor with the Inflammatory Bowel Diseases journal. His main research interests are the epidemiology and etiology of IBD and conducting translational studies in IBD.

Searching for a Cause of Inflammatory Bowel Disease (IBD)

We have established the largest validated population-based database of IBD in North America and have used it to explore issues related to disease burden, clinical outcomes and even etiology. Epidemiological studies can be vehicles for translational research and I will show how our program has developed data at a community level and have used it to explore issues on a cellular level from a population-based perspective. While Canada has amongst the highest incidence rates of IBD in the world, the emergence of IBD in developing nations warrants a systematic search for environmental changes in those countries to explain the evolution of IBD. The hygiene hypothesis suggests that an alteration in the microbial environment experienced by the host facilitates the evolution of chronic immune mediated diseases. In this presentation I will discuss worldwide epidemiological trends worldwide in IBD and consider factors that may be associated with these trends. I will also discuss how we have used our University of Manitoba IBD Epidemiology Database and our University of Manitoba IBD Research Registry to explore the role of the gut microbiome in the etiology of IBD.



DAVINDER JASSAL, MD, FACC, FRCPC

Section of Cardiology, Department of Internal Medicine
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre

Dr. Davinder S. Jassal was born in Thompson, Manitoba, obtained an International Baccalaureate Degree at Sisler High School in Winnipeg, and graduated from the University of Manitoba with an M.D. in 1998. He completed a residency in Internal Medicine at the University of Manitoba from 1998-2001 and then a residency in Cardiology at Dalhousie University in Halifax, Nova Scotia, Canada from 2001-2004. Subsequently, he completed a clinical and research fellowship in multimodality cardiac imaging from 2004-2006, specializing in echocardiography, computed tomography, and MRI at Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, US.

Dr. Jassal joined the University of Manitoba in 2006 as an Academic Clinician Scientist, where half of his time is devoted to patient care in the Coronary Care Unit and cardiac imaging and the other half devoted to translational research. Currently, as a distinguished contributor to the field of noninvasive cardiovascular imaging, he holds numerous academic and administrative positions at the University of Manitoba. Dr. Jassal is Assistant Professor of Medicine, Radiology and Physiology; Principal Investigator of the Cardiovascular Imaging Laboratory in the Institute of Cardiovascular Sciences at the St. Boniface General Hospital and Research Centre; Program Director of Adult Cardiology Residency; Director of the Coronary Care Unit; Co-director of the WRHA Cardiac CT and MRI programs; and Postgraduate Cardiology Research Director. Additionally, Dr. Jassal holds affiliated scientist positions with both the Institute of Biodiagnostics at the National Research Council of Canada and the Canadian Centre for Agri-Food Research in Health and Medicine (CCARM), and is a cofounder of the Cardiovascular Research and Health Outcomes in Manitoba (CHARM) research group.

Dr. Jassal holds the Heart and Stroke Foundation of Canada New Investigator. He was recently nationally awarded the Royal College of Physicians and Surgeons of Canada Mentor of the Year Award, Canadian Cardiovascular Society Young Investigator Award, the Liam Murphy Young Investigator Award from the Department of Internal Medicine in 2008, and the University of Manitoba Rh Award for Outstanding Contributions to Scholarship and Research in the Health Sciences Category in 2010. Dr. Jassal has secured grant support from a total of 26 local, provincial and federal agencies amounting to 3.0 million dollars in funding. With over 250 peer reviewed publications consisting of original research, editorials, chapters, and abstracts, he has published in high impact journals including the New England Journal of Medicine, Circulation, Journal American College of Cardiology, and the European Heart Journal.

Trastuzumab (Herceptin) and Heart failure: A Tale of Two Cities

Cardiovascular disease and breast cancer are major public health concerns in Canada. The two diseases are intricately involved as treatment of one disease may lead to detrimental effects in the other. Although the current combination of surgical resection, radiotherapy, and chemotherapy may lead to remission in breast cancer patients, the administration of chemotherapeutic based agents, in particular Doxorubicin, are associated with an increased risk of cardiotoxicity. The introduction of novel monoclonal antibodies in breast cancer therapy which target growth factor receptors further compounds this issue of drug induced cardiac dysfunction.

Trastuzumab (Herceptin), a humanized monoclonal antibody against the extracellular domain of the HER-2 protein, is used in both the adjuvant and metastatic settings of breast cancer. Despite its clear therapeutic benefits, cardiotoxicity is a major concern, especially when trastuzumab is used in combination with anthracyclines. A brief review of the prevalence of Trastuzumab mediated cardiotoxicity in Manitoba, the use of noninvasive cardiac imaging for its early detection, and the use of preventative therapy will be presented.



ESTELLE SIMONS, BSc, MD, FRCPC, FAAP, FACAAI, FAAAAI

Section of Allergy and Clinical Immunology
Department of Pediatrics and Child Health

Dr. Estelle Simons founded the Section of Allergy and Clinical Immunology in the Department of Pediatrics & Child Health at the University of Manitoba, and headed the Section from 1975-2005. Recently, she served as the elected President of the American Academy of Allergy Asthma and Immunology (AAAAI). Previously, she served as President of the Canadian Society of Allergy & Clinical Immunology (CSACI), Chair of the Royal College Clinical Immunology Examining Board, Chair of the Royal College Clinical Immunology Specialty Committee, Chair of the Allergy Section of the Canadian Pediatric Society, and founding President of the Manitoba Allergy Society. Her research has focused on the pharmacologic and immunologic modification of allergic diseases such as anaphylaxis and asthma. She has authored or co-authored 500 peer-reviewed articles, invited editorials, reviews, and book chapters, as well as 285 published abstracts. She has also edited or co-edited seven books, including *Middleton's Allergy: Principles & Practice 6th edition (2003)* and *7th edition (2009)*. She has been honored with the Medical Research Council Queen Elizabeth II Scientist Award, the CSACI Research Award, the Manitoba Medical Association Scholastic Award, the Canadian Medical Association Medal of Service, the Canadian Who's Who in Healthcare Award, the Anaphylaxis Canada Research Award, the Commemorative Medal for the Queen's Golden Jubilee, the World Allergy Organization Scientific Achievement Award, and the AAAAI Distinguished Service Award.

Anaphylaxis: New Frontiers in the 21st Century

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Several active areas of translational research in this disease will potentially lead to major advances in diagnosis and treatment in the future.

Diagnosis of anaphylaxis is based primarily on clinical criteria. There are no validated laboratory tests that are specific for the disease; however, biomarkers such as platelet-activating factor and mast cell carboxypeptidase A3 are currently being studied as promising new diagnostic tests. Moreover, although allergen skin tests and allergen-specific IgE levels in serum are widely used to confirm sensitization to anaphylaxis triggers, these tests do not predict anaphylaxis recurrence, severity, or fatality. In vitro tests such as allergen-specific cytokine responses and component-resolved diagnostics are currently being studied for their potential usefulness in predicting clinical risk in anaphylaxis.

In the treatment of anaphylaxis, none of the medications currently used has ever been studied in randomized, double-blind, placebo-controlled trials in acute anaphylaxis episodes. Based on the best evidence available, prompt injection of epinephrine is universally recommended as the essential life-saving intervention. Recent research has focused on why epinephrine is under-utilized in the first-aid treatment of anaphylaxis and on improved epinephrine auto-injector design and development of non-injectable epinephrine formulations. Recommendations vary greatly with regard to use of adjunctive medications such as H₁-antihistamines, H₂-antihistamines, and glucocorticoids in anaphylaxis. The possibility of conducting randomized placebo-controlled trials with these adjunctive medications, particularly with glucocorticoids, is currently being considered in order to guide clinical decision-making in this life-threatening disease.



PETER JONES, PhD

Director, Richardson Centre for Functional Foods and Nutrition
Professor, Departments of Food Science and Human Nutritional Sciences
Canada Research Chair I in Nutrition and Functional Foods

Peter J. Jones, the Canada Research Chair in Functional Foods and Nutrition joined the University of Manitoba on November 1, 2005 as Director of the Richardson Centre for Functional Foods and Nutraceuticals.

Currently, Dr. Jones serves as President of the Danone Institute for Nutrition in Canada and Past-President of the Canadian Society for Nutritional Sciences. He serves as Chairman of the Functional Foods and Nutraceuticals Board of the Vancouver-based Forbes Medi-tech group. Dr. Jones also has sat on the Food and Agriculture Organization of the United Nations, World Health Organization, and United Nations University (FAO/WHO/UNU) Expert consultant Panel for Energy and Protein Requirements in Human Nutrition.

Dr. Jones' research interests cover cholesterol, fat and energy metabolism. He has applied novel stable isotope methodologies to examine the response of these areas of metabolism to dietary intervention. His research group has been active in exploring the dietary determinants which control cholesterol biosynthesis in humans, as well as how plant sterols act in functional foods as cholesterol-lowering agents. Other areas of research have included re-establishing energy needs in sub-groups of the Canadian population and exploring what fats confer optimal health during weight reducing diets. Dr. Jones has published over 200 peer-reviewed research articles and reviews in international journals, as well as chapters in leading nutrition textbooks. Dr. Jones received the Young Investigator Award for Excellence in Nutrition Research in 1997.

Plant Sterols in Foods: From Research Bench to the Corner Store

Over past decades a panoply of diet based ingredients have been marketed with purported health benefits, however, only certain of these have passed muster in terms of solid evidence based science. One such category is plant sterols. Dietary supplementation with plant sterols has been demonstrated to reduce cholesterol absorption in the gut suppressing circulatory low density lipoprotein cholesterol (LDL-C) levels. As such, considerable basic and clinical trial evidence supports the use of plant sterols and their analogs in the modulation of heart disease risk. Similarly, the inhibitory action of plant sterols on lung, stomach, as well as ovarian and breast cancer has been proposed. Plant sterols appear to act through a wide range of mechanisms of action including suppression of key intestinal absorption as well as reducing cancer cell growth and promotion of apoptosis. In concert with the sound science now available supporting the efficacy and safety of plant sterols, recent regulatory approval for health claims on foods containing these materials has paved the way for public acceptance and benefit. As of May 2010, plant sterol containing foods were permitted for sale in stores in Canada as safe alternatives or adjuncts to drugs in cardiovascular disease and cancer risk management. Furthermore, it has been calculated that penetration of plant sterol foods into the Canadian marketplace will translate into direct and indirect health care cost savings of as much as CAN\$ 2.45B. Thus, the plant sterol functional food category represents a melding of basic science and regulatory policy to provide consumers with an effective new dietary-based avenue for health promotion.



LEIGH MURPHY, BSc (Hons), PhD

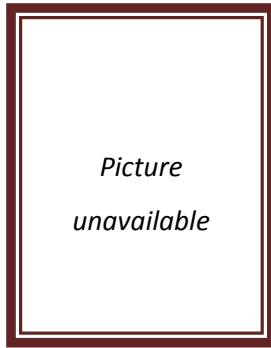
Department of Biochemistry and Medical Genetics
Chair, Breast Cancer Research Group
Senior Scientist, Manitoba Institute for Cell Biology

Leigh Murphy obtained her Phd in reproductive endocrinology in 1977 from Sydney University, Australia, followed by postdoctoral training at the Ludwig Institute for Cancer Research, Sydney University and the Dept of Physiology, University of Manitoba. She is currently Professor in the Department of Biochemistry and Medical Genetics, University of Manitoba; Chair, Breast Cancer Research Group, Director of the Manitoba Institute for Cell Biology and Director of the Manitoba Breast Tumour Bank. She has published over 170 publications mainly on estrogen signaling in human breast cancer tissues *in vivo*. Research funding has been from MRC/CIHR, MHRC, NCIC/CBCRA, CFI, CBCF, CCMF and PCFC. She has held prestigious career awards including the NCIC and MRC Scientist Awards. In 2005, she received a YMCA-YWCA Women of Distinction Award for her internationally recognized research in the areas of hormones and breast cancer.

Her research focuses on estrogen receptors (ERs) in particular ER profiling in human breast tumours as better treatment response biomarkers. One aspect is the expression of ER-alpha and ER-beta in tumours. Her lab was first to show that ER-beta mRNA is expressed in human breast tumours such that two types of tumour exist, those expressing both ER-alpha and ER-beta and those expressing ER-beta alone. Her results suggest that the function of ER-beta when expressed with ER-alpha is different to when it is expressed alone. Her second focus is post-translational modifications of ER. Her lab was the first to demonstrate that phospho-Serine 118 ER-alpha was detectable in multiple human breast tumours, and more recently detection of several other novel phosphorylation sites on ER-alpha in breast tumour was found such that she has identified a novel phosphorylation code for ER-alpha with the potential to be a more precise biomarker of treatment response in breast cancer. This phosphorylation code is based on the presence and absence of 7 different phosphorylated sites on ER-alpha. More recently she has been investigating the role of ER-beta in both prostate and lung cancers.

A Phosphorylation Code for Estrogen Receptor Alpha: A Better Biomarker for Prediction of Prognosis in Human Breast Cancer

The estrogen receptor (ER-alpha) status of breast tumors, measured as a binary factor (+/-) is a clinically useful important but imperfect treatment response biomarker in human breast cancer. There is a need for more precise markers of response and outcome to endocrine therapies such as Tamoxifen and aromatase inhibitors. ER-alpha is regulated by several factors including phosphorylation. Multiple sites of phosphorylation on ER-alpha have been identified. Using novel phosphorylation site specific antibodies to ER-alpha we have detected multiple phosphorylated sites on ER-alpha in multiple breast tumour biopsy samples using tissue micro-arrays constructed by and available in the Manitoba Breast Tumour Bank and Clinical Database. Thus providing evidence of their relevance to human breast cancer *in vivo*. Our data suggest that detection in primary breast tumours of phosphorylation at some sites on ER-alpha is associated with a better clinical outcome while phosphorylation at other sites is associated with a poorer clinical outcome in breast cancer patients who have been treated with the endocrine therapy, Tamoxifen. This suggests the hypothesis that phospho-profiling of ER-alpha in human breast tumours to establish an "ER-alpha phosphorylation code", may be a more accurate marker of prognosis and/or response to endocrine therapy in human breast cancer.



ALEX SILAGHI, BSc, MSc

MD Program, Undergraduate Medicine
PhD Program, Medical Microbiology

Alex Silaghi obtained a BSc in Microbiology and a MSc in Immunology from University of Manitoba and is currently enrolled in the MD and PhD programs at University of Manitoba. His PhD is focused on the pathogenesis of highly virulent influenza viruses.

Influenza Evades Type 1 Interferon Response Through an ERK 1/2-Dependent Pathway

Evasion of the type I interferon pathway by influenza virus is essential for replication in mammals and pathogenesis. The current evasion model for influenza centers around inhibition of type I interferon induction, yet we hypothesize that inhibition of response to type I interferon may be also important. We investigated the role of ERK1/2 since these molecules are activated during influenza infection and in some cancers activation of ERK1/2 was involved in resistance to type I interferons.

Influenza A/WSN/1933 or a recombinant vesicular stomatitis virus (VSV) were used to infect J774A.1 murine macrophages. WSN and VSV induced similar levels of interferon, yet MHCI expression, a type I interferon-induced protein, and anti-viral state levels were significantly higher for VSV, suggesting that response to type I interferon is reduced during influenza infection. Inhibition of ERK1/2 enhanced MHCI expression and anti-viral state levels, and reduced influenza replication. Blockage of the type I interferon receptor abrogated the enhanced MHCI expression and anti-viral response observed after ERK1/2 inhibition, indicating that the anti-viral effects caused by ERK1/2 inhibition are dependent on type I interferon response. Thus, we propose that inhibition of ERK1/2 may be a viable anti-influenza therapeutic strategy.



ALLAN BECKER, MD, FRCPC

Head, Section of Allergy and Clinical Immunology
Department of Pediatrics and Child Health

Dr. Becker is Professor and Head of the Section of Allergy and Clinical Immunology in the Department of Pediatrics and Child Health at the University of Manitoba and a consultant allergist at Children's Hospital of Winnipeg. He led development of asthma educator education program (*AsthmaTrec*) and of national Asthma Educator certification in Canada. He is a member of the Asthma Committee of the Canadian Thoracic Society and of the Scientific Committee of the Global Initiative for Asthma (GINA) and was primary author of the first Canadian Pediatric Asthma Guidelines.

Dr. Becker's primary research interest is the origins of allergy and asthma in early life. He is co-PI of "The Canadian Asthma Primary Prevention Study" and leads two CIHR teams in asthma research. He is co-PI of the Canadian Healthy Infant Longitudinal Development (CHILD) study.

Allergy Prevention: Have We Created More Allergy as a Result of Our Recommendations?

The epidemic of allergic diseases has been best recognized in the increase in asthma prevalence beginning in the 1970s. It is now clear that food allergy has also increased particularly over the last decade and most apparently for peanut allergy. Data from questionnaires, cohort studies, and health care databases all have demonstrated this increase. In the 1990s there was concern that pregnancy and early life were vulnerable periods of time for the fetus and infant's developing immune system. Based on this, paediatric authorities in the US, UK, Canada and Australia produced dietary recommendations for mothers during pregnancy and while breastfeeding as well as for infants and toddlers in the terms of delayed introduction of "highly allergenic" foods. And since then there has been a clear and dramatic increase in food allergy. Our Canadian Asthma Primary Prevention Study began in 1994 and included advice on food avoidance during pregnancy, lactation and for the infant's early years. In that study there was a (fortunately non-significant) trend at 7 years of age for more peanut allergy. More recently, we studied approximately 14,000 children born in Manitoba in 1995 also followed through to 7 years of age. In that cohort we clearly showed that the most vulnerable children (i.e. those born prematurely and of low birth weight) have no increase in current food allergy. This would appear to negate the argument that foods should be delayed because of an immature immune system or poorly developed gastrointestinal tract. Current evidence does not support the need for maternal dietary restrictions during pregnancy or lactation. Data do support the importance of breastfeeding for a variety of reasons but physicians ought not to advise patients that breastfeeding will prevent development of allergy. There may be a decrease in transient cow's milk sensitization and wheezing in early childhood and delay of atopic dermatitis with exclusive breastfeeding for at least 4 months but this does not translate into decrease in food allergy nor allergic diseases. In addition, breastfeeding is associated with less obesity in children in our 1995 Manitoba birth cohort and a trend to less asthma. For children at 7 years of age who were breastfed less than 12 weeks, who are overweight and who have a mother with asthma, there is a fourfold increased likelihood of asthma in that cohort. Recent recommendations from the American Academy of Pediatric Committee of Nutrition and Section of Allergy and Immunology support breastfeeding and note that "There is little evidence that delaying introduction of complementary foods beyond 4 – 6 months of age prevents atopic disease".



MANEESH SUD, BSc (Hons)

MD Program, Undergraduate Medicine

Maneesh Sud completed his BSc (Hons.) degree in Pathobiology at the University of Toronto in 2007, where he won the gold medal in the Department of Laboratory Medicine and Pathobiology. He began his undergraduate medical education at the University of Manitoba's BSc (Medicine) summer research program. He is currently a 4th year medical student interested in pursuing a career in Internal Medicine.

At the University of Toronto, under the supervision of Drs. Herman Yeger and Ernest Cutz, Maneesh was involved in localizing NADPH Oxidase in small cell lung tumours. He did work under Dr. Philip Marsden in endothelial biology and received the John D. Schultz Science Student Scholarship from the Heart and Stroke Foundation (2007) to investigate the role of promoter methylation of the endoglin gene in hereditary hemorrhagic telangiectasia and atherosclerosis. He is currently working on characterizing the gene expression patterns of EVI1+ acute myeloid leukemias under Dr. Mark Minden at the Ontario Cancer Institute. He recently won the Katie Hamauer Award in Oncology and Cancer Cell Biology at the National Student Research Forum in Galveston, Texas (2010) and 1st place in translational research at the Canadian National Medical Student Research Forum in Winnipeg, Manitoba (2010).

Maneesh has participated in numerous published systematic reviews, most notably the use of mechanical ventilation in the prone position and high frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome under the supervision of Drs. Jan Friedrich and Neill Adhikari. He currently works with Dr. David Swajcer to characterize the outcomes of patients receiving hematopoietic stem cell transplants who are diagnosed with acute myeloid leukemia in the province of Manitoba.

Gene Expression Characterization of EVI1+ Acute Myeloid Leukemias

Acute myeloid leukemia (AML) is a group of hematological malignancies characterized by genetic abnormalities resulting in aberrant gene expression and variable responsiveness to chemotherapy. A subset of AML patients over-express the EVI1 transcription factor that resides at 3q26. The clinical outcome of EVI1⁺ patients is poor with conventional chemotherapy. This suggests that the identification of transcriptome features unique to EVI1⁺ patients may explain this resistance and provide a path to improved therapy.

We used a microarray-based gene expression approach to characterize the signatures associated with EVI1⁺ positivity in peripheral blood blast samples from the Princess Margaret Hospital Leukemia Tissue Bank. Results were validated using quantitative RT-PCR. *In vitro* drug sensitivity of an EVI1⁺ cell line was determined using an MTS assay.

We identified 10 patients with 3q26 abnormalities over-expressing EVI1 (3q26⁺/EVI1⁺), 5 patients without 3q26 abnormalities over-expressing EVI1 (3q26⁻/EVI1⁺) and 11 patients with neither 3q26 abnormalities nor EVI1 expression (3q26⁻/EVI1⁻) for microarray analysis. Unsupervised cluster analysis revealed 3 distinct gene expression signatures correlating with 3q26 and EVI1 status. EVI1⁺ blasts up-regulated genes within the mTOR pathway and numerous other signalling pathways relative to EVI1⁻ blasts. A 3q26⁺/EVI1⁺ patient-cell line was susceptible to *in vitro* treatment with an mTOR inhibitor, rapamycin.

We conclude EVI1⁺ AML has a distinctive gene expression profile that indicates high-level activation of cancer-associated pathways. Among these is the mTOR pathway for which inhibitors are available and already in clinical use.



PAUL FERNYHOUGH, BSc, PhD

Pharmacology & Therapeutics
St. Boniface Hospital Research Centre

Dr. Fernyhough was born and educated in East London, UK, and performed his BSc degree in Biological Sciences at the University of Essex. Dr. Fernyhough performed his Phd in biochemistry in the Department of Biochemistry (department of Sir Hans Krebs) at University of Sheffield in the UK. He also performed postdoctoral research at Colorado State University, Kings College London (department of Maurice Wilkins) and as a Wellcome Trust Postdoctoral Fellow at St Bartholomew's Medical College (department of Sir John Vane). All of these positions spanned 1985-1998. Dr. Fernyhough subsequently worked for 5½ years (1998-2004) as a fully tenured lecturer in the School of Biological Sciences (now the Faculty of Life Sciences) at the University of Manchester. Dr. Fernyhough came to Winnipeg in 2004 and has helped to set up a neuroscience research group at St Boniface Hospital Research Centre with strong links with the Department of Pharmacology & Therapeutics at the University of Manitoba that now numbers 40 staff and currently holds approximately \$8 million in external funding. Dr. Fernyhough's general research interest is in the cell biology underlying neurodegenerative disorders of the peripheral and central nervous systems with a focus on the impact of diabetes.

Can Fishing Expeditions Bring Home the Translational Bacon?

In North America 19 million people have diabetes and the epidemic in obesity is raising the impact of the disease. Diabetic neuropathy is a common complication of diabetes. For example, 80% of aboriginal persons with diabetes exhibit neuropathic symptoms. The disease leads to incapacitating pain, sensory loss, foot ulceration, infection, gangrene, poor wound healing and amputation. This neurodegenerative disease is associated with structural changes in peripheral nerves resulting in irreversible dying-back of nerve endings.

A unique capability of the laboratory is the development of a medium throughput screening assay involving culture of adult sensory neurons. This assay combined with high content imaging permits quantification of effects of compounds on levels of axon outgrowth, an in vitro measure of nerve fiber plasticity and tissue innervation. A drug screen of previously FDA-approved compounds identified a novel receptor antagonist as a candidate molecule for treatment of diabetic neuropathy. This compound enhanced axon regeneration in cultures from normal, type 1 diabetic and type 2 diabetic rodents. In vivo studies in type 1 streptozotocin diabetic mice (a model of type 1 diabetes) have shown the drug to be efficacious in preventing and reversing indices of diabetic sensory neuropathy.

The general strategy is to now position the drug to proceed to clinical trials in 2-3 years. In the least the compound or related analogues should be ready to move into the NIH RAID program within 2 years for further drug development in readiness for clinical trials. (*Funded by the Juvenile Diabetes Research Foundation.*)



BARBARA TRIGGS-RAINE, BSc, PhD

Department of Biochemistry and Medical Genetics
Scientist, Manitoba Institute of Child Health

Dr. Triggs-Raine completed her undergraduate and graduate training in microbiology at the University of Manitoba in 1987. Fascinated by a graduate course that she took in human genetics, she opted to develop this interest through postdoctoral training at Toronto's Hospital for Sick Children and then the McGill University-Montreal Children's Hospital Research Institute. In 1991, she returned to the University of Manitoba, where she is now a Professor in Biochemistry and Medical Genetics. Her early work included molecular studies of metabolic disease, and underlies several of the current standards for Tay-Sachs disease screening. Collaborations with other researchers, and the application of new technologies, have led her in new research directions. One of these directions has been a successful collaborative effort with local geneticists, Drs. Greenberg, Wrogemann, and Zelinski, as well as members of the Hutterite community, leading to the identification of the Bowen-Conradi Syndrome gene.

Bowen-Conradi Syndrome: From Gene Discovery to a Diagnostic Chip

Bowen-Conradi Syndrome (BCS) is an autosomal recessive disorder characterized by severely impaired prenatal and postnatal growth, profound psychomotor retardation, and death in early childhood. BCS is of major concern to the Hutterite communities of the Canadian Prairies and the United States Great Plains due to its morbidity, mortality, and high frequency (~1/355 births). Our group mapped the BCS gene to a 1.9 Mbp interval, containing 59 candidate genes, on human chromosome 12p13.3. Through characterization of the candidate genes, we identified an A to G mutation that results in a deficiency of EMG1 (Essential for Mitotic Growth 1) protein as the cause of BCS in Hutterites. Although EMG1 has not been studied in humans, its absolute requirement for ribosome biogenesis in yeast attests to its likely importance in humans. Consistent with this, a complete deficiency of Emg1 in mice is pre-implantation lethal (Ding et al, unpublished). BCS is one of several disorders in Hutterites where a single mutation underlies the disease of interest. This has led us to design a DNA CHIP that will have potential application to genetic testing and diagnosis for members of the Hutterite population. *(Funded by the Manitoba Institute of Child Health and the Canadian Institutes of Health Research.)*

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Dr. Redwan Moqbel (Chair), Professor and Head, Immunology
Dr. Kevin Coombs, Assistant Dean (Research), Faculty of Medicine; Professor, Medical Microbiology
Dr. David Eisenstat, Director, Advanced Degrees in Medicine Program
Dr. Spencer Gibson, Provincial Director, Research, CancerCare Manitoba &
Director of Translational Research, Manitoba Institute of Cell Biology
Dr. Kelly Kaita, Director, Viral Hepatitis Investigative Unit (VHIU), Health Sciences Centre
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Mrs. Susan Ness, Program Assistant, National Training Program in Inflammation and Allergy
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