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### Reports: Research Institutes

#### Population Health Research Institute

The Population Health Research Institute (PHRI) was established in 1999, having evolved from the highly successful Preventive Cardiology and Therapeutics Research Program initiated in 1992 by Salim Yusuf. The primary objective of PHRI is to provide leadership in international health research focused on the causes of chronic diseases and how they can be prevented or treated. The PHRI also plays an active role in the education of individual researchers, and in building capacity internationally for the development of global research programs. The PHRI resides in the new David Braley Cardiac, Vascular and Stroke Research Institute, a dedicated state-of-the-art research facility that provides increased capacity to PHRI for managing global clinical trials and epidemiology studies, while also providing multidisciplinary space for basic sciences and knowledge transfer. This facility is shared with the Thrombosis and Atherosclerosis Research Institute (formerly the Henderson Research Institute) led by Dr. Jeffrey Weitz, creating a trans-disciplinary research environment for collaborations and integrated health care initiatives with Hamilton Health Sciences.

The PHRI involves over 300 scientists, researchers, and other support professionals, and conducts studies in more than 1500 centres in 83 countries from all inhabited continents of the world. Eight members hold research chairs, more than 12 hold career scientist awards from CIHR, HSFO or MOH. PHRI is funded from peer-reviewed grants (CIHR, HSFO, MOH, NIH), the World Health Organization and industry. PHRI has trained over 50 graduate students and research fellows. Its scientists publish more than 150 papers a year, with several (about 15-20) every year in leading journals such as NEJM, Lancet, JAMA, BMJ, and Circulation. Several of the papers are among the highest-cited papers in the world. For example, the main HOPE paper published in NEJM 2000 is the highest-cited paper in clinical medicine in November/December 2001 and the INTERHEART paper in Lancet was the highest-cited research paper from Canada from April 2004-February 2006. Collectively the scientists are the highest-cited clinical research group in Canada, with S. Yusuf the only Canadian in the top 10 in the world. Publications from PHRI scientists have influenced national and international guidelines for treatment and prevention of cardiovascular diseases such as ACS, heart failure, CABG surgery and secondary prevention.

#### Program Specialties:

- **Acute Coronary Syndromes** (S. Mehta, S. Jolly, C. Buller, J. Eikelboom)*
- **Aboriginal/Ethnicity Health** (S. Anand)*
- **Atherosclerosis Imaging** (E. Lonn, T. Sheth)
- **Arterial Physiology** (S. Connolly, C. Morillo, J. Healey)*
- **Cardiovascular Prevention** (H. Gerstein, K. Teo, E. Lonn, M. O’Donnell, C. Chow, A. Mente)*
- **Childhood Risk Factors** (K. Morrison, K. Teo, S. Anand, S. Atkinson)*
- **Coronary Interventional Health Delivery** (M. Natarajan, S. Mehta, S. Jolly, C. Buller)
- **CV Surgery** (A. Lamy, K. Teo, R. Whitlock)
- **Developing Countries** (K. Teo, C. Morillo, R. J. Devereaux, J. Bosch)*
- **Diabetes/Dysglycemia** (H. Gerstein, Z. Punthakee, J. Bosch)*
- **Heart Failure/LV Dysfunction** (R. McKeilvie, C. Demers, K. Teo, H. Dokainish)*
- **Knowledge Translation** (KT1) (S. Connolly, R. Nieuwlaat)*
- **Translational Medicine** (KT1) (J. Eikelboom, H. Gerstein, J. Hirsh, S. Anand)*
- **Perioperative Ischemia** (P.J. Devereaux, M. Walsh)*
- **Population Genomics** (S. Anand, G. Paredes, M. McQueen)*
- **Population Health** (S. Anand, K. Teo, M. O’Donnell, A. Mente, C. Chow, S. Ranganathan)*
- **Stroke/Cognitive Function** (M. O’Donnell, J. Bosch)*
- **Women’s Health** (S. Anand, H. Arthur)

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The PHRI also runs the CIHR-funded CANNeCTIN program, now beginning its third year of operation. CANNeCTIN (PI: S. Yusuf) brings together investigators from across Canada with a wide range of expertise and research achievement in cardiovascular disease and diabetes to work collaboratively toward major discoveries which are likely beyond the capacity of an individual centre. CANNeCTIN aims to develop research capacity across Canada in the field of randomized clinical trials. CANNeCTIN’s 32-member national steering committee and 14 working groups involve every Canadian medical school and other Canadian research institutions. To date CANNeCTIN has funded 18 collaborative, multi-centre, peer-reviewed research projects (including both trials and registries) and brought together over 300 collaborators nationally and internationally. The CANNeCTIN projects are:

1. Vascular events in noncardiac surgery patients cOhort evaluatioN (VISION)
2. IMPI: Investigation of the Management of Pericarditis
3. Perioperative Ischemic Evaluation-2 Trial (POISE-2)
4. Understanding the Increased Cardiovascular Risk after Preeclampsia/ Eclampsia (ACRE)
5. Cluster RCT to assess the effect of using a simple warfarin dosing algorithm on INR control among Canadian general practices
6. Heart Failure and Conditioned Nutritional Deficiency in the Myocardium: Studies of cardiac nutritional deficiencies and Targeted Supplementation to Improve Markers of Improvement in Cardiac Function in Chronic Systolic Heart Failure
7. Left Atrial Appendage Occlusion Study II (LAACOS II)
8. Prevention of Arrhythmia Device Infection Trial (PADIT)
9. Ontario Bariatric Registry
10. Canadian Pediatric Weight Management Registry (CANPWR)

Top 25 Publications from PHRI*

Papers with the highest citations of PHRI papers (Top 25 only; 109 papers have been cited >100 times.)

**As of August 2010**

- HOPE-2, Homocysteine lowering, NEJM 2006
- INTERHEART Psychosocial, Lancet 2004

Major Discoveries in 2009

1. Oral direct thrombin inhibitor (dabigatran) is more effective and safer than oral anticoagulation in atrial fibrillation.
2. Clopidogrel plus aspirin (dual antiplatelet therapy) is superior to aspirin in preventing strokes in AF vs. PCI Alone in patients with STEMI undergoing primary PCI
3. Double dose clopidogrel is superior to regular dose clopidogrel in ACS patients undergoing PCI

11. Covert Stroke in Canada: An MRI and Outcome Assessment Study (PURE-MRI)
12. Effects of Beta Adrenergic Blocker and Angiotensin Receptor Blocker On Aortic Dilatation in Adults with Bicuspid Aortic Valve (BAV)
13. Remote Ischemic Preconditioning in Cardiac Surgery Trial (Remote IMPACT)
14. Steroids In Cardiac Surgery: Impact on Atrial Fibrillation (SIRS AF)
15. SUperventricular and Pharmacological novel iNterventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting surgery: An International Multicenter RCT (SUPERIOR SVG PATENCY CABG Trial)
16. TOTAL trial: randomized trial of routine aspiration ThrOmbecTomy with percutaneous coronary intervention (PCI) vs. PCI Alone in patients with STEMI undergoing primary PCI
17. RIVAL: Radial vs. Femoral access for coronary intervention in patients presenting with ACS
18. RAAS data analysis: Are inhibitors of the Renin-Angiotensin-Aldosterone System beneficial even in normotensive individuals?

PHRI also houses the CARING network which examines issues related to women and heart disease. New areas of research include peripoperative medicine, childhood risk factors, population genomics, societal and upstream determinants of health, CV surgery and strokes. PHRI houses one of the largest research biobanks with 2.4 million aliquots of bloods and urine from approximately 380,000 subjects linked to clinical outcomes, which is an invaluable resource for discovery research.

Recent Major National/International Awards:

- Sonia Anand 2009 Indo-Canada Chamber of Commerce Professional Female Award
- P.J. Devereaux 2009 POISE paper identified as a fast breaking paper in the field of clinical medicine by Thomson Reuters Essential Science Indicators
- Carlos Morillo 2010 One of the 10 Most Influential Hispanic Canadians
- Salim Yusuf 2009 Henry N. Neufeld Memorial Lecture and Award, Israel Heart Society
- 2009 Robert Tagerstedt Award of the Finnish Hypertension Society
- 2009 Annual Clinical Science Lecture of Karolinska Institutet, Stockholm, Sweden
- 2009 Lifetime Career Feature in European Heart Journal, CardioPulse
Thrombosis & Atherosclerosis Research Institute (TaARI)

After more than two decades of success, the Henderson Research Centre relocated to the David Braley Research Institute at the Hamilton Health Sciences in January 2010. In celebration of its new location, the institute was renamed the Thrombosis & Atherosclerosis Research Institute (TaARI). The new facility not only provides space for further expansion, but also creates synergies with the Population Health Research Institute (PHRI). As before, the mission of TaARI is to reduce death and disability from thrombotic diseases by conducting research into the pathogenesis, prevention, diagnosis and treatment of thrombosis and vascular disease.

Dr. Jeffrey Weitz, Executive Director, continues to provide leadership to the core research programs at TaARI which include:

1. Experimental Thrombosis and Atherosclerosis (ETA) Program, which is under the directorship of Dr. Jeff Weitz and conducts fundamental research on the interplay between thrombosis, atherosclerosis, diabetes, obesity, cancer, and inflammation.

2. Clinical Thromboembolism Program (CTP), which is led by Dr. Sam Schulman and performs research that informs optimal prevention, diagnosis and treatment of patients with thrombotic problems, as well as research in knowledge translation aimed at optimal transfer of this information to the bedside. This regional program includes all Hamilton Health Sciences hospital sites as well as St. Joseph’s Healthcare and provides clinical care to patients in the hospital and in the community who have, or are at risk for, thrombotic disorders.

3. Comparative Medicine Program, which is under the directorship of Dr. Shawn Petrik, and focuses on the translation of basic research findings into clinically relevant models prior to evaluation in humans.

4. Biometrics Group, which is led by Professor Robin Roberts, and provides biostatistical support for all faculty and students in the various TaARI programs. Professor Roberts also leads the statistical core for the Neonatal Research Program, which is led by Dr. Barbara Schmidt.

The funding for TaARI is primarily derived from peer-reviewed sources, such as the Canadian Institutes of Health Research, Canada Research Chairs, the Heart & Stroke Foundation of Canada/Ontario, Canadian Diabetes Association, National Cancer Institute of Canada and the National Institutes of Health. Hamilton Health Sciences and McMaster University continue to provide invaluable support to help fund faculty and students, as well as operational funding for infrastructure.

Consistent with its academic mission of providing an excellent environment for learners, faculty members at TaARI have trained 18 MSc and 9 PhD candidates, and 10 postdoctoral fellows in 2009-10. In addition, the facility also has provided many undergraduate students with a site to conduct their fourth year thesis projects.

Fluorescently labeled micro particles have been infused into the vascular system, a network of small blood vessels, that surround and supply the walls of large vessels. The image shows a section of the aortic arch.

Dr. G. Warstuch lab

Firestone Institute for Respiratory Health

Following the development of a respiratory service with a research arm at St. Joseph’s Healthcare Hamilton 40 years ago, the Firestone Regional Chest and Allergy Unit, now the Firestone Institute for Respiratory Health (FIRH), has developed into a world-renowned centre for the investigation and treatment of respiratory diseases.

FIRH provides comprehensive inpatient and outpatient respiratory care as the regional respiratory service for the City of Hamilton and the Hamilton Niagara Haldimand Brant Local Health Integrated Network. FIRH has a unique Chest Program that encompasses the spectrum of respiratory medicine together with affiliated head-and-neck and thoracic surgery services; all are located on one site. In 2009-10, FIRH Clinics handled over 65,000 patient contacts, a considerable increase since 2005. Currently thirty physicians hold over 75 separate clinics during a typical week. FIRH’s patient-centred focus on care is achieved through the tremendous efforts of allied health care professionals, including nurses, respiratory therapists and technicians, and through the efforts of FIRH’s administrative staff.

Clinical, research and educational activities are integrated and collaborative within FIRH. The intent is to provide exemplary clinical care, in tandem with basic and translational research inquiry, while educating and mentoring health care professionals to treat, research, teach, and lead. The strength of FIRH continues to be its focus on improving patient outcomes.

The proximity of research teams to clinical services has, on the one hand, allowed conduct of highly relevant and well-powered clinical studies, and on the other, has ensured rapid incorporation of new knowledge into the care of patients. This integration also strongly influences the education of physicians and allied health care professionals.

This year FIRH hosted three significant international education events. The ‘Inhalation Challenge for Airway Disease Symposium’ involved over 45 physicians from the United States and Canada who participated in an interactive session. The summary of this meeting appeared recently in a peer-reviewed publication. The ‘Firestone Institute for Respiratory Health Symposium on Asthma Management’ program saw 25 physician specialists from Mexico participate in a two-day workshop. The ‘Current and Emerging Therapies in Respiratory Diseases: Difficult Challenges, Fresh Approaches’ program provided a two-day accredited CME event for over 150 physicians from Spain.

FIRH conducts research to increase understanding of respiratory health and disease across the life cycle through collaborative basic and clinical investigations with the expectation of improving patient care. Research is wide-ranging, from studies of smooth muscle physiology and intracellular signalling through experimental disease models to clinical trials which enhance patient quality-of-life and extends not only from bench to bedside, but to population health and policy. The research productivity of FIRH is attested to by the high quality and impact of the peer-reviewed publications. In 2009-10, FIRH faculty authored 83 peer-reviewed publications, including several in high impact international publications. The research efforts also resulted in FIRH faculty registering three patents. In addition, FIRH faculty mentored several postdoctoral, graduate and undergraduate students.

Providing leadership and strategic direction for the Firestone Institute in 2009-10 are Dr. Paul O’Byrne, Executive Director; Dr. Stewart Pugsley, Clinical Director; and Dr. Martin Kolb, Research Director. Members of the FIRH faculty hold important administrative posts locally, including Dr. Paul O’Byrne, who is the current Chair of the Department of Medicine at McMaster University; Dr. Gerard Cox, who is the Division Director of Respiratory Medicine; Dr. Lori Whitehead, who is the Program Director for Respiratory Training at McMaster University; and Dr. Malcolm Sears, who is the Principal Investigator for the national Canadian Healthy Infant Longitudinal Development (CHILD) Study.

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Faculty and staff wish to acknowledge and thank those who continue to support the efforts of the Institute. In particular, we thank the St. Joseph's Hospital Foundation and the many people who contributed to support our clinical, research and educational initiatives this past academic year.

AllerGen NCE Inc.

AllerGen NCE Inc., the Allergy, Genes and Environment Network, is one of 20 national Networks of Centres of Excellence (NCE) funded by Industry Canada through the NCE program. AllerGen is based at McMaster University and led by Scientific Director and CEO, Dr. Judah A. Denburg. Through his scientific direction, Dr. Denburg leads AllerGen’s research, networking, commercialization, knowledge mobilization and capacity building activities, which contribute to reducing the morbidity, mortality and socio-economic impacts of allergy, asthma and related immune diseases. AllerGen-funded research aims to accelerate the development of new diagnostic tests, better medications, and more effective public policies. AllerGen’s investments in education and training improve public education, allergy, asthma and anaphylaxis management, and increase the number of medical professionals researching and practicing in these areas.

AllerGen currently brings together more than 269 investigators and collaborators, 284 highly qualified students and young professionals and 164 full-time equivalent network research personnel. In addition, AllerGen works closely with over 164 partners across different sectors, including academia, industry and government, on 52 research projects. As a highly integrated, multi-disciplinary and multi-sectoral national research network, AllerGen has also established strong ties with international organizations and academic institutions. This has been possible through AllerGen’s successful implementation of an International Partnership Initiative (IPI) program, supported by NCE-IPI and International Development Research Council grants totaling over one million dollars. This past year, AllerGen’s Scientific Director has also initiated new collaborative partnerships aimed at expanding AllerGen’s internationalization with a network of genetic, environmental and allergy, asthma and allergic disease researchers in Germany, China and Australia.

AllerGen’s Clinical Investigator Collaborative (CIC), a national clinical trials consortium, led by Dr. Paul O’Byrne, Muran Campbell Professor in Respiratory Medicine and Chair of the Department of Medicine at McMaster University, is adding two international collaborating sites to the six existing Canadian sites for clinical trials. Joining the collaboration will be Sweden’s largest centre for medical training and research, the Karolinska Institutet, and the Netherlands’ Erasmus University Medical Centre in Rotterdam in September 2010. McMaster University researchers, Drs. Gail Gauvreau, Petra Ark and Mark Larché are also involved in collaborative research projects with the Karolinska Institutet investigators alongside AllerGen’s Scientific Director Judah Denburg and CIC leader Paul O’Byrne. Activities with the Karolinska Institutet also involve capacity building exchanges involving post investigators and doctoral and graduate students.

In addition to AllerGen’s international successes, McMaster University researchers are currently leading a $12 million study supported by AllerGen in partnership with the Canadian Institutes of Health Research (CIHR) to investigate the genetic and environmental factors that influence the development of asthma and allergies in children. This project, known as the CHILD Study, is led by AllerGen Investigator Dr. Malcolm Sears, of the Firestone Institute for Respiratory Health and Professor of Medicine for the Michael G. DeGroote School of Medicine. The CHILD Study is investigating the roles of indoor and outdoor environmental exposure, infections, nutrition and genetics in the development of childhood asthma and allergies.

AllerGen is committed to knowledge translation (KT) and has developed Knowledge Translation Planning Tools for Allergic Disease Researchers, available on the AllerGen website at www.allergen-nce.ca. The AllerGen KT tool can be applied across disciplines to develop effective knowledge translation plans for research projects, optimizing social and economic research benefits. AllerGen has also supported an e-learning program developed by McMaster University’s Dr. Anthony Levinson, Associate Professor, Department of Psychiatry and Behavioural Neurosciences and the John R. Evans Chair in Health Sciences Educational Research and Instructional Development. This program consists of online courses based on best practices for dealing with anaphylactic individuals and is directed at teachers, daycare staff, and restaurant managers and staff. Since training capacity is limited and costly, e-learning is an efficient, cost-effective model for human resource training on how to deal with anaphylaxis. Dr. Levinson has built upon his AllerGen-supported project in partnership with the Government of Alberta in order to implement this e-learning program, known as the Alberta Education Pilot Study.

AllerGen’s food allergy research program has also made tremendous progress due to the work of McMaster University allergy specialists Drs. Susan Waserman and Manel Jordana, who are both part of AllerGen’s Canadian Group on Food Allergy Research, or CanGoFAR team. In addition, Drs. John Bienenstock, Petra Ark and Paul Forsythe of McMaster University have applied their expertise in allergic and immune related disease to AllerGen-funded projects in the area of diagnostics and therapeutics, with a strategic focus on biomarkers, immune monitoring and drug development and discovery. Also noteworthy in the area of food allergy research is AllerGen’s involvement in the study, Surveying Canadians to Access the Prevalence of Common Food Allergies and Attitudes towards Food Labelling and Risk (SCAAALAR), launched in 2008. McMaster University’s Dr. Susan Elliott, Professor, School of Geography and Earth Sciences, and alongside other AllerGen researchers from McGill University, designed the study to estimate the prevalence of food allergies responsible for the majority of severe and/or fatal anaphylactic reactions. The breakthrough study, the first ever to provide this type of Canadian data, was published in the June 2010 issue of The Journal of Allergy and Clinical Immunology and has been featured in a number of media outlets, including a recent article in Allergic Living Magazine, and has also resulted in a follow-on partnership with Health Canada.

Looking ahead, AllerGen will continue to support excellence in research and to foster social innovation and knowledge translation that will enable Canadians to better prevent, manage and treat allergy, asthma, anaphylaxis and related immune diseases.
Farncombe Family Digestive Health Research Institute

The Farncombe Institute was formed in January 2009, building on the success of the Intestinal Disease Research Program. The Institute is an integrated group of clinical and basic scientists dedicated to understanding the impact of digestive health and nutrition on disease across the life span. It is focused on developing new strategies for the diagnosis, treatment and prevention of intestinal diseases such as Crohn’s disease and ulcerative colitis, which will have global benefits. However, the focus of research in the Institute is not limited to digestive diseases; rather, it includes diseases of many other organ systems that may be caused and/or profoundly influenced by digestive health and nutrition.

A donation of over $18 million from the Farncombe family of Oakville has allowed for the building of a state-of-the-art Axenic Gnotobiotic Facility, as well as providing extensive renovations to the office and laboratory area on the 3rd floor of the Health Sciences Building. The new office suite was completed in May 2010, and a new atrium will be completed by September 2010. The atrium will be the focal point of the Institute, providing a central place for interactions among faculty and trainees and as a facility for educational events, research symposia and group meetings. The official opening of the atrium will be held in October 2010.

Considerable effort is being made to recruit a number of outstanding researchers to the Farncombe Institute. While our application for a Canada Excellence Research Chair was scored very highly, it was not approved. Nevertheless, we were still successful in recruiting our nominated candidate, in part because of the resources that the Farncombe donation provided for capacity building. Dr. Michael Surette, an outstanding microbiologist, will join the Farncombe Institute in October 2010. In addition, another leading microbiologist, Dr. Philippe Langella, has joined the Farncombe Institute in 2010–2011 as a visiting scientist for one year. Drs. Surette and Langella are key members of a CIHR Team Grant application that was submitted by the Farncombe Institute in 2010, an initiative headed by Dr. Stephen Collins. A number of other recruitments are also underway.

Despite ongoing construction, the Farncombe Institute hosted a visit of 150 delegates from the Crohn’s and Colitis Foundation of Canada’s national congress, and hosted a research symposium on digestive disease that included presentations by several McMaster and University of Toronto research trainees.

The 14 full members of the Farncombe Institute published 53 peer-reviewed articles in the 2009-2010 academic year, a significant increase over the previous year. This included two papers in Science, one in PNAS and five in Gastroenterology, the leading digestive disease publication. Peer-reviewed funding to Institute members also increased significantly over the previous academic year, rising from $2.5 million to $4.3 million. In addition, Dr. Walid Khan obtained $250,000 in funding from the Ontario Research Fund and $250,000 from the Canadian Foundation for Innovation.

Strategies to increase the effectiveness of the Institute’s website and to enhance awareness of the Farncombe Institute have been implemented this year and will be enhanced in the coming year. As part of this process, a study of the impact of the research conducted at the Farncombe Institute was commissioned. That study demonstrated that among digestive disease researchers in Canada, those in the Farncombe Institute rank highest in terms of the impact of their publications, assessed on the basis of Hirsh factor and total number of citations.

Several Institute members received distinguished honours in 2009-2010, including:

- Elena Verdu, J.A. Campbell Research Award from the Canadian Celiac Association
- Walid Khan, New Investigator Award from the Canadian Institutes of Health Research
- Paul Moayyedi, named co-Editor of the American Journal of Gastroenterology (the first non-American ever to hold this post)
- Jan Huizinga, named Honorary Professor of Wuhan University, China

Control

Reduced villous/crypt ratio

Intraepithelial lymphocytes

Experimental model showing gluten-induced Marsh II, celiac-like lesions, consisting of reduced villous crypt ratios and intraepithelial lymphocytosis. CD3+ lymphocytes (brown stain) were counted in villi tips per 100 enterocytes.

Dr. E. Verdu lab
Dr. Austin's research program is to better understand the underlying cellular and molecular mechanisms of atherosclerosis and its risk factors, including hypercholesterolemia, diabetes, obesity and renal disease. The overall goal of Dr. Austin's research program is to better understand the underlying cellular and molecular pathways that mediate atherosclerotic disease. Some of the major discoveries in Dr. Austin's laboratory include: (i) defining the role of endoplasmic reticulum (ER) stress in atherosclerotic lesion growth and plaque destabilization, (ii) demonstrating a causal association between the ER stress response and atherosclerosis, and (iii) establishing a resounding success.

Amgen Canada Chair in Nephrology
Dr. Richard C. Austin

Dr. Austin is a Professor of Medicine in the Division of Nephrology, McMaster University and St. Joseph's Healthcare Hamilton. He is a Career Investigator of the Heart and Stroke Foundation of Ontario and holds the Amgen Canada Research Chair in Nephrology. Currently, Dr. Austin holds grant-in-aid funding from the Heart and Stroke Foundation of Ontario and Canadian Institutes of Health Research. Dr. Austin is also Director of a Heart and Stroke Foundation of Ontario Program Grant that aims to identify and characterize novel targets and therapeutic strategies that decrease atherothrombosis.

In the past two years, his work has focused on determining the role of TDAG51 in lesion development, plaque rupture and vascular calcification, and establishing a causal relationship between the ER stress response and atherosclerosis. Furthermore, Dr. Austin and colleagues have shown that attenuation of ER stress can suppress many of the downstream pathways that contribute to atherogenesis and obesity. Additional strategies to inhibit the ER stress response pathways are now being investigated as a potential therapy to prevent or delay the onset of cardiovascular disease. Dr. Austin and his research team have utilized state-of-the-art biochemical and molecular approaches as well as established mouse models of atherosclerosis, obesity and hypercholesterolemia in their studies to better explain the underlying mechanisms responsible for atherothrombosis.

Reports: Endowed Chairs

Alliance for Better Bone Health Chair in Rheumatology
Dr. Jonathan D. Adachi

Over the past academic year, the chair has been used to further our research interests in the effective transfer of guidelines to practice in the primary care setting and to further our research in osteoporosis and arthritis. We have used portions of these funds to support two individuals in their research endeavours in rheumatology.

Dr. Richard C. Austin

Dr. Austin is a Professor of Medicine in the Division of Nephrology, McMaster University and St. Joseph’s Healthcare Hamilton. He is a Career Investigator of the Heart and Stroke Foundation of Ontario and holds the Amgen Canada Research Chair in Nephrology. Currently, Dr. Austin holds grant-in-aid funding from the Heart and Stroke Foundation of Ontario and Canadian Institutes of Health Research. Dr. Austin is also Director of a Heart and Stroke Foundation of Ontario Program Grant that aims to identify and characterize novel targets and therapeutic strategies that decrease atherothrombosis.

In the past two years, his work has focused on determining the role of TDAG51 in lesion development, plaque rupture and vascular calcification, and establishing a causal relationship between the ER stress response and atherosclerosis. Furthermore, Dr. Austin and colleagues have shown that attenuation of ER stress can suppress many of the downstream pathways that contribute to atherogenesis and obesity. Additional strategies to inhibit the ER stress response pathways are now being investigated as a potential therapy to prevent or delay the onset of cardiovascular disease. Dr. Austin and his research team have utilized state-of-the-art biochemical and molecular approaches as well as established mouse models of atherosclerosis, obesity and hypercholesterolemia in their studies to better explain the underlying mechanisms responsible for atherothrombosis.

Dr. Dr. Austin has collaborated with clinicians and has recently worked on the identification of patients with arthritis. This was accomplished through a CIOA grant titled Validation of the GALS (Gait, Arms, Legs, Spine) Examination for Use by Family Physicians in Primary Care. This feasibility study was conducted, completed, presented and published all within one year and was the basis of a larger study awarded to her for using the GALS examination in primary care to identify those with inflammatory arthritis and has again been funded through a CIOA grant. Modifications to include an osteoporosis component to the examination were accomplished through a grant from the Ontario College of Family Physicians.

Finally, Dr. Beattie has participated in a system of reporting bone density measurements as a reflection of ten-year fracture risk. This work is novel and seems to be as effective, if not more so, than several other tools that have been developed. This work has been presented at several national and international meetings and has met with very positive responses. We have implemented this program in Hamilton with resounding success.

Amgen Canada Chair in Nephrology
Dr. Richard C. Austin

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Andrew Bruce Douglas Chair in Neurology

Dr. John Turnbull

The Andrew Bruce Douglas Chair in Neurology was established in March 2006 to further the clinical, educational, and research aspects of Amyotrophic Lateral Sclerosis (ALS) at McMaster. From a clinical point of view, we have established a position as a premier clinical site in Canada for the treatment of ALS, and patients come to the clinic from South Central Ontario, and indeed, all Ontario and beyond. We are grateful to Hamilton Health Sciences for their ongoing support of the clinic. Staff from ALS Canada and ALS Ontario have often come to the clinic to gain a clearer appreciation for ALS issues, as well as, over the years, interested federal and provincial politicians, and many health science and medical students and residents. Ms. Ishtar Gabriel, our clinic coordinator, has decided to remain home with her young family and she has been replaced by Ms. Jane Allen, formerly of the ALS Society of Ontario. Our research continues to evolve in an exciting way. Last year we felt that we had discovered a key mechanism that might explain SOD1 familial ALS, and that might be applicable to at least some cases of sporadic ALS. All confirmatory tests in cell culture and in mouse models have proven positive to date, and we are planning on two additional exploratory studies in humans to strengthen the hypothesis. (These are not therapeutic trials but designed to confirm the mechanisms underlying ALS.) This last year we have been involved in one clinical trial, and I have served on the steering committee of a joint Canadian / American clinical trial funded by ALS Canada and the US National Institutes of Health. I continue to meet with officials within the Ontario Ministry of Finance and the Insurance Industry in Canada, to develop new rules surrounding supplemental health insurance which should benefit patients with ALS.

AstraZeneca Chair in Respiratory Epidemiology

Dr. Malcolm Sears

The majority of time is committed in directing Canadian Healthy Infant Longitudinal Development (CHILD) Study which is jointly funded by CIHR and the AllerGen NCE. This study, which will recruit 5000 pregnant women across Canada over the next two years and follow their infants through to age five years, is designed as a broad multidisciplinary intensive investigation of factors responsible for development of allergy and asthma, with a particular emphasis on gene-environment interactions. The environment is defined very broadly, including not only indoor and outdoor air, but psychosocial environment including maternal stress, infections and nutrition. Currently some 800 mothers have been recruited, approximately 200 in a vanguard wave of the study and a further 600 using the final methodologies developed from assessment of the vanguard sample. Over 40 investigators from across Canada are participating in various components of the study, which is directed from the National Coordinating Centre for CHILD at the Firestone Institute for Respiratory Health, St. Joseph’s Healthcare Hamilton. The study is guided by an Executive Committee, including the co-principal investigators who are leading the study at each of the four recruitment sites in Vancouver, Edmonton, Winnipeg and Toronto, a Scientific Advisory Committee of international experts in allergy, asthma, and epidemiology, and a Strategic Planning Committee whose mandate is ensuring the long-term viability and success of the study.

I continue to be involved in the Dunedin Multidisciplinary Health and Development Research Study being conducted in New Zealand, where the participants (born 1972-73) are returning in 2010-2011 for detailed assessments at age 38 years. This cohort has already generated more publications (over 1050) than the 1037 original cohort members, including over 50 publications related to epidemiology of asthma, allergy and respiratory disease. As the participants are now well established in adulthood, respiratory investigations have become increasingly related to chronic obstructive pulmonary disease, the impact of smoking and occupational exposures, built on the solid foundation of childhood respiratory history and objective data. This study has achieved over 90% retention of study members to date, providing a wealth of data not only in respiratory outcomes but development, psychosocial, dental, cardiac, gene-environment interactions, and parenting, to name a few. This is one of the longest running birth cohorts with objective respiratory data in the world, and our aspiration is that the new Canadian study will also become long lived with excellent retention, providing a platform for many studies of respiratory and other health issues in the future.

The third major component of my work in respiratory epidemiology has focused on asthma management and drug safety, particularly through involvement in the ongoing controversy over the safety or otherwise of long-acting beta-agonists in asthma. This has involved consultations and meetings with pharmaceutical companies and with the U.S. Food and Drug Administration, reviewing data from clinical trials of asthma management, and discussing potential new studies designed to address safety issues more clearly than in the past, including the feasibility and necessity for such studies.

Through the coming year, the primary focus will be ensuring the CHILD study is firmly established, and additional funding obtained to ensure its successful completion. Mentoring of the younger leadership of the study as they prepare to direct this study through the longer term is a key priority.
REPORTS: ENDOWED CHAIRS

David Braley and Nancy Gordon Chair in Thromboembolic Disease

Dr. Jeffrey Ginsberg

I have continued to collaborate with colleagues at Harvard University, Emory University and Tulane University on a textbook that will be published by McGraw-Hill, which also publishes one of the reference standards for Internal Medicine, Harrison’s Textbook of Internal Medicine. The book, entitled Principles and Practice of Hospital Medicine is scheduled to be published in 2011 and will be the most comprehensive textbook written on the topic. Hospital Medicine is a relatively new specialty that is becoming increasingly important as the role of the Hospitalist in patient care becomes more prominent. Progress has been rapid, as we have assembled five senior editors, including myself as the only Canadian representative. We now have over 75% of the finished chapters at the publishers and I am happy and proud to say that my colleagues at McMaster University have been key contributors and represent much of the Canadian content of the textbook, particularly in advancing the incorporation of Evidence-based Medicine into day-to-day practice. Many of the recommendations for the diagnosis, prevention, and management of thromboembolic problems in pregnancy have been based on studies performed and/or spearheaded by investigators at McMaster University. We continue to publish key studies unraveling the mysteries behind the propensity for clotting in pregnant women. Recent studies have defined key differences in the distribution of DVT in the veins of pregnant women and non-pregnant subjects. These studies lead us to conclude that the “thrombophilia” of pregnancy is probably largely due to anatomic changes rather than an intrinsic tendency for the blood to be hypercoagulable. The differing anatomic distribution suggests a different mechanism of DVT formation in pregnant compared to non-pregnant patients, necessitating a different approach to the diagnosis of DVT in pregnancy. To this end, we have, in separate publications, developed a clinical prediction rule that is unique for pregnancy, established that D-dimer testing is useful for the exclusion of DVT in pregnancy using different cutpoints than in non-pregnant subjects, and developed diagnostic algorithms for suspected DVT in pregnancy using venous ultrasonography as a pivotal test.

Eli Lilly Canada Chair in Osteoporosis

Dr. Alexandra Papaioannou

Dr. Papaioannou is a Professor in the Department of Medicine and a Geriatrician at Hamilton Health Sciences. She is past Director of the Division of Geriatric Medicine, with a joint appointment in the Division of Rheumatology. She is an Associate Member in the Department of Clinical Epidemiology and Biostatistics and faculty in the Medical Sciences Program. Dr. Papaioannou is a member of the Scientific Advisors of the International Osteoporosis Foundation. She leads the Ontario Ministry of Health and Long-Term Care Strategy for Fracture Prevention in Long-Term Care. Dr. Papaioannou mentors a number of PhD and Masters students in Medical Sciences and the Health Research Methodology Program. Recent Internal Medicine resident research projects with Dr. Papaioannou have included the prevalence of Vitamin D deficiency in the elderly in acute care. She had 19 peer-reviewed publications in 2009 including JAMA publications identifying that hip fracture rates have decreased in Canada over the past 20 years. (For a complete listing of Dr. Papaioannou’s 2009 publications, see the publications section of this book.) Dr. Papaioannou completed a CIHR-funded scoping review that found Vitamin D to be the most effective intervention to reduce falls in long-term care. She is leading the Osteoporosis Society 2010 Osteoporosis Guidelines.

Eli Lilly / May Cohen Chair in Women’s Health

Dr. Sonia Anand

With the support of the Endowed Chair in Women’s Health Research, Dr. Sonia Anand leads the CIHR/HSFO funded CARING Network which focuses on sex/gender determinants of cardiovascular disease diagnosis, treatment, and knowledge translation. The specific theme areas in which Dr. Anand is involved include acute coronary syndromes and the metabolic syndrome. Dr. Anand has a particular interest in conducting intersectoral research including ethnicity, sex/gender, and social factors. She is currently initiating a maternal-child study among South Asians in Ontario (START Birth Cohort) which includes a detailed study of the role of social support, social networks, and acculturation stress among South Asian immigrants. Dr. Anand also collaborates with a number of researchers outside of McMaster and is a co-investigator on projects of gender/sex determinants in the areas of cardiac rehabilitation (Dr. Sherry Grace), diabetes and hypertension (Dr. Nadia Khan, Dr. Baiju Shah). Dr. Anand chairs the Expert Research Panel for the Ontario Ministry of Health Agency ECHO which aims to improve knowledge translation for women’s health issues in Ontario. Recently Dr. Anand was named one of Canada’s Top 100 Most Powerful Women in 2010 in the Trailblazers & Trendsetters category.
**Farncombe Family Chair in Digestive Health Research**

**Dr. John Wallace**

Dr. John Wallace’s research is aimed at gaining a better understanding of the regulation of inflammation. By identifying key events in inflammatory reactions and the chemicals that mediate those events, it is hoped that novel anti-inflammatory therapies can be developed for a number of common diseases. His research also involves investigating the processes of injury and repair, particularly in the digestive system. For example, Dr. Wallace is investigating the pathogenesis of inflammatory bowel disease (Crohn’s disease and ulcerative colitis) and of gastrointestinal ulcers caused by anti-inflammatory drugs. This work is mainly done using animal models of human disease, but in the past few years Dr. Wallace has increasingly been performing studies of human tissue samples. This translational research led to a major publication recently in the Proceedings of the National Academy of Science. The research suggested that a key inflammatory mediator, called prostaglandin D2, is produced in higher than usual levels in the colon of patients that are in long-term remission from ulcerative colitis. Levels of this mediator were not elevated in patients with active disease or in patients in drug-induced remission. Further studies are underway to better understand the importance of this mediator in inflammatory bowel disease, and to explore the therapeutic implications of this discovery.

Dr. Wallace also continues to perform studies aimed at developing safer and more effective anti-inflammatory drugs. To this end, he is exploiting the potent anti-inflammatory effects of hydrogen sulfide-releasing drugs. He has developed derivatives of several commonly used anti-inflammatory drugs (such as for colitis, arthritis and irritable bowel syndrome) and is evaluating their effectiveness and safety. One such drug, which is a derivative of a commonly used arthritis medicine (naproxen), has been shown not to produce any gastrointestinal injury or bleeding, even when given to laboratory rats at extremely high doses. In humans, the ulcers and bleeding caused by drugs such as naproxen is the major limitation to their use. (These side effects can be severe, leading to death in some cases.)

**GlaxoSmithKline Chair in Gastroenterology**

**Dr. Stephen Collins**

My work continues to investigate the role of gut bacteria in health and in the expression of gastrointestinal diseases at both a basic scientific and clinical level. In previous work, I had developed an animal model that provided proof of concept that an acute enteric infection could trigger persistent dysfunction of gastrointestinal tissue and showed that this was due to immune activation and the induction of chronic subclinical infection in the gut. This had been prompted by observational studies showing that up to one third of patients recovering from acute Salmonella food poisoning went on to develop chronic gastrointestinal symptoms and disability. Later we were fortunate enough to gain access to the residents of Walkerton, Ontario following the massive contamination of the town’s water supply by a pathogenic bacteria and parasites in May 2000. With John Marshall, we studied the epidemiology of this outbreak and found that close to 30% of those infected went on to develop Irritable Bowel Syndrome (IBS), and some have gone on to develop Crohn’s Disease. We have genetically Walkerton residents, screening 79 functional variants of genes with products that have been associated with other GI disorders and found that the development of IBS post-infection is associated with polymorphisms of genes that encode proteins involved in epithelial barrier function and the innate immune response to enteric bacteria. We also found that post-infective IBS was accompanied by an increase in intestinal permeability. Taken together, these observations support a conceptual model of PI-IBS in which chronic gut dysfunction is maintained in genetically susceptible individuals by a leaky mucosal barrier and low-grade inflammation. This prompted us to question the role of resident bacteria in the pathogenesis of this condition.

IBS, as well as other GI diseases such as inflammatory bowel disease (Crohn’s and Ulcerative Colitis), exhibit psychiatric co-morbidity in up to 80% of cases, but it is not known whether this simply reflects the disability caused by the GI condition, or whether there is a shared pathophysiological basis for dysfunction in both the gut and brain. This prompted an investigation of the potential influence of gut bacteria on gut and brain function – that is, on the gut brain axis. Using murine models in our photobiological facility (the only one of its kind in Canada), we have examined whether perturbation of the normal bacterial composition of the gut causes changes in gut and brain function. Our results indicate that transient perturbation of the gut flora (microbiome) results in sub-clinical inflammation in the gut and an increase in visceral pain perception. Furthermore, in separate experiments we showed that altering the microbiome produced changes in Brain-Derived Neurotropic Factor, a key modulator of brain function and behaviour, and that this was associated with changes in exploratory behaviour in the mice. To confirm the role of the flora, we performed adoptive transfer experiments in which we were able to successfully transfer, via the flora, components of the behavioural phenotype of a donor mouse into a germ free mouse of a different strain that has a different behavioural phenotype. Our current work examines the mechanisms whereby commensal bacteria influence brain chemistry and behaviour.

We believe that this work will provide insights into the basis of the co-existence of psychiatric and GI disease, and identify novel therapeutic approaches to both components of disease. The work described above has resulted in ten publications in the past year and has been enabled by a CIHR operating grant and grants from the Crohn’s and Colitis Foundation of Canada.
This past academic year has been quite successful through ongoing collaborations with various groups. I am working closely with Drs. Raha and Ewart on a project aiming to identify novel antibodies in various forms of acquired peripheral neuropathies. We have confirmed preliminary findings that type 2 diabetes worsens neuropathy in individuals with CMT1A. These findings were enabled by the development of the database which was begun last year. I have teamed up with Dr. K. Boycott, from CHEO, for a groundbreaking study employing a gene chip for the diagnosis of patients with CMT and related inherited neuropathies. Dr. S. Vernino, University of Texas, and I have collaborated on the first case of transient neonatal autoimmune autonomic ganglionopathy.

I contribute as a medical advisor to Dr. Stuart Phillips’ laboratory. His group has been very productive this past year publishing numerous manuscripts on the complex genetic signaling induced in skeletal muscle by resistance training/exercise. Dr. Tarnopolsky and I continue to explore the diverse clinical entity of statin myopathy and two invited manuscripts are in preparation on this topic. Finally, I was elected to the editorial board of Muscle & Nerve.

Dr. Jeffrey Weitz

Dr. Weitz has held this endowed chair since 2000, with renewals granted in 2005 and 2010. With a $1 million endowment from the Heart and Stroke Foundation of Ontario and a matching amount from McMaster University, the interest from this Chair has been used to support the Thrombosis and Atherosclerosis Research Program. Funds have been used to supplement the salaries of new investigators, including Drs. Patricia Liaw, Geoffrey Wernstuck, and Shirya Rashid.

Heart and Stroke Foundation / J. Fraser Mustard Chair in Cardiovascular Research

With this Chair, the thrombosis group has expanded over the past five years with recruitment of Drs. Fred Spencer, Wendy Lim, Peter Gross, John Eikelboom, Sam Schulman, Lori-Ann Linkins, Howard Chan, Shirya Rashid, and Alex Spyropoulos. The increased critical mass has expanded our research capabilities. Currently, the thrombosis research group oversees research projects that span the full spectrum from basic research, to translational studies that link basic science with patients, to clinical trials, to health outcomes research and on to knowledge translation.

Dr. Salim Yusuf

Areas of Research
1. Causes of vascular disease, diabetes and obesity
2. Global health and the role that ethnic, environmental and cultural diversity plays in the causal pathway
3. Identifying better methods of preventing and treating heart disease and stroke

Publications in the last 12 months: 43 (out of a total of 529)

Highlights include:
1. CFI grant of $39.6 million for the David Braley Cardiac, Vascular and Stroke Research Institute
2. CFICRI grants of $19.6 million for CANNeCTIN, a national network for CVD of diabetes research.
4. First global study on risk factors for stroke indicating that 10 risk factors are associated with 90% of the risk of stroke (INTERSTROKE study. Lancet 2010; 376(9735): 112-23.)
Heart and Stroke Foundation of Ontario / Michael G. DeGroote Chair in Population Health Research

Dr. Sonia Anand

Dr. Anand received the Heart and Stroke Foundation of Ontario/Michael G. DeGroote Chair in Population Health Research at McMaster University in 2008. The mandate of this Chair is to improve research in population health as it relates to cardiovascular disease. Dr. Anand’s research is aimed at understanding the contribution of environmental and genetics factors on the development of cardiovascular risk factors and cardiovascular disease. She has a particular interest in conducting intersectoral research including ethnicity, sex/gender, and social factors. Dr. Anand is currently 1) investigating the role of genetic factors and type 2 diabetes risk in various ethnic populations, 2) evaluating the effectiveness of culturally-tailored multimedia intervention to modify risk factors for cardiovascular disease in the South Asian population, and 3) initiating a birth cohort study in the South Asian community in Ontario to determine the role of intrauterine programming on the early development of adiposity and related metabolic factors in this high risk community.

McMaster University / GlaxoSmithkline Chair in Lung Immunology at St. Joseph’s Healthcare

Dr. Mark Larché

Dr. Mark Larché was appointed to the McMaster University/GSK Chair in Lung Immunology at St. Joseph’s Healthcare in March 2008. Partnered funding for the Chair was obtained from CIHR and St. Joseph’s Healthcare to support the group over the period 2009-2013. In 2010 further funding has been obtained from the Ontario Thoracic Society and the Scleroderma Society of Ontario. The current research focus within the laboratory is (1) the role of T lymphocytes in the pathogenesis of asthma/allergic airways disease (together with Dr. Mark Inman), (2) mechanisms of peptide-induced immune tolerance, which may lead to novel therapeutic avenues, (3) the development of novel allergen challenge models (together with Dr. Helen Neighbour) and (3) the pathogenesis and treatment of scleroderma (systemic sclerosis). Dr. Larché is a member of the newly constituted Hamilton Scleroderma Group which has been funded by the Scleroderma Society of Ontario to conduct research into this devastating disease. Collaborative projects are currently underway with other faculty at St. Joseph’s Healthcare within the Firestone Institute for Respiratory Health and the Division of Nephrology.

McMaster University / St. Joseph’s Healthcare Regional Academic Chair in Critical Care Medicine

Dr. Deborah Cook

Most practices in the ICU were based on theory or physiologic reasoning several years ago. However, today, promising physiologic observations documented in the laboratory during critical illness clearly require confirmation or refutation in high quality randomized clinical trials. Interestingly, refutation sometimes seems more common than confirmation. For example, Hamilton intensivists recently identified harm when benefit was expected (e.g. increased mortality associated with targeting euglycemia using intensive insulin therapy); we also identified no impact when benefit was expected (e.g. no effect on survival from vasopressin infusion for severe septic shock).

The quality, quantity, and relevance of trials in critical care medicine have increased recently as critical care medicine has gained academic traction globally. Another trend is an increase in trial sample size since the 1990’s when the average enrolment was only 100 patients. This trend is evident in all of our successful CIHR funded work. Dr. Maureen Meade is now leading the largest international trial of high frequency oscillation for adult acute lung injury. Dr. Deborah Cook and Drs. Andreas Freitag, Tim Karachi and Meade just completed the third largest ICU trial ever conducted on thromboprophylaxis. Drs. Patricia Liaw and Alison Fox-Robichaud are starting an observational study to identify whether plasma DNA predicts mortality during critical illness. Additional CIHR-funded trials in Hamilton are examining the effect of standard issue vs. fresh red blood cells, antioxidant supplements vs. placebo and computerized vs. clinician-directed weaning from mechanical ventilation.

There is also growing recognition in our community that patient outcomes may be best improved not by just making new discoveries, but also by the systematic implementation of interventions which we know are beneficial. To that end, quality improvement programs abound in Hamilton, focused on safe, timely and appropriate best evidence application at the bedside. Today, quality improvement efforts require scientifically sound performance measures and interdisciplinary teamwork that is incremental and continuous.

In Hamilton, we have also been actively training junior colleagues devoted to academic careers. Drs. Maureen Meade and Deborah Cook hold monthly tutorials with multidisciplinary research fellows in ACCADEMY (Academy of Critical Care: Development, Evaluation and Methodology), to assist with project development, Masters and PhD course work in the Health Research Methods Program, and professional development as independent investigators.
Medard DeGroote Chair in Medicine
Dr. Akbar Panju

In my role as the Medard DeGroote Chair in Medicine, the last 12 months have been busy in the planning of the Michael G. DeGroote Pain Clinic and McMaster Ambulatory Care Centre. We had multiple meetings with members of the present pain clinic and also with the Department of Medicine. Both these academic clinics will have an academic vision with educational component and research activities.

In addition to the planning of the educational activities, I have been involved in exploring innovative management strategies for treatment of post-stroke central pain. I am also collaborating with other individuals in the field of post-stroke central pain to do a meta-analysis of motor cortical stimulation and deep brain stimulation for the treatment of post-stroke central pain.

Other activities include following the academic visioning of the Division of General Internal Medicine. I have continued to be the Division Director of Academic GIM and also Service Head of GIM for Hamilton Health Sciences. We have been very fortunate in attracting high calibre individuals who have joined our Fellowship Program in GIM. We have also recruited excellent individuals to our General Internal Medicine Division at McMaster University and we are well positioned to be one of the leading Divisions of GIM in the country.

With the movement of inpatient activities from McMaster University Medical Centre, we have a great opportunity to build two major academic ambulatory activities for pain and for the Department of Medicine.

Michael G. DeGroote Professorship in Stroke Management
Dr. Demetrios (James) Sahlas

Work by Dr. Sahlas and his colleagues using the Registry of the Canadian Stroke Network established a decrease in hemorrhagic complications following treatment of acute ischemic stroke with IV tPA, based on the actual time patients were “last seen normal”. The results were presented at the 35th International Stroke Conference in San Antonio, Texas and were the subject of a press release issued in February by the American Heart Association, which resulted in several U.S. media interviews in conjunction with the international conference.

Additional work involving dose miscalculation of intravenous tPA due to estimation of patients’ weight was presented at the 1st Canadian Stroke Congress in Quebec City, and formed the basis of a successful grant application in collaboration with colleagues from the University of Toronto Stroke Program. A dedicated weight stretcher is now housed in the emergency room of the Hamilton General Hospital for accurate dose calculation of tPA in acute ischemic stroke patients.

Dr. Sahlas has been a proponent for the role of advanced imaging techniques such as CT perfusion as an adjunct to the evaluation of acute ischemic stroke patients, and coordinated a collaboration between the Department of Radiology at the Hamilton General Hospital and an established Heart and Stroke Foundation research project led by Dr. Richard Aviv at Sunnybrook Health Sciences Centre in Toronto. His other work involving emerging technologies include promoting the uptake of telemedicine for acute stroke, and neurosonology in the acute care setting.

Finally, he has continued in his role as Best Practice Champion across the Continuum of Care on the Provincial Coordinating Committees of the Ontario Stroke Network. His work at a provincial level over the past year has included working to facilitate revisions to the paramedic prompt card in order to incorporate the recently expanded time window for treatment of acute ischemic stroke, as well as recommending changes to the Ministry of Health and Long Term Care’s carotid surgery wait time strategy to more accurately reflect best practice.
Moran Campbell Chair in Respiratory Medicine
Dr. Paul M. O’Byrne

Dr. Paul O’Byrne has had a longstanding research interest into the causes and treatment of asthma. In particular, his research is focused on the roles of environmental allergens in causing airway inflammatory responses and the associated changes in physiological responses of the airways, which are a hallmark of asthma. These studies have demonstrated mechanisms by which the airways signal the bone marrow to increase production of eosinophils which then traffic into the airway to participate in allergen-induced responses. Eosinophils and other airway cells, including mast cells, release a group of mediators known as cytokine leukotrienes, which Dr. O’Byrne’s research group has demonstrated to be critical mediators for a number of allergen-induced responses including bronchoconstriction, the further influx of inflammatory cells, and the trafficking of dendritic cells, which are the professional antigen-presenting cells in the airways. In addition to this, Dr. O’Byrne’s laboratory has used the clinical models of allergen-induced airway responses and airway inflammation as a mechanism to study the potential efficacy of new drugs in asthma, as well as the mechanisms by which established drugs work. Recently, the first documented evidence of anti-sense treatment to inhibit the production of cytokine receptors was shown to be beneficial in this clinical model. Other studies have focused on humanized monoclonal antibodies directed against a number of cytokines thought to be possible mediators of allergic inflammation. This included the first study with an anti-IL5 monoclonal antibody to show benefit in severe asthma. Finally, research in his laboratory has identified a pivotal role for Th2 cytokines such as IL4, IL5 and IL13 in inducing airway responses and a possible role for interferon-Y in inhibiting allergen-induced airway inflammation.

Population Health Institute Chair in Diabetes Research and Care
Dr. Hertzel Gerstein

This Chair was established in 2001 to provide broad support for research activities focused on the prevention and treatment of diabetes and its serious consequences. Dr. Gerstein is pursuing these goals through a broad range of research-related activities at the international, national and local levels. Some of these activities include his role as an international PI and leader of: a) the ongoing NIH-funded 10,000 person ACCORD outcomes trial and ACCORD extension, which is assessing the short and long-term role of glucose, blood pressure and lipid management in people with type 2 diabetes; b) the 12,000 person ORIGIN outcomes trial of thiazolidinediones and/or Vitamin D in people with established type 2 diabetes. He is also co-leading epidemiologic and ancillary analyses of data collected in the recently completed DREAM trial of diabetes prevention in 5,000 people and the 20,000 person EpIDREAM cohort study. In addition, he founded Diabetes Hamilton 11 years ago and continues to lead this program that supports self-management of diabetes for more than 4,200 people in Hamilton and includes knowledge translation research in collaboration with other individuals at McMaster. In addition to these clinical research activities, he continues to collaborate with colleagues at McMaster in research using animal and cellular models of dysglycemia to identify the mechanisms underlying the development of diabetes, and the relationship between dysglycemia and cancer, cognitive decline, and cardiovascular diseases. Dr. Gerstein’s research is funded by CIHR, NIH, CDA, the Heart and Stroke Foundation and industry, and much of his clinical research is accomplished through the Population Health Research Institute, where he is Deputy Director. During the last academic year he published 24 articles in major medical journals and participated widely as an invited guest in international and local diabetes-related meetings and programs.

Richard Hunt / AstraZeneca Chair in Gastroenterology
Dr. Paul Moayyedi

This chair was established to increase the clinical component of the Farncombe Family Digestive Health Research Institute and strengthen population-based gastroenterology research as well as evidence-based medicine within the Institute. Dr. Paul Moayyedi has held the Chair since 2004. During this time he has published 112 papers that have been cited over 1,500 times. He was appointed Director of the Division of Gastroenterology in 2006 and the division has continued to thrive under his leadership. Dr. Moayyedi is responsible for the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) Review Group moving from the University of Leeds, U.K. to McMaster University. The UGPD group has received funding from CIHR for the next five years through a $9.6 million grant to Cochrane Canada. The UGPD group is responsible for commissioning all Cochrane systematic reviews relating to the upper GI tract and annually updating these reviews on the Cochrane Library. This provides evidence on the most effective health care interventions to doctors and patients worldwide. The systematic reviews that he has conducted have informed guidelines that will better serve the needs of patients with gastro-esophageal reflux disease, dyspepsia and H. pylori infection. This work has also had an international impact and been a major feature of guidelines in Canada, the U.S., and the U.K.

Dr. Moayyedi has chaired a working party for the Canadian Association of Gastroenterology (CAG), which has provided valuable information on GI manpower in Canada. This systematic review work has also been central to Asian Pacific guidelines on the prevention of gastric cancer, which has the potential to save 600,000 lives each year. He has also recently provided evidence for an American College of Gastroenterology (ACG) Task Force on Irritable Bowel Syndrome, which has shown that traditional therapies may be more efficacious than previously thought. This may have a large impact on the management of this common disorder. The work has been published in highimpactfactor medical journals and has also been cited in the U.K. and Canadian press. He is currently conducting work to support the ACG inflammatory bowel disease monograph. He also has been appointed joint Editor-in-Chief of the American Journal of Gastroenterology. This is the world’s highest impact factor general clinical gastroenterology journal and he is the first person not to reside in the U.S. to be appointed to this prestigious position.
Salim Yusuf Chair in Cardiology
Dr. Stuart J. Connolly

The Salim Yusuf Chair in Cardiology is designated for the Director of the Division of Cardiology at McMaster University, currently Dr. Stuart Connolly.

The Division of Cardiology continues to play a major role in the Local Health Integration Network in clinical service and is one of the strongest divisions in teaching. It is the leading clinical research division in the country.

The objectives for the coming year are to continue to develop the arrhythmia service with the establishment of a centre for the treatment of some of the more complex cardiac rhythm disorders. The program continues to be enriched by an outstanding faculty that is productive in both basic science investigations and clinical research. The mandate of this endowed chair is to develop research in internal and vascular disease, particularly in the area of stroke. Over the past year, there has been an expansion in our program of stroke research. INTERSTROKE, a large case control study designed to evaluate traditional and emerging (e.g. genetics) risk factors for stroke has been expanded to 18 countries, and we have completed Phase 1 (Drs. Yusuf and Xavier).

St. Peter’s / McMaster Chair in Aging
Dr. D. William Molloy

Dr. Molloy’s research this year has been dominated by the multi-centred randomized controlled trial of doxycycline and rifampin for Alzheimer’s disease (DARAD). This investigator-initiated multi-centred clinical trial is funded by CIHR and includes fourteen centres from Edmonton to Halifax. In May this year, an interim analysis of 306 patients was performed. The results showed that doxycycline and rifampin did not slow or stop the progression of Alzheimer’s disease. Although the treatment was well tolerated, the active treatment groups fared no better than the placebo group. The trial has been stopped on the basis of futility. In total, 406 patients had been entered into the study. One hundred and seventy-seven of those were enrolled at the St. Peter’s Hospital site, which has required a substantial clinical commitment from Molloy.

The basic science investigations into the mechanisms of Alzheimer’s, which paralleled the DARAD trial, continued during the past year. The results of the trial have caused a re-evaluation and modification of the aims of each of those investigations. Ninety-eight patients taking the study treatment also contributed cerebrospinal fluid samples so that biomarkers of treatment effects might be identified. The remaining CSF samples are being reserved for future analysis. With the collaboration of Drs. M. Warsi and M. Noseworthy at St. Joseph’s Brain-Body Institute, a subset of DARAD patients have undergone a novel form of MRI imaging (susceptibility weighted imaging- SWI) before and after study treatment. SWI quantifies elements in the brain such as iron and calcium, which can be measures of Alzheimer staging and potentially reflect the response to treatment. This investigation is proceeding. Dr. Monica Marchese, research fellow, is using triple transgenic mice which have the Alzheimer’s gene to measure the progression of their “Alzheimer’s” and test their behaviour with the aim of developing better studies in humans. The rapid life cycle of the mice allows results to be seen quickly. This research is ongoing.

William Walsh Chair in Internal Medicine
Dr. Martin O’Donnell

This will be my last report as the William J. Walsh Endowed Chair in Internal Medicine. I have taken up a position in Ireland, but will keep my association and interaction with McMaster University. The Dr. William J. Walsh Endowed Chair in Internal Medicine is named after a founding father of McMaster’s Faculty of Health Sciences and renowned physician. The mandate of this endowed chair is to develop research in all three areas of academic internal medicine, achieving objectives for performance in clinical, educational and research endeavours. In the clinical arena, Dr. Denburg continues to attend to one of the largest and most intensive specialist academic internal medicine practices in Canada, specifically in immune aspects of disease affecting many organ systems. He has continued his referral-based outpatient and inpatient activities, seeing patients with complex medical problems. Additionally, he has continued involvement in clinical trials for some of these disorders.

His main research thrusts include examination of the mechanisms of allergic inflammation, with particular emphasis on hematopoietic cytokines and their role in activating the differentiation and recruitment of inflammatory cells such as eosinophils, basophils and mast cells. This includes an understanding of the growth and differentiation of human basophil and eosinophil precursors, with the development of in vitro assays to monitor clinically relevant fluctuations in these cells during allergic responses. The specific diseases studied have included allergic rhinitis, nasal polyposis and asthma. These studies have established the biological importance of hematopoietic mechanisms in allergic inflammation and emphasize important and clinically-recognised links among rhinitis, asthma and other allergic disease manifestations (“allergy as a systemic disease”). Findings have been published in high-impact journals, and are the subject of ongoing peer-reviewed and industrial grants.

As creator, forger and Scientific Director and CEO of AllerGen NCE Inc., Dr. Denburg has overseen the continued development of this applied research and training network in allergy and asthma in Canada, now with global outreach in several continents. The Walsh Professorship has been a critically important asset in support of Dr. Denburg’s role in developing and maintaining AllerGen’s activities. For a summary of AllerGen’s major accomplishments over the past year, see the report included elsewhere in this publication.
Reports: Canada Research Chairs

Canada Research Chair in Neuroimmunology

Dr. Petra Arck

Fetal development is greatly dependent on the mother. However, pregnancy maintenance and hence fetal development are highly sensitive to disruption, i.e. upon prenatal stress challenge. However, research on the effect of stress during human pregnancy was long plagued with methodological problems and lacked a solid theoretical framework. Employing the expanding availability of established, high-validity tools to define stress perception in humans, coupled with experiments in basic science models, Dr. Arck and her team have shown that prenatal stress challenge causes negative repercussions on immune responses of the offspring. This impaired immune maturation appears to originate from an impaired adaptation as early as pregnancy, i.e. the lack of dampening inflammation at the fetomaternal interface along with a decrease of pregnancy maintaining hormones, such as progesterone. Interestingly, Dr. Arck and her coworkers were the first to report an inverse correlation between maternal levels of progesterone during pregnancy and the subsequent risk for allergies in the children, which was particularly profound in girls.

These insights, complemented by ongoing functional and reductionist studies in mouse models pursued by Dr. Arck's team, will then allow early identification of a risk for allergic diseases, which can subsequently lead to the proposal of primary allergy prevention strategies in utero.

Canada Research Chair of Research Transfer in Intensive Care

Dr. Deborah Cook

Critical care is intensive and expensive. Critically ill patients are acutely ill and require basic and advanced life support. The ICU is complex, replete with multiple technologies to monitor, diagnose and treat patients. Care is ministered by multiple professionals with different backgrounds such as nurses, respiratory therapists, physicians, pharmacists, and nutritionists. Clinicians must obtain, interpret, communicate, and act upon large amounts of diverse, dynamic patient-specific data. The consequences of critical illness are sustained physical, cognitive and emotional disability among survivors, and psychological trauma to families. In Canada, up to 25% of all hospital deaths occur in critical care venues, the majority as a result of a decision to limit advanced life support.

The Canada Research Chair in Intensive Care held in 2010 affords the privileged opportunity to focus exclusively on the conduct of investigator-initiated studies. Such investigations have many different foci, such as testing established drugs and devices, evaluating multidisciplinary approaches to care and guideline implementation. Investigator-initiated studies, as compared to industry-initiated studies, are more likely to address broad health concerns of citizens and health care systems, and are less likely to be influenced by corporate directives.

I therefore devote the work made possible by this Canada Research Chair to understanding critical illness, reducing morbidity, increasing survival, and improving the satisfaction and quality of life of patients and their families. At St. Joseph's Healthcare, systematic screening of ICU patients by highly specialized research coordinators using a computerized clinical information system followed by bedside assessment resulted in efficient screening and enrolment of nearly one thousand patients into 27 academic ICU studies in the last four years.

Canada Research Chair in Cardiovascular Medicine

Dr. John Eikelboom

Dr. Eikelboom’s Canada Research Chair in Cardiovascular Medicine supports a program of research into the mechanisms and management of antiplatelet drug “resistance”, optimal antithrombotic strategies for the prevention and treatment of arterial and venous thrombosis, and outcomes after bleeding and red cell transfusion in patients.

The results of the recently completed CURRENT OASIS-7 study provide no evidence for a benefit of higher doses of aspirin compared with low-dose aspirin for the prevention of cardiovascular events. This finding contrasts with the results of Dr. Eikelboom’s laboratory studies demonstrating that higher doses of aspirin are superior to low-dose aspirin for inhibition of urinary concentrations of thromboxane, a marker of platelet activation that independently predicts cardiovascular risk. This apparent paradox of aspirin’s dose-dependent effect on laboratory markers of cardiovascular risk but dose-independent effects on clinical events, is the subject of Dr. Eikelboom’s ongoing research. Utilizing a combination of genetic, biochemical and pharmakokinetic markers, Dr. Eikelboom is continuing to explore the determinants of response to aspirin as well as other commonly used antiplatelet therapies.

New antithrombotic therapies that are currently under evaluation or have completed testing in phase III trials have important efficacy advantages over established treatments but may cause more bleeding. The results of studies conducted by Dr. Eikelboom have shown that both bleeding and red blood cell transfusions that are used to treat bleeding are associated with adverse outcomes. Building on these findings, his research conducted with collaborators at McMaster University is exploring the potential benefits of transfusing the freshest available red blood cells compared with standard issue red cells (i.e. oldest available blood) on mortality in hospitalized patients.

Dr. Eikelboom’s program of research is funded by the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, Hamilton Health Sciences Corporation, and industry, and supports the education and training of fellows and students from Australia, the Netherlands and China, as well as Canadian trainees.
Obesity levels of resistin—a protein secreted in high quantities by obese fat tissue—increases neutral lipid content in a human liver cell line more than the fatty acid oleate. These findings suggest that resistin may cause fatty liver in humans.

**Canada Research Chair in Molecular Hemostasis**

Dr. Catherine Hayward

Dr. Hayward's Canada Research Chair in Molecular Hemostasis is supporting work on hemostatic mechanisms and the cause of an inherited Canadian bleeding disorder called the Quebec platelet disorder, with a unique, gain-of-function defect in fibrinolysis. In 2010, her group reported the genetic cause of the defect is a duplication of the gene for the fibrinolytic enzyme urokinase plasminogen activator. This is the first bleeding disorder identified to be caused by a gene duplication event and also the first inherited disorder attributed to a mutation of the urokinase plasminogen activator gene. Since this report, her team has identified new cases of Quebec platelet disorder among individuals from Canada and the United States whose bleeding disorder cause was previously unknown. Dr. Hayward's team is investigating the fundamental mechanisms of platelet hemostatic function and how they are altered by diseases. Her team reported that platelet adhesion and thrombus formation is uniquely supported by the polymeric platelet protein multimerin 1, an adhesive ligand that promotes platelet adhesion and binds to collagen and von Willebrand factor. Her team identified that multimerin 1 binds coagulation factor V with high affinity, which inhibits coagulation by reducing thrombin generation and factor V activation. Their group mapped the sites in factor V that mediate multimerin binding and reported on acquired bleeding problems due to an autoantibody against the multimerin binding domain of factor V. In collaboration with Nancy Heddle, Dr. Menaka Pai, Dr. Kathryn Webert and the Transfusion Medicine Research Group, her team is pursuing evidence-based assessments of platelet function. They were first to describe the valuable diagnostic utility of several platelet function tests for the assessment of bleeding disorders. Her team is also developing practical, evidence-based questionnaires for the assessment of bleeding disorders and bleeding risks. Separately, Dr. Hayward led the development of North American Guidelines on platelet aggregation testing. As President of the North American Specialized Coagulation Laboratory Association, Dr. Hayward led international research initiatives to improve the quality of blood coagulation testing, and successfully launched proficiency testing exercise programs for laboratories that assess platelet function disorders.

**Canada Research Chair in Allergy and Immune Tolerance**

Dr. Mark Larché

Dr. Larché was appointed Canada Research Chair in Allergy and Immune Tolerance in September 2006. His group, based at both McMaster University Health Sciences Centre and St. Joseph's Healthcare, currently consists of approximately 15 researchers including physicians, postdoctoral fellows, technicians, graduate students and undergraduate thesis/summer students. The laboratory is currently investigating both pathogenesis and treatment of a variety of immunological diseases including allergic and non-allergic asthma, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, transplant rejection and autoimmunity thrombocytopenia. Funding has been obtained from CIHR, Ontario Thoracic Society, Scleroderma Society of Ontario, AllerGen NCE, Circassia Ltd., Adiga Life Sciences and St. Joseph’s Healthcare. In March 2009, Dr. Larché was the founding scientist of a new joint venture, 'Adiga Life Sciences', between McMaster University and Circassia Ltd (a company he founded in the UK in 1998). The joint venture will act as a vehicle for the commercialization of certain aspects of research within Dr. Larché’s laboratory and other laboratories at McMaster University. Adiga Life Sciences is currently conducting clinical trials of peptide-based vaccines for cat allergy, ragweed allergy, house dust mite allergy and grass allergy, all of which were developed in the Larché laboratory. Further vaccines are under development. Dr. Larché’s group continues active collaborations with other researchers based at McMaster University and St. Joseph’s Healthcare including members of the Divisions of Rheumatology, Nephrology, Respiratory and Hematology.

**Canada Research Chair in Gastrointestinal Immunology**

Dr. Kathy McCoy

Our research aims to understand how our intestinal microbiota interact with our mucosal and systemic immune systems and how this interaction can shape the developing immune system. Our goal is to elucidate the mechanisms involved in maintaining a homeostatic balance between our immune system and the billions of bacteria within our gut.

In this past year we have been able to develop a system to reversibly colonize germ-free mice such that the immune system is exposed to intestinal bacteria but then the gut becomes germ-free again. Using this tool has allowed us to investigate immune memory to intestinal microbiota and the longevity of an antibody response. We have found that even transient exposure to intestinal bacteria is able to induce a robust mucosal IgA response, which is extremely long-lived even when the bacteria are no longer present. However, this bacterial-specific IgA starts to decline when there are other bacteria present that can stimulate IgA of other specificities. This work has implications for mucosal vaccination strategies and has now been published in Science. We are continuing to use this system to investigate many other aspects of the mucosal immune system.

We have also made significant progress on our study of microbial influences on B cell development. We have found that exposure to intestinal bacteria alters many different steps in B cell development in the bone marrow and spleen. We now know that these effects are due to a combination of cell death and increased proliferation, which occur at different stages of development. We have been investigating the pathways of microbial stimulation that lead to cell death versus proliferation in the bone marrow and are continuing to investigate how these changes may alter subsequent immune responses.
During the past year we have also made progress in understanding how hygiene status can affect systemic levels of IgE, which is the major antibody involved in allergic responses. We previously found that IgE levels are abnormally elevated in germ-free animals. Despite the fact that germ-free animals have never been exposed to bacteria, elevated IgE seems to be dependent on signaling through Toll-like Receptors, which recognize microbial patterns. We have now investigated whether food antigens could be driving this increased IgE by generating antigen-free mice. Surprisingly, we have found that in the absence of both microbiota and food antigens, IgE levels are increased even further. These results indicate that exposure to intestinal antigens is crucial for the suppression of IgE. We will continue these studies and we hope that our findings will have an impact on understanding the increase in allergic diseases in Westernized countries.

Canada Research Chair in Airway Inflammometry

Dr. Parameswaran Nair

Inflammation is a key component of most airway diseases such as asthma and COPD. The CRC-funded research program established methods to measure airway inflammation in sputum. The methods helped identify the types of inflammation and are now leading to identifying specific therapies for the different types of inflammation. This has now been recommended by Canadian and international guidelines to treat asthma, chronic cough and COPD. The research also demonstrated that such treatment strategies are more effective and less expensive than the currently available strategies. The program has identified new targets for drug development. Currently, we are exploring proteomic and genomic technologies to identify new biomarkers in sputum.

The major impact of the research in the past year can be summarized as follows:

1. Eleven peer-reviewed publications in major scientific journals.
2. Twelve lectures at major universities or scientific societies in Europe and North America including state-of-the-art lectures at the International Eosinophil Society meeting in Brugges and the John Seiner Allergy Conference in Aspen, CO.
3. Research grants worth over $1 million, major accomplishments were two collaborations with Dr. Carl Richards (McMaster) and Dr. Richard Cook (Waterloo) that were funded by CIHR.
4. New collaborations were established with the University of Seattle, University of Galveston, University of Newcastle, Sydney and McGill University Severe Asthma Program.
5. Airway Inflammometry laboratory served as a central reference laboratory for five large multi-centre clinical trials and trained personnel from over 20 academic centres.
6. The prototype product Accufilter™ has been moved into clinical and research use as part of our research commercialization process.

Canada Research Chair in Metabolism, Obesity and Type 2 Diabetes

Dr. Gregory Steinberg

The rapid rise in rates of obesity has become an important health issue for the developed world. This is because obesity is associated with a number of metabolic diseases such as type 2 diabetes, cardiovascular and fatty liver disease. In addition, emerging data also support obesity as a risk factor in the development of many other diseases including asthma, osteoarthritis and even certain cancers. Given these wide-ranging implications of obesity, we have collaborated with a diverse range of scientists from across the McMaster campus within the last year.

An important aspect of our research program involves studying the role of the evolutionary conserved metabolic sensor AMPK-activated protein kinase (AMPK). AMPK controls energy balance in all eukaryotes through phosphorylation of key substrates in multiple biochemical pathways to help increase ATP production while reducing energy utilization. At the whole-body level this results in AMPK integrating stress responses such as exercise as well as nutrient, hormonal and inflammatory signals to control food intake, energy expenditure and substrate utilization. In the past year we published 12 papers on AMPK regulation of metabolism in journals such as Circulation, Cancer Research, Diabetes, Journal of Biological Chemistry and Physiological Reviews. These studies were funded through grants and fellowships from the Canadian Research Chairs Program, CF, Michael DeGroote Fellowship Awards, CIHR, NSERC and the Canadian Diabetes Association.

Canada Research Chair in Thrombosis

Dr. Jeffrey Weitz

Dr. Weitz has held this Tier 1 chair since 2001; the chair was renewed in 2008. This chair provides salary support for Dr. Weitz and has been used to fund his research program. In addition to the chair, the Canada Foundation for Innovation has twice provided funds to purchase state-of-the-art equipment that is used by Dr. Weitz and other investigators at the Thrombosis and Atherosclerosis Research Institute. Focusing on thrombosis, this chair prompted the successful Canadian Institutes of Health Research Team Grant in Venous Thromboembolism that was awarded to Dr. Weitz and the McMaster Thromboembolism Group in 2006. Providing $4.2 million over five years, the Team Grant has funded new initiatives in thrombosis research that span the spectrum from basic science, to clinical trials, to research in knowledge translation, and created new collaborations at Queen’s University, McGill University, the University of Toronto and the University of Michigan.