

**MEDICAL CAREERS**

## Developing Clinician-Scientists: The MD/PhD Program at McMaster University

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### ABSTRACT

There has been increasing global investment in the clinician-scientist as MD/PhD programs and various other initiatives prioritize translational and patient-oriented research. The Faculty of Health Sciences at McMaster University is uniquely suited to provide a solid foundation for a MD/PhD program. McMaster University has long built a solid reputation as a research-intensive institution. This history of educational innovation in the Michael G. DeGroot School of Medicine means that we can develop programs that optimize the integration of clinical learning and basic research from the very beginning. Since its inception in 2007, the McMaster MD/PhD program has accepted four students, with preparations underway to admit its newest cohort for 2009. The goal of the program is to train students in both clinical medicine and biomedical research. MD/PhD students enrolled at McMaster have the opportunity to choose from a broad array of internationally recognized researchers as supervisors and to be exposed to the latest and most innovative research technology. As a program, we encourage MD/PhD students to gain exposure to collaborative and translational research that will underpin a broad basic research education. The breadth and international recognition of the research environments in which our MD/PhD students are working are detailed in the student highlights at the conclusion of the paper.

In September 2007, McMaster University admitted the first students to its new concurrent MD/PhD program. This program was developed by Carl Richards, PhD, associate dean of graduate studies for the Faculty of Health Sciences with the goal of training students in both clinical medicine and biomedical research. It is envisioned that these students will include a significant research component in their careers, and will be well-placed to become leaders in the advancement of medicine and medical research. As we prepare to enroll our third class to this program, we take this opportunity to examine the role of an MD/PhD program in the present medical research environment, and to give you a glimpse of the future of this nascent program.

University of Toronto initiated the first Canadian MD/PhD program in 1984, and there are now eight MD/PhD programs across Canada. Canadian and American MD/PhD curricula share similar structures. They usually begin with two years of clinical education, followed by four years of research work, and finishing with two years of clinical edu-

cation. The McMaster program is structured differently, with an initial research year followed by 15 months of medical and clinical education (Medical Foundations 1 to 5), three years of research, followed by a final 18 months of clinical clerkship (Figure 1).

The goal of the McMaster MD/PhD program is to train clinician-scientists. Although not a universally accepted definition,<sup>1</sup> a clinician-scientist is an individual with a medical degree who spends the majority of his or her time in research while continuing to have a minor clinical responsibility.<sup>2</sup> Historically, medical research was the sole domain of the clinician-scientist.<sup>3</sup> Over the past 50 years, with the explosion of basic biomedical research, the clinician-scientist has been eclipsed by a cadre of highly trained PhD researchers who continue to answer fundamental questions about human disease and develop novel therapies. This apparent decline in the MD researcher role was recognized, and in 1964 the National Institutes of Health in the USA stepped in with a broad funding program for students pur-

MD/PhD Program Timeline

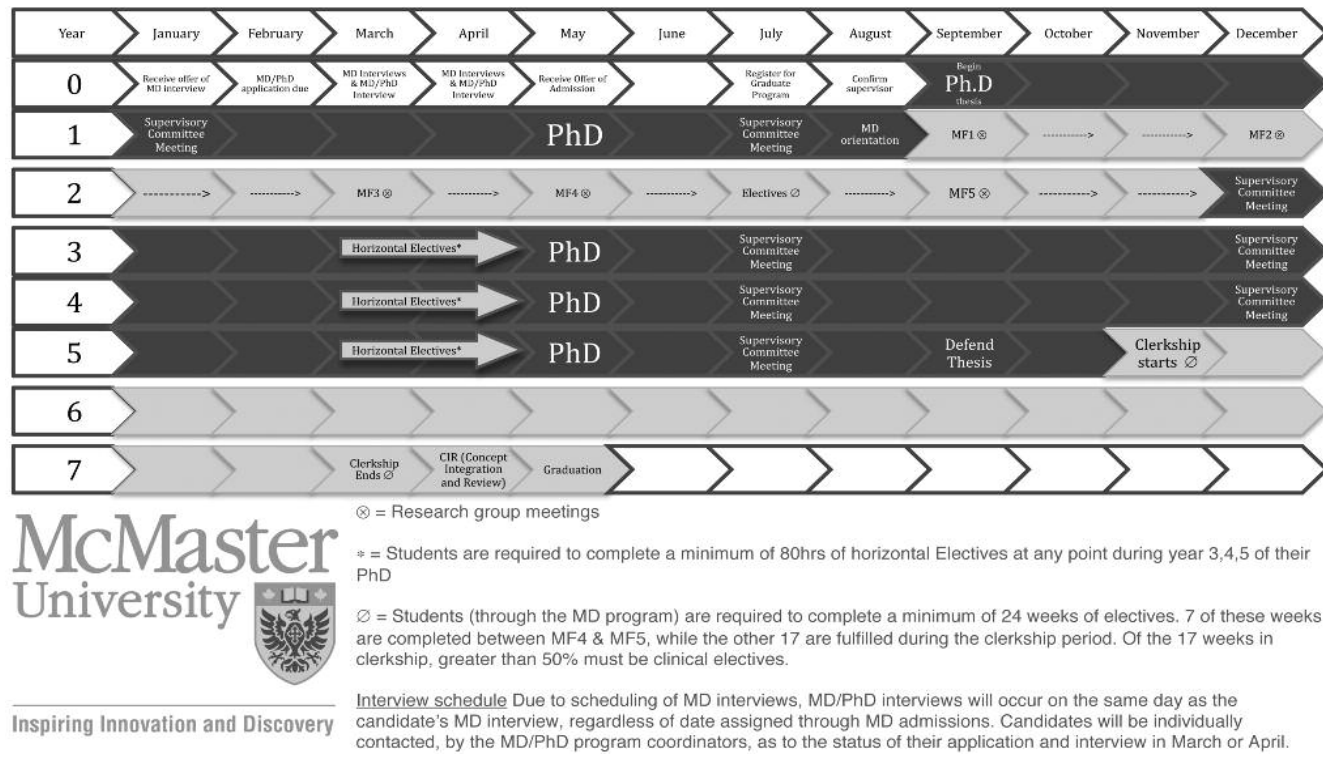


Figure 1. McMaster University MD/PhD program timeline.

using a combined MD/PhD program (the Medical Sciences Training Program, MSTP). Today, the MSTP provides \$42M yearly in funding in order to create and maintain a pipeline of clinician-scientists.<sup>4</sup> A similar but significantly smaller program has been instituted through the Canadian Institutes of Health Research.

The decline of the clinician-scientist has been associated with a significant decline in patient-oriented research.<sup>5,6</sup> The medical research landscape can be viewed through the multiple spectra of basic to clinical research and fundamental to patient-oriented research (Figure 2). Patient-oriented research involves questions that develop from clinical observations which are taken to the laboratory for further understanding. It implies direct contact between the clinician-scientist and the patient. Disease-oriented research involves the understanding of, and development of treatments for, a specific disease process. Fundamental research focuses on basic biological or epidemiological questions.<sup>2,5,7</sup> The investment in the clinician-scientist, through MD/PhD and various other initiatives, was felt to be important in order to rescue patient-oriented research that has essentially disappeared in the tidal wave of basic, fundamental biomedical research.

There is little or no published Canadian data on the effectiveness of these programs in training academic clinician-scientists. American data suggest that MD/PhD programs and the MSTP have been effective at creating a core of trained clinician-scientists,<sup>8</sup> although recent editorials have

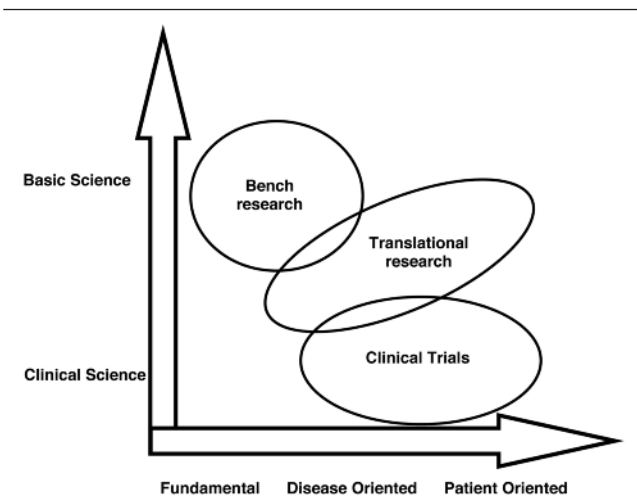


Figure 2. The landscape of biomedical research. Although MD/PhDs can work in any area of research, their education is uniquely suited to bridging the gap between basic and clinical research which is called translational research.

lamented the lack of more recent outcome data and have questioned the cost effectiveness of the MSTP.<sup>4</sup> Program questionnaires have recently been published that give us insight into important characteristics of American MD/PhD students.<sup>1,9</sup> MD/PhD graduates make up about 3% of the US graduating medical class. Sixty to 80% of these students

receive full funding, which covers academic expenses and a small stipend. Although 99% of students surveyed planned to carry out some research, only 56% stated that research would be the major focus of their career (clinician-scientist by definition). Although most MD/PhDs were headed for an academic research career, it should be remembered that numerically, MDs still make up the majority of clinician-scientists.<sup>10</sup> The National Institutes of Health (NIH) K23 grant encourages patient-oriented research, but MDs rather than MD/PhDs hold the majority of these awards.<sup>7</sup>

As further criticism of US MD/PhD programs, they tend to underrepresent women and visible minorities.<sup>10</sup> Andriole and colleagues used data from approximately 80,000 MD graduates, including 1,833 MD/PhD students, from the Association of American Medical Colleges Graduation Questionnaire, 2000 to 2006. They found 45.5% of all MD graduates were female compared with 30% in the MD/PhD group. Similarly, they found that 12.6% of MD students were from an underrepresented minority as opposed to 7.4% in the MD/PhD graduates. Both of these were significant differences ( $p < 0.001$ ) by univariate analysis. The struggle of the female academic researcher is compounded in the clinician-scientist role. Of those MD/PhD students surveyed, 70% of the males, compared with 50% of females, planned to take on a clinician-scientist role.

In light of these observations, what is the benefit of the MD/PhD program in the current medical research environment? Is there a synergism in combining intensive research training with an MD degree? It could be argued that the fundamental research questions are best tackled by a well-trained PhD scientist who can dedicate the majority of his or her time to research and not be distracted by clinical responsibilities. Likewise, patient-oriented and clinical research is perhaps best tackled by an MD who is intimately associated with the clinical question addressed. Where then does the MD/PhD trained clinician-scientist fit in all this? Clearly MD/PhD training is suited to provide a unique approach to fundamental research questions and, from a practical point, MD/PhD applicants have a small but consistent advantage in NIH grant success.<sup>7</sup> However, biomedical research continues to move rapidly, using increasingly complex technology. It may be difficult in the future for a clinician-scientist to maintain clinical competence while keeping up with the rapid advances in basic sciences. Therefore, the MD/PhD of the future may be best placed to work in larger collaborative efforts where he or she can understand and ask the clinical question, as well as co-ordinate the basic approach to answering this question. Likewise, new observations and discoveries made in the laboratory could more quickly be translated to the clinical realm by someone well versed in both arenas. This rapid transfer of clinical and basic research questions, so-called "translational research", is increasingly viewed as the ideal strategy for meaningful future biomedical research.

How do we evolve the McMaster MD/PhD program to educate students to fulfill the clinician-scientist role of the future? Clearly, there are unique facets within the Faculty of Health Sciences at McMaster that will provide a solid foundation for the MD/PhD program. The history of educational innovation in the Michael G. DeGroot School of Medicine means we can develop programs that optimize the integration of clinical learning and basic research from the beginning. In existing MD/PhD programs, there is an observed difficulty with re-entry to clinical education, usually at the clerkship level, after a prolonged period of bench research.<sup>11</sup> With integration of a minimal clinical component into the research time, this hurdle can be avoided. This integrated approach will also more closely mimic the future daily job description of the clinician-scientist. Ongoing clinical exposure throughout the MD/PhD program will allow students to fully evaluate future residency options. The eventual residency choice is important, as the clinician-scientist career path is optimized if the clinical area of expertise coincides with the research focus.

The MD/PhD program is only one component of creating a clinician-scientist. It has recently been shown that of the physicians who have both an MD and PhD degree, those who get their PhD at the end of all medical training are more productive in their research career than those who have PhD training before their MD degree.<sup>12</sup> Part of this may be the time lag between research training and initiating a research intensive career.<sup>13</sup> There is a need to restructure residency programs to accommodate MD and MD/PhD's interested in a clinician-scientist career. Again, integration of ongoing research training with medical training throughout the residency program would be ideal. The newly developed Clinician Investigator Program is a program recognized by the Royal College of Physicians and Surgeons of Canada that accommodates further research training as part of an integrated clinical specialty; in essence, it is a research residency program. This important support allows for re-entry to research after clinically-focused training in early residency. Finally, and most importantly for the clinician-scientist to succeed, there needs to be encouragement from academic clinical departments to support this rare but important career choice, and there needs to be ongoing and increasing support from government and funding agencies to support medical research in Canada.

McMaster University has built a strong reputation as a research intensive institution. MD/PhD students enrolled at McMaster can expect to have a choice of a broad array of internationally recognized researchers as supervisors and to be exposed to the latest and most innovative research technology. As a program, we encourage MD/PhD students to gain exposure to collaborative and translational research that will develop a broad, basic research education. As seen in the following descriptions of the four students presently enrolled in the McMaster MD/PhD program, the breadth and international recognition of the research environments where they are working is indeed very exciting.

**Lindsey MacGillivray**  
**MD/PhD Student (Year 2), Medical Sciences**

The challenges of an MD/PhD program, especially one that is just breaking ground, are many and varied. Administrative hurdles, long hours and a struggle to mesh detail-laden research with clinical medicine are but few of the obstacles I have encountered since starting my studies at McMaster four years ago. But I relish challenge – and my eventual arrival in an MD/PhD program has suited perfectly my ambitions to balance scientific curiosity with clinical pursuits.

My journey to the program was an exciting and convoluted adventure. I graduated from the Honours BSc Biology program at St. Francis Xavier University in 2005. I entered the Master of Science medical sciences program at McMaster later that fall, transferred one year later to the PhD program and again a year later to the newly formed MD/PhD program. I recently completed the pre-clerkship MD curriculum and have made the transition back to near full-time research. I consider it an exceptional opportunity to be a member of the charter MD/PhD class here at McMaster University. The true spirit of the program is an integrative educational experience in which a clinical perspective informs basic science research and vice versa. I have chosen to pursue an MD/PhD degree because no other program will afford me the same opportunities to integrate the challenges and satisfaction of basic research science with the broader clinical context of health and disease. Already, I have noticed the positive impact of clinical knowledge on my research. I have returned to my research with renewed energy and a fresh perspective on how my research can contribute to enhanced patient care.

Since Prozac was approved for commercial use in 1988, selective serotonin reuptake inhibitor (SSRI) antidepressants have been prescribed with staggering frequency.<sup>14</sup> Though initially held as largely benign, it is known now that the therapeutic efficacy of SSRI antidepressants is mitigated by both acute and persistent side effects that are thought to be related to alterations in serotonergic function. Long term use of SSRI medications is associated with sleep disturbances, sexual dysfunction and nausea, and discontinuation of SSRI medications induces a clinically relevant withdrawal syndrome that may persist over time.<sup>15-17</sup> It is well established that SSRI medications inhibit serotonin reuptake via blockade of serotonin transporters.<sup>18</sup> However, neither the onset of therapeutic properties nor the induction of persistent side effects correlates with transporter blockade;<sup>18</sup> this suggests a mechanism more complex than simple inhibition of serotonin reuptake.

Thus, the goals of my research, supervised by Dr. Michael Mazurek, are to investigate whether acute and or chronic SSRI administration induces changes in rat brain monoaminergic neurons, to delineate a time course for such phenomena if present, and ultimately, to develop a model by which SSRI

medication exerts its therapeutic and toxic effects. The clinical relevance is obvious; though SSRI antidepressants are the current first line treatment for depression, their associated toxicities and mechanism of action remain poorly understood. My work addresses this gap and I am confident that it will make a positive contribution toward our understanding of depression and best practices for treatment.

**Jeremy Hernandez**  
**MD/PhD Student (Year 2), Medical Sciences**

A seven-year combined MD/PhD program may appear intimidating but, in reality, it is not as daunting as it seems. As someone who loathes monotony, and who thrives on diverse and novel challenges, the flexibility and variety offered by the McMaster MD/PhD program seemed tailor-made for me. Following my undergraduate education in Physiology (Honours BSc) at the University of Western Ontario, I entered graduate school at McMaster University. After two years in the Master of Science Medical Sciences program, I transferred into the MD/PhD program. This pathway enabled me to build on my current graduate studies in asthma research to complete the PhD component of the program.

The prevalence, health care expenditures and deaths due to asthma have increased in Canada over the past 20 years;<sup>19,20</sup> and yet the gold standard treatment options for this disease,  $\beta_2$ -agonists and inhaled corticosteroids, were developed decades ago. Both of these treatment options fall short of providing complete relief of symptoms, especially in severe asthmatics. While the development of the bronchial thermoplasty technique,<sup>21</sup> with studies performed at the Firestone Institute for Respiratory Health (FIRH) at McMaster University, provides optimism for the future, there remains a great deal of research to be done. My research project, supervised by Dr. Luke Janssen (FIRH), involves studying the structure and function of intact airway smooth muscle in response to acute stretch. In a healthy individual, there is a bronchodilatory effect caused by a deep inhalation to total lung capacity. This beneficial effect is lost in the hyper-responsive airways of an asthmatic individual and a deep inhalation may even cause bronchoconstriction in severe asthmatics.<sup>22,23</sup> Thus, by elucidating the pathways involved in this response, potential therapeutic treatments may be developed to more effectively maintain airway caliber in asthmatics.

As mentioned above, the main role of a physician-scientist is to perform research that bridges the gap between the laboratory and clinical settings. The structure of the MD/PhD program at McMaster has enabled me to complement my basic science skills with clinical skills by pursuing horizontal electives in disciplines such as respirology, cardiology and family medicine. This opportunity has allowed me to see the real-world applications of my medical research as well as caveats to current therapies and patient care. Pursuing a career in translational research and providing a stronger connection between the research and clinical realms is a future goal of mine.

Lastly, the McMaster MD/PhD program provides students with the opportunity to get involved in a wide range of extracurricular activities such as journal clubs, medical interest groups, student council, intramural sports and horizontal electives. These are invaluable opportunities to foster networking skills with future colleagues, professors and health care professionals, while creating a healthy diversion from work. Midway through my second year of the MD/PhD program, I realize that there is still a long road ahead. However, with a program as diverse and flexible as this one, time will surely fly by.

### **Chelsea Maedler MD/PhD Student (Year 1), Biochemistry**

In the past decade, large advances have been made in the fields of stem cell biology and cancer research. In 1994, a seminal paper published by the Dick Lab, revealed that only a small subset of leukemia cells were capable of reproducing the disease upon injection in non-obese diabetic, severe combined immunodeficiency (NOD-SCID) mice.<sup>24</sup> These cells, with a distinct phenotype, shared many similarities with normal hematopoietic stem cells.<sup>25</sup> Further studies led to a model in which leukemogenesis (the progression of leukemia) was organized in a hierarchy, with primitive leukemic cells at the apex capable of self-renewal and differentiation into more mature progenitors.<sup>26</sup> The aforementioned two properties are broadly used to define a stem cell and these findings helped form the basis of the still-controversial theory of cancer stem cells (CSCs).<sup>27</sup>

In leukemia, the notion of CSCs helps explain why current treatments, such as chemotherapy, do not produce complete remission in a number of patients, as they usually target the rapidly cycling bulk population of leukemia cells, while missing quiescent CSCs.<sup>27</sup> My PhD thesis, under the supervision of Mick Bhatia (Director of the McMaster Stem Cell and Cancer Research Institute), focuses on understanding the basic molecular pathways that govern the self-renewal and differentiation of these leukemic/cancer stem cells, which will help shed light on how to better eradicate leukemia in patients.<sup>27,28</sup>

New breakthroughs in the treatment and diagnosis of cancer are discovered on all fronts of scientific research, whether through clinical trials, epidemiological findings, molecular biology or instrumentation and technological advances. The one common trend in all of the above is the need for researchers who can deconstruct and translate clinical problems into scientific questions and systematically gather information to help solve them. Having the expertise and training to do so comes with experience in both clinical medicine and applied research. As a future clinician-scientist, I know that the training I receive throughout my MD/PhD will help me bridge future dialogue between scientists and physicians and design experiments which allow for the translation of findings into concepts for the treatment of leukemia.

Currently in my first year of the combined program, I have engaged in both basic research through my thesis and clinical involvement by attending hematology rounds and shadowing clinicians. My interest is to specialize in hematology or oncology and pursue research in the field of regenerative medicine. It is evident early into my degree that, for the most part, a large divide exists between basic researchers and clinicians. As an MD/PhD student, I am helping to connect this divide. The very notion that McMaster University supports this program resonates with members of faculty and health care professionals and invites them to question their own involvement in translational medicine.

I look forward to the seven years ahead but also understand the obstacles that come with the pursuit of a combined degree. It is also clear that I will have the capacity to play a leading role in medical research; however, it is important that the public and healthcare system understand, foster and be amenable to clinician-scientists as they become a larger influence on Canadian health care.

### **Derek Kuo-Cheng Chu MD/PhD Student (Year 1), Medical Sciences**

My affinity towards medical research and clinical practice has been influenced by my life-threatening peanut allergy. My allergy has driven me to attempt to gain an understanding of it through knowledge acquisition – to try to “figure it out”. On reflection about the rising prevalence, potentially lethality and lack of treatments for peanut allergy, two fundamental questions come to mind: Why do individuals develop allergies (so that we can cure them) and what causes anaphylaxis (so that we can control and/or prevent the deaths it causes)?

Under the guidance of Dr. Manel Jordana, Tier 1 Canada Research Chair in Immunobiology of Respiratory Diseases and Allergy, I will study peanut allergy and anaphylaxis. My main project revolves around investigating mechanisms behind allergic sensitization to peanut. The Hygiene Hypothesis states that increased microbial exposure early in life reduces the risk of developing allergies. In line with this hypothesis is the notion that the extensive and life-long communication between the immune system and more than  $10^{14}$  commensal gastrointestinal bacteria critically influences whether tolerance or allergic disease develops upon antigen ingestion.<sup>29</sup> Importantly, differences in the composition of gut flora between normal and atopic individuals have been repeatedly reported. However, whether this relationship is causal and the direction of any such causality remains untested.

Our main approach to investigate this line of inquiry will involve our previously established mouse model of peanut allergy.<sup>30</sup> Briefly, peanut administered along with an adjuvant, cholera toxin, by oral gavage (i.e., forced feeding) once a week for four weeks causes mice to develop hypersensitivity to peanuts. Subsequent systemic challenge of these

mice results in the development of several biological and clinical features similar to those observed during human anaphylaxis. In particular, mice rapidly exhibit (within less than 40 minutes) severe clinical symptoms, significant increases in hematocrit, marked mast cell mediator release and pronounced increases in vascular permeability. Collaboration with professor Kathy McCoy will allow us to assess the impact of the gastrointestinal microbiota on allergic sensitization/tolerance to peanut through the use of germ-free (i.e., devoid of any commensal bacteria) and selectively colonized mice. Importantly, McMaster is the only facility in Canada, and one of few in the world, with the capabilities to house such stringently sterile mice. Knowledge gained through these studies may lead to preventative and/or therapeutic strategies for peanut allergy through the alteration or manipulation of gastrointestinal commensal bacteria.

As an MD/PhD student, it is important not only to learn clinical practice, but also to question, develop and alter it through medical research. This career path requires us to engage in productive dialogue with clinicians and scientists, bridge the gap between them to create collaborative relationships and, most importantly, integrate information from both sides in order to advance health care in unique and important ways. I welcome these responsibilities with eager anticipation to contribute to both science and society.

The depth, quality and clinical relevance of research being conducted by McMaster MD/PhD students demonstrate the program's commitment to advancing clinical medicine through science. The health sciences milieu at McMaster, a combination of cutting-edge research and an internationally recognized medical program, provides MD/PhD students with a learning environment that is uniquely suited to optimize the integration of clinical medicine and basic science. With the MD/PhD program, McMaster continues a tradition of excellence and innovation by ideally equipping students for leadership in the increasingly overlapping areas of clinical work and research. †

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### Author Biography

**Peter Margetts** is an associate professor in the Department of Medicine at McMaster University. He is a staff nephrologist at St. Joseph's Hospital with an interest in chronic kidney disease and peritoneal dialysis. He supervises a research program in basic mechanisms of peritoneal and kidney fibrosis and treatment with gene therapy. In September 2008, he was appointed the Director of the McMaster MD/PhD program.