KRESCENT

KRESCENT Award Recipients:

2005-2009

kidney FOUNDATION

FONDATION DU rein

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

CIHR IRSC
Institute of Nutrition, Metabolism and Diabetes
Institut de la nutrition, du métabolisme et du diabète

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2005 KRESCENT Award Recipients

Dr. David Cherney

Ortho Biotech-KRESCENT Joint Fellowship



Supervisor: Dr. Judith Miller

Institution: Toronto General Hospital

Year: 2005-2008

Dr. David Cherney will complete his post-doctoral fellowship with Dr. Judith Miller at the Toronto General Hospital, where he will study the renal complications of diabetes. Forty percent of patients with End-Stage Renal Disease (ESRD) have an underlying diagnosis of diabetic nephropathy. Dr. Cherney will study the relationship between the Renin-Angiotensin System (RAS), a specific hormone known as angiotensin II and an enzyme (PKC) that causes many diabetes-related diseases. Understanding this relationship and how to block the increase of PKC may reduce kidney complications in diabetes.

Dr. Todd Fairhead

Amgen-KRESCENT Joint Fellowship



Supervisor: Dr. Joaquin Madrenas

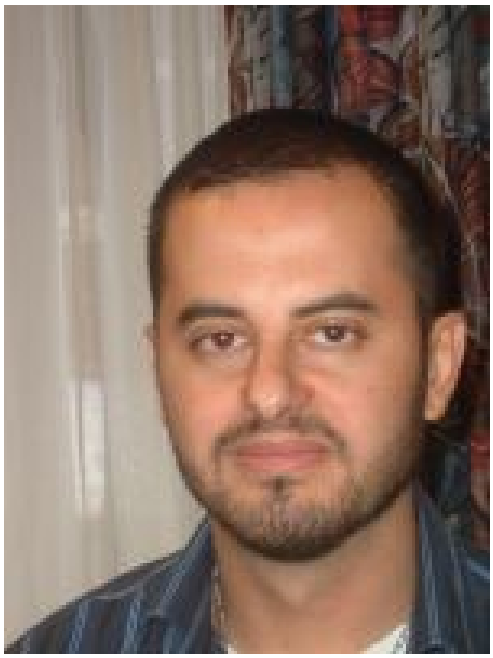
Institution: Robarts Research Institute

Year: 2005-2008

Dr. Todd Fairhead will complete a post-doctoral fellowship in the laboratory of Dr. Joaquin Madrenas at the Robarts Research Institute in London, Ontario. Dr. Fairhead is a young researcher who has charted a consistent path in immunology with a particular focus on transplant immunology. In his research he will examine the role of a specific protein, (RIP 2), in the immune response and its association with infections of the peritoneal cavity amongst individuals on peritoneal dialysis as well as renal allograft injury.

Wissam Faour, PhD

Merck-Frosst-KRESCENT Joint Fellowship



Supervisor: Dr. Chris Kennedy

Institution: Ottawa Health Research Institute

Year: 2005-2008

Dr. Wissam Faour will complete his post-doctoral fellowship in the laboratory of Dr. Chris Kennedy at the Ottawa Health Research Institute. Dr. Faour is a Ph.D. scientist who will be investigating both the beneficial and harmful role of prostaglandins in glomerular disease, building on his expertise in molecular mechanisms. Diseases of the glomerulus, or filter of the kidney, are one of the most important single causes of end-stage kidney failure that affects over 4,000 Canadians each year.

Dr. Lakshman Gunaratnam

KRESCENT Fellowship



Supervisor: Dr. Joseph V. Bonventre

Institution: Brigham and Women's Hospital, Boston

Year: 2005-2008

Dr. Lakshman Gunaratnam obtained his M.D. from the University of Ottawa and will complete a post-doctoral fellowship with Dr. Joseph Bonventre at Brigham and Women's Hospital in Boston, Massachusetts. Dr. Gunaratnam's training will focus on immunology and transplant biology. One third of the patients receiving a kidney transplant have previously received a kidney that failed. Dr. Gunaratnam will be examining the role of certain types of blood cells (CD4+ T cells), which when activated can either promote – or protect against – rejection. His research will explore how a rejection response can be changed into a protective response by altering the activities of molecules in CD4+ T cells.

Dr. Jaqueline Ho

KRESCENT Fellowship



Supervisor: Dr. Jordon A. Kreidberg

Institution: Boston Children's Hospital

Year: 2005-2008

Dr. Jacqueline Ho is a paediatric nephrology fellow who obtained her M.D. from the University of Western Ontario in London. She will complete a post-doctoral fellowship with Dr. Jordan Kreidberg at the Boston Children's Hospital in Massachusetts. Dr. Ho will study the regulation of kidney development. In children, congenital anomalies of the kidney are amongst the most common causes of renal failure. Ultimately, a better understanding of normal kidney development may lead to better strategies to prevent the onset of renal failure.

Dr. Michele Zappitelli

Shire Biochem-KRESCENT Joint Fellowship



Supervisor: Dr. Stuart L. Goldstein

Institution: Texas Children's Hospital

Year: 2005-2007

Dr. Michele Zappitelli is a fellow in paediatric nephrology who obtained his M.D. at McGill University in Montreal and will complete a post-doctoral fellowship with Dr. Stuart Goldstein at Baylor College of Medicine and Texas Children's Hospital in Houston, one of the largest pediatric centres in North America. Dr. Zappitelli's research will explore the nutritional and energy needs of critically ill children who develop acute renal failure in the intensive care unit. Poor nutrition can hinder recovery, delay wound healing and contribute to negative outcomes, and his research is intended to increase understanding of the nutritional needs of critically ill children with acute renal failure and, ultimately, contribute to improved recovery.

Shao-Ling Zhang, PhD

KRESCENT New Investigator Award



Institution : Centre de recherche du CHUM – Campus Hôtel Dieu

Year: 2005-2008

KRESCENT Infrastructure Support: 2005-2006

Dr. Shao-Ling Zhang is a new investigator in kidney development at the Centre Hospitalier de l'Université de Montréal (CHUM) – Campus Hôtel Dieu. Dr. Zhang has returned to Canada after completing a post-doctoral fellowship at Harvard Medical School in the United States. Dr. Zhang's research addresses the role played by prenatal events in kidney development and prenatal programming of adult diseases, and she will be exploring the premise that the intrauterine hormonal environment influences kidney development and contributes to adult health in the long-term.

2006 KRESCENT Award Recipients

Mélanie Béland, PhD

KRESCENT Fellowship



Supervisor: Dr. Maxime Bouchard

Inst tut on: McGill Cancer Centre

Year: 2006-2009

Dr. Mélanie Béland will complete her post-doctoral fellowship in the laboratory of Dr. Maxime Bouchard at the McGill Cancer Centre in Montreal. She will be investigating the role of Pax2 in the initiation and progression of renal cell carcinomas. Kidney cancer accounts for nearly 3% of all tumors diagnosed in Canada; in 2005, approximately 4,500 new cases were reported.

Marie-Luise Brezniceanu, PhD

KRESCENT Fellowship



Supervisor: Dr. John Chan

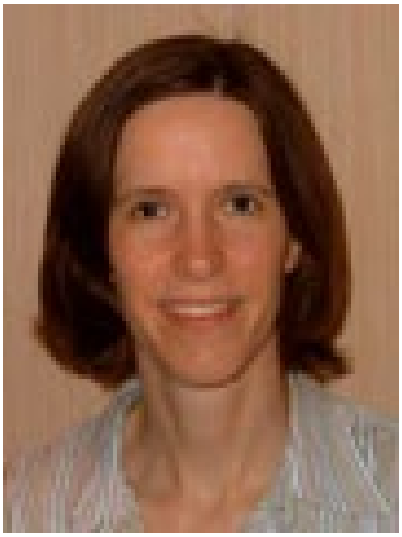
Institution: Hôtel Dieu – CHUM

Year: 2006-2008

Dr. Marie-Luise Brezniceanu will complete her post-doctoral fellowship with Dr. John Chan at the Hôtel-Dieu Hospital (CHUM), where she will study hyperglycemia and activation of the Renin-Angiotensin System (RAS) in the initiation and progression of diabetic nephropathy. Forty percent of patients with End-Stage Renal Disease (ESRD) have an underlying diagnosis of diabetic nephropathy. Dr. Brezniceanu will study the molecular mechanisms of high glucose and intrarenal Reactive Oxygen Species (ROS) action in the hypertrophy and programmed cell death of proximal tubular cells in the kidney. An increase in our understanding of the role(s) of intrarenal ROS in the pathogenesis of diabetic nephropathy will directly contribute to improved clinical treatment.

Dr. Bethany Foster

KRESCENT New Investigator Award



Institution: McGill University

Year: 2006-2009

KRESCENT Infrastructure Support: 2006-2007

Dr. Bethany Foster is a new investigator in kidney transplantation at the Montreal Children's Hospital. She recently returned to Canada after completing a post-doctoral fellowship at the University of Pennsylvania in the United States. Dr. Foster's research addresses the cardiovascular health of children and young adults who need dialysis or a kidney transplant. Cardiovascular mortality in kidney transplantation recipients is lower than in dialysis patients but remains 10 times higher than their healthy counterparts. Once critical post-transplant cardiovascular abnormalities have been determined and risk factors for ongoing cardiovascular disease have been identified, treatments to improve or eliminate these risk factors will be tested and clinically applied.

Dr. Jagbir Gill

KRESCENT Fellowship



Supervisor: Dr. John Gill

Institution: University of California – Los Angeles

Year: 2006-2008

Dr. Jagbir Gill obtained his M.D. from the University of British Columbia. He will complete a post-doctoral fellowship with Dr. Gabriel Danovitch and Dr. Michael Cecka at the University of California in Los Angeles (UCLA), where he will train in kidney transplantation and epidemiology. The shortage of kidneys is a dominant issue in kidney transplantation today, and Dr. Gill will examine the influence of donor age on the survival and outcomes relating to the kidney graft, particularly in living donation.

Sunny Hartwig, PhD

KRESCENT Fellowship



Supervisor: Dr. Jordan Kreidberg

Institution: Boston Children's Hospital, Harvard University

Year: 2006-2009

Dr. Sunny Hartwig obtained her Ph.D. from the University of Toronto. She will complete her post-doctoral fellowship with Dr. Jordan Kreidberg at the Boston Children's Hospital in Massachusetts, where she will study the role of WT-1 (Wilms' Tumor Suppressor) during early kidney development. Mutations in the Wilms' Tumor Suppressor gene cause severe dysplastic kidney disease, (malformation of the kidney), the single most common cause of End-Stage Renal Disease (ESRD) in children.

Dr. Heather Reich

KRESCENT Fellowship



Supervisor: Dr. James W. Scholey

Institution: University of Toronto

Year: 2006-2009

Dr. Heather Reich will complete her post-doctoral fellowship with Dr. Daniel Cattran and Dr. James Scholey at the University of Toronto, where she will study glomerular-based diseases (disease of the filters of the kidney) which account for the majority of cases of End-Stage Renal Disease (ESRD). \\ Since patients with glomerular disease have a variable prognosis, the ability to predict disease outcomes is extremely limited. Dr. Reich will investigate the level of proteinuria (high protein levels in the urine) and gene expression in kidney biopsies as predictors of outcomes of End-Stage Renal Disease in order to better understand kidney disease progression and identify high risk patients.

Dr. Michael Walsh

KRESCENT Fellowship



Supervisor: Dr. David Jayne

Institution: Addenbrooke's Hospital – United Kingdom

Year: 2006-2009

Dr. Michael Walsh obtained his M.D. from the University of Calgary and will complete his post-doctoral fellowship with Dr. David Jayne at Addenbrooke's Hospital in Cambridge, U.K. Dr. Walsh's training will focus on epidemiology and clinical research. In particular, Dr. Walsh will be involved in multi-centre clinical trials in vasculitis and lupus nephritis. Lupus nephritis is a common cause of glomerulonephritis and is an important cause of chronic kidney disease.

Dr. Dongcheng Wu, PhD

KRESCENT Fellowship



Supervisor: Dr. Joan C. Krepinsky

Institution: McMaster University

Year: 2006-2008

Dr. Dongcheng Wu will complete his post-doctoral fellowship in the laboratory of Dr. Joan Krepinsky at McMaster University in Hamilton. High blood pressure is a leading cause of kidney failure, and Dr. Wu will study the effects of high blood pressure on the molecular mechanisms of the glomeruli cells in the kidney. When the mesangial cells in the glomerulus sense high blood pressure in the blood vessels, signaling pathways inside the cells are activated, resulting in the formation of scar protein.

2007 KRESCENT Award Recipients

Dr. R. Todd Alexander, PhD

CIHR Clncal Scentist Phase I Award



Supervisor: Dr. René Bindels

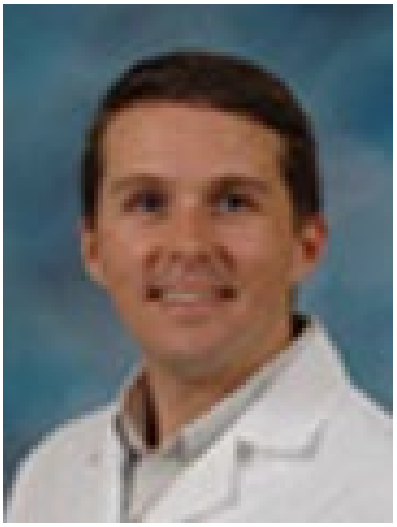
Institution: Radboud University, Netherlands

Year: 2007-2010

Dr. Alexander obtained his M.D. from the University of Western Ontario and Ph.D. from the University of Toronto. He will complete his post-doctoral fellowship with Dr. René Bindels at Radboud University in Nijmegen (the Netherlands). His research project focuses on how the kidney regulates whole body calcium levels in both good health and kidney disease. The aim of the project is to understand how a recently discovered hormone, Klotho, increases the activity of transport proteins, enabling them to retain calcium in the blood and thereby preventing the development of kidney stones and osteoporosis.

Scott Harvey, PhD

KRESCENT Fellowship



Supervisor: Dr. Jeffrey Miner

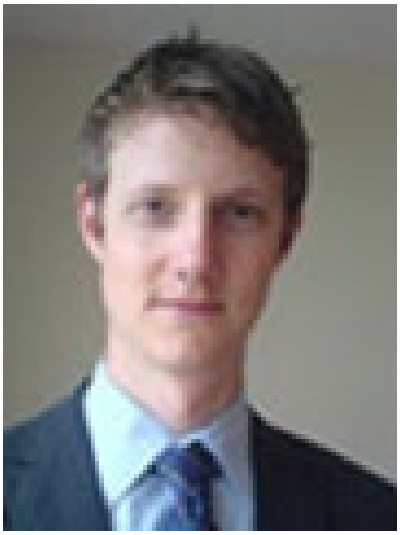
Institution: Washington University – St. Louis, Missouri

Year: 2007-2009

Dr. Scott Harvey will complete his post-doctoral fellowship with Dr. Jeffrey Miner in the Renal Division of Washington University in St. Louis, Missouri. His research will explore the importance of microRNAs in kidney development and function. MicroRNAs are regulatory molecules that act to dampen or silence gene expression. Dr. Harvey will identify microRNAs present in the kidney and disrupt their actions using genetic strategies. His work may lead to the discovery of new pathways that are disrupted in certain kidney diseases, and in doing so, point to new therapeutic targets.

Dr. Matthew James, PhD

Shire Biochem - KRESCENT Joint Fellowship



Supervisor: Dr. Brenda Hemmelgarn

Institution: University of Calgary

Year: 2007-2010

Dr. Matthew James obtained his M.D. from the University of British Columbia and will complete his post-doctoral fellowship with Dr. Brenda Hemmelgarn at the University of Calgary. Dr. James's training will focus on the clinical epidemiology of acute and chronic kidney disease. His research focuses on the long-term effects of acute kidney injury on kidney function in people with pre-existing chronic kidney disease. In particular, he will study changes in kidney function that may occur after coronary angiography. The results of this project will help inform patients and physicians on the relative risks and benefits of these medical procedures and guide the care of patients with kidney disease after they undergo coronary angiography.

Dr. Jean-Philippe Lafrance

KRESCENT Fellowship



Supervisor: Dr. Donald R. Miller

Institution: Boston University

Year: 2007-2009

Dr. Jean-Philippe Lafrance obtained his M.D. from the University of Montreal. He will complete his post-doctoral fellowship with Dr. Donald R. Miller at Boston University, where he will study the risks of developing side effects from various NonSteroidal Anti-Inflammatory Drugs (NSAIDs), the most commonly used form of medication worldwide. Principally used to treat pain, inflammation and fever, NSAIDS can have various side effects on the stomach and kidney, ranging from leg swelling to kidney dysfunction. New NSAIDs with fewer negative effects on the stomach have been developed but their effect on the kidney is not clear. Dr. Lafrance's research findings may assist primary health care practitioners in prescribing the most suitable drug for their patients and may ultimately reduce NSAID-related side effects on the kidney and related hospitalizations.

Dr. Joseph Ly

KRESCENT Fellowship



Supervisor: Dr. S. Quaggin

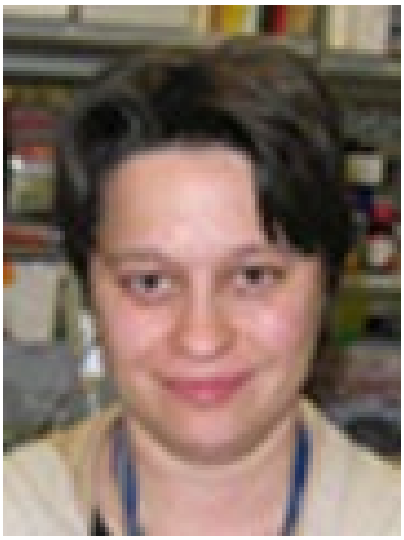
Institution: University of Toronto

Year: 2007-2010

Dr. Joseph Ly obtained his M.D. from the University of Toronto, where he also completed a nephrology fellowship with Dr. K. Kamel. He will complete a post-doctoral fellowship with Dr. S. Quaggin of the Samuel Lunenfeld Research Institute in Toronto, where he will study cystic kidney disease, a major genetic cause of kidney failure. His research will define the pathology and protein expression of a newly identified mutant called “sweet pee” that results in dramatic cystic changes in the kidneys (including the glomerulus) and glucosuria (sugar in the urine) on urinalysis. Characterizing the gene involved is expected to further medical understanding of cystic kidney diseases and may lead to potential therapeutic interventions.

Dr. Katalin Szaszi

KRESCENT New Investigator Award



Institution: St. Michael's Hospital

Year: 2007-2010

KRESCENT Infrastructure Support: 2007-2008

Dr. Katalin Szaszi is a new investigator at St. Michael's Hospital in Toronto. She completed her M.D. and Ph.D. in molecular and cellular physiology at Semmelweis University in Hungary and a post-doctoral internship in cell biology at The Hospital for Sick Children in Toronto. She will be studying the cellular connections central to the structural integrity of the epithelium of the kidney’s functional units or tubules. Regulation of these connections is pivotal for normal functioning of the kidney, but a number of diseases can alter them. Dr. Szaszi’s research aims to study the molecular activities that associate these structures with negative outcomes such as kidney inflammatory responses, scarring and organ failure.

Chih-Chang Wei, PhD

KRESCENT Fellowship



Supervisor: Dr. Joseph V. Bonventre

Institution: Brigham and Women's Hospital

Year: 2007-2010

Dr. Chih-Chang Wei obtained his Ph.D. in the Faculty of Medicine at the University of Montreal. He will complete his post-doctoral fellowship with Dr. Joseph Bonventre at the Brigham and Women's Hospital in Boston where he will study kidney injury molecule-1 (KIM-1), which is strongly expressed in various diseased kidneys. Understanding the function of KIM-1 will provide important insight into the role of this protein in kidney injury and repair processes and may identify KIM-1 as an important therapeutic target for acute and chronic renal disease.

2008 KRESCENT Award Recipients

Karen Hornby

PhD Candidate



KRESCENT Allied Health Doctoral Scholarship

Supervisors: Dr. Ivan Pless and Dr. Sam Shemie

Institution: McGill University

Year: 2008-2011

Karen Hornby will complete her doctoral degree in epidemiology at McGill University in Montreal. Ms. Hornby will study Canadian transplant tourism with Dr. Ivan Pless and Dr. Sam Shemie at the Montreal Children's Hospital. The demand for transplantable kidneys far exceeds the supply in Canada and internationally, thereby pushing individuals to go abroad to purchase a lifesaving kidney transplant. Her research will compare outcomes of people who get kidney transplants abroad with those who have their transplants in Canada and those who remain on waiting lists. Results of the study will provide much needed public health information to inform discussions and policy decisions pertaining to potential solutions to the kidney transplantation shortage.

Nina Jones, PhD



KRESCENT New Investigator Award

Institution: University of Guelph

Year: 2008-2011

Dr. Nina Jones is a new investigator at the University of Guelph in Ontario. Injury to the basic blood filtration unit (glomerulus) of the kidney is one of the leading causes of kidney disease. She is investigating protein interactions in the kidney and is particularly interested in the signalling pathways that are regulated by nephrin, a central component of the kidney filtration barrier. Her research will contribute to our knowledge of the molecular basis of normal kidney development and help identify new molecular targets for therapies that could be used to potentially slow and reverse kidney disease.

Dr. Heather Reich

KRESCENT New Investigator Award



Institution: University of Toronto

Year: 2008-2011

Dr. Heather Reich is a new investigator at the University of Toronto, where she obtained her Ph.D. in the Faculty of Medicine and previously held a KRESCENT Post-Doctoral Fellowship (2006 – 2008). Her current study, Molecular markers of kidney disease progression, is aimed at identifying "high risk" and "low risk" individuals to either facilitate early intervention or spare patients the toxicity of unnecessary therapy. Profiling makes it possible to determine the molecular characteristics of an individual patient's disease, thus allowing for personalized treatment strategies. Dr. Reich has established a biobank of kidney tissue samples linked to long-term clinical database. She has already identified a "profile" of kidney tissue gene expression that relates to protein in the urine, one of the most important factors of kidney failure. The next stage of her work will be to relate this profile to kidney disease outcome.

Dr. Navdeep Tangri, PhD

KRESCENT Fellowship



Supervisor: Dr. Andrew Levey

Institution: Tufts Medical Centre

Year: 2008-2011

Navdeep Tangri obtained his M.D. from the University of Manitoba and has worked extensively with clinical researchers in nephrology at McGill and the University of Toronto. Dr. Tangri will complete his post-doctoral fellowship under the mentorship of Dr. Andrew Levey at the Tufts Medical Centre in Boston. He previously used artificial neural networks to predict outcomes in patients on peritoneal and hemodialysis, and his present study will focus on creating a simplified model to identify patients at high risk for kidney failure and test its accuracy in an external population.

Dr. Darren Yuen, PhD

KRESCENT Fellowship



Supervisors: Dr. Richard Gilbert and Dr. Susan Quaggin

Institution: St. Michael's Hospital

Year: 2008-2011

Dr. Darren Yuen will complete his post-doctoral fellowship in the laboratory of Dr. Richard Gilbert at the University of Toronto, where he will study blood vessel repair in kidney injury. Evidence suggests that the kidney endothelium (the inner lining of the blood vessel wall in the kidney) is important for the kidney to work properly, and recent studies have found that regenerative cells in human bone marrow can repair damaged endothelium. Dr. Yuen's research will determine whether injected regenerative cells can improve the endothelium and if there are better ways to target regenerative cells to the injured kidney, with the potential to identify new opportunities in the treatment of kidney disease.

Dr. Michele Zappitelli

KRESCENT New Investigator Award



Institution: McGill University

Year: 2008-2011

Dr. Michele Zappitelli is a new investigator in pediatric nephrology at McGill University. Last year he returned to Canada after completing a KRESCENT Post-Doctoral Fellowship at Baylor College of Medicine and Texas Children's Hospital in Houston, one of the largest pediatric centres in North America. Dr. Zappitelli will evaluate Cystatin C and urine proteins as tests of acute kidney injury (AKI) in critically ill children. Presently, there is no treatment for AKI. His research will evaluate multiple ways of detecting AKI as early as possible, which in turn, will increase the ability to offer new treatments.

2009 KRESCENT Award Recipients

Dylan Burger, PhD

KRESCENT Fellowship



Supervisors: Dr. Rhian Touyz

Institution: Ottawa Hospital Research Institute

Year: 2009-2012

Dylan Burger will undertake his post-doctoral fellowship under the mentorship of Dr. Rhian Touyz at the Kidney Research Centre, Ottawa Hospital Research Institute, where he will study how microparticles may contribute to hypertension. Microparticles are tiny pieces of cells that are released from dying cells in the body. Recent research indicates that microparticle levels in the blood are increased in many diseases, including hypertension. These tiny pieces of cells appear to exert significant effects on the body such as promoting the clotting of blood. Understanding the proteins carried by microparticles and the signaling that microparticles activate in living cells can potentially lead to the development of new drug treatments for hypertension as well as other disease processes such as heart and kidney failure.

Ghada Kurban, PhD

KRESCENT Fellowship



Supervisors: Dr. Brenda Gallie and Dr. Michael Jewett

Institution: Ontario Cancer Institute

Year: 2009-2012

Dr. Ghada Kurban will pursue her post-doctoral research project under the supervision of Dr. Brenda Gallie and Dr. Michael Jewett at the Ontario Cancer Institute, located at Princess Margaret Hospital and part of the University Health Network. She aims to identify the genomic changes that distinguish small renal masses that will progress into advanced renal cell carcinoma (RCC) from those that will not. RCC is the most common type of kidney cancer with a mortality rate greater than 33% in Canada, and her work will determine what role these genes play in the progression of kidney cancer. In the short term these results may avoid unnecessary surgery in

patients whose small renal masses will not progress. In the long term this research may provide important insight into the onset of RCC, as the identified target may lead to early-stage therapeutic intervention when a cure is still possible.

Dr. Sacha de Serres

KRESCENT Fellowship



Supervisor: Dr. Nader Najafian

Institution: Harvard Medical School

Year: 2009-2012

Sacha De Serres is a nephrologist from Université Laval. He has started his post-doctoral fellowship at Brigham and Women's Hospital at Harvard University, where as a fellow in the immunology of transplantation in Dr. Nader Najafian's laboratory he will attempt to identify biomarkers of chronic and acute kidney rejection in cohorts of renal transplant recipients. It is expected his findings will contribute to the development of new, non-invasive tools that will prove valuable in the adjustment of immunosuppressive drugs. The objective is to make these tools useful in the delivery of antirejection therapy, not only for renal transplant recipients but for other organ recipients as well. Upon completion of his training Dr. De Serres intends to return to Université Laval in order to pursue his career as an independent clinician-scientist.

Dr. Mona Sedeek, PhD

KRESCENT Fellowship



Supervisors: Dr. Rhian Touyz and Dr. Richard Hébert

Institution: Ottawa Hospital Research Institute

Year: 2009-2012

Dr. Mona Sedeek will carry out her post-doctoral research project under the supervision of Dr. Rhian Touyz and Dr. Richard Hébert at the Kidney Research Centre, Ottawa Hospital Research Institute. Diabetic nephropathy is a leading cause of kidney disease. Processes underlying this mechanism are unclear, but increased production of derivatives of oxygen called Reactive Oxygen Species (ROS) may be important. These molecules are toxic and cause damage to many tissues, including the kidney. Many enzymes produce reactive oxygen species, including a special protein found in the kidney called Nox4. Dr. Sedeek will try to determine the effects of diabetes on the expression and activity of Nox4, which may prove to be a therapeutic target in patients with type 2 diabetes mellitus.

Dr. R. Todd Alexander, PhD

KRESCENT New Investigator Award



Institution: University of Alberta

Year: 2009-2012

KRESCENT Infrastructure Support: 2009-2010

R. Todd Alexander is a new investigator at the University of Alberta and a pediatric nephrologist at the Stollery Children's Hospital. In 2007, he completed his PhD in Cell Physiology at the Hospital for Sick Children, followed by a KRESCENT Post-Doctoral Fellowship at St. Radboud University (Nijmegen, the Netherlands) under the supervision of Dr. René Bindels. His research aims to understand how calcium, once it has been filtered by the glomerulus (the filtration unit of the kidney) is reabsorbed back into the blood by the proximal tubule, a section of the kidney responsible for the reabsorption of the majority of necessary ions, minerals, vitamins, proteins etc. The molecular details of renal calcium regulation will provide novel insight into renal calcium wasting and its consequences: kidney stones and osteoporosis. Through these insights, he intends to help generate new therapies for these disorders.