The Kidney Foundation of Canada Research Awards

2018 Awardees and Lay Summaries

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ALPORT SYNDROME FOUNDATION GRANT

Dr. Alessandra Renievi

University of Siena

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Alport Syndrome

AAV2-CRiSPR/Cas9 preclinical trial on a naturally occurring ATS dog model

Alport syndrome (ATS) is a clinically heterogeneous nephropathy caused by mutations in collagen IV genes and characterized by ultrastructural lesions of the glomerular basement membrane (GBM) (Gubler et al., 2008). Podocytes have a predominant role in disease onset and progression, and we have recently proven that it is possible to isolate COL4-expressing podocyte-lineage cells from urine obtained from ATS patients (Daga et al., 2018). An efficient therapy for ATS is still missing, and functional disruption of podocytes can be only partially recovered by symptomatic treatments with RAAS-inhibitors. Transformative gene-based medicines for patients with rare diseases are now aiming to cure diseases at the molecular level using innovative gene-editing tools. The proposed project is designed to use a CRISPR/Cas9 gene editing approach in order to efficiently correct a causative mutation of Alport syndrome in dogs to achieve wild-type COL4 chain production and reversion or slowing-down of the ATS phenotype. The naturally-occurring ATS dog model has a 10-base-pair deletion in the COL4A5 gene. Using podocytes derived from urine, we first aim to establish the efficiency of adeno-associated virus (AAV)2-CRISPR/Cas9 gene therapy to restore the wild-type genotype in canine ATS podocytes in-vitro. We then propose a gene therapy in-vivo preclinical pilot trial using a single femoral artery catheterization to deliver the AAV2-CRISPR/Cas9-based correction system, injecting into both renal arteries.

The proposed AAV2-CRISPR/Cas9 strategy can provide the proof-of-principle for a gene therapy strategy for ATS treatment. If evidence for efficacy and safety is found, this approach will open up the possibility of in-vivo clinical trials on ATS patients based on a personalized, transformative medicine tailored to the pathogenic mechanism and performed directly on the disease-relevant cells.

Dr. Melissa Little

Murdoch Children's Research Institute

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Alport Syndrome

Modelling Alport Syndrome using iPSC-derived glomeruli

One of the main roles of the kidney is to filter the blood, removing waste products and toxins. The units responsible for this filtration are called glomeruli, inside which two specialized cell types, the podocytes and the endothelial cells, create a barrier separating the bloodstream from the waste solution which will become urine. When the kidneys are made and the glomeruli develop, a layer of podocyte cells forms on the outside of the blood vessels and a layer of endothelial cells coats the inside. Both cell types then produce a special meshwork of proteins which forms a barrier to prevent important components within the blood from being lost. This barrier is called the glomerular filtration barrier. A tight glomerular filtration barrier is critical to prevent loss of blood cells and proteins.

Alport syndrome is a kidney disease caused by defects in a particular protein which makes up this barrier: collagen IV. These defects cause the barrier to be leaky. As a result, patients lose proteins and even blood through the barrier and into the urine. Different Alport patients have different mutations, hence the severity and onset of their disease can vary. However, we have no treatment for this disease as we are not yet able to understand why the leakiness occurs or how to fix the problem. This is in part because recreating a model of the glomerular filtration barrier in the laboratory is extremely difficult as the podocytes do not function normally when grown in the laboratory. As a result, research into this disease has largely relied on the use of animal models.

In an important breakthrough we have developed a novel method to recreate three dimensional human glomeruli using stem cells. We can create this model from the stem cells of any individual, including Alport disease patients. As a result, we believe this represents a unique way to accurately model the glomeruli of Alport syndrome patients and compare these to the glomeruli of healthy individuals. This will allow us to investigate what is causing the disease patient by patient, potentially allowing us to screen for drug treatments that will work for individual cases.

In this project we aim to investigate the role of both cell types in the glomeruli, the podocytes and the endothelial cells, to the normal form and function of the glomerular filtration barrier in disease by comparing glomeruli made from the stem cells of an Alport patient with an X-linked COL4A5 mutation and their unaffected sibling. This will show whether or not this approach can be used for drug screening.

Dr. Peter Santi

Regents of the University of Minnesota



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Alport Syndrome

Investigation of cochlear pathology and hearing loss in an X-linked mouse model of Alport syndrome

Alport syndrome (AS) is primarily characterized by renal failure and deafness in humans due to the absence of type IV collagen **αα**3.**αα**4.**αα**5 and the presence of **αα**1.**αα**2.**αα**1 chains in basement membranes in kidney and cochlea. However, the site and mechanism for hearing loss in humans with AS is not yet known. We propose to examine hearing and cochlear basement membranes in X-linked mutant male mice that lack the **αα**3.**αα**4.**αα**5 type IV collagen chains to determine if it mimics the human defect. Establishment of a murine model of AS is essential for the development and testing of early intervention therapies to prevent or minimize hearing loss in humans with AS, since renal dysfunction can be corrected with dialysis and kidney transplantation, whereas, hearing loss can only be treated using hearing aids.

ALLIED HEALTH RESEARCH GRANTS

Dr. Diana Mager

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$99,889	Diabetes

Vitamin D and frailty: longitudinal assessment of risk factors in adults with diabetes and chronic kidney disease

One of the most common problems in people with kidney disease is the high frequency of having several coinciding medical conditions such as osteoporosis and frailty leading to bone fractures, falls, lifelong health problems and reduced health related quality of life (HRQOL). Frailty in particular is very common in adults with chronic kidney disease and it can result in significant muscle weakness, which can in turn result in increasing difficulties performing daily activities such as walking. One of the factors that are thought to contribute to an increased risk for frailty is suboptimal vitamin D (vitD) status.

VitD deficiency is very common in Canada (especially in northern Alberta) because winter is very long. Most people also don't eat or drink enough foods that are high in VitD (like milk) and so they don't have enough Vit D in their body to keep muscles strong. Although many people can feel their muscles are getting weaker because it's harder to walk or climb stairs, they are not sure of the best course of action or whether vitD can help. Right now, we are not sure exactly how much Vit D people with diabetes and kidney disease need to take to prevent them from developing weak muscles (frailty). This is important to understand as frailty can lead to an increased risk for falls and has been shown to also be associated with increasing hospital visits and reduced HRQOL.

We recently showed that people with diabetes and kidney disease who take daily vitamin D pills over a 2-3-year time horizon have stable bone health. However, we also observed that some individuals over the same time period who did not take their vitamin D supplements every day reported increasing difficulties in their ability to perform activities of daily life, (such as walking and climbing stairs), experienced greater loss of muscle mass and more visits to the hospital than those who took their vitD supplements every day. As we know that vitD is an important nutrient to ensure muscles stay strong and work well, we want to study all of the people we

originally studied for an additional three years. Our plan is to measure vitD levels in the blood, and to measure muscle strength/muscle mass, ability to perform activities of daily life (walking, climbing stress, etc.) and HRQOL on a yearly basis for another three years in these same people so we can understand if taking vitamin D supplements can help prevent frailty. This information will help us to understand the best way to prevent frailty over the long term in patients with diabetes and chronic kidney disease.

Lisa Lillebuen

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$5,000	Nursing

Facilitators and barriers to rural treatment of PD emergency care

As dialysis numbers continue to grow, more Albertans are choosing peritoneal dialysis (PD) as their primary dialysis modality. Home dialysis therapies have also been associated with better patient survival and quality of life. As Alberta is geographically diverse, many patients do not live near a center that offers PD. When complications arise, urgent treatment may be needed in a rural emergency department (ED). However, not all rural EDs are willing to provide this treatment. Hence, the purpose of my study is to explore the facilitators and barriers to rural treatment of PD emergency care.

Since nurses are key members of the health care system, their clinical competency in specialized care for PD patients is crucially important. There are no studies that explicitly address barriers and facilitators to PD patients receiving care in a rural emergency department. Since limited literature is available on facilitators and barriers of emergency care for rural PD patients in rural EDs, I am planning a qualitative study to explore these factors to address issues to enhance care of rural PD patients. If the current mandate to encourage home modalities such as PD continues, patients will need additional supports in their home communities to be successful. I plan to conduct a qualitative interpretive description study by conducting semi-structured interviews with nurses who work in rural EDs in Northern Alberta. I have chosen four emergency departments in rural Alberta where I hope to be able to interview 6 to 10 nurses to identify common themes around facilitators and barriers.

Dr. Tania Janaudis-Ferrier

MUHC Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Quality of Life

Development of a self-management workbook to improve quality of life in kidney transplant recipients

Organ transplantation is a lifesaving procedure that prolongs the life of people with kidney disease. Although it is well known that, in comparison to dialysis, transplantation improves the quality of life (QOL) of patients with end-stage kidney disease, the recovery of physical health and other aspects of QOL post-transplant is poor. Many of the challenges that affect QOL are not related to the malfunction of the kidney, but rather to the negative effects of the experience and physical and psychological problems that are carried over from the transplant phase and that cannot be readily addressed as part of the standard outpatient clinical care. In preparation for this project, 51 kidney transplant recipients were evaluated by a personalized questionnaire of QOL to identify particular areas affected by the experience of a kidney transplant. The top identified areas were physiological function, restrictions in leisure, work and socialization, nutrition, mobility, pain, mood/emotions, fatigue and health. Optimization of QOL post-transplant is best managed by the patients themselves. To be able to do so, however, patients need to be provided with training and tools for self-management.

Self-management is a lifelong task where patients are coached to maintain wellness through the development of five core skills: problem solving, decision making, resource utilization, forming patient/health care provider partnership, and taking action. We will develop a workbook to help kidney transplant patients develop the skills and attitudes required to effectively take charge of their health. Our project is in line with the Kidney Foundation of Canada's mission, as its overall goal is to improve quality of life of kidney transplant recipients.

BIOMEDICAL RESEARCH GRANTS

Dr. Amber Molnar

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Dialysis

Risk factors for sub-optimal dialysis initiation

Summary:

Chronic kidney disease affects approximately 730,000 Canadian adults. Patients with kidney disease are at risk of developing kidney failure. Patients with kidney failure require dialysis or a kidney transplant. Most patients are treated with dialysis. Ideally, dialysis should be started with a fistula or graft in the arm or a catheter placed into the abdomen. Creation of a dialysis access can require months of advance planning under the care of a kidney specialist (nephrologist). Unfortunately, many patients start dialysis urgently during a hospital admission or start with a less desirable dialysis access, known as a central venous catheter (CVC). A CVC can be used immediately for dialysis and does not require advanced planning. Patients who start dialysis with a CVC or urgently during a hospital admission have an increased risk of poor outcomes, including death. Our study will provide a better understanding of why patients start dialysis so frequently with a CVC or in hospital. We will then design and test a treatment plan to help reduce the number of patients who start dialysis with a CVC or in hospital. Ultimately, our goal is to improve the care of patients with advanced kidney disease.

Biography:

Amber Molnar started as a staff nephrologist at St Joseph's Healthcare in Hamilton, Ontario in August 2015. She is an Assistant Professor with the Department of Medicine, Division of Nephrology at McMaster University and holds a cross appointment with the Department of Health Research Methods, Evidence and Impact. She completed her nephrology and research training at the University of Ottawa. She was awarded a KRESCENT Post-doctoral Fellowship Award to support her research training and now holds a KRESCENT New Investigator Award. She is an Adjunct Scientist with the Institute for Clinical Evaluative Sciences. In this role, she is able to use large, provincial healthcare databases to answer research questions pertinent to patients with kidney disease. Her research program focuses on chronic kidney disease; specifically, improving the pre-dialysis

care of patients with advanced chronic kidney disease and reducing cardiovascular complications in patients with chronic kidney disease.

Dr. Amit Garg

Lawson Health Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$49,500	Renal Failure

Risk of acute kidney injury in patients randomized to a restrictive versus liberal approach to red-blood-cell transfusion in cardiac surgery

Summary:

When people have heart surgery their kidneys can sometimes be injured. This is known as “acute kidney injury”. This condition is very serious and sometimes causes kidney failure or death. To diagnose acute kidney injury, blood tests are needed before and after the surgery. These blood tests can show if the patient’s kidney function has dropped significantly, which means acute kidney injury has occurred.

We are conducting a kidney sub-study of a large clinical trial of patients undergoing heart surgery. This trial is comparing two approaches to blood transfusions during heart surgery: restrictive and liberal approaches. The main trial will determine if clinical outcomes such as death and heart attacks are different between transfusion groups. We have added extra kidney measurements to this trial in order to compare the number of patients who get acute kidney injury in each transfusion group.

We want to make sure that the restrictive approach to transfusion is as safe as the liberal approach in patients undergoing heart surgery. We also want to know if the restrictive approach is safe in patients with chronic kidney disease.

Biography:

Dr. Garg practices nephrology at the London Health Sciences Centre and is a Professor of Medicine, Epidemiology and Biostatistics at Western University. He has contributed to the landscape of Canadian kidney research over the last 18 years with over 450 publications (including several studies published with teams in the highest-ranked medical journals). More importantly, several findings have had a demonstrable impact in improving the health and care of persons living with kidney disease. His various leadership roles help him translate research findings into better patient care, practice and policy. He currently serves as the President for

the Canadian Society of Nephrology. He has used his Master's in Education and research activities to deliver mentorship and training to help over 75 prior trainees realize their professional goals.

Dr. Andrey Cybulsky



MUHC Research Institute

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Glomerulo-nephritis

Protein kinase SLK in the kidney

Summary:

The health of an organism largely depends on the accuracy of signals sent among constituent cells. Much of this information is transmitted inside cells through specific proteins called protein kinases. Activity of protein kinases contributes to the maintenance of normal cell structure and function, while disorders in protein kinase activation or function can contribute to disease. Diseases of the renal glomerulus, (the filtering unit of the kidney), especially those initiated by immunological processes, ("glomerulonephritis"), account for approximately half of the causes of chronic kidney disease in Canada. Treatment of patients with kidney disease with dialysis and kidney transplantation has resulted in a dramatic improvement in the survival of patients, but at a large cost to the Canadian economy. Fundamental research into the disordered mechanisms that lead to glomerulonephritis is essential to the understanding of these diseases, an understanding that will ultimately lead to therapy and prevention. In this proposal we will study abnormalities in cellular pathways in the glomerulus involving a protein kinase called SLK, and how disordered regulation of SLK leads to kidney disease. The proposed studies will use a tissue-culture system and animal models of glomerulonephritis to characterize abnormalities contributing to the cause of the disease. The elucidation of basic mechanisms of the causes of disease and testing of therapies in preclinical (animal) models is likely to be the most productive approach to the development of treatment strategies to human glomerulonephritis. The results of the proposed studies will eventually lead to improved strategies for therapies of kidney disorders.

Biography:

Dr. Cybulsky is a clinician-scientist, and currently a Professor of Medicine and Director of Nephrology at the McGill University Health Centre, Montreal, Canada. He holds the Catherine McLaughlin Hakim Chair. Dr. Cybulsky obtained his MD degree at the University of Toronto and completed Nephrology clinical and research training at Boston University. He has been an active investigator at McGill University since 1988. Dr. Cybulsky's research is directed at understanding mechanisms of renal cell injury. He employs experimental animal models, and molecular, biochemical and cell imaging approaches to elucidate the pathophysiology of human glomerular

diseases, primarily those involving the podocyte. Dr. Cybulsky's studies have characterized various mediators of podocyte injury, including the complement system, protein kinases, phospholipases and stress proteins. The ultimate goal of Dr. Cybulsky's research is to comprehensively understand the pathophysiology of podocyte injury in order to develop diagnostic bioassays and mechanism-based therapies for human glomerular diseases.

Dr. Alp Sener

Lawson Health Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Transplantation

Evaluating the protective role of a novel mitochondria-targeted hydrogen sulphide donor molecule against ischemia reperfusion injury

Summary:

Kidney failure is on the rise, with 1 out of every 1000 Canadians currently on dialysis. Sadly, this number continues to increase by 5% each year. Half of these dialysis patients will die from complications of kidney failure within 5 years. Although kidney transplantation is the best manner in which to treat kidney failure, only a limited number of donor organs are available. To overcome this, centers have begun to transplant kidneys from donors after cardiac death (DCD). This involves the use of organs from donors whose hearts have stopped beating prior to donation. Unfortunately, these kidneys are very prone to injury that occurs as a result of the decreased blood flow and oxygen they experience during the dying process. This damage leads to increased organ rejection, and poor transplant kidney function in patients.

We have previously shown, in animal models of kidney transplantation, that the supplementation of organ preservation solutions with NaHS, a hydrogen sulphide (H2S) donor and a naturally occurring compound in all animals, leads to an impressive improvement in kidney function and recipient survival. With this grant, we propose to evaluate and understand the protective role of H2S using a novel H2S donor molecule (AP39) which targets the mitochondria, the powerhouse of the cell, in DCD models which we have developed in the lab using discarded human kidneys. Our findings will not only enable future human clinical trials but also play a role in improving existing organ preservation techniques. Ultimately, the proposed work has the potential to positively alter the outcomes of patients receiving kidney transplants.

Biography:

Dr. Alp Sener earned his biology degree from the University of Texas at Austin in 1994. Upon concluding his undergraduate studies, he obtained his PhD in renal physiology in 1999, followed by his MD in 2002 from the University of Calgary. Subsequently, Dr. Sener completed his Urology residency at Western University and became a fellow of the Royal College of Physicians and Surgeons of Canada in 2007. Dr. Sener spent two years at the University of Maryland Medical Center in Baltimore as the American Society of Transplant Surgeons/Novartis Fellow in Transplantation. While in Maryland, he was trained in kidney and pancreas transplantation and completed a research fellowship in transplant immunology. Dr. Sener joined the Division of Urology in 2009 as an Assistant Professor of Surgery and of Microbiology & Immunology, and was the first surgeon to receive the Schulich Clinician Scientist award from the Western University.

Dr. Sener has been the recipient of local, national and international research contribution awards, including the Western University Dean's Award of Excellence, the Canadian Society of Transplantation Research Excellence Award and the Vanguard Award from the American Society of Transplant Surgeons. He has published 86 peer-reviewed articles and 139 conference abstracts. He is the Founder and Chair of the Canadian Association of Chairs of Surgical Research. Dr. Sener also serves as the Chair of the Surgical Research Committee for the Department of Surgery and is the Director of the Kidney/Pancreas Transplant Fellowship program and of the Urology Residency Program at Western University.

In addition to a general urology and kidney/pancreas transplant-directed clinical practice, Dr. Sener maintains an active basic sciences and translational research laboratory focusing on the innate and adaptive immune responses in graft rejection as well as in developing novel methods of mitigating organ injury associated with transplantation. His laboratory has pioneered the use of hydrogen sulphide in mitigating organ injury associated with transplantation, in modulating neovascularization and metastasis of renal cell carcinoma cell lines and in mitigating tissue fibrosis following chronic urinary obstruction. He is heavily involved in promoting research and education through his national and international active roles in both Urology, (American Urological Association Research Advocacy Committee, AUA Northeastern Section Board of Directors; Canadian Urological Association Research and Education Committees and as President of the Urological Society of Transplant and Renal Surgeons), and Transplant organizations (Canadian Society of Transplantation Research Committee and American Society of Transplant Surgeons Vanguard Committee).

Dr. Christopher Kennedy

Ottawa Health Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Hypertension

Nox5-containing urinary microparticles in renal injury associated with diabetes and hypertension

Summary:

Early detection of injury in the leading causes of kidney disease – diabetes and hypertension – is urgently needed to help guide therapies in order to slow down the disease process. We are studying an enzyme known as Nox5 that converts oxygen molecules into highly volatile and reactive oxygen molecules that damage the cells of the kidney. One of the ways in which this damage takes place is by causing the cells to release microscopically sized pieces of their outer membrane. These are called microparticles and we are able to detect them in the urine of humans with diabetes and in mice with high blood pressure. We will test whether Nox5 is found in these microparticles and whether it leads to their formation. Ultimately, Nox5 might become a biomarker for kidney damage and might also become a target for future drugs in order to slow or reverse kidney disease.

Biography:

Christopher Kennedy is a Senior Scientist within the Chronic Disease Program and Kidney Research Centre at the Ottawa Hospital Research Institute and a Full Professor in the Faculty of Medicine / Department of Medicine at the University of Ottawa. He is interim director of the Faculty of Medicine's Awards and Prizes for Excellence in Education and Research.

Dr. Kennedy served as Chair and Scientific Officer of the CIHR Hematology Digestive Diseases and Kidney open operating grant peer review committee and is an Advisory Board member of the CIHR's Institute of Nutrition, Metabolism and Diabetes. Currently, he is a member of the Board of Directors for the Canadian Council on Animal Care and has served for over 10 years on the University of Ottawa's Animal Care Committee. He is also chair of the Kidney Foundation of Canada's Biomedical Research Grants Committee and a member of the CIHR College of Reviewers.

Dr. Kennedy's research program is a fertile training environment for undergraduates, graduates and postgraduates and is funded by the Canadian Institutes for Health Research (CIHR), the Kidney Foundation of Canada (KFOC), and the Canada Foundation for Innovation. Using animal models his research seeks to identify how the kidney's filtration system and vasculature are damaged in diabetes and high blood pressure – the two

leading causes of kidney disease in Canada – with the goal of translating his work into novel therapies that would slow down or prevent kidney disease progression.

Dr. Clara Bohm

University of Manitoba



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$99,973	Dialysis

Effect of an exercise rehabilitation program on symptom burden in hemodialysis: a randomized controlled study

Summary:

People with kidney failure who require hemodialysis to sustain life have multiple symptoms, such as fatigue, pain, and difficulty sleeping which are difficult to treat.

This affects their ability to perform everyday activities, enjoy life, and likely increases the risks of hospitalization and dying. This study will assess whether an exercise rehabilitation program improves symptom burden (the number and severity of symptoms) and quality of life (QOL) in individuals on hemodialysis. We will enroll 150 volunteers who are receiving hemodialysis. Half of the participants will be randomized to receive usual care, which includes exercise counseling. The other half will be randomized to receive usual care plus a 12-week exercise rehabilitation program. We will compare symptom burden and QOL between groups immediately after the program.

The improvement of symptoms and QOL in individuals on dialysis has been identified as a key research priority in Canada. We hope to address this knowledge gap by showing that exercise rehabilitation improves symptom burden and QOL in people receiving hemodialysis. Such improvements are important for individual health and could also reduce burden and costs to the health care system.

Biography:

Dr. Clara Bohm received her medical degree from McMaster University. She completed her postgraduate clinical training at the University of Saskatchewan and Dalhousie University and completed a Master of Public Health at John's Hopkins Bloomberg School of Public Health. She is an Assistant Professor and clinical researcher in the Department of Internal Medicine, University of Manitoba. She also works as a clinical nephrologist in the Manitoba Renal Program. As the Medical Lead of the Manitoba Renal Program's Exercise and Wellness Program,

she has been involved in the design and implementation of evidence-based exercise initiatives for individuals with all stages of chronic kidney disease. She is also a Research Affiliate with the Health, Leisure and Performance Research Institute in the Faculty of Kinesiology at the University of Manitoba. Dr. Bohm's primary research interests lie in fully characterizing the benefits of activity promotion and exercise programming in individuals with chronic kidney disease and translating these findings into clinical practice to improve health outcomes. She is also involved in several projects seeking ways to redesign care delivery to improve clinical care for individuals with kidney disease.

Dr. George Yousef

St. Michael's Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Cancer

Understanding the attributes of papillary renal cell carcinoma subtypes

Renal cancer includes multiple types. Papillary renal cell carcinoma (PRCC), the cancer we are proposing this research for, is the second most common form of kidney cancer. However, PRCC itself is divided into 2 subtypes: PRCC type 1 and PRCC type 2. This is based upon the way they look under the microscope. Previous researchers have noted that type 2 is usually a more aggressive form of cancer than type 1. As such, patients with these cancers should be followed differently. Other studies as well as ours have found that the types have a different biology. Therefore, their response to cancer drugs is expected to be different. However, to date they are treated by doctors as one entity. Part of the dilemma is that nearly half the cases are hard to subtype using the microscope alone. There is a need for tests (biomarker) that can help pathologists (cancer microscope doctors) distinguish between them. Our previous work identified some promising possible markers. We need to confirm these results in another set of cancer patients, which is part of our research proposal. The findings will help doctors divide patients properly in the right group for follow up and treatment.

Yet another confounding factor is that even though the types are known to have different biology, the exact nature of these changes and how they affect the cancer response to drugs is not properly understood. Our previous research shows that the cancer types should respond differently to certain cancer drugs. We propose further studying these differences and assessing the response of the cancer cells, (cancer cells made and grown for research, corresponding to our particular tumor types), to a number of current cancer medications. We will be examining that effect both in petri dishes and on mice. The results are expected to guide doctors into treating patients with the right kind of medicine for the right kind of cancer. Lastly, we will study early kidney lesions that

are thought to eventually give rise to the cancer, in the hopes that they will tell us more about how to detect these cancers and how to prevent them.

Dr. Indra Gupta

MUHC Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Urology

Claudin function in kidney development and in disease

The incidence of kidney stones is on the rise and studies in Canada estimate that 1 in 10 adults may be affected. In addition to the acute severe pain caused by the stone, in the long-term kidney stones can contribute to chronic kidney disease in children and adults. Unfortunately, treatment options for stones are extremely limited. New, individualized treatment strategies are needed.

Kidney stone development is impacted by dietary salt intake and regulation of salt levels in blood and urine. Salt is absorbed from the intestine into the blood. It then passes from the blood into the kidney, where salt balance is controlled by hundreds of thousands of filtering units called nephrons. In the nephron, some salt is reabsorbed back into the circulation to maintain the correct balance in the blood. Too little salt reabsorption leads to excessive salt in the urine, which forms crystals that develop into kidney stones. Claudin proteins regulate the barriers that control the movement of salt between the nephron and the blood; some make the barrier tighter, and others make it leakier.

Individuals within the population can have different versions of each claudin, which when combined determine their “claudin genetic signature”. We will perform studies to determine the correlation between different claudin signatures and the propensity to develop kidney stones and ultimately chronic kidney disease. We will create a diagnostic tool to assess claudin signatures to determine if this predicts who will get kidney stones repeatedly. Finally, we will test a novel claudin-targeted treatment using the leaf of a plant known as Bryophyllum pinnatum that regulates claudin barrier function in the nephron. We will give tablets with the leaf contents or a placebo and determine if patients have less salt in their urine, suggesting a lower risk of having a kidney stone.

Dr. Joan Krepinsky

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Hypertension

Role of miR-299a in regulating renal fibrosis

Summary:

In patients with chronic kidney disease, the filtering units of the kidney, (called glomeruli), develop scars. As these scars become larger the kidney or a kidney transplant to survive. The protein TGFbeta is an important cause of this scarring. It makes cells found in these filtering units – called mesangial cells – produce scar proteins. Blocking TGFbeta actions in patients would offer a way to slow or prevent the decrease in kidney function that is often seen in patients with chronic kidney disease. Our studies show that a molecule called miRNA-299a-5p is important to allowing TGFbeta to work in kidney mesangial cells. Blocking miRNA-299a-5p can prevent kidney mesangial cells from responding to TGFbeta and from making scar proteins. In kidneys taken from mice with chronic kidney disease, miRNA-99a-5p is increased. This suggests that miRNA-299a-5p is an important player in kidney scarring. In our studies, we would like to understand how miRNA-299a-5p allows TGFbeta to direct kidney mesangial cells to make scar proteins, and whether blocking the function of miRNA-299a-5p will prevent kidney scarring and help to prevent kidney function from getting worse in mice with chronic kidney disease. Drugs which block other molecules like miRNA-299a-5p have already been used successfully in patients. If our studies show that blocking miRNA-299a-5p prevents kidney scarring and helps to keep kidney function from getting worse over time, this will give us a new treatment to test in patients with chronic kidney disease.

Biography:

Dr. Krepinsky is a clinician-researcher with the Division of Nephrology, McMaster University. She see's patients with general kidney problems, chronic kidney disease and kidney failure who are being treated with dialysis. Her research goal is to better understand the process of kidney scarring in chronic kidney disease, especially that associated with high blood pressure. This is because kidney scarring over time builds up and leads to failure of kidney function. The focus of Dr. Krepinsky's current work, funded by the Kidney Foundation of Canada, is to evaluate the role of a particular molecule (micro-RNA) in the scarring process, and to test whether blocking this micro RNA will improve kidney function and decrease scarring in a model of chronic kidney disease associated with high blood pressure.

Dr. Maxime Bouchard

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
		Kidney Development

Collective cell migration in urinary tract morphogenesis and disease

Summary:

Our laboratory works on the identification of genes affected in patients with “Congenital Anomalies of the Kidney and Urinary Tract” or CAKUT. This disease group is not well defined and includes patients with only one kidney, smaller kidneys, obstruction of the ureter or ureteral reflux. CAKUT affects 1 in 100 newborns and is the most frequent cause of chronic kidney disease and renal transplant in children.

The way we address the problematic of CAKUT is to try to reproduce the kidney and ureter defects in mice. Over the years we have generated and published about 10 different mouse strains with CAKUT-like urinary tract defects. Most of the genes affecting kidney and ureter development act at a very early stage of urogenital system formation. They typically affect the formation of the primitive kidney (mesonephros) or the early stages of adult kidney development.

In this proposal, we used advanced molecular techniques (single cell RNA sequencing) to identify potential regulators of mesonephros development. We used the CRISPR approach to identify which candidates affected mesonephros development in the mouse embryo. This work identified a gene called Ymo1 that is involved in the formation modification of the cell skeleton. Changes in the structure of the cell skeleton (cytoskeleton) is responsible for the changes in cell shape that are necessary for cells to move (by themselves or in group) or become stiff and packed together.

We therefore propose to study our new mouse model to understand how the cell skeleton regulates the formation of the mesonephros but also the adult kidney and ureter. The genes – important for early kidney development - are often also involved at later stages of kidney formation, which can generate other forms of CAKUT-like defects. To fully understand the implication of our new regulator of kidney development in CAKUT, we also propose to sequence the DNA of 95 patients (children) with CAKUT and determine if they carry mutations in this gene.

This work will be beneficial to public health and is relevant to the KFOC mission in several ways. It will document the importance of the cell cytoskeleton in kidney development (for which we know little); it will generate murine models to better understand how defects in kidney development lead to CAKUT; it will help

better define the disease group CAKUT for which there is no clear molecular definition at this time; and finally, it will help pediatric nephrologists decide on the best diagnostic and method of intervention when they are referred patients affected with kidney and ureter malformations at birth.

Dr. Nicoletta Eliopoulos

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Cancer

Treatment of renal cell carcinoma using gene-modified mesenchymal stem cells

Summary:

Kidney cancer is among the 15 most common cancers in men and women worldwide, with an incidence of about 338,000 new cases and 144,000 deaths yearly, the highest rates being in North America, Europe and Australia/New Zealand. In Canada, kidney cancer is the 10th most frequently arising cancer, with more than one quarter of cases being diagnosed at stage 4 when it is fatal for most patients. 80-90% of kidney cancers are renal cell carcinoma (RCC).

PTEN, (phosphatase and tensin homologue deleted on chromosome ten), is a tumor suppressor that is absent or reduced in many advanced cancers which include kidney cancer. PTEN levels are frequently decreased in advanced RCC, and this is associated with tumor progression and poor outcome. A variant of PTEN, named PTEN-Long, is capable of being released from cells and penetrating into other cells. Like PTEN, PTEN-Long also has anti-tumor actions. Injection of the PTEN-Long protein in mice with RCC, led to tumor regression, suggesting the potential of recombinant PTEN-Long protein as a treatment strategy. However, recombinant protein use in patients has several disadvantages. An alternative is to use mesenchymal stem cells, (MSCs), a type of adult stem cell, as a cellular vehicle for delivering PTEN-Long.

The main goal of our research is to determine if MSCs genetically modified to produce PTEN-Long can be used to combat kidney cancer. Our specific aims are to: (1) Determine if human MSCs from fat can be genetically modified to produce PTEN-Long and reveal its effects on human RCC cells in culture; (2) Evaluate in mice with RCC if administration of MSCs producing PTEN-Long leads to anti-tumor effects; (3) Reveal the location and duration of these MSCs following their administration in mice.

Our proposed research is very promising. The use of the easily isolated fat-derived MSCs to deliver PTEN-Long is intended to permit clinically relevant production of PTEN-Long and its various antitumor effects to

effectively combat RCC (locally and at metastatic sites), aiming for a curative response and therefore relevant to the mission of the KFOC. Our study is novel, as it will be the first to evaluate the delivery of PTEN-Long by any cellular vehicle in any cancer model.

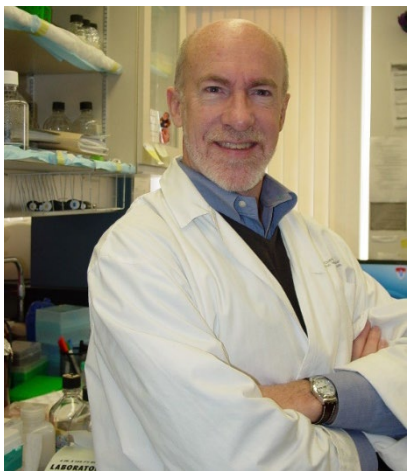
Biography:

Dr. Nicoletta Eliopoulos is an Investigator at the Lady Davis Institute for Medical Research (LDI), Jewish General Hospital (JGH), and Assistant Professor in the Department of Surgery, Division of Surgical Research, at McGill University in Montreal. She is also the Laboratory Director of the JGH Cell Processing Center, a clinical-grade cell handling facility which is committed to fostering early-phase trials testing cell-based technologies. Dr. Eliopoulos has a B.Sc. degree in Physiology from McGill University, M.Sc. and Ph.D. degrees in Pharmacology from the Université de Montréal and received her postdoctoral training at the LDI in the laboratory of Dr. Jacques Galipeau.

Dr. Eliopoulos is a scientist with expertise in stem/progenitor cells for cell and gene therapy of various diseases, such as kidney injury and cancer. Her research laboratory currently performs studies on the pre-treatment, gene-enhancement and therapeutic use of mesenchymal stem cells (MSCs). She is very grateful to the Kidney Foundation of Canada for supporting her research exploring the use of gene-enhanced MSCs for the treatment of renal cell carcinoma.

Dr. Paul Goodyer

MUHC Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Kidney Development

Priming the renal progenitor cell

Summary:

Every year in Canada about 4,000 Canadians develop sudden kidney injury (AKI), often from low blood pressure as a complication of some other illness. Among patients in the Intensive Care Unit, the occurrence of AKI doubles the chance of dying. There are no effective therapies for AKI and physicians are usually limited to supportive care such as dialysis while waiting to see if the kidneys will recover. In the past decade investigators have tried to treat AKI by infusing cells from the patient's bone marrow in the hope that these cells will replace the damaged kidney cells; while this cell-based therapy has some helpful effects, the hoped-for goal of repopulating the damaged kidney with viable cells has been unsuccessful. However, we recently discovered that

special cells from the kidney have properties which allow them to enter areas of the damaged kidney and repopulate the renal tubule. Similar cells can be gathered from the urine of premature babies. In this project we will study how to optimize the features of these cells might allow us to use them as a treatment for AKI.

Biography:

A graduate of Harvard University, Dr. Goodyer has been Director, Division of Pediatric Nephrology at the Montreal Children's Hospital since 1998. His research career spans over 20 years with a particular interest in molecular genetics, a research field that focuses on genes as determinants of all life processes. Author of more than 100 peer-reviewed articles in prestigious journals, Dr. Goodyer is a popular and highly-anticipated speaker at international conferences. He has also played a key role in supervising graduate students and post-doctoral fellows throughout his career.

Dr. Paul Ronksley

University of Calgary



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Dialysis

Predicting emergency department use among patients receiving hemodialysis care

Summary:

Chronic kidney disease (CKD) affects approximately 10% of the Canadian population and places patients at high risk of requiring acute medical care for related health problems. Patients living with CKD are among the highest users of acute care medical services given their level of illness. This is particularly true for those with kidney failure who require dialysis as a life-sustaining therapy. Research has shown that patients that are dialysis-dependent are frequent users of emergency department (ED) and acute care hospital services due to their chronic medical conditions and its complications. While the ED is essential for providing urgent care in a timely manner, identifying ways to improve efficiency, improve patient experience, and decrease ED wait times have been recognized as research priorities by both patients and health policy makers.

The goal of our research is to identify hemodialysis-dependent patients at greatest risk of having an ED visit which is potentially preventable. We will use clinical and administrative data sources from Alberta to develop a tool to identify those at highest risk. Upon development and testing of the performance of this tool in Alberta, we will then assess the generalizability of this strategy in another group of patients from British Columbia.

Identifying ways to improve quality of life and health outcomes has been identified as a priority among patients receiving dialysis care. There is also a need for accurate tools to identify patients at highest risk of using the ED to potentially reduce the strain that is currently placed on this portion of the healthcare system. This project has the ability to identify high-risk hemodialysis patients that may require additional care to not only reduce unnecessary ED use but to improve patient experience, quality of life, and health outcomes.

Biography:

Paul Ronksley, PhD is an Assistant Professor and health services researcher in the Department of Community Health Sciences, University of Calgary. He has a PhD in Epidemiology from the University of Calgary and completed a post-doctoral fellowship in Clinical Epidemiology at the Ottawa Hospital Research Institute. Dr. Ronksley has considerable experience in the use of administrative data and data linkage methodologies to study health system use and outcomes among patients with chronic kidney disease. He is a member of the Alberta Kidney Disease Network (AKDN), a co-investigator within the Interdisciplinary Chronic Disease Collaboration (ICDC), and devotes 75% of his time to health research.

Dr. Rulan Parekh

Hospital for Sick Children Research Institute

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$99,994	Glomerulo-nephritis



Patient centered outcomes in childhood onset nephrotic syndrome

Nephrotic syndrome is the most common childhood kidney disease in the world. The rates of nephrotic syndrome have doubled over the past ten years in Ontario, where 5 children per 100,000 children are affected. South Asian children are affected by nephrotic syndrome more frequently, with a 6-times higher occurrence than European children. Steroids are the basis of treatment not only at initial presentation, but also at each subsequent relapse. If the child is steroid resistant, dependent, or frequently relapsing, steroid-sparing immunosuppressive medications are often used. Overall most children do well, and in about 85% of children the disease has been cured by adulthood. Unfortunately, there is a significant exposure to steroids and at least half of the children have a prolonged and repeated exposure to other immunosuppressive drugs. Despite prolonged exposure to medications, the risks of developing other chronic diseases related to repeated exposure to steroids and other steroid-sparing medications are unknown. Specifically, we do not know if these children develop chronic kidney disease, cardiovascular disease, diabetes, fractures, infertility or cancer. Our goal is to determine

the risk of these long-term complications in individuals with childhood nephrotic syndrome as they age into young adults. We will compare the overall risk of complications to that in healthy children from Ontario.

We propose to study around 1500 children with idiopathic nephrotic syndrome from 4 pediatric centers in Ontario (Toronto, Hamilton, Ottawa and London) with equal access to healthcare. We will collect health data from the medical charts of these children and link it with provincial health administrative data to determine the rates of complications. Results of the study will provide the rationale for clinical practice guidelines on screening for comorbidities and potentially alternative treatment strategies to lessen the risk. If there is no difference in risk, we can reassure families about prolonged steroid use and choice of steroid sparing agent. We will also develop methods to determine specific kidney outcomes in children using administrative data. Our overall goal is to provide more robust estimates of the burden for these important outcomes that result from having childhood nephrotic syndrome or arise from treatment with steroids and other nonsteroidal immunosuppressive drugs. This study addresses important patient-centered outcomes and will provide key information in counselling patients and families on the risks of nephrotic syndrome and related medications.

Dr. Sandra Turcotte

Université de Moncton

	FUNDING AMOUNT	CATEGORY
	$100,000	Cancer



Studying the interaction between miR-2355 and the Sushi-domain-containing protein 4 to investigate a role for the complement system in VHL-inactivated renal cell carcinoma

There are 6,600 adults in Canada that will be diagnosed with kidney cancer in 2017 and about 2,000 will die from this disease. It is one of the ten most common types of cancer diagnosed worldwide. Renal Cell Carcinoma (RCC) incidence increases with age (median age is 64 years) and is higher in men than women by a 2:1 ratio. In addition to obesity, hypertension and smoking, medical conditions such as chronic kidney disease, haemodialysis and kidney transplantation are risk factors associated with RCC. Importantly, intratumor heterogeneity showed variability in mutational signatures across the tumor. Furthermore, these tumors are highly vascular at the metastatic stage and no molecular markers or curative treatments are available. Thus, a better understanding of kidney carcinogenesis is crucial to develop new approaches to detect and treat this disease.

Alterations (mutations) that inactivate the von Hippel-Lindau (VHL) tumor suppressor gene are an important discovery reported in up to 85% of RCC cases. Our lab investigates the molecular functions of the VHL tumor suppressor gene using genomics to metabolomics approaches to further improve our knowledge of VHL-inactivated tumors. This research program focuses on microRNAs (miRNAs), which are negative regulators of gene expression. Dysregulation of miRNAs have been implicated in several diseases, including kidney cancer. We previously identified a signature profile of 32 VHL-regulated miRNAs in cells and in a cohort of patients with mutations in the VHL gene. From this, we found an overexpression of miR-2355 associated with a negative regulation of the Sushi Domain-Containing Protein 4 (SUSD4). Here, our work aims to characterize the interaction between miR-2355 and SUSD4 to demonstrate their functional role in clear cell RCC carcinogenesis. Outcomes from this study will provide new insights into VHL-inactivated tumors that could lead to the development of therapeutic targets for kidney cancer.

Dr. Serge Lemay

MUHC Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Kidney Failure

Role of Dok-4-mediated interactions in growth factor signaling and acute kidney injury

In response to acute kidney injury, growth factors produced naturally in the kidney help the damaged tissue to regenerate. In animals with acute kidney injury, systemic administration of excess growth factors further improves tissue repair. Unfortunately, these beneficial effects have not been seen in human clinical trial of growth factors in acute kidney injury. We propose that the beneficial effects of growth factors in acute kidney injury could be increased by inhibiting Dok-4, a protein that normally attenuates the function of several growth factor receptors at multiple steps of their action. We have identified novel protein-protein interactions that help Dok-4 perform its function. In this study, we will examine the molecular events that underlie Dok-4 function in cells and will examine if genetic mutation of Dok-4 in mice can indeed facilitate kidney recovery following acute kidney injury. The goal is to target Dok-4 itself or its key interacting partners to facilitate recover of acute kidney injury.

Dr. Tomoko Takano

MUHC Research Institute

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Glomerulo-nephritis



Role of the Rac1 activator, beta-PIX, in the pathogenesis of proteinuria

Summary:

Leakage of proteins into urine (proteinuria) is a hallmark of many kidney diseases. When you have a lot of proteinuria, you are more likely to progress to kidney failure. This is why it is important to find effective treatments to stop proteinuria. Current treatments are non-specific; they are not always effective while they can cause a lot of undesired side effects. What is blocking the discovery of specific and effective treatments is the fact that we do not know how proteinuria develops. Normal kidneys have a barrier function that allows the passage of water and waste products into the urine while retaining proteins that are essential for body function. In the kidney, cells called podocytes are maintaining this barrier function. When podocytes are injured, this causes proteinuria. The proposed research will define what is happening in podocytes when they are injured. Our recent research identified that in proteinuric kidney diseases, the molecule called Rac1 is activated in podocytes and this leads to podocyte malfunction. When the Rac1 activation is persistent, podocytes are eventually lost in the urine and that leads to kidney failure. Thus, blocking Rac1 is a promising treatment strategy for proteinuria. However, Rac1 is expressed in all the cells in the body and blocking Rac1 itself will likely harm the body. Instead, we have identified a protein, called beta-PIX, which regulates Rac1 activity in podocytes. We will study how beta-PIX works in podocytes and establish if it could be a good therapeutic target. The results of the research will help us understand how proteinuria occurs and allow the development of a better therapeutic approach.

Biography:

Tomoko Takano is a Professor of Medicine at McGill University, staff adult nephrologist at the McGill University Health Centre (MUHC) and senior scientist at the MUHC Research Institute. Dr. Takano received her M.D. from University of Tokyo and completed residency in Internal Medicine and Nephrology at University of Tokyo. Following clinical training in Nephrology, she obtained a Ph.D. in Biochemistry at University of Tokyo and completed post-doctoral training at the Brigham and Women's Hospital in Boston and Royal Victoria Hospital in Montreal. Dr. Takano's research focuses on glomerular podocyte biology and pathogenesis of proteinuria. Clinically, she contributes to the Chronic Kidney Disease Centre and the Glomerulonephritis Clinic. She is a founder and co-Director of the MUHC Kidney Disease Biorepository and the Chair of the Scientific Committee of

the Canadian Society of Nephrology. She has been a member of various scientific committees including the Canadian Institute of Health Research and the Kidney Foundation of Canada.

Dr. Xing-Zhen Chen

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$100,000	Kidney Biology

Regulation of PKD2 function and associated disease via the S4-S5 linker to C-terminus interaction

Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in the PKD1 or PKD2 protein. It affects 0.2% of adults worldwide and has no effective cure. Recent clinical trials targeted to known regulatory pathways but only Tolvaptan was approved as the first ADPKD drug in Canada. However, effectiveness of this drug is marginal, and the US FDA has not approved it because it has an unclear risk-benefit ratio. There is thus a pressing need for alternative routes to therapies for ADPKD. Because these tested drugs all act on regulatory pathways rather than on PKD1 or PKD2 itself, the drug efficacy and specificity are questionable. Our goal is to identify molecules that directly act on PKD2 to compensate for pathogenic PKD2 function.

PKD2 has 6 membrane spans (S1-S6) and an intracellular N- and C-terminus. Our preliminary experiments revealed the interaction of the intracellular S4-S5 linker with the C-terminus (termed L-C interaction) in PKD2 and its close homologue PKD2L1, and that the interaction is required for channel function. We also found that phospholipid PIP2 inhibits the PKD2L1 L-C interaction. We hypothesize that PIP2 binds to the PKD2 linker, which undermines the L-C interaction and thus inhibits PKD2 function.

In this project, using mutagenesis, molecular biology, protein-protein interaction, electrophysiology, and cellular models we will determine: 1) that the intra-molecular L-C interaction in PKD2 is functionally critical and is inhibited by PIP2, and 2) that PKD2 peptides that disrupt the L-C or PIP2-PKD2 interaction can compensate for PKD2 pathogenic mutants function. Further, using zebrafish models that mimic human loss-of-function PKD2 pathogenic mutants, we will identify PKD2 peptide modulators (as candidate drugs) that regulate disease phenotypes through inhibiting the L-C or PIP2-PKD2 binding. This research will give us new insights into how PIP2 regulates the PKD2 L-C binding and channel function and determine how cystic diseases can be treated by PKD2 peptide modulators that directly act on the PIP2/L-C binding axis.

Dr. Ziv Harel

St. Michael's Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2018-2020	$61,344	Screening & Prevention

Assessing kidney disease and its outcomes in pregnancy

Pregnancy is marked by dramatic changes in kidney function, especially by the amount of blood filtered by the kidneys to make urine – called the "glomerular filtration rate" (GFR). GFR can be measured by a woman's serum creatinine (SCr), her estimated glomerular filtration rate (eGFR), or her estimated creatinine clearance (CrCl). However, which of these measurements is most accurate in pregnancy is unknown. Pre-existing or acquired kidney injury in pregnancy can lead to poor outcomes for mother and fetus, including maternal preeclampsia and newborn prematurity. Currently, it is not well-established what changes in SCr, eGFR, and CrCl are associated with such poor outcomes. The first goal of this study is to establish "normal" and "abnormal" metrics for these three markers of kidney function in pregnancy among a large proportion of pregnant women in Ontario. Second, based on this new information we will determine which of the three markers, when abnormal, is most associated with poor outcomes among mother and fetus/newborn. We will use these "big data" metrics to help doctors better: detect kidney injury in early, middle and late pregnancy; enable affected women and their fetuses to have better surveillance; use preventive medications like aspirin; and improve decision-making about the optimal timing of delivery.