The Kidney Foundation of Canada Research Awards

2019 Awardees and Lay Summaries

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2019 SPECIAL RESEARCH PROJECT GRANT: Predictive Biomarkers

Dr. Ana Konvalinka

University Health Network



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2023	$450,000	Predictive Biomarkers

Urine markers of kidney transplant scarring

Kidney scarring is a major problem in clinical nephrology and kidney transplantation. Kidney transplant scarring develops primarily as a result of immune injury. This scarring is progressive and irreversible, but difficult to detect until advanced. Unfortunately, there are currently no effective treatments or clinical markers of early scarring. Improved markers of early scarring would lead to detection of the problem when it could still be treatable. Dr. Konvalinka previously discovered urine proteins that were able to identify patients with kidney scarring in a small group of kidney transplant patients. Her goal is now to develop improved ways of monitoring scar formation in the kidney by measuring urine levels of the proteins in larger groups of patients with kidney transplant. This study thus has the potential to improve the lives of patients with kidney transplant and native kidney disease through better monitoring and more precise treatment of kidney scarring.

ALPORT SYNDROME FOUNDATION GRANT

Dr. Benjamin Humphreys

Washington University (Missouri)

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$125,000	Alport Syndrome

Tubulointerstitial Profiling for Alport Syndrome Target Identification

Dr. Humphreys was awarded $125,000 over two years for his tubulointerstial profiling project. Dr. Humphreys has successfully mapped the complex protein "communication" pathways between the cells of the glomeruli and the cells of the neighboring tubules of the kidneys. His premise is that cell-specific profiling of the cell type that drives scarring of the kidney – the myofibroblast – and the cell that causes its activation – proximal tubule – will reveal pathways for drug intervention to prolong kidney function. The pathways for which drugs already exist for other indications will then be tested to slow progression of the disease in a mouse model of Alport syndrome.

Dr. Ron Korstanje

University of Maine

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$125,000	Alport Syndrome

Pharmaceutical Targeting of Alport Syndrome Modifier Genes

Dr. Korstanje was awarded $125,000 over two years for his project which targets specific modifier genes that might reduce or delay the symptoms of Alport syndrome. There is large variation in the age of onset and severity of Alport syndrome in humans, even among patients with similar mutations. It is widely accepted that modifier genes contribute to this variation. Because modifier genes have been shown to be effective therapeutic targets in other diseases, they have potential to serve similarly in Alport syndrome. Using new mice models, Dr. Korstanje will determine if therapeutic intervention using a drug shown to reduce chronic kidney disease in other animal models could prolong kidney function.

ALLIED HEALTH SCHOLARSHIP

Rani Redoruk

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2020	$5,000	Quality of Life

Frailty and the elderly in Chronic Kidney Disease

Summary:

Frailty is a common condition in the elderly that is associated with decreased functional ability to perform activities of daily life due to reduced muscle function/strength and declining cognition that leads to increased vulnerability to falls, hospitalization, disability and death. Frailty has been closely associated with increased morbidity and mortality in adults with chronic kidney disease (CKD) and diabetes, but the evolution of this disorder has not been well described. Rani Fedoruk is proposing to comprehensively study the risk for frailty and to look at its evolution over time as it relates to Vitamin D status, quality of life, mental health and cognition, body composition and health care use, in a cohort of patients with CKD (stage 1 to 5) and diabetes currently receiving routine Vitamin D supplementation. This group has already been followed by Dr. Mager for the past three years. Rani Fedoruk also proposes to develop a new and innovative home-based rehabilitation program which will include the use of video technology for community dwelling adults with diabetes and CKD to prevent frailty and its progression.

Biography:

Rani Fedoruk is a registered dietitian who works in Chronic Disease Management and Prevention. She has become aware of the critical importance of developing dietary and physical activity interventions to ameliorate frailty in those with Chronic Kidney Disease and Diabetes. She will be conducting research towards that end while at the University of Alberta as she works towards obtaining a master's degree in Nutrition and Metabolism under the supervision of Dr. Diana Mager.

ALLIED HEALTH DOCTORAL FELLOWSHIP

Arrti Anil Bhasin

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$50,000	Quality of Life

The epidemiology of depression and anxiety in patients with CKD

Summary:

Depression and anxiety are the most reported psychological disorders in patients with chronic kidney disease (CKD). Presence of these symptoms impairs quality of life and depression specifically, increases the risk of mortality by about 50% in patients with renal failure. The proportion of CKD patients with depression is 3-4 times higher than that of the general population or individuals with diabetes and heart disease. Though studies of the prevalence of depression and anxiety in advanced CKD patients receiving dialysis exist, how the incidence changes as kidney function evolves and whether patients receive care similar to patients without CKD is uncertain. Ms. Bhasin's project will examine the incidence and prevalence of depression and anxiety across the spectrum of kidney function, and the association between kidney function and mental health care resource use in those that have a diagnosis of anxiety and depression.

Biography:

Ms. Arrti Bhasin is currently pursuing her PhD in Health Research Methodology at McMaster University, under the primary supervision of Dr. Michael Walsh. She is also supervised by Dr. Amber Molnar. Her background includes a Bachelor of Science in Biochemistry from Queen's University, awarded in 2015. She also held a position in the nephrology research team at Sunnybrook Health Sciences Centre, under the supervision of Dr. Michelle Hladunewich. In 2017, Ms. Bhasin was admitted to the Master of Science in the Health Research Methodology program, and in 2019 she directly transferred to the doctoral program. Ms. Bhasin is passionate about improving the quality of life and care of patients with renal dysfunction. Her thesis will explore the mental health and symptom burden of patients with advanced chronic kidney disease.

Lilly Yeung

University of Toronto



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$58,000	Quality of Life

Predicting patient participation and their outcomes during End Stage Kidney Disease treatment decisions

Summary:

About three million Canadians have chronic kidney disease (CKD). When CKD progress to end-stage kidney disease (ESKD), patients decide between different treatment pathways such as dialysis, transplantation, and comprehensive conservative renal care. Deciding between these options is important and challenging for patients and families, as well as healthcare providers. Patient participation in treatment decisions is a priority but despite this, the literature suggests that many patients with CKD do not achieve their preferred level of participation in the treatment decisions. Research on patients' preferred roles and whether these are congruent with their perceived role is scarce. Lily Yeung proposes to address this gap in knowledge by studying what leads to patients engage in decision making and how they want to engage. Do patients' engagement in decision making relate to outcomes like feeling sad or nervous and their wellbeing? Finding out answers to these questions will help healthcare providers understand patients' challenges and develop programs to support them.

Biography:

Ms. Lily Yeung obtained her Honours Bachelor of Science in Integrative Biology from University of Toronto (2010) and her Bachelor of Science in Nursing from Ryerson University (2014). She has worked as a Registered Nurse in the Hemodialysis units of Toronto General Hospital. In 2016, she started her Master of Science in Nursing at the University of Toronto and transferred into the PhD in Nursing Science program in 2017. She is now entering her third year of the program with her research thesis focusing on patient participation in treatment decisions for end-stage renal disease.

ALLIED HEALTH RESEARCH GRANTS

Dr. Mary Smith

Queen's University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$97,710	Quality of Life

Circles towards Indigenous solutions for kidney health: a strength-based approach

Summary:

Indigenous people in Canada have Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD) up to four times more often than that of the general Canadian population. In addition to receiving fewer kidney transplants, Indigenous communities face numerous challenges in managing and treating kidney disease. For some remote and isolated communities, travel costs, time commitments to receive dialysis and lack of home dialysis hinders quality of life. For most, further challenges exist with participation in health care systems delivered through non-Indigenous contexts. Beyond focusing on deficits, Dr. Smith project will build upon strength-based approaches or Indigenous knowledge systems that seeks solutions towards CKD and ESRD. The objectives are to create partnerships with Indigenous peoples, stakeholders and community representatives to identify culturally-safe approaches to 1) foster kidney health and prevention of kidney disease; 2) increase kidney donation and transplantation; 3) promote accessible or home dialysis modalities.

Biography:

Dr. Mary Smith holds a PhD in Nursing from the University of Victoria and is a Primary Health Care Nurse Practitioner in Ontario. Presently, she is also an Assistant Professor at Queen's University in the School of Nursing and is keenly interested in pursuing Indigenous renal and mental health research. This interest has been fueled through her own experiences as a live kidney donor and as a member of a First Nations community. She has also been a volunteer with the Kidney Foundation of Canada and continues to offer peer support within her own community, the Beausoleil First Nation. Dr. Smith has provided presentations throughout Canada, the United States and Australia on her experiences with kidney organ donation. Her recent doctoral research concerning kidney disease within a First Nation community has been accepted by the International Journal of Indigenous

Health for publication during the fall of 2019. Thorough the Kidney Foundation of Canada's Allied Health Grant, Dr. Smith and her research team are inspired towards finding strength-based Indigenous solutions towards kidney health.

Dr. Sheryl Zelenitsky

University of Manitoba



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$99,980	Dialysis

Optimizing Antibiotic Dosing for Patients on Hemodialysis: A High-Risk Population

Summary:

According to the World Health Organization, antibiotic resistance is one of the most serious threats to global human health. Dialysis patients are among the most vulnerable to infectious diseases, along with those with cancer or organ transplants. Dialysis patients are more likely to receive antibiotics and become infected with resistant bacteria. They are also more likely to fail antibiotic therapy, and even die from infectious diseases.

Given the limited pipeline of new anti-infectives, existing antibiotics are the mainstay for treating infectious diseases today and in the future. The importance of selecting the right antibiotic at the right dose for the right duration is well established. In fact, optimal antibiotic dosing has been shown to improve the activity, safety, and even survival in patients with serious infections. Antibiotic dosing is particularly important in special populations such as the elderly, and those with kidney disease, poor immune function, or critical illness.

Despite significant advances for other high-risk populations, research to optimize antibiotic dosing for hemodialysis patients is very limited. Three of the most commonly used antibiotics include cefazolin and ceftazidime that are given by injection, and ciprofloxacin that is taken in tablet form. Despite their significant use in hemodialysis patients, cefazolin dosing is based on a single study, and there are no studies of ceftazidime or ciprofloxacin. As such, "one-dose-fits-all" approaches are often used regardless of the patient's age, gender, body weight, and dialysis.

Dr. Zelenitsky project aims to optimize the dosing of cefazolin, ceftazidime, and ciprofloxacin for hemodialysis patients. For each antibiotic, she will study 20 patients receiving antibiotic therapy for infection.

She will measure blood levels to show how antibiotics are handled differently in hemodialysis patients compared to individuals without kidney disease. She will also use these results to develop new customized dosing recommendations. Her findings will provide valuable information for those involved in the management of hemodialysis patients and will be widely disseminated to benefit as many patients as possible. Overall, her project will improve the treatment of serious, often life-threatening infections in hemodialysis patients.

Biography:

As a pharmacy professor at the University of Manitoba, Dr. Sheryl Zelenitsky integrates teaching, research, and practice in the area of infectious diseases. She received her BScPharm from the University of Manitoba and PharmD from the State University of New York in Buffalo. She teaches in the undergraduate and graduate programs and serves as Chair of Graduate Studies in the College of Pharmacy. Sheryl maintains a pharmacy practice licence and holds a cross-appointment at the St. Boniface Hospital where she sits on the Antimicrobial Stewardship Committee. She also serves on the Board of the Canadian Society of Hospital Pharmacists Foundation, supporting patient-centred pharmacy practice and research across Canada.

Sheryl leads research on antimicrobials, specializing in pharmacometrics and the study of dosing strategies that maximize efficacy while minimizing the risks of adverse effects and antibiotic resistance. She focuses on high-risk populations such as those who are critically ill, immunocompromised, undergoing surgery, or requiring dialysis. Through laboratory, clinical, and simulation studies, Sheryl also emphasizes the translation of research to patient care. She collaborates with clinicians and researchers from various disciplines including those in the St. Boniface Hospital and Manitoba Renal Programs. In this work, she has developed antibiotic dosing protocols for dialysis patients, and has characterized the microbiological trends in peritonitis, bloodstream and exit site infections. Sheryl continues her research to better understand and treat the serious, often life-threatening infections that affect dialysis patients.

BIOMEDICAL RESEARCH GRANTS

Dr. Todd Alexander

University of Alberta

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Renal Failure



Phosphate added to food moves between intestinal cells and is therefore more readily absorbed

The most common cause of death in persons with kidney failure is cardiovascular disease. In persons with chronic kidney disease (CKD) and end stage renal disease (ESRD), blood phosphate levels directly correlate with cardiovascular diseases including heart attack and stroke. This is because phosphate can bind calcium in the blood forming calcifications in blood vessels and the subsequent sequela; heart attack and stroke. It has been appreciated that inorganic phosphorus (such as is added to food to preserve it) is more readily absorbed by the intestine than organic phosphorus, which exists in protein. Unfortunately, we do not completely understand, at a molecular level, why inorganic phosphate (a common food preservative) is better absorbed into the blood than organic phosphorus, such as occurs in protein.

Importantly, if we can explain this it will justify patients with chronic kidney disease and end-stage renal disease (i.e. patients on dialysis) eating a low inorganic phosphorus diet. This would also enable people with kidney disease to eat more foods with organic phosphorus such as is in protein. This could significantly improve well being and nutrition. Dr. Alexander's team predict; do to the electrophysiological properties of the types of phosphorus in the diet (i.e. inorganic vs organic) that inorganic phosphorus moves between the cells of the intestine into blood uninhibited, while organic phosphorus moves through the cell, a more difficult and energy consuming process. To test this hypothesis, his team will feed rodents different types of phosphorus containing diets in the presence of either a drug that inhibits the movement of phosphorus through the intestinal cells or use a model lacking a protein that blocks the movement of phosphate between cells. They predict that the phosphorus absorption inhibitors through the cell pathway will only inhibit phosphate absorption in animals fed an organic phosphorus diet while the converse will be true, i.e. animals lacking a gene blocking phosphorus

absorption between the cells will only have altered phosphate absorption when fed an inorganic phosphorus diet. Ultimately, these studies will provide strong rationale for a diet low in inorganic not organic phosphorus for patients with CKD/ESRD.

Dr. Rahul Chanchlani

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Renal Failure

Long-term kidney and heart outcomes after acute kidney injury among newborns and children

Acute kidney injury (AKI) is sudden damage to the kidneys that causes them to not work properly. It occurs in one in five and one in three hospitalized adults and children, respectively. If the kidneys shut down completely, this may require temporary support in form of dialysis until the kidney function recovers. Occasionally, AKI causes loss of kidney function or chronic kidney disease (CKD), hypertension, and death. Recently, in adults, AKI has been shown to cause a 9-fold risk of CKD and a 2-fold risk of death compared to those individuals without AKI. However, there is a limited understanding of the risk of these complications after AKI among newborns and children. Most of the studies in this population done so far have been of variable quality, with short follow-up and small sample size. There is also a lack of information on how much the health care costs are increased after AKI and whether rates of AKI have increased among newborns and children in Ontario over the last 20 years.

Dr. Chanchlani will determine how often newborns and children with AKI develop CKD and hypertension compared to those without AKI in Ontario. He will compare the risk of permanent kidney damage (end-stage kidney disease) and death in newborns and children with AKI compared to those without AKI. He will also determine the increased costs of healthcare in 1, 5, and 10 years after the development of AKI and whether or not AKI rates have increased in Ontario over the last 20 years among newborns and children. Currently, doctors cannot provide information on the future risk of kidney and heart problems to the families, and there is no follow-up policy on such patients. The study results will help identify which newborns and children are more likely to develop CKD and hypertension after AKI so that they can be seen by doctors regularly to improve their kidney and heart health.

Dr. Jeffrey Dickhout

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

Preventing Kidney Disease by Preventing Protein Misfolding

The overall goal of Dr. Dickhout's project is to determine how the response of kidney cells to problems with protein production and folding can lead to the death of these cells and to find a way to counteract this process. Kidney cells die when the kidney does not receive enough blood; this is called renal ischemia. Cell death can also occur when the kidney is exposed to harmful chemicals. Both of these processes lead to acute kidney injury and prevent the proteins that form the kidney cells from folding properly. This type of injury involves acute tubular necrosis (death of cells inside the kidney), which contributes to acute kidney injury and prevents the kidney from filtering blood effectively. Acute kidney injury is a cause of kidney failure and can be life-threatening because it can also lead to heart or lung failure. This project will allow researchers to discover whether correcting problems with protein production in the cells that make up the kidney will help people with kidney damage.

Dr. Amit Garg

Lawson Health Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Renal Failure

Does a strategy to avoid low blood pressure during surgery protect the kidneys?

During surgery, a patient's blood pressure can sometimes drop very low. This can starve the body's vital organs of blood and oxygen. POISE-3, a randomized controlled trial, is testing a new strategy to keep the blood pressure from falling too low during surgery. POISE-3 started in June 2018 and will determine if patients who receive the new strategy have fewer heart attacks than those who receive a usual-care strategy.

Dr. Garg want to conduct a sub-study of POISE-3 to see if this strategy can also protect the kidneys during surgery. This is an important question: each year, 20 million patients who have surgery have their kidneys injured and 20,000 develop kidney failure. Researchers are trying to find better ways to protect the kidneys during surgery.

To conduct this substudy, additional kidney measurements are needed in the POISE-3 trial. The leaders of the POISE-3 trial have agreed to add these measurements. At the end of the trial, the team will determine if the risk of acute kidney injury is lower in patients who receive the new strategy compared to patients in the control group who receive a usual-care strategy. By adding kidney measurements to this large trial, the team can efficiently examine whether a new strategy to avoid low blood pressure during surgery protects the kidneys. They will also determine if this strategy works well in patients who have kidney disease before surgery.

Dr. Richard Hebert

University of Ottawa



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Hypertension

The role of prostaglandin E2 and their receptor subtypes on kidney disease

Hypertension and diabetes are leading causes of chronic kidney disease and both have reached epidemic status worldwide. Despite the many efforts aimed at understanding the pathogenesis of hypertensive kidney disease, to this day the therapeutic approaches are inadequate. Novel targets are needed to effectively manage disease outcomes.

Prostaglandin-E2 (PGE2) is a hormone-like substance that is released by blood vessel walls in response to infection or inflammation. In the kidney, it regulates blood flow in the glomerulus (kidney component responsible for filtration), renin (enzyme that controls blood pressure) secretion, and tubular transport (process by which solutes and water are removed from the tubular fluid and transported into the blood), via four PGE2-EP receptor subtypes (EP1-4). In general, two receptor subtypes, namely EP1 and EP3 promote disease processes, but the receptor subtypes EP2 and EP4 are beneficial. Dr. Hebert showed that the receptor subtype EP1 or EP3 deletion prevents diabetic hyperfiltration, kidney growth, and proteinuria (presence of protein in urine) in diabetic mice. The EP3 receptor deletion attenuates the excessive or an abnormally large production of urine by improving urine concentrating function. Whether protective effects of this receptor subtype EP1 or EP3 deletion apply to hypertensive kidney disease is unknown.

Dr. Herbert's lab has produced a mice model to be able to study the different role of these receptors in the hypertensive kidney. His project will clarify the importance of EP3 receptor in the absence of EP1 receptor, in preventing water and sodium disturbances in the mice model.

Dr. Nina Jones

University of Guelph



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

Hold on tight! - A molecular approach to understand podocyte adhesion

Chronic kidney disease (CKD) is a major public health issue that continues to rise, and ~3 million Canadians are already living with this devastating illness. Very few treatments are available for advanced CKD, and these approaches are associated with considerable mortality and healthcare costs. Despite the burden of disease, the molecular and cellular basis of CKD is poorly understood, limiting opportunities for development of new therapies.

Fundamental discoveries over the past decade have highlighted the key role of the podocyte in the pathogenesis and progression of CKD. Podocytes are highly specialized cells of the glomerulus (kidney component responsible for blood filtration) that play an active role in preventing plasma proteins from entering the urinary filtrate by providing a barrier comprising filtration slits between foot processes. Their ability to remain anchored to the basement membrane and maintain filtration despite fluctuating blood flow forces is closely tied to their unique morphology. Podocytes extend a series of foot processes that respond to their environment and alter their shape via a specialized cell junction known as the slit diaphragm. One of the earliest features of kidney disease is remodeling of podocyte foot processes, and though this is reversible, prolonged dysfunction culminates in podocyte detachment.

Dr. Nina Jones' lab provided some of the first evidence that signaling from the slit diaphragm directly regulates foot process morphology, and they have since validated the importance of such signaling in podocyte injury and repair. For this project, her team will use cutting-edge microscopy techniques, mutant mouse models and complementary cell lines to explore the role of specific molecules in podocytes cell adhesion dynamics. The long-term objective is to translate knowledge gained here into rational design of more targeted therapeutics.

Dr. Andras Kapus

St. Michael's Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

The role of injured kidney tubules in chronic kidney scarring

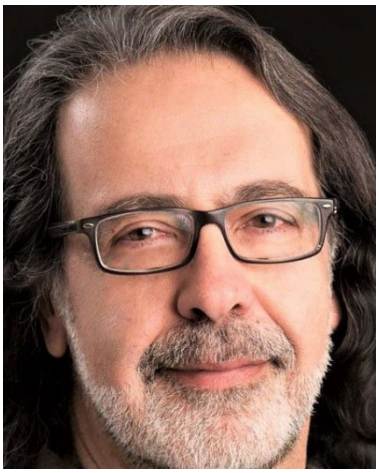
Chronic kidney disease (CKD) is a major health problem, which is often called an “epidemic” as it affects 12% of the population. In Canada 2.6 million people suffer from or are at risk for CKD, which most often develops as a consequence of common conditions such as diabetes, hypertension, obstruction of free urine flow and polycystic kidney disease (PKD), the most common inherited disorder. Unfortunately, we have no cure for CKD, which usually progresses toward chronic kidney scarring (called fibrosis). This process destroys the kidney architecture and function, necessitating dialysis or transplantation as the only means to prolong life.

These “solutions” are associated with profound human suffering, are extremely expensive (e.g. dialysis costs more than $80.000/patient/year and there are >23,000 dialyzed patients in Canada) and require lifelong medication, putting a huge burden on the patients and society alike. Therefore, there is a dire need to understand the cellular and molecular basis of kidney fibrosis, since without this knowledge we cannot hope to reverse the disease process and restore function.

Recent research from Dr. Kapus’s lab has identified critical proteins that, upon injury, reprogram gene expression in the main fluid-handling cells of the kidney, the tubular epithelium. However, we do not understand the molecular events underlying this reprogramming process, which ultimately leads to disease. The researchers hypothesize that two such proteins (so called transcription factors) play essential role in the production of a connective tissue molecule that propagates scarring. Moreover, they surmise that the same proteins are responsible for inducing fibrosis not only in acquired kidney injury, but also in genetic defects, namely PKD. They propose a mechanism whereby the underlying gene error in the kidney tubules turns on the implicated transcription factors and induces chronic scarring. They will use a variety of cellular and molecular techniques, animal models as well as human PKD specimens to explore the critical events leading to excessive scarring. They will also use specific drugs and test their capacity to inhibit these deleterious processes. Ultimately, these studies will help the development of new treatments that halt or lessen fibrosis in both acquired and inherited kidney diseases.

Dr. Andrew Karaplis

Jewish General Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Renal Failure

Preventing polycystic kidney disease

Polycystic kidney disease (PKD) is a genetic kidney disorder. It causes fluid-filled cysts to form in the kidneys, thereby changing the shape of the kidney and making them much larger. PKD decreases kidney function and eventually causes kidney failure, requiring dialysis or kidney transplantation. It is the fourth leading cause of kidney failure. Presently, in some forms of the disease, a drug called tolvaptan has been shown to have modest beneficial effects, but it causes a number of very bothersome (frequent urination, increased thirst) and at times dangerous side effects that are difficult to manage. Dr. Karaplis will use as a model of the human condition, a mouse that develops PKD. Using kidney tissue from these mice, he will explore the cause of this rapid growth in cell number and the inability of the kidney to deal with this problem, eventually causing kidney cysts. Finally, he will feed these mice chow containing either tolvaptan or TUDCA, a product that eliminates the undesirable consequences of rapid cell growth with minimal side effects, each alone or in combination, and then determine their effects on kidney size and function. He anticipates that TUDCA will provide a beneficial effect on these measures and offer a novel potential therapeutic alternative to tolvaptan for the treatment of patients with PKD.

Dr. Andrew Makrigiannis

Dalhousie University

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

Regulation of immune responses in the kidney

Kidneys are the filtration units of the body where blood is filtered to remove toxic wastes, which are then expelled from the body in the form of urine. Diseases affecting kidney function are associated with poor quality of life, increased risk of cardiovascular disease and premature mortality. Understanding the mechanisms causing chronic kidney disease, or contributing to the progression of the disease, is necessary for the design and development of effective therapies.

Immune reactions are often associated with the cause and progression of kidney diseases. Mechanisms are in place to regulate the type and vigor of immune reactions in the body. Failure of this regulation lead to unnecessary immune reactions causing tissue damage and autoimmunity. Immune cell functions are controlled by cell surface proteins called receptors. They bind to other proteins in different tissues as a mean of communication between cells and a way to determine the health of the tissue. Dr. Makrigiannis will study an immune receptor using a mice model that develop a kidney disease characterized by inflammation and tissue damage. The main goal of his project is to identify which immune cells bear a specific receptor and how its interaction with other proteins in the kidney is necessary to maintain health in the organ.

Dr. Itsvan Mucsi

Toronto General Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$99,670	Quality of Life

A study of patient-reported distress measures

Chronic kidney disease is a life-changing illness. People living with chronic kidney disease have high rates of distress, such as anxiety, depression, social or physical difficulties, pain or sleep problems. When combined, these emotional and physical difficulties can lead to poor health outcomes for patients. For example, patients may fail to take their medication, end up in hospitals more often, have higher rates of other diseases or even die sooner. Their overall quality of life can suffer. However, the current treatment for kidney disease does not include methods for screening or treating distress symptoms. Thus, distress experienced by patients often goes unrecognized and undertreated.

Some doctors who treat patients with chronic illnesses use tools called Patient Reported Outcome Measures to detect distress and physical symptoms. These tools are usually computer- or paper-based questionnaires. They do better in recognizing distress than routine assessments by healthcare providers. Using Patient Reported Outcome Measures can improve doctor-patient communication and give patients a greater say in their care. It will also enhance their satisfaction with their treatment and can also help improve patients' survival. Thus, the use of Patient Reported Outcome Measures in kidney care can improve patient care and should be of high priority. To do so, we need tools that are comprehensive, highly accurate, and not too long.

To generate such tools, the National Institutes of Health developed a system called the Patient-Reported Outcomes Measurement Information System – Computer Adaptive Testing (PROMIS CAT). Its questions are designed to detect distress and symptoms both in healthy individuals and in patients with chronic diseases.

Based on the answer to the previous question the computer will determine what the next best question will be for that particular participant. Dr. Mucsi's project will compare the PROMIS CATs to current questionnaires and investigate if they are precise enough to help clinicians detect distress. He will develop a toolkit to guide clinicians in using the PROMIS CAT in clinics and test if a subsequent study is feasible and acceptable for patients and healthcare professionals. He predicts that PROMIS CATs will become a useful tool for kidney care teams, helping them provide more effective, patient-centred care.

Dr. Daniel Muruve

University of Calgary



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

How the Immune System of the Kidney Contributes to Disease

The kidney contains its own internal immune system. This immune system gets activated when the kidney gets sick or is exposed to toxins, medications and other harmful substances. Activation of the kidney's immune system results in kidney inflammation which can leave to kidney failure. Dr. Muruve's project will examine how the kidney immune system is activated in response to harmful medications and how it contributes to kidney disease. The hope is by understanding these new immune pathways, we will one day develop new drugs or therapies to better treat kidney inflammation and help patients with kidney diseases.

Dr. Frances Plane

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

How blood flow to different parts of the kidney is coordinated

The vascular system brings blood to the tissues, where nutrients are exchanged for wastes, and returns blood to the heart. We talk about the arterial “tree” because of structural similarities to actual trees. A single trunk, the aorta, leaves the heart and progressively gives off major arteries (branches) to supply organs such as brain, liver, kidneys, etc. Within each organ the artery branches progressively into smaller and smaller arteries, eventually arriving at about 1 billion capillaries, the tiny vessels where exchange of nutrients and waste occurs. Blood pressure generated by the heart pushes blood flow and blood flow is controlled by the smallest arteries, just upstream from the capillaries. These arteries are muscular and contract (just like closing a tap) when blood pressure increases. Like a real tree, there is random variation in the structure of arterial branches, and this translates into varied blood flow in each branch. Every organ faces what can be called the “3 bears” problem – how to deliver, not too much, not too little, but “just right” blood flow to all capillaries.

High blood pressure (hypertension) causes damage to the tiny capillaries. The kidney is protected against hypertension by stabilization of the blood flows when blood pressure rises (it "autoregulates" its blood flow). Previous work showed that this autoregulation is a network process so that all the branches receive "just right" blood flow. But, just like the plumbing in a house, not all the pipes are the same length and some mechanism is needed to make sure that all the taps get the same flow at the same pressure. That means that the different branches must talk to each other. This communication occurs via transmission of electrical signals that instruct cells in the artery walls to contract. These types of signals are unique to the kidney and the underlying mechanism is unknown. Previous studies demonstrated the importance of this electrical communication pathway by showing that blocking it impairs autoregulation and "just right" flow in the whole kidney.

Dr. Planes’s project objective is to investigate the basis for this kidney-specific electrical signalling pathway that is crucial to controlling blood flow in the kidney and protecting it from changes in blood pressure. She will use a genetically modified rat that lacks a specific protein, connexin40. This breaks the communication pathway along the vessels. Using this model, she expects to show in more detail how the kidney blood flow is regulated and how kidney damage occurs when it fails.

Dr. Pietro Ravani

University of Calgary



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Dialysis

Individualizing the method of connecting people with kidney failure to the hemodialysis machine

Hemodialysis requires a reliable method of connecting the patient to the blood-purification machine, called vascular access. The two most common forms of vascular access are catheters and fistulas. A catheter is a plastic tube inserted into a vein in the neck; a fistula is a vein surgically connected to an artery in the arm that is accessed by needles. Many expert committees consider fistulas the preferred form of vascular access and actively promote them. However, these recommendations are based on studies that may have overestimated the benefits of fistulas and underestimated the potential risks associated with procedures required to achieve and maintain fistula patency. We do not have sufficient data to provide patients with enough information to allow them to make an informed decision about pursuing a fistula creation attempt or using a hemodialysis catheter without attempting a fistula. We cannot offer decision support to promote shared decision-making because we do not know patient, caregiver and healthcare provider decision needs.

Dr. Ravani will study people who start hemodialysis with a catheter in six large renal programs in Canada. He will follow participants from the start of hemodialysis to determine the benefits and harms associated with attempting fistula creation, and whether they vary with sex, age or presence of disease conditions. He will also assess decision needs of patients and caregivers, and healthcare providers. This project will leverage multicenter, high-quality data describing vascular access procedures and our expertise in this area of research. It will provide important data on potential benefits and possible harms of attempting or avoiding fistulas and will identify the attributes of hemodialysis access-related decisions that are important to patients and caregivers, and healthcare providers in order to inform the design of a tool to support decision-making about the vascular access for hemodialysis.

Dr. Darren Richard

Laval University

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Renal Failure



Roxadustat, a drug to treat anemia in chronic kidney disease, may cause arterial calcification

Patients with chronic kidney failure often develop heart problems and are prone to stroke. This is caused by blood vessel stiffening in these patients, often the result of calcium deposition in blood vessels. Unfortunately, little is known about mechanisms involved in the development and progression of calcium deposition and blood vessel calcification. Our research has identified an essential factor involved in responses to low oxygen (hypoxia), known as hypoxia-inducible factor-1 (HIF-1), as an important component for blood vessel calcification. Our research also indicates that HIF-1 plays a central role in calcification by translating different signals associated with cell stress. Roxadustat, an experimental drug used to treat anemia in patients with kidney failure is a potent activator of HIF-1. Therefore, it may cause important side effects on patients by causing arterial calcification. The goal of Dr. Richard's proposal is to gain in-depth insights into this unexplored role of HIF-1 in kidney disease and vascular calcification and to determine the effect of Roxadustat in this context. Researchers believe that understanding this important process will identify an important, and potentially detrimental, consequence of Roxadustat treatment, and will support the development of safer and more effective treatments to reduce the burden of cardiovascular disease in this population.

Dr. Katalin Szaszi

St. Miachael's Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Kidney Biology

Claudin-2 in kidney disease

Chronic kidney disease is a significant problem that poses a large burden on individuals and society. Kidney disease is associated with very common conditions such as diabetes and high blood pressure. We currently do not have a treatment and more research is essential to understand the fundamental processes that contribute to development of kidney disease.

The kidney tubules are made of specialized cells called epithelial cells, which create and maintain a barrier and allow only highly regulated exchange of materials through the layer. These cells are vital for kidney function, but their changes also contribute to disease.

Dr. Szaszi discovered that a protein residing at the points were two tubular cells come together, named claudin-2, is a suppressor of kidney damage. Further, experimental data show that in animal models of kidney disease this protein is lost. When researchers mimicked experimentally loss of claudin-2, they found that tubular cells had augmented production of disease-causing mediators, suggesting that claudin-2 is a regulator of this important process.

Therefore, in this project, they will define how claudin-2 is regulated and assess interventions to prevent its loss. Using cultured tubular cells and animal models, Dr. Szaszi will use biochemical techniques to determine abundance of claudin-2, and microscopy to assess its localization within cells. She will interfere using pharmacological and genetic methods with candidate molecular pathways to interrogate their role in claudin-2 reduction. A key candidate is an enzyme that is known to be a central energy sensor molecule in cells, termed AMPK, that is implicated in many diseases including diabetes. Using the drug metformin, an inhibitor of this enzyme, in a kidney disease model, she will assess whether it can prevent claudin-2 loss. Overall, her project will uncover new mechanisms underlying molecular events during kidney disease and will start assessing approaches that could be beneficial by slowing the disease process.

Dr. Tomoko Takano

MUHC Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Glomerulo-nephritis

How can we treat children with nephrotic syndrome without using steroids?

Nephrotic syndrome is the most common kidney disease among children. Affected children have massive leakage of protein into the urine and, as a consequence, develop body swelling (edema). Most children respond to treatment with steroids, however many of them require repeated courses for frequent relapses of the disease. Long-term use of steroids causes many side effects including obesity, growth retardation, hypertension, cataracts, poor bone health, and cosmetic effects. Minimizing the use of steroids has been identified as the number one priority of the patients and families.

A non-steroid drug, rituximab, is now known to be effective in the treatment of nephrotic syndrome, but it is entirely unclear how it works. In this study, we will investigate the mechanisms by which rituximab alleviates the symptoms associated with nephrotic syndrome, allowing patients to go into remission. Blood collected from affected patients when their disease is active, and after successfully treated with steroid or rituximab, will be analyzed using the state-of-the-art technique called immunophenotyping. One of the investigators in the research team, Dr. Piccirillo, is the leading researcher of this technology in Canada. Moreover, Dr. Takano will use another cutting-edge technology called single cell RNA sequencing, which will tell which genes are active or inactive in individual blood cells from patients. The analyses will allow identification of the blood cells that are active and causing the disease and become inactive after treatment. She will also find out if steroids and rituximab have different effects on blood cells.

With this approach, researchers are likely to uncover how this common pediatric disease occurs - it has been a mystery for over five decades. Furthermore, understanding how rituximab works in nephrotic syndrome will enable the identification of patients who are most likely to respond to rituximab thus avoiding steroids. Finally, if the culprit cells are known, new drugs specifically targeting these cells can be developed. The hope is that steroids will not be used at all in the future.

Dr. Bradley Urquhart

University of Western Ontario



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Predictive Biomarkers

Finding better ways to detect and monitor kidney disease

Kidney disease is a progressive disease that is characterized by decreasing function of the kidney over time. Currently, kidney disease is diagnosed and tracked by a single blood test. In this blood test, the amount of molecule called creatinine is measured in the lab and the result of this test informs the treating doctor whether the patient has kidney disease and how severe the kidney disease is. The majority of experts in the field consider this test inadequate. The reason the test is inadequate is because kidney function has to decline by a large amount before the test is able to identify patients with kidney disease. This means many people actually have kidney disease, but the test is unable to diagnose it. In addition, the test for kidney disease is inadequate because it can be influenced by the body composition of the patient. For example, a very muscular patient with perfectly functioning kidneys may be identified falsely as having kidney disease using the current blood test. A better test for kidney disease would be able to identify patients with kidney disease earlier, more accurately and allow better tracking of their progression from mild decreases in kidney function to severe kidney failure.

Dr. Urquhart will use a novel technology called metabolomics to find better tests for kidney disease. Metabolomics seeks to measure all metabolites in a sample (example: blood or urine sample). Researchers then use sophisticated data analysis techniques to determine which metabolites differ between people with normal kidney function compared to those with various stages of kidney disease. This allows the discovery of new patterns in metabolites that can be used to better diagnose kidney disease and track its progression. Dr. Urquhart will apply those methods to measure metabolite levels in two distinct, very large sets of blood samples collected from kidney disease patients across Ontario and Canada. One of these collections of blood samples has over 2500 kidney disease patients and the other will have samples from 500 patients.

Dr. Urquhart expects that his metabolomics methods will identify better tests for kidney disease. This would allow earlier identification of kidney disease, which would help doctors to intervene, and help slow the rate at which patients lose their kidneys and prevent the onset of kidney failure. Researchers anticipate that development of better tests would greatly improve the quality of life for patients with kidney disease and decrease the number of patients that progress to kidney failure.

Dr. Michele Zappitelli

Hospital for Sick Children



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Cancer

Long-term kidney and blood pressure problems in children treated for cancer

About 1400 Canadian children per year are treated for cancer. Child cancer survival has increased in the last 30 years; about 30,000 Canadians are childhood cancer survivors today. Higher cancer survival in children has not come without a cost. There is now a large population of people living with many long-term organ complications due to the cancer treatments they received to save their lives. Children treated for cancer commonly have kidney complications later in life, also called chronic kidney disease. They also seem to be at higher risk than expected for having high blood pressure (or hypertension). Chronic kidney disease and hypertension are very important risk factors for developing heart disease, reduced quality of life and death. However, especially if caught early, chronic kidney disease and hypertension are treatable.

Major pieces of information are missing, which are preventing the development of clear recommendations (to hospitals, doctors and families) on how to protect childhood cancer survivors from and treat long-term kidney and blood pressure problems: 1) It is not clear how often childhood cancer survivors develop chronic kidney disease and hypertension; 2) Specific factors (like treatments, events that happen during cancer treatment) that cause chronic kidney disease and hypertension are unclear; and 3) Whether treating chronic kidney disease and hypertension in childhood cancer survivors might improve overall health, well-being and heart health in the long-term, is unclear.

Dr. Zappitelli will use information available at an Ontario health data organization which contains health, diagnosis and treatment information from across the province, to achieve the following goals: 1) determine how often children treated for cancer since 1993 in Ontario develop chronic kidney disease and hypertension and find risk factors that predict who develops chronic kidney disease and hypertension after cancer treatment. 2) seek to know if the childhood cancer survivors that do develop chronic kidney disease or hypertension, have higher risk for dying and for being hospitalized later in life. In the next 2 years, he will have the information needed to recommend/improve how childhood cancer survivors are followed for kidney and blood pressure problems, to hopefully decrease kidney and heart long-term health problems and improve long-term health and quality of life. His team will be able to achieve these goals, because they have included kidney, cancer and research specialists, pediatricians (who care for these patients) and parents of children treated for cancer.

Dr. Shao-Ling Zhang

CHUM Research Center



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$100,000	Diabetes

Hedgehog Interacting Protein Expression in Diabetic Kidney Disease

Diabetes is characterized by high blood sugar and is often associated with several complications as a result of poor blood sugar control, the most serious complications including heart disease and kidney failure. People with kidney failure may require treatment by artificial kidney (dialysis) or by kidney transplant to survive. Despite the use of currently available medications to lower blood sugar and blood pressure, kidney function continues to decline in most people with diabetic kidney disease (also called diabetic nephropathy or DN). New alternative treatments are therefore urgently needed.

A molecule called hedgehog interacting protein (Hhip) is a key regulatory component of Hedgehog signalling, which controls organ development during gestation (in the womb) and optimizes cell functions in adults. Dr. Zhang recent work led to the discovery that high blood sugar levels turn on the Hhip expression in diabetic kidney, causing kidney damage. In this project, she will study how Hhip gene in responding to elevated glucose levels could target one specific type of kidney cells called podocyte since podocyte loss and/or injury may directly impact kidney function. She will use podocyte grown in petri dishes and in diabetic mouse models to understand Hhip pivotal roles in the pathogenesis of DN, ultimately, providing new treatment strategies to prevent kidney damage in patients with diabetes.

CDTRP KFOC RESEARCH INNOVATION GRANT

Dr. Bethany Foster

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$30,000	Transplantation

Associations between Sex Hormone Levels and Immune Profiles among Kidney Transplant Recipients

Organ transplant recipients must take medications to suppress their immune systems for life. The way these immune suppressing medications are used varies little from patient to patient; regardless of sex or age, the approach is about the same. However, there are important sex and age differences in the immune system. Dr. Foster have previously showed substantial sex differences in graft failure risk which depended on age: girls and young women show higher graft failure rates than boys and young men, whereas graft failure rates do not differ between women of post-menopausal age and men of the same age. This age dependent pattern of sex differences suggests that sex hormones may have an influence on the immune response. Dr. Foster's project will gather preliminary data regarding the associations between sex hormone levels and the immune profile among 41 kidney transplant recipients treated with immune suppressing medications and 40 healthy people. She will use advanced methods to identify different types of immune cells, their relative numbers, and their responses to stimulating agents, and ultrasensitive methods to measure blood sex hormone levels. She will then determine whether these measures of immune function are associated with sex hormone levels.

This study may provide clues as to the biological reasons for higher graft failure rates in women compared with men. It will lead to future larger studies to develop personalized strategies, with the goal of developing personalized, age- and sex-specific immunosuppression strategies, and recommendations regarding the use of oral contraceptives and hormone replacement therapy, ultimately improving graft outcomes.

Dr. Marie-Chantal Fort n & Dr. Tania Jaudis-Ferreira

McGill University and Université de Montréal

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2019-2021	$30,000	Transplantation



Acceptability and feasibility of the kidney transplant physical activity and social club (Keep ACTIVe Club)

Kidney transplant recipients face numerous challenges after transplantation. One of the challenges is the high frequency of diabetes, hypertension and heart disease. In addition, the majority of kidney transplant recipients face several barriers to engaging in and maintaining a good level of physical activity even years post-transplant which can increase the risk of mortality and developing poor organ function. They also experience feelings of isolation and loneliness after transplantation. The goal of this study is to develop the Kidney Transplant Physical Activity and Social Club" (KEeP ACTIVe Club) to offer support for kidney transplant recipients to improve their levels of physical activity, knowledge in risk factors for heart and circulatory diseases and break the isolation and loneliness after transplantation. Specifically, we aim to determine whether the KEeP ACTIVe Club is acceptable to kidney transplant recipients and feasible to be delivered and if participation in this club can increase levels of physical activity, knowledge in risk factors for heart and circulatory diseases and decrease socialization restrictions among kidney transplant recipients. We will offer participation in the KEeP ACTIVe Club for six months which consists of a face-to-face educational session about benefits of physical activity and risk factors for heart and circulatory diseases, online social networking (a Facebook closed group), peer and professional mentorship, and a menu of options for physical activities that patients can choose from based on their personal preferences. At the end of the study we will make recommendations for future versions of the KEeP ACTIVe Club.