The Kidney Foundation of Canada Research Awards

2020 Awardees and Lay Summaries

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ALLIED HEALTH SCHOLARSHIP

Kelly Picard

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2020	$5,000	Nutrition

Nutrition in Chronic Kidney disease patients

Do you eat bananas? Stop! Eat doughnuts instead. Sounds crazy doesn't it? Well, if you are living with kidney disease, your health care provider may inadvertently be sending you this message. That is because people with kidney disease often need low potassium diets. We know how much potassium is in fruits and vegetables. What we don't know is how much potassium is in processed foods.

Because of this knowledge gap, patients are told to avoid fruits and vegetables, but of course, they have to eat something. When processed foods are not mentioned on the teaching materials or by health care providers, these foods seem like good alternatives. Unfortunately, over 56 different potassium-based food additives are approved for use in Canada and their use is expected to increase.

Using grocery store receipts collected from patients with CKD, Kelly Picard's team is going to complete a large-scale survey of foods sold in Alberta. The foods will be examined for the presence of additives and the amount of potassium additives whenever it is listed on the label. Using the information gathered from the grocery stores, two similar menus will be developed – one that uses unprocessed foods and one that uses processed foods. The team will analyze both menus for minerals important in kidney disease, including sodium, potassium and phosphorus to see what the difference is for the mineral content between these two menus.

Providing patients and health care professionals with information about the potassium content in processed food will help ensure patients have access to the best information possible about what foods to avoid.

ALLIED HEALTH DOCTORAL FELLOWSHIP

Penny Jarrin

The University of Western Ontario



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$58,000	Dialysis

Improving hemodialysis tolerability through innovation

Although dialysis is a needed treatment, we know that there are risks that come with this therapy. The long-term effects of kidney disease put patients at risk for heart disease. The treatment of dialysis makes this and other risks worse. This is very concerning for the people (doctors and nurses) that care for those on dialysis. Because of this harm patients don't feel well, their quality of life is low, they are hospitalized more often and do not recover.

Until recently, the bad things that dialysis caused were either not understood or not known. We know now that the longer patients are on dialysis the more damage is done to organs including the heart, brain, liver and gut. This is because of low amounts of blood flowing to the body during dialysis. Penny Jarrin's research project proposes to make dialysis better by finding ways to decrease risks before they happen and to change the care for dialysis patients. Her goal is to make patients feel safe, improve how they feel and live longer.

ALLIED HEALTH KIDNEY RESEARCH GRANTS

Dr. Samantha Anthony

Hospital for Sick Children



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Transplantation

Improving health equity: Access to living donor kidney transplantation

Ethnocultural inequities in access to living donor kidney transplantation (LDKT) have been described both globally and within the Canadian context. Chinese Canadians are the largest visible minority population in Canada with an increased risk of end-stage kidney disease (ESKD) but have markedly reduced access to LDKT compared to Caucasians. However, potentially modifiable barriers to LDKT are largely unknown in this population. This major knowledge gap prevents the development of an effective, culturally-tailored strategy to increase LDKT in this population. Therefore, Dr. Anthony aim to conduct the first study of ethnocultural perceptions and barriers to LDKT among Chinese Canadians, as well as education needs and strategies to facilitate LDKT within this community. The overarching objective of her research is to promote equitable access to LDKT for Chinese Canadians. Ultimately, this health promotion program will contribute to excellence in kidney health, optimal quality of life and reduce the burden of kidney disease for this population.

KIDNEY HEALTH RESEARCH GRANTS

Dr. Mohsen Agharazii

Laval University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Hypertension

Accelerated CKD-related vascular calcification: side effects of diuretics drugs

Patients with kidney failure develop heart failure and stroke as a result of blood vessel stiffening which is caused by the deposition of calcium in blood vessels. This is referred to as calcification of blood vessels or vascular calcification. Dr. Agharazii's group of research aims to identify why patients with kidney disease develop calcification of blood vessels and propose ways to prevent vascular calcification and improve the quality of life of patients with kidney disease. During their previous studies, they discovered that one of the medications that is frequently used to reduce fluid retention (a water pill or a diuretic), seems to exacerbate vascular calcification. This is very important as most patients with kidney disease take these drugs and this potential side effect had never been described before. To better understand why this happens, they will use an animal model of kidney disease and vascular calcification. They will examine if the negative effects of these water pills are related to their interaction with a hormone called aldosterone. Indeed, their preliminary results indicate that aldosterone increases with water pills. Using drugs to block aldosterone, they want to examine if they can counteract these negative effects and potentially use these drugs for the treatment of patients.

Dr. Dylan Burger

Ottawa Hospital Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$118,012	Dialysis

Sex Differences in Platelet Microparticles in Chronic Kidney Disease patients on dialysis

Women are at reduced risk of death from a heart attack or stroke compared with men. However, when women are on hemodialysis, they lose this protection. Why this protection disappears on hemodialysis is unclear. Recently Dr. Burger's lab discovered that women undergoing hemodialysis have a much higher level of particles released from blood cells involved in clot formation than men. These particles, known as microparticles, not only signal activation of these clot forming cells (termed platelets), but they also directly damage blood vessels. The purpose of this study is to determine if these platelet microparticles are higher in women because of chronic kidney disease or specifically due to hemodialysis. They will also test whether microparticles from women cause more damage to the blood vessels than those from men on dialysis. They predict that platelet microparticles will be higher in women on hemodialysis only and that these microparticles will cause greater damage to blood vessels. If confirmed these studies will set the stage for testing aimed at developing new therapies to protect women on dialysis from heart attack and stroke.

Dr. Xing-Zhen Chen

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Kidney Biology

Discovering new therapeutic targets for polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in membrane receptor PKD1 or cation channel PKD2. Clinical trials were recently conducted based on known PKD1 or PKD2 regulatory pathways. The outcomes were rather negative except that Tolvaptan was approved as the first ADPKD drug. However, its effectiveness is marginal and with debatable risk/benefit ratio. These tested drugs all act on regulatory pathways but not directly on PKD1 or PKD2. Because PKD1 and PKD2 are regulated by multiple pathways which also regulate other targets, the drugs specificity and efficacy are questionable.

Dr. Chen is proposing to investigate the molecular function of PKD1 and PKD2 using cell models and a technique called electrophysiology. This project will potentially discover therapeutic targets based on the new knowledge on the molecular interactions involved in PKD1 and PKD2 mutations.

Dr. Emmanuelle Cordat

University of Alberta



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Water, Salt, and Calcium Handling by the Kidney

Understanding the role of claudin-4 in calcium balance to find therapies for kidney stones

Kidney stones affect approximately 1 in 10 people in Canada during their lifetime and this predisposes to chronic kidney disease. Today, no drug efficiently treats or prevents these painful events, mainly because we still do not understand what causes the formation of these "stones" in our kidneys.

Dr. Cordat's study of a rare disease called distal renal tubular acidosis led her to identify a protein, claudin-4, which when eliminated from mice kidney results in elevated urinary calcium, a pre-requisite to the formation of kidney stones. She hypothesizes that claudin-4 contributes to calcium balance in our body. In the first Aim of this project, she will dissect the contribution of this protein to calcium reabsorption in the kidneys, using a renal cell line mimicking the section of the kidney where claudin-4 is expressed. In the second Aim of the project, she will turn to mice where claudin-4 have been eliminated to dissect the physiology associated with calcium imbalance in these animals.

At the end of the project, she hopes to improve our understanding of the role of claudin-4 in calcium balance and will be in an ideal position to start identifying drugs that can target claudin-4 as a potential remedy to treat kidney stone formers.

Dr. Andrey Cybulsky

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Glomerulo-nephtritis

Studying the dysregulation of protein kinase SLK that leads to glomerulonephritis

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, Dr. Cybulsky 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.

Dr. Mélanie Dieudé

Université de Montréal



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Predictive Biomarkers

Mechanisms of injury to renal microvessels in the autoimmune disease Lupus Nephritis

Lupus nephritis (LN) is a serious renal manifestation in patients suffering from the autoimmune disease systemic lupus erythematous (SLE). Up to 60% of lupus patients will develop LN which, if not controlled, can lead to kidney failure. SLE is much more common in women than in men and most often strikes during the child-bearing years. Nine out of 10 people who have SLE are women.

Dr. Dieudé's group has showed that injury and loss of microscopic blood vessels that provide oxygen and nutrients to the kidneys are of major importance for predicting renal failure. However, there is currenlty no reliable means of assessing injury to renal microvessels in patients with LN. They recently identified anti-LG3 autoantibodies as important player in the loss of renal microvessels in other renal disease context. They have also recently showed that anti-LG3 are elevated in mice model of lupus and in human LN patients.

In this project, they will build on these new observations to study the mechanisms of injury to renal microvessels triggered by anti-LG3 responses and characterize novel biomarkers of renal microvascular damage in LN. They will use a multifaceted strategy combining animal models and patient samples to define novel means of predicting and preventing renal failure in LN patients.

Dr. Meghan Elliot

University of Calgary



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Dialysis

Promoting the patient voice: understanding the implementation of patient-reported outcome measures in hemodialysis care

Persons with kidney failure receiving hemodialysis commonly report clusters of symptoms (such as fatigue and itching) and poor quality of life. Patient-reported outcome measures, or PROMs, are questionnaires used to assess individuals' perspectives on their symptoms, quality of life, and function without interpretation by clinicians or anyone else. Whereas PROMs have been used primarily as research tools, they are becoming more widely adopted in clinical settings to support person-centered care. As part of the patient-oriented research initiative, EMPATHY, patients will complete PROMs (i.e., symptom questionnaires) every 2 months for one year. Their responses will be fed back to their clinicians who will review results and address symptoms using patient and provider educational tools. Whereas the EMPATHY initiative will examine the impact of PROM use on communication and clinical outcomes quantitatively, a qualitative study is needed to more fully understand the experiences of patients, family/support persons, and clinicians with PROM use in routine hemodialysis care.

Dr. Elliott's project will explore the experiences of hemodialysis patients, family/support persons, and clinicians with implementation of PROMs, perspectives on their use, and barriers and facilitators to their integration in routine care. She will also explore how patient partners on the research team observe PROM use in routine HD care through analysis of their field notes, with the intent of understanding how lived experience with kidney failure might influence the nature of their observations and interpretations.

She will conduct interviews and focus groups with hemodialysis patients, their family/support persons, and clinicians (e.g. nurses, allied health professionals, nephrologists) after 4-6 months of PROM use across 10 Southern Alberta hemodialysis centres. Findings from this qualitative study will enhance the overall EMPATHY initiative by helping identify aspects of PROM use that could be tailored to promote sustainable, person-centered hemodialysis care. This project also addresses priority areas identified in partnership with hemodialysis patients and stakeholders. Findings will have implications for the patient-oriented research community, including teams seeking to develop meaningful research partnerships with patients.

Dr. Marie-Chantal Fortin

Université de Montréal



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$79,346	Transplantation

Studying stakeholders' perspectives on ethical and logistical issues related to advanced and voucher donation in kidney transplantation in Canada

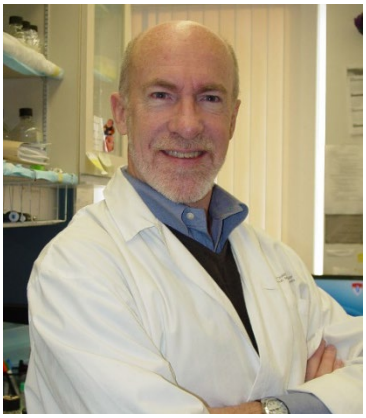
Living kidney transplantation offers the best medical outcomes for end stage renal disease (ESRD) patients. Prior to the launch of kidney paired donation programs (KPDs), the living kidney donor had to be compatible with his intended recipient. KPD provides the ability to circumvent this incompatibility obstacle by matching a donor who is incompatible with his intended recipient with a different recipient who is also incompatible with his donor and vice versa. Since its beginning, the Canadian KPD program has facilitated 682 living donor kidney transplantations which would not have been possible before.

Recently, advanced donation programs with vouchers have been developed in the US. This program allows the living donor to donate at the most appropriate moment for him and provides a voucher for named persons (up to five) who are not currently ready to receive or could potentially receive a kidney transplant, to receive a living donor kidney transplant at the end of KPD chain in the future. Advanced donation raises numerous ethical and logistical issues such informed consent, fairness and justice, gift-exchange, etc.

The objective of this exploratory study is to gather key stakeholders' perspectives, with qualitative interviews and surveys, on the ethical and logistical issues related to advanced donation and to develop preliminary ethical guidelines adapted for the Canadian transplant context. The results of this study will provide important topical information to the transplant community and may inform future discussions on any advanced donation programs developed for the Canadian KPD program.

Dr. Paul Goodyer

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Genetics

New therapy for a rare form of hereditary kidney stone disease, cystinuria

About 15% of patients with any hereditary kidney disease carry a type of genetic error (a “nonsense mutation”) that blocks translation of our genetic code into a functional protein. Remarkably, a newly developed drug (ELX-02) related to the antibiotic gentamycin can bypass this block. Using cells isolated from patients with the rare disease, cystinosis, we showed that ELX-02 partially restores protein production from a nonsense mutant CTNS gene; on the strength of our findings, a clinical trial of ELX-02 in cystinosis was initiated at McGill recently.

In this project, Dr. Goodyer proposes that ELX-02 may be able to help patients with nonsense mutations causing many other hereditary kidney diseases. To establish proof-of-principle, he will focus on a rare form of hereditary kidney stone disease, cystinuria. His team has worked out methods to isolate tubular cells from patient urine and they will use nonsense mutant cells as a model system to test ELX-02 effects. This research offers a completely new therapy for some patients with cystinuria and will open the path toward a similar strategy in many other genetic kidney diseases.

Dr. Lakshman Gunaratnam

University of Western Ontario



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Renal Failure

Role of Kidney Injury Molecule-1 in the Acute Kidney Injury to Chronic Kidney Disease Transition

In acute kidney injury, decreased blood flow, medication toxicity, or other causes suddenly damage the kidneys. While most people with acute kidney injury will eventually recover kidney function, some can develop chronic kidney damage and scarring, and would eventually need dialysis. Methods to predict who will recover and who will develop chronic kidney disease are imprecise. Moreover, there are no effective treatments to prevent the transition from acute to chronic damage.

Dr. Gunaratnam will study the molecular mechanisms behind the transition from acute kidney injury to chronic damage. This knowledge will help us develop interventions to prevent end-stage kidney failure after an episode of acute kidney injury.

His team has identified a molecule called “Kidney Injury Molecule-1” (KIM-1) that would be critical for the body to repair damage during the first few weeks of acute kidney injury. However, preliminary data suggests that if KIM-1 remains “on” for prolonged periods of time – for example, when the acute kidney injury is very severe – KIM-1 can paradoxically lead to fibrosis (scarring) of the kidney and cause chronic kidney disease. They have found that KIM-1 activates a gene called TBX-1 after severe acute kidney injury and they suspect TBX-1 is involved in kidney scarring. In this study, they will confirm that TBX1 is responsible for causing kidney scarring after severe acute kidney injury; verify that TBX-1 is a key factor activated by KIM- 1 and test a previously unknown treatment strategy to prevent kidney scarring in severe kidney injury. This work will greatly increase our understanding of processes that cause chronic kidney disease after severe acute kidney injury and potentially identify an effective treatment.

Dr. Paul Isenring

Laval University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Water, Salt, and Calcium Handling by the Kidney

Understanding the mechanisms by which salt, acid base balance and blood pressure is regulated in the kidney

Cells are the living units of all organisms. Each unit corresponds to a fluid-filled space that is contained by a lipid envelop (also called surface membrane), and within the fluid itself, there are many additional fluid-filled spaces that are also contained within lipid envelops. These envelops are naturally impermeable to molecules. However, they must be able to allow the passage of such molecules in a very controlled manner so that cells can maintain a normal function. They achieve such a task through the presence of various transport proteins that are designed to allow the movement of very specific molecules. It is for these reasons that transport proteins come into several varieties that each play a very precise and exclusive role based on the types of molecules that must be transported and the types of cells where they must be present.

One of the transport systems that is involved in molecule exchanges across cellular membranes is known to catalyze the movement of potassium (K) along with chloride (Cl) simultaneously: it is thus called the K-Cl cotransporter system. This protein has also been shown to catalyze the movement of hydrogen (H) along with Cl. Through these various functions, the K-Cl cotransporter system allows all cells to maintain their ion and water content, and it enables specialized cells, those included in the kidney's filtration systems (called nephrons), to control how much of these ions are retained or excreted by the kidney. It is thus not surprising that the renal K-Cl cotransporter system has been shown to play a role in blood pressure control and to regulate urinary acid excretion.

Humans possess 4 different types of K-Cl cotransporters (KCCs) that belong to a larger family of proteins called cation-Cl cotransporters (CCCs). Not surprisingly, each type of KCC exerts its role in a relatively unique way, but we still do not know exactly how. Dr. Isenring project proposes to decipher the precise role and localization of the KCCs in the nephron and gain insight into some of the mechanisms by which humans regulate their salt and acid base balance as well as their blood pressure. Such studies could thus lead to the identification of new targets for the treatment or prevention of disorders that are very common in the general population.

We already know of human syndromes that are due to abnormalities in the operation of ion transporters and that manifest as renal salt-losing disorders with or without low blood pressure or as renal salt-retaining disorders

with or without high blood pressure. Importantly, these studies will help understand how abnormal K-Cl cotransport leads to various manifestations and will have to be carry out before any new drugs are generated. Otherwise, researchers will not know precisely which of the KCCs should be targeted and how these transporters should be altered to generate beneficial effects.

Dr. Joan Krepinsky

McMaster University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Diabetes

Role of Lasp1 in the pathogenesis of diabetic kidney disease

Diabetes is the most common cause of kidney failure, leading to scarring of the filtering units of the kidneys. High glucose causes kidney cells called mesangial cells to make scar proteins. These scar proteins accumulate in the filtering units of the kidneys and prevent them from functioning properly. It is not yet known how high glucose levels cause mesangial cells to produce these scar proteins. Dr. Krepinsky previous studies have shown that a protein called ADAM17 directs mesangial cells exposed to high glucose to make scar proteins. In studying how ADAM17 function can be blocked, she found that a protein called LASP1 is important in regulating both the activity and the levels of ADAM17 in mesangial cells exposed to high glucose. She also found LASP1 to be increased in diabetic kidneys. In this project, she plans to investigate how LASP1 functions to regulate ADAM17 activation and levels, and whether blocking LASP1 can slow or prevent the development of diabetic kidney disease.

Dr. James Lan

University of British Columbia



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$119,560	Transplantation

Improved laboratory tests for kidney recipients to optimize transplantation

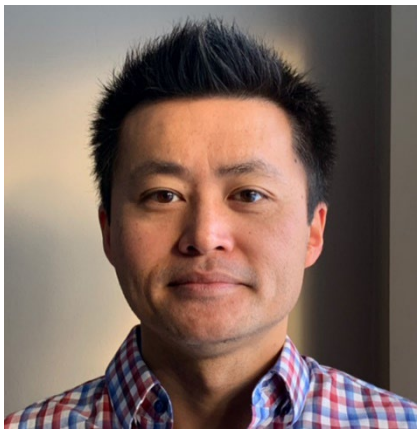
Kidney transplantation improves both the quality of life and longevity of patients with end-stage kidney disease. Despite major improvements in the science of transplantation, a particularly severe form of kidney rejection known as antibody-mediated rejection (AMR) accounts for more than half of organ loss in the long-term. AMR is caused by the presence of circulating antibodies in the patient's bloodstream which react with unique molecules called HLA (human leukocyte antigen) expressed on donor cells. Under the normal circumstance patients do not have anti-HLA antibodies, unless they have been previously exposed (sensitized) to foreign molecules through blood transfusion, pregnancy, or previous organ transplant. When a patient develops antibodies through these pathways, donors carrying HLA proteins which are the targets to the recipient's circulating antibodies are considered incompatible with the patient. Thus, the more antibodies that are found in a patient's blood the lower the likelihood of finding suitable donors in the population.

The main laboratory test used to detect antibodies in patients' blood is called the single-antigen bead (SAB) test. Although this test is very good at detecting low-level antibodies, it has come to scientists' attention that more than half of kidney patients never exposed to sensitizing events have apparent HLA antibodies on the test. It is important to understand the cause and significance of this phenomenon – without this knowledge many patients could be unfairly denied access to kidney donors solely on the basis of unexplained antibodies, which researchers predict to be largely harmless in the context of transplantation.

In this study, Dr. Lan will apply innovative machine learning approaches to study the pattern and cause of unexplained antibodies in 1000 kidney patients enrolled from 5 leading transplant centers. He will then assess the significance of these antibodies in the test tube by running them through a series of sophisticated laboratory tests that evaluate their chemical and functional properties. Finally, patients with unexplained antibodies that are determined to be harmless through these tests will have the opportunity to transplant across them under a rigorous clinical trial designed to improve transplant access while safeguarding against high rates of rejection.

Dr. Fabrice Mac-Way

Laval University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Hypertension

Nanoparticles to understand and treat vascular calcification in chronic kidney disease

Cardiovascular disease is a major complication in chronic kidney disease (CKD) patients. For reasons that are not completely understood, these patients develop, within their vessels, the equivalent of bone tissue (called calcification) that will damage their vessels leading to increased heart disease, amputations, chronic wounds, etc. There is currently no available treatment to reverse the process of calcification. There have been attempts to verify whether some drugs, when given orally, could reverse calcification in the vessels but the results have been disappointing. This may be explained by the fact that only a small proportion of these drugs are actually reaching the sites of calcification in the vessels.

To develop a targeted therapy for blood vessel calcification, Dr. Mac-Way started a collaboration with an expert in nanoparticles (NP). NP are small particles that can be injected in the blood vessels and delivered to specific diseased organs. The use of these NP is better known in the field of cancer where NP-bound chemotherapy is used to target cancer sites and to avoid potential secondary effects in healthy organs. In this research proposal, he wants to verify: 1) if these NP could have an effect on blood vessel calcification and 2) if he can incorporate drugs that have anti-calcifying properties within these NP to decrease or prevent blood vessel calcification. Blood vessel calcification is responsible for reduced quality of life and increased mortality rate in CKD. Dr. Mac-Way proposes a unique strategy that has the potential to generate an innovative therapy in this area. If results are positive, the next step will be to test these NP in human.

Dr. York Pei

Toronto General Hospital



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Genetics

Improving diagnosis of atypical polycystic kidney disease by Next Generation Sequencing

Polycystic kidney disease (PKD) comprises a collection of common and rare genetic diseases. With a prevalence of ~1 per 1000 births, autosomal dominant polycystic kidney disease (ADPKD) is the most common cause. Correct diagnosis of ADPKD is important since we now have a drug, Tolvaptan, which can be used to slow kidney failure in ADPKD, but not in other forms of PKD. When there is a family history, ADPKD is typically diagnosed by an ultrasound scan. However, patients without a positive family history, with an atypical kidney imaging patterns, with extreme disease variability in their family, with very mild disease but no PKD1 and PKD2 mutations, or with discordant results of their PKD severity between kidney imaging and kidney function tests, are said to have "atypical PKD". Identifying the cause of "atypical PKD" in any given patient (i.e. identifying the specific cystic disease gene mutations) typically requires mutation screening of multiple disease genes beyond those involved in ADPKD and is expensive and time consuming. Additionally, some patients with "atypical PKD" may have a condition called "somatic mosaicism" in which PKD was acquired during early embryo development affecting only one of several stem cells which eventually give raise to a mixture of normal and mutated cells that made up the different organs and tissues. As a result, the disease is diluted and presents in an atypical pattern. Currently mutation screening by Sanger sequencing will miss mosaic mutations because their mutation signal is very low.

Recent advances in Next Generation Sequencing (NGS) has revolutionized novel disease gene discovery and is transforming our approach in molecular diagnostics by providing high-throughput mutation screening of multiple genes at a modest cost. Furthermore, by providing extremely high DNA sequence read depth permitting detection of low mutation signals for a disease gene of interest, NGS is a promising technology for identifying mosaic mutations. Using this new technology, Dr. Pei will identify the genetic causes of ~300 patients with atypical PKD. The identification of cystic disease gene mutations is expected to provide important insights into the causes of atypical PKD. His work will accelerate the development of cost-effective molecular diagnostic testing for this challenging clinical problem.

Dr. Janusz Rak

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$120,000	Cancer

Investigating cancer cell metabolism and tumor microenvironment to discover new treatment options for kidney cancer

There is a growing population of patients suffering from metastatic renal cancer. Notably, this cancer is resistant to chemo- and radiotherapies and therefore it is treated with drugs that target blood vessels or stimulate the immune system. Unfortunately, many tumours escape their effects, and new therapies are badly needed.

Dr. Rak's study focuses on understanding the cellular function and therapeutic values of targeting a protein, which is over-expressed in renal cancer. His preliminary studies suggest that this protein regulates a metabolic process which is critical for cancer cells and thereby lead to tumor growth and metastasis. In addition, from his initial analyses it appears that this protein has also impacts on interactions between tumor cells and other cells and tissues surrounding them. In this project, he proposes to study these effects in detail and to examine the potential of inhibiting this protein for treatment of renal cancer. This project will characterize a nexus between cancer cell metabolism, and microenvironment, opening avenues for combating resistance to standard care and paving the way to better treatments.

Dr. Yasser Riazalhosseini

McGill University



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$119,996	Cancer

Finding better ways to detect and monitor kidney disease

Incidence rates for kidney cancer are rising worldwide. Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer accounting for about 80% of all cases. Most patients undergo surgical removal

of the kidney or tumor but a third of these patients develop relapse or metastasis, which is life-threatening. However, it remains difficult to predict risk of relapse or metastasis post-surgery among ccRCC patients. Thus, there is an urgent need to identify factors that can reliably predict risk of relapse/metastasis to establish personalized and effective management strategies for ccRCC.

Dr. Riazalhosseini and others have shown that gene mutations in ccRCC tumors may be used to estimate the risk of relapse in patients and that certain gene mutations may be predictive of metastasis in female patients only while other gene mutations are specific to male patients. Further, his team has shown that cell-free tumor DNA (ctDNA) released by tumor cells can be identified in biofluids (blood or urine) offering unique opportunities for non-invasive genetic tests through liquid biopsy screening in ccRCC.

The objectives of this study are therefore to develop a sex-appropriate, robust, non-invasive assay that will allow for sensitive and specific detection of tumor mutations in the blood or urine of kidney cancer patients (liquid biopsy).

There is a growing population of patients, suffering from metastatic kidney cancer and long-term side effects of treatment. The emotional/economic burdens on patients, families and society are significant. Identifying and implementing prognostic genetic markers in clinical practice will help clinicians improve health-care delivery to patients based on individualized risk assessment on the basis of patient's sex. Outcomes of this study have the potential to significantly impact patient management, allowing accurate risk stratification for recurrence/progression, timely identification of patients with failure, better adapted follow up regimens, and potentially better selection of candidates for adjuvant treatments.

Dr. Samuel Silver

Queen's University

FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$178,279	Renal Failure



Promoting Kidney Recovery after Acute Kidney Injury Receiving Dialysis

Acute kidney injury (AKI) is a rapid decline in kidney function, and it is a common complication for patients in the hospital. Dialysis is an important treatment for patients with severe AKI, but we do not know which patients are likely to recover after severe AKI that requires dialysis or how to increase the likelihood of kidney recovery. This study's goal is to identify characteristics in patients that make kidney recovery more likely and test the

feasibility of a new dialysis strategy to promote kidney recovery in patients with AKI who remain on dialysis after the initial illness has resolved.

This study will have 2 parts. In Part 1, patients with AKI who remain on dialysis at 5 hospitals in Ontario will be asked if the research team can collect health information for up to 6-months. This information will be collected through the medical record, and the only extra tests needed are weekly blood tests and urine collection. In Part 2, the same patient population will be asked if they are also willing to be randomized, like the flip of a coin, to a new dialysis strategy (based on a standard protocol of expert opinion and best practices) or usual care (based on the patient doctor's opinion). Dr. Silver will follow the progress of all patients until they recover enough kidney function to stop dialysis or 6-months after the first dialysis session.

Results from Part 1 will help determine which patient characteristics (like age, heart disease, and urine output) can predict which patients still on dialysis are likely to recover kidney function. Results from Part 2 will help determine if the new dialysis strategy is acceptable and followed by patients and healthcare providers, as well as which parts of the strategy work and which ones should be changed. Dr. Silver will also securely link the collected data to government databases, so that he can study other long-term outcomes (like death and hospitalizations).

This research will be the first to study a group of patients with the potential to recover kidney function after severe AKI, as well as the first to test a dialysis strategy to promote kidney recovery. These results will help design patient-centered decision-making tools to ease anxiety for patients likely to recover and speed chronic dialysis planning for patients less likely to recover. It will also make ongoing testing of potential recovery strategies easier because they can be targeted at the patients most likely to get off dialysis. In this way, patients with AKI still on dialysis can begin to receive more accurate information about their prognosis and personalized care.

Dr. Manish Sood

Ottawa Hospital Research Institute



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$111,967	Screening & Prevention

Development, validation and dissemination of a survey-based prediction equation targeting the general public: PREDICT-CKD Lifestyle

Chronic disease prevention is a policy priority and pillar of healthcare in Canada. Chronic kidney disease (CKD) is an incurable, progressive condition affecting an estimated 276 million persons worldwide in 2016 (13% of adults in Canada); an increase of 87% since 1990. This is attributable to global increases in key CKD risk factors such in diabetes, hypertension, obesity and an aging population; however, the development of CKD is not universal and remains variable. The ability to improve CKD awareness and accurately predict high risk individuals for disease surveillance remain major impediments to reduce or prevent the major adverse health outcomes associated with CKD. In the general population, kidney disease awareness is poor (below 10%) and this lack of awareness hampers disease prevention strategies. For healthcare providers there is uncertainty identifying patients at risk for progression and who may benefit from evidence-based therapies. This need not be the case as with the recent widespread availability of key laboratory tests, clinical and lifestyle data, the development of new onset CKD is a predictable event.

Dr. Sood proposes to develop a survey-based prediction equation targeting the general population to identify individuals at risk for incident CKD called PREDICT-CKD lifestyle.

His project has three objectives:

1. Develop a predictive algorithm using self-reported lifestyle data to predict new onset CKD (termed PREDICT-CKD lifestyle);
2. Validate PREDICT-CKD lifestyle internally;
3. Integrate PREDICT-CKD lifestyle into educational knowledge translation tools that will engage and allow the general public to determine their individual CKD risk.

This proposed study will be unique as it targets the general population and aims to improve CKD awareness. To date Dr. Sood has established an international research team consisting of world leaders in kidney disease, prediction analytics, and administrative data. Furthermore, they have developed inclusion/exclusion criteria,

estimated sample size, performed a systematic review to identify candidate predictor variables from existing prediction models and identified validated study outcomes. To improve uptake and usability of PREDICT-CKD lifestyle, it will be widely disseminated by knowledge translation partnerships using freely available web-based systems to broadly reach end-users. The PREDICT-CKD lifestyle equation aligns with identified research priorities of patients, healthcare workers, and policy makers. The timely, accurate, and reliable self-identification of individuals at risk of CKD would facilitate disease awareness and the targeting of lifestyle-based preventative therapies.

CDTRP KFOC RESEARCH INNOVATION GRANT

Dr. Lakshman Gunaratnam

University of Western Ontario



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$30,000	Transplantation

Therapeutic use of recombinant AIM to improve renal transplant outcomes

A kidney transplant has the potential to prolong the life of people with kidney failure and immensely improve their quality of life. A major limitation of organ donation is the short lifespan of the organs when transplanted into a person. The damage that happens to an organ during the transplant process (e.g. lack of blood flow to the organ), and then from the person's immune system (i.e. rejection) are major factors that determine the lifespan of transplanted kidneys. At the molecular level, this damage is caused by dying kidney cells which release their contents into the body and activate an immune response. Our laboratory has discovered a potential therapeutic agent, called "AIM", which, when given immediately following transplant surgery, can help remove the contents that are released from dying cells and prevent further damage to the transplanted kidney. We now would like to test whether AIM can help prolong the lifespan of transplanted kidneys in an animal model that is similar to human transplantation, where the animals have different genetic backgrounds from each other. We expect that giving AIM to people that receive kidney transplants will reduce the damage caused by transplantation surgery and the effects of the immune response. AIM may become a revolutionary treatment used to make kidney transplants last longer in people with kidney failure.

Dr. Darren Yuen

McGill University and Université de Montréal



FUNDING PERIOD	FUNDING AMOUNT	CATEGORY
2020-2022	$30,000	Transplantation

Nanobubbles: a new way to non-invasively measure donor kidney ischemia-reperfusion injury

While kidney transplantation can be a “gift of life”, we know that kidneys are injured during the transplant surgery, and that this injury can affect kidney function. This damage is due to the loss of blood flow when a kidney is taken out from the donor (“ischemia”) and put into a recipient (“reperfusion”). This process, called “ischemia-reperfusion injury” (IRI), occurs in every transplanted kidney. A major feature of IRI is blood vessel damage, resulting in less blood flow in the kidney after it is transplanted, and leaky blood vessels that allow fluid to inappropriately accumulate in the kidney. IRI severity determines how well the kidney will work after transplant. Doctors have no way of measuring IRI severity, and so can not easily predict how well a kidney will work. Thus, doctors can not tell patients what to expect after transplantation, and scientists can not easily test new anti-IRI drugs. We have developed a new ultrasound technique that measures kidney blood vessel damage. This technique can be done quickly, and based on our preliminary experiments seems to measure IRI in the kidney. We want to test if our new technique can accurately measure kidney IRI severity, and predict how well the kidney will function after IRI. These initial experiments will be done in mice, but if successful, will lead to studies in large animals and then a first-in-human clinical trial. Our hope is to provide a new tool for doctors to help better manage kidney IRI, and thus improve transplant outcomes.