2018 FUNDED RESEARCHERS
Medical and Scientific Advisory Committee

The role of the Medical and Scientific Advisory Committee is to advise the Leukemia & Lymphoma Society of Canada’s Board of Directors on a range of issues, including periodically reviewing the organization’s medical affairs and providing guidance to the research grant process. The committee is comprised of leading experts in their fields who volunteer their time to the LLSC and receive no compensation for their generous support.

Scientific Review Panel

The Scientific Review Panel is responsible for the evaluation of research grant applications. It consists of experienced researchers and clinicians who convene to discuss and rank applications based on rigorous criteria. Each member of the panel is carefully selected by the LLSC, in consultation with the appointed Chair, with varying expertise on blood cancer types and pose no conflict with the applicants. Once the applications are reviewed, the panel presents a recommendation for funding to the Medical & Scientific Advisory Committee.
Funding blood cancer research

The Leukemia & Lymphoma Society of Canada has a long-standing history of funding cancer research that began in 1955 when five Toronto women concerned about the lack of leukemia research started fundraising. Today, we are the largest voluntary health agency in Canada that is dedicated not only to leukemia but to all types of blood cancers.

Donations to The Leukemia & Lymphoma Society of Canada contribute to blood cancer research funding. There are many scientists in hospitals and cancer centres across the country who are looking for financial support in order to start or continue their projects in blood cancer research.

Once a year, our Scientific Review Panel selects research projects led by established and new scientists working in various cancer centres across Canada. Our Operating Grants offer funding over a two-year term to basic research that contribute to the advancement of science aimed at preventing, detecting and treating blood cancers. Our New Idea Awards provide funding over a one-year term to support the initial exploration of untested but potentially transformative ideas that challenge the manner in which we approach blood cancer diagnosis or treatment.
Discovering epigenetic vulnerabilities in poor prognosis

Some leukemia groups are very difficult to treat and the patients have poor survival. We propose to investigate how to inhibit the driving factor in these leukemias by targeting the epigenetic processes that the driver is dependent on. The inhibition will be achieved by drug-like molecules that have a potential to suppress the leukemia cells and be developed for leukemia therapy.

Real-time monitoring of leukemic stem cells in the bone marrow

Acute myeloid leukemia (AML) arises in the bone marrow, but we know little about how cells enter, live and exit the bone marrow. A better understanding of AML behavior will help optimize the delivery of emerging immunotherapies and improve outcomes. We will use imaging methods to answer these questions in mouse models of AML to inform the design of future immunotherapy-based AML trials in patients at high risk of relapse.

The RANK-RANKL axis in B-ALL

Nearly 90% of children with B cell leukemia (B-ALL) are cured. However, many survivors have late effects of the disease including secondary cancers and bone fractures. Cure rates for children who relapse are much poorer due to chemotherapy resistance. How can we protect childhood survivors from late effects of leukemia, and how do leukemic cells gain resistance to therapy? Our project, a collaboration between cancer biologist and a pediatric bone physician, examines how B-ALL damages bone and how the bone protects B-ALL cells from therapy.

AID expression sensitizes B cell lymphoma to UNG inhibition

A large proportion of non-Hodgkin lymphomas become resistant to the available therapies, so new alternatives are needed. We propose to exploit a vulnerability created by the enzyme AID, which is present in many lymphomas, to specifically target these cancer cells. We will show that inhibiting the non-essential DNA repair factor UNG allows AID to produce catastrophic damage at the chromosome ends, permanently arresting lymphoma cells proliferation and thereby tumor growth.
Preclinical development of an anti-AML small molecule, JP-4-94

We have developed a molecule which targets STAT5, an important driver of blood cancers. The compound exhibits potent killing of AML cells while not killing normal cells at same concentrations, is orally bioavailable, and most importantly, penetrates bone marrow and other blood producing organs. We seek to optimize the drug structurally, identify mechanism of action against STAT5, and conduct preclinical trials in animal models of AML to identify an advanced preclinical candidate for treatment of AML.

Development of new prognostic markers in acute myeloid leukemia

Acute myeloid leukemia (AML) is a deadly cancer treated with intensive chemotherapy to achieve remission followed by consolidation treatment to prevent relapse. Consolidation with chemotherapy or stem cell transplantation is chosen according to the risk of relapse which is determined by genetic anomalies in leukemia cells. This research aims to identify new prognostic markers to improve the risk stratification of AML patients and help clinicians select the most appropriate treatment.

An innovative approach to selectively target dormant leukemic stem cells

Despite encouraging advances in the treatment of leukemia, many blood cancers resist therapy or come back after initially responding. This is because the inability of current therapies to eradicate slow-growing blood cancer stem cells and their supporting cells in the bone marrow. This proposal aims to develop new combination therapies against other key proteins (ILK), so that these critical cells can be eliminated to improve survival in blood cancers.

Mechanisms of Lenalidomide resistance

Myelodysplastic syndrome (MDS) is a type of blood cancer that has very few types of treatment available. The aim of this project is to understand why patients with a specific type of MDS become resistant to the only treatment they have available. We hope that understanding this mechanism will also provide clues to overcome resistance to the therapy.
Developing a biomarker for limited-stage follicular lymphoma

Our proposal focuses on a particular subtype of non-Hodgkin lymphoma, namely follicular lymphoma. We will study tumour biopsies from those patients who have disease that is localized, meaning that it is amenable to treatment using radiation therapy. Unfortunately, half of these patients experience a relapse after treatment. We propose to develop an assay that would tell us which patients are at high risk of presenting with recurrence of their lymphoma.

Impact of a CMV-induced NK cell subset in cancer therapy

Host and virus interactions have been established over millions of years of evolution, exhibiting multifaceted consequences. Notably, some interactions are uniquely advantageous to hosts. A recently identified subset of long-lasting Natural Killer (NK) cells that develop post-cytomegalovirus (CMV) infection appears to confer enhanced protective immunity against cancer. Intrigued by this new discovery, we propose to investigate the roles of this subset of NK cells in cancer.

Role of follicular helper T cell subsets in chronic lymphocytic leukemia

Leukemia cells disrupt the immune system by invading immunological tissues such as lymph nodes and bone marrow, where they interact with other cells that help the leukemia proliferate and become resistant to chemotherapy. Dr. Marshall’s group has discovered specific abnormalities of T lymphocytes in leukemia patients and is determining how these T cell abnormalities contribute to disease progression. These discoveries will identify new biomarkers predictive of disease outcomes and new targets for therapy.

Critical care outcomes in hematologic malignancy and stem cell transplant

Patients with leukemia (blood cancer) may become critically ill because of their disease or complications of treatment; and may require intensive care unit (ICU) admission. Approximately 1/3 of patients die in ICU, and survivors may be left with significant longterm disability. Our study will evaluate long-term outcomes of patients who develop critical illness and identify factors we can modify to improve their outcome.
Podoplanin is a key new player in acute promyelocytic leukemia

Acute promyelocytic leukemias (APL) are uniquely characterized by frequent severe bleeding episodes which are the leading cause of early deaths in these patients. Our proposal capitalizes on a new observation that involves the protein podoplanin as a novel player involved in these complications. We will determine the contribution of this protein compared to other known factors, and investigate the potential benefit of targeting this new protein in APL patients.

Improving Ibrutinib therapy in chronic leukemia by targeting janus kinases

Chronic lymphocytic leukemia (CLL) is the commonest leukemia in Canada and is often fatal. A new drug called Ibrutinib has been of great help to CLL patients but does not cure them. Dr. Spaner’s group has found that CLL cells are kept alive in the presence of Ibrutinib by proteins called cytokines. Learning the best way to block the effects of cytokines should improve the lives of patients on Ibrutinib.

Characterization of leukemia-causing oncogenes using Drosophila

Acute myeloid leukemia or AML is a cancer of blood cells. Despite significant progress in recent years, a considerable proportion of afflicted children (40%) and adults (60%) still succumbs to the disease. Based on the conservation of cell division mechanisms among multicellular organisms, we exploit Drosophila fruit flies as a tool to identify functional collaborators of AML-causing oncogenes. This approach will accelerate the discovery of promising targets for therapeutic intervention.
The following researchers are winners of the 2018 Operating Grants (listed in alphabetical order by last name).

**Acute Myeloid Leukemia (AML)**

**Biology of S100A8 and S100A9 proteins in human AML**

Our team has recently studied the role of S100A8 and S100A9 proteins in acute myeloid leukemias. We found that S100A8 maintains the undifferentiated state of leukemic cells while S100A9 can induce their differentiation. In the current proposal, we aim to better understand the effects of the proteins, their receptors and their cellular pathways both in vivo and in vitro to move towards clinical application in the next few years.

**Leukemia**

**DNAJC21 a novel leukemia predisposition gene in Shwachman-Diamond Syndrome**

Mutations in a gene called DNAJC21 were recently found to cause Shwachman-Diamond syndrome (SDS). Patients affected by SDS have low numbers of white blood cells, characteristic physical findings, and an increased risk of developing leukemia. In this study, Zebrafish, which have similar blood development to humans, will be genetically modified to contain this mutation and loss of the related TP53 gene to determine their contribution to normal blood development and leukemia.

**Acute Myeloid Leukemia (AML)**

**Defining targets of MDS to AML progression**

Leukemia impacts thousands of Canadians. Developing effective treatments is limited by incomplete understanding of how normal blood cells become leukemic in the first place. Using our recently created model system where normal blood cells can be progressively turned into leukemia, we aim to define the genes that are activated and inactivated when healthy cells turn leukemic, and use new drugs to inhibit these changes to prevent leukemia from starting.
**Acute Myeloid Leukemia (AML)**

**Evaluation of N-myristoyltransferase in acute myeloid leukemia**

NMT2 is a protein that plays an important role in cells. We have found that expression of NMT2 is very low in most leukemia cells from patients with acute myeloid leukemia (AML). One main purpose of this study is to test NMT2 levels in leukemia cells, as a way of predicting the outcome in AML patients who receive chemotherapy. That may help us to find out which patients are less likely to be cured with chemotherapy. We also have a new agent, PCLX-001, that is able to kill cells that have low levels of NMT2. In this study we will also test the effectiveness of PCLX-001 in killing leukemia cells in the lab and in mice with AML. This may lead to a new treatment for AML.

**Lymphoma**

**Clonal Hemopoiesis is a Risk Factor for Chemotherapy-Related Complications**

This study will screen 188 lymphoma patients, over the age of 60, prior to their commencement of chemotherapy. Clonal mutations (called CHIP) are present in 20-30% of lymphoma patients above the age of 70. The hypothesis being tested is that those patients exhibiting a clonal CHIP mutation may have a greater chance to develop chemotherapy-related complications. Testing will also occur at 6 and 12 months post-chemotherapy to investigate possible increased or decreased CHIP mutation levels, and/or any new emerging mutations. This study will have important implications for other types of cancer as well.

**Pediatric acute myeloid leukemia (AML)**

**Uncovering the role of NEO1 in NUP98 acute megakaryoblastic leukemia**

AML represents 20% of pediatric leukemia, but accounts for most of disease-related mortality in children. The goal of our project is to characterize an emerging subgroup of high fatality leukemia harboring specific genetic lesions (NUP98 gene fusions). This subgroup of aggressive leukemia is rare. To overcome this impediment, novel in vitro systems and animal models will be developed to better define the disease and find therapeutic avenues.
Multiple myeloma

Role of Epigenetic Modulation in Myeloma Drug Resistance

Multiple myeloma (MM) is a B-cell tumor with survival ranging from several months to a few years. It remains incurable due to the development of a drug-resistant phenotype after prolonged therapy. Current studies focus on the targeted therapy with molecular signaling blockade by inhibitors to increase tumor septicity, reduce toxicity, and prevent drug-resistance in multiple myeloma. We propose to investigate the molecular mechanisms of epigenetic modulations in the drug resistance and evaluate lead inhibitors in MM. We will establish a model to target specific genes and overcome drug resistance in MM. Thus, our study will provide a potential novel therapeutic strategy to improve the outcome of patients with MM.

B-cell acute lymphoblastic leukemia (B-ALL)

Characterization of driver mutations in a mouse model of B-cell leukemia

We have developed a new mouse model of pediatric precursor B-cell acute lymphoblastic leukemia (B-ALL). Our goal is to identify mutations responsible for driving cancer development in these mice. This will be done by sequencing and comparing genomic DNA from leukemia cells and normal cells. We are confident that the scientific community will make use of this model to develop new molecular targeted approaches for treatment of leukemia.

Lymphoma and leukemia

Developing and testing AID inhibitors for leukemia/lymphoma treatment

We are studying a molecule called AID which mutates the DNA of lymphocytes thus transforming them into leukemia or lymphomas. Many studies have shown conclusively that AID expression in lymphomas correlates with poor prognosis. We have identified small molecule drug-like compounds that attach specifically to the part of AID which is responsible for mutating DNA, and thereby inhibit its activity. The goal of this proposal is to (1) refine these molecules to make them more effective, (2) test the hypothesis that these inhibitors can block AID-mediated gain of drug resistance in leukemia or lymphoma. The outcome of this work will pave the way for pre-clinical testing and therapeutic development.
B-cell lymphoma

Identifying non-coding driver mutations in diffuse large B-cell lymphoma

DNA sequencing studies of Diffuse large B-cell (DLBC) lymphoma patients have revealed that 99% of their cancer-associated mutations involve non-protein coding DNA. This project will examine the hypothesis that some of these non-coding mutations promote the cancerous behavior of DLBC lymphoma cells by affecting the regulation of important genes. This collaborative study will examine combinations of coding and non-coding mutations that will reveal which biochemical signaling pathways are implicated in determining the treatment response of lymphoma cases. Once identified many of these pathways can be targeted with new drugs.

Burkitt’s lymphoma

Uncovering novel chemoresistance driver mutations in Burkitt’s lymphoma

Blood cancers disrupt the normal functioning of our blood cells and can be diagnosed during childhood up to late adulthood. Although anti-cancer therapies have dramatically improved over the past decades, patients affected by these diseases are still at high risk of being unresponsive or developing resistance to the current standard treatments. The goal of this research proposal is to use newly developed technologies that allow editing of the genome to identify new diagnostic tools for a specific subtype of blood cancers, named Burkitt’s Lymphoma (BL). We aim at functionally characterizing mutations observed in patients that have experienced chemotherapy relapse in a mouse model and determine which mutations provide a selective advantage to the tumour. This work will not only provide help in the diagnosis of BL but will also greatly enhance the development of new therapies for BL patients that fail conventional treatments.

Acute myeloid leukemia (AML)

The molecular landscape of leukemia-specific antigens

The goal of our project is to develop therapeutic vaccines against acute myeloid leukemia (AML). We therefore need to discover molecules that are present only on leukemic cells and that can be recognized by the immune system. To this end, we have developed a disruptive method based on next generation sequencing, mass spectrometry and bioinformatics. Using this proteogenomic method, we have discovered mouse leukemia antigens that elicit strong protective immune response and lead to elimination of leukemic cells. Using our unique method, we now looking to discover leukemia antigens that can be used as therapeutic AML vaccines. Preventive vaccines against various pathogens represent the most cost-effective way to save lives. We believe that almost anybody would wholeheartedly trade a course of chemotherapy for a vaccine.
Acute myeloid leukemia (AML)

Identification of microRNAs essential for AML chemoresistance

Chemoresistance is one of the primary targets of AML research because there is tremendous potential to increase survival if overcome. Nevertheless, little progress in the understanding and treatment of resistant AML has been made. This proposal represents fundamental studies to identify microRNAs that drive and maintain chemoresistant AML, and which will serve as novel therapeutic targets or chemosensitising agents in AML. This collaborative venture will provide an exceptional opportunity to produce exciting results that can be rapidly applied to the diagnosis, future treatments and management of AML.

Pediatric leukemia

Validation of pediatric chronic graft-versus-host disease biomarkers

When children have leukemia, we treat them using transplantation of blood or bone marrow donated from another person. Unfortunately, this “cure” can cause a new life-threatening disease, called chronic graft-versus-host-disease, in which the donor’s immune system attacks the patient’s healthy organs. We are working to find blood tests that can help us personalize treatment by knowing when it is best to intervene to prevent cGvHD and guide treatments selection.
New Idea Awards

We want to leave no stones unturned when it comes to finding cures. We introduced a research award to funnel a stream of projects that support innovative approaches that may fundamentally change our understanding, diagnosis and/or treatment of blood cancers.

The New Idea Award recognizes researchers who are investigating potentially transformative ideas to significantly improve clinical outcomes for patients with blood cancers.
Acute myeloid leukemia (AML)

**eIF4E drives production of extracellular vesicles in AML**

Dysregulation of a cancer-causing protein, eIF4E, is linked to many cancers including acute myeloid leukemia (AML). We discovered that eIF4E overexpression drives changes to the surface architecture of cancer cells, coating them in a sugar called hyaluronan, which supports the cancer phenotype. We also found that eIF4E drove the formation and release of hyaluronan-based vesicles into the space between cells. We will investigate whether these vesicles carry cargoes that can reprogramme the environment to support the growth of cancer cells and allow them to evade the effects of chemotherapy.

Pediatric acute lymphoblastic leukemia (ALL)

**Targeting eIF2(alpha) phosphorylation in T-cell acute lymphoblastic leukemia**

Standard of care in pediatric T-cell acute lymphoblastic leukemia (T-ALL) result in high cure rates, however the long duration of such drastic chemotherapy in young people irreversibly alters their quality of life. Moreover, prognosis is appalling in adolescent/adult T-ALL. We previously showed that leukemia initiating cells are slowly dividing cells that ‘lie low’ to resist chemotherapy. We will identify the mechanism that refrain these cells from dividing, with the objective of releasing the brake and sensitizing these cells to treatment.

Leukemia

**Novel histone mutations in leukemia**

Leukemia often develops when the master genes that govern how all other genes are ‘read’ are broken by mutation. This disrupts how a cell functions and can result in uncontrolled growth and behaviour, leading to leukemia. In particular, the genes that control how DNA is packaged and organized have been shown to be drivers of leukemic development. In our present study, we will examine new genes in this category for involvement in leukemia.

The following researchers are winners of the 2018 New Idea Award (listed in alphabetical order by last name).

**Acute myeloid leukemia (AML)**

**eIF4E drives production of extracellular vesicles in AML**

- Dr. Katherine Borden
  University of Montréal
  Montréal, Québec

**Pediatric acute lymphoblastic leukemia (ALL)**

**Targeting eIF2(alpha) phosphorylation in T-cell acute lymphoblastic leukemia**

- Dr. Colin Crist
  Jewish General Hospital/Lady Davis Institute for Medical Research
  Montréal, Québec
  Co-Applicant: Dr. Trang Hoang
  IRIC, University of Montréal

**Leukemia**

**Novel histone mutations in leukemia**

- Dr. Kolja Eppert
  McGill University Health Centre
  Montréal, Québec
  Co-Applicant: Dr. Margret Shirinian
  American University of Beirut
**Leukemia**

**Self-assembling multi-subunit chimeric antigen receptors to target leukemia**

Current therapies using chimeric antigen receptor (CAR) therapy show great success in treating patients with various types of leukemia. However, this approach has been fraught with pitfalls such as aberrations in receptor signaling, which can cause severe side effects such as death. One current pitfall is that current CARs have the ability to compete or associate with endogenous receptors. The novel CAR architectures proposed in this research will abrogate these interactions and enable a more predictive immune response outcome.

**Leukemia**

**The onco-ribosome as a novel drug target in leukemias**

In our lab, we discovered a cancer-specific variation in T-cell leukemia in the ribosome, a cell component essential to synthesize proteins. Interestingly, this variation is located in a ribosomal region that is the target of a major group of antibiotics. The goal of this project is to test the hypothesis that leukemia cells with this ribosomal variation can be selectively killed by antibiotics, which would provide a new therapeutic option.

**Acute myeloid leukemia (AML)**

**High level expression of SOCS2 in high risk acute myeloid leukemia**

SOCS2 is a protein which suppresses cytokine signaling and is encoded on chromosome 12. It appears to inhibit Acute Myeloid Leukemia (AML) cell growth by targeting and binding to several key proteins within these AML cells. SOCS2-AS1 is the RNA transcribed from the SOCS2 gene. This project will examine the potential role of SOCS2-AS1 on the growth and chemotherapy resistance of AML cells.