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.
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.
Operating Grants

Year after year, The Leukemia & Lymphoma Society of Canada invests in research projects that take on the toughest challenges in blood cancer.

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. These grants recognize scientists whose work will contribute to the tremendous momentum in blood cancer research and yield groundbreaking results in treating patients and extending lives.

In 2019, we are funding 18 new Operating Grants.
The following Operating Grant winners from 2018 continue to receive funding in 2019 (listed in alphabetical order by last name).

**Biology of S100A8 and S100A9 proteins in human acute myeloid leukemia**

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.

**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.

**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.
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.

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.

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.
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.

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.

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.
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.

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.

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.
Identification of microRNAs essential for AML chemoresistance

Chemosensitivity 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.

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.
Draining the batteries: a novel approach to treatment strategies in CLL

Cancer cells, specifically chronic lymphocytic leukemia cells are charged with energy when compared to normal B-lymphocytes. We have identified that certain markers on the leukemia cells, such as one called ZAP 70, predicts which cells have higher energy levels. We do not, however, know what factors outside the cell or within the cells actually alter ZAP 70 to change the energy status of the cell. We believe learning this information is important for two main reasons: 1) It could be used to predict what doses of new drugs may best be used for patients to ensure they are working without side effects, and 2) Inform us how drugs should be combined together to avoid side effects while maximizing the effect of treatment. By determining how to best assess energy changes in cancer cells under certain conditions, we can best learn about how different drugs “drain the batteries” of the leukemia cells.

Role of inflammation in acquired clonal hematopoiesis in aging individuals

Aging is associated with the acquisition of small changes (mutations) in the genes of blood cells. Some of these mutations can give a growth advantage to the affected cells, which will outgrow the normal ones. This phenomenon is called Age-Related Clonal Hematopoiesis (ARCH). The presence of ARCH is associated with a 10-fold increased risk of developing a blood cancer such as leukemia, and it also doubles the risk of having a heart disease. This proposal will determine the role of inflammation as an initiator of ARCH but also as a factor of progression to cancer and/or cardiovascular diseases. Our results could lead to the development of a test allowing early identification of individuals at risk, and pave the way for the development of intervention strategies based on microbiota modification and/or anti-inflammatory treatment.

Improved T-cell expansion and differentiation for adoptive immunotherapy

The injection of immune cells (T-cells) grown in specialized laboratories can be very effective to treat blood cancers. Unfortunately, these immune cells can get “tired” and are less effective at killing cancer cells after their expansion in the laboratory. We have found that by blocking natural “brakes” on these cells, we can prepare large quantities of effective cancer-killing immune cells. We now seek to better manipulate these brakes to produce better cancer-fighting immune cells for therapy. This project is entirely oriented towards the treatment of blood cancers and will be relevant to all forms of T-cell immunotherapies. Based on our expertise translating innovative T-cell therapies in the clinic, we aim to provide better more effective cancer-killing T-cells to use as a treatment for blood cancers.
Understanding the role of exosomes/microvesicles in the CLL microenvironment

We are studying the most common form of adult leukemia called chronic lymphocytic leukemia (CLL). Though there are many new treatments available, there is still no cure for CLL. Cancer cells can release particles that contain material that act as messengers to the cells around them. We have found that CLL patients that have more particles in their blood have more aggressive disease. We will investigate if these particles are playing a role in the development of drug resistance. It is also possible that these particles could be changing the function of other cells in the body, creating an environment that makes it easier for the cancer cells to survive. Finally, we will use a 3D model of cellular tissues to see if blocking the release of these particles will increase the amount of cell death in the cancer cells. Drug resistance remains a significant clinical barrier to treat CLL patients. By understanding the role these particles play in promoting cell survival in CLL cells, effective therapeutic strategies could be developed to overcome drug resistance.

Bypassing resistance to lenalidomide in del(5q) MDS

Myelodysplastic syndromes (MDS) are a type of blood cancer that have poor outcomes and for which few therapeutic options exist. About 1/3 of MDS patients progress to an incurable acute leukemia, with the rest dying of bone marrow failure. One type of MDS (del(5q) MDS) is normally treated by a medicine called lenalidomide (LEN). However, more than half of these patients do not respond or stop responding to treatment, indicating a need for new therapies. Our goal is to determine whether MDS patients who are resistant to lenalidomide might benefit from blocking a cell signaling pathway called IGF1R. Our work will lead to the potential of new treatment options for LEN-resistant MDS patients.

Enhancing epigenetic therapies in B-cell lymphoma

This proposal will focus on aggressive B-cell lymphoma, which represents the most common form of lymphoma in Canada, with over 4,000 new diagnoses per year. Identifying novel treatment strategies for these patients is a critical, unmet need, given that relapse occurs in 40% of patients and is often life-limiting. Our understanding of how lymphoma arises has significantly improved over the last decade. Novel drugs are now available that precisely target critical proteins that are important for lymphoma cells to proliferate and survive. However, lymphoma cells often find ways to develop resistance. Consequently, most novel drugs have relatively low response rates and, even when patients have responsive disease, the duration of the response can be short. In our research, we aim to identify optimal drug combinations as a means to more effectively treat lymphoma. We will focus on drugs that can be combined with inhibitors of two proteins, namely EZH2 and HDAC3. We will not only apply cutting-edge methods to identify novel combination partners, but we will also aim to understand the mechanisms that explains the synergy that we observe. Our ultimate goal is to translate findings herein into a clinical trial that can benefit patients.
Therapeutic targeting of the miR-106a-363 cluster in acute myeloid leukemia

Despite improved therapies, the 5-year relative survival for acute myeloid leukemia (AML) is currently 21% in Canada, with especially unfavorable prognosis for elderly patients. Therefore, new treatments that target the root of AML, leukemic stem cells (LSCs), are necessary. The current standard of care in elderly patients with AML, a combination of Venetoclax and azacytidine, has significantly improved overall survival. However, one third of responders relapsed, suggesting incomplete eradication of LSCs and thus making further investigation critical. MicroRNAs (miRNAs) exert key functions in LSCs and their dysregulation affects prognosis and outcome in AML patients. Furthermore, modulation of miRNA levels has shown promising results in preclinical models. Here we explore targeting LSCs through inhibition of a cancer-causing microRNA cluster in combination with Venetoclax and azacytidine. The proposed combination potentially intensifies depletion of LSCs and therefore has clinical potential not only in AML but also in other cancers such as lymphomas, multiple myeloma and solid tumors.

Exploiting metabolic vulnerabilities in aggressive non-Hodgkin lymphoma

Non-Hodgkin lymphomas (NHLs) are the fifth most commonly diagnosed cancer in Canadians and the most prevalent of all the blood cancers. New treatment options are urgently needed for NHL in patients that have cancers that return following primary treatment. To date, novel drug development initiatives in NHL have been largely unsuccessful in identifying new agents to improve on standard of care therapies. It is known that aggressive lymphomas need a constant and increased supply of nutrients to fuel cell division and proliferation. In devising strategies to cut off nutrient supplies, we uncovered adaptations that allow lymphoma cells to survive leaner times. We believe that preventing access to the nutrient sources represents an attractive method to combat NHL. We have developed novel drugs that act by inhibiting lymphoma cells from adapting to stress for use as combination therapies thereby exploiting metabolic vulnerabilities.
Targeting telomere maintenance in Hodgkin’s lymphoma

Inside our cells our genes are arranged along twisted, double-stranded molecules of DNA called chromosomes. At the ends of the chromosomes are stretches of DNA called telomeres which protect our genetic data, make it possible for cells to divide, and hold some secrets to how we age and get cancer. Telomere length maintenance is critical for cell division and cell survival. Normally, when telomeres reach a critical length the cells stop dividing and start to deteriorate and die. In Hodgkin’s lymphoma, however, the cells activate a protein called telomerase that maintains telomere length and prevents cell death. In this project, we will explore how Hodgkin’s Lymphoma cells maintain telomere length and then target their telomere maintenance pathways to prevent growth of cancer cells. We expect that treatments that target telomere maintenance pathways present in all cells of HL patients may alter the current treatment outcome of HL.

STAT6 mutations in relapsed/refractory diffuse large B cell lymphoma

Lymphoma is a cancer of the lymphocytes that can be treated with chemotherapy, but is often fatal once resistance develops. We profiled mutations in one type of relapsed lymphoma, diffuse large B cell lymphoma (DLBCL). Here we found that the protein STAT6 is more frequently mutated in relapsed samples than those taken when the disease is first diagnosed. STAT6 is a protein that binds DNA and controls genes important in lymphocyte survival. In our preliminary experiments, we found that cells with these mutations grow faster. This has led us to try to understand how mutated STAT6 leads to increased cancer cell growth. We will then test whether cells with the mutant STAT6 protein relapse more quickly following treatment with chemotherapy. Furthermore, we think that these tumors may respond to a new class of drugs targeting this pathway alone or in combination with chemotherapy. We believe that this mutant STAT6 protein is a marker for tumors who will not response well to chemotherapy, but also a marker for those tumors that might respond to these STAT6-targeted therapies.
**Exploration of nanopore sequencing in the diagnosis and prognosis of AML**

Many Acute Myeloid Leukemia (AML) subtypes consistently swap between the same chromosomes (called a translocation). At the time of diagnosis, the translocation is identified and can be monitored after chemotherapy to guide further treatment. This is called residual disease monitoring (RDM). A subtype of leukemia associated with translocations is Mixed Lineage Leukemia (MLL). In this project we are using MLL as a model to identify chromosomal translocations in acute leukemia. Diagnosis can be complicated and there is no established test for RDM in MLL leukemia. Our first aim is to use a novel technology called nanopore sequencing to identify chromosomal translocations involving the MLL1 gene. Our second aim is to use the nanopore sequencing results to develop patient specific probes for residual disease monitoring. If successful, this project will potentially allow us to develop a patient specific approach for residual disease monitoring in many diseases, not just AML.

**Exploring MYSM1 as a potential drug-target for cMYC-driven B cell lymphoma**

cMYC is an important regulator of gene expression and abnormal increase in cMYC activity is a major cause of cancer. In recent work we demonstrated that cMYC works together with another protein MYSM1 in the regulation of gene expression in the blood and immune systems. Loss of MYSM1 therefore can protect mice from cancers of the blood and immune system. The molecular mechanisms involved in the MYSM1 and cMYC interaction will be analyzed in our proposed project. The long term goal is to determine whether inhibition of MYSM1 will also inhibit cMYC activity, and thus provide another potential treatment option.

**Platelet-packaged organelles: A novel outsourcing of cancer modulators**

Inflammation is tightly linked with the development and progression of cancer. Amongst the inflammatory components participating in these processes are platelet cells. Platelets, initially discovered as clotting agents, are the second most abundant circulating blood cells in the human body. Interestingly, platelets also shed small vesicles (similar to escape pods) which package biologically active molecules. We have recently identified a new type of these vesicles, termed mitoMPs. These mitoMPs contain mitochondria which are known as the power and energy producing components of every cell. Our preliminary results show that mitoMPs bind and get enveloped by leukemia cells to transfer their content (mitochondria). As a result, these cancer cells have greater viability and have increased resistance to cellular death. We believe that mitoMPs represent important cancer modulators which will result in increased disease progression. In this study, we propose to define the significance of mitoMPs in chronic lymphocytic leukemia (CLL). Most importantly, we will determine the disease mechanisms which will then allow for the development of new strategic therapeutic approaches.
Targeting the ubiquitin E1 ligase, UBA1, in AML

TAK-243 is a new drug that blocks the cell’s garbage disposal system. We have shown that TAK-243 kills AML cells in culture and mouse models while sparing normal cells. Based on these data, we propose a clinical trial of TAK-243 in patients with refractory AML. In support of this clinical trial, we will develop a laboratory-based test to determine whether TAK-243 can bind and inhibit its target. We will also investigate mechanisms by which cells become resistant to TAK-243. Finally, we will test new drug combinations that could enhance the ability of TAK-243 to kill AML cells while continuing to spare normal cells.

PRAME alterations in DLBCL: Clinical and functional significance

Lymphomas are the 5th most common cancers in Canada. The current standard of care in many B cell lymphomas consists of chemotherapy and therapeutic monoclonal antibodies, and has significantly improved patient outcomes over the past 15 years. A large proportion of patients, however, suffer from refractory or relapsed disease. Therefore, the development of new therapeutic strategies for these patients represents an important unmet clinical need. We will investigate the roles of a new gene, PRAME, which is frequently deleted in patient’s tumors. However, the functional role of PRAME down regulation remains unknown. We will study how these deletions lead to lymphoma formation and how tumor cells escape from the patients’ own immune system surveillance, thus aiding in the development of new therapeutic avenues to simultaneously treat the tumor and the host.

Diagnosis, prognosis and novel therapy for Ph-like ALL in Canada

While cure rates for childhood acute lymphoblastic leukemia (ALL) have improved significantly in the current era, relapse remains the most common cause of treatment failure and death. Teenagers and young adults with ALL have a worse outcome compared to younger children. Advances in cancer genetics have recently made several important discoveries, such as the identification of a particular group of patients who display a “genetic signature” similar to that of Philadelphia (Ph) chromosome-positive ALL but lacking the Ph chromosome. This is known as Ph-like ALL, and comprises approximately 15% of childhood ALL and over 25% among adults with ALL. Despite modern chemotherapy regimens, this group has poor survival rates compared to those without the “Ph-like” signature. Testing for Ph-like ALL remains limited in Canada and about 500 ALL patients do not have access to such testing each year. Given the poor prognosis and the possibility for outcome improvement, the main goal of this study is to develop a national screening program for Ph-like ALL using a novel sequencing technology. This screening will allow to identify Ph-like ALL patients who could benefit from the addition of TKI in combination with conventional chemotherapy in order to improve their outcomes.
Late neurocognitive deficits in ALL survivors: DNA methylation biomarkers

Treatment of childhood leukemia is very effective; however, treatment can interfere with normal brain development in up to 50% of children treated. Brain functions such as attention, memory and intelligence can be affected leading to problems with learning and social skills. Importantly, these effects may only appear years after treatment has ended and are therefore called late effects. Our recent research suggests that patterns in epigenetic markers, i.e. changes to the DNA that controls whether genes are turned on or off, can help us understand how late effects develop in leukemia survivors. These epigenetic markers are stable over the years following treatment and have the potential to be used as a predictive tool for damaging effects on brain development. Our study aims to identify epigenetic markers in bone marrow cells collected during routine testing early in chemotherapy treatment to learn more about the possible causes of late effects. This information could help us predict which children are most susceptible to late effects. Additionally, these findings will enable the advancement of our understanding of the mechanisms of late effects, the development of early biomarkers, and the potential for early more personalized interventions.

Engineering proT-cells from stem cells for adoptive cell immunotherapy

In current CAR-T cell therapies, mature T-cells are collected from the patient’s blood, engineered to kill leukemia and lymphoma cells, and transplanted back into the patient. Successful implementation of this strategy is limited by high treatment costs, low cell yields, and long-term safety concerns. Many CAR T-cells recognize both cancerous and healthy cells, causing undesirable side effects. A ‘universal’ source of progenitor (pro) T-cells engineered to target certain cancer cells could be transplanted into the patient where they would develop into mature T-cells that would be tolerated by the patient’s immune system, thus minimizing the potential side effects. We have developed a way to grow proT-cells from stem cells and aim to demonstrate that CAR proT-cells are an effective way to treat blood cancers. Optimization of CAR-proT therapy should reduce targeting of healthy tissue, reduce side-effects, and increase potency against many types of leukemia and lymphoma. Furthermore, development of proT-cells would allow for scalable production of ‘off the shelf’ cancer immunotherapies which would result in lower costs for patients.
New Idea Awards

The Leukemia & Lymphoma Society of Canada is proud to play a leading role in the fight against blood cancers.

We want to leave no stones unturned when it comes to finding cures. The New Idea Award funds 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.

In 2019, we are funding 5 New Idea Awards.
The following researchers are winners of the 2019 New Idea Award competition (listed in alphabetical order by name).

**Targeting repressive chromatin complex mutations in acute myeloid leukemia**

PRC2 is a multi-protein complex that controls the genes important for normal blood cell development and leukemia progression. Mutations in the genes encoding the components of PRC2 are found in myelodysplasia, myeloproliferative disorders and Acute Myeloid Leukemia (AML) and are often associated with poor prognosis. We have previously investigated AML patient samples and have shown that drugs targeting the PRC2 complex drastically reduced the ability of these cells to grow thus providing a potential option of treatment. We propose to undertake further studies to understand the role of the mutant PRC2 complex in AML. This information gathered here will provide justification to explore PRC2 as a drug target, or biomarker for other drugs, and help identify an important patient population that may most benefit from such agents.

**Therapeutic potential of variable lymphocyte receptor antibodies**

Conventional antibodies play an increasingly important role in cancer therapy because of their ability to bind to target cells with very high specificity. However, it remains a great challenge to identify targets that are uniquely expressed on cancer cells so as to avoid damage to non-cancer cells. The recently identified variable lymphocyte receptor (VLR) antibodies of the evolutionarily distant sea lamprey provide an equally diverse and specific antibody system. However, the structure of VLR antibodies is radically distinct from the commonly used mammalian antibodies. Various studies have demonstrated that the antibody-antigen interactions of VLR antibodies are different from those of conventional antibodies and that they interact with structures not easily recognized by conventional antibodies. Humanization of VLR antibodies will provide a strategy to take advantage of the highly specific recognition of targets which conventional antibodies may not be able to bind. The ultimate goal of our research is to harness the unique VLR antibodies of the sea lamprey as a novel therapy aimed at treating cancer.
Uncovering tumor specific antigens in ETP acute lymphoblastic leukemia

Early T-cell Precursor Acute lymphoblastic leukemia subtype (ETP-ALL) is associated with resistance to chemotherapy and poor prognosis, especially in adults. Stem cell transplantation is beneficial in a large proportion of patients which suggests high potential for immunotherapy for treatment of ETP-ALL. Our goal is to uncover tumor specific antigens (TSA), proteins on cancer cells. These proteins are present exclusively on leukemic cells and can be targeted for immunotherapy in ETP-ALL. This will pave the way to developing novel therapeutic vaccines for treatment of ETP-ALLs.

A novel method to identify synergistic lethality in B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a common and aggressive lymphoma subtype in which relapse after front-line treatment remains a major challenge. Such patients have very poor outcomes. Better therapeutic strategies are thus urgently needed to increase upfront cure rates. We propose to uncover combinations of drug targets that, when inactivated, kill tumour cells synergistically. We are aiming to accelerate the discovery of promising drug combinations by using large-scale screens in which we can explore the effect of inactivating pairs of genes, in addition to inactivating such genes individually. Our goal is to uncover unexpected vulnerabilities and prioritize treatment strategies for subsequent clinical evaluation. Our project will discover novel ways of treating DLBCL patients including: identify strategies to improve upfront cure rates, decrease the morbidity from relapsed lymphoma, and ultimately improve survival of diffuse large B-cell lymphoma patients.

Small molecule targeting of CYP26B1 in myeloid leukaemia

Retinoic Acid (RA) has been used since the 1980s to treat certain types of blood cancers. AML is a blood cancer characterized by the growth and accumulation of immature cells, known as blasts, in the bone marrow and blood. RA is able to change the blast cells that cause cancer in a way which limits their cancer-causing potential but, unfortunately, it has been unsuccessful for treating Acute Myeloid Leukemia (AML). The cells for this type of cancer are protected by bone marrow cells which rapidly metabolize RA due to activity of a protein called CYP26, discovered previously in our lab. We believe that compounds that block the CYP26 in these patients will restore the therapeutic effects of RA. We have designed and developed a series of potential drugs which are able to block CYP26. We have found that that blocking CYP26 can be an effective strategy to sensitize leukemic cells to RA. This would be the first drug of its kind for treating MDS (a precursor of AML) and AML, and could completely revolutionize treatment for these patients and significantly increase the rate of remission.