Cancer research covers a variety of activities and many areas of scientific study because cancer is not one disease but a multitude of diseases, each with its own subtypes and related disorders. When we think about finding a cure for blood cancers, we are really trying to understand and find effective treatments for 137 types of blood cancers and related disorders.

Understandably, research progress happens slowly with consideration for every aspect of the research cycle. Each year, The Leukemia & Lymphoma Society of Canada forms a new group of medical experts with the task of reviewing research projects taking place in Canada that show the greatest promise in advancing our understanding of different blood cancers, ability to test therapies and ultimately, to find cures.

In 2016, our scientific review panel selected 16 research projects led by established and new scientists working in various cancer centres from coast-to-coast. Our Operating Grants focus on basic and translational research aimed at preventing, detecting and treating blood cancers.

Our Operating Grant award winners for 2016, listed in alphabetical order by last name, are:
Challenging the Leukemia Stem Cell Theory in Human Acute Leukemias

Testing human leukemic cells in immunodeficient mice is the state-of-the-art approach to understand their *in vivo* behavior and assay their engrafting and self-renewing capacities. In the past 20 years, the data generated in such models led us to believe that a subset of cells, called leukemic stem cells, are at the apex of the tumor hierarchy. However, our recent results challenge this dogma and new sequencing technologies will help testing it.

Elucidating pathogenesis and downstream targets in NUP98-NSD1 induced AML

Acute myeloid leukemia (AML) is an aggressive blood cancer requiring better treatments. We will use zebrafish to determine why children with a newly discovered gene abnormality have a particularly deadly form of AML. We will put NUP98-NSD1 and FLT3 human cancer genes into zebrafish. We will study how these genes impact zebrafish blood development causing leukemia. Compounds that restore normal blood development in zebrafish may represent new treatments for leukemia.

Defining epigenetic determinants of MDS to AML towards novel therapeutics

Leukemia impacts and affects thousands of Canadian families. However, developing effective treatments is limited by an incomplete understanding of how normal blood cells become leukemic. Using our recently created model system where normal blood can be progressively turned into leukemia, we aim to understand the steps that contribute to leukemia initiation in the first place, and use changed characteristics to define new drugs that prevent leukemia from even starting.

Determinants of oncogenic penetrance of TET2 mutations in aging individuals

The incidence of blood cancers greatly increases with age. However, there is no test to identify individuals at risk. We have documented mutation in a gene called TET2 in a small proportion of aging individuals. Since this gene is frequently mutated in blood cancers of older people, we think that it may be a predisposing factor. To prove our hypothesis, we need to study a larger number of individuals and see if they develop such cancers with time. Fortunately, we have started our study 10-15 years ago with several thousand subjects. Therefore, we will be able to answer this question in a short lapse of time. If our hypothesis holds true, we will be able to identify individuals at risk of blood cancer as it is done for other cancers such as prostate, colon or breast.
Role of Mitochondrial Biogenesis and Mitophagy in AML Stem Cells

Acute myeloid leukemia is an aggressive type of blood cancer that kills over 1,000 people every year in Canada. Current therapies are often ineffective because they fail to kill a special type of cells known as leukemia stem cells. Our proposed studies will study how mitochondria, the powerhouses of the cell, function in leukemia stem cells and explore new strategies to destroy these cells by targeting the mitochondria.

Rational co-stimulation modulation for adoptive immunotherapy

The treatment of blood cancer using immune cells that have been previously “educated” in the laboratory is highly promising. However, several limitations need to be overcome before this form of therapy reaches its full potential. This proposal is about modulating certain signals the immune cells receive in the laboratory and in vivo, so that they acquire the best characteristics to recognize and kill leukemia cells.

Role of MYC in a new de novo model of MYC-induced human AML

The roles of specific gene alterations in patients’ leukemic cells are difficult to study because of many other mutations typically also present. The applicants have recently discovered a method of creating human leukemia experimentally by forcing normal human blood precursors to overexpress a single gene broadly implicated in human leukemia. They will now analyze the cells and molecules affected and thereby identify important targets to later test in patients’ cells.

Regulation and interactions of the oncogenic transcription factor MEIS1

MEIS1 is a protein that controls gene expression. Overexpression of MEIS1 is involved in many blood cancers including leukemias. Using a powerful new tool to modify the genome of human or mouse cells we have modified the MEIS1 gene in both human leukemic cell lines and in a novel mouse strain so that we can more easily detect its expression (via a fluorescence reporter) and purify it along with associated proteins (via a special tag sequence). We will now exploit these models to better understand how MEIS1 expression is regulated and with what proteins it interacts with in order to identify new methods to block MEIS1 expression or function in leukemia.
A developmental checkpoint in Pro-T cells and acute leukemia

Acute lymphoblastic leukemia is the most common childhood cancer and 25% of those are of T cell origin (T-ALL). Approximately 20% of childhood and 60% of adolescent and adult patients succumb to this disease. Furthermore, even though the disease is of good prognosis in children and treatment can achieve more than 80% long term cure, current chemotherapy compounds impose a severe burden on the patient and the immediate family, due to undesirable severe side effects. There is an urgent need to identify compounds that are more specific towards leukemic cells and spare normal cells. To this end, we used a multilevel approach to identify the complete set of molecular alterations that lead to T-ALL, with the ultimate goal of identifying more specific drug-like compounds that can efficiently inhibit T-ALL maintenance and propagation. We uncovered a novel mechanism that controls disease onset, due to alterations of a critical quality control checkpoint in T-cell development.

We propose a global approach combining large scale genomic, bioinformatics and cell based screening with in vivo models of T-ALL to identify more specific drugs. Our research opens possibilities for new treatments of T-ALL.

Inhibiting mitochondrial RNA polymerase in acute myeloid leukemia

Acute myeloid leukemia on a particular cellular energy pathway for growth and viability. One enzyme, mitochondrial RNA polymerase, controls the level of this energy pathway. In the current application we propose an animal model and cell culture proof-of-concept study with a selective inhibitor of the enzyme. This project will help us understand whether designing drugs against this enzyme might be a useful therapeutic strategy for AML.

Optimization of autologous immune therapy using MRD expansion

The presence blood cancer cells in children completing the first phase of treatment is a strong indicator that the disease may return later. The low numbers of the cells at this stage, however, have made it difficult to evaluate their sensitivity to other treatments. Here, we will develop a new approach to increase the number of cancer cells and use these cells to develop better approaches to limit their growth and survival.
Investigating a novel role for INPP4B in leukemic stem cell maintenance

Dr. Salmena’s research group has identified INPP4B as a biomarker to identify leukemia patients that are likely to fail therapy. Subsequently, they have discovered that INPP4B is important for maintaining the ‘health’ of the leukemia stem cells (LSC) that drive aggressive disease and relapse in leukemia. The Salmena group will study how INPP4B contributes to stemness and use this knowledge to identify new therapies to treat leukemia.

Blocking mitochondrial protein import and folding in acute leukemia

The mitochondria are the energy producing factories in the cell. Most of the proteins in the mitochondria are made in the cytoplasm and transported into the mitochondria through the mitochondrial protein import pathway. In our preliminary data, we demonstrated that blocking mitochondrial protein import using genetic approaches or drug-like molecules preferentially killed a subset of AML (acute myeloid leukemia) cells over normal blood cells. In this application, we will explore blocking mitochondrial protein import as a new strategy to treat leukemia. Specifically, we will study the mechanism by which blocking mitochondrial protein import kills AML cells. We will also determine whether blocking mitochondrial protein import can kill primary AML stem cells over normal cells. Finally, we will determine the effectiveness and safety of blocking mitochondrial protein import in mouse models of leukemia. Thus, through this proposal we will discover new biological insights about the role of mitochondria in AML. In addition, we will highlight a potential new treatment of this disease.

Estrogen receptor beta as a novel target in acute myeloid leukemia

Patients with acute myeloid leukemia are faced with poor disease outcomes. Our research shows that targeting estrogen receptor beta selectively kills leukemia cells. The objective of this project is to determine how drug targeting of this receptor imparts this selective killing. The end goal of this work is to develop new drugs aimed at extending the lives of leukemia patients.
Therapeutic targeting of adenosine in chronic lymphocytic leukemia

We want to investigate a new approach for treatment of chronic lymphocytic leukemia (CLL). We have shown that blocking adenosine makes the immune system better at destroying many cancer cells. We will use a mouse model of CLL and test the effect of blocking adenosine alone or in combination with other treatments. In addition we will see if CLL patients that fail treatment have a lot of adenosine.

B cell lymphoid neoplasms, such as chronic lymphocytic leukemia (CLL), are very common and often incurable diseases, despite recent introduction of targeted therapies. For patients in whom currently available treatments fail to control their disease, the identification of novel therapeutic targets may prove beneficial. These tumours are often associated with immunosuppression, induced either directly by the cancer cells themselves, or as a consequence of the expansion of distinct suppressive and immunoregulatory cell populations, such as Treg.

N6-methyladenosine (m6A) RNA modification in Acute Myeloid Leukemia

We study how mRNAs in cancer cells are modified by a mechanism called m6A methylation, and how such modifications contribute to the origin and progression of cancer. The outcome of this project will help develop novel cancer therapeutics targeting mRNA methylation in deadly cancers such as leukemia.
Operating Grant Summaries 2017

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.

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.

In 2017, we invested $3.8 million in blood cancer research – our largest annual investment in research since our inception. A part of this year’s investment supported our Operating Grants for 2017 through which 15 scientists, in addition to those selected in 2016, were added to a growing list of blood cancer research we currently fund.

Our Operating Grant award winners for 2017, listed in alphabetical order by last name, are:
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

Acute Myeloid Leukemia (AML) is the most common acute leukemia in adults. Worldwide, AML affects forty individuals per million annually. The majority of AML patients respond to toxic chemotherapy initially, but due to therapy resistant relapses, the 5-year overall survival is below 50%, and below 20% for patients >60 years. There is an intense medical need for new therapeutic options. Furthermore, demographic change and improved medical care will lead to more AML cases in the future. For example, many current chemotherapeutic interventions promote AML. The major hurdle in identifying an effective AML drug, is that it must be capable of entering blood producing organs like bone marrow to efficiently kill leukemic cells. 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.
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.
2017 NEW IDEA AWARD SUMMARIES
2017 New Idea Award Summaries

We want to leave no stones unturned when it comes to finding cures. This year, 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.

The 10 winners of our New Idea Award, listed in alphabetical order by last name, are:
In Vivo Studies of Acute Myeloid Leukemia and its Hypoxia Status within the Bone Marrow Microenvironment

Acute myeloid leukemia (AML) is a disease of the bone marrow (BM) that spreads throughout the BM of affected patients. The BM microenvironment supports the development of leukemic cells, and typically the BM is hypoxic (low oxygen). In solid tumors, hypoxia is associated with poor prognosis and resistance to therapy. Since leukemia is not considered a solid tumor, the influence of a hypoxic microenvironment on disease progression has not been adequately studied. Moreover, the study of hypoxia in hematological diseases, like AML, has been slowed by the lack of reliable experimental methods. Recent studies have shown that hypoxia influences leukemic cell proliferation, differentiation, maintenance and resistance to chemotherapy. Despite recognizing that the importance of the hypoxic BM microenvironment in developing new treatment strategies, much of past and current research has been carried out in suspension cultures or in histological sections which fail to replicate the patient setting and only tell us what is happening at a fixed period in time. Drs. Ralph DaCosta and Mark Minden’s teams at the Princess Margaret Cancer Centre, for the first time, will apply state-of-the-art optical imaging methods in animal models of AML to visualize AML cells and their complex behaviors in the hypoxic BM microenvironment in real-time and at the single cell level. Findings from this research will improve our understanding of how AML cells grow in the BM which could lead to new treatments for this disease. The experimental tools developed in this unique bench-to-bedside collaboration will also open up new avenues for basic research in leukemia which could help overcome previous technological barriers in the field.

Developing an innovative treatment monitoring tool in multiple myeloma

Multiple myeloma does not yet have a cure, but because of research investments it can be controlled. To control myeloma, we need very sensitive medical tools. These tools detect when the myeloma flares up and needs to be treated. The sooner we know when to treat, the better quality of life a myeloma patient can have. The more we know about myeloma the better treatments can get. Here, we will use a new tool to chemically fingerprint myeloma. The tool uses Nanotechnology Surface Enhanced Raman Light Scattering (NanoSERS) to find the unique by-products of myeloma cells. This technique is simple, easy to set-up and low-cost. If successful, oncologists and patients could be better informed about the progress of myeloma. In the future, this new tool could provide new information to help improve myeloma therapy.

Dr. Ralph DaCosta
University Health Network
Toronto, Ontario

Dr. Keith Brunt
Dalhousie University
Halifax, Nova Scotia
Manipulating Gamma Delta T-cell metabolism for Improved Cytotoxicity in Hematological Malignancies

Harnessing the potential of the immune system to combat blood cancers represents a new approach that has started to change the standard of care. A growing body of evidence indicates that as immune cells switch from an inactive mode to a cancer-killing mode they undergo radical changes in how they take up and use nutrients and metabolites. In this proposal we aim to explore how gamma/delta T-cells change their nutritional requirements upon activation to a cancer-killing state. Having determined which nutrients these cells rely on to and how they are re-programmed to kill lymphoma cells, we will then attempt to genetically manipulate the metabolism of these cells them for optimal anti-lymphoma activity. This could lead to the development of an entirely new type of cellular therapy to treat blood cancers.

Impact of clonal hematopoiesis in donors on allogeneic hematopoietic stem cell transplantation outcomes

Allogeneic hematopoietic stem cell transplant still remains the only curative treatment modality in many of hematologic malignancy treatment. It requires transfer of hematopoietic stem cells from healthy donor to the recipient, i.e. patient with hematologic malignancy. Suitable donors may be matched related donor followed by matched unrelated individuals or half matched family members. As donors themselves may have abnormalities of their blood forming cells called clonal hematopoiesis, it is important that we should be able to identify the most appropriate donor incorporating this information in donor selection. Incorporating this novel genomic information from donors together, we can develop a new recommendation on donor selection process for allogeneic stem cell transplantation.

Elucidation of the functional role of Complement Factor D in Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the second most common type of leukemia in both children and adults for which the survival rate remains poor. The proposed research intends to elucidate the function of a novel prognosis marker in AML. In particular, we will characterize its role on cancer cells aggressiveness and communication with their specialized microenvironment. This marker is a potentially actionable target for the development of innovative therapies to cure leukemia.
Mutual Antibody T cell Engagers (MATEs): a safe, flexible alternative to CAR-T cells for the treatment of leukemia and lymphoma

The world has seen a major breakthrough in the treatment of leukemias and lymphomas using “CAR-T cells”, a new strategy in which T cells are genetically engineered to express “Chimeric Antigen Receptors” that enable them to recognize and destroy cancer cells. Remarkably, CAR-T cells are achieving 50-90% response rates in patients with advanced leukemias and lymphomas expressing a marker called CD19. Despite these unprecedented results, the current version of CAR-T cells can bring serious side effects. Moreover, a significant number of patients eventually relapse after CAR-T cell treatment. The goal of this project is to develop a safer, more flexible alternative to CAR-T cells, which we refer to as “Mutual Antibody T cell Engagers”, or MATEs. Our approach will give clinicians exquisite, failsafe control over the number and activity of engineered T cells after they are infused into the patient’s bloodstream. It will also enable clinicians to aim the T cells at different targets on tumors, minimizing the risk of relapse. This will not only provide a safer and more effective alternative to CAR-T cells, it will enable application to a wide range of malignancies that otherwise cannot be safely targeted. Thus, the MATEs strategy will ultimately yield a new arsenal of highly selective immunotherapies for a broad range of cancers.
Assessment of minimal residual disease in patients undergoing treatment for acute myeloid leukemia using an *in vivo* xenotransplantation model

Acute Myeloid Leukemia (AML) is an aggressive blood cancer. About 80% of people can achieve a remission with our standard treatments but the majority of patients will relapse and die from their disease. Only about 40% of patients under the age of 60 and about 10-15% of patients over the age of 60 live for more than 5 years. These relapses are thought to happen because of leukemia cells that are left over after the initial treatments. Despite our best efforts to find these leukemia cells we have been unsuccessful in predicting whose leukemia is going to come back and whose is not. For this grant we are proposing an entirely new way of finding leukemia cells. Instead of trying to find leukemia in a lab using test tubes and machines we want to take the bone marrow from patients (bone marrow is where leukemia is found) and inject this into mice that are used for leukemia research. If the mice develop leukemia then we know that the patient still has leftover leukemia-causing cells and still has the potential to have leukemia come back. For these patients we can potentially offer other treatments.

Microfluidic detection of leukemia cells by electronic biomolecular sensors

Acute myeloid leukemia (AML) is a disease caused by the uncontrolled growth of primitive myeloid progenitor cells. Patients with AML are usually treated with chemotherapy that will destroy the bulk of the tumor cells. Some cells can acquire resistance to this treatment however, leading to a “minimal residual disease” (MRD) and eventually, relapse. The ability to track MRD levels in the clinic is valuable, allowing doctors to intervene earlier, however this typically requires painful and invasive bone marrow sampling. This project, performed in collaboration with the Bouilly lab, will test an entirely new way of detecting AML cells, using a microfluidic electronic sensor that is triggered by the presence of proteins or DNA that are specific to the tumor cells. The work supported by this grant will allow prototype devices to be built and tested, in order to optimize their design and function. Because these sensors are extremely small, they have the potential to eventually provide a much faster, cheaper, and less invasive technique for monitoring MRD and improving patient treatment.
Oncometabolite-induced DNA replication defects in leukemia

Unlike normal blood cells which divide only when necessary, leukemic cells divide uncontrollably and in doing so are constantly duplicating their genetic material (i.e., their DNA) in a process called “DNA replication”. Chemotherapy drugs cause lethal damage specifically to replicating DNA in cancer cells, but spare normal cells which rarely undergo DNA replication. This explains in large part how such drugs can preferentially kill cancer cells over normal cells. Our laboratory studies biochemical mechanisms that protect cancer cells against DNA damage caused by chemotherapy drugs, thereby decreasing the efficacy of cancer-killing treatments. To fit in the tiny confines of the cells, DNA is wrapped around molecules called “histones” that strongly influence how cancer cells respond to DNA damage caused by chemotherapy. We also know that leukemia cells produce abnormal chemicals that modify the function of histones in unwanted ways. We propose to directly evaluate the impact of these chemicals on the ability of cancer cells to respond to chemotherapy. We expect that our research will lead to new, more efficient and personalized strategies to treat leukemia.