The Princess Margaret Cancer Foundation UHN

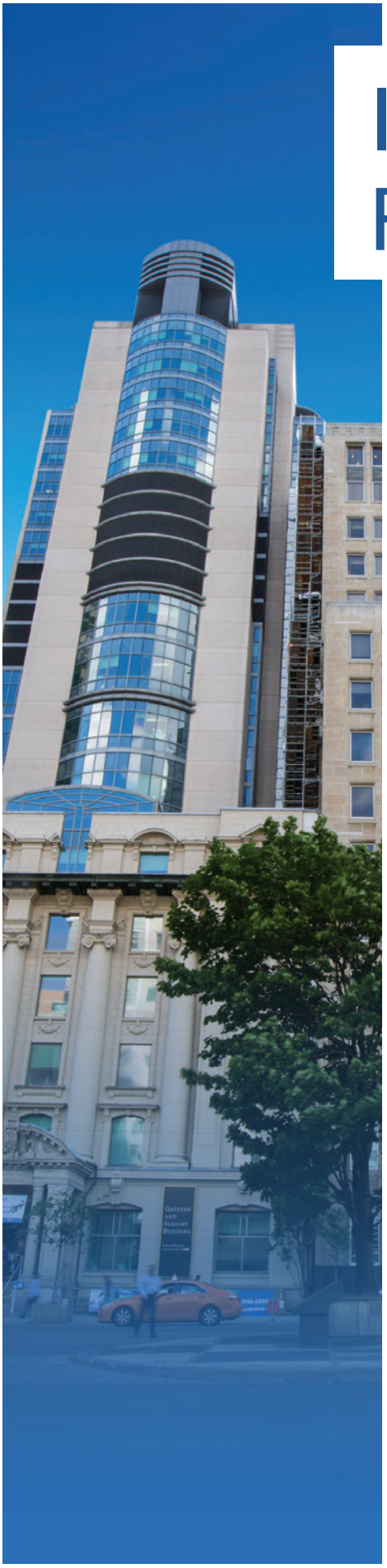
IMPACT REPORT

Invest in Research Program

Driving Tomorrow's Breakthroughs Today

Invest in Research

January 2022



Invest in Research 2022

Every year, the Invest in Research program gives scientists at The Princess Margaret a grant to do something bold: test their most cutting edge, innovative ideas.

Because of visionary donors like you, each recipient receives $100,000 to support their work. This important, competitive source of funding enables these scientists to overcome a common obstacle in the world of research. New, high-potential ideas need funding to pull together data and validate hypotheses; research bodies tend to favour later stage ideas where data has already been collected.

The success of Invest in Research speaks for itself. As noted by Dr. Aaron Schimmer, the Research Director at Princess Margaret Cancer Centre and a past Invest in Research grant recipient, scientists typically leverage every dollar donated to research at The Princess Margaret by raising an additional dollar and thirty cents. “But when you invest a dollar in Invest in Research,” he explains, “it’s leveraged over tenfold. The more than $2 million raised to date has helped secure over $36 million in additional grant support from external agencies. That is truly spectacular.”

The interest from our scientists continues to be strong. This year, we had over 30 applicants. At our Fall 2021 meeting, Dr. Schimmer shared with you the top six projects, which were selected by a committee of top scientists at the Cancer Centre. In the recent past, two grant proposals earned funding per year. Because the investor group has grown, we now support three grant recipients – something that started last year. We are deeply grateful to all our supporting members, both new and established, whose leadership has helped to create a dynamic and magnetic program.

In this report, we are excited to share with you the results of your vote to select the 2022 new grant recipients – as well as an update on last year’s grant recipients.

"Year over year, Invest in Research continues to be among the most popular programs amongst our scientists. That's because it funds projects at the earliest stages of research, a high risk point that other programs might not be willing to support. Importantly, it also gives the scientists the opportunity to compete on a level playing field, where they can each submit ideas and see which ones the donor panel ultimately decides to fund. It's always exciting to be a part of this process, and I thank you very much for your continued support."

— Dr. Aaron Schimmer,

Research Director,
Princess Margaret Cancer Centre

2021-2022
Grant Recipients

Investigating Ciliopathy as a Predisposition for Pediatric Leukemia

Dr. Eric Lechman,

Affiliate Scientist

The Problem

Down syndrome is caused by the presence of an extra chromosome – chromosome 21. Children with Down syndrome also have a 150-fold increased risk of developing pre-leukemia that can evolve into leukemia. Dr. Lechman was involved in a landmark study in 2021 that demonstrated that pre-leukemia in Down syndrome arises only within rare hematopoietic stem cells (HSC). What remains unclear is how an extra copy of chromosome 21 predisposes HSC toward leukemia.

The Solution

Preliminary data from Dr. Lechman suggests that Down syndrome-related HSC express a gene signature consistent with dysfunctional primary cilia – a previously unexplored connection. The primary cilium is a solitary, hair-like appendage required for cells to respond appropriately to their environment. In the context of Down syndrome, it's possible that the hair on the blood cells becomes abnormal, which in turn misinterprets environmental cues and leads to leukemia.

The Plan

Dr. Lechman and his team plan to study approximately 60,000, single blood progenitor cells with state-of-the-art DNA structure, RNA and Protein analyses. This will create the first high-resolution dataset revealing differences between Down syndrome and normal blood cells.

The Potential Impact

The proposal has the potential to understand how chromosome 21 influences leukemia initiation in children with Down syndrome. More broadly, the mechanisms it uncovers may also reveal the genetic alterations that cause leukemia in adults as well. That's because it will shed light on the little-understood cellular origins that initiate leukemia and possibly govern the properties of the resultant disease.

Accelerating Lung Cancer Diagnosis Through Liquid Biopsy

Dr. Natasha Leighl,

Medical Oncologist

The Problem

Lung cancer remains the deadliest cancer in Canada, accounting for 25% of all cancer deaths. For advanced non-small cell lung cancer (NSCLC) patients, survival is directly impacted by the time from symptom onset and diagnosis to the start of treatment. Unfortunately, the cancer journey for advanced NSCLC patients is often drawn out. In the era of precision medicine, molecular testing of tumour tissue with a biopsy is the gold standard for directing treatment decisions for advanced NSCLC patients. However, 15-40% of patients do not have enough tissue for successful molecular testing, and delays obtaining tumour tissue and molecular results mean most patients do not have results when they see their oncologist. These days, such time lags are further exacerbated by the COVID-19 pandemic, causing immense stress for patients and costing precious time for oncologists to implement effective therapy.

The Solution

To drastically reduce the time delay before treatment, Dr. Leighl would like to trial a new technology: liquid biopsies. Liquid biopsies are non-invasive blood tests that detect circulating tumour DNA (ctDNA), biology markers that indicate cancer in the blood. Molecular information from liquid biopsies can help diagnose and discover molecular targets much faster than standard tumour tissue biopsy testing. Liquid biopsies are also more convenient and safer than tumour biopsies for patients, and can result in cost savings.

The Plan

Dr. Leighl has designed a study to use liquid biopsy for advanced NSCLC patients. The tests will be implemented at the time of diagnosis to determine what biological markers the liquid biopsies detect, and to see how they can be used to accelerate time to treatment. While the technology is still new, Dr. Leighl and her team believe they will see meaningful results that might point to a new gold standard when it comes to diagnostics.

The Potential Impact

It is anticipated that this approach will significantly reduce wait times between diagnosis and treatment for advanced NSCLC patients. Accelerating molecular diagnosis and time to treatment will have important implications for survival, symptom control and quality of life, ensuring the best possible outcomes for those afflicted with lung cancer.

Dynamic heterogeneity of the prostate microenvironment in patients undergoing external beam radiotherapy

Dr. Shane Harding,

Scientist

The Problem

Radiotherapy is used to treat half of all cancer patients but fails if the cancer has spread throughout the body. In some patients, adding immunotherapy to their radiotherapy has led to dramatic cures. Unfortunately, this combination treatment does not work in all patients for reasons that we do not fully understand. One major gap in our knowledge is that we do not actually know how cells in patients respond to radiotherapy at the molecular level, despite the fact that radiotherapy has been used in treatment for decades.

The Solution

Dr. Harding is assembling a multi-disciplinary team to study radiation in the context of prostate cancer, with the hope of better understanding how cells respond to radiotherapy at the molecular level, and therefore how it can be better utilized with immunotherapy to improve survival rates. Work from the Harding Lab and many others has already shown that the molecular signals produced by cells after radiotherapy can recruit and activate the immune cells that are necessary for immunotherapy to be effective.

The Plan

With this proposal, Dr. Harding and his team plan to identify a cohort of prostate cancer patients at high risk for recurrence after radiotherapy. Biopsies will be collected before and after their treatment. Using modern technologies, the team will profile thousands of individual cells. This approach allows the team to address several fundamental questions, including:

- How do different cell types that comprise a tumour respond to radiotherapy?
- How does radiotherapy change the types of cells within a tumour?
- How do cells within a tumour communicate with each other and the cells of the immune system?

The Potential Impact

This study is going to shed new light on how radiotherapy affects cells. Ultimately, it will offer the opportunity to improve the effectiveness of radiotherapy – an important if not entirely understood treatment for cancer patients.

2020-2021 Grant Recipients: Update On Progress

Lung Cancer Earlier Detection to Intercept Cancerous Relapsing Tumours (Lung EDICT)

Dr. Geoffrey Liu,

Senior Clinician-Scientist and Medical Oncologist

The Problem

In Canada, lung cancer is the leading cause of cancer death, comprising 13% of all cancer diagnoses and 25% of all cancer deaths. The disease is not inherently less curable than other forms of cancer. However, many patients are not diagnosed until they are in a late stage, when survival rates are less than 10%. Screening is now delivering some improvements in earlier detection, but current screening practices, which rely on CT scans, are reserved for the highest-risk lifetime smokers, which comprise 43% of cases. That means 57% of patients fall through the cracks. With lung cancer now increasing even among those who have never smoked, a group accounting for 15% of diagnoses, there is an urgent need for improved methods of early detection for a wider array of people. Moreover, even among patients who are diagnosed at Stage I or II, substantial proportions will relapse after surgery, which typically leads to death. Therefore, identifying patients at high risk of relapse is another key imperative, along with early detection, when it comes to improving outcomes for patients.

The Solution

Blood-based liquid biopsies are a promising, accessible and affordable approach for early detection and monitoring of lung cancer. Tumours, including those in the lungs, release free-floating genetic traces into patients' blood called circulating tumour DNA (ctDNA). By sampling blood and studying ctDNA, clinicians can potentially both detect and monitor changes in patients' cancer. Because taking blood is an accessible and non-invasive treatment, this can be done more easily and more frequently than other sampling techniques, enabling clinicians to be more agile in detecting cancer and monitoring treatment response. However, current experimental and commercially available blood-based technologies are not sensitive enough to reliably detect early signs of cancer or relapse, and physicians cannot be confident they are getting a complete and accurate picture of a patient's cancer through ctDNA analysis. Dr. Liu is working to improve these blood-based technologies to make them more clinically useful. To do so, he's testing different liquid biopsy technologies, including those developed by Drs. Scott Bratman and Daniel De Carvalho, both past Invest in Research grant recipients. Dr. Bratman and Dr. De Carvalho's diagnostics start-up, Adela, recently raised $60 million in investment financing.

The Progress

2021 was a challenging time for research because of the ongoing COVID-19 pandemic, which made it more difficult to hire key research staff. Despite some initial set backs, Dr. Liu and his team are making great progress. Their Invest in Research funding helped attract a CIHR grant to run parallel research, expanding the scope of their liquid biopsy work. By the end of 2021, the team had collected all the necessary samples, and hope to have results to better understand the liquid biopsy technology in early 2022.

Your Investment Leveraged to Attract Funding

The Invest in Research grant was leveraged for two additional funding opportunities. The Canadian Health Institutes of Health Research granted Drs. Liu and Bratman $995,295 over five years to refine the use of liquid biopsy in the early detection of lung cancer. A further collaboration of at least $500,000 was also negotiated with Adela to develop this technology into a pan-cancer early detection signature. This work is expected to take two to three years to complete and will involve international samples across multiple cancer sites.

Targeting Colorectal Cancer Cells in the Drug-tolerant Persister State

Dr. Catherine O'Brien,

Surgeon-Scientist

The Problem

Treatment resistance is a significant clinical challenge across many types of cancer. Some patients respond well to chemotherapy or targeted therapy at first — their tumour shrinks, for example, or their blood shows signs that their leukemia is abating — but then improvement stops and the cancer progresses. Research has shown that during the period when patients are initially responding to therapy, their cancer cells can enter what is called a drug-tolerant persister (DTP) state. The DTP state occurs in many cancers, and in response to both chemotherapy and targeted agents. Understanding the biology of cells in the DTP state and learning how to overcome this barrier to sustained treatment efficacy is an important focus for research.

The Solution

In studying treatment resistance, many researchers have focused on genetic mutations in cancer cells that make the cells permanently resistant to therapies. Dr. O'Brien discovered that prior to developing permanent treatment-resistance underpinned by genetic mutations, all colorectal cancer cells enter the DTP state. At this time, they exhibit a temporary,

reversible resistance. To describe the DTP state in cancer cells, Dr. O'Brien uses the metaphor of a hibernating bear: like bears resisting the harsh environment of winter, cancers may "hibernate" to resist the toxic environment of chemotherapy, dividing much more slowly and conserving their energy while they wait out the chemotherapy. When treatment ends, however, the cells are capable of resuming their original rhythms: their division accelerates, and the patient's cancer returns. Dr. O'Brien has been investigating methods, including combinations of therapies, to ensure that the cancer cells don't merely hibernate, but are killed permanently.

The Progress

Using extensive studies in mice, Dr. O'Brien's team have discovered that when cells enter the DTP state, clinicians have a valuable therapeutic opportunity: a window of time when cancer cells are present but lying low. In this window, cancer cells have developed mutations that make their resistance to therapy permanent. Dr. O'Brien's research has explored the potential of therapies to make targeted attacks on cancer cells while they're in the DTP state. Specifically, she has successfully tested an intervention designed to destroy cancer cells by preventing them from deriving nourishment from their own proteins — a survival mechanism cells rely on in the DTP state. After testing these interventions in mice, Dr. O'Brien is now co-principal investigator on a clinical trial led by Dr. Eric Chen to test whether these interventions will be successful in patients diagnosed with colorectal adenocarcinoma. Dr. O'Brien is thrilled to see her research continuing to the next level of potential impact in patients. This trial would not be possible without the funding received from the Invest in Research grant. This funding made it possible to carry out preclinical in vivo testing which was leveraged to obtain funding for the clinical trial.

Your Investment Leveraged to Attract Funding

Combined, Dr. O'Brien has recieved grants totaling just under $1 million, including a Canadian Cancer Society Challenge Grant to continue the research.

Detecting and Monitoring Molecular Residual Disease (MRD) in High-Risk Melanoma Patients through Novel Circulating Tumour DNA (ctDNA) Profiling Technologies

Dr. Anna Spreafico,

Medical Oncologist and Clinician Investigator

The Problem

Melanoma, a form of skin cancer, is sometimes easily cured through the removal of a superficial growth. The disease becomes much more serious if it

spreads to other parts of the body. When patients are diagnosed before their cancer has spread, surgical removal of the melanoma is the obvious first step. Clinicians then face the question of whether patients are at a high risk of recurrence and should receive additional treatment. Insufficient treatment can cause localized cancers to progress to an incurable stage. However, anticancer therapies can cause potentially long-lasting or toxic side effects. Therefore, their use should ideally be limited to patients who will benefit most. One important research goal is to improve our ability to predict which patients are at high risk of recurrence, so we can plan personalized treatments or avoid unnecessary treatments altogether. Tailored therapies not only have the potential to improve cure and survival rates, they could also result in a more efficient use of the limited resources available for cancer care and research. The process would involve the identification of measurable indicators called biomarkers that can accurately predict disease progression, survival outcomes and treatment response. However, there is currently no reliable molecular method to identify which melanoma patients are at most risk of recurrence or most likely to benefit from certain therapies.

The Solution

Circulating tumor DNA (ctDNA) has recently emerged as a promising biomarker that can identify cancer cells through an easily accessible blood draw, also called a liquid biopsy, even before CT scan detection. The development of such a biomarker is a critical step toward enhancing clinical decision-making, accurately measuring the extent of a patient's disease, assessing prognosis, and predicting treatment response. With SAMBA, an observational study of patients with high-risk melanoma, Dr. Spreafico is assessing the sensitivity of liquid biopsies to detect ctDNA. The study aims to compare the ctDNA in melanoma patients receiving different kinds of therapies and determine if liquid biopsies can predict cancer recurrence. This sophisticated blood test might detect cancer cells in cases where clinicians believe the disease has been eliminated. This early detection tool could allow doctors to intervene with more treatment before a patient's cancer regrows. Ultimately, results from this project will help the design of clinical trials evaluating ctDNA as a biomarker to detect residual disease and to better guide and personalize treatment decisions.

The Progress

Dr. Spreafico and her team recruited 81 patients to SAMBA; all had surgically removed melanoma. Using over 300 blood samples collected from these patients at different stages of disease and treatment, the team has started analysis of the melanoma DNA. Early results have been promising. The liquid biopsies detected the presence of cancer that was also confirmed by CT scans in the same patients, suggesting that the tests have the potential to be incorporated in clinical decision-making steps. Patients stand to benefit significantly if these blood tests enable clinicians to detect cancer earlier than ever. Liquid biopsies could also provide other genetic details to help personalize treatment for each patient.

Your Investment Leveraged to Attract Funding

Your support for Dr. Spreafico's research has provided a springboard for new grant applications for a further study, Clear Molecular Residual Disease in patients with Melanoma or CLEAR-Me. This trial will build on the early-detection capabilities of the liquid biopsy technology validated through SAMBA for a new high-risk group of patients.

The Princess Margaret difference is that our researchers always ask, and try to answer, the hard questions. Whether that is looking for new ways to detect lung cancer, understanding the root causes of why some cancer cells persist despite treatment, or decreasing wait times between diagnosis and treatment – we always strive to take a step beyond. Invest in Research is vital to enabling our scientists to pursue highly challenging, highly rewarding projects. Thank you. Your partnership is having a deep impact on cancer research here and around the world."

– Dr. Miyo Yamashita

President & CEO
The Princess Margaret Cancer Foundation

Enhancing the Patient Experience and Clinical Research

For more information please contact:

Michael Wilson
Chair, Invest in Research
(416) 229-5560
michael.s.wilson@cibc.ca

Karina Wong
Senior Manager, Leadership Giving
(416) 992-0080
karina.wong@thepmcf.ca

To learn more visit thepmcf.ca/investinresearch

The Princess Margaret Cancer Foundation UHN

610 University Avenue, Toronto, ON M5G 2M9
Charitable Organization No. 88900 7597 RR0001