2015 New Frontiers Program Project Grants Competition Recipient ~ Quebec

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

PROJECT TITLE: Oncometabolism and the Molecular Pathways that Fuel Cancer

AWARD TOTAL: $5,317,448

DURATION: 2015-2019

CO-FUNDING PARTNER:
McGill University's Rosalind & Morris Goodman Cancer Research Centre Fund: $554,512

The Quebec Breast Cancer Foundation: $500,000

PROJECT LEADER: Vincent Giguère

INVESTIGATORS: Russell Jones, Nahum Sonenberg, William Muller, Julie St-Pierre, Arnim Pause, Peter Siegel, Ivan Topisirovic, Michael Pollak

Dr. Vincent Giguère

Dr. Vincent Giguère, an international leader in the field of nuclear receptors, is a professor in the Departments of Biochemistry, Medicine and Oncology at McGill University and a researcher at the Goodman Cancer Research Centre. Dr. Giguère identified several members of the superfamily of nuclear receptors and revealed mechanisms demonstrating how these proteins work at the molecular level. His groundbreaking work also led to major advances in our understanding of the roles played by nuclear receptors and their natural and synthetic ligands in embryonic development, adult physiology and several diseases, most notably breast cancers. His most recent work has focused on understanding of how cancer cells meet the energy and resource requirements to sustain the needs of rapidly growing tumours, which intra-cellular metabolism is different from normal cells. Dr. Giguère and his team has identified a nuclear receptor referred to as ERRa that acts as a key regulator of cancer cell metabolism, and has shown that ERRa activity contributes to promote metabolic adaptations required for cancer cells to survive and then become resistant to the insult of anti-cancer drugs.

Quebec team focuses on metabolic causes of cancer with goal of preventing its growth, spread in diseases like breast cancer

Cancer cells flourish in our bodies by overcoming significant internal and external stresses and constantly adapting to new environments. Armed with new funding from the Terry Fox Research Institute and partners*, Montreal-based researcher Dr. Vincent Giguère is leading a team at McGill University with the goal of unravelling the mysteries of cancer metabolism.

Metabolism is defined as the chemical processes occurring within living organisms or cells that are necessary for life, such as utilizing oxygen and nutrients. Most normal cells in our body get their energy from fatty acids while cancer cells preferentially use sugar glucose, which makes both energy and building blocks - something fat can't do as well.

"People have tried for many years now to block the cancer cells from utilizing glucose, and that doesn't work so well," says Dr. Giguère, project leader and a professor of biochemistry at the Rosalind and Morris Goodman Cancer Research Centre. "We have to better understand how cells take up and metabolize glucose and the pathways that are used to enable this process if we are to successfully kill the cancer cells."

The team is working on various strategies to block the key metabolic pathways necessary for growth and survival of cancer cells. Interrupting these metabolic processes could prevent cancer from metastasizing or becoming resistant to treatment – two problems that cause 90 per cent of breast cancer deaths.

"Our main goal is to study the relationship between metabolic processes and metastasis in cancer cells," says Dr. Giguère. "We are trying to find the metabolic functions that allow cells to survive under stresses such as chemotherapy, targeted therapy, as well as adapting to new environments."

Dr. Giguère says that TFRI is the "prime driver" of this team's exciting new project, which brings together leading cancer researchers from McGill's Goodman Cancer Research Centre, including many long-time funded Terry Fox investigators.

"This is a very new aspect of cancer research that we think will be very successful, especially in combating cancer metastasis and the resistance to drugs that are used currently in the clinic," says Dr. Giguère. "It's really new and exciting, and there's a great future for this."

2015 New Frontiers Program Project Grants Competition Recipient ~ British Columbia

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

PROJECT TITLE: Discovery and Therapeutic Development of Antibody-Based Targets in Oncology

AWARD TOTAL: $2,250,000

DURATION: 2015-2018

CO-FUNDING PARTNER: BioCanRx: $750,000

PROJECT LEADER: Steven Jones

INVESTIGATORS: John Babcook (SFU), François Bénard, Gregg Morin, Kuo-Shyan Lin, Tomas Hudlicky (Brock University), Paul Schaffer (TRIUMF)

Dr. Steven Jones

Dr. Steven Jones is associate director and head of bioinformatics for Canada's Michael Smith Genome Sciences Centre at the BC Cancer Agency and a professor at both the University of British Columbia (Department of Medical Genetics) and Simon Fraser University (Department of Molecular Biology & Biochemistry).

Dr. Jones gained his PhD at the Sanger Institute, Cambridge, UK in 1999, where he was involved in the *C. elegans* genome project. He has played a role in numerous other genome projects, including that of the human, mouse, rat, bovine, fruitfly and the SARS coronavirus. Dr. Jones' major research focus is in the computational analysis of DNA sequence and the analysis of genomic and transcriptomic data. In health care research, he has applied next generation DNA sequencing technology to detect mutations arising in both patient samples and in cancer cell lines in various cancer types and under the influence of different therapeutics.

Keeping normal cells healthy, reducing negative side-effects of chemo-drugs are aims of team developing better therapeutics for patients

Many chemotherapeutic drugs used to treat cancer result in tremendous toxicities for patients that can have many negative side effects, including some that are long-lasting, without ever actually curing the disease. Dr. Steven Jones' TFRI-funded PPG team is working to improve this reality for many patients and their clinicians.

"Chemotherapeutics are, in many cases, poisons that seem to affect the rapidly growing tumours more than normal cells," says Dr. Jones, associate director of Canada's Michael Smith Genome Sciences Centre at the BC Cancer Agency in Vancouver. "We are trying to develop new ways of treating cancer patients to make drugs that are more targeted to the actual tumours, instead of poisoning both cancerous and normal cells."

Cytotoxic effects from chemotherapy often have long-lasting consequences, for example: hair loss, nausea and vomiting, problems in the blood and bone marrow, and infertility.

Dr. Jones' three-year PPG, which is funded in partnership with BioCanRx, aims to identify protein markers on the surface of tumour cells that don't exist in many normal tissues and cell types. Antibody drug conjugates will then be developed to bind only with these proteins and specifically target tumour cells, leaving the normal cells unharmed.

"The idea is that by attaching a drug to an antibody you're specifically targeting it to a certain place or cell type in the body, decreasing the cytotoxic effects and increasing the concentration where you want it," he adds.

An advantage to his team's approach is they are not targeting any cancers in particular, says Dr. Jones. All data will be examined to determine the tumour type that has the best markers on it, making it most receptive to this method of treatment. Investigators on the project also come from the Centre for Drug Research and Development, Simon Fraser University and TRIUMF, all in BC, and Brock University (ON).

"I think this project encompasses the paradigms of personalized medicine," says Dr. Jones. "Imagine a world where we could be identifying patients that have that particular markers, and then tailoring the specific antibody drug conjugate to that patient….It's very exciting!"

2015 New Frontiers Program Project Grants Competition Recipient ~ Ontario

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

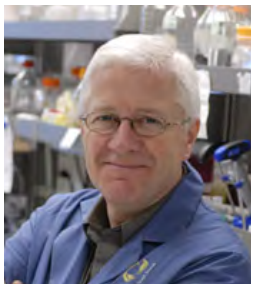
PROJECT TITLE: Development of Stemness-Based Prognostic Biomarkers and Therapeutic Targets

AWARD TOTAL: $6,228,373

DURATION: 2015-2020

PROJECT LEADER: John Dick

INVESTIGATORS: Norman Iscove, Rodger Tiedemann, Peter Dirks, Gary Bader, Carl Virtanen, Mathieu Lupien, Mark Minden, Aaron Schimmer, Thomas Kislinger, Donna Reece, Stephane Angers, Quaid Morris



Dr. John Dick

John Dick is a senior scientist at the Princess Margaret Cancer Centre and the McEwen Centre for Regenerative Medicine of the University Health Network and professor of molecular genetics at the University of Toronto. Dr. Dick is also director of the Cancer Stem Cell Program at the Ontario Institute for Cancer Research. Dr. Dick's research has revolutionized the study of normal and leukemic stem cells. Two of his most important achievements were developing a system for transplanting normal and malignant hematopoietic cells into immune-deficient mice to identify and characterize both normal and leukemic stem cells. His lab established that only a small proportion of leukemic cells were capable of initiating leukemia within the immune-deficient mice, providing direct evidence for the cancer stem cell hypothesis.

Dr. Dick's seminal contributions to the fields of molecular hematology, stem cell biology and oncology have been recognized by his election as a Fellow of both the Royal Society of Canada (2004) and the Royal Society of London, UK, (2014) and numerous prestigious awards at the national and international level.

Toronto team focuses on better understanding cancer 'stemness' to improve therapy and increase survival for patients with high-risk cancers

There is an analogy senior scientist Dr. John Dick uses when explaining his TFRI-funded cancer stem cell (CSC) research. He compares cancer to a weed that has a separate root to the stem, branches and leaves, with the tumour as the leafy top.

"Cancer, just like a weed, can only be killed if the root is removed entirely – not just the tumour at the top," says Dr. Dick, from his laboratory in Toronto's Princess Margaret Cancer Centre. "In our studies, cancer stem cells were found to act like the root and were responsible for initiating and sustaining cancer growth."

Not all cancer cells in a tumour are created equally or function the same, he remarks, much like parts of a plant. It is the "stemness" characteristic of CSCs that is responsible for both patients' response to treatment and the cancer's ability to regenerate and spread.

Building on his previously funded program project grants and important findings, Dr. Dick's latest funded, five-year project aims to understand the nature of the CSCs in high-risk cancers, including two blood cancers (acute myeloid leukemia and myeloma) and one solid tumour (glioblastoma, a type of brain tumour). These are cancers with poor outcomes that are urgently in need of better treatments.

"Our discoveries will provide us with a better understanding of cancer recurrence that can reappear months or years later from the surviving CSC," he says. "We want to find the Achilles heel of these cells and target them to be able to reduce therapy failure and ultimately increase patient survival."

Dr. Dick credits TFRI with giving his team the opportunity to "delve into unexplored areas" and expand on their groundbreaking cancer stem cell discoveries.

"We've had a great team and we've worked on this very collaboratively, says Dr. Dick. "We're looking forward to harnessing our collective insights in a concerted way. It's very gratifying to get this support from TFRI again for another five years."

2015 New Frontiers Program Project Grants Competition Recipient ~ Ontario

The Terry Fox Research Institute
L'Institut de recherche Terry Fox

PROJECT TITLE: Li-Fraumeni Syndrome: Applying Genetic Determinants of Cancer Risk to Cancer Surveillance and Prevention

AWARD TOTAL: $2,249,993

DURATION: 2015-2018

PROJECT LEADER: David Malkin

INVESTIGATORS: Andrea Doria, Anna Goldenberg, Adam Shlien, Jason Berman (Isaac Walton Killam Health Centre)

Dr. David Malkin

Dr. Malkin is a professor of pediatrics and medical biophysics, POGO Chair in Cancer Control in the Faculty of Medicine at the University of Toronto, and medical director of the Pediatric Oncology Group of Ontario (POGO). He is a pediatric oncologist in the Division of Hematology/Oncology, Director of the Cancer Genetics program at The Hospital for Sick Children (SickKids), and a senior scientist in the Genetics and Genome Biology Program in the SickKids Research Institute. His laboratory focuses on 1) genetic and genomic mechanisms of childhood cancer susceptibility, in particular the Li-Fraumeni Syndrome; and 2) signaling pathways and novel therapeutic targets in rhabdomyosarcoma. Recently, his work has focused on application of this genetic/genomic information to develop rational clinical surveillance and treatment guidelines for children and adults deemed at genetic 'high risk' for cancer. He has been an invited speaker for the volunteer kick-off events for the annual Terry Fox Runs and has participated in these runs for many years.

Team hopes to develop new ways to detect and prevent tumours for families living with Li-Fraumeni Syndrome

What would you do if you were diagnosed with a rare disease in which patients have an almost 100 per cent chance of developing cancer in their lifetime – in any part of the body and at any age – and the options for treatment were limited? These are just a few of the dilemmas posed by Li-Fraumeni Syndrome (LFS), a rare and primarily inherited disease that Toronto researcher Dr. David Malkin and his TFRI-funded PPG group are working on.

"The challenges faced by these children and families are devastating," says Dr. Malkin, the project's principal investigator based at The Hospital for Sick Children in Toronto. "There is currently no way to predict which individual will develop cancer, when that cancer might occur, or what types of cancer will actually develop in an individual. Families are basically just waiting for something to happen."

LFS is caused by inherited mutations in a gene called TP53, one of the most frequently mutated genes in human cancers, and affects around one in 2,000 to 5,000 people.

Dr. Malkin's project will sequence the DNA of all the study's participants to create a predictive model for determining both the type of cancer and at what age a patient would be most likely to develop it. All of the molecular testing and genetic studies will be done primarily on children, with some adults also involved.

The team is comprised of researchers from two Canadian cities, Toronto and Halifax. The Toronto team members will also develop a surveillance blood test to detect tumours in LFS patients before a patient has any symptoms, while the Halifax team is using mutated zebra fish to identify drugs that may be able to prevent tumours from developing in patients with LFS.

This PPG is very unique, says Dr. Malkin, and is a great example of a successful interdisciplinary collaboration to improve the lives of families living with LFS.

"TFRI is allowing us to take a major problem and come at it from four or five very different ways under one umbrella," says Dr. Malkin. "We've got human genetics, diagnostic imaging, radiology, zebra fish modeling, and computer science on one project – and that is an incredible breadth of scientific expertise working together to solve this…and that's so exciting!"