general overview

Terry Fox (1958-1981)

Terry Fox has become an inspiration to us all. Terry Fox was 18 when he was diagnosed with cancer and lost one leg to it by amputation. In 1980 he started to run across Canada in his Marathon of Hope to support cancer research. He wrote in his letter seeking support, "I will be ready to achieve something that for me was once only a distant dream reserved for the world of miracles—to run across Canada to raise money for the fight against cancer. We need your help. The people in cancer clinics all over the world need people who believe in miracles."

He has received many honours and awards and today is recognized by many as Canada's greatest hero. His legacy lives on through The Terry Fox Foundation, the millions of people who participate in Terry Fox Runs around the world, the millions of generous donors worldwide who give to cancer research, and the Terry Fox Research Institute.

The Terry Fox Foundation (TFF)  

www.terryfox.org

The Terry Fox Foundation (TFF) maintains the vision and principles of Terry Fox while raising money for cancer research through the annual Terry Fox Run, National School Run Day and other fundraising initiatives. To date, over $700 million has been raised worldwide for cancer research in Terry Fox's name. The first Terry Fox Run was held in 1981, with The Terry Fox Foundation being created in 1988. Its national headquarters are located in Burnaby, BC and it has offices in 9 provinces.

The Foundation invests in cure-oriented, biomedical research through its flagship program, The Terry Fox New Frontiers Program Project Grants. It also supports capacity-building research through its New Investigator awards. The Foundation research portfolio is managed by The Terry Fox Research Institute and affiliated partners.

The Terry Fox Research Institute (TFRI)  

www.tfri.ca

Launched in October 2007, The Terry Fox Research Institute (TFRI) is the brainchild of The Terry Fox Foundation and today acts as its research arm, overseeing its complete portfolio of cancer research projects. TFRI seeks to improve significantly the outcomes of cancer research for the patient through a highly collaborative, team-oriented, milestone-based approach to research that will enable discoveries to translate quickly into practical solutions for cancer patients worldwide. TFRI collaborates with over 73 cancer hospitals and research organizations across Canada. Headquartered in Vancouver, BC, the Institute has six nodes across Canada which interact with regional partners and support the mission and vision of the Institute.

Annual scientific participants visit the statue of Terry Fox during an early morning run in May 2015.
The projects and publications listed in this summary of Terry Fox research represent some of the best cancer research being conducted in Canada. Provided by our project leaders, these scientific summaries describe research funded by The Terry Fox Foundation and its partners. Funding partners are acknowledged for specific projects. We are deeply grateful to the patients who participate in this research, and to our researchers, clinicians, scientists and their staff for their dedication, expertise and commitment to making a difference for all cancer patients.

The Terry Fox Research Institute supports five areas of cancer research:

**Terry Fox New Frontiers Program Project Grants**  These programs support Canadian research teams exploring new frontiers in cancer research through the funding of three or more outstanding independent research projects around a common theme. An open competition is offered annually through TFRI to select the best program projects for funding.

**Terry Fox New Investigator Awards**  These awards provide a three-year operating grant to independent cancer researchers within the first five years of their first faculty appointment. New Investigators are sponsored and mentored by an existing translational project or New Frontiers Program Project team.

**Terry Fox Translational Pan-Canadian Cancer Research**  These programs support Canadian multidisciplinary teams to develop collaborative pan-Canadian research projects to align with its translational research mandate. These projects mostly target a specific cancer with a focus on moving discoveries and knowledge into practical solutions for patients within a relatively short time frame. This is accomplished via an iterative process of developing milestone-driven “business plans” to focus on the outcomes impact of the research. An open competition is offered annually through TFRI to select the best project for funding. TFRI provides one award per year.

**Terry Fox Cancer Research Training Program**  TFRI currently supports five integrated training programs across the country.

**Terry Fox International Run Program Grants**  Globally, The Terry Fox Foundation fundraises through its International Run Program. Funds raised support research projects in countries where the run is held. [www.terryfox.org/InternationalRun/](http://www.terryfox.org/InternationalRun/)

On the occasion of the 35th anniversary of the Marathon of Hope, TFRI’s 6th Annual Scientific Meeting was held in St. John’s, Newfoundland, where Terry began his run in 1980.

Oral poster presentation trainees are congratulated by Terry’s brother Darrell Fox (sixth from left) and Judith-Fox Alder (right), Terry Fox’s sister, at our meeting in May 2015.
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A personalized oncolytic vaccine: Using oncolytic viruses to exploit neo-antigens derived from the tumour mutanome

Terry Fox New Investigator Operating Grant (2012-2015)

Investigator: Rebecca Auer, Ottawa Hospital Research Institute

Mentoring Program: Canadian Oncolytic Virus Consortium (COVCo)

Scientific Summary: The immune system plays a central role in the cancer outcomes of most solid tumours, in particular in the eradication of micrometastatic disease following surgical resection of the primary tumour. Cancer immunotherapies must effectively target ‘self’-derived tumours while avoiding autoimmune side effects, a potentially fatal penalty for effective immunotherapy. A recent focus in the field of cancer immunotherapy is “immunomics”-combining immunology with genomics to identify neo-epitopes, based on tumour-specific somatic mutations (the ‘mutanome’), with the goal of designing personalized cancer vaccines that are less likely to produce autoimmune pathology.

The rapid advances in next-generation sequencing means that personalized cancer vaccines will be realized in the next five years. A promising cancer vaccine platform is based on oncolytic viruses (OV). OVs selectively replicate in tumour cells resulting in immunogenic cell death. Oncolytic vaccines (OV expressing tumour antigens) provide an even more powerful boost to pre-existing antitumour immunity by combining viral oncolysis with the presentation of tumour antigens. The Terry Fox Canadian Oncolytic Virus Consortium is a leader in the development of oncolytic vaccines and combining this strategy with a personalized approach to antigen selection, based on the tumour ‘mutanome’ represents a highly novel application of both technologies. When used in combination with surgery, this cancer vaccine strategy has the potential to impact over 65,000 Canadians who undergo surgical resection of their solid tumour every year.

Hypothesis: We hypothesize that the antitumoural immunity induced by viral oncolysis can be utilized to identify immunogenic neo-antigens derived from the tumour ‘mutanome’. We further hypothesize that immunizations with oncolytic vaccines expressing these mutated sequences will result in a therapeutic antitumour immune response without development of autoimmunity and that this strategy can be successfully combined with surgical resection of the primary tumour to eradicate micrometastatic disease.

Specific Aims:

(1) Determine the effect of tumour oncolysis on the in-vivo generation of T cell mediated immune responses to mutant peptide neo-antigens derived from the B16 ‘mutanome’.

(2) Assess the therapeutic and autoimmune effects of a prime-boost vaccination strategy using a recombinant adenovirus vaccine vector and a complementary replicating rhabdoviral oncolytic vaccine expressing selected mutant peptide neo-antigens derived from the B16 ‘mutanome’.

(3) Evaluate a perioperative prime-boost immunization strategy to treat metastatic disease in combination with surgery in a B16 tumour model

Methods: In this project we will make use of the murine B16 melanoma model, one of the most widely used models for scientific validation of T cell-based immunotherapies, and for which the ‘mutanome’ has been published. This project will establish the pre-clinical ‘proof of concept’ for a personalized oncolytic vaccination strategy that can ultimately be employed in patients following deep sequencing of their own tumour.
List of Key Publications:


The systems biology of tumour hypoxia

*Terry Fox New Investigator Operating Grant (2014-2016)*

**Investigator:** Dr. Paul C. Boutros, Ontario Institute for Cancer Research  
**Mentoring Program:** A research pipeline for hypoxia-directed precision cancer medicine

**Scientific Summary:** Human cancers reside in a local micro-environment unlike that of any normal tissue. Through a variety of processes, tumour cells interact with and modulate their immediate micro-environment. These micro-environments contain areas of very low oxygen concentration, called hypoxic regions, which can contain cells that have adapted to severe metabolic stressors and are resistant to cytotoxic chemotherapy and radiotherapy. These cells can also acquire genetic instability and lead to an increased capacity for metastatic spread. A greater understanding of tumour hypoxia within a clinical context is critical to improving outcomes across multiple cancer types. To achieve this, I am creating computational techniques that relate the molecular characteristics of hypoxic cells and their surrounding micro-environment to clinical heterogeneity in patient response to therapy and overall prognosis.

**Aims:** The first key aim of this project is to develop ways to accurately predict specific micro-environmental phenomena from molecular data. We are taking two complementary approaches to this problem: one based on using Bayesian probabilistic models to distinguish distinct cellular populations, and the other employing genomic data to predict specific micro-environmental characteristics. The second key aim of this project is to create joint micro-environmental-molecular models to predict patient outcome and response to therapy. We are extending our previous graph-theory-based approaches for biomarker prediction, integrating known functional pathways with micro-environmental and other molecular characteristics. Validation of both aims is occurring with new datasets being generated by the TFRI Tumour Hypoxia Program Project.

**Updates:** We have created a way of merging tumour microenvironmental and genomic data into a model that very accurately predicts patient survival. This model is now undergoing validation in new cohorts in a CLIA setting, with the aim of it being used in routine clinical practice. We also developed a series of computational tools that are now in wide-use by scientists both within and outside of Canada to improve the way that they analyze cancer genomic data. Finally, we created the first spatial map of genomic heterogeneity within prostate cancer, giving specific guidance on how biomarkers for personalized medicine can account for this inherent variability in tumours.

**List of Key Publications:**
Evaluation of oncolytic immunotherapy in canine cancer trials: A stepping stone towards successful translation into human patients

*Terry Fox New Investigator Operating Grant (2015-2018)*

**Investigator:** Byram W. Bridle, University of Guelph

**Mentoring Program:** Canadian Oncolytic Virus Consortium (COVCo)

**Collaborators:** J. Paul Woods, Anthony Mutsaers and Geoffrey Wood, University of Guelph; Jean-Simon Diallo, Hesham Abdelbary and Joel Werier, Ottawa Hospital Research Institute

**Scientific Summary:** Osteosarcoma (OSA) is the most common form of primary bone cancer. When patients present with metastases, the prognosis is dismal despite aggressive surgical resection and chemotherapy. Dogs have a 10-fold higher incidence of OSA and its pathogenesis closely mimics the human disease, with a similarly poor prognosis. The hypothetical basis of this proposal is that adjunct oncolytic immunotherapy can augment the standard of care in OSA patients. The applicant has published a strategy to synergize cancer immunotherapy that directs the power of the immune system against tumours, with oncolytic virotherapy that utilizes viruses that replicate in and kill only cancerous cells. This synergy could be achieved by using an oncolytic rhabdovirus as a tumour-associated, antigen-expressing vaccine to boost adenovirus-primed, tumour-specific immune responses. The primary objective of this proposal is to test this novel biotherapy in the context of a clinical canine OSA trial. The long-term goal is to refine the approach for translation into human patients. Primary, secondary and tertiary endpoints of the trial are induction of detectable OSA-specific T-cell responses and increase median progression-free and overall survival between dogs receiving the standard of care with adjunct oncolytic immunotherapy versus those treated with the standard of care alone. Predicted benefits include prolonged remission time, extended survival and enhanced quality of life. Attempts will be made to correlate tumour-antigen expression, intra-tumoural gene and cytokine signatures with clinical outcomes in an effort to identify novel biomarkers and new therapeutic targets. Two small-scale projects will assess the potential benefits of incorporating histone deacetylase inhibition or treatment with liposome-encapsulated clodronate into the oncolytic vaccine therapy. The goal of these pre-clinical projects is to develop more advanced forms of the therapy that can be tested in future canine clinical trials. Access to the state-of-the-art Animal Cancer Centre at the University of Guelph, which has a huge catchment area, combined with the logistical infrastructure, intellectual property (e.g. the potential to license novel veterinary therapeutics) and expertise developed through this project will be a valuable and unique Canadian resource that can be leveraged by the sponsoring partner (COVCo) and TFRI to facilitate translation of the most promising and highly refined biotherapeutics into human cancer patients.

**Aims:**

1. **Primary objective:** Evaluate the efficacy of an MG1-vectored oncolytic booster vaccine in a canine osteosarcoma clinical trial.
2. **Pipeline project #1:** Test a more advanced iteration of the oncolytic vaccine therapy that incorporates histone deacetylase inhibition. This study will determine a safe dose of the MG1 oncolytic booster vaccine that can be used in combination with the HDI entinostat in a dose-escalation study in Ad-vaccinated purpose-bred research dogs. The objective is to develop the rationale to propose testing of a next-generation therapy in a new clinical canine osteosarcoma trial at the time of renewal of this grant.
3. **Pipeline project #2:** Use liposome-encapsulated clodronate to deplete splenic marginal zone macrophages to simultaneously enhance oncolytic vaccine-induced secondary T-cell responses, improve intratumoural delivery of the virus, remove immunosuppressive myeloid-derived suppressor cells and deplete osteoclasts that cause bone loss and spontaneous fractures in osteosarcoma patients. This represents an extremely novel pre-clinical project and aims to generate data to inform the design of a future study in purpose-bred research dogs.

**Updates:** Although funding only commenced three months ago, a PhD-level graduate student and postdoctoral fellow have been recruited to conduct research. In addition, two summer students were hired to assist with the research.
The graduate student has begun constructing the viral vectors needed for the pre-clinical, mouse-based project that has been proposed. The postdoctoral researcher is constructing the viruses needed for the clinical canine osteosarcoma trial. One of the summer students optimized a flow cytometry-based method to quantify activated T-cells. This will be used to monitor immune responses in the upcoming dog trial. The other summer student confirmed, by Western blotting, that our proposed target antigen (survivin) is highly expressed by osteosarcomas in our companion animal tumour bank but not matched normal tissues. We have also optimized a method to transiently deplete splenic marginal zone macrophages as well as the method needed to assess this. Once viral vectors are rescued, the next steps will include: working with collaborators to produce veterinary clinical trial-grade batches and then assessing their safety in a Canadian Food Inspection Agency/Canadian Centre for Veterinary Biologics approved study.

List of Key Publications:


Deciphering the role of chromatin demethylases in high-risk pediatric acute myeloid leukemia

*Terry Fox New Investigator Operating Grant (2015-2017)*

**Investigator:** Sonia Cellot, CHU Ste-Justine  
**Mentoring Program:** Core pathogenic pathways in human leukemia  
**Funding Partner:** The Cole Foundation, La Fondation CHU Sainte-Justine, La Fondation du Centre de Cancérologie Charles-Bruneau

**Scientific Summary:** Chromatin methylation patterns impact on cell fate decisions, such as stem cell self-renewal and differentiation, in both hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs). Regulators of chromatin methylation dynamics are involved in normal blood development, and their perbutation can lead to cancer. This is best exemplified by the histone methyl transferase MLL (mixed lineage leukemia), which is critical in regulating normal HSC fate decisions, while mutations in the MLL gene are found in more than 70% of infant leukemia. Like MLL, several epigenetic regulators are deregulated in aggressive forms of leukemia. Epigenetic regulators are under active pharmacological scrutiny as promising drug targets in leukemia, and chemical probes now become available at a rapid pace. Pediatric acute myeloid leukemia (AML) is a heterogeneous disease with sub-optimal survival rates. Using an RNAi- and chemical-based screening strategy, we want to identify demethylases that are critical to sustain leukemia, and assess their their role in normal HSC fate regulation. The research program greatly benefits from synergistic collaborations with stem cell biology leaders and members of the thematically related TFRI Program Project Grant in Core Pathogenic Pathways in Human Leukemia, led by Dr. K. Humphries (BC Cancer Agency).

**Aims:** To develop a functional screening platform using RNAi- and chemical-based approaches to assess the role of epigenetic regulators, and in particular chromatin demethylases, in the context of pediatric acute myeloid leukemia. We anticipate that AML subtypes will display specific demthylase dependencies, given the heterogeneity of the disease, and in particular the distinct entity that represents pediatric leukemia. A counterscreen will be performed using cord blood isolated HSC, to gauge for potential toxicity of demethylase inhibition on the normal hematopoietic system, a critical step in drug target identification. Identified hits will be validated *in vivo* using xeno-transplantation based assays. Epigenetic landscapes and expression profiles of HSC and LSC will be determined.

**Updates:** We have performed functional genetics screens to identify HSC regulators, using a pipeline of standardized HSC isolation, transduction and transplantation strategies. Among the Jumonji family of histone demethylases, we identified both positive (Jhdm1f/Phf8) and negative (Kdm5b/Jarid1b) regulators of mouse HSC activity, through an RNAi-based approach. These studies suggest that Jarid1b contributes to transcriptional repression of stemness associated genes and promotes cell differentiation. We now want to identify demethylases that modulate human HSC/LSC fate, using newly optimized culture conditions that sustain human cells *ex vivo* and novel high-risk acute myeloid leukemia (AML) models. For epigenetic and expression profile studies of AML specimens, we will exploit the pediatric branch of the Quebec Leukemia Cell Bank (www.bclq.gouv.qc.ca). Overall, we aim to identify pediatric leukemia specific drug targets, and investigate the role demethylases in normal human HSC.

**List of Key Publications:**


Epigenetic basis of myeloid malignancies

*Terry Fox New Investigator Operating Grant (2015-2017)*

**Investigators:** Martin Hirst, UBC; R. Keith Humphries, Aly Karsan, BC Cancer Agency;

**Mentoring Program:** Core pathogenic pathways in human leukemia

**Funding Partner:** BC Cancer Foundation

**Scientific Summary:** Acute myeloid leukemia (AML) remains one of the most lethal of adult malignancies, with long-term survival rates of <20% in patients under 65 and little improvement in treatment options for several decades. The goal of our research is to dissect the role of the epigenome in the pathogenesis of primary AML and quantitate the molecular and phenotypic changes associated with exposure to ascorbic acid (Vitamin C) in the context of AML harbouring inactivating *TET* or neomorphic *IDH* mutations. Comprehensive and quantitative epigenetic profiling of clinically annotated and genotyped primary leukemic cells combined with the study of an essential nutrient recently shown to have the capacity to activate TET will enhance our understanding of the mechanisms of epigenetics in cancer and the potential to reverse genetically driven epi-mutations.

We have recently demonstrated that vitamin C alters DNA methylation homeostasis and, in turn, the expression of specific genes by enhancing TET activity. In a TET dependent manner, vitamin C reduces CpG methylation at CpG islands (CGIs) via a hydroxymethyl-cytosine intermediate promoting a more primitive DNA methylation state in normal hematopoietic stem cells. My hypothesis is that vitamin C will partially or completely reverse epigenetic effects specifically of heterozygous *TET* and *IDH* mutations in AML via activation of the remaining wild type TET protein and hmC driven demethylation of aberrantly methylated CGIs. If successful, our research will provide evidence for a new class of therapeutics that act by upregulating endogenous epigenetic pathways and the opportunity of rapid translation for Canadian patients diagnosed with this deadly cancer type.

**List of Key Publications:**


Epithelial polarity in tumour invasion and metastasis

Terry Fox New Investigator Operating Grant (2011-2015)

Investigator: Luke McCaffrey, McGill University

Mentoring Program: Unraveling metabolic adaptations associated with disease progression and therapeutic response in metastatic breast cancer

Scientific Summary: Under the mentorship of the Preclinical Models and Therapeutic Targets for Metastatic Breast Cancer Program, our objective is to build a molecular understanding of how cell polarity regulates invasive and metastatic breast cancer with the goal of identifying novel prognostic markers and therapeutic targets. Metastatic progression correlates strongly with loss of tissue structure and organization; accordingly, cell polarity proteins are frequently disrupted in tumours, but the role of these key regulators in breast cancer progression is not understood. Accumulating evidence indicates that atypical protein kinase C (aPKC) isoforms, which are key transducers of polarity signalling, are disrupted in breast cancer and may have either oncogenic or tumour suppressive functions. Furthermore, we have found that the Par3 polarity protein is a key regulatory of aPKC in normal and tumourigenic epithelial cells. In this project we are further exploring the contribution of Par3 and aPKC in breast tumour progression. To address the objectives of our project, we have three primary questions:

- What are the mechanisms by which Par3/aPKC polarity organizes the mammary epithelium, and how this is disrupted in breast cancer?
- How do aPKC isoforms promote or suppress breast cancer progression?
- Does aPKC polarity mediate cancer stem cell activity to control the differentiation state of breast tumours?

Key Findings: We found that Par3 silencing dramatically reduced tumour latency in breast cancer mouse models and produced invasive and metastatic tumours that retained epithelial marker expression. Par3 depletion was associated with induction of matrix metalloproteinases, destruction of the extracellular matrix, and invasion, all mediated by atypical PKC-dependant JAK/Stat3 activation. Importantly, we found that Par3 expression is significantly reduced in human breast cancers, which correlates with active aPKC and Stat3. These data identify Par3 and aPKC as regulators of signaling pathways relevant to invasive breast cancer.

List of Key Publications:

Exploring clonal evolution in non-Hodgkin lymphomas using serial tumour sampling and liquid biopsies

*Terry Fox New Investigator Operating Grant (2015-2017)*

**Investigator:** Ryan Morin, Simon Fraser University  
**Mentoring Program:** Molecular correlates in treatment failure in lymphoid cancers  
**Funding Partner:** BC Cancer Foundation

**Scientific Summary:** We are studying the patterns of clonal evolution in aggressive non-Hodgkin lymphomas (NHLs) including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Substantial effort to date has been placed on understanding the genes that are commonly mutated in these two deadly cancers but little is currently known regarding clonal evolution patterns under the selective pressure applied by the standard treatments, such as chemotherapeutic agents and immunotherapy. We are performing genomic analysis of serial tumour biopsies to infer these changes and patterns of clonal evolution in individual patients. We are also seeking evidence for genes that are more commonly mutated at relapse due to clonal selection. In parallel, we are implementing methods for detecting and tracking somatic mutations non-invasively using a method known as “liquid biopsies” that involves sequencing genomic DNA shed from tumour cells that is present in blood plasma.

**Aims:** We aim to identify genes that are more commonly mutated at relapse in MCL and DLBCL and to determine the means by which these become enriched at relapse by more general clonal analysis of these tumours. Clonal architecture will be determined through computational analysis of bulk tumour sequencing data and single-cell analysis of disassociated tumour tissue. Liquid biopsies have shown utility for identifying clonal mutations in a variety of solid tumours but little is known regarding their utility in detecting and accurately representing mutations present at different clonal frequencies. We aim to firmly establish the extent to which clonal and subclonal mutations can be detected and differentiated via liquid biopsies in these NHLs.

**Updates:** We have analyzed 38 uniformly treated DLBCL tumour biopsies collected at relapse using exome sequencing and have identified the commonly mutated genes. For a subset of these cases, we sequenced matched diagnostic tumour DNA and observed patterns of clonal evolution in some of these patients. By comparing mutation prevalence to published cohorts, three genes were found significantly enriched for mutations at relapse. We found evidence for clonal enrichment of mutations in several of these genes in one or more patient, suggesting that aggressive subclones that contribute to relapse exist in some patients at the time of diagnosis. We are also studying liquid biopsies from each of these patients to determine the correspondence of mutation abundance in the plasma and tumour. In parallel, we have begun characterizing additional MCL patients using exome sequencing and single-cell analysis and await subsequent blood and biopsy samples from these patients for liquid biopsy applications.

**List of Key Publications:**


Understanding cancer stem cell heterogeneity and dynamics: Implications for therapy in human colorectal cancer

Terry Fox New Investigator Operating Grant (2013-2016)

Investigator: Catherine A. O’Brien, Princess Margaret Cancer Centre
Collaborator: Jason Moffat, University of Toronto
Mentoring Program: Genetic dissection of actionable targets required for maintenance of metastatic disease

Scientific Summary: We are developing and applying methods to better understand functional tumour dynamics at the level of the single cell. In the cancer stem cell (CSC), field experiments typically involve isolating CSC and non-CSC fractions and injecting them separately into immunocompromised mice at limiting dilution. Our hypothesis is that current experimental models in solid tumour CSC research, although widely accepted, do not provide a complete picture because they do not assess how CSC subsets interact with each other and with non-CSCs. The ability to track and isolate viable individual clones provides a powerful tool to study the clonal structure of tumours and how the clones interact with each other in the context of tumour formation. This model also provides a means to better understand the clonal composition of metastatic lesions, as compared to the primary tumour site. Finally, we are using lentiviral barcoding of individual cells to study response to therapeutic intervention, including standard-of-care chemotherapies and “stem cell” directed therapies at the clonal level. This work will provide unprecedented insight into how tumours recur following treatment, at the level of the individual cell.

Aims: Our work uses shRNA lentiviral barcode libraries to uniquely label individual cancer stem cells and follow them in the context of the bulk tumour, using human colorectal cancer (CRC) xenograft models.

In our first aim we are working towards demonstrating how clonal co-operation and competition influence overall tumour structure and growth patterns. In our second aim we are using the lentiviral barcoding system to study the effect of therapeutic intervention on the clonal structure of tumours at the level of the single cell. Another advantage of our model is that it will allow us to viably isolate, characterize, and test the therapy resistant clones we identify. In our final aim, we are studying clonal composition in the context of an orthotopic xenograft metastasis model of colorectal cancer. This work will allow us to identify patterns of clonal spread and help us to determine if there is a subset of CRC stem cells that are predisposed to metastasize. If we can identify clones that preferentially metastasize, we can viably isolate and characterize these specific CSCs.

Updates: We have successfully labeled and tracked individual cancer cells in vivo using three colorectal cancer xenograft models. We started by carrying out the gold standard test to enumerate CSCs, the in vivo serial passage limiting dilution assay. At limiting dilution we expected tumours to arise from a single CSC; however, we found that this is not always the case. Instead we are detecting clonal structures that suggest the existence of clonal co-operation and competition. We have isolated and are currently combining individual clones in vivo and in vitro to functionally define how individual clones interact with and influence each other’s growth.

The focus of the first aim is to better understand cancer cell co-operation and competition, at the level of the individual cells. The ability to understand how individual clones functionally interact is key to developing novel strategies aimed at targeting the tumour as a whole.

In our second aim we are treating barcoded CRC xenografts with standard of care chemotherapies and stem cell directed therapies. As a first step we are testing the efficacy of treatment strategies that decrease the relative abundance of all clones versus those strategies that decrease the overall clonal complexity. There is an assumption that less complexity would be favourable; however, this remains to be experimentally proven. The results obtained from our work will have important implications for the field.
In our final aim we have lentivirally barcoded CRC cells that have been orthotopically injected into immunocompromised mice and are currently awaiting the formation of liver metastases, the plan being to viable isolate tumour cells from both the primary tumour and liver metastases and sequence the barcodes to determine the clonal structures of each tumour site. Our aim is to determine whether metastatic spread is random or if we can use the barcode labeling to predict the subset of clones that is predisposed to metastasize.

**List of Key Publications:**


Understanding the impact of cancer cell fate decisions during ovarian cancer treatment

Terry Fox New Investigator Operating Grant (2014-2016)

Investigator: Francis Rodier, Université de Montréal  Collaborators: David Huntsman, BC Cancer Agency; Anne-Marie Mes-Masson, Université de Montréal

Mentoring Program: A pan-Canadian program for the development of biomarker-driven, sub-type specific management of ovarian cancer

Scientific Summary: This project aims to develop new tools that will help select the best treatment options for ovarian cancer (OvCa) patients. OvCa is one of the most lethal malignancies affecting women with poor five-year survival rates, mostly because it is often detected late, at an aggressive stage. The success of any cancer treatment is usually calculated based on long-term parameters such as patient survival and increased quality of life. Surprisingly, while general health effects in response to cancer treatments are well-documented, very little is known about the cellular biology behind tumour regression. For example, the immediate responses of cancer cells to damages initiated by radiotherapy or chemotherapy remain unknown. In reality, damaged cells have many options: they can repair the lesions (very often cancer therapy causes DNA lesions), they can die, or they can enter a state of permanent growth arrest termed senescence. Every cancer is unique, and theoretically, cancer cells may select any of these decisions. Whether these cellular decisions taken during treatment will influence the outcome of cancer treatment is currently unknown.

Aims: Our hypothesis is that decisions taken by single OvCa cells in response to treatment will impact long-term patient survival. In this research program, we propose to extensively characterize OvCa cell responses to therapy and to define whether each different response has a clinical impact on patient survival. This knowledge could help us to detect early whether a cancer is susceptible or is responding appropriately to a treatment and would improve our ability to select the appropriate treatment. We also think that this knowledge could benefit treatment outcomes by generating novel innovative pharmacological targets.

Updates: We have now determined that two particular subsets of OvCa, the diseases called high-grade serous and clear cell carcinoma, both prefer to use a response to treatment termed “cellular senescence”, which is a phenomena akin to accelerated cellular aging. Moreover, we observed that the occurrence of senescence in OvCa tumours is apparently beneficial for the patient. We are now designing senescence-specific biomarkers to predict whether a particular OvCa tumour can undergo senescence and to follow in real-time the occurrence of senescence during treatment. As a long-term goal, we propose that pharmaceutically enhancing OvCa senescence during treatment could improve overall treatment success.

List of Key Publications:


Are genomic instability and clonal diversity prognostic indicators of high-grade serous ovarian cancer?

Terry Fox New Investigator Operating Grant (2012-2015)

Investigator: Sohrab Shah, BC Cancer Agency
Mentoring Program: A pan-Canadian program for the development of biomarker-driven, sub-type specific management of ovarian cancer

Scientific Summary: In North America, ovarian cancer is the leading cause of death due to gynecological malignancies. The majority of women diagnosed with this disease are not expected to survive beyond five years. This project focuses on the most common subtype, high-grade serous ovarian cancers which account for 70% of ovarian cancers. The current standard of treatment involves platinum-based chemotherapies, however, though they are effective in treating the primary tumour, in almost all instances, the cancer will reform and are resistant to any of the currently available therapies. Current clinical markers are ineffective in determining which patients will respond more effectively to chemotherapy and live longer without evidence of disease. High-grade serous carcinomas are genomically diverse and heterogeneous, i.e., their genetic make-up vary from tumour to tumour and within the same tumour, populations of cells can be very different from one another.

Our research group recently observed that there are, in fact, global patterns of diversity that exist amongst this group of tumours. This proposal will examine whether these global patterns of genomic diversity can be used to segregate patient populations and predict which patients fare better than others. We have assembled a highly productive and multidisciplinary team to undertake this research. State-of-the-art genome sequencing technology and novel bioinformatic and algorithmic approaches developed in our lab will be used to decipher the entire DNA sequence of the tumours which will be compared to the patient’s normal DNA to identify global patterns of change. In addition, using state-of-the art single-cell microfluidic devices developed by our group, we will be able to sequence the DNA in individual cells to determine whether there are subpopulations of cells within the primary tumour that are resistant to platinum-based therapy and emerge as dominant clones in relapsed patients. All the tools, infrastructure and tissue specimens required for the discovery phase of this project are available within the BC Cancer Agency and UBC.

We will validate our findings in a much larger patient population (>500 samples) using a national ovarian cancer resource (COEUR) funded by the Terry Fox Research Institute. The ultimate goal is to develop biomarkers or parameters that can be used clinically to predict a patient’s response to chemotherapy. The discoveries from this research can be immediately translatable to other cancer types that follow similar patterns of evolution and progression.
**The role of the CD73-adenosinergic pathway in prostate cancer**

*Terry Fox New Investigator Operating Grant (2015-2017)*

**Investigator:** John Stagg, PhD, Centre de Recherche du Centre Hospitalier de l’Université de Montréal  
**Mentoring Program:** The Canadian Prostate Cancer Biomarker Network  
**Funding Partner:** Fonds de Recherche du Québec-Santé

**Scientific Summary:** Immunotherapy is a promising approach for treatment of prostate cancer (PC). Nevertheless, clinical benefits from immunotherapy have traditionally been modest in PC, due at least in part to the ability of PC to successfully evade immune control. The general objective of this proposal is to validate CD73 as a therapeutic target in PC. Previous studies from our group have highlighted the importance of the CD73-adenosine axis for tumour immune escape (1-5). Adenosine produced by CD73 activates four adenosine receptors (A1, A2A, A2B and A3), each possessing variable tissue distribution and affinity to adenosine. A2A adenosine receptor plays a dominant role in the suppression of T-cell responses against cancer. Through this proposal, we hope a better understanding of the role and place of the adenosinergic pathway in PC will lead to the development of new therapeutic agents able to synergize with existing immunotherapies.

**Aims:** We will investigate the prognostic value of CD73 in human PC and its association with immune infiltrates and tissue hypoxia. Using mouse models of PC, we will investigate the role of CD73 in the prostate tumour microenvironment. Finally, we will perform pre-clinical studies to test whether targeted blockade of CD73, or downstream A2A adenosine receptors, can synergize with immune-checkpoint inhibitors and cell-based prostate vaccines.

**Updates:** By crossing TRAMP transgenic mice, which spontaneously develop PC, with CD73 knockout mice, we established the first proof-of-concept that CD73 promotes PC in mice. CD73 deficiency was associated with a significant reduction of PC growth and an increased infiltration of CD8+ T-cells (3). Moreover, anti-CD73 mAb therapy effectively suppressed the growth and metastasis of transplanted TRAMP-C1 tumours. Our preliminary data thus suggest that CD73 is a potential target in PC.

**List of Key Publications:**

**Transcriptional and epigenetic consequences of MLL-AF9 translocations**

_Terry Fox New Investigator Operating Grant (2014-2017)_

**Investigator:** Brian Wilhelm, University of Montreal  
**Mentoring Program:** Improved assignment of best-available therapy for patients with MDS/AML  
**Funding Partners:** Fonds de Recherche du Québec-Santé; The Cole Foundation; L’Institut de Recherche en immunologie et cancérologie

**Scientific Summary:** Translocations of the mixed-lineage leukemia (MLL) gene are particularly frequent in acute myeloid leukemia (AML) in infants and young adults, and are associated with a poor prognosis. While some MLL translocations have been studied in a murine setting, the analysis of pediatric MLL-AML patient samples is complicated by their scarcity and very high genetic heterogeneity. To overcome these limitations, we have used a novel model system that allows multiple leukemias to be generated from individual human CD34+ cord blood (CB) samples. This is the equivalent of having a single patient developing multiple independent MLL-AF9 (MA9) leukemias, removing the problem of patient genetic heterogeneity. As a result, the data from our model AML system gives us a novel and unique advantage when compared to RNA-seq data from MA9 AML patients. The step-wise analysis of AML development has enabled us to clearly identify expression and splicing changes that are specific to MA9 leukemias but which could not have been identified using the “noisy” patient data alone.

By filtering our data to identify genes expressed specifically in MA9 AML but which are not expressed in normal blood cells, we have discovered 34 MA9-specific candidate genes that are biomarkers of this disease. We now wish to exploit this system to interrogate the changes highlighted by our model leukemias, to elucidate the mechanisms of MA9 tumorigenesis in human cells.

**Aims:** The overall aim of this project is to study the mechanisms by which MLL-AF9 forces leukemia development and to use this information to develop more effective treatments for patients. The first specific aim is to characterize which of our candidate genes may be essential for leukemia development, through a small-scale shRNA screen. The second aim is to perform a structure/function study of one of the candidates, a receptor tyrosine kinase, where we already have evidence for its importance for this type of leukemia. Lastly, because our model leukemia data suggests collaborating mutations are not required for MLL-AF9 AML, we will perform _in vitro_ functional studies of the gene _NCOR2_. We have identified this nuclear co-repressor protein as consistently losing a critical interaction domain as a result of alternative splicing in our model and patient MLL-AF9 AMLs.

**Updates:** To date, we have generated and performed RNA-seq on 22 independent leukemia samples from 4 single CB donors and we have also analyzed the patterns of DNA methylation at each stage of development. Initial shRNA knock-down experiments have highlighted several genes whose loss causes profound growth defects, and additional experiments are now underway to try and better define the role of these proteins. In addition, several of our candidate genes have been validated for use in a diagnostic test, which will improve patient diagnosis compared to standard cytogenetics. Lastly, our work studying the function of _NCOR2_ has uncovered connections to another protein that regulates the differentiation of cells, potentially implicating it in the development of AML. We will test this hypothesis to validate whether or not this protein may also represent a novel therapeutic target in MA9-AML.

**List of Key Publications:**


Exploring novel mechanisms of tumour vascularization in malignant brain tumours

*Terry Fox New Investigator Operating Grant (2012-2015)*

**Investigator:** Gelareh Zadeh, UHN  
**Mentoring Program:** Genetic analysis of signaling pathways for vascular development and tumour angiogenesis

**Scientific Summary:**
Angiogenesis involves a highly regulated and co-ordinated interaction of multiple angiogenic factors and is critical for both embryonal development and physiological vessel formation in adults. Angiogenesis is also proven to significantly contribute to the progression of various disease processes, including cancer.

Glioblastoma (GBM) is among the most angiogenic tumors, and it therefore makes sense from an investigative perspective to understand the mechanisms of angiogenesis in these tumours as a means for identifying new therapeutic opportunities. However, despite initial positive early response to anti-angiogenic therapy in GBMs, the clinical benefits of anti-angiogenic treatment is limited and GBM recurrence within a few months remains inevitable. This is, in part, due to unidentified mechanisms of neo-vascularization that can evade radiation and targeted therapy. Therefore, recent research interest has focused on the possibility of new vessel formation through progenitor cells that are replenished at a constant and continuous level and as a result they can avoid therapeutics.

Neovascularization has traditionally been considered to occur through two distinct processes, angiogenesis and vasculogenesis. Angiogenesis is the process by which new vessels form from sprouting and branching of pre-existing vessels, whereas vasculogenesis or *de novo* vessel formation, occurs by differentiation of endothelial precursor cells (EPC). It has long been thought that vasculogenesis was restricted to embryonal vessel development while post-natal vessel formation occurs primarily through angiogenesis. However, emerging evidence suggests that vasculogenesis can occur in adult life and it has been argued to provide a potential mechanism for cancer neovascularization through mobilization of EPCs from the bone marrow (BM) or circulation. This hypothesis remains highly controversial and there is debate as to whether bone marrow derived progenitor cells (BMDCs) actually differentiate to endothelial cells (ECs) or contribute to formation of vascular channels in neoplastic processes.

Additional open questions include whether BMDC vasculogenesis is influenced by tumor type, microenvironmental factors, tumour growth stage and response to therapy. To do this, however, we needed a model that could examine the process of vasculogenesis *in vivo*, and in real time. This is the impetus for us to establish the experimental strategies outlined above in (Ai), using a two-photon laser microscopy (2PLM) system, coupled with an intra-cranial window in mouse models of GBM to obtain *in-vivo* real-time longitudinal imaging of normal brain and GBM associated vasculature. This strategy complements traditional immunohistochemical (IHC) and immunofluorescent (IF) analysis, as it allows visualization at single cell resolution of fluorescent bone marrow derived progenitor cells, and fluorescent GBM cells. It then goes beyond the traditional IHC and IF techniques by the examination of these processes in real time, in a living mammalian organism. In a series of carefully controlled experiments, we observed that bone marrow-derived cells (BMDCs) are recruited to the brain in response to cranial radiation (CR).

We demonstrated that BMDCs are recruited specifically to the site of CR, in a radiation dose and temporal-spatial manner. We showed that BMDCs do not form endothelial cells but rather they differentiate predominantly into inflammatory cells and microglia. Using a GBM *in vivo* model, we show three distinct patterns of BDMC activity in response to tumour growth. While these cells do support GBM neo-vascularization, we definitively show that there is no evidence of direct differentiation of BMDCs into endothelial cells and, moreover, no contribution to vasculogenesis or to *de novo* vessel formation. This result is in contrast to prior studies by other groups, and we strongly believe that the careful use of our 2PLM high-resolution *in vivo* optical imaging single-cell resolution system in real time was critical in resolving this controversial topic in the field of GBM angiogenesis. Additionally, these findings support the concept that a disruption of the region-dependent contribution of BMDCs to vasculogenesis may be an important therapeutic opportunity.
The Terry Fox New Frontiers Program Project Grant: Canadian Oncolytic Virus Consortium (COVCo)

Terry Fox New Frontiers Program Project (2012-2017)

Project Leader: John Bell, OHRI

Investigators: Harold Atkins, Jean-Simon Diallo, OHRI; David Stojdl, Children’s Hospital of Eastern Ontario; Brad Nelson, Deely Research Institute/BC Cancer Agency; Patrick Lee, Dalhousie University; Nahum Sonenberg, McGill University; Brian Lichty, Dr. Jonathan Bramson, Dr. Yonghong Wan, Dr. Karen Mossman, McMaster University; Andrea McCart, UHN

Scientific Summary: Our program is directed toward the discovery and testing of novel replicating anti-cancer viruses, and complimentary biotherapeutic strategies for the treatment of cancer. We are focused on the most promising oncolytic therapeutics including three that are currently in clinical development. We are also exploring cutting-edge immunotherapies including genetically modified immune cell platforms and personalized anti-tumour vaccines, and how best to combine OVs with immune-based therapies for cancer. We are carrying out fundamental studies to understand how viral therapeutics interact with the host, the tumour and tumour microenvironment. Small-molecule screening and functional genomics approaches are being used to identify therapeutic targets that can be modified to enhance virus killing of tumour cells.

Our ongoing studies include:

- Understanding how best to manipulate or engineer the host immune system to both facilitate virus delivery and potentiate anti-tumour immune responses.
- Delineating signaling pathways that sensitize tumour vascular endothelium and cancer-associated fibroblasts to virus infection and destruction, and developing methods to modulate these pathways in favour of enhanced therapeutic activity.
- Characterization of the innate anti-viral response in normal and tumour cells that determine virus selectivity.
- Identification of tumour-specific pathways that can sensitize cancer cells to virus killing.
- Mechanism of action of small molecules that uniquely inactive the anti-viral interferon response.
- Role of protein translation regulation in determining virus therapeutic activity.
- Optimization of combination strategies using viruses and immunotherapies for synergistic anti-cancer activity in preclinical models.

Highlights:

We have made substantial gains in understanding how to manipulate the host immune system to maximize the therapeutic impact of oncolytic viruses, how to target, select and/or optimize OV vectors for activity in resistant tumours, and revealed the influence of the normal cell component of the tumour microenvironment, in the therapeutic action of OVs. Notably, adipocytes render tumours significantly less sensitive to virotherapy, a key observation considering the prominence of fat as a risk factor for cancer. It is also clear that combination approaches addressing barriers in the tumour microenvironment, or enhancing the anti-tumour immune responses will have a dramatic impact on OV therapeutic efficacy. In 2015 our investigators opened a first in man phase I/II clinical trial of an oncolytic rhabdovirus (Maraba MG1) in combination with anti-MAGE A3 vaccination, which has arisen from the heterologous prime-boost approach in subproject 5. Also in this past year, we have established pre-clinically that this oncolytic vaccination approach is readily adaptable to HPV associated cancers, and relevant prostate cancer antigens. This first trial has paved the way for follow-on trials targeting HPV associated cancers and prostate cancer over the next 2-4 years. Importantly, we plan to follow this phase I/IIb trial with a subsequent trial evaluating the prime-boost approach in combination with checkpoint inhibition, in partnership with BioCanRx, Turnstone Biologicals, OICR, and Merck.
List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in ultrasound and MRI for cancer therapy (2014-2017)

Investigators: Gregory J. Czarnota and Gregory J. Stanisz, Sunnybrook Research Institute; Michael C. Kolios, Ryerson University.

Scientific Summary: We are proposing to develop and enhance the use of ultrasound and MRI techniques to improve cancer treatments. Our focus is on making chemotherapy and radiation therapy, two of the most common cancer treatments, significantly better. We will continue our highly productive track record of developing quantitative ultrasound and MRI methods to detect and track the progression of the effects of cancer therapies on cell death. In addition we will continue to develop ultrasound (with a goal to MRI guidance) to significantly enhance the effects of radiation.

The research here firstly focuses on using ultrasound to track responses to chemotherapy. We have demonstrated that quantitative ultrasound can be used one week into a 4-6 month course of chemotherapy to determine as a new function imaging method whether it is working or not. This will be combined with new MRI methods and photoacoustic imaging as new methods for tumour response tracking. For therapy we have also recently demonstrated that ultrasound-stimulated microbubbles can be used to increase the efficacy of radiation treatments whereby a 2 Gy dose of radiation combined with these treatments. We will scale up that research here to large animal models and clinically compatible MRI systems with a view to having clinical impact through the introduction of these new methods in the near term.

Specifically, there are four highly interrelated projects proposed which complement each other and are critical to bringing these technologies ultimately to the clinic. The first will see the continued development of quantitative ultrasound methods and new photoacoustic methods for the detection of tumour responses to cancer therapies at high and low frequency, for preclinical and clinical applications, respectively. We will specifically expand this component to include new work on photoacoustics to obtain functional measurements based on blood content and oxygenation. The second will focus on correlative analyses which will be integrated with the quantitative ultrasound approaches and will focus on evaluating new MRI methods and correlating these with whole-mount, three-dimensional histopathological data and ultrasound data. We will be integrating these into our analyses as they are rapidly becoming clinical standards. The third project will be centered about evaluating quantitative ultrasound data from patients receiving cancer therapy and will draw on background established methods in quantitative ultrasound and be guided by ongoing developments from the first two projects. The last project will further develop recent innovations in using ultrasound as an enhancing agent for cancer therapy based on our discovery of bubble-enhanced ultrasound potentiation of tumour response and as targeting method to deliver radio-sensitizers. The effects of these will be tracked using our new imaging methods as they are prepared for clinical implementation.

List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in the development of stemness-based prognostic biomarkers and therapeutic targets (2015-2020)

**Investigators:** John Dick, Norman Iscove, and Rodger Tiedemann, Princess Margaret Cancer Centre, University Health Network; Gary Bader, University of Toronto; and Peter Dirks, The Hospital for Sick Children.

**Scientific Summary:** Tumour heterogeneity plays a major role in therapy failure resulting in disease progression and recurrence. Our team is guided by the central hypothesis that both sub-clonal genetic diversity and the existence of cellular hierarchies contributes to tumour heterogeneity and it is the unified effect of both that influences the stemness properties of individual tumour cells; ultimately, stemness is the key biological property that governs patient outcomes.

We are focused on defining the determinants of stemness for high-risk cancers including acute myeloid leukemia (AML), myeloma and glioblastomas multiforma (GBM) that have poor outcome and urgently require effective therapies. Our vision is translating the unique knowledge we have gained into a new generation of clinically relevant biomarkers and therapeutics that target the vulnerabilities of CSCs, reducing therapy failure and increasing patient survival.

Each project is built upon state-of-the-art CSCs assays, using either primary human cancer cells or engineered murine models, and novel approaches to screen for vulnerabilities of cancer cells in general, and CSCs specifically. We will also define the genetic basis for subclonal diversity in myeloma and GBM. Our focus is to deploy specific functional assays that measure self-renewal, the key hallmark of the stemness state, to gain mechanistic insight into how selected genetic, epigenetic or metabolic targets govern CSCs function for each cancer type.

The vast amount of data will be integrated into a single bioinformatic core to gain insight into stemness at a pathway level, which will be central to therapeutic target identification. The specific aims for each project coalesce around three major translational outcomes: the development of stemness-based biomarkers for predicting clinical features that will enable improved clinical cancer management; the identification of new therapeutic targets that ensure eradication of bulk tumour cells as well as the CSCs that lie at the root of the cancer; and pre-clinical development of targets using state-of-the-art primary cancer xenografts that our team pioneered.
The Terry Fox New Frontiers Program Project in killing the hydra: Genetic dissection of actionable targets required for maintenance of metastatic disease (2014-2019)

Investigators: Sean Egan, Michael Taylor, The Hospital for Sick Children, UofT; James Woodgett, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, UofT; Eldad Zacksenhaus, Toronto General Research Institute, UofT

Scientific Summary: The majority of cancer deaths occur secondary to metastatic disease, as primary tumours are often controllable with a combination of surgery and radiotherapy. Despite this, most studies are focused on primary tumours. In 2012, the Taylor lab reported on results of a Sleeping Beauty transposon-based screen that revealed substantial divergence between metastatic medulloblastoma and matching primary tumour. The Egan and Zacksenhaus labs have performed similar screens in mouse models of breast cancer associated with mutations in p53, Pik3ca and Rb. Indeed, the metastatic genes identified so far are very different from mutations associated with primary tumour formation in these models. Finally, the Woodgett lab has defined novel tumour suppressor functions associated with a Wnt pathway kinase. As a group, we have developed a series of innovative tools and assays to define the role of specific signaling proteins and pathways in metastatic breast cancer and medulloblastoma. These include doxycycline-repressible transgenics that can be used to probe the function of PI3K and β-catenin in circulating tumour cells and disseminated disease. In addition, we have established “Lazy Piggy” transposon-containing mice that can be used to screen for genes that are required for continued survival of primary and disseminated tumour cells.

We hypothesize that the best targets for rationale therapy to treat metastatic disease is the subset of mutational events that is required for tumour maintenance.

We will define critical maintenance genes for metastatic cancers of the brain and breast through the following projects and cores:

- Targeting novel transcriptional pathways in metastatic BC
- Targeting metastatic maintenance pathways in medulloblastoma
- Contributions of Wnt and PI3K signaling in breast & brain tumour dissemination
- Defining and targeting metastatic events in RB1/p53 tumour suppressor pathway-driven breast and brain cancer
- Bioinformatics and genomics core

List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in molecular correlates of treatment failure in lymphoid cancers (2013-2016)

Investigator: Randy Gascoyne, BC Cancer Agency

Co-Investigators: Marco Marra, BC Cancer Agency, Genome Science Centre; Sohrab Shah, BC Cancer Agency; Christian Steidl, Joseph Connors, BC Cancer Agency

Scientific Summary: Most lymphoid cancers are easily treated and, in specific subtypes, treatment is given with curative intent. Diffuse large B-cell lymphoma (DLBCL) accounts for 30 to 40% of all non-Hodgkin lymphomas (NHL) and is curable even when widely disseminated at the time of diagnosis. Seminal work from our group has recently characterized the mutational landscape of these tumours and now the current renewal of this TFRI New Frontiers Program Project Grant will investigate at unprecedented resolution, the molecular correlates of treatment failure through the study of clinical samples from patients who were not cured with state-of-the-art therapy. Similar studies will also be conducted in follicular lymphoma (FL), the second most common form of NHL.

The BC Cancer Agency is recognized as a world leader in using next-generation sequencing technologies of lymphoid cancers to understand the fundamental biology and identify the recurrent genetic abnormalities (so-called driver mutations) that represent the underpinnings of these cancers. Building on previous work from our group, we will leverage prior discoveries to determine if tumours from patients with primary treatment failure are different from those experiencing complete remissions through the study of relapsed or recurrent disease. We hypothesize that a limited number of cellular pathway perturbations underlie the biology of treatment failure and by studying these cases we will identify the candidate molecules and pathways that could be used to explore novel, targeted therapies. We plan to study the functional consequences of these genetic alterations and develop a small suite of tests that could be used to recognize at the time of diagnosis those patients destined to not be cured with current treatments. We strongly believe that these studies will ultimately improve the outcome for patients with both DLBCL and FL and fulfill our mandate of delivering precision medicine for patients with lymphoid cancers.

List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in oncometabolism and the molecular pathways that fuel cancer (2015-2019)

Investigators: Vincent Giguère, Julie St-Pierre, Russell Jones, Arnim Pause, Nahum Sonenberg, William Muller, Peter Siegel, Goodman Cancer Research Centre; Ivan Topisirovic, Michael Pollak, Lady Davis Research Institute.

Funding Partners: McGill University Rosalind and Morris Goodman Cancer Centre; The Quebec Breast Cancer Foundation

Scientific Summary: The purpose of this program project grant is to foster a comprehensive research platform to study the links between metabolic reprogramming and cancer progression. The overall goals are to identify and integrate regulatory pathways and metabolic networks that impact the cancer phenotype with a focus on metastatic progression and mechanisms of therapeutic resistance. Long-term goals are to discover and develop novel therapeutic strategies to induce or target metabolic vulnerabilities leading to inability of tumours to overcome metabolic stresses and reprogram their biosynthetic pathways to support aberrant growth, ultimately sensitizing them to anti-cancer drugs. Poor-outcome breast cancer will constitute the central focus of the proposed studies as our group has developed strong expertise in mouse models of human breast cancers, thus providing a unifying theme for the group. However, other cancer types, such as prostate cancer, will be incorporated in certain studies to test specific hypotheses.

Recent Discoveries and Accomplishments:

- Established that the LKB1-AMPK energy-sensing pathway mediates tumour suppression and metabolic reprogramming in cancer.
- Showed that loss of LKB1 enhances the development ErbB2-driven breast cancer through metabolic reprogramming of breast cancer cells.
- Identified the tumour suppressor FLCN as an evolutionary-conserved negative regulator of AMPK.
- Showed that constitutive AMPK activation promotes PGC-1-mediated mitochondrial biogenesis, which stimulates HIF transcriptional activity and metabolic reprogramming in cancer cells.
- Discovery that miR-378* is both a component and a regulator of the PGC-1β/ERRγ axis, and that ERBB2-activated breast cancer cells can specifically exploit this pathway to reprogram their energy metabolism and thus increase their growth potential.
- Demonstrated that PGC-1α, along with ERRα, is a positive regulator of the expression of glutamine metabolism genes in ERBB2+ breast cancer cells.
- The biological relevance of the control of glutamine metabolism genes by the PGC-1α/ERRα axis was demonstrated by consequent regulation of glutamine flux through the TCA.
- Showed that PGC-1α expression is positively correlated with that of the glutamine pathway in ERBB2+ breast cancer patients, and high expression of this pathway is associated with reduced patient survival.
- Demonstrated that metformin exerts its cell-autonomous effects by directly inhibiting mitochondrial complex I.
- Established that the expression of ERRα is restored in lapatinib-resistant breast cancer cells through constitutive re-instatement of mTOR signalling, thus providing the optimal metabolic settings required for cell survival in the presence of the lapatinib insult.
- Demonstrated that loss of ERRα promotes hepatocarcinogenesis development via metabolic and inflammatory disturbances in the tumour cells and resident macrophages.
- Determined that mTOR inhibitors, as well as biguanides exert their biological effects by altering translation of a specific subset of mRNAs encoding proteins known to promote neoplastic growth such as cyclins.
- Demonstrated that the anti-neoplastic effects of biguanides are attenuated by a compensatory activation of glycolysis and that the anti-proliferative effects of biguanides are potentiated in cells that are deprived of serine.
- Showed that the mTORC1/4E-BP pathway maintains cellular energy homeostasis by modulating translation of mRNAs encoding mitochondria-related genes.
- Determined the role of LKB1 in promoting ErbB2-mediated breast cancer progression and metastasis.
Validated claudin-2, a tight junctional protein, as a clinically relevant and functionally important mediator of breast cancer liver metastasis.

The Metabolomic Core Facility contributed to the advancement of all research projects through the development of novel technologies related to the study of metabolomics.

List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in Prostate Cancer Progression (2011-2016)

Investigators: Martin Gleave, Colin Collins, Emma Guns, Michael Cox, Chris Ong, Paul Rennie, Amina Zoubeidi, YZ Wang, VPC, UBC; Kim Chi, Shoukat Dedhar, Poul Sorensen, BC Cancer Agency

Scientific Summary: Progression to castrate resistance following androgen ablation is the main obstacle to improving survival for men with advanced prostate cancer and the central focus of our Terry Fox New Frontiers Program Project Grant, comprised of a multidisciplinary team of 20 scientists and clinicians. Androgen ablation precipitates a cascade of changes in transcriptional and signalling networks that provide a selective survival and growth advantage for sub-populations of the tumour cells, thereby accelerating progression and rendering cells more resistant to therapy.

Objectives:
- Elucidate genomic, molecular and cellular mechanisms responsible for progression to castrate resistance.
- Use this information to develop new therapies aimed at biologically relevant and tumour-specific targets and pathways to delay progression of late stage disease.
- Partner with national clinical trials networks and industry to accelerate bench-to-bedside translation of our discovery science.
- Since our ongoing TF program cycle renewal in December 2011, we have published over 530 papers, applied for or obtained >130 patents, initiated 65 clinical trials and enrolled 814 patients. Since the beginning of support of our Terry Fox New Frontiers Program on Prostate Cancer Progression we have outlicensed 6 novel therapeutics and completed 8 Phase I/II trials of novel agents discovered as a direct consequence of laboratory research performed under this program. Two more novel drug products that target SEMA3C and the DNA binding domain of the AR are ready for clinical development; these novel agents were discovered as a direct consequence of pre-clinical laboratory research performed under the auspices of the program.

Leading in this regard is OGX-011 (Custirsen), now in global Phase III trials. The AFFINITY trial (second-line metastatic Castrate-Resistant Prostate Cancer (CRPC)) and ENSPIRIT trial (non-small-cell lung cancer (NSCLC)) are ongoing, while the SYNERGY trial failed to achieve its primary end point as a first-line therapy in CRPC. We also led the bench-bedside translation of a second novel inhibitor targeting Hsp27, OGX-427, which is currently in six randomized Phase II studies in CRPC, bladder, NSCLC and pancreatic cancer. The Borealis-1 TM Phase II Trial of OGX-427 in metastatic bladder cancer has been completed and data recently presented showing 50% reduction in risk of death in patients with low performance status. This direct translation of basic science to the clinic is how our team works and is in keeping with the mandate of the Terry Fox Foundation.

Our program consists of six individual but highly integrated research projects grouped into four relational areas:
- **Target Discovery**: Project #1 is using next-generation sequencing technologies to identify changes in the genomes and transcriptomes of tumours mechanistically linked to castrate resistance, with a particular focus on androgen receptors and androgen biosynthetic pathways.
- **Cell Biology Mechanisms**: Project #2 is continuing studies on the stress response and cytoprotective chaperones in treatment resistance, focusing on the role of clusterin in endoplasmic reticular stress and autophagy. Project #3 is investigating mechanisms of ERG-mediated prostatic carcinogenesis and progression.
- **Molecular & Cellular Targets**: Projects #4 and #5 are investigating the anti-apoptosis proteins, BIRC6, and Semaphorin 3C, respectively, in treatment resistance of prostate cancer and as potential therapeutic targets.
- **Clinical Evaluation**: Project #6 is performing correlative measures to test biologic activity for a combination of a potent anti-androgen in combination with an inhibitor of clusterin (OGX-011) or Hsp27 (OGX-427, both developed in our Program) in a Phase II clinical trial in CRPC patients. In this regard we have initiated a multi-center randomized trial of OGX-427 +/- abiraterone in post ABI CRPC. All sub-projects within the Terry Fox program are supported by a shared core facility with five major components: Advanced Genomics & Bioinformatics, Pathology & Molecular Imaging, Animal Models, Analytical Pharmacology, and Translational Trials.
In summary, our Program Project Grant on Prostate Cancer Progression is a major catalyst for translational research that has enabled us to have already brought several new therapies from bench to bedside. The program will help further accelerate discovery and validation of novel cellular and molecular targets and uncover mechanisms for treatment resistance.

By pooling our talents and resources into a single co-operative effort, we maximize our potential for solving the problem of prostate cancer progression in the most efficient manner. This program is an ideal example of how team science enables the discovery of underlying mechanisms of prostate cancer progression, facilitates the development of new multimodality therapies, and accelerates translation of research into clinical practice. The many publications related to this program listed below are evidence of our team-based interactions and productivity.

List of Key Publications:


The Terry Fox New Frontiers Program Project Grant in core pathogenic pathways in human leukemia (2012-2017)

Investigators: R. Keith Humphries, Connie J. Eaves, Aly Karsan and Andrew Weng, BC Cancer Agency; Martin Hirst, UBC

Scientific Summary: Acute leukemias remain one of the most devastating and costly cancers with less than 1 in 5 adult patients surviving 10 years and some childhood patients failing current treatments. Research into how normal blood cells are formed and perturbations in leukemia have provided major insights into why cures are so hard to achieve, with many seminal contributions provided by this longstanding program project. These indicate that most human leukemias are sustained by a rare subset of “leukemia stem cells” which are often resistant to currently used drugs. Cures, thus, require treatments that effectively target these leukemia stem cells, ideally with little toxicity for normal cells.

This now seems possible with the advent of modern tools that can identify every change in every gene in cells, and that can also determine whether and why every gene is being expressed. In addition, vast libraries of naturally occurring and synthetic chemicals that can target specific molecules in cells are now available. Our group now brings powerful genetic engineering tools to enable human models of aggressive leukemia to be rapidly created in the lab so that mechanisms of treatment resistance and new drugs and biomarkers can be efficiently analyzed and tested directly and repeatedly in human cells that mimic, but do not rely on, patients’ cells. Our projects focus on examples of the worst types of leukemia known, with the goals to develop human models of these and, in concert with two groups of world experts in the molecular analysis of cells, to use these models to search for common therapeutic targets.

Our research findings are providing powerful new platforms to study the process of initiation and progression of several aggressive leukemias and are leading to the identification of relevant genes and pathways, many linked to the epigenome (e.g. Ikaros in CML, IGF-R in MDS, HIF1alpha in T-ALL). Insights gained promise new therapeutic targets and biomarkers.

List of Key Publications:

The Terry Fox New Frontiers Program Project Grant in the genomics of forme fruste tumours: new vistas on cancer biology and treatment (2013-2018)

Investigators: David Huntsman, Samuel Aparicio, Carl Hansen, Martin Hirst, Chenghan Lee, Marco Marra, Gregg Morin, Ryan Morin, Torsten Nielsen, Sohrab Shah, Poul Sorensen, T. Michael Underhill, Stephen Yip

Co-applicants: Paul Clarkson, Jessica McAlpine, David Schaeffer, Anna Tinker

Scientific Summary
This PPG is an innovative approach to making clinically meaningful cancer discoveries. Forme fruste tumours are clinically and pathologically homogenous tumour types that we believe our driven by a limited number of genetic events. This property makes them ideal for research, but equally important, these tumours are in critical need of improved diagnostics and treatments.

Additionally, discoveries made from the study of forme fruste tumours often have broader clinical relevance. Our research program addresses the objective in three ways: (1) Attacking the cancer problem through the unique perspective gained from the study of rare forme fruste tumour types; (2) Using state-of-the-art technology including next generation sequencing and microfluidics to achieve our objectives; and (3) Addressing commonly overlooked areas of cancer biology such as RNA editing and non-coding alterations, and alterations in epigenetic signatures. Our team has been studying forme fruste tumours since 2010, and we have had an exceptional track record of identifying mutations that are characteristic of forme fruste tumours and uncovering how these mutations drive tumour biology.

We have developed four inter-related sub-projects and one core facility that will work together to study these cancers:

Sub-project one is the main sequencing/discovery project and it will generate a complete catalogue of genomic alterations in forme fruste tumours using a comprehensive suite of next-generation sequencing techniques.

Sub-project two will combine some of the deep sequencing data from sub-project one with newly generated sequencing data for selected forme fruste tumours with known alterations to comprehensively describe the clonal sub-populations within these tumour types. This deep sequencing data will be analyzed to characterize the genotype of individual cell populations within the tumours and how the different clonal mutation profiles have evolved. As part of this sub-project, model xenograft systems will be studied, pre- and post- treatment, to determine how these tumours evolve under the pressure of targeted therapeutics.

Sub-project three will use isogenic tumour cell line models to validate how genomic alterations identified in sub-projects one and two will affect the epigenome, mutant protein expression, protein interaction networks, and tumourigenic cellular phenotypes. Sequence based methods will query the epigenome, and proteomic methods will identify effects on protein networks and the translatome. Drug screens will be used to confirm therapeutically actionable targets and processes.

Sub-project four will optimize methods for measuring levels of circulating tumour DNA in forme fruste cancers as a novel diagnostic and tumour monitoring tool. The circulating tumour DNA levels will be correlated with clinical parameters.

These four sub-projects will be supported by a Data Analysis Core for bioinformatics analysis, statistical analysis, and data analysis. The discoveries from this project will be translated into the clinic through our collaboration with the SMART (Shared Access Medicine: An Approach to Rare Tumours), through the Center for Drug Research and Development, and through collaborations with clinical trials groups. The work described in this program will help improve the management and treatment for forme fruste tumours and provide general insights into the biology of cancer.
List of Key Publications:

The Terry Fox New Frontiers Program Project Grant in unraveling metabolic adaptations associated with disease progression and therapeutic response in metastatic breast cancer (2014-2015)

Investigators: Russell Jones, Nahum Sonenberg, Vincent Giguère, William Muller, Peter Siegel, Morag Park, McGill University

Scientific Summary: Tumour cells reprogram a variety of their central metabolic and bioenergetic pathways to fuel growth, survival and metastatic progression. In the context of breast cancer, these metabolic adaptations allow cancer cells to deal with ever-changing conditions in the primary tumour (hypoxia) and foreign metastatic microenvironments. Oncogenes and tumour suppressor genes encode proteins that regulate cellular metabolic pathways, causing a shift from oxidative phosphorylation to aerobic glycolysis (“Warburg effect”). However, the mechanisms that induce and control these metabolic adaptations remain largely undefined. Also, the impact that metabolic reprogramming has on metastatic progression and therapeutic resistance, two key challenges in breast cancer management, remains to be elucidated.

Goals: The overall goals of this program are to identify and integrate key regulatory signaling and metabolic networks that impact on poor outcome in breast cancers with a focus on metastatic progression and mechanisms of resistance of HER2 and basal breast cancer.

Each of the individual projects addresses a unique issue regarding metabolic adaptation in breast cancer. Project # 1 (Dr. Jones) investigates the impact of AMPK signaling as a key metabolic checkpoint in basal and HER2+ breast cancers. Project # 2 (Dr. Sonenberg) unravels mTOR and translational regulation of metabolism during the development of therapeutic resistance to targeted and chemotherapeutic agents. Project # 3 (Dr. Giguère) will define transcriptional networks governed by the ERR/PGC-1 axis that regulate metabolic programming in breast cancer. Project # 4 (Dr. Muller) will investigate how receptor tyrosine kinase (HER2) signaling modulates metabolic networks and therapeutic resistance. Project # 5 (Dr. Siegel) explores how mitochondrial dysfunction drives the acquisition of aggressive breast cancer phenotypes and how tumour/stromal interactions with the metastatic microenvironment alter tumour cell metabolism in basal breast cancers.

List of Key Publications:

1. ERBB2 deficiency alters an E2F-1-dependent adaptive stress response and leads to cardiac dysfunction.
   Perry MC1, Dufour CR2, Eichner LJ1, Tsang DW1, Deblois G1, Muller WJ3, Giguère V4.

2. Serine deprivation enhances antineoplastic activity of biguanides.
   Gravel SP1, Hulea L2, Toban N3, Birman E4, Blouin MJ4, Zakikhani M4, Zhao Y4, Topisirovic I5, St-Pierre J6, Pollak M7.

3. Lyn modulates Claudin-2 expression and is a therapeutic target for breast cancer liver metastasis.
   Tabariès S1,2, Annis MG1,2, Hsu BE1,2, Tam CE1,2, Savage P1,2, Park M1,2,3,4, Siegel PM1,2,3.

4. PDK1-Dependent Metabolic Reprogramming Dictates Metastatic Potential in Breast Cancer.
   Dupuy P1, Tabariès S2, Andrzejewski S1, Dong Z2, Blagih J3, Annis MG4, Omeroglu A5, Gao D6, Leung S5, Amir E6, Clemons M7, Aguilar-Mahecha A8, Basik M8, Vincent EE9, St-Pierre J1, Jones RG9, Siegel PM10.

   Vincent EE1, Sergushichev A2, Griss T1, Gingras MC1, Samborska B1, Ntimbane T4, Coelho PP5, Blagih J1, Raissi TC1, Choinière L4, Bridon G2, Loginicheva E3, Flynn BR1, Thomas EC6, Tavaré JM6, Avizions D8, Pause A3, Elder DJ9, Artyomov MN7, Jones RG9.
The Terry Fox New Frontiers Program Project Grant in discovery and therapeutic
development of antibody-based targets in oncology (2015-2018)

Investigators: Steven Jones, John Babcook, François Bénard, Kuo-Shyan Lin, Gregg Morin, Paul Schaffer, Tomas Hudlicky

Funding Partner: BioCanRx

Scientific Summary: This proposal brings together a multidisciplinary team of experts from academia and industry focused on developing therapeutic antibody-based diagnostics, theranostics and therapeutics for newly discovered tumour-associated targets. It stands to bring together world-class genomics, bioinformatics, and proteomics capabilities (Genome Sciences Centre, GSC) with both an established and a novel antibody-drug conjugate platform (Centre for Drug Research and Development, CDRD) and a clinically integrated imaging platform (BC Cancer Agency, BCCA). Underlying all of these individual programs is the cutting-edge antibody generation platform established at the CDRD which will generate panels of antibodies and derivatives to validate the targets identified from the bioinformatics program, and become the basis of therapeutics for the antibody-drug conjugate program and companion theranostics for the imaging program. Together this team will generate a suite of fully validated antibody-based therapeutics with matched theranostics which could be used individually or combined for next-generation targeted therapy.

List of Key Publications:


The Terry Fox New Frontiers Program Project in Li-Fraumeni Syndrome: Applying genetic determinants of cancer risk to cancer surveillance and prevention (2015-2018)

**Investigators:** David Malkin, Adam Shlien, Anna Goldenberg, Andrea Doria, Hospital for Sick Children, University of Toronto; Jason Berman, IWK Health Centre, Dalhousie University

**Scientific Summary:** Li-Fraumeni Syndrome (LFS) is a highly penetrant autosomal dominantly inherited predisposition syndrome associated with a remarkably heterogeneous presentation of early onset cancers. In 1990, the PI (Malkin) discovered that germline *TP53* mutations cause >80% of LFS. Since then, this group has demonstrated that *TP53* mutations occur with striking frequency in a wide spectrum of patients with component LFS tumours, with or without a family history of cancer.

In addition, epigenetic, genomic and genetic events have been found to modify the phenotypic effects of an underlying germline *TP53* mutation. We have elucidated a mechanistic model to explain tumour initiation/progression in LFS in which a constitutional (or possibly early somatic) *TP53* mutation favours accumulation of epigenetic or genetic events that facilitate accelerated telomere attrition, chromothripsis, and subsequent somatic cell transformation. We developed a clinical surveillance protocol that takes advantage of innovative imaging techniques such as rapid sequence whole body MRI (WB-MRI), ultrasonography and biochemical tests to detect occult malignancy. This approach improves survival and reduces treatment-related morbidity. Our protocol has been rapidly adopted worldwide.

Notwithstanding this extraordinary progress, patients with LFS continue to face seemingly insurmountable challenges: 1) It is impossible to prevent cancers from developing; 2) It is impossible to prevent therapy-induced cancers from developing; 3) It is impossible to predict what types of cancer will develop and at what age; and 4) It is extremely difficult to effectively treat these patients who face dismal survival rates with devastating treatment-related toxicities.

We propose to address these challenges through the following interwoven projects:

**Projects 1-2:** We will define the epigenetic and genetic modifiers that confer specific phenotypes in *TP53* mutation carriers and create multi-level algorithms merging genetic and clinic-pathologic data to refine tumour type and age of onset risk estimates in *TP53* mutation carriers.

**Project 3:** We will use this information to refine and implement novel MRI-based surveillance strategies, and to create molecular surveillance techniques for early tumor detection.

**Project 4:** We will explore potential chemoprevention strategies for *TP53* mutation carriers using a powerful zebrafish p53 model (1).

Each project complements the others and addresses a key element of the continuum from molecular genotyping through risk stratification to translational strategies for early tumour detection and cancer prevention in Li-Fraumeni Syndrome. We anticipate that these studies will lead to a better understanding the role of early p53 alterations in cancer generally, and to transform the care of patients with Li-Fraumeni Syndrome.
The Terry Fox New Frontiers Program Project Grant in the genetic analysis of signaling pathways for vascular development and tumour angiogenesis (2010-2015)

Investigators: Andras Nagy, Anthony Pawson, Jeff Wrana, Susan Quaggin; Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Hao Ding; University of Manitoba, Janet Rossant; Hospital for Sick Children

Scientific Summary: Anti-angiogenic therapy is one of the most promising cancer treatments. It prevents the formation of new blood vessels and thereby hinders tumours from growing. This treatment, however, comes with a long list of severe side effects, including high blood pressure and kidney failure, which limits the full utilization of this powerful approach to fighting cancer. In this program project, we join the expertise of six laboratories to overcome these limitations.

- The Nagy Lab is committed to obtain mechanistic insights into the broad range of consequences of anti-angiogenic therapies on normal physiology including the immune system.
- The Quaggin Lab focuses on finding ways to protect the kidney and other organs from damage during anti-angiogenic therapy.
- The Rossant Lab uses stem cells to increase the quality of blood vessels so that the delivery of chemotherapy can be enhanced. They also develop robust cell-based screening tools to test new anti-angiogenic therapies.
- The Wrana Lab has developed a system to measure the movement of cancer cells. They use this to define novel pathways mediating cancer metastasis via stromal tumour interactions.
- The Ding Lab investigates how the PDGF gene, that plays an important role in vessel formation, is involved in medulloblastomas, the most common type of brain tumour in children.
- The Pawson Lab studies how disruptions of cell-cell interactions can cause cancer.
- There are two core facilities serving our laboratories; one maintains and distributes genetically modified mouse lines for cancer modeling and the other provides high throughput screens.

List of Key Publications:


Molecular and cellular differentiation: New targets and treatments (2009-2015)

Investigators: Christopher Paige, (Project Leader), Norman Iscove, John Dick, Robert Rottapel, Ben Neel, Juan Carlos Zuniga-Pflucker (OCI, UHN); Tak Mak and Pam Ohashi, (Campbell Family Institute for Breast Cancer Research, OCI, UHN).

Scientific Summary: Fully functional mature cells differentiate from progenitors through a series of stages regulated by genes and proteins. Our Terry Fox Program Project group studies both the normal process of differentiation and the changes that occur when malignancies arise. We define the molecular differences that serve to drive the transformation and progression of cancer cells. Based on this information we develop and use novel technologies to find targets for therapeutic intervention. We study both solid and dispersed cancers using both mouse and human models with a particular emphasis on ovarian cancer, as an example of solid tumors, and leukemia. In addition to molecules which might be targets of drug or biological therapy, we also use the latest understanding of the cells and cytokines which drive immunity to develop novel protocols to harness the power of the immune system to recognize and eliminate cancer cells.

List of Key Publications:


**Investigators:** Brian Wilson, Princess Margaret Cancer Center (Project Leader and Sub-project 3 Leader); Stuart Foster, Sunnybrook Research Institute (Sub-project 1 Leader); Gang Zheng, UHN (Sub-project 2 Leader); John Trachtenberg, Ralph DaCosta, Princess Margaret Cancer Centre; Norman Marcon, Cathy Streutker, Maria Cirocco, St. Michael’s Hospital; Theo van der Kwast, Robert Weersink, UHN; Linda Sugar, Masoom Haider, Sunnybrook Research Institute

**Scientific Summary:** This new project aims to develop a novel technology platform to be applied to two significant unmet clinical needs. The first technology component is photoacoustic imaging, combining the molecular specificity of light with the deep imaging of ultrasound, and which Dr Foster has pioneered. The second is all-organic nanoparticles (“porphysomes”) discovered in Dr Zheng’s lab that have an exceptional properties for imaging and therapeutics. Here, they are to be used primarily for their high photoacoustic image contrast. The first unmet need is to treat patients with low/intermediate-risk “focal” prostate cancer (PCa) with minimal risk to normal tissues. This builds on previous work using laser photothermal therapy. The nanoparticle-enhanced photoacoustic imaging platform is intended to improve the efficacy and safety of this approach and to facilitate its cost-effective dissemination and clinical adoption. The second unmet need is to detect high-grade dysplasia in patients with Barrett’s Esophagus (BE) and to ensure absence of submucosal invasion so that minimally-invasive endoscopic mucosal resection can be performed, reducing the need for esophagectomy and associated morbidity. In both applications, the long term goal is to change the balance between achieving effective tumor control and the side effects of radical therapies that significantly impact quality of life. The project comprises three subprojects, as follows:

**Sub-project 1:** “Photoacoustic Imaging Technology” focuses on the design, fabrication, testing and optimization of hardware and software for photoacoustic imaging. The technology is based on prior development of high-resolution ultrasound imaging, extending this to photoacoustic mode. Two different photoacoustic probes are under development. The first is a transrectal device for imaging of the prostate, while the second is intended for endoscopic use. These two probes will be validated in animal models before translating to the first-in-human studies in Sub-project 3. The transrectal probe is under constructed in collaboration with industry partners. The endoscopic probe has been designed to incorporate a miniaturized ultrasound transducer using a novel fabrication technique.

**Sub-project 2:** “Porphysomes for Photoacoustic Imaging” comprises further development and optimization for the clinical applications of two different forms of porphysomes. The first, pyro-porphysomes, are intended as photoacoustic image contrast agents and have been validated for intrinsic tumor targeting in various tumor models. Both photoacoustic and fluorescence imaging are possible with the same nanoparticles, which is particularly valuable for endoscopic applications. An animal model of BE has been established to enable pre-clinical testing and optimization of porphysomes for this specific application. The second, J-porphysomes, are designed to enable real-time 3-D imaging of the temperature distribution during photothermal treatment of focal prostate cancer, enabling optimal treatment delivery. The principle of this approach has been demonstrated. In order to translate porphysomes into clinical trials (Sub-project 3), scale-up, gmp (good manufacturing practice) and toxicity testing are required. These are in progress, with additional internal and external support.

**Sub-project 3:** “First-in-Human Studies of PAI and Porphysomes in PCa and GI” comprises a series of small-scale studies in patients, piggybacking on current clinical practice or ongoing clinical trials, with the intent to obtain first-in-human data on safety, technical feasibility and performance of the different photoacoustic/porphysome combinations. The first human ex vivo tissue studies of intrinsic photoacoustic contrast are in progress: a) in intact prostatectomy specimens to assess tumor delineation and b) in endoscopic mucosal resection specimens to assess altered microvascular patterns. Investigations of quantitative imaging with topically-applied porphysomes is also in progress. Additional planned PCa studies comprise: intrinsic and porphysome-enhanced photoacoustic imaging in combination with MRI for tumor localization; photoacoustic imaging during and post photothermal treatment to assess response; and thermal mapping using J-porphysomes during treatment. In the GI track, the transrectal system will also be used.
to image rectal cancer, while the endoscopic system will be used for *in vivo* imaging in BE patients. These studies will inform subsequent definitive clinical trials of the new technologies.

**References:**

The Terry Fox New Frontiers Program Project Grant: A research pipeline for hypoxia-directed precision cancer medicine (2014-2019)

**Investigators:** Robert Bristow, Bradley Wouters, Marianne Koritzinsky, Michael Milosevic, Anthony Fyles, and David Jaffray

**Scientific Summary:** Cancer cells sense and respond to hypoxia through complex biological pathways that also adversely affect patient prognosis. These include changes in cell signaling, proliferation, metabolism, angiogenesis, DNA repair, and metastasis. However, these pathways may also be amenable to precise targeting to offset aggressive hypoxia-based phenotypes.

Our new TFRI program constitutes a research pipeline with short-, medium-, and long-term interactive goals aimed directly at improving patient outcome by targeting or exploiting hypoxic cell phenotypes in tumours. This program consists of five projects that include novel mechanistic studies to understand how hypoxia influences protein expression relevant to metastasis, identification of new therapeutic targets and development of new biologics, understanding the relationship between hypoxia and genetic instability, investigating the therapeutic potential of targeting hypoxia and IFP-driven chemokine and bone marrow cell recruitment in tumours, and implementing imaging and genomic-based personalized medicine approaches in hypoxia-directed clinical trials with new agents.

Our team will focus on using these innovative and combined approaches to improve cures in cervix, head and neck, prostate, and pancreatic cancer using a “pipeline of basic science to clinical trials”.

**Recent Discoveries and Accomplishments:**
- Secretion of hypoxia-induced proteins is supported by superior disulfide bond formation in hypoxia.
- APEX2-mediated affinity tag purification facilitates cargo-specific interactions in the secretory pathway.
- Fumarate hydratase mediates metabolic reprogramming during hypoxia through PKM2.
- Expression of OCT3 is important for metformin uptake and response in cancer cells.
- Metformin as a novel biological modifier of radiotherapy.
- Flavoprotein POR is shown as a key determinant of sensitivity to the hypoxia-activated prodrug SN30000.
- Targeting tumour hypoxia to prevent cancer metastasis.
- Showed chromosomal instability as a prognostic marker in cervical cancer.
- Developing a prognostic micro-RNA signature for human cervical carcinoma.
- Establishment of an orthotopic primary cervix cancer xenograft model.
- Completed functional genomic screens on 29 head and neck cell lines
- Identified Notch3 as a therapeutic target in head and neck cancer
- Characterized the dynamic interactions among the tumor microenvironment, chemokines, BMDCs and radiotherapy in curable cervix cancers.
- Developed a unique, image-guided targeted radiation protocol in mice to administer localized beams specifically to the cervix tumour xenograft.
- Production of FAZA for hypoxia
- PET imaging is produced on site for clinical trials and pre-clinical studies.
- Initiation of Phase II study: metformin as a novel personalized biologic therapy in women with hypoxic cervix cancer.
- Demonstrated that Plerixafor with combined standard treatment of radiochemotherapy was successful in reducing tumour growth and metastasis.

**List of Key Publications:**


STP collaboration with the Centre for Drug Research and Development (CDRD)


Investigators: John Babcook, CDRD; Rob Rottapel, Ben Neel, Brad Wouters, OCI; David Andrews, McMaster University; Peter Dirks, Hospital for Sick Children; Daniel Durocher, Frank Sicheri, Samuel Lunenfeld Research Institute, Mount Sinai Hospital; Jason Moffat, Sachdev Sidhu, UofT

Scientific Summary: The Selective Therapies Program (STP) is a translational program whose objective is to identify novel cancer targets for which new anti-cancer therapeutics can be developed with heightened selective properties. The STP has been able to identify novel cancer targets using high-throughput RNA interference (RNAi) screening technologies and new high-throughput screening strategies. Dr. Sidhu has led the development of novel synthetic antibodies to promising cancer drug targets identified by the STP. To further exploit the therapeutic potential of these novel targets and antibodies, the Centre for Drug Research and Development (CDRD) will select antibodies generated by the STP and conjugate their novel, potent cytotoxins to generate antibody-drug conjugates (ADCs). These ADCs will be assessed for their ability to specifically deliver the toxin payloads and kill target-expressing tumour cells. Lead ADC candidates will then be selected for further therapeutic development.
Canadian Colorectal Cancer Consortium (C4) (2012-2017):

Investigators: Gerald Batist, Jewish General Hospital, McGill University; and Steven Gallinger, Mount Sinai Hospital, UHN

Scientific Summary: Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract, and the second leading cause of cancer death among Canadians. The more advanced the disease is at the time of diagnosis, the greater the risk of metastases. The main strategies proven to ameliorate the health of Canadians with colorectal cancer are: 1.) reducing risk, by improving outcomes through earlier diagnosis; and 2.) increasing therapeutic responses for those with more advanced disease.

The uptake of CRC screening in most Canadian provinces remains too low for the potential impacts of screening to be achieved across the population, even after recent efforts to increase screening rates. Although a variety of innovations in treatment have dramatically improved the outcome for patients with Stage III and IV disease, the inevitable development of therapeutic resistance remains the major obstacle to improving survival.

The overall objective of this project is to establish a molecular-based approach to translational cancer care that will improve the outcome of CRC patients by:

1.) Increasing the impact of early diagnosis, decreasing mortality and the cost of managing CRC through targeted screening of families stratified by risk (Screening Axis).

2.) Improving the life expectancy and reducing the cost of the management of advanced CRC through the study of drug-resistant metastatic disease and the development of a biomarker panel to predict drug resistance (Therapeutic Axis).

This will be achieved by creating the C4, a Canadian multidisciplinary and inter-institutional network. A major outcome of the C4 will be an integrated infrastructure for the development of a large-scale, molecular based approach to translational cancer care for CRC. The C4 aims to use genetic data for the breadth of clinical challenges faced from the time of diagnosis to the time of treatment. The C4, supported by TFRI, will put Canada at the forefront of translational cancer research allowing us to establish a unique and high-impact program.

List of Key Publications:


Development of new treatment and biomarker for hepatocellular carcinoma: From woodchuck to human

NSC-TFRI International Collaborative Research (2013-2016)

Investigators: John Bell, OHRI; Pei-Jer Chen, National Taiwan University College of Medicine

Scientific Summary: Lack of sensitive biomarkers for timing diagnosis and effective therapeutics for advanced tumours are the two main reasons for the poor outcome of hepatocellular carcinomas (HCC). Therefore, there is a pressing demand to develop new diagnosis and treatment strategies for HCC. Chronic hepatitis B virus (HBV) infection is one of the major causes of HCC and the woodchuck (Marmota monax) chronically infected with woodchuck hepatitis virus (WHV), a virus with high similarity to human HBV, recapitulates the complex liver milieu and natural course from chronic HBV infection to HCC. It represents, and has been used, as an ideal preclinical model for HBV-related translational studies. Despite the approval of the molecular targeted agent, sorafenib, for advanced HCC treatment, its efficacy has been modest. New regimens, such as oncolytic viruses, are promising anti-cancer agents that deserve further investigation to optimizing efficacy and safety in the relevant woodchuck model.

Therefore, the objectives of this project are:
- To adapt oncolytic virus-based therapeutics based on vaccinia virus or rhabdovirus platforms for testing against liver cancer in the woodchuck hepatitis B model;
- To use surgical explants from woodchuck or human HCC subjects to study their susceptibilities to oncolytic virus infection and to identify transcriptional or genomic markers that predict animal/patient HCC permissiveness for oncolytic virus infection and treatment responses;
- To develop unique viral integration cellular junction DNA as a biomarker for follow-up of HCC growth and treatment in woodchucks.

List of Key Publications:

Development of 2-[18F]fluoro-2-deoxy-D-galactose as a new molecular imaging probe for hepatocellular carcinoma diagnosis

NSC-TFRI International Collaborative Research (2013-2016)

Investigator: François Benard, BC Cancer Agency

Scientific Summary: Liver cancer is a major cause of death among patients of east or southeast asian descent, as well as other population groups, notably in central and west Africa. Diagnosis of liver cancer requires a combination of several imaging techniques and biopsies. Despite this, diagnosis can remain inconclusive or difficult to establish in patients at risk for liver cancer.

The purpose of this joint Taiwanese / Canadian research project is to evaluate novel imaging methods developed to diagnose the most common form of liver cancer, hepatocellular carcinoma. We propose to use novel imaging probes that have been reported to bind to liver cancers but not benign liver lesions that can be confused with liver cancer. Three such imaging probes will be evaluated. 2-[18F]-fluoro-2-deoxy-D-gulcose, called [18F]FDG, is a radioactive sugar that is widely used for cancer imaging with a device called positron emission tomography, or PET scans. We already know that [18F]FDG cannot detect some liver cancers that are slow growing. 2-[18F]Fluoro-2-deoxy-D-galactose([18F]FDGal), another radioactive sugar, has been recently reported to be highly effective at detecting liver cancer. [18F]Fluorocholine ([18F]FCH), another molecule, is currently being evaluated in Taiwan and other jurisdictions for this purpose. In 2010, a French researcher reported 80-90% detection rate by using [18F]FCH alone or in combination with [18F]FDG. In 2011, a Danish researcher reported an even better result by using [18F]FDGal alone.

The Taiwan group will compare [18F]FCH and [18F]FDGal. The Canadian (Vancouver) group will compare [18F]FDGal and [18F]FDG, which could be complementary to each other. Both groups will evaluate 50 patients each over a period of three years. The results will be correlated with those of biopsies and clinical follow-up. Having two patient groups will allow the researchers to compare two strategies, while minimizing the number of diagnostic tests that research participants will have to undergo to evaluate the best diagnostic strategy. After the completion of these two trials, we will compare the results with another on going multi-centre trial now already on schedule in Taiwan by 10 medical centres using [18F]FCH vs. [18F]FDG.

This study will provide valuable data on whether these imaging agents can successfully differentiate malignant liver lesions from benign ones. It will also provide information about whether these imaging agents can successfully assess whether the cancer has spread outside the liver. It will provide data that will allow physicians to determine the optimal imaging protocol to properly diagnose liver cancer.
Modeling and therapeutic targeting of the clinical and genetic diversity of glioblastoma  
(2012-2017)

Investigators: Gregory Cairncross, Stephen Robbins, Samuel Weiss, University of Calgary; David Kaplan, UofT; Warren Mason, Queen’s University; Marco Marra, UBC

Scientific Summary: Glioblastoma (GBM) is a deadly brain cancer that has eluded major treatment advances. While all agree that new therapies for GBM are needed, there is no consensus on how best to find them. With this project, we employ a unique collection of cell lines established from GBM. These lines, referred to as brain tumour initiating cells (BTICs), capture and retain the major genetic alterations that are present in the tumours from which they were derived, in addition to maintaining many of the histological features of the parent tumour when grown in vivo.

This cell-based model system now provides our team at the universities of British Columbia, Calgary and Toronto with the foundation for an innovative drug discovery and genome-sequencing program with real potential for rapid clinical translation. Our experimental strategy begins with BTIC lines as a research tool for drug and target discovery and ends with new therapeutics in early phase human testing in molecularly defined subpopulations of GBM, via a collaboration with the NCIC Clinical Trials Group and its many participating Canadian centres. Our approach, which combines a superior model system with high-throughput drug screening and genomics technologies, holds great promise.

Our singular objective is the discovery of new drug therapies for GBM within five years that will improve tumour control and quality of life for patients with this disease. This project will also ensure that specialized laboratory models of GBM are in hand to support future drug discovery.

Specific Aims:
- High-throughput screening of toolkit, NIH, and kinase inhibitor libraries against a panel of BTICs to enable rapid identification of targeted drug therapies for GBM.
- Genome and transcriptome sequencing of BTICs, their parent tumours, and normal DNA to enable the discovery of new drug targets, as well as correlate genotype with drug response.
- Continued establishment of BTIC lines from common and rare types of glioma.
- Pre-clinical testing of promising compounds in vivo.
- Clinical trials of promising compounds.

List of Key Publications:


Investigation of the pathogenesis of ASXL1 mutation in acute myeloid leukemia
NSC-TFRI International Collaborative Research (2013-2016)

Investigators: Keith Humphries, Aly Karsan, BC Cancer Agency; Hwei-Fang Tien, Yuan-Yeh Kuo, Wen-Chien Chou, National Taiwan University College of Medicine

Scientific Summary: ASXL1 is the human homolog of Drosophila additional sex combs (Asx), which encodes a chromatin-binding protein required for normal determination of segment identity in the developing embryo. ASXL1 was found to be mutated in AML and other myeloid malignancies. A team of researchers at the National Taiwan University have analyzed the clinical implications of this mutation in a large cohort of their de novo AML. They found several features of this mutation, including not correlating with a normal karyotype, frequent association with older age, male sex, isolated trisomy 8, RUNX1 mutation, and expression of HLA-DR and CD34, but mutual exclusion with t(15;17), complex cytogenetics, FLT3-ITD, NPM1 mutations, WT1 mutations, and expression of CD33 and CD15. Several studies have shown that ASXL1 mutation is a poor prognostic factor. However, the pathophysiology underlying the mutation remains largely unknown. In this collaborative project, the Taiwan and Canadian researchers propose to explore the mechanisms of ASXL1 that would be of great value in understanding the processes of leukemogenesis and in searching for novel therapy.

Specific Aims:
- To investigate the nature of human ASXL1 mutation in vivo. Is ASXL1 mutation a loss-of-function, gain-of-function, or dominant-negative mutation in human AML?
- To understand how the ASXL1 mutation affect epigenetic regulation in vivo.
- To answer if ASXL1 mutation alone is sufficient for leukemogenesis.
- To explore the co-operation between mutations of ASXL1 and other genes such as RUNX1.
- To search for any novel therapy.
- Canadian investigators Drs. Humphries and Karsan will work closely with the Taiwan collaborators to analyze the miRNA/mRNA expression profiles, characterize the ASXL1 mutant "knock-in" mouse model, validate the findings in mutations from the discovery cohort, and provide expertise, training, and re-agents for retroviral/lentiviral gene transfer (shRNA and mRNA) to identify collaborating genes with mutant ASXL1 that would accelerate leukemogenesis or suppress leukemogenesis.

List of Key Publications:

Investigators: Stephen Lam, Ming Tsao; British Columbia Cancer Agency, University Hospital Network-Princess Margaret Hospital (Co-Directors)

BCCA-VCH (Annette McWilliams, John Mayo, Richard Finley, John Yee, Ken Evans, Paola Nasute)

University of Calgary (Alain Tremblay, Paul Burrowes, Paul MacEachern)

University Hospital Network-Princess Margaret Hospital (Heidi Roberts, Geoff Liu, Frances Shepherd, Kam Soghrati, Kazurhiro Yasufuku, John Thenganat, Charlie Chan, Natasha Leigh)

Juranvinski Cancer Centre (John Goffin, Serge Puksa, Lori Stewart, Allan McLellan, Bill Evans)

Ottawa Hospital Regional Cancer Centre (Garth Nicholas, Glen Goss, Jean M Seely, Kayvan Amjadi)

University of Laval (Simon Martel, Francis Laberge, Michel Gingras, Christian Couture)

Dalhousie University (Michael Johnson, Daria Manos)

Memorial University (Rick Bhatia)

Lung Cancer Risk Modeling (Martin Tammemagi, Don Sin, Geoff Liu)

Health Economics & QOL (Stuart Peacock, Bill Evans, Martin Tammemagi, Natasha Leigh, Sonya Cressman)

Blood Biomarkers (Geoffrey Liu, Don Sin)

COLD Network (Lung Function) (Wan Tan)

Quality Assurance (Nestor Muller (Radiology), Tom Sutedja (Bronchoscopy), Adi Gazdar (Pathology)

Scientific Advisory Committee (Christine Berg, John Field, James Jett)

Funding Partners: The Canadian Partnership Against Cancer, Lung Cancer Canada, Princess Margaret Cancer Centre Foundation, BC Cancer Foundation

Scientific Summary: Sophisticated but relatively expensive technologies such as low dose spiral computed tomography (CT) and autofluorescence Bronchoscopy (AFB) exist for detection of early lung cancer. The inclusion of low cost risk modeling and biomarkers to select population cohorts with the highest risk of lung cancer development may provide a cost effective application of relatively expensive, yet effective, detection methods. Our objective is to develop a new multi-modal early detection strategy that integrates risk modeling, spirometry, AFB and blood biomarkers with CT for early detection of lung cancer.

The study has a 6.4% cancer detection rate. Seventy-six percent of the cancers were detected from abnormalities observed at the baseline scan and 24% were incidence cancers. CT scan data from the study was used as a development data set to determine the malignancy of lung nodules on first screen CT. The study has produced a highly predictive tool based on patient and nodule characteristics to accurately estimate the probability that lung nodules detected on baseline screening CT are malignant. The results were published in the N Engl J Med 2013;369:910-919. The study aims to complete a third round of screening on enrolled participants to contribute additional information regarding the frequency and duration of LDCT screening.

Pending Manuscripts:

4. Predication of lung cancer in abnormal computed tomography screens in the national lung screening trial and pan-Canadian early detection of lung cancer study. Martin Tammemagi. Comment: this study will extend our existing NEJM nodule.
6. prediction model and will be applicable in post-baseline screening situations. This model is expected to receive a great deal of attention and application, as our initial model did.


List of Key Publications and Abstracts:


2. Ritchie, Alex. Computer vision tool and technician as first reader of lung cancer screening CT. IASLC Mini 36.05 Denver CO, Sept 2015


15. 15th World Conference of Lung Cancer, Sydney, Australia. Lung Density versus emphysema as predictor of malignancy risk of pulmonary nodules detected on first screening CT. (Oral Presentation) October 2013. Keishi Ohtani

Translational research in lung cancer: From molecular markers/targets to therapeutic applications
NSC-TFRI International Collaborative Research (2013-2016)

Investigators: Stephen Lam, Wan Lam, BC Cancer Agency; Pan-Chyr Yang, Chong-Jen Yu, National Taiwan University Medical College and Hospital

Scientific Summary: Lung cancer is the leading cause of cancer mortality worldwide as well as in Taiwan. Delayed diagnosis, early metastasis, poor treatment outcome and rapid emergence of drug resistance are the present obstacles for the management of lung cancer patients. Dr. Martin Tammemagi has developed a lung cancer risk prediction model in never smokers using the PLCO dataset (from the NCI sponsored Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) (PMID: 21606442). Drs. Tammemagi and Stephen Lam demonstrated that pulmonary function and sputum DNA image cytometry added value to their lung cancer risk prediction model (PMID: 21411501). Dr. Lam’s team validated this prediction model in a pan-Canadian lung cancer biomarker screening trial, which was supported by TFRI (PMID: 24004118). The utility of this prediction tool can be tested in never and ever smoker populations in Taiwan. Furthermore, the incremental value of the inclusion of specific genetic biomarkers can be investigated. We hypothesize that the pan-Canadian risk model is applicable for predicting lung cancer risk in the Taiwan population. The goal is to validate our PLCO model (validated in a TFRI sponsored pan-Canadian trial) in a Chinese population and determine if genetic markers add incremental value to risk assessment in never and ever Chinese and Caucasian population.

Specific Aims:

- Evaluate the utility of the Tammemagi PLCO model risk model in the Taiwanese population.
- Optimize such a model for early detection of lung cancer in Taiwan.
- Test the incremental value of genetic markers to predict lung cancer risk versus the Tammemagi PLCO model that includes family history and lung function (FEV1%).

Impact: Early detection is critical to the reduction of lung cancer mortality. The development of a risk model optimized for the Taiwan population will have the potential for improving clinical practice. Furthermore, such a risk model can be adapted for other populations in Asia and worldwide.
A pan-Canadian platform for the development of biomarker-driven subtype specific management of ovarian carcinoma (2010-2018)

Investigators: Anne-Marie Mes-Masson, Diane Provencher, Kurosh Rahimi, Francis Rodier, John Stagg, CHUM Research Centre; David Huntsman, Aline Talhoukr, Anna Tinker, Dianne Miller, Blake Gilks, Brad Nelson, Peter Watson, BC Cancer Agency, VGH; Martin Koebel, Helen Steed; Alberta Health Services; Hal Hirte, Hamilton Health Sciences Centre; Ted Brown, Joan Murphy, Barry Rosen, Helen Mackay, Marcus Bernadini, Patricia Shaw, Blaise Clarke, Amit Oza, UHN; Trevor Shepherd, London Health Sciences Centre; Janet Dancey, Barbara Vanderhyden, Johanne Weberpals, Michele Fungkee Fung, Ottawa Regional Cancer Center; Walter Gotlieb, Jewish General Hospital, Montreal; Mark Natchigal, University of Manitoba; Patricia Tonin, McGill University; Alain Piché, University of Sherbrooke; Isabelle Bairati; Dimcho Bachvarov, Marie Plante, Bernard Tetu, CHUQ, Université Laval; Robin Uqhart, Dalhousie University; Eva Grunfeld, OICR

Scientific Summary: Ovarian cancer is the second most common gynecological cancer and the leading cause of death from gynecological malignancies. Early detection of ovarian cancer is rare and little is known about the natural history of disease progression. More recently, the notion that ovarian cancer is a single disease has given way to a more sophisticated concept of subsets of ovarian disease that may be associated with very different molecular events. While platinum/taxane-based treatment is currently the gold standard in first-line therapy, failure of this treatment in a significant portion of patients remains a serious problem. Identifying non-responders, and offering these individual alternative first-line treatments remains one of the most important aspects in the initial clinical management of the ovarian cancer patient, and is the focus of future clinical trials.

In order to address these issues, the research team proposes the following specific aims:

- A validated classification system for ovarian cancer that stratifies cases into groups with different natural histories and chemotherapy response rates, and a trained pathology community ready to effectively perform this classification with QA program to maintain excellence.
- A cohort of over 2,000 ovarian cancer sub-typed cases (COEUR) to be interrogated for biomarkers predictive of treatment response, and analysis would be extended to address response in sub-type specific ovarian disease.
- The biomarkers with the highest predictive value will be carried forward for correlative studies in sub-type specific ovarian cancer trials.
- A pan-Canadian team of clinical researchers working within a collaborative framework to reduce ovarian cancer mortality.

List of Key Publications:

Selective Therapies Program Collaboration: Therapeutic targets validation in ovarian cancer (2012-2015)

Investigators: Anne-Marie Mes-Masson (Institut du cancer de Montréal/CRCHUM, Medicine Dept., Université de Montréal, Montreal - PI), Robert Rottapel (Ontario Institute for Cancer Research, Dept. of Medical Biophysics, University of Toronto Toronto - PI), Diane Provencher (Dept. Ob/Gyn, University of Montreal, Montreal - PI) and Laudine Communal (Institut du cancer de Montréal/CRCHUM, Montreal - Project Manager)

Collaborators: Mauricio Medrano (Ontario Institute for Cancer Research, Toronto), Fabrice Sircoulomb (Ontario Institute for Cancer Research, Toronto).

Scientific Summary: Ovarian cancer is the most lethal of gynecological cancer and effective therapies are still lacking as the majority of patients develop resistance to first-line chemotherapy. In order to improve cancer outcomes, the Selective Therapy Program (STP) was launched by the Terry Fox Research Institute (TFRI)/Ontario Institute for Cancer Research (OICR). This program has identified new promising therapeutic targets using an integrative genomic, proteomic and functional approach\(^1\). Here we characterized and validated the relevance of selected candidates as therapeutic targets or biomarkers in High Grade Serous Epithelial Ovarian Cancer (HGS-EOC).

A systematic candidate characterization includes a first step of expression evaluation by western blot in EOC cell lines\(^2\). Candidate expression is then evaluated by immunofluorescence (IF) on a tissue-microarray (TMA) consisting of 101 cases of HGS-EOC. Multi-labeling IF conditions were defined to allow the discrimination of epithelial and stromal cells as well as nuclei and cytoplasmic compartments\(^3\). Candidate expression levels are accurately quantified in relevant compartments with a powerful image analysis procedure (Visiomorph\(^TM\)) and are correlated with patient clinical parameters in order to determine their relevance and to prioritize them for further studies.

Promising results were obtained for three candidates so far. High expression of CD151 and APBB3 protein were correlated with poor patient prognosis in our HGS-EOC TMA and in the pan-Canadian TFRI COEUR cohort comprised of 983 HGS tumours. Further analyses showed that CD151 depletion impaired survival, proliferation and tumor growth in murine models of a subset of HGS-EOC cell lines. In addition, low JAMA protein expression was correlated with poor prognosis in the 101 cases HGS-EOC TMA. Further analyses are ongoing to confirm the potential of CD151, APBB3 and JAMA as biomarkers and/or therapeutic targets.

All the candidates showed a good expression in HGS-EOC suggesting that they can be further studied as therapeutic targets. In addition, some of the candidates seem promising as prognostic markers. Systematic review of all candidates will reveal those best suited to be further studied as therapeutic targets or prognostic markers.

List of Key Publications:


2. Fleury H*, Communal L*, et al.: Novel high-grade serous epithelial ovarian cancer cell lines that reflect the molecular diversity of both the sporadic and hereditary disease. Genes & Cancer 2015. Accepted. *These co-authors have contributed equally.


Efficacy of optically guided surgery in the management of early-stage oral cancer: The Canadian optically guided approach for oral lesions surgical (COOLS) trial (2010 -2016)

Investigators: BCCA/BCCRC/UBC: Catherine Poh, Scott Durham, Calum MacAulay; BCCA/BCCRC/SFU: Miriam Rosin, Stuart Peacock, Kitty Corbett; University of Calgary: Joseph Dort; University of Alberta: Hadi Seikaly, University of Manitoba: Paul Kerr; Sunnybrook Health Sciences Centre: Kevin Higgins; London Health Sciences Centre: John Yoo; Dalhousie University: Robert Hart.

Scientific Summary: The COOLS trial is a multicentre Phase III randomized control trial that is evaluating the clinical efficacy of an optical tool to reduce local recurrence of oral cancers and severe dysplasia. The tool identifies alteration of tissue autofluorescence (FV) around oral lesions and uses such change to delineate surgical margins. The study will recruit a total of 400 patients with oral severe dysplasia or higher. Patients will be randomized into either FV-guided (experimental arm) or white light (current standard of care) surgery.

The trial has four goals: 1) To collect clinical evidence of the comparative effectiveness of the two treatments. 2) To collect molecular and phenotypic evidence in margins to test if FV produces a shift in surgical field, sparing normal tissue while catching high-risk occult tissue. 3) To collect relative cost-effective evidence of the two treatments in both the cost per avoided recurrence and the cost per quality-adjusted life years (QALYs) gained. 4) To develop a knowledge translation (KT) strategy that will foster the dissemination of FV-guided surgery across Canada and globally.

As of September 30, 2015, we have seven sites actively engaging in steady patient follow-up: Our final accrual number stands at 427 patients (246 cancerous and 181 high-grade lesions). All of them are being actively followed up with 84% of the projected visits completed at the end of this reporting period. To date, there have been 29 cases of local recurrence, the primary endpoint during the follow-ups.

On June 8th 2015, we held the 5th COOLS annual meeting in Winnipeg, with all the site co-ordinators and the participating site surgeons in attendance. We committed to continue collaborating with the PanCanNOCC network with the consensus that this historical teamwork provides a valuable infrastructure for knowledge sharing, improves patient care and clinical results, and pushes forward Canadian oral cancer disease prevention and treatment.

Continuation of sample pipeline and molecular analysis for margin samples: We have developed a pipeline for sample flow from acquisition to documentation, histological review, and sample selection for analysis, processing and delivery to laboratories for molecular and phenotypic analysis. Preliminary quantitative tissue pathology (QTP) and loss of heterozygosity (LOH) analysis shows positive correlations of these endpoints with margin evaluation using histology and FV status. Early data suggest that we may be able to spare low-risk tissue at surgical margins.

Health Economics Team: The Health Economics Team (Goal 3) has been developing its analysis plan using interim data from the COOLS Trial. Unit costs for time and equipment have been applied to surgical capture forms and sub-population analyses have been applied to investigate differences in clinical populations. These methods and some interim findings have been submitted and presented at national and international conferences, with feedback from health economics experts. A qualitative “face-to-face interview” component has been appended to this goal, and has received provisional approval from the University of British Columbia Research Ethics Board – interviews began in fall 2013. Interim data analysis will continue as the trial increases its recruitment and follow-up.

Knowledge Translation: Knowledge translation (KT) in the COOLS trial entails health service data collection to prepare for dissemination and scale-up of fluorescence visualization (FV)-guided surgery beyond the trial, if warranted by study results. KT discovery and application throughout the trial is informed by Social Marketing and Diffusion of Innovations change theories. The discovery phase, which has been completed, involved data collection from study site surgeons, pathologists, clinic staff, and patients that explored factors and processes of FV-guided surgery important for clinical practice change. Future application-phase activities will include developing and testing of an acceptable, appropriate
KT scale-up strategy. Both phases use a between-case, compare and contrast approach concurrent with qualitative data collection to identify emerging themes and inform subsequent steps.

List of Key Publications:


The Canadian Prostate Cancer Biomarker Network (CPCBN) (2010-2016)

Investigators: Fred Saad, Anne-Marie Mes-Masson, Mathieu Latour, Pierre Karakiewicz, Jean-Baptiste Lattouf, Louis-Mathieu Stevens, Mathieu Latour, Dominique Trudel, John Stagg, CHUM; Marie-Paule Jammal, Cité de la Santé de Laval; Jean-Benoît Paradis, Complexe Hospitalier de la Sagamie; Armen Aprikian, Simone Chevalier, Simon Tanguay, Jacques Lapointe, Fadi Brimo, McGill University Health Center; Louis Lacombe, Alain Bergeron, Yves Fradet, Hélène Larue, CHUQ; Neil Flesner, Rob Bristow, Theodorus van der Kwast, Antonio Finelli, Shabbir Alibhai, Natasha Leigh, UHN; Laurence Klotz, Margaret Fitch, Sunnybrook Hospital; Darell Drachenberg, Manitoba Prostate Center; Martin Gleave, Ladan Fazli, Alan So, Colin Collins, VPC; Simon Sutcliffe, BCCA.

Scientific Summary: Prostate cancer is the most commonly diagnosed cancer with an estimated 23,600 new cases in 2013 and it is the third leading cause of cancer-related death in Canadian men. The introduction in the 1990s of prostate specific antigen (PSA) as a screening tool greatly facilitated the diagnosis of prostate cancer and in particular favoured the detection of early stage, and, in some, cases low-grade (Gleason 6 or less) tumours. In patients with low-grade tumours, it is presently difficult to differentiate between low- and high-risk disease, which contributes to the overtreatment of men for whom interventional therapy is neither required, nor appropriate, to ensure a lifespan uncompromised by cancer or its therapeutic consequences. Therefore, there is an urgent need for new prognostic tools that will allow the distinction between low-grade tumours requiring definitive therapy and those that are best suited for observation. When patients are under active surveillance (AS), practitioners routinely measure PSA levels and monitor signs of disease progression through regular biopsies and digital rectal exams. This delays curative treatment in low-risk patients until there are indications that the disease is progressing, at which time active treatment is initiated. Moreover, there is also a need to identify biomarkers that will add to the currently used clinical and pathological parameters to identify patients at high-risk of cancer recurrence and/or progression that may benefit from adjuvant or neo-adjuvant therapies. This would have the potential of directing high-risk patients to multi-modal therapy and/or trials with novel therapies in order to limit their disease. Accurate and individualized risk stratification may have profound individual (lower recurrence rates, better quality of life) and societal (lower cost, better use of health resources) implications.

To accomplish its goals, the CPCBN assembled a large tissue microarray (TMA) series of 1,508 radical prostatectomy specimens associated with extensive clinico-pathological data. This important resource is presently being shared among Canadian researchers to validate biomarkers related to prostate cancer patient prognosis. In addition, the CPCBN also created a TMA series of 125 biopsy specimens from intermediate-risk patients treated by radiotherapy in combination or not with hormonotherapy. Due to the nature of biopsy specimens, this TMA will be used only for binary markers in immunohistochemistry. In collaboration with GenomeDx, the CPCBN moved towards an RNA/DNA approach for its cohort of patients treated by radiotherapy. Microarray expression data GenomeDx signature category of risk and copy number alterations from over 200 patient specimens will be available for researchers. The CPCBN will also move towards a RNA/DNA approach for the active surveillance cohort of 250 patients. To access the CPCBN TMA series and extracted material or profiling data, researchers must fill an application form for their proposal to be evaluated by the study committee.

The CPCBN is focused on the identification of biomarkers that predict risk in order to inform clinical management decisions. Despite the fact that there are clear advantages from a health/quality of life/health economic viewpoint to AS, its uptake within the Canadian context has not been studied. Indeed, the extent to which it is practiced, the barriers to its implementation, and health professional/societal views on its acceptance in the Canadian context are poorly documented. Using database interrogation and chart review approaches in four different provinces (Quebec, Ontario, Manitoba, British Columbia) the CPCBN monitored AS in men that underwent a biopsy in 2010 to provide evidence for the extent of active surveillance uptake in Canada. In depth analysis will be performed to understand the root of any significant differences that might exist between provinces/centres.

In parallel, using a focus-group approach, patients and health care providers of the same four provinces were interrogated to identify perceived barriers and facilitators to AS. The rich data collected during the focus-group approach will be used to inform questionnaires that can provide a quantitative measure of the importance of different barriers and facilitators to AS from the patient and practitioner point of view.
Ultimately, the CPCBN aims to reduce the impact of prostate cancer by incorporating key molecular information about expression, prognosis, response and outcome into algorithms defining optimized, individualized therapy.

The program is also defining how best to transfer this new knowledge within the Canadian health care setting. In particular, this approach has the potential to stratify patients with low-risk disease, as determined by current criteria, into a larger group for whom no further therapy is required to achieve survival unimpeded by prostate cancer (active surveillance) from a small group whose disease, despite being apparently low-risk, will progress and result in premature death if left untreated.

**Specifics Aims:**

**Biomarker Core**

- Assembly of tissue micro-array- (TMA) based validation platforms:
  - 1,500 radical prostatectomy specimens
    - 125 biopsy specimens from intermediate risk patients treated by radiotherapy
  - DNA/RNA extraction with profiling/copy number variation
    - >200 biopsy specimens from intermediate risk patients treated by radiotherapy
    - 250 biopsy specimens from low-risk patients followed by active surveillance – profiling to be confirmed
- Validation of biomarkers:
  - Specific to low-risk disease that will not progress (biopsy based) to safely follow them by active surveillance and avoid therapeutic complication
  - Specific to patients with a high-risk of progression/recurrence to combine their initial treatment with adjuvant therapies.
- Establishment of a nomogram to facilitate prostate cancer patient management.

**Knowledge to Action Core**

- Snapshot of active surveillance uptake in Canada for the year 2010.
- Identification through focus groups of the barriers in the offer, acceptance and adherence to active surveillance in Canada.

**List of Key Publications:**

## Glossary

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<th>Abbreviation</th>
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<tr>
<td>BCCA</td>
<td>BC Cancer Agency</td>
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<td>BCCRC</td>
<td>BC Cancer Research Centre</td>
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<td>CDRD</td>
<td>Centre for Drug Research and Development</td>
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<td>CHUM</td>
<td>Centre hospitalier de l’Université de Montréal</td>
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<td>CHUQ</td>
<td>Centre hospitalier de l’Université de Québec</td>
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<td>CRCHUM</td>
<td>Centre de recherche du Centre hospitalier de l’Université de Montréal</td>
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<td>MSGSC</td>
<td>Michael Smith Genome Sciences Centre</td>
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<td>OCI</td>
<td>Ontario Cancer Institute</td>
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<td>Vancouver General Hospital</td>
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<td>VPC</td>
<td>Vancouver Prostate Centre</td>
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The Terry Fox Research Institute from coast to coast

TFRI is an Institute without walls linking the capabilities of 73 leading cancer care and cancer research institutes and universities organized through six regional “nodes”.

**NATIONAL PARTNERS**
- Canadian Institutes of Health Research
- Canadian Tumour Repository Network (CTRnet)
- Genome Canada
- Lung Cancer Canada
- The Terry Fox Foundation

**BRITISH COLUMBIA**
- BC Cancer Agency
- BC Cancer Foundation
- The Centre for Drug Research and Development
- Genome British Columbia
- St. Paul’s Hospital (Providence Health)
- Simon Fraser University
- Team Finn Foundation
- University of British Columbia
- Vancouver Coastal Health Research Institute

**ALBERTA**
- Alberta Cancer Foundation
- Alberta Health Services
- Alberta Innovates – Health Solutions
- Cross Cancer Institute
- Genome Alberta
- Tom Baker Cancer Centre
- University of Alberta
- University of Calgary

**PRAIRIES**
- CancerCare Manitoba
- Children’s Hospital Research Institute of Manitoba
- Saskatchewan Cancer Agency
- Research Manitoba
- University of Manitoba
- University of Saskatchewan

**ONTARIO**
- BioCanRx
- Brock University
- Children’s Hospital of Eastern Ontario
- Hospital for Sick Children
- Juravinski Cancer Centre
- London Health Sciences Centre
- McMaster University
- Mount Sinai Hospital
- Ontario Cancer Institute
- Ontario Institute for Cancer Research
- Ottawa Hospital Research Institute
- Queen’s University
- Sunnybrook Research Institute
- Thunder Bay Research Institute
- University Health Network (Princess Margaret Cancer Centre)
- University of Guelph
- University of Ottawa
- University of Toronto

**QUEBEC**
- Centre hospitalier de l’Université de Montréal
- Centre hospitalier Universitaire du Québec
- CHU Saint-Justine Fondation
- Institut Universitaire de Cardiologie et de Pneumologie de Québec
- Jewish General Hospital
- Institut de recherche en Immunologie et cancérologie
- Fonds de recherche Québec – Santé
- Fondation centre de cancérologie Charles-Bruneau
- L’Institut de Recherches Cliniques de Montréal
- McGill University Goodman Cancer Centre
- McGill University Health Centre
- McGill University
- Quebec Breast Cancer Foundation
- The Cole Foundation
- Université de Montréal
- Université Laval
- Université Sherbrooke

**ATLANTIC**
- Atlantic Cancer Research Institute (Moncton)
- Capital District Health Authority
- Dalhousie University (Halifax)
- Isaac Walton Killam Health Centre
- New Brunswick Health Research Foundation
- Memorial University of Newfoundland (St John’s)
- New Brunswick Cancer Network
- QEII Health Sciences Centre (Halifax)
- The University of New Brunswick
- The University of Prince Edward Island