BC Cancer Agency

CARE + RESEARCH

An agency of the Provincial Health Services Authority

2016 RESEARCH REPORT

2016 FAST FACTS BC Cancer Agency Research

52 full-time scientists

124 clinical investigators

149 health professionals

341 research papers published

6 new technology licensing agreements signed

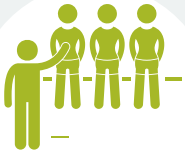
303 active clinical trials

99.3 million
in research funding

Construction of the Conconi Family Immunotherapy Lab completed

317 patients
participated in the POG Program

4 researchers named among World's Most Influential Scientific Minds



416 trainees

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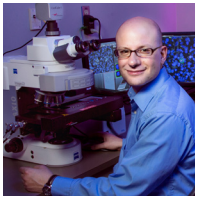

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A message from Dr. François Bénard, Vice President, Research

Research has always been an integral part of the BC Cancer Agency. As the Agency's new vice president of Research, my goal is to embed research even more deeply into the fabric of daily work at the BC Cancer Agency. By increasing the integration of our clinicians and researchers, we can learn more from our patients, be more efficient with research funding and accelerate our research progress.

What sets BC Cancer Agency research apart: our strong sense of community and a common purpose. This spirit of collegiality and cooperation extends to our research partners at the universities, hospitals and health research institutes. I hope to strengthen and grow these relationships so that we can increase collaboration.

Our biggest strength: our fantastic researchers, many who are pioneers in their fields. We are learning about the value of teamwork, and how people with very specialized but highly complementary expertise are very effective when it comes to tackling problems together. Now is the time to start recruiting the next generation of scientists, who can be mentored by our experts and then bring us to the next level of cancer research.

BC Cancer Agency's most powerful opportunity: the ability to view cancer on a population-wide basis. We are the organization that cares for all the cancer patients in British Columbia over the long term, which is extremely powerful from a research perspective. Although it will be a challenge, we need to improve the interaction between the population-based data sets and the genomic infrastructure.

Cancer research is evolving rapidly. We have the ability to learn from our patients and generate new knowledge and new treatments. We now need to bring our research back into the clinic so that we can help our patients do even better. This is what I am hoping to achieve.

Cancer research is evolving rapidly. We have the ability to learn from our patients and generate new knowledge and new treatments.

A message from Sarah Roth, President & CEO, BC Cancer Foundation

The BC Cancer Foundation is proud to be the largest charitable funder of cancer research in BC, because we see the difference breakthroughs in the lab make in the lives of cancer patients each day: Two new targeted therapies are in the clinic, specific to the deadliest forms of breast and prostate cancer. This is a direct result of donor support fuelling drug development in our labs. The construction of the Conconi Family Immunotherapy Lab was completed to catapult T Cell Therapy research into patient trials to bring promising new treatment options for a wide range of cancers. Three hundred and seventeen patients took part in the Personalized Onco-Genomics—POG—Program, providing a tailored approach for their care while building knowledge into the genetic factors that drive individual cancers. We invite you to learn more at bccancerfoundation.com

The BC Cancer Agency celebrates just a few of our many outstanding women and their research achievements and awards in 2016.

Celebrating the Leadership of Women in Cancer Research

Women in science continues to be an important topic of discussion, with a heightened awareness that relatively few women proceed from doctoral studies to senior positions in academia or biotech. The BC Cancer Agency is proud of our many outstanding women scientists who work in cancer research. They have risen to be stars in their respective fields, have major scientific and administrative leadership roles and serve as important mentors and role models for the next generation of female scientists.

The BC Cancer Agency celebrates just a few of our many outstanding women and their research achievements and awards in 2016.

Dr. Connie Eaves is an internationally recognized leader in normal and cancer stem cell research and a distinguished scientist in the Terry Fox Laboratory at the BC Cancer Agency. She was a cofounder and former director of the Terry Fox Laboratory and the former vice president, Research of the BC Cancer Agency. She is also a professor in the Department of Medical Genetics at the University of British Columbia, a fellow of the Royal Society of Canada and a corresponding fellow of the Royal Society of Edinburgh. In 2016, Dr. Eaves was awarded the 2016 **Dr. Chew Wei MBBS [HK] FRCOG [ENG] Memorial Prize in Cancer Research**. This is arguably the most prestigious award for cancer research in Canada, and honours a Canadian physician or scientist who has made

outstanding contributions to improving the treatment of cancer. This award acknowledges her distinguished record of discovery and seminal contributions to understanding normal and cancer stem cells of the blood and mammary gland, and their application to clinical advances. The award also celebrates her remarkable ability in promoting research partnerships fostering collaborative cancer research advances and their clinical implementation. Importantly, the award also speaks to her success in cultivating future leaders in the field, as her support and mentorship have launched the careers of many BC Cancer Agency researchers, as well as others who have gone on to major scientific leadership positions around the world.

In 2016, Dr. Mager's laboratory demonstrated that IFR5, or Interferon regulatory factor 5, a key transcription factor in Hodgkin lymphoma, is driven by an ancient retroviral promoter.

Dr. Dixie Mager, distinguished scientist, Terry Fox Laboratory, is

a pioneer and an international leader in the field of study focused on a form of genetic material derived from ancient retroviruses that is now recognized as playing important roles in a wide range of cancers including lymphomas. Her laboratory developed a novel strategy to identify gene expression abnormalities, and has used this method to study the role of transcriptional promoters - that drive gene expression - in cancers. In 2016, Dr. Mager's laboratory demonstrated that IFR5, or Interferon regulatory factor 5, a key transcription factor in Hodgkin lymphoma, is driven by an ancient retroviral promoter. In addition to research, Dr. Mager has mentored many other scientific trainees, both in her own laboratory and as a past Chair of the Medical Genetics Graduate Program at the University of British Columbia. Her research is supported by the Natural Sciences and Engineering Research Council of Canada, Canadian Cancer Society Research Institute and Canadian Institutes of Health Research.

Dr. Marianne Sadar, distinguished scientist, Michael Smith Genome

Sciences Centre, and her collaborators at the BC Cancer Agency and UBC identified a novel imaging agent, I-EPI-002, that may be useful for prognosis or selection of treatment options for advanced prostate cancers that are resistant to current treatments. In July 2016, they published their findings in the journal *JCI insight*. I-EPI-002 is an analogue of EPI-506, a first-in-class prostate cancer drug candidate brought to clinical trials by her research group at the BC Cancer Agency the previous year. Dr. Sadar's work is supported by the BC Cancer Foundation and National Cancer Institute/National Institutes of Health, USA.

Dr. Xiaoyan Jiang, distinguished scientist, Terry Fox Laboratory,

is working to identify molecules and pathways leading to new, rationally designed, more effective and less toxic, personalized molecularly

targeted therapies. Her work focuses on understanding the molecular mechanisms of several newly identified cancer driver genes as potential therapeutic targets, and to develop new predictive and prognostic tests and improved treatments for human leukemia. In 2016, she was invited to present her seminal work in several national and international conferences, including as keynote speaker at the 16th Annual McGill Biomedical Graduate Conference in Montreal, where she received her PhD in 1995. Dr. Jiang is not only involved in many key scientific collaborations but has mentored numerous students who have gone on to prominent positions in academia and biotech, and been the lead collaborator on high profile research with major drug companies.

Dr. Pamela Hoodless, distinguished scientist, Terry Fox Laboratory, is a developmental biologist working to understand how

embryonic genes are reactivated in cancer. In 2016, she identified the Hippo signaling pathway as part of the switch between embryonic and adult gene expression in the liver, and is now studying how the epigenetic and biochemical mechanisms involved in this pathway relate to cancer. In 2016, she also led research initiatives relevant to hematologic, pancreatic and ovarian cancer. As the leader of the BC Cancer Agency gene modeling core, Dr. Hoodless is implementing CRISPR-Cas9 gene editing techniques, which allow precise gene alterations to be made in many different types of cells. Her work is supported by Canadian Institutes of Health Research, the Cancer Research Society, Canadian Foundation of Innovation, the Natural Sciences and Engineering Research Council of Canada and the Heart & Stroke Foundation.

Mary L. McBride distinguished scientist, Cancer Control Research,

BC Cancer Agency. This year Ms. McBride was part of a multi-province team that examined gaps in quality and coordination of care between oncology and primary care throughout the cancer care continuum. Her BC Cancer Agency collaborators included **Dongdong Li** and **Yang Zhang**. The study uses available data on British Columbian cancer patients to assess key aspects of the delivery of quality medical care – defined as effective, appropriate, efficient, timely, accessible, equitable and safe - from diagnosis to end of life. The goal of the project is to improve care for cancer patients. The work was published in the *Canadian Family Physician* in October of 2016. Her work was supported by the Canadian Institutes of Health Research.

As the leader of the BC Cancer Agency gene modeling core, Dr. Hoodless is implementing CRISPR-Cas9 gene editing techniques, which allow precise gene alterations to be made in many different types of cells.

Dr. Barbara Melosky, medical oncologist, BC Cancer Agency. In 2016, the results of the Pan Canadian Rash Trial were published in the prestigious *Journal of Clinical Oncology*. Dr. Melosky was the principal investigator of the

Canada-wide randomized cancer trial, which demonstrated that preventing or treating skin rash in patients being treated for metastatic lung cancer did not compromise the efficacy of the targeted therapy and should be considered for all patients. Other BC Cancer Agency investigators who were involved in this study included **Drs. Cheryl Ho**, **Nevin Murray**, **Sophie Sun** and **Janessa Laskin**.

Dr. Cheryl Ho, medical oncologist, specializes in lung and head and neck cancer. With her colleagues, **Dr. Janessa Laskin** and **Kelly Zibrik**, she piloted the integration of a lung cancer nurse navigator at the BC Cancer Agency. The intention was to improve referral practices, timelines and the availability of molecular testing. Having a lung cancer nurse navigator at the BC Cancer Agency improved care for patients by increasing the proportion of patients receiving systemic treatment, shortening the time to treatment and increasing the rate of molecular testing and the number of patients with molecular testing results available at time of initial consultation. A framework for implementing nurse navigators at other institutions was also developed. This work was published in the *Current Oncology* and *Journal of Oncology Practice*.

Dr. Kasmintan Schrader, from the Department of Molecular Oncology, and her collaborators including Dr. David Huntsman, discovered three genetic mutations in a known cancer susceptibility gene called APC, which causes a rare gastric condition called gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This condition is a variant of Familial Adenomatous Polyposis (FAP) and can lead to gastric cancer. The discovery has important implications for the potential gastric cancer risk in FAP patients and for colon cancer risk in families identified as having GAPPS. As a result, the BC Cancer Agency now offers clinical genetic testing for families presenting with GAPPS to help them understand their risk for gastric cancer. The finding was published in the May 2016 issue of *American Journal of Human Genetics*. The work was led by an Australian group, but the BC-based work was supported by the BC Cancer Foundation, the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research.

Dr. Cathie Garnis, senior scientist, Integrative Oncology Department, BC Cancer Agency Research Centre, investigates molecular profiles of early-stage head and neck cancers. In 2016 she published a paper in the journal *Genes, Chromosomes and Cancer,* which reported that the EYA4 gene may function as a "tumour suppressor" gene, with a role in preventing the development of oral cancer. She found that the gene is turned off in pre-cancer cells through epigenetic modification. Her lab is further investigating EYA4 as a potential prognostic biomarker and as a candidate for novel targeted therapies.

Dr. Miriam Rosin, senior scientist, Cancer Control Research, BC Cancer Agency Research Centre, conducts human studies using

genetic and phenotypic biomarkers of exposure and risk, focusing on the reduction in cancer risk through chemoprevention. In 2016, she published a paper in *BMC Cancer* that demonstrated how socioeconomic status impacts the stage of oral cancer diagnosis and survival. Using data from the British Columbia Cancer Registry, she assessed how socioeconomic status is related to staging trends and cancer specific survival rates in patients with oropharyngeal and oral cavity cancer. Her research study concluded that lower socioeconomic status is related to later stage of diagnosis and poorer survival for oral cancer, highlighting the need for more oral cavity cancer screening programs to be targeted towards less-affluent neighbourhoods.

The research contributions of **Dr. Donna Hogge**, senior scientist, Terry Fox Laboratory, focus on the

cellular and molecular characterization of malignant stem cells from patients with acute myeloid leukemia (AML), with the aim of developing new therapies to target and destroy these cells. In 2016, Dr. Hogge along with her collaborators, published a paper in *Cancer Research* which described an integrated method to test novel anticancer agents and to also identify predictive biomarkers in AML. The approach integrates a number of different methods including biobanking, xenografting and multiplexed phospho-flow cytometric profiling. Although Dr Hogge retired from the bench in 2015, she served as the medical director of the Clinical Cell Therapy Laboratory and as senior hematologist in the Leukemia/Bone marrow transplant Program of BC.

Dr. Karen Gelmon, senior scientist

and medical oncologist at the BC Cancer Agency and professor of medicine at the University of British Columbia, not only maintains a busy clinical practice, but has an active research career as a clinical trial investigator. In 2016, she was successful as part of Stand Up to Cancer Canada – Canadian Breast Cancer Foundation Dream Team, along with her BC Cancer Agency colleague Dr. Sam Aparicio. The Dream Team will conduct clinical trials in six Canadian provinces, with the aim of developing new targeted therapies to treat triple-negative breast cancer and other aggressive types of breast cancer. The team is funded over four years, with $6 million support provided by Stand Up to Cancer Canada, the Canadian Breast Cancer Foundation and the Canadian Imperial Bank of Commerce.

The Dream Team will conduct clinical trials in six Canadian provinces, with the aim of developing new targeted therapies to treat triple-negative breast cancer and other aggressive types of breast cancer.

Additional achievements by **Dr. Connie Eaves, Dr. Sharon Gorski** and **Dr. Angela Brooks-Wilson** are highlighted on pages 22, 11 and 29 respectively.

Distinguishing pseudo-metastasis from metastasis in synchronous endometrial and ovarian cancers

Dr. David Huntsman and the OVCARE research team have made a breakthrough in understanding the origin and development of synchronous endometrial and ovarian (SEO) cancers. These tumours appear at the same time in the endometrial lining of the uterus and the ovary, and this synchronous occurrence happens in five to ten per cent of endometrial and ovarian cancer cases. Until now, researchers haven't known if these represent two separate cancers or if one has metastasized from one organ to another, suggesting that the cancer is more advanced and requires an aggressive approach to treatment.

To determine the origins of the cancers, Dr. Huntsman and his team sequenced frequently mutated cancer genes from 18 pairs of SEO tumours. They demonstrated that these cancers invariably share mutations and thus are indeed metastasis. To explain the excellent prognosis of these cancers, Dr. Huntsman and colleagues coined the term "pseudo metastasis," which likely occurs through the fallopian tubes and not the bloodstream as with regular metastasis.

This discovery has important implications for treatment. In British Columbia, SEO cancer patients have been treated conservatively by surgically removing the tumours. On a global scale, however, many women with SEO tumours have received aggressive treatment designed to fight late-stage metastatic cancer.

The results of this study, which were published in the *Journal of the National Cancer Institute,* not only confirm that we are taking the correct approach in British Columbia but will have an immediate impact on the management of ovarian and endometrial cancers globally. The researchers hope women elsewhere no longer have to undergo a needlessly aggressive treatment.

The next step of the research team is to more fully understand the process of pseudo-metastasis: whether the initial event takes place in the ovary or the endometrium and what keeps cells temporarily restricted to these organs without metastasizing to the rest of the body.

This collaborative research study included Dr. Huntsman and the OVCARE team at the BC Cancer Agency. The lead, author Dr. Anglesio, is a recently appointed faculty member at the University of British Columbia. Partner institutes included the Vancouver Coastal Health Research Institute, University of British Columbia and the University of Tuebingen. The study was supported by the Gray Family Ovarian Clear Cell Carcinoma Research Resource, the BC Cancer Foundation, the Vancouver General Hospital and University of British Columbia Hospital Foundation and the Canadian Cancer Society.

Cancer of the uterus is the fourth most commonly diagnosed cancer in BC in women and the fifth most common cause of cancer death overall.

Autophagy and breast cancer subtypes

Dr. Sharon Gorski and her research team at the BC Cancer Agency Genome Sciences Centre have uncovered a novel association between a subtype of breast cancer and an autophagy protein called ATG4B. This discovery holds promise for therapeutic strategies for HER2-positive breast cancer patients.

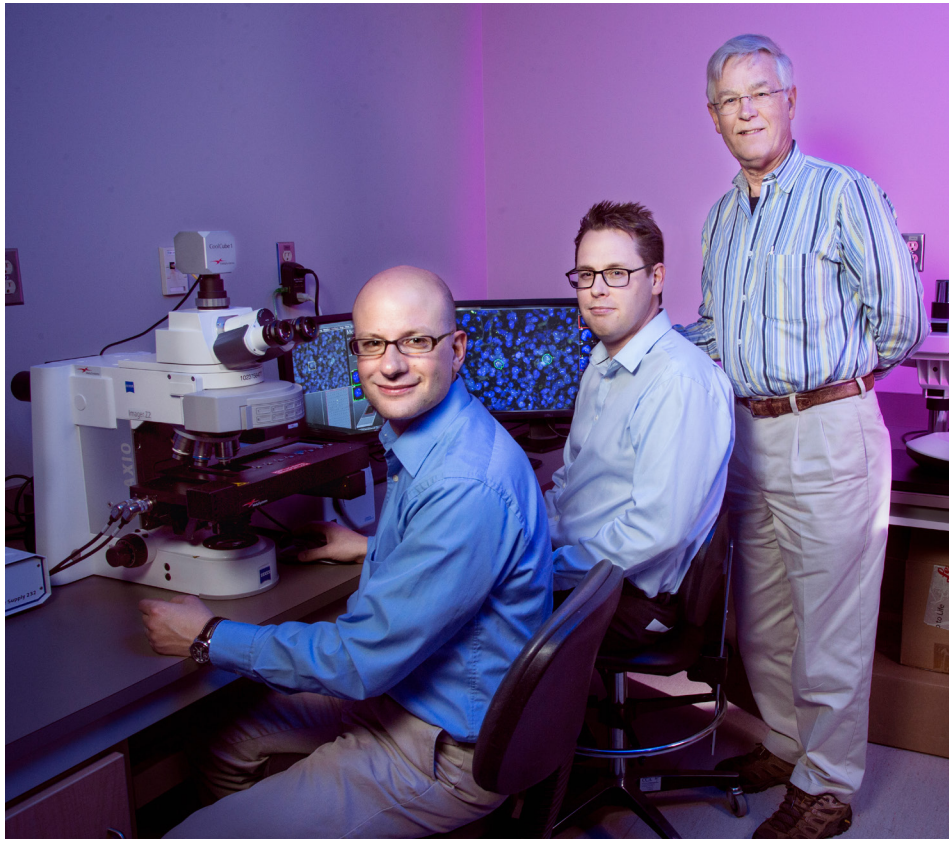
Dr. Gorski's laboratory at the BC Cancer Agency is a world leader in the study of autophagy and its relevance to cancer biology. Autophagy is a cellular self-digestion and recycling process, which has wide ranging implications for normal physiology and diseases including cancer. Cancer cells can use autophagy to adapt to stress, resist treatment and fuel their growth. Consequently, the autophagy process and specific autophagy proteins (e.g. ATG4B) are under investigation as therapeutic targets, but the contexts in which ATG4B inhibition may be beneficial are not well understood.

This study was the first to identify the HER2 subtype as a suitable context for emerging ATG4B inhibition strategies. Approximately 20 per cent of breast cancers are characterized by overexpression of the HER2 protein, which initiates signaling events that support cell growth and survival. Although advances in anti-HER2 therapies have led to significant improvements in patient survival, treatment resistance in advanced cases of HER2-positive cancers has not yet been effectively addressed. Dr. Gorski's team found that HER2 regulation influenced ATG4B levels and the inhibition of ATG4B sensitized treatment-resistant HER2-positive breast cancer cell lines to anti-HER2 treatment.

Dr. Gorski was selected to give an oral presentation on her team's work at the Keystone Symposium on Autophagy in June 2016, and the study was subsequently published in *Oncotarget* in October 2016. Other BC Cancer Agency team members include Dr. Svetlana Bortnik, Dr. Courtney Choutka,Dr. Jennifer H. Baker, Dr. Chandra Lebovitz, Dr. Wieslawa H. Dragowska, Dr. Nancy E. Go, Dr. Marcel B. Bally, Dr. Andrew I. Minchinton and Dr. Karen A. Gelmon. Other team members include Hugo M. Horlings and Samuel Leung, and research partners include Simon Fraser University, University of British Columbia, Vancouver General Hospital and Netherlands Cancer Institute.

This research was supported by a Canadian Institutes of Health Research Team Grant and a Canadian Institutes of Health Research in partnership with Avon Foundation for Women-Canada grant.

The approach integrates a number of different methods including biobanking, xenografting, and multiplexed phospho-flow cytometric profiling.



Personalized treatment for lymphoid cancers is a daily reality for patients in British Columbia

Researchers at the BC Cancer Agency's Centre for Lymphoid Cancer continue to explore ways to provide precision and personalized treatment for each patient with lymphoid cancer in British Columbia. Although highly effective treatments are currently available for most lymphoid cancers, these treatments can be difficult to tolerate and ultimately only cure about half of patients. Providing a more personalized and accurate diagnosis of a patient's cancer gives physicians the option to choose more appropriate treatments that are specifically designed for that individual's cancer, and ultimately improve patient outcomes.

More than a decade ago, the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) first suggested the potential of increasingly personalized treatment for lymphoid cancers. A technique called gene expression profiling is used to describe and compare the specific genetic characteristics of normal and malignant cells to develop a "profile" or "signature". This signature is studied to learn how malignant cells will behave and can be used to predict treatment responses.

Although the gene expression profiling technique holds much promise, the consortium collaboration led by Dr. David Scott and collaborators Dr. Joseph Connors and Dr. Christian Steidl, worked hard to refine the technique further. They developed these "signatures" into tests that could be applied to the same tissue that was taken from the patient to make the diagnosis of lymphoma. Their refinements have allowed

them to characterize different subsets of patients with increasing precision and to identify those who may require more innovative treatment approaches.

In 2016, Drs. Scott, Connors and Steidl's research initiatives further advanced personalized treatments for lymphoid cancer:

- A paper describing the development and validation of the **MCL35 assay (or test) for mantle cell lymphoma** was accepted for publication in a major cancer journal and a patent was filed. This assay uses a gene expression-based signature for proliferation that can be applied to routine formalin-fixed paraffin-embedded biopsies using the NanoString Technologies platform. The assay will allow the development of trials that will match treatment regimens to the risk of relapse of the patient.
- The **Chronic Lymphocytic Leukemia (CLL) Project and Biobank** were launched. While collection and biobanking for other cell types was routine, developing the methodology for CLL cells took a great deal of additional effort. Now, samples can be systematically gathered from CLL patients across the province of British Columbia, enriched for tumour cells and banked for future studies. Current projects using these samples involve targeted and genome wide sequencing along with fluorescence in situ hybridization (FISH) analyses. This initiative will allow the researchers to study and understand the events leading to disease activation in the patients who have a more aggressive form of this disease.
- Until recently, the genomic personalization of cancer treatment has only been applied in research settings, not day-to-day medical care. Researchers are evaluating how **practical, rapid and cost effective** personalized diagnosis and treatment can be integrated into routine patient management in British Columbia. In addition to carefully analysing all the costs and cost savings, they are also determining if outcomes for these patients are improved because of personalized lymphoid cancer care. British Columbia is functioning as a real-world laboratory to show how to use genomic analysis to cost-effectively cure more cancer patients in a way that can readily be duplicated elsewhere around the world.

Many other BC Cancer Agency researchers were involved in these projects including Drs. Graham Slack, Diego Villa, Randy Gascoyne, Andy Weng, Marco Marra, Dean Regier, Stuart Peacock and Andrew Mungall.

Funding for this series of projects was provided by: National Institutes of Health, Terry Fox Research Institute, BC Cancer Foundation, Genome Canada, Genome BC and Canadian Institutes for Health Research.

More than a decade ago, the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) first suggested the potential of increasingly personalized treatment for lymphoid cancers.

These ideas will continue to move forward with the renewal of two large scale team grants.

The Terry Fox Research Institute and the Canadian Institutes of Health Research recently awarded grants to the investigators of the department of Lymphoid Cancer Research.

- The TFRI New Frontiers Program Project Grant in *Overcoming Treatment Failure in Lymphoid Cancer* is co-led by Drs. Connors and Steidl and involves 26 interdisciplinary investigators and collaborators across Canada and the USA. State-of-the-art genomics and proteomics platforms will be used including next-generation sequencing of archival formalin-fixed paraffin-embedded tissues (FFPET), circulating tumour DNA (ctDNA), mass cytometry (CyTOF), single cell genomic tools and genome editing tools for *in vitro* and *in vivo* model development. Serial tissue biopsies are available in the tissue repositories of BC Cancer Agency's Centre for Lymphoid Cancer and additional biopsies are acquired through prospective clinical trials. This $7.5 million grant was awarded to support the interdisciplinary team in identifying the patients early on who are in need of alternative treatments. The grant will focus on patients with follicular lymphoma, diffuse large B cell lymphoma, Hodgkin lymphoma and mantle cell lymphoma.
- The $1.5 million Canadian Institutes of Health Research Foundation grant is led by Dr. Christian Steidl and involves Drs. Marcel Bally, Gregg Morin, Kerry Savage, Sohrab Shah and Andrew Weng. Investigators will research the lymphoma microenvironment focusing on two related subtypes of lymphoid cancer – Hodgkin lymphoma and Primary mediastinal B-cell lymphoma, which often affect adolescents and young adults. The investigators will study the mechanisms of immune system escape in tumour cells, focusing on genes that were found to be altered in earlier studies. The goal of this research will be to characterize novel drug targets, to develop genetic tests that predict therapy resistance in childhood and adult Hodgkin lymphoma, to identify patients who are at high risk of relapse and to pave the way for innovative clinical trials.

The Terry Fox Research Institute and the Canadian Institutes of Health Research recently awarded grants to the investigators of the department of Lymphoid Cancer Research.

Dr. Randy Gascoyne is awarded the 2016 Lifetime Achievement Award: Terry Fox Medal

Dr. Randy Gascoyne was presented with the 2016 Lifetime Achievement Award: Terry Fox Medal at Terry Fox Research Institute – BC Node Research Day. This award celebrates his many contributions to lymphoid cancer research, clinical care and the establishment of provincial Hematopathology resources, and his significant influence on the next generation of clinicians and scientists.

As an internationally recognized hematopathologist, Dr. Gascoyne has had a long and productive career at the BC Cancer Agency. He is a clinical professor at the University of British Columbia and a distinguished scientist at the BC Cancer Research Centre. He is known for his work investigating the pathogenesis of lymphoid cancers using genomic approaches, gene expression profiling studies, and biomarker and prognostic factor development in in Hodgkin lymphoma and non-Hodgkin lymphoma. He is prolific, with over 442 peer-reviewed manuscripts, hundreds of abstracts and many book chapters. He has also been an investigator or co-investigator on research grants totalling over $94 million and has served on many advisory and editorial boards. In addition, he was listed as one of the World's Most Influential Scientific Minds for three consecutive years.

In July 2016, Dr. Gascoyne retired from the BC Cancer Agency.

Some of the World's Most Influential Scientific Minds work at BC Cancer Agency

In December 2016, Drs. Marco Marra and Steven Jones of the Genome Sciences Centre were included in the list of the World's Most Influential Scientific Minds of 2016 by Thomson Reuters, along with Drs. Joseph Connors and Randy Gascoyne of the Lymphoid Cancer Research Department at the BC Cancer Agency. Membership on this list was determined by analyzing citation data over the last 11 years to identify those who have published the highest impact work. This is the third consecutive year that Drs. Marra, Connors and Gascoyne have received this recognition. This achievement demonstrates the international recognition and leadership of BC Cancer Agency researchers.

Successes in commercialization: Celator, Aquinox and ARTMS

Commercialization is part of the innovation process in cancer research. The BC Cancer Agency Technology Development Office (TDO) saw several significant commercialization milestones in 2016.

Commercialization is part of the innovation process in cancer research. The BC Cancer Agency Technology Development Office (TDO) saw several significant commercialization milestones in 2016. Located at the BC Cancer Agency Research Centre, the TDO serves researchers across the Provincial Health Services Authority by providing a range of services that ultimately transfer knowledge from research into the public domain.

Celator Pharmaceuticals is a start-up company that was co-founded by Drs. Marcel Bally and Lawrence Mayer in 1999. In 2016, the results of a Phase III clinical study demonstrated that elderly patients with high-risk (secondary) Acute Myeloid Leukemia (AML) treated with the lead product VYXEOS (cytarabine:daunorubicin liposome injection) experienced a statistically significant improvement in overall survival. As a result, the USA FDA granted Breakthrough Therapy designation to VYXEOS for treatment of high-risk secondary AML and in July 2016, Jazz Pharmaceuticals acquired Celator Pharmaceuticals for $1.5 billion.

Aquinox Pharmaceuticals is a start-up company co-founded by Dr. Gerald Krystal and incorporated in 2006. The company specializes in novel targeted small molecule therapeutics for the treatment of inflammatory disease and cancer. In September 2016, Aquinox initiated a phase III study of their lead molecule, AQX-1125, in patients who suffer from Interstitial Cystitis/Bladder Pain Syndrome. AQX-1125 is an anti-inflammatory product candidate targeting SH2-containing inositol-5'-phosphatase 1, or SHIP1, which is a key regulator in the PI3K pathway, an important cellular signalling pathway in immune cells. Market capital of this company is currently valued at $350 million USD.

ARTMS™ Products Inc. executed a license agreement between TRIUMF, the BC Cancer Agency, Lawson Health Research Institute and the Centre for Probe Development and Commercialization. This agreement is a major milestone and marks the beginning of a new era in Tc-99m production and supply. Tc-99m is the most widely used medical isotope in the world and is in over 80 per cent of all nuclear medicine imaging procedures and in more than 35 commercial radiopharmaceutical products. The Chalk River Nuclear Reactor license was extended to March 2018, at which time it will cease routine production of molybdenum-99 (Mo-99), the parent isotope of Tc-99m. The agreement will lead to the commercialization of a decentralized, green and Canadian-made technology that will allow Technetium-99m (Tc-99m) to be produced daily at hundreds of hospital-based cyclotrons around the world.

Completion of the ASCENDE-RT clinical trial

The trial demonstrated that men randomized to receive a brachytherapy boost halved the recurrence rate compared to those randomized to external radiation alone.

Clinical trials require years, and sometimes decades, of hard work from conception to analysis, with many steps and milestones in between. December 2016 marked the completion of the ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) trial, with the final publication of study results in *The International Journal of Radiation Oncology, Biology and Physics*. The trial has been ongoing since the first subjects were enrolled in August 2002.

ASCENDE-RT trial was led by Dr. W James Morris and compared two methods of delivering dose escalation for men with unfavourable risk localized prostate cancer. The trial demonstrated that men randomized to receive a brachytherapy boost halved the recurrence rate compared to those randomized to external radiation alone. The trial also had the highest benchmarks for disease-free survival ever seen in any prospective, randomized study for poor prognosis prostate cancer patients; at the median followup of 6.5 years, 83 per cent of high-risk and 94 per cent of intermediate-risk patient randomized to brachytherapy were free of disease. The results of this study, which involved almost 400 patients, have already begun to change practice in Canada, the USA, Europe and Australia.

The study was supported by unrestricted educational grants to the BC Cancer Agency received from Oncura corporation, a division of GE Healthcare, which manufactured the model 6711 125Iodine RapidStrand® sources used in this trial, and Sanofi-Aventis Canada, the maker of the Suprefact® and Eligard® LHRH depot injections used in this trial.

The principal investigator for this multicentre randomized trial was Dr. W James Morris, and involved numerous other BC Cancer Agency investigators, and most importantly the close to 400 patients that agreed to randomization in this practice-changing trial.

AVAILABLE PROVINCE-WIDE: a more personalized approach for the analysis of myeloid cancers and solid tumours

Researchers at the BC Cancer Agency and the Genome Sciences Centre have changed the way that patients throughout British Columbia will be diagnosed and treated for cancer. Two next-generation sequencing-based panels are now being offered to all eligible cancer patients on a province-wide basis. Newly diagnosed patients with advanced lung cancer, colorectal cancer, melanoma, gastrointestinal stromal tumours (GIST) or low grade gliomas are now eligible for **OncoPanel** testing, which is a clinical test that can detect multiple different mutations in several genes simultaneously. Newly diagnosed patients with acute myeloid leukemia, myeloproliferative neoplasms and myelodysplastic syndromes are eligible for the **Myeloid Panel**, which is also a clinical test that detects multiple mutations in several genes. Each year in British Columbia, an estimated 2,000 cancer patients are eligible for OncoPanel testing, while an estimated 600 cancer patients are eligible for the Myeloid Panel.

Dr. Aly Karsan, Genome Sciences Centre, developed the OncoPanel and Myeloid Panel, and Dr. Hagen Kennecke co-led the study to validate the OncoPanel across British Columbia. Drs. Marco Marra, Donna Hogge, Inanc Birol and Steven Jones helped to co-develop the myeloid panel. Multiple single gene sequencing tests are integrated onto a single Next-Generation sequencing panel and provide a detailed genetic fingerprint of each patient's cancer. The gene mutations that are included on each panel were carefully selected based on clinical relevance with respect

to publicly funded treatment or ongoing clinical trials. The panels were validated in two clinical trials, involving 600 patients and 79 oncologists.

The panels are adaptable and new gene tests can be added as more clinically significant biomarkers are identified. As well, the capacity of the panels is being expanded to detect more types of genetic alterations including copy number variants and gene rearrangements.

The OncoPanel and Myeloid Panel are translating science into clinical applications and improving patient care. The advanced and specific information from the panels is sent to treating oncologists and hematologists within two to three weeks, enabling them to make critical and timely treatment decisions. As more patients are matched with the best treatment options available, British Columbia is moving towards personalized cancer care and a targeted treatment approach. In addition to clinical applications, researchers will gain research knowledge of how both common and uncommon mutations contribute to cancer, and this may provide insights into future treatment strategies.

The panels were developed with significant support from the BC Cancer Foundation and Genome BC, as well as from Canadian Institutes of Health Research, Terry Fox Research Institute, Pfizer, Amgen, Hoffman LaRoche and the Provincial Health Services Authority.

British Columbia is the first jurisdiction in Canada to provide this type of analysis on a provincial scale, meaning a more personalized approach to treatment for thousands of eligible cancer patients. These are the first gene panels to be available province-wide and as part of standard cancer care in Canada for acquired cancers.

Patients eligible for the OncoPanel include:

British Columbians newly diagnosed with advanced lung cancer, colorectal cancer, melanoma, gastrointestinal stromal tumours (GIST) or low grade gliomas. After a biopsy is performed, samples are sent to the BC Cancer Agency where the DNA is processed. OncoPanel results will be sent to the patient's oncologists two to three weeks after the biopsy.

Patients eligible for the Myeloid Panel include:

British Columbians newly diagnosed with acute myeloid leukemia, myeloproliferative neoplasms and myelodysplastic syndromes who meet testing guidelines. A bone marrow sample is taken and sent to the BC Cancer Agency laboratory for processing. Myeloid Panel results will be sent to the patient's hematologist two to three weeks after the sample is extracted.

In 2016, Dr. Aly Karsan was the recipient of the John Auston BC Cancer Foundation Clinical Investigator Award. This five-year award will support his research into myelodysplastic syndromes (MDS), which are cancers of the blood-forming cells in the bone marrow. The goal of this work is to develop clinical tests to inform physicians about the best treatments for patients with MDS. The award was named in honour of past BC Cancer Foundation board director John Auston, who was an avid supporter of cancer research in BC and who lost his life to cancer.

Dr. Poul H. Sorensen awarded the Canadian Cancer Society Robert L. Noble Prize

Dr. Poul H. Sorensen, distinguished scientist at the BC Cancer Agency, was awarded the Robert L. Noble Prize by the Canadian Cancer Society for outstanding achievements in basic biomedical cancer research. He is a globally renowned molecular pathologist with a worldwide reputation in pediatric oncology research. His work focuses on the molecular abnormalities that underlie childhood sarcomas and brain cancers, and adult cancers of the breast, brain and prostate.

Dr. Sorensen's research program is remarkably diverse and has led to important advances in both cancer genetics and cancer biology. Early in his career, Dr. Sorensen discovered several new genetic alterations in solid childhood cancers, which typically have less genetic complexity than adult tumours. He used these findings in an innovative way to better understand the biology of adult cancers. This included the identification of the ETV6-NTRK3 gene fusion in both childhood sarcoma and a form of breast cancer, which pointed to a new treatment strategy for these diseases. Dr. Sorensen has also used his genetic findings to develop new tests to improve the classification of childhood cancers, which are used by clinicians around the world. More recently, Dr. Sorensen's work has drawn attention to the crucial role of cancer proteins in cellular stress responses that allow cancer to grow and spread.

Dr. Sorensen is a prime example of excellence in cancer research and demonstrates continued dedication to the scientific community. He regularly volunteers his expertise on grant review panels and is recognized for his extraordinary mentorship and commitment to training the next generation of excellent scientists.

The Robert L. Noble Prize is given for outstanding achievements in basic biomedical cancer research. It honours Dr. Noble, an esteemed Canadian investigator whose research in the 1950s led to the discovery of vinblastine, a widely used anticancer drug. At the time, vinblastine was one of the most effective treatments available for Hodgkin lymphoma.

PANCREOX: Results of a BC Cancer Agency-led Canadian phase III clinical trial in advanced pancreatic cancer

Patients with advanced pancreatic cancer who have failed their first line of chemotherapy have limited options and a guarded prognosis. Trials in this patient setting are few and challenging given the nature of the disease. Understanding the efficacy and the risks of therapy are extremely important in this palliative setting.

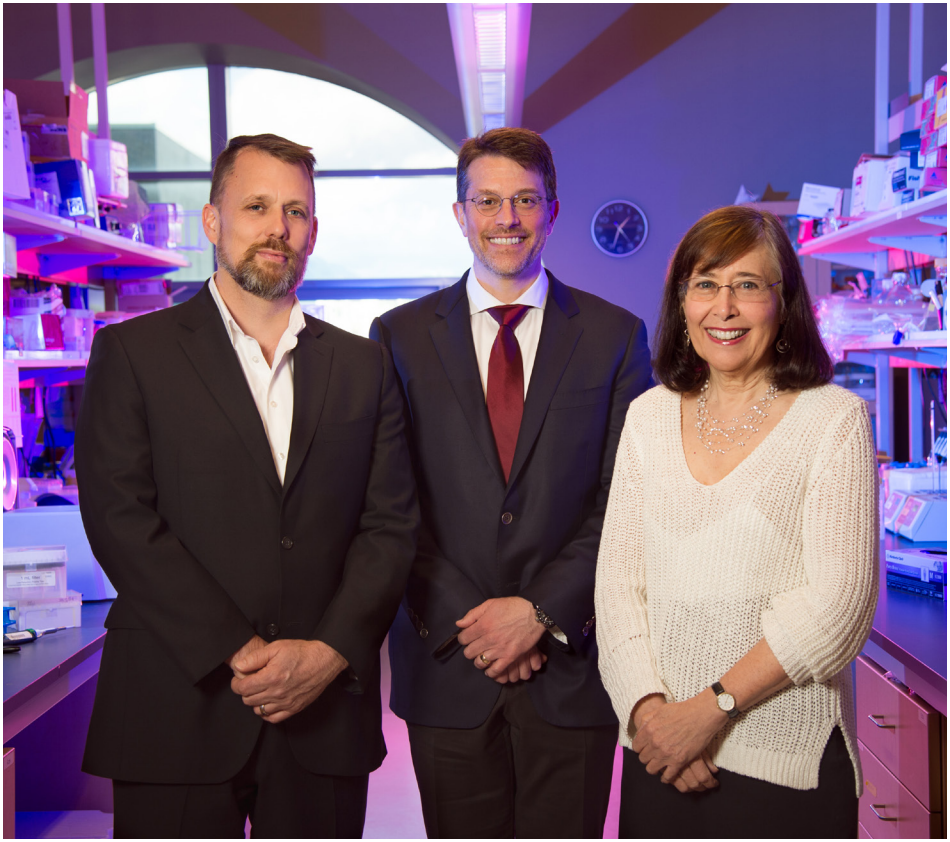
The PANCREOX (Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy) study conclusively demonstrated that the use of a combination oxaliplatin-containing regimen did not improve survival over a single agent fluoropyrimidine regimen and was associated with greater toxicity. The study was conducted in 108 patients who had advanced pancreatic cancer who had failed first-line gemcitabine therapy.

As a result of this trial, patients can now be offered a less toxic therapy without a concern that efficacy is being compromised. As well, the trial demonstrated that studies in this advanced setting are feasible.

Results of this study were reported in the *Journal of Clinical Oncology* in September 2016. BC Cancer Agency team members included Drs. Sharlene Gill, Malcolm Moore, Dan Renouf, Hagen Kennecke, Howard Lim, Christian Kollmannsberger, Barbara Melosky, Winson Cheung, Thuan Do and Muhammed Zulfiqar. The study involved multiple academic centres across Canada including the Princess Margaret Hospital, Sunnybrook Hospital, Tom Baker Cancer Centre, Juravinski Cancer Centre, The Ottawa Hospital Cancer Centre, Sherbrook University and Burnaby Hospital. The trial was supported by Sanofi Canada.

As a result of this trial, patients can now be offered a less toxic therapy without a concern that efficacy is being compromised.

EPIGENOMICS: BC Cancer Agency's leadership role in a coordinated publication release with the International Human Epigenome Consortium project



BC Cancer Agency scientists contributed three of the 41 research papers that were released by the International Human Epigenome Consortium (IHEC) on November 17, 2016. The studies involved researchers from across Canada, the USA, the European Union, Germany, Japan and Singapore. The coordinated release was named as one of the top five epigenetics stories of 2016 by the Epigenetics Literacy Project. The papers covered a broad range of topics and were published in a number of scientific journals, including 27 in *Cell* family journals.

The epigenome is a series of chemical modifications to DNA and its packaging proteins that act to control how genes are expressed in the genome during development, during normal and disease processes and in response to different environmental and chemical stimuli. Understanding how genes are switched on and off in different cell types and situations provides scientists with insights into normal human development and disease. Not surprisingly, epigenomic mechanisms are deregulated in many diseases, with some types of cancers – including Acute Myeloid Leukemia (AML) and pediatric cancers – particularly susceptible to epigenetic deregulation.

As Chair of the IHEC international scientific steering committee, Dr. Martin Hirst, scientist at the BC Cancer Agency and Head of Epigenomics at the Genome Sciences Centre, played a key leadership role in coordinating the publication of the 41 papers, the release of all associated data and the development of associated commentaries and news releases. In addition, he was an author on several of the papers along with his BC Cancer Agency colleagues.

- Dr. Hirst, with his colleague Dr. Connie Eaves, a distinguished scientist at the BC Cancer Agency, published the first comprehensive epigenetic profiles of normal cell types in human breast tissue. This information will help scientists understand how human mammary cells are normally regulated, and the information will serve as a baseline against which cells perturbed by disease can be compared. This paper was published in *Cell Reports*.
- A second paper identified epigenetic changes that are thought to contribute to the development of a rare childhood cancer called malignant rhabdoid tumour. This work was conducted by a team led by Dr. Marco Marra, distinguished scientist at the BC Cancer Agency and director of the Genome Sciences Centre. This paper was published in *Cancer Cell*.
- Dr. Hirst's group also published a third study describing a novel method for analyzing stem cell epigenomes. This new ChIP-Seq method enables researchers to extract additional information about protein-DNA interactions from even very small samples. This publication was published in *Cell Reports*.

These papers establish important technological and reference frameworks, which are essential to understanding what normal epigenomes look like. The next step will be to determine the degree to which the epigenome varies in populations of similar cells, how it becomes deregulated in disease and if such deregulation may be reversed. Dr. Hirst's lab has already classified different types of epigenomic effectors and is working to understand how these can be manipulated to potentially address disease. These important efforts will help to inform clinical trials already underway evaluating new ways to modulate epigenetic changes and reverse disease.

All DNA sequencing work for these three papers was performed at the Genomes Science Centre, the Centre for Epigenome Mapping Technologies led by Drs. Hirst and Marra, and the Epigenomic Data Coordination Centre led by Dr. Steven Jones of the BC Cancer Agency, Simon Fraser University and the University of British Columbia. Support for this work was provided by the Canadian Institutes of Health Research, the Canadian Cancer Society Research Institute, the Canada Foundation for Innovation, Genome Canada and Genome BC, the National Cancer Institute, National Institutes of Health and the BC Cancer Foundation.

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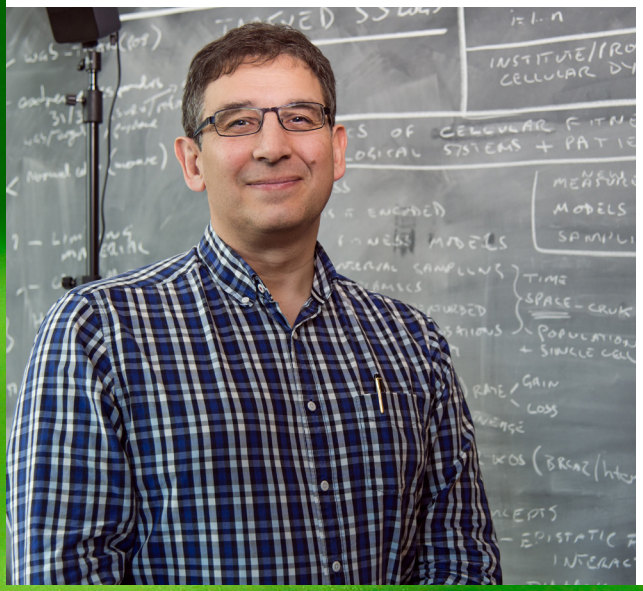
Dr. Sam Aparicio named Fellow of the Royal Society

Dr. Samuel Aparicio, senior scientist and head of the Department of Breast and Molecular Oncology at the BC Cancer Agency, was named fellow of the Royal Society of Canada as part of the Life Science Division on November 18, 2016. The Royal Society of Canada is considered the highest honour a scholar can achieve in the arts, humanities and sciences in Canada.

Dr. Aparicio's work on the genomes of breast cancers has provided new insights into the tremendous breadth of tumour genetic heterogeneity. The cells within tumours are not identical, and tumours are now best thought of as complex communities of cells composed of genetically distinct cellular sub-populations. His work has linked this genetic heterogeneity to cancer evolution and recurrence, providing a much-needed explanation for how treatment-resistant cancers may arise.



Most recently, Dr. Aparicio was the co-corresponding author of a study that analyzed somatic mutation profiles of 2,433 breast cancers, and refined their genomic and transcriptomic landscapes. The results of the study emphasize the importance of genome-based stratification in a heterogeneous disease such as breast cancer and have important implications for designing therapeutic strategies. This adds to the METABRIC project, an important resource characterizing the combined genomic profiles of a large number of primary breast tumours from patients with long-term follow up data. The study was published in *Nature Communications* in May 2016 and involved collaborators in the UK, Norway, Australia and from across Canada. The METABRIC project was funded by Cancer Research UK, the BC Cancer Foundation and Canadian Breast Cancer Foundation BC/Yukon.

Dr. Aparicio's work on the genomes of breast cancers has provided new insights into the tremendous breadth of tumour genetic heterogeneity.

Dr. Sohrab Shah: UBC Killam Research Prize winner

This open-source software overcomes some of the limitations of previous methods and can robustly infer clonal genotypes from single cell sequencing data.

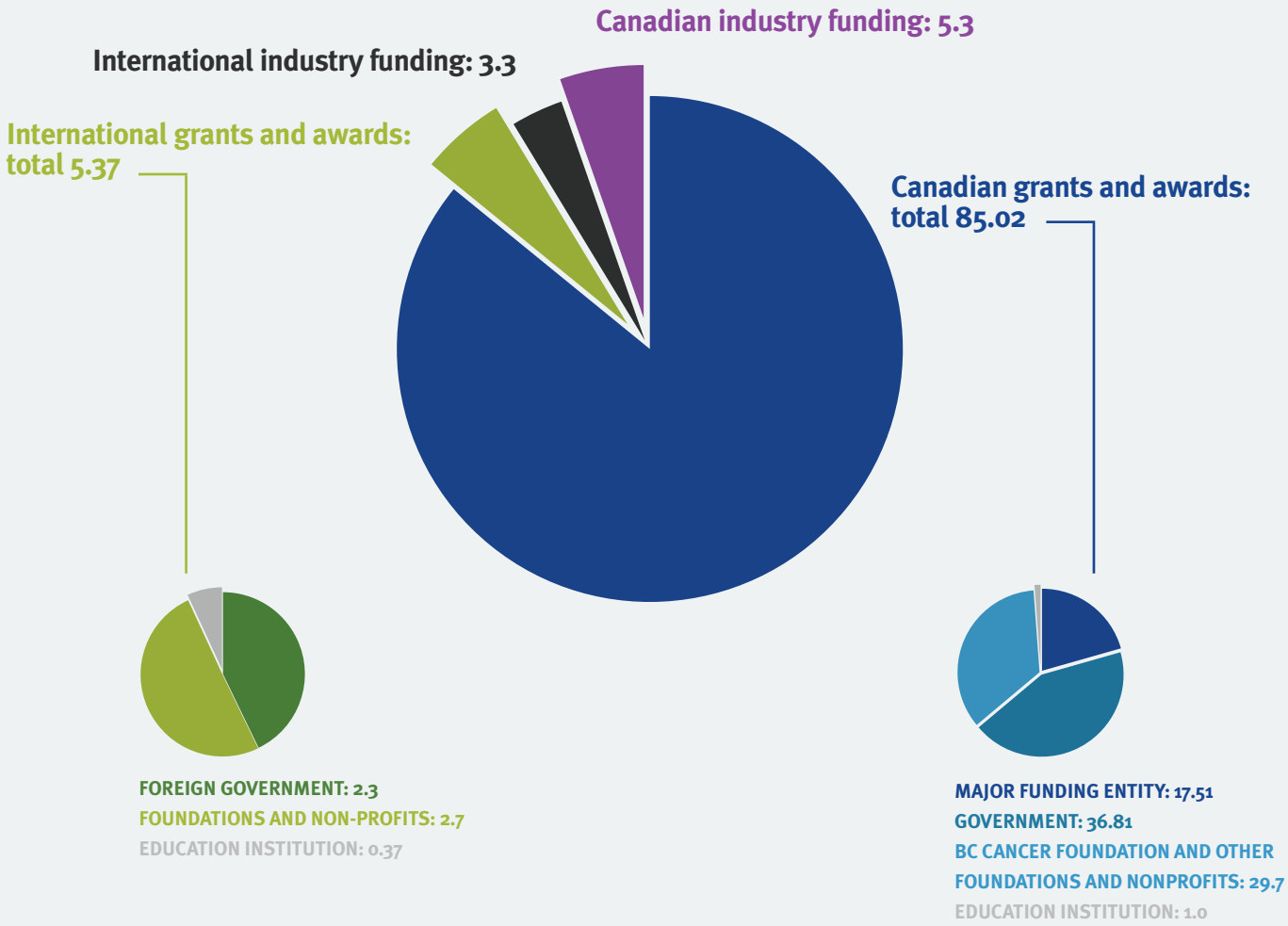
Dr. Sohrab Shah, scientist, Department of Molecular Oncology at the BC Cancer Agency, was awarded the Killam Research Prize for Applied Science in the Junior category. He was one of only seven members of the Faculty of Medicine, from seven different departments, that were recognized by UBC's Faculty Research Awards.

The award recognizes Dr. Shah's outstanding research and scholarly achievements in the area of analysis of single cell genomics and clonal evolution. Dr. Shah's work is in the field of computational cancer genomics and involves the development of statistical models and machine learning algorithms to interpret next generation sequence data for defining mutational landscapes and quantifying clonal evolution in ovarian and breast cancers.

In this last year, with his research team that included many of his colleagues from the BC Cancer Agency Department of Molecular Oncology, Simon Fraser University and the University of British Columbia, Dr. Shah published a paper in *Nature Methods* describing the Single Cell Genotyper. This open-source software overcomes some of the limitations of previous methods and can robustly infer clonal genotypes from single cell sequencing data.

In addition, he published a paper in *Nature Genetics*, tracking clonal migrations among metastatic sites in the peritoneal cavity of high-grade serous ovarian cancer patients. In mapping the cell migration, Dr. Shah's team identified at least two divergent modes of intraperitoneal metastasis and showed how cells are able to settle and thrive in specific regions of the body causing widespread, life-threatening disease.

TOTAL FUNDING: $99,332,395



Liquid biopsy for patients with advanced prostate cancer

Cell free, or circulating tumour DNA (ctDNA), is genetic material that is released by tumours into a patient's blood. Analysing this ctDNA from a blood sample is like a "liquid biopsy" and permits researchers to identify genetic changes in cancer and to measure how a tumour is responding to therapy in real time. Dr. Kim Chi, medical oncologist and senior scientist at the BC Cancer Agency, in collaboration with Dr. Alex Wyatt, senior scientist at the Vancouver Prostate Centre, developed and validated a liquid biopsy technique to predict the likely disease course and to monitor responses to therapy in patients with advanced prostate cancer.

They examined the ctDNA from blood collected from 65 men with metastatic castrate-resistant prostate cancer, before and after they received treatment with enzalutamide, an androgen-receptor antagonist. They conducted integrated genomic profiling of the ctDNA to identify changes that occurred in the androgen receptor gene; as well as changes in 19 other genes associated with primary and acquired resistance. They found that the genetic changes were related to how the men were responding to prostate cancer treatment.

This study demonstrated that the approach taken to obtain and analyse the ctDNA from the study participants was feasible and could be used to predict responses of individual patients to treatment. Dr. Chi and his colleagues could determine when therapy resistance occurred, and identify other potential targets that may be used to treat advanced prostate cancer.

With further work, they hope that this minimally invasive ctDNA-based method can be used to choose the right therapy for each patient and to avoid treatments that will not work. Additional advantages of the liquid biopsy method are that blood samples are easy and relatively painless to obtain, can be repeated on a regular basis to monitor treatment and may reduce or delay the need for a core biopsy.

This work was published in *JAMA Oncology* and has been highlighted as one of the five key advances in prostate cancer research in 2016. This work has also resulted in the launch of an umbrella trial (a type of trial where a patient is assigned a treatment based on their molecular profile) with the Canadian Cancer Trials Group led by Dr. Chi.

This study was supported by the Canadian Cancer Society Research Institute, Prostate Cancer Canada, Movember, BC Cancer Foundation, Nation Cancer Institute Specialized Programs of Research Excellence and Terry Fox Research Institute.

Quantitative proteome profiling: development of the SP3-CTP technology

The Genome Sciences Centre Proteomics Platform led by Dr. Gregg Morin and Dr. Chris Hughes has developed the innovative "SP3-Clinical Tissue Proteomics (CTP)" technology. This technology allows researchers to comprehensively identify and quantify the proteins in single formalin fixed paraffin embedded (FFPE) tumour tissue sections. This highly sensitive method enables biomarker discovery, therapeutic target identification and identification of tumourigenic biological processes.

This technology was developed entirely by the Proteomics Platform, and is the first demonstration of in-depth proteomics using practical amounts of clinical FFPE tissues.

This novel protocol based on mass spectrometry allows the measurement of >8,000 proteins from the archival tumour samples at unmatched sensitivity compared with other leading international research groups. The BC Cancer Agency has many thousands of such archived samples and associated clinical information available for these studies.

As proof of principle for this new technology, Dr. Morin's team in collaboration with Dr. Huntsman and his OVCARE team, performed in-depth quantitative analyses of clinical ovarian tumour specimens. Results showed that in depth proteomic analysis of clinically annotated patient materials can be effectively used as a biomarker discovery tool and perhaps ultimately as a diagnostic approach.

The SP3-CTP technology is being integrated in the BC Cancer Agency's precision medicine Personalized Onco-Genomics (POG) clinical trial to provide improved guidance to oncologists for treatment decisions. This technology was the central methodology for three awarded grants that seek to identify protein markers for patient sub-classification for improved diagnosis in breast, ovarian and rare tumours from multiple sites including gynecological, gastrointestinal, lung and brain cancers. It is also a component of three large Terry Fox Research Institute grants in the BC Cancer Agency for lymphoma, antibody-based cancer drug development and pediatric cancer personalized medicine. Support for this work was provided by a Canadian Cancer Society Research Institute Impact Grant, the BC Cancer Foundation and donors Charles and Elaine Schnier.

BC Cancer Agency collaborators include Drs. Melissa McConechy and Dawn Cochrane. Other research partners include the University of British Columbia.

This technology allows researchers to comprehensively identify and quantify the proteins in single formalin fixed paraffin embedded (FFPE) tumour tissue sections.

Understanding genetic characteristics of super seniors:

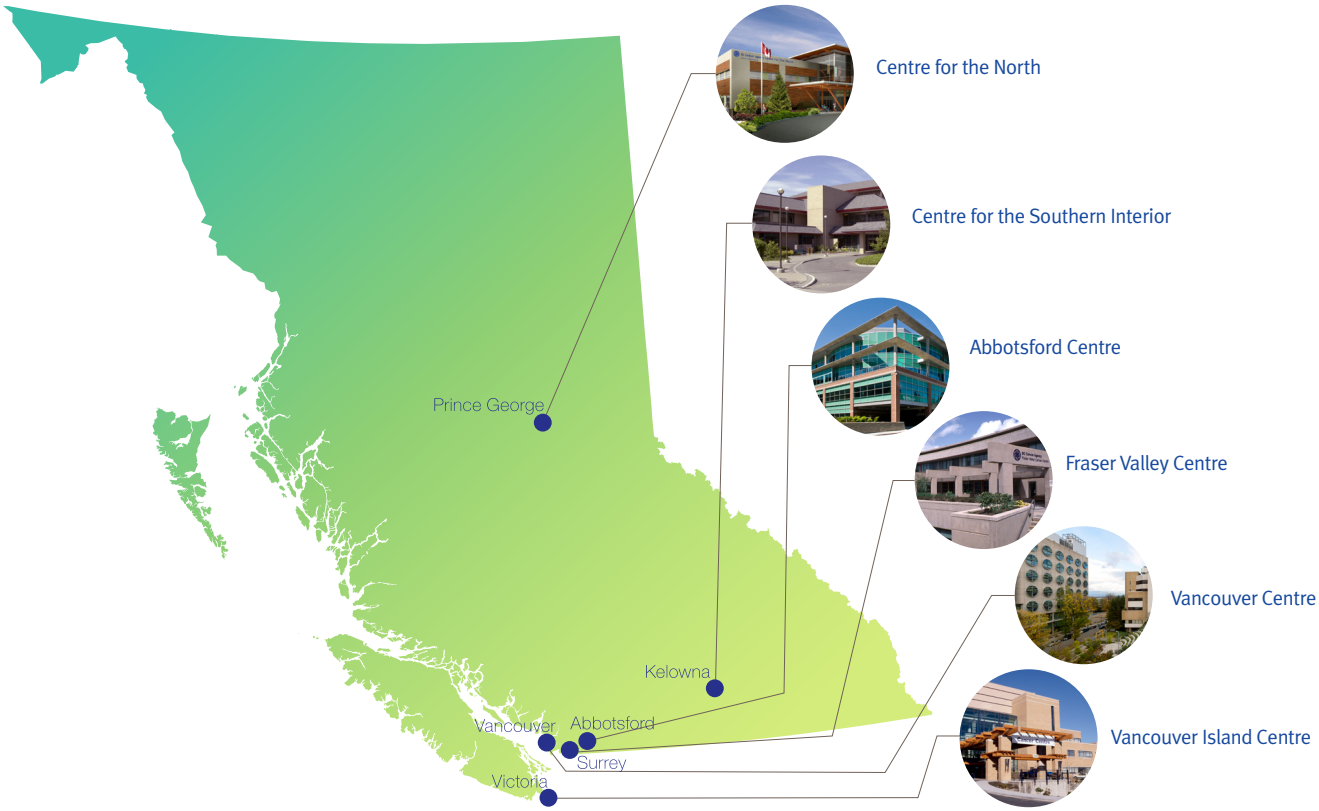
exceptionally healthy individuals over the age of 85

Dr. Angela Brooks-Wilson, distinguished scientist, Genome Sciences Centre, is leading the Healthy Aging Study, which was recently awarded $761,272 in funding from the Lotte and John Hecht Foundation. This unique BC Cancer Agency-based research study is examining why some exceptionally healthy seniors remain free of cancer and other common age-related diseases such as cardiovascular or pulmonary disease, diabetes or Alzheimer's disease.

While some aspects of aging are related to lifestyle choices and environmental exposures, genetic factors may come into play. The study will help determine if individuals lack susceptibility factors that contribute to disease or possess resistance factors that enhance their ability to resist disease and prolong lifespan. The knowledge of genetic variants associated with healthy aging and protection against specific common age-related diseases may help physicians to tailor disease prevention programs for individual patients.

This funding from the Lotte and John Hecht Foundation was used to expand the study with the collection of an additional 200 biological samples from super seniors from across Canada, increasing the number of super seniors to 700.

The study will help determine if individuals lack susceptibility factors that contribute to disease or possess resistance factors that enhance their ability to resist disease and prolong lifespan.



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