



**BC
CANCER** RESEARCH
Provincial Health Services Authority

2018

BC CANCER RESEARCH

ANNUAL REPORT

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MESSAGE FROM THE VICE PRESIDENT OF RESEARCH, DR. FRANÇOIS BÉNARD

Researchers in British Columbia are having a global impact on cancer care. While our research offers hope to improve how we prevent, diagnose and treat cancer, there is much work ahead of us.

At BC Cancer we strive to be a global leader in cancer care and research. Our everyday work is driven by our vision of a world free of cancer.

Our 2018 Research Report focuses on blood cancer research, which has had several achievements and milestones in the past year. One of our top clinician scientists, Dr. Joseph Connors, retired from clinical practice after 37 years at BC Cancer and left a huge legacy behind him, with a landmark publication showing improved efficacy of a new treatment combination for patients with advanced Hodgkin’s disease. Dr. Christian Steidl, who now leads the Centre for Lymphoid Cancer (CLC), received a prestigious Allen Distinguished Investigator Award. Our leukemia research team is growing with the addition of a new clinician scientist and our immunotherapy research program is gearing up to offer innovative cell-based therapies through clinical trials.

We are entering a new era of blood cancer research exploring ground-breaking diagnostic approaches

to better stratify patients, and implementing new treatments to improve the outcomes for our patients. Each year, more than 2,000 British Columbians are diagnosed with blood cancer – leukemia, lymphoma, and multiple myeloma – and we are committed to bringing new discoveries and tailored treatments to provide our patients with the best care.

Working collaboratively with our valuable partners and patients, we are using genomics and other technologies such as proteomics to identify patients who could benefit from more tailored approaches to improve our ability to control their cancer while minimizing undesirable effects. It is an exciting time as we uncover new technologies that can greatly improve our ability to understand what is happening when cancers fail to respond to treatment. An example is the development of single cell genomics, the ability to decode the genome of individual cancer cells and understand how they manage to resist the effects of treatment.

We are immensely proud of our scientists, clinicians and trainees who continue to be recognized for their outstanding work in cancer research. This report shows how BC Cancer continues to be internationally renowned for excellence in



research and care – from winning prestigious awards to being cited in high ranked scientific journals.

We also need to plan for the future. The success of BC Cancer is driven by the people and their passion to reduce the impact of cancer on people and society. Our future lies in our students and trainees and the significant contributions they make to cancer research and care. We are proud of their accomplishments in 2018, and will continue to do everything we can to attract the best and brightest talent to work at BC Cancer.

We are certainly in the midst of exciting times in cancer research and this will continue as we work towards a better future where we minimize the impact of cancer on families in B.C.

MESSAGE FROM BC CANCER FOUNDATION PRESIDENT AND CEO, SARAH ROTH



Photo credit: BC Cancer Foundation.

The BC Cancer Foundation is proud to share a common vision with our partner, BC Cancer: a world free from cancer.

BC Cancer has a deep history of innovative breakthroughs in blood cancer research and treatment. This year, the Foundation was delighted to focus its fundraising on this hard-to-treat cancer at our annual *Inspiration Gala*.

During the evening, a courageous mother took to the stage to share the experience of her five-year-

old daughter, Morgan May, and her battle with leukemia. A story no mother wants to tell, Kelly May inspired hundreds, eliciting a record number of donations. Thankfully, Morgan is nearing the end of her two-year treatment regimen.

In total, the *Inspiration Gala* raised an extraordinary \$4.3 million toward blood cancer research which helped the Foundation achieve a record-setting fundraising year – \$63.7 million – in support of BC Cancer.

The continued generosity of our community means hope is in sight for patients and families facing cancer. Together, we are entering a new era in research and care, and we believe that BC Cancer CAN change the outcome for thousands of families.

As BC Cancer's committed fundraising partner, we look forward to growing philanthropic dollars to fuel life-changing work.

**2018
FAST
FACTS**

342
researchers,
including clinical
scientists

592
staff

580
trainees

\$86
million in
funding

524
total
publications

443
journal
articles

95%
peer
reviewed

10
patents
filed

26
patents
issued

34
active
licenses

10
spin-offs
(1 new)

43%
industry
funded trials

309
active clinical
trials

34,573
patients
enrolled in
clinical trials

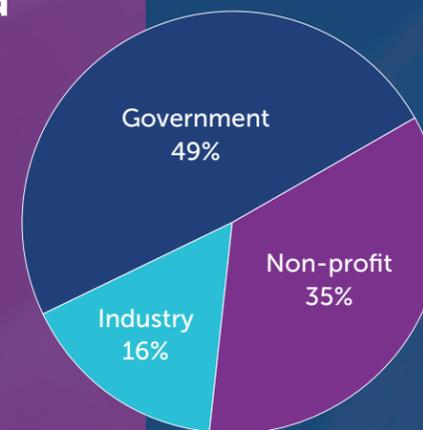
11
researchers
named among the
World's Most Influential
Scientific Minds

FUNDING

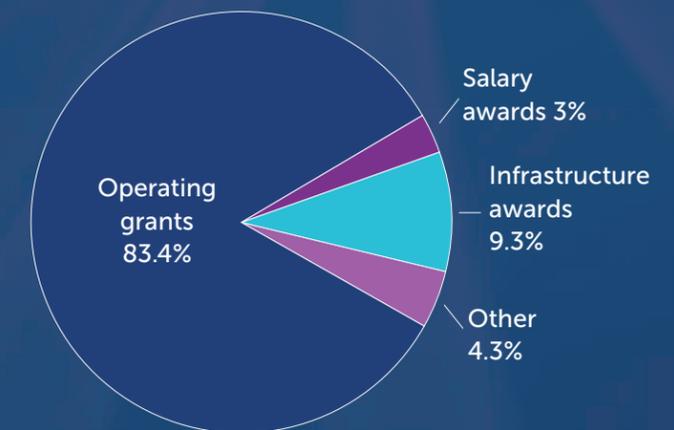
**\$86 million
Total Grants
Awarded**

2017-18 Fiscal Year

33% of CIHR
competitions above
National Average
Success Rate
in FY 17-18



By Sector



By Award Type

2018

AWARDS AND FUNDING

January

◆ In the CIHR Fall 2017 Project Grant competition, four grants were awarded to Principal Investigators at BC Cancer:

1. **Dr. Xiaoyan Jiang** received \$787,950 to investigate targeting key autophagy proteins/pathways for treatment of human leukemia. 
2. **Drs. Haishan Zeng and Isabella Tai** received \$508,724 to investigate real-time endoscopic raman spectroscopy for improving dysplasia/colorectal cancer detection in patients with inflammatory bowel diseases.
3. **Dr. Dean Regier** received \$200,000 to investigate preference analyses and development of an e-health app facilitating communication of test results for hereditary cancer syndromes.
4. **Dr. Rob Holt** received \$150,000 to investigate engineering T cells to overcome an immunosuppressive solid tumour microenvironment.

February

◆ Canadian Cancer Society Research Impact (CCSRI) Grants are designed to accelerate knowledge from science into outcomes for patients, including improved cancer treatments and reduced cancer burden. BC Cancer laboratories and research teams led by **Drs. David Huntsman, Samuel Aparicio, Sohrab Shah, and Torsten Nielsen** received four of the available seven 2018 CCSRI Grants. Below is an overview of the grants:

1. **Molecular pathogenesis of clear cell carcinoma of the ovary: towards better prevention and management strategies:** Clear cell carcinoma, the second most common type of ovarian

cancer, is poorly understood and there are no effective treatments for advanced disease. Improved understanding of this disease is critical to developing effective diagnosis, treatment and prevention strategies. **Dr. David Huntsman**, a leading expert in ovarian cancer, and his team will use a variety of cellular and molecular techniques to examine the biology and behaviour of this disease. By understanding how this cancer starts and grows, and where there may be opportunities to stop it, the researchers plan to help shape clinical practice.



2. **Decoding the clonal dynamics and evolution in breast cancers at single cell resolution: improving diagnostics and expanding treatment approaches:** Cancers can be made up of cells with different characteristics that affect how likely they are to become resistant to treatment. These characteristics may even change over time, making diseases like triple-negative breast cancer (TNBC) hard to treat. **Dr. Samuel Aparicio** and his team will use advanced techniques to study the genetic and molecular features of single tumour cells from people with TNBC to predict how they will respond to different combinations of treatments. This research could help guide targeted treatment and diagnostic strategies for many hard-to-treat cancers.



3. **The determinants of drug response in high-grade serous ovarian cancer: a single cell population genetics approach:** Many ovarian cancers respond to chemotherapy, but some subtypes are resistant and the cancer often returns. The

molecular reason for why this occurs is unknown, and new and effective treatments are needed.



Dr. Sohrab Shah and his team will study the molecular processes and genetics that underlie why individual ovarian cancer cells are susceptible or resistant to standard and experimental treatments. They will also design a new diagnostic test that can match a woman's specific ovarian cancer subtype to an effective treatment, paving the way for precision medicine in the treatment of ovarian cancer.

4. **Adolescent and young adult sarcomas: translating basic science into clinical care:** Sarcomas are a group of over 50 types of cancer affecting the connective tissues of the body, especially in the limbs. Sarcomas most often affect adolescents and young adults, are particularly difficult to diagnose and treat, and have a relatively high mortality rate.



Dr. Torsten Nielsen and his team will address these issues by studying DNA structure in sarcoma cells utilizing new models systems, and developing improved diagnostic tests. With this project, the team is poised to bring novel diagnostic and treatment strategies into clinical trials.

- ◆ **Dr. David Huntsman** received the **Michael Smith Foundation for Health Research (MSFHR) 2018 Aubrey J. Tingle Prize**. This award is given annually to a B.C. clinician scientist whose work in health research has had a significant impact on advancing research and improving health, and the health system, in B.C. and beyond. Dr. Huntsman's work on the genetics of cancer has advanced the

understanding and treatment of hereditary stomach cancer. He has also contributed greatly to the understanding of ovarian cancer with his research team at OvCaRe. The impact of Dr. Huntsman's research is dramatic, with 340 published papers, many in high impact journals, and 21,000 citations in the past five years alone. He has also committed significant time to supporting up-and-coming researchers, mentoring more than 30 trainees to this point in his career, whilst also attracting more than \$20 million in funding as a principal investigator and \$73 million as a co-investigator.

- ◆ **Dr. Connie Eaves** received the **LifeSciences BC Dr. Don Rix Award for Lifetime Achievement**. These awards are presented annually to recognize talented individuals and organizations that represent the life sciences ecosystem in B.C. including academia, health institutions, government, and industry.



March

- ◆ **Drs. Daniel Renouf and David Schaeffer** received the **Terry Fox Pan-Canadian Enhanced Pancreatic Profiling for Individualized Care (EPPIC) Program grant** of \$5 million over five years. The Terry Fox Translational Research Program provides funding to Pan-Canadian projects that accelerate the development and adoption of new treatments and technologies for the benefit of cancer patients across Canada. The goal of EPPIC is to improve personalized treatments for patients with pancreatic ductal adenocarcinoma, a disease with just a nine per cent five-year survival rate.

2018

AWARDS AND FUNDING

March

- ◆ Dr. Marco Marra was awarded with a **Canadian Cancer Society Innovation Grant** co-funded with CIHR-ICR for his research titled "Dissecting tumour heterogeneity using single cell genomics, epigenomics and transcriptomics". Innovation Grants support the development and testing of unconventional concepts and approaches to address problems in cancer research, enhance our understanding of cancer, and generate new approaches to confront the challenges we face in defeating cancer.



April

- ◆ Dr. Connie Eaves received the **American Society of Hematology E. Donnall Thomas Lecture and Prize** for her outstanding contributions to the field of hematopoiesis and stem cell research. This lectureship and prize is named after the late Nobel Prize laureate and past president of American Society of Hematology, E. Donnall Thomas, MD. The E. Donnall Thomas Lecture and Prize recognizes pioneering research achievements in hematology that represent a paradigm shift or significant discovery in the field.
- ◆ Dr. Dianne Miller was awarded the **Presidential Medal** from the **Society of Gynecologic Oncology of Canada** for her outstanding leadership. Her (international vision and far reaching collaborative spirit has led to an innovative strategy for the prevention of ovarian cancer and advances in care of women with gynecologic cancers in Canada and abroad.



- ◆ Drs. Andrew Minchinton, Jeffrey Bacha, and David Perrin received \$259,381 from the **CIHR Collaborative Health Research Program** to investigate hypoxia-selective inhibitors of DNA repair. The proposed work involves the development of a drug that will improve the effectiveness of radiation therapy.

May

- ◆ Dr. Ryan Brinkman received the **International Society for Advancement of Cytometry (ISAC) Distinguished Service Award**. Dr. Brinkman has established himself as a world leader in the application of bioinformatics techniques to flow cytometry data to advance our understanding of human health and disease. His early work focused on creating data standards and free open source computational infrastructure to support high throughput computational statistical analysis of flow data.



June

- ◆ Dr. Marianne Sadar received an honorary doctorate from **Thompson River University** for contributions to cancer research. Dr. Sadar is a celebrated cancer researcher whose development of therapeutics for advanced prostate cancer has important benefits the future of cancer treatment.
- ◆ Dr. Dean Regier received an outstanding academic performance award from the **Faculty of Medicine, University of British Columbia**. This award is for outstanding academic productivity in relation to other faculty members.



- ◆ Dr. Connie Eaves was a **YMCA Women of Distinction – Research and the Sciences Award Nominee**, which honours individuals and organizations whose outstanding activities and achievements contribute to the well-being and future of the community. Dr. Eaves also received the **2018 International Society for Stem Cell Research (ISSCR) Tobias Award** for her innovative research in hematology.
- ◆ BC Cancer and UBC researchers, **Drs. David Huntsman, Samuel Aparicio, Poul Sorensen, Gregg Morin, Sohrab Shah, Stephen Yip, Torsten Nielsen, Martin Hirst, Michael Underhill, Peter Stirling, Alexandre Bouchard-Côté and Cheng-Han Lee** will continue their ground-breaking research into rare tumours after receiving renewal funding from the **Terry Fox Research Institute**. The team has received \$6 million (between July 2018 and June 2023) to study how different cellular features impact the development of rare tumours, known in oncological circles as *forme fruste* tumours. The project's overall objective is to understand how mutations interact with non-mutational features to promote tumour development, progression and metastasis. Using this information, the goal is to develop new diagnostic and therapeutic opportunities that target both the mutations and the epigenetic mechanisms through which they operate.



- ◆ Dr. Jenny Ko received the **Michael Smith Foundation 2018 Health Professional Investigator Competition Award**. Dr. Ko's research facilitates surgical evaluation of breast cancer resection by real-time, accurate and rapid point-of-care assessment of response to systemic therapy utilizing Diffuse Optical Imaging (DOI). This research has implications for the use of hand-held DOI-Scan probe (an optical probe) to facilitate appropriate cancer care in rural and remote areas, as equipment is portable, relatively inexpensive and easy to use with simple training.

July

- ◆ In the **CIHR Spring 2018 Project Grant** competition five grants were awarded to Principal Investigators at BC Cancer:
 1. Dr. Sharon Gorski received \$956,250 to investigate the relationship between HER2 and ATG4B in breast cancer.
 2. Dr. Kevin Bennewith received \$956,250 to investigate hypoxia in tumour-draining lymph nodes as an indication of immune activation and immunotherapy response.
 3. Dr. Peter Landsdorp received \$856,800 to investigate replication of guanine rich DNA.
 4. Dr. Peter Stirling received \$845,326 to investigate mutagenic replication-transcription conflicts in cancer-initiation.
 5. Dr. Pamela Hoodless received \$742,050 to investigate SOX9-dependent transcriptional networks in heart valve development.



2018

AWARDS AND FUNDING

July

- ◆ Dr. Cheryl Duzenli was awarded the **Canadian Cancer Society 2018 Innovation to Impact Grant** to research reducing toxicity in whole breast adjuvant radiotherapy using a novel breast positioning device. Dr. Duzenli and her team will use the breast positioning device to reduce skin folding and the dose to skin, which often leads to these adverse reactions, with the added benefit of reducing heart and lung dose.

September

- ◆ Dr. Yuzhou Wang was inducted into the **Canadian Academy of Health Sciences (CAHS)** as a fellow, one of the highest honours within Canada's academic community. CAHS fellows are nominated by their institutions and peers and selected in a competitive process based on their internationally recognized leadership, academic performance, scientific creativity and willingness to serve.



- ◆ Drs. Poul Sorensen and Gregg Morin were awarded a **National Institutes of Health (NIH) grant** led by Drs. John Maris and Crystal Mackall at **Children's Hospital of Philadelphia**. The research grant titled "Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers", seeks to discover the fundamental mechanisms leading to high-risk childhood cancer phenotypes, including how these malignancies evolve to evade the immune system and resist modern therapies.



October

- ◆ A new **molecular imaging and therapeutics program** will be established thanks to an **\$18 million anonymous donation** to the **BC Cancer Foundation**, the largest donation ever made by a single donor. The new molecular imaging and therapeutics program will accelerate and scale up scientific development of radioactive isotope treatments and fund a clinical trial for targeted radioligand therapy in prostate cancer. Radioligand therapy may be applied to other cancers as well; therefore this new program will ultimately improve targeted radioligand cancer therapies for British Columbians.

- ◆ Drs. Samuel Aparicio and Stephen Chia received \$1.2 million from the **BC Cancer Foundation** to establish a platform to study circulating tumour DNA (ctDNA) in blood plasma in breast cancer patients. The study, titled "New Frontiers in Breast Cancer Research + Care: Harnessing the Power of Circulating Tumour DNA", will help develop a blood test that can monitor breast cancer and guide treatment. The discovery has opened an entirely new field of diagnostics – minimally invasive and cost effective "liquid biopsies" which can detect early breast cancer and help predict a woman's response to therapies. This intensive two-year study will have wide-reaching implications beyond breast cancer.



November

- ◆ Prime Minister **Justin Trudeau** announced federal funding for the construction of the new **Institute for Advanced Medical Isotopes (IAMI)**. The IAMI is Canada's first nuclear medicine hub and houses BC Cancer and other industry partners to advance medical isotope production, drug development, cancer therapy, clinical imaging and radiopharmaceutical research. IAMI will be part of TRIUMF at the University of British Columbia campus.

- ◆ Dr. Christian Steidl received the **Allen Distinguished Investigator Award**, making him the first Canadian recipient and ranking him among the most celebrated scientists in North America. The prestigious award comes with \$1.5 million in research support from **The Paul G. Allen Frontiers Group**, a division of the **Allen Institute**. Knowledge gained from this research will lead to development of novel biomarkers and immunotherapies targeting tumour-host interactions, which will ultimately improve patient outcomes.



- ◆ Dr. Dean Regier received funding to create the **Health Economics Analytic Support and Research Unit (HEASRU)** at BC Cancer. The goal of HEASRU is to generate evidence that supports BC Cancer's executive team in making timely, real-world decisions for the adoption and management of therapies, interventions and technologies. Dr. Regier is leading a team of health economists who generate evidence on the cost-effectiveness and budget impact of new drugs, technologies and programs under consideration for implementation in the province.



- ◆ Dr. Shoukat Dedhar was elected as a fellow of the **Royal Society of Canada**. The fellowship of the Royal Society of Canada comprises over 2,000 Canadian scholars, artists, and scientists, peer-elected as the best in their field. These are distinguished men and women from all branches of learning who have made remarkable contributions in the arts, the humanities and the sciences, as well as in Canadian public life.



- ◆ Eleven scientists were listed by **Clarivate Analytics** as **Highly Cited Researchers**: Drs. Samuel Aparicio, David Huntsman, Marco Marra, Steven Jones, Robert Holt, Inanc Birol, Martin Hirst, Richard Moore, Andy Mungall, Angela Tam, and Jacquie Schein. This list recognizes world-class researchers selected for their exceptional research performance, demonstrated by production of multiple highly cited papers that rank in the top one per cent by citations for field and year in Web of Science.

- ◆ Stanford University recognized **Dr. Andrew Minchinton with the 2018 Robert F. Kallman Award** for his academic leadership, scientific excellence, service to the profession and commitment to colleagues and students. Dr. Minchinton is the second BC Cancer scientist to receive the award after Peggy Olive in 2008 and makes BC Cancer the only institution to have two awardees.



AWARDS AND FUNDING

November

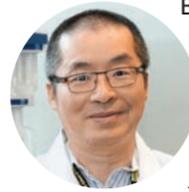
- ◆ The BC Cancer Foundation hosted the **2018 Inspiration Gala** to raise funds specific for blood cancers including lymphoma, leukemia and myeloma as well as for related research programs such as the Large-Scale Applied Research Project (LSARP) grant, immunotherapy research program (CAR-T cell therapy), and recruitment of a newly appointed clinician scientist focused on leukemia and myeloma at BC Cancer, Dr. Florian Kuchenbauer. Together with the Foundation, the lymphoma and leukemia teams successfully raised \$4.3 million at this event to support the continuation of the world-leading research in blood cancers at BC Cancer.

December

- ◆ **Dr. Marcel Bally** received the **2018 John McNeill Excellence in Health Research Mentorship Award**. This award is offered annually by UBC's Faculty of Pharmaceutical Sciences and recognizes faculty members in any of UBC's health-related disciplines who have been identified as mentors that exemplify a deep commitment to fostering the professional and personal development of faculty colleagues, graduate students, and post-doctoral fellows, in the early stages of their academic career. Marcel was nominated by the Faculty of Medicine, Department of Pathology and Laboratory Medicine.



- ◆ **Drs. Kuo-Shyan Lin** and co-investigator **Dr. François Bénéard** received the **Neuroendocrine Tumour Research Foundation (NETRF) Pilot Award** to develop novel radioligands for better management of neuroendocrine tumours. Dr. Lin will explore a novel strategy to develop more efficacious therapeutic agents to treat neuroendocrine tumours. Dr. Lin's design is based on a novel and very stable chemical compound that can bind to the neuroendocrine tumour tissues more tightly, and the resulting therapeutic agents are expected to produce a higher treatment efficacy than 177Lu-DOTATATE.



- ◆ The Stand Up to Cancer Canada Metastatic Breast Cancer Dream Team led by Drs. Nahum Sonenberg and Michael Pollak, including BC Cancer investigators **Drs. Poul Sorensen, Brad Nelson, Gregg Morin, Samuel Aparicio, Karen Gelmon** and an integrated team of Canadian researchers have been assembled to conduct a phase 1b clinical trial of a novel drug candidate eFT508 in patients with metastatic breast cancer, and to study innovative pharmacodynamics as well as clinical endpoints of this trial. BC Cancer – Vancouver and Victoria is leading the pathology core and clinical sites will be in Vancouver, Montreal and Edmonton. The research titled "Targeting mRNA Translation to effectively treat Metastatic Breast Cancer" is sponsored by the **American Association for Cancer Research International-Canada, Canadian Cancer Society, Canadian Institutes of Health Research, and Stand Up To Cancer Canada**.

RECOGNIZING OUR NEW RECRUITS IN 2018

Dr. Florian Kuchenbauer is a clinician scientist in the Terry Fox Laboratory and the Leukemia/Bone Marrow Transplant Program of BC. As a physician, he specializes in hematopoietic stem cell transplantation (HSCT) in adults. Over the past few years, he has been working in the stem cell transplantation unit of the University Hospital Ulm, Germany, and developed an interest in optimizing conditioning regimens as well as thrombotic microangiopathy (TA-TMA) during HSCT. His research focuses on non-coding RNAs, especially microRNAs (miRNAs) in acute myeloid leukemia (AML) and normal hematopoiesis, and he has made significant contributions to the field over the past decade. His expertise in AML and stem cell transplantation is of great value to BC Cancer both as a researcher and a clinician, and he aims to establish a translational bone marrow transplantation research program.



Photo credit: BC Cancer Foundation

Dr. Arman Rahmim is a provincial medical imaging physicist at BC Cancer and associate professor of Radiology and Physics and Astronomy, Faculties of Medicine and Science at the University of British Columbia. His work involves conducting research in image analysis, machine learning, radio-omics and radionuclide therapy. He has participated as principal investigator or co-investigator on a range of grants towards quantitative tomographic imaging, including translation to clinical applications. Dr. Rahmim was elected as an Institute of Electrical and Electronics Engineers (IEEE) senior member and is president of the Physics, Instrumentation and Data Sciences Council of the Society of Nuclear Medicine and Molecular Imaging.



Dr. Andrew Roth is a principal investigator in the Department of Molecular Oncology, joining expanding programs in the areas of single cell biology, cancer evolution and relevant machine learning and artificial intelligence approaches to data. Dr. Roth is an assistant professor in the Departments of Pathology and Laboratory Medicine, and Computer Science at the University of British Columbia and a scientist at BC Cancer. His interdisciplinary research focuses on the application of statistical machine learning to problems in high dimensional cancer biology. This research program encompasses the development of computational methods for studying clonal population structures and tumour evolution, as well as methodological work in computational statistics. His research will focus on developing computational approaches for studying the spatial and temporal dynamics of the malignant-cell immune interface.



Dr. Parveen Bhatti is the scientific director, cancer prevention and principal investigator of the BC Generations Project, a cohort of 30,000 British Columbians with extensive data and pre-diagnostic biospecimens that he aims to enrich and utilize as a cross-disciplinary platform for research in precision medicine, particularly in the areas of cancer prevention and early detection. Dr. Bhatti is also the principal investigator of a National Institutes of Health (NIH) funded birth cohort study in Guangzhou. His team is in the process of recruiting 1,000 children who will be followed from birth to five years of age to study the complex interactions of environmental pollution and the developing gut microbiome on health outcomes that may influence cancer risk later in life, such as childhood obesity.



A NEW ERA OF BLOOD CANCER RESEARCH

It's an exciting time in blood cancer research – we've come a long way over the past decade and the future ahead is a promising one. Each year, over 2,000 British Columbians are diagnosed with blood cancer. BC Cancer is looking at innovative treatment solutions to reduce the burden of cancer in B.C. and beyond.

We spoke to clinician scientists Drs. Joe Connors, Christian Steidl and Florian Kuchenbauer about how blood cancer research has changed over the years and the work currently happening at BC Cancer to develop more effective targeted cancer drugs and treatments.

Blood cancer research: then and now

Twenty years ago, cancer research was empiric and had a trial and error type of approach. Fast forward to the present and we now have greater tools to perform elaborate blood cancer research investigation, including genomic analyses, which are leading to treatment approaches that are more effective and minimize toxicity.

"Back in the day, we would think of a good idea and just try it out. The shift occurred 10 to 20 years ago – and that was a shift to focusing with much greater detail on the underlying biological events that lead to the development of cancers and why they may be resistant to treatment," says Dr. Joe Connors. "The fundamental biology of cancer cells is now being revealed and it suggests specific ways to intervene and get rid of the cancer by concentrating on it and avoiding unwanted effects on the person's body."

Blood cancer treatment will also see a more tailored approach in the future. "Treatment of blood cancers will rely more on reprogramming the patient's immune system and tailoring the treatment to respond to the individual patient's disease. This will eventually be combined with disease specific drugs for a deeper remission and to prevent relapse. Eventually, we will move away from unspecific treatments such as chemotherapy. Treatment decisions will be guided by personalized high-resolution disease monitoring such as next-generation sequencing," says Dr. Kuchenbauer.

Significant progress in blood cancer research

Several projects are underway at BC Cancer to improve treatment outcomes for patients. Earlier this year, Drs. Christian Steidl, Marco Marra and David Scott were awarded a \$11.9 million Large-Scale Applied Research (LSARP) grant to fill a major knowledge gap and an unmet clinical need. The project addresses the most significant knowledge gap in lymphoma care – the genome level biology of relapsed lymphoid cancers. This research focuses on developing genomics-based clinical tests to improve patient outcomes and quality of life, while integrating tests into the health care system by sequencing relapsed tumours to identify targeted treatment options. The team is also looking at the health-system impact from an economic perspective and identifying ways to develop e-health applications to assist patients with treatment decision-making.

“Our focus is trying to understand why blood cancers relapse and get a better understanding of tumour dynamics. It is important to examine how the cancer cells work, how they evolve and what it means for therapy,” says Dr. Steidl.

In addition to the LSARP program, Dr. Steidl was awarded a \$1.5 million Allen Distinguished Investigators grant that will help his team study the dynamic, complex networks of normal and cancer cells constituting the tumour microenvironment. Using novel, multidimensional imaging and single cell genomics approaches, this project aims to comprehensively characterize the microenvironment composition and spatial architecture of classical Hodgkin lymphoma (cHL) in correlation with somatic gene alterations in the malignant Hodgkin Reed Sternberg (HRS) cells to potentiate therapeutic advancements. This knowledge will lead to development of novel biomarkers and immunotherapies targeting the tumour-host interactions, which will improve patient outcomes.

The Centre for Lymphoid Cancer (CLC) has also established a centralized ctDNA acquisition and analysis platform as part of the BC Cancer biobank programs. Next generation sequencing can be performed to determine “driver mutations” using patient biopsy samples, with the goal to design personalized treatment approaches that are specific to the patient’s mutational profiles.

A large international Phase 3, multi-center trial was led by Drs. Connors and Kerry Savage to evaluate the efficacy of brentuximab vedotin with chemotherapy (doxorubicin, vinblastine, and dacarbazine: A+AVD) in previously untreated patients diagnosed with stage III or IV cHL. The results of this trial have shown that A+AVD had superior efficacy over the standard frontline regimen of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in treatment of advanced stage HL.

Dr. Kuchenbauer is currently working on bridging the Leukemia/ Bone Marrow Transplant Program of BC with state-of-the-art research at BC Cancer’s Terry Fox Laboratory. He is focused on finding more effective, less toxic treatments to deliver to leukemia and multiple myeloma patients. “The sheer amount of new drugs that have been approved for diseases like multiple myeloma or chronic lymphocytic leukemia totally changed the field and treatment outcome. In addition, immunotherapies such as CAR-T cells are game changers,” says Dr. Kuchenbauer.

The future of blood cancer research

We have made major steps in understanding what sets up the conditions under which blood cancer develops and encourages the cell to become malignant. We have more important work ahead of us.

“The most pressing problem is understanding how cells become resistant to the treatments that we have available. We need to characterize the elements that are crucial to the initiation of treatment resistance and then, even more importantly, figure out specific maneuvers that we can use to overcome those abnormalities and reverse their treatment resistance to make these cancers responsive to treatment,” says Dr. Connors.

The future of blood cancer research continues to be an exciting one with new advances to personalize cancer treatment for patients. The results of this work will provide patients with more treatment options, less toxicity and better outcomes.



Dr. Joe Connors



Dr. Florian Kuchenbauer



Dr. Christian Steidl

OUTSTANDING TRAINEE PUBLICATIONS 2018

The Office of the VP, Research once again held a **Publication Awards** competition for papers of outstanding scientific merit first-authored by BC Cancer students, residents, post-doctoral fellows and graduate students for work performed at, or in collaboration with, BC Cancer during the previous year. Awards were given in the categories of Basic Research (two prizes awarded: 1st place prize \$1000, 2nd place prize \$500), Clinical Research (one prize awarded: \$1000), and Cancer Control Research and Health Services Research related to cancer (including Health Economics) (one prize awarded: \$1000).



In the category of Basic research, first-place was awarded to **Allen Zhang**, an MD/PhD graduate student supervised by **Dr. Sohrab Shah** in the Department of Molecular Oncology, for the paper "Interfaces of Malignant and Immunologic Clonal Dynamics in Ovarian Cancer" published in *Cell*. In this work, Zhang and colleagues identified three different immunologic subtypes across metastatic sites in patients with high-grade serous ovarian cancer (HGSC), the most common type of ovarian cancer. This finding may be exploited in future immuno-oncologic therapeutic strategies for HGSC.



Second-place in the category of Basic Research was awarded to **Damian Lai**, an MSc graduate supervised by **Dr. Xiaoyan Jiang** from the Terry Fox Laboratory, for the paper "PP2A inhibition sensitizes cancer stem cells to ABL tyrosine kinase inhibitors in BCR-ABL+ human leukemia" published in *Science Translational Medicine*. In this paper, Lai and colleagues identified the protein phosphatase 2A (PP2A) as a critical therapeutic target in drug-resistant blood cancer cells, including blood cancer stem cells from chronic myeloid leukemia (CML) patients, which may have implications for other malignancies where PP2A is highly increased.



The award for the best Clinical Research paper was given to **Daniel Louie**, a PhD student studying at the School of Biomedical Engineering at the University of British Columbia, supervised by **Dr. Tim Lee** from the department of Cancer Control Research for the paper "Degree of optical polarization as a tool for detecting melanoma: Proof of principle" published in the *Journal of Biomedical Optics*. In this study, Lee and colleagues present the first clinical use of a novel probe utilizing the degree of polarization (DOP) to detect differences between cancerous and benign skin lesions, demonstrating DOP as a potentially useful diagnostic property to detect melanoma.



In the category of Cancer Control Research and Health Services Research related to cancer (including Health Economics), the award was presented to **Dr. Ryan Woods**, a PhD student supervised by **Dr. John Spinelli** in the department of Cancer Control Research for the paper "Breast screening participation and retention among immigrants and non-immigrants in British Columbia: A population-based study" published in *Cancer Medicine*. In this publication, Dr. Woods and colleagues examined breast cancer incidence by birth country, and discovered important variation in risk that is not observable when data are aggregated at the world region level.

SPOTLIGHT ON
ORAL CANCER
RESEARCH EXPERT
DR. CATHERINE POH



Dr. Catherine Poh leads the way when it comes to oral cancer research and understanding the complex stages involved in malignant transformation. She is currently one of two practicing oral maxillo-facial pathologists in B.C. and is actively involved in developing processes by which new research information can be transferred into dental communities.

As a clinician scientist of the BC Oral Cancer Prevention Program (BCOCP) at BC Cancer and an associate professor at the Faculty of Dentistry at the University of British Columbia, Dr. Poh's primary research focus involves application of molecular and imaging tools for community screening, early detection, and management of cancerous and precancerous oral lesions. She is also a Canadian Institutes of Health Research (CIHR) clinician scientist and a scholar of the Michael Smith Foundation for Health Research.

We had a chance to speak with Dr. Poh about her oral cancer research and how her work is providing clinicians and patients a better understanding of treatment options.

What is the focus of your research?

Oral cancer has a huge impact globally. Worldwide more than 300,000 new cases of oral cancer are reported each year, with half of the individuals dying of the disease. Those who survive often suffer from significant functional and cosmetic compromises. It is important to identify the disease early and to develop new ways of treating it in early stages. Being a clinician and scientist, my primary research focus involves the application of molecular and imaging tools for community screening, early detection, risk assessment, and management of cancerous and precancerous oral lesions.

What are your thoughts on the future of oncology?

The future of oncology is in prevention. Cancer diagnosis and treatment imposes a heavy societal burden. The introduction of more sophisticated imaging and diagnostic techniques and advanced drugs has led to increasingly expensive treatments, which may be affordable only for few patients. Following the success of cervical cancer screening, screening for breast cancer and colorectal cancer has shown significant improvement in early detection. Prevention programs are an important part of the effort to control cancer, as they are able to reduce both the incidence of cancer and mortality.

What do you think is the most pressing problem facing cancer research now?

The advances in molecular technologies have made significant progress in the identification of new biomarkers that can potentially be used in early detection, diagnosis, and prognosis prediction. However, few of them have successfully translated to the clinical side to truly improve patient care. Additionally, a lot of research funding and resources have been used to support either cancer types (e.g., breast cancer or prostate cancers, or those at late stages). Few funding dollars and institutional supports have been available for prevention, screening and early detection.

What advice would you offer to young clinician scientists?

Clinician scientists play key role in translational research. They are the key to identifying clinical problems in oncology patient care. Meaningful and impactful translational research relies on them to take the initiative to find solutions from researchers and gradually improve patient care.

SCREENING AND DIAGNOSIS

Circulating tumour DNA (ctDNA) platform establishment

The Centre for Lymphoid Cancer (CLC) has established a centralized ctDNA acquisition and analysis platform as part of the BC Cancer biobank programs. The cell free circulating tumour DNA (ctDNA) are released from cancer cells into circulation; there is increasing evidence to support the potential clinical utility of ctDNA as an inexpensive detection tool to monitor patients. The ctDNA acquisition

and analysis platform established at the CLC is scalable to provincial expansion utilizing the infrastructure already built for the BioCancer Initiative, which is the multi-disciplinary collaboration between different tumour groups, mainly the lymphoma, breast and gastro-intestinal programs to create a province-wide Biobank and patient consenting system to support comprehensive, translational research at BC Cancer.

BC Generations Project

The BC Generations Project (BCGP) led by Drs. Nhu Le, Trevor Dummer, and Parveen Bhatti, supported seven research studies with data or bio-samples. Among these, BCGP supported two ancillary studies. BCGP continued collecting additional questionnaire data from their 30,000 participants. BCGP's first follow-up health and lifestyle questionnaire was completed with an 80 per cent

response rate and an occupational history questionnaire was initiated. The BCGP resource was enriched with environmental data through linkages with federal agencies. 2018 also saw publications for our regional cohort and national cohort, including being published in the *International Journal of Epidemiology* and *Canadian Medical Association Journal*.

SCREENING AND DIAGNOSIS

Early skin cancer detection using artificial intelligence (AI)

2018 was an important year for the Skin Sciences Research Program in establishing a new team in applying artificial intelligence (AI) techniques for skin cancer detection. The team led by Dr. Tim Lee built a deep learning system for identifying and localizing blood vessels from



dermoscopic images of basal cell carcinoma (BCC). These vessels are extremely subtle and hard to detect because of their small size and low contrast. The AI system achieved an accuracy of 95 per cent in detecting the vessels, and along with patient demographic information, the system is being developed

further to differentiate BCC from non-BCC with an accuracy of 91 per cent. This program also developed a handheld prototype for analyzing the polarization properties of skin. In a pilot study the prototype showed an impressive ability to differentiate melanomas and nevi (a precursor of melanoma).



SCREENING AND DIAGNOSIS

Canadian Centre for Applied Research in Cancer Control (ARCC)

ARCC led a number of large international and national research projects in 2018. In particular, ARCC has been undertaking world-leading research into deliberative public engagement and real-world evidence in cancer directly engaging broad representation from communities across Canada to inform high priority policy issues such as cancer drug funding, gene therapies and palliative care. In October, **Dr. Stuart Peacock** was invited to present this work to the American Association of Cancer Institutes in Chicago – the leadership from all of the cancer institutes in the United States.



Work on real-world evidence is determining whether new drugs and technologies actually deliver the effectiveness promised by clinical trials for our real-world patients. This work is critical in the era of precision medicine, where trials are becoming smaller and harder to interpret.

These research programs are being conducted with world-leading research teams, as well as the senior leadership of provincial cancer agencies and ministries of health. Their results are allowing the public to have a real voice in cancer policy as well as the effectiveness of therapies in the real-world to be properly understood.

ARCC was also successful in obtaining a number of grants from leading funding agencies. Of note, **Dr. Helen McTaggart-Cowan** is leading the health economics component of a Canadian Institutes of Health Research (CIHR) grant examining colorectal cancer in young adults (PI: **Dr. Mary de Vera** at the University of British Columbia) and **Stuart Peacock** is leading the health economics component of a large Prostate Cancer Canada grant on radioligand therapy (PI: **Dr. François Bénard**, BC Cancer). ARCC is additionally leading the health economics component of the HPV FOCAL Study led by **Dr. Gina Ogilvie**.

Improving the prevention and treatment of oral cancer

The BC Oral Cancer Prevention Program (BC OCPP) is a translational research program focused on the prevention and treatment of oral cancer. At the core of the BC OCPP is the Oral Cancer Prevention Longitudinal Study (OCPL), a globally unique study that follows patients identified with pre-cancer over the long term. Over the past 21 years, the BC OCPP team has followed more than 2,200 patients with oral cancer and precancerous lesions and has built one of the

world's largest clinically annotated biobanks of oral premalignant lesions as they progressed to cancer.

As part of this research, **Drs. Miriam Rosin** and **Denise Laronde** have developed guidelines for screening, technology for assessing lesion risk, and markers to help predict outcomes and identify what progresses to oral cancer. In 2018, work began looking at microenvironmental influences on disease progression. The BC OCPP has developed

the only validated biomarker for the malignant transformation of low-grade premalignant disease, and pilot experiments have begun into validating Next Generation Sequencing against this model. The BC OCPP is now examining further developing omics prevention research offering the opportunity to improve our understanding of precision treatment interventions, including chemoprevention in premalignant disease.

SCREENING AND DIAGNOSIS

HPV FOCAL Trial compares HPV testing to LBC testing for cervical cancer screening

The HPV FOCAL Trial is a very large randomized controlled trial, comparing primary human papillomavirus (HPV) testing every four years, to liquid based cytology (LBC) every two years for cervical cancer screening. The main objectives of the trial led by **Drs. Gina Ogilvie, Laurie Smith, and Andrew Goldman** were to evaluate histologically confirmed cumulative incident

cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+) and grade 2 or worse (CIN2+) detected at 48 months. Results from the HPV FOCAL Trial were published in the *Journal of the American Medical Association* in 2018, and were featured in many international TV news shows and newspapers, including the *Washington Post*, CNN, NBC, ABC and the CBC. Funding was also obtained

from the National Institutes of Health (NIH) to follow the HPV FOCAL cohort to 10 years post baseline to provide long-term information regarding the use of primary HPV testing in an organized cervical cancer screening program. HPV FOCAL was also named as one of the top ten achievements of the year at the University of British Columbia, where Gina Ogilvie holds a CRC (Tier 1) in Global Health and HPV.

Gene Environment Interactions in Cancer Program (GENIC)

Non-melanoma skin cancer (keratinocyte carcinoma) is the most common cancer in Canada and counts for about one-third of all cancer cases. The prevention and management strategy of the disease depend on precise statistics. **Drs. Nhu Le** and **Tim Lee** successfully built algorithms using doctor billings and pharmacy data that could accurately determine the statistics of non-melanoma skin cancer.

Stage II and III melanoma patients have highly varying survival rates. For example, the five-year survival rate of IIIA patients is 88 per cent, which is same as IIA patients, but higher than the patients of IIB (82 per cent) and IIC (75 per cent). BC Cancer along with a group of international experts are working on a five-year National Institutes of Health grant to determine the genetic and clinical prognosis factors

of these patients. New knowledge acquired from the study could be used to improve the treatment options for these patients. The risk of ovarian cancer has also been

published in several publications, including the *International Journal of Epidemiology*, *International Journal of Gynecological Pathology*, and *Cancer Research*.



CANCER PREVENTION

Opportunistic salpingectomy and ovarian cancer prevention

As an effort to prevent ovarian cancers in the general population, in September 2010, OVCARE sent all gynecologic surgeons in B.C. a letter and DVD recommending that they consider the following: 1) performing bilateral salpingectomy at the time of hysterectomy (even when the ovaries are being reserved) and 2) performing bilateral salpingectomy in place of tubal ligation for sterilization. These two procedures are collectively known as opportunistic salpingectomy (OS). The knowledge translation campaign led by Drs. **Dianne Miller, Sarah Finlayson and Blake Gilks** included discussing the recommendations for OS at an annual provincial obstetrics and gynecologist meeting, a media outreach campaign, local champions spearheading the recommendations in B.C. communities, and presenting the recommendations at various meetings including hospital rounds, community clinics, provincial continuing medical education for family doctors, and local women's groups. Since then, research led by Drs. **Gillian Hanley, Jessica McAlpine, David Huntsman, and others in OVCARE** showed that the knowledge translation initiative had a profound effect on clinical practice in B.C.: the proportion of hysterectomies (without oophorectomy) that had an associated salpingectomy increased from 8 per cent in 2008 to 75 per cent in 2013, and the proportion of

sterilizations by salpingectomy increased from 0.5 per cent in 2008 to 48 per cent in 2013. No other Canadian provinces were targeted by such a knowledge translation initiative and rates of adoption were lower. In 2011, when B.C. was performing nearly 40 per cent of hysterectomies with bilateral salpingectomy, Canada's most populous province Ontario was only doing approximately 10 per cent. The success of OVCARE's knowledge translation initiative is striking when considering the overall success rates and the length of time taken to translate scientific research into clinical practice: it takes an estimated average of 17 years for only 14 per cent of new scientific discoveries to enter day-to-day clinical practice. To date, 13 societies representing 14 countries have statements regarding opportunistic salpingectomy. Nine of the 13 statements (from Canada, Finland, USA, Great Britain, Australia and New Zealand, Denmark, Austria, Turkey, and Japan) support consideration of opportunistic salpingectomy in appropriate women and four (from Germany, Sweden, Norway, and France) are ambivalent. All 13 societies with statements represent developed countries likely because ovarian cancer is a greater concern in developed countries compared to other countries, reflecting the burden of ovarian cancer in developed countries.

TREATMENT

Patient-Centred, Accessible, and Efficient Applications of Precision Medicine (PACER)

Dr. Dean Regier's Research Lab, PACER (patient-centred, accessible, and efficient



applications of precision medicine) has increased its national and international with team members presenting at seven health economics, health services research and oncology conferences, four of which were at International conferences. PACER published 10 peer-reviewed manuscripts in leading academic health journals, with an additional seven manuscripts currently under review and two in press. Dr. Regier was awarded \$500,000 in grant funding from

Genome British Columbia to conduct health economic analyses in context to precision medicine implementation for rare diseases in B.C. and England. PACER's ongoing research in precision medicine sustainability includes international collaborations with health economics and clinical leaders from Oxford University and Genomics England, Manchester University, University of Washington, and the University of Alabama. PACER's emerging presence and outstanding performance were recognized in 2018 with two conference presentation awards (Weymann, Pollard) and a trainee publication award from BC Cancer (Weymann).

Potential combination therapy for small cell carcinomas of the ovary, hypercalcaemic type – a rare and lethal ovarian cancer that affects young women and children

A research team led by Dr. **David Huntsman** found that EZH2 is a



promising therapeutic target for small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) and combination treatment of an EZH2 inhibitor and an HDAC inhibitor

synergistically suppresses the growth of SCCOHT cells and tumours, which have now been published in *Journal of Pathology* and *Molecular Cancer Therapeutics*, respectively. These findings are the first promising biologically-driven potential therapeutic strategy for this rare and lethal ovarian cancer type which affects young women and girls.

TREATMENT

“Evolutionary arms race” between ovarian cancer and immune system

BC Cancer and UBC scientists have uncovered some of the tricks used by the deadliest ovarian cancer to escape the immune system, setting the stage for a better understanding of how and why patients respond to promising new immunotherapies. The study, published May 10 in *Cell*, used DNA sequencing, advanced molecular measurements, and

computer algorithms to analyze how immune cells infiltrate tumours. Through those strategies, the scientists identified combinations of genetic changes that help high-grade serous ovarian cancer (HGSC) cells escape attack from a type of immune cell, called killer T-cells. This study provided some of the first clues in understanding why the

most common ovarian cancer HGSC often responds poorly to current immunotherapies – this paves the way for development of more potent immunotherapies for gynecological cancers. **Drs. Brad Nelson and Rob Holt** are ready to launch the first of a series of clinical trials for ovarian and other gynecological cancers.

BC Cancer leading national program on radioligand therapy for prostate cancer

Dr. François Bénard and his team are leading the national initiative on bringing transformative prostate cancer treatment to Canadian patients. Men with advanced and metastatic prostate cancer are not cured by standard treatments. They urgently need additional targeted approaches to treat their disease when endocrine treatments fail. Radioligand therapy (RLT)



targeting prostate specific membrane antigen (PSMA), an abnormal protein found in prostate cancers, is a promising treatment for patients with prostate cancer that has become unresponsive to endocrine treatments. RLT delivers radiation to all tumour sites following the intravenous injection of a radioactive drug. RLT has yet to be introduced in Canada for the

treatment of prostate cancer. This program will address the practical issues of making and distributing the radioactive drugs used for diagnosis and treatment, build up the infrastructure to deliver the treatment and improve upon the efficacy of RLT. The program will implement and conduct a research study to compare this treatment with chemotherapy, evaluating its tolerability, efficacy, and economic impact.

Development of new radiotherapy technique for patients with second cancer incidences

Patients requiring treatment for second cancer incidences present unique radiotherapy plan development challenges. Historical dose delivered to organs at risk must be accounted for to properly estimate lifetime toxicity risks, but historical dose delivered to the region now occupied by tumours does not contribute to the prescription dose.

Drs. Haley Clark, Fred Cao, Carson Leong, and **Eric Berthelet** developed a new radiotherapy technique for patients with second cancer incidences. This work proposes a new radiotherapy technique. The cohort of patients this work is applicable to are patients with cancers that come back in the same or nearby location is growing

significantly. Previously, there was no good way to manage this cohort. This study, titled “A practical radiotherapy treatment planning technique for second-incidence cancers that incorporates complete organ-at-risk dose history” was published in the *Journal of Medical Imaging and Radiation Sciences*.

TREATMENT

Heterochromatin protein 1a mediates development and aggressiveness of neuroendocrine prostate cancer

Neuroendocrine prostate cancer (NEPC) research led by **Dr. Yuzhuo Wang’s** group has led to the development of a unique first-in-field, clinically relevant experimental model, consisting of patient-derived prostate cancer grafts in immune-deficient mice, that can be used to study the



development of NEPC following androgen deprivation therapy of the mice. Using this model, they have recently discovered that a heterochromatin gene, called HP1α, plays a crucial driving role in the transdifferentiation of prostate cancer into NEPC. Their study for the first time reports an NEPC-specific

heterochromatin gene signature that can be applied for precision diagnosis of the disease. HP1α with its early and powerful function in NEPC development and aggressiveness also provides a promising therapeutic target for not only treatment of NEPC, but also preventing the disease from happening.



TREATMENT

First demonstration of in vivo anti-tumour activity of a hypoxia-activated DNA-PK inhibitor

Drs. Andrew Minchinton, Alastair Kyle, Jennifer Baker, and Judit Banath achieved the first demonstration of in vivo anti-tumour activity of a hypoxia-activated DNA-PK inhibitor.

A clinically effective DNA-PK inhibitor would increase the efficacy, cure rate, response rate of radiotherapy for all cancers treated. It overcomes the well characterized radiation resistance of

cells at low oxygen tension. BC Cancer provided the laboratory to carry out this research and a new class of drug was developed to improve radiation therapy.

Leading the way in a new standard of care in an international trial

Dr. Kim Chi co-led and established a new standard of care in an international trial. The study, titled "Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial", was published in *Lancet Oncology* and explored the improved



quality of life with treatment intensification of standard androgen deprivation therapy (ADT) for metastatic castration sensitive prostate cancer. This helped to establish ADT + abiraterone as a new international standard of care. Dr. Chi also researched how circulating tumour DNA (ctDNA) genomics correlate with resistance to abiraterone and enzalutamide for prostate cancer, in the first trial to compare abiraterone

and enzalutamide directly, in an investigator sponsored grant funded study conducted at BC Cancer, as published in *Cancer Discovery*. As published in *Annals of Oncology*, Dr. Chi also explored the first report of the first trial comparing chemotherapy versus hormone therapy in patients with poor risk castration resistant prostate cancer; this was selected as an oral presentation at the European Society for Medical Oncology (ESMO) Congress 2018.

New method for visualization of delivered radiation dose

In collaboration with UBC Okanagan and Duke University, Dr. Michelle Hilts has developed a way to measure the volume of radiation treatment dose delivered directly at the time of treatment using the same imaging system that is used to guide the treatment itself. Termed "cone beam CT polymer gel dosimetry", the technique will enable the

measurement of the exact 3D location of dose deposited by highly localized and complex radiation fields such as those used in the treatment of brain metastases. Using the imaging system that guides the radiation treatments, on-board cone beam CT, means that practitioners automatically know precisely how the dose is aligned in the

same imaging coordinate system used for patient alignment and treatment. This advancement may enable further development of new complex and highly spatially distributed radiation fields used in cancer care. Ultimately, the hope is that this new technology will improve the accuracy of radiation treatments and improve patient outcomes.

TREATMENT

Introduction of guide system for breast brachytherapy treatments

Our BC Cancer - Kelowna research team are world leaders in permanent breast seed implant (PBSI) and along with our collaborators have an exceptional record in innovation in PBSI brachytherapy as published in *Medical Physics*, *Practical Radiation Oncology*, *Brachytherapy*, and *Clinical Oncology*. Drs. Michelle Hilts, Deidre Batchelar, and Juanita Crook, in collaboration with researchers at the University of British Columbia, University of Victoria, and Western University, are working to develop a

better way of guiding implants using 3D ultrasound. This will enable more doctors to perform the treatment and thus allow many more women to benefit from this successful treatment. This research, based around developing 3DUS for PBSI, is moving PBSI towards wide spread implementation so that many more women can benefit from this one day treatment for breast cancer. This achievement is an important clinical research milestone for BC Cancer as it stands to significant advance breast cancer care in B.C.

Supporting patients throughout their journey of breast cancer

A quality improvement project led by radiation nurse Crystele Montpetit has improved the management of radiation induced skin dermatitis with the use of InterDry®, a moisture-wicking fabric with antimicrobial silver complex that effectively manages complications associated with skin folds. The use of InterDry® for radiation dermatitis has provided comfort to countless

women at BC Cancer - Surrey. A protocol for the use of InterDry® has been developed at the Surrey centre and is now being used on a regular basis at the Surrey centre by request of BC Cancer's oncologists. Patients are being supported with additional skin assessments and emotional support while using the InterDry® for radiation dermatitis.

Towards cardiac gated and synchronized radiotherapy

Drs. Kirpal Kohli, Steven Thomas, Devin Schellenberg, and Justin Poon engaged in a clinical study to treat cancer based on the interaction between light and matter. The focus of the research is to synchronize radiation delivery to the target area based on cardiac motion. During the

course of cardiac radiation treatment, the heart is always in motion and must be accounted for to deliver dosage to cancerous tissue and not healthy tissue. This team worked to adjust beam delivery speed in response to heart rate and showed successful synchronization with a sample cardiac signal.

Bioimpedance measurement in head-and-neck cancer patients undergoing radiotherapy predicts malnutrition complications

Dr. Kirpal Kohli along with R. Corns, K. Vinnakota, P. Steiner, C. Elith, D. Schellenberg, W. Kwan, and A. Karvat studied bioimpedance parameters such intracellular water content, extracellular water content, and cell membrane integrity of head-and-neck cancer patients undergoing radiation therapy. Because patients with head and neck cancer can suffer from malnutrition while undergoing radiation treatment, a calculation determined that measured body composition including intra and extracellular water content and cell membrane integrity helps to better correlate body mass indicators with each other to predict which patients might succumb to complications related to malnutrition. Ultimately this study will facilitate better outcomes for head-and-neck cancer patients undergoing radiotherapy.

BIOLOGY AND GENETICS

Large-Scale Applied Research Project (LSARP) Launch

The BC Cancer research team led by **Dr. Christian Steidl** successfully won a Large-Scale Applied Research (LSARP) project worth \$11.9 million funded by Genome Canada, Genome BC, Canadian Institutes of Health Research and the BC Cancer Foundation to address the most significant knowledge gap in lymphoma care: the genome biology of relapsed lymphoid cancers. Lymphoid cancers are the fifth most common cancers in Canada. Despite recent improvements made in therapies for lymphoma, the mortality results almost exclusively from relapsed disease when the standard of care fails to cure the cancer. Furthermore, treatment of relapsed lymphoid cancers is estimated to cost over \$315 million, representing approximately 10 per cent of the expected cancer drug budget for 2022 in Canada, adding a major burden for the health care system. Therefore, prevention of relapse and



successful treatment of secondary progression are the utmost significant unmet clinical needs.

The team's large-scale, pan-Canadian study was launched last year to discover novel, actionable markers of relapsed lymphoma from which clinically relevant assays can be developed. This study also aims to implement genomic-based clinical tests, which have been previously developed by their research team, in the publicly funded health care system across the country to enhance more patient centric approaches and improve outcomes for lymphoma patients.

This research will significantly improve the management of relapsed disease and help implement personalized treatment approaches into the health care system using the two approaches: application of state-of-the-art sequencing technology to decipher relapsed-linked genetic aberrations and performing detailed economic analyses and patient engagement into joint decision making.



Clinical trials and outcomes research

The clinical investigators at the Centre for Lymphoid Cancer (CLC) have been involved in numerous clinical trials and contributed significantly to outcomes research. A large Phase 3 multi-centre trial was led by **Drs. Joe Connors** and **Kerry Savage** to evaluate the efficacy of brentuximab vedotin



with chemotherapy (doxorubicin, vinblastine, and dacarbazine: A+AVD) in previously untreated patients diagnosed with stage III or IV classical Hodgkin lymphoma (cHL). Brentuximab vedotin is an anti-CD30 antibody-drug conjugate which has been approved for relapsed and refractory HL. The results of this Phase 3 trial have shown that A+AVD had superior efficacy over the standard frontline regimen of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in treatment of advanced stage HL (Connors et al., N ENGL J Med, 2018).



Similarly, the efficacy of this new drug in combination with chemotherapy was evaluated for CD30 positive T-cell lymphomas in another Phase 3 trial, to which the clinical team at BC Cancer led by Dr. Savage had contributed. This study showed the significant improvement in outcomes of patients treated with brentuximab

vedotin with chemotherapy as frontline therapy (Horwitz et al., Lancet, 2018). Another Phase I/II clinical trial led by **Dr. Laurie Sehn** was conducted to evaluate toxicity and efficacy of polatuzumab vedotin (Pola) in combination with the standard frontline therapy of bendamustine and rituximab (BR) in relapsed/refractory FL and DLBCL patient cohorts. The study showed tolerable toxicity in both cohorts and superior efficacy of Pola+BR combination when compared to BR-alone in DLBCL.

To assess outcomes following the introduction of frontline therapy with BR in patients diagnosed with FL, the clinical and pathology teams at the CLC have conducted a population-based study in 2018. This analysis has shown that patients with advanced stage FL have excellent outcomes after frontline BR in the absence of transformation or progression within 24 months after BR. Furthermore, in collaboration with the Lunenburg Lymphoma Biomarker Consortium (LLBC), Dr. Sehn evaluated prognostic significance of MYC single, double and triple hit translocations in the context of its translocation partner in DLBCL. In this study, MYC double/triple hit DLBCL with an IG partner were found to have the worst overall survival and progression-free-survival compared to single, double or triple hit with a non-IG partner. This suggests that identification of the MYC partner gene is needed in

addition to the routine clinical MYC testing to help design and interpret future clinical trials. The data generated from the clinical research team at the CLC will continue to have impact on clinical practice and management of lymphoma.

New Phase 1b clinical trial in metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)

An open-label, multi-center, Phase 1b study to investigate the safety and tolerability of SLC-0111 (WBI-5111) in combination with Gemcitabine in metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) subjects positive for Carbonic Anhydrase IX (CAIX) was launched in 2018.

This is the second clinical trial with the new compound, SLC-0111, discovered and developed in the research laboratory of **Dr. Shoukat Dedhar**. The Phase 1b trial is specifically targeted in



patients with pancreatic ductal adenocarcinomas which are positive for CAIX expression, the target of SLC-0111. The trial will determine whether the safety of gemcitabine/SLC-0111 combination as well any responses in patient survival. Trial principal investigators are **Drs. Daniel Renouf and Jonathan Loree**.

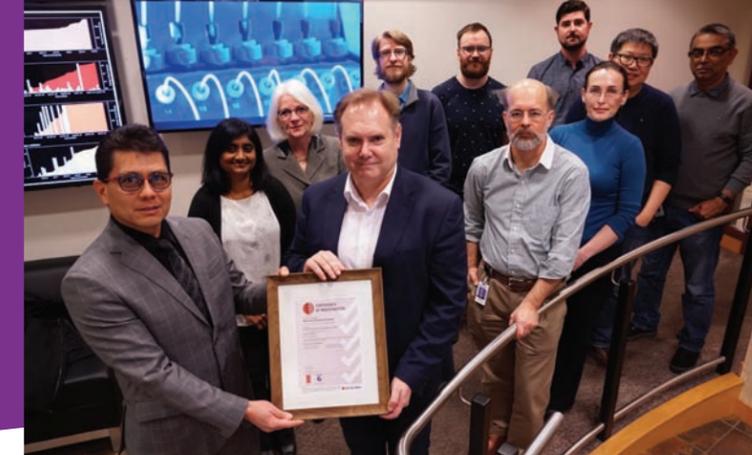
BIOLOGY AND GENETICS

BC Cancer's Genome Sciences Centre is now ISO certified

BC Cancer's Genome Sciences Centre (GSC) is now ISO 27001 certified and is the only genomics facility in Canada to comply with this comprehensive international standard for information security management. The ISO 27001 standard addresses nearly everything related to information security across an organization. When the GSC started processing patient data, the need for a stringent information security management system became clear. New processes for managing patient data were put in place, including College of American Pathologist (CAP)

certification in 2011 for cancer gene panel testing. The Centre for Clinical Genomics at the GSC, which received the CAP certification, past its fifth CAP inspection on February 1, 2019. The ISO audit itself was conducted by a senior auditor with 25 years of experience from SAI Global. It took five days with intensive interviews and extensive document and record verification to confirm that all requirements were met with zero non-conformances.

Dr. Steven Jones and the ISO implementation team at the GSC receive the ISO certificate from SAI Global.



Molecular characterization and subtyping of primary mediastinal large B-cell lymphoma

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare disease, accounting for two to three per cent of all non-Hodgkin lymphomas (NHL). The research team at the Centre for Lymphoid Cancer (CLC) has developed a robust clinical classification assay, Lymph3Cx, which accurately distinguishes PMBCL based on gene expression of

58 genes using routinely produced formalin-fixed paraffin-embedded biopsies (Mottok et al., Blood, 2018). Currently, they are collaborating with North American clinical trials groups, in particular with investigators at the University of Pennsylvania to further validate the clinical utility of this assay for routine diagnostic purposes. Moreover, to further characterize

PMBCL, their research team has applied next generation sequencing technology to discover novel somatic *IL4R* mutations in a subset of PMBCL patient samples (Vigano et al., Blood, 2018), enabling an accurate classification assay which can be readily implemented into clinical practice.

Molecular profiling of aggressive B-Cell lymphoma

Diffuse large B cell lymphoma (DLBCL) is an aggressive form of B-cell non Hodgkin lymphoma (NHL) and the most common type of NHL. With its heterogeneous nature in clinical behaviour, reliable biomarkers are needed to accurately categorize the tumour subtypes. Recent advancement in gene expression profiling has defined clinically important predictive biomarkers based on "cell-of-origin" (COO), which categorizes DLBCL into two specific subtypes with distinct mutational patterns and clinical outcome. MYC and BCL2



translocations are other genomic characteristics which are used as an additional prognostic tool to further characterize the COO subtypes to determine prognosis for DLBCL patients. The team led by Dr. David Scott has revealed clinically relevant architecture of MYC rearrangement in DLBCL (Chong et al., Blood Advances, 2018). A new clinically relevant assay was developed based on 104-gene double-hit signatures (DHITsig), showing that DHITsig positive patients have inferior outcomes compared to DHITsig negative patients. Another new assay,

DLBCL90, identifies a clinically and biologically distinct group within Germinal centre B-cell like DLBCL (GCB-DLBCL) helps guide clinical management of this aggressive disease (Ennishi et al., J. Clin. Oncol, 2018).

In 2018, Dr. Scott and the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) were granted a National Institutes of Health P0-1 Team Grant for USD \$12 million, led by Dr. Rimsza at Mayo Clinic and co-led by other leading researchers around the world. Dr. Scott is the lead of the aggressive B-cell lymphoma project within this grant.

Centre for Epigenome Mapping Technologies (CEMT) contributes to International Human Epigenome Consortium (IHEC)

Drs. Martin Hirst, Marco Marra, Steven Jones, Connie Eaves, Joseph Connors, Andrew Weng, Aly Karsan, and Christian Steidl contributed to a major milestone of phase 1 of the International Human Epigenome Consortium (IHEC). The objective of IHEC is to understand the extent to which the epigenome has shaped human populations over generations and in response to the environment. A major goal of phase 1 of IHEC was to generate reference maps of human epigenomes for key cellular

states relevant to health and disease. By generating and publishing 85 full reference epigenomes by March 31, 2018, the Centre for Epigenome Mapping Technologies (CEMT) in the BC Cancer Genome Sciences Centre (GSC) played a pivotal role in facilitating IHEC's goal. In fact, the team at the GSC contributed almost a quarter of the total reference epigenomes generated globally. Scientists at the GSC have also provided critical leadership to IHEC in the form of coordinating the development of

common bioinformatics standards, data models and analytical tools to organize, integrate and display the large quantities of epigenomic data generated. Indeed, in addition to being a contributing member of almost all of the IHEC working groups, Dr. Martin Hirst chairs the International Scientific Steering Committee of the consortium. IHEC is now working towards the target of generating 500 reference epigenomes and GSC researchers remain at the forefront of this effort.

Hematopoietic stem and progenitor regulation in Myelodysplastic syndromes (MDS)

Dr. Aly Karsan's group published a study in *Nature Communications* describing how miRNA haploinsufficiency activates TGFβ in myelodysplastic syndromes (MDS). MDS are the most common myeloid cancer that progresses to bone marrow failure or acute leukemia. Matched for age and stage, outcomes in MDS are worse than that for lung cancer. With our population aging, the incidence of MDS is expected to rise significantly. We have known for a while that an interstitial deletion of the long arm of chromosome 5 is the most common chromosomal alteration in



MDS, but the role of different genes that occupy the deleted region is still under active investigation. The Karsan lab has been investigating the role of small noncoding RNAs that are deleted on chromosome 5q. In a recent study published in *Nature Communications* they discovered that the loss of two microRNAs, miR-143 and miR-145, activates the TGFβ signaling pathway in bone marrow. This aberrant signal activation suppresses the creation of blood stem cells while expanding the number of more mature progenitor cells being created in the bone

marrow. This explains why MDS can lead to bone marrow failure caused by low levels of healthy blood cells, while also causing acute leukemias associated with the proliferation of malignant cells derived from progenitor cells that flood the bone marrow. The discovery opens the door for the development of potential therapies that could improve outcomes for patients with MDS by identifying a new therapeutic target. Specifically, these findings suggest that clinical trials with inhibitors of the TGFβ pathway may be warranted in MDS patients with deletions on chromosome 5.

BIOLOGY AND GENETICS

New findings on ETV6-NTRK3



Dr. Poul Sorensen's group published new findings on ETV6-NTRK3

in *The Journal of Biological Chemistry and Oncogene*. This was timely, as 20 years ago they were the first to show that NTRK kinase fusions are recurrent alterations in human tumours. It is now estimated that NTRK1, 2, and 3 fusions occur in ~1% of human cancers, leading to a new classification of NTRK fusion cancers, and directly prompting the pharmaceutical industry to develop NTRK inhibitors. This includes Larotrectinib, which was approved by the FDA on Nov. 26, 2018. This was satisfying to the Sorensen group as an actual bench-to-bedside application of their translational research program. In one study, STAT1 was identified as a crucial mediator of ETV6-NTRK3-induced tumorigenesis. In the other study, a potential strategy was identified for targeting chimeric tyrosine kinases in cancer.

Multidisciplinary team identifies and characterizes a new autophagy inhibitor

The cysteine protease ATG4B is a key component of the autophagy machinery. The roles of ATG4B and autophagy in cancer and other diseases are context dependent but are still not well understood. To help further explore ATG4B functions and potential therapeutic applications, a multidisciplinary team led by Dr. Sharon Gorski of the BC Cancer Genome Sciences Centre employed a chemical biology approach to identify ATG4B inhibitors. The team demonstrated that LV-320 inhibits ATG4B enzymatic activity, blocks autophagic flux in



cells, and is stable, non-toxic and active in vivo. These findings suggest that LV-320 will serve as a relevant chemical tool to study the various roles of ATG4B in cancer and other contexts. The team is exploring the potential of ATG4B (and other ATG4 family members) modulation of HER2+ breast cancer and pancreatic cancer; two research grants were awarded in 2018 for these studies – a Canadian Institutes of Health Research (CIHR) for HER2+ breast cancer, and a PanCAN Translational grant for pancreatic cancer.

Annotation and visualization of de novo genome and transcriptome assemblies

Establishing a fundamental understanding of the specific molecular biology of a species begins with reconstructing its genome (DNA) and transcriptome (RNA). This research led by Dr. Inanc Birol is enabled by modern sequencing technologies, which generate large volumes of data. And for over a decade, assembling this data into coherent information has been a primary focus of the bioinformatics field. However, linking the sequence information to biological phenomena by interpreting the assembled data remains a significant challenge. Annotating the genes of a particular species plays a



critical role in that interpretation. Dr. Birol is building methods to improve the quality of assembled genomes and transcriptomes by detecting misassembled sequences. He will also develop tools and resources to facilitate gene annotation and predict their function. Dr. Birol and his team will further develop visualization tools to assess the quality of assemblies and their associated annotations. The tools will be made available through Dr. Birol's software portal and will help researchers worldwide better understand the world around us at the genomic and transcriptomic levels.

Breast cancer risk in postmenopausal women: a causal inference approach in a case-control study

Drs. Héctor A. Velásquez García, Boris G. Sobolev, Carolyn C. Gotay, Christine M. Wilson, Caroline A. Lohrisch, Agnes S. Lai, Kristan J. Aronson and John J. Spinelli conducted a study on the mammographic non-dense area and breast cancer risk in postmenopausal women. The association between high mammographic density and elevated breast cancer risk is well established. However, the role of absolute non-dense area remains unclear. The team estimated the effect of the mammographic non-dense area and other density parameters on the risk of breast cancer. This study utilized data from a population-based case-control study conducted in Greater Vancouver, with 477 female post-menopausal breast cancer cases, and 588 female post-menopausal controls. To examine the marginal (causal) effect of mammographic density parameters (with emphasis on the non-dense area) on breast cancer risk among postmenopausal women causal inference methods were implemented. These analyses conclude that the non-dense area is an independent risk factor after adjustment for dense area and other covariates, inversely related with the risk of breast cancer. It is also confirmed that that both dense area and percent mammographic density are directly related risk factors for breast cancer.

These evaluations also indicate that the non-dense area parameter does not improve discrimination in prediction models over that offered by percent mammographic density or dense area alone. These findings confirm that mammographic density parameters are important risk factors for breast cancer. This information could be helpful to public health efforts such as screening strategies. This work makes use of modern methods to examine the effect of mammographic density on breast cancer risk among postmenopausal women. The findings provide further evidence about the importance of mammographic density in the risk of breast cancer, as well as insights regarding potential future methods of breast cancer prevention.

POPULATION ONCOLOGY

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Childhood, Adolescent and Young Adult Cancer Survivors Research Program (CAYACS)

The Childhood, Adolescent, and Young Adult Cancer Survivor (CAYACS) Research Program tracks a cohort of all British Columbians diagnosed with cancer under the age of 25 years from 1970 and studies cancer survivors to understand health risks in later years. Using linked health care and other administrative records, the program conducts studies on the risks of health, education, and employment problems for survivors in later years, and inequities in the quality of long-term follow-up



In 2018, the team led by **Mary McBride** explored changes in health risks as treatments change, and are examining approaches to better coordination of care among physician specialists for this special population. Linking to Statistics Canada data, the long-term effects of cancer on earnings of childhood adolescent and young adult cancer survivors were measured. The CAYACS data have also been used to develop and test new statistical methods for analysis of large health care databases.

This unique study, that uses a novel approach of ongoing record linkage of registries, clinical data, and health and other administrative databases, has generated high-quality evidence that has led to better care for these survivors in B.C.

732 "Super Seniors" have participated in the Healthy Aging Study to date

The Healthy Aging Study has had 732 "Super Seniors" participate to date. Super-Seniors are healthy, long-lived individuals who were recruited at age 85 years or older with no history of cancer, cardiovascular disease, diabetes, dementia, or major pulmonary disease. **Dr. Angela Brooks-Wilson** and her research team want to know why a rare few of us live into a healthy old age. BC Cancer's role is research design, study participant recruitment, genetic and genomic analyses, and bioinformatics support. Drs. Brooks-Wilson and Denise Daley of UBC have received funding from the Canadian Cancer Society for three years to investigate genetic factors that may protect against cancer as part of the Healthy Aging Study. The study now welcomes anyone aged 85 or older, regardless of their health. If you are or you know someone 85 or older that may be interested in being part of this study, please call 604-675-8151.

Project MOVE's microgrant model makes physical activity more accessible for breast cancer survivors

Dr. Susan Ellard's research focused on innovative interventions to increase physical activity in breast cancer survivors. Physical activity is an effective way to help improve the many mental and physical side effects of breast cancer treatment. Yet, studies show up to 70 per cent of breast cancer survivors are not getting enough activity. Called Project MOVE, the program offers 'action grants'—a combination of microgrants up to \$2,000 and additional financial incentives—to prompt and sustain physical activity. Project MOVE used

the microgrant model to make physical activity more accessible and enjoyable for breast cancer survivors. The effectiveness, acceptability and satisfaction of the program were evaluated at 6 and 12 months. More than 86 per cent of the participants were satisfied with their program, 70 per cent learned about new physical activities and more than 96 per cent agreed that Project MOVE was appropriate for breast cancer survivors. Many participants agreed that they would continue with physical activity following positive experiences with the project.

IN MEMORY: PEGGY OLIVE, WORLD FAMOUS BC CANCER SCIENTIST DEDICATED TO IMPROVING RADIOTHERAPY

Professor Peggy L. Olive worked at the BC Cancer Research Centre for over 25 years and enriched the understanding of hypoxia and DNA damage in cancer. She is most famous for two techniques that measure DNA damage, the comet assay and gH2AX staining. Using these methodologies she probed the way in which radiation therapy and chemotherapy damages cellular DNA and how that damage is repaired.

She was a prolific author with over 200 peer reviewed and meaningful publications covering a wide range of topics associated with the tumour microenvironment, DNA damage and radiation oncology. Although she worked ultimately to increase the effectiveness of radiotherapy and was universally admired by the radiation research community, her friends and colleagues will also remember her keen sense of humour and formidable work ethic.

Born in Montreal, Peggy received an MSc and PhD from the universities of Western Ontario and McMaster's respectively. Following a post-doctoral fellowship at Johns Hopkins she was recruited by Lloyd Skarsgard to the Medical Biophysics Department at the BC Cancer Research Centre. Peggy received numerous NIH(US), CIHR and CCS peer reviewed operating grants and served on peer review granting committees in Canada and worldwide. Peggy became head of medical biophysics prior to her retirement in 2009 after which she dedicated her energy to volunteering, gardening and writing fiction under the *nom de plume* Margaret Durand and was short-listed for the 2015 Cedric Literary Awards.

Peggy declined a public funeral or celebration of life, but suggested donations be made to the Canadian Cancer Society. Visit www.mydaffodil.ca



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