

Provincial Health Services Authority

**2019** BC CANCER RESEARCH

REPORT

# Table of Contents

3	Message from the Senior Executive Director of Research, Dr. François Bénard
4	Message from BC Cancer Foundation President and CEO, Sarah Roth
5	2019 Fast facts
6	Awards and funding
14	Celebrating 20 years of Canada's Michael Smith Genome Sciences Centre at BC Cancer
16	New recruits in 2019
16	Food for thought: Dr. Rachel Murphy dissects diet and disease
17	Down to the roots: Dr. Ly Vu looks for leads in acute myeloid leukemia
18	Service spotlight: the graduate student and post-doctorate society at BC Cancer
19	Service spotlight: BC Cancer Libraries and Cancer Information Centres
20	Dr. Leah Lambert pushes to improve the circle of care
22	Medical resident spotlight: Dr. Erica Tsang searches for solutions for pancreatic cancer
24	Scientist spotlight: 2019 highlights of distinguished scientist Dr. Connie Eaves
26	Outstanding trainee publications 2019
27	Biology and genetics
34	Health economics and cancer control
35	Screening and diagnosis

- 38 Treatment
- 46 Cancer immunology and immunotherapy
- 50 Personalized OncoGenomics



#### On the cover

Genome Sciences Centre Head of Laboratory Operations, Paul Lythgo with a portion of the GSC computer cluster at the GSC's Echelon technology platform. With 30,000+ hyper-threaded cores, 20+ PetaBytes of storage and 24 deep learning GPU devices, the GSC is home to some of Canada's largest computation infrastructure, used almost entirely for the storage and analysis of genomic data. Last year alone, the GSC sequenced 391,012,881,130,938 bases of DNA, bringing its total to more than 2.74 petabases (2,740,000,000,000)—roughly equivalent to the number of base-pairs in nearly 900,000 human genomes.

# Message from the Senior Executive Director of Research, Dr. François Bénard



Our 2019 report showcases how BC Cancer continues to be internationally recognized for our excellence in cancer research and its integrated model of cancer planning and care. While our researchers and trainees continue to receive a remarkable number of awards and publish their work in the world's most prestigious scientific journals, we are reminded every day that our research is not a pure academic exercise. We do this for our patients, friends and families whose lives are affected every day by cancer. Our research has purpose and we intend to make sure it delivers a positive impact for everyone affected by cancer.

Many of the groundbreaking research discoveries were made possible thanks to Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer, which celebrated its 20th anniversary in November. In a tribute to this inspiring milestone, our 2019 research report focuses on genomics and the inspiring success of the GSC. Over the past two decades, the GSC has participated in thousands of national and international collaborations and produced DNA sequence equivalent to approximately 900,000 human genomes. Globally, we have entered a new era of precision medicine through the power of cancer genomics research which continues to improve outcomes for patients through the identification of new approaches for cancer diagnostic and treatment strategies. At cancer research centres across Canada, 2019 marked the launch of the new Marathon of Hope Cancer Centres Network (MOHCCN) through the Terry Fox Research Institute (TFRI), with support from the Government of Canada. The MOHCCN will bring together our national cancer centres to focus collective effort towards new precision medicine strategies for patients utilizing genomic approaches applied for Canadians. This will mean sequencing and comprehensive genomic profiling for over 15,000 Canadians across the country in the next five years. BC Cancer is proud to be one of the first centres piloting the MOHCCN, along with cancer centres in Montreal and Toronto.

The new five-year Strategic Plan for BC Cancer Research was also implemented in July of 2019, with approval by the Provincial Health Services Authority (PHSA) Research Board. The ultimate goal for the plan is to strengthen our research capabilities and align our strategies with the BC Cancer Foundation, PHSA, Terry Fox Research Institute, regional health authorities, the University of British Columbia (UBC) and other partner universities, including Simon Fraser University (SFU), University of Victoria (UVic) and the University of Northern British Columbia (UNBC). This new plan for research provides clear direction that improves our ability to generate knowledge, enhance the impact of our research and support innovation in clinical care.

While there is still much work ahead of us at BC Cancer, we are optimistic for the future as we continue to be a global leader in cancer care and research and every single day we are reminded that our work is driven by our vision of a world free of cancer.

# Message from BC Cancer Foundation President & CEO, Sarah Roth

As I reflect on 2019 at the BC Cancer Foundation, I am excited by the outstanding research achievements and innovative projects at BC Cancer that inspire our donors and advance cancer care in B.C. As BC Cancer's fundraising partner, we are proud to support the extraordinary work that happens across BC Cancer's vast research enterprise.

Many of the initiatives that take place at BC Cancer's research centres are fueled by our generous community of 95,000 donors who see the impact of innovation. This includes the ground-breaking work underway in the area of genomics.

Since its inception, the BC Cancer Foundation has been a major funder of the Genome Sciences Centre. Over the past 20 years, the GSC team has brought patients and families hope through advancements in technology and scientific and clinical collaborations. Genomics is now a global movement and BC Cancer is a leader-there is no other facility in Canada like the GSC.

Last November, at our annual Inspiration Gala, our community rallied together to raise an incredible \$3 million to advance genomics research. Funds raised will allow BC Cancer's brilliant oncologists, bioinformaticians, pathologists and scientists to get closer to achieving our mission to break down cancer for the more than 27,000 British Columbians diagnosed each year.



Genomics represents a paradigm shift, ensuring the health of our children and grandchildren for years to come.

Our donors are also enabling clinicians and scientists to push the envelope, driving innovation across borders. The BC Cancer Foundation has partnered with the Terry Fox Research Institute and other large cancer centres and funding partners under the Marathon of Hope Cancer Centres Network, a pan-Canadian initiative to accelerate the adoption of precision medicine. This is an example of BC Cancer expertise co-leading a powerful collective on a national stage to change outcomes for all Canadians facing cancer.

As your partner, the BC Cancer Foundation is motivated by our united vision of a world free from cancer. Together, we won't stop advancing life-saving research and, ultimately, changing outcomes for all British Columbians.





### January

Dr. Shoukat Dedhar, distinguished scientist with Integrative Oncology, received the University of British Columbia Killam Research Prize in recognition of his outstanding research and scholarly contri-



butions. Dr. Dedhar has pioneered a large body of work in the cellular and molecular biology of cell-extracellular matrix interactions, including significant insights into the roles of tumour microenvironments and hypoxic stress as driving forces for metastatic potential in cancers. His research in this area has led to the identification of Carbonic Anhydrase IX (CAIX) as a therapeutic target in aggressive forms of breast cancer, brain cancer (glioblastoma) and pancreatic cancer. Dr. Dedhar is also the scientist that discovered Integrin-Linked Kinase (ILK), which is an essential protein involved in the regulation of Integrin function and Integrin-mediated signal transduction. ILK deregulation plays a major role in cancer progression, kidney disease, inflammatory diseases, myelination disorders and neurodegeneration.



Dr. Robert Holt, distinguished scientist with Canada's Michael Smith Genome Sciences Centre, was awarded Grand Challenge funding from Cancer Research UK. One of the most ambitious cancer research funding programs in the world, Grand Challenge awards provide freedom

for scientists to try novel approaches in the pursuit of life changing discoveries. Dr. Holt is part of an international team of 14 investigators that will examine how the microbiome can influence a person's risk of developing bowel cancer, how cancer cells and gut microbes interact, how it can influence treatment response and how it may be manipulated to treat bowel cancer. Dr. Holt's lab specifically will research new therapeutic strategies like vaccinations and antibiotics that target key organisms.

Dr. Ryan Morin, senior scientist with Canada's Michael Smith Genome Sciences Centre, received a 2019 American Society of Hematology (ASH) Scholar Award, which funds hematologists in the North America who conduct basic, translational and



clinical research as they transition from training programs to careers as independent investigators. Dr. Ryan Morin has been studying the genetic nature of lymphoid cancers using genomic methods for more than a decade. During his doctoral training at UBC and BC Cancer, he pioneered the use of transcriptome and whole genome sequencing to identify driver mutations in non-Hodgkin lymphomas. Over the course of his training, he published a series of papers describing some of the most common genetic features of diffuse large B-cell lymphoma (DLBCL) and follicular lymphomas including EZH2, KMT2D, CREBBP and MEF2B. Dr. Morin was the only Canadian to receive the ASH Scholar Award in 2019.

Dr. Dan Le, medical oncologist at BC Cancer–Surrey and Dr. Christine Simmons, medical oncologist at BC Cancer–Vancouver, were awarded \$177,500 over two years from the 2019 Pfizer Canada ASPIRE Breast Cancer Early Investigator Research Award for a clinical study examining the use of the drug Gabapentin in reducing chemotherapy induced joint and muscle pain.

Dr. Robert Olson, radiation oncologist at BC Cancer–Prince George, received a \$500,000 research grant from Varian Medical Systems to operate the SABR-COMET-3 Phase III clinical trial—a large randomized study investigating whether stereotactic ablative radiotherapy (SABR) can prolong the life of cancer that has spread from

one to three locations. Dr. Mark Carey was appointed as Gynecologic Committee

Chair for the Canadian Cancer Trials Group (CCTG)

#### CIHR Fall 2018 Project Grants

- Dr. Cathie Garnis was awarded \$539,324 over four years to study blood-based biomarkers for the early detection of recurrent head and neck cancer.
- Dr. Aly Karsan, was awarded \$1.2 million over five years to investigate hematopoietic stem cell (HSC) aging and define the role of noncoding RNAs as determinants of aging in the hematopoietic system. Specific goals include elucidation of the mechanisms of HSC aging in response to loss of miR-146a, determination of the role of miR-146a in the aging of HSC and whether aging of HSC can be reversed.

- Dr. Arman Rahmim was awarded \$631,124 over four years to study the quantitative PSMA targeted imaging of prostate cancer patients.
- Dr. Yuzhuo Wang was awarded \$956,250 over five years to investigate the function and therapeutic potential of SUV420H2 in neuroendocrine prostate cancer.
- Dr. Julian Lum was awarded a \$1.08 million to study the role of sugar in regulating T cell responses and derive new avenues to enhance T cell immunotherapy.
- Dr. Kuo-Shyan Lin was awarded \$772,650 over five years to develop a general strategy to reduce kidney uptake of peptide-based radiopharmaceuticals with the aim to enhance their detection sensitivity and minimize their undesired side effects.

### **February**

Dr. Marco Marra, distinguishedscientist and director of Canada's Michael Smith Genome Sciences Centre at BC Cancer and professor and head of Medical Genetics at UBC, received the 2019 Don Rix Lifetime Achievement Award from LifeScience BC. In

honour of Dr. Donald Rix's memory and his many achievements, the award recognizes exemplary leadership and determination.

Throughout his career, Dr. Marra has been instrumental in demonstrating the pivotal role that genomics can play in human health and disease research, including contributions to the Human Genome Project, leading the sequencing of the first SARS coronavirus genome (SARS-CoV-1) and the first proof-of-concept study demonstrating the effective use of whole genome analyses in personalized cancer medicine. His research has uncovered new cancer mutations, candidate biomarkers and therapeutic targets as well as illustrating the functional interplay between the cancer genome and epigenome. Since 2014, he has been named as among the World's Most Influential Scientific Minds with more than 400 scientific publications, placing him in the top one per cent of cited scientists in his discipline worldwide.

# 2019

#### CIHR Fall 2018 Special Operating Grants

Dr. Rachel Murphy was awarded a CIHR Operating Grant of \$100,000 to lead a study aiming to identify risk factors—other than smoking—that may increase the risk of developing lung cancer. The study will use



large datasets of health information about Canadians from across the country, including the BC Generations Project based out of BC Cancer, which includes a cohort of nearly 30,000 B.C. participants who have volunteered their health information and biological samples to help researchers learn more about how environment, lifestyle and genes contribute to cancer and other chronic diseases.

> Dr. Aly Karsan was awarded a CIHR Operating Grant of \$910,350 over five years to investigate the role of endothelial Meis1 in definitive hematopoiesis and vascular development, and to characterize the cellular heterogeneity

within the homogenic endothelial cell population. This study will better define the transcriptional programs that drive endothelial-to-hematopoietic transdifferentiation, which has implications for optimizing the *ex vivo* production of hematopoietic stem cells and potentially for the development of therapeutics for blood and vascular disorders.

### March

With new support from BC Cancer Foundation's Neil MacRae Hereditary Cancer Research Fund, three teams of BC Cancer scientists will help to shed light on the genetic origins of rare male breast cancers. Drs. Steven Jones (PI), Kasmintan Schrader (co-PI), Marco Marra, Aly Karsan, Janessa Laskin, Sophie Sun, MyLinh Thibodeau and Stephen Yip will use novel DNA sequencing technologies to analyze hereditary mutations associated with the disease. Drs. Connie Eaves (nominated PI) and Martin Hirst will design pilot studies to elucidate relevant early and targetable events in the genesis of male human breast cancer that will also set the stage for testing new therapies for patients. Drs. Intan Schrader (nominated PI), Sophie Sun (co-PI), Aly Karsan, Dean Regier and MyLinh Thibodeau aim to identify inherited mutations from deceased male breast cancer patients by performing genetic testing on their cancer samples.

#### April



The NanoMedicines Innovation Network (NMIN), which includes Dr. Marcel Bally, Head of Experimental Therapeutics and Research Management Leader with NMIN, was awarded \$18.5 million from Networks of Centres of Excellence to demonstrate the

health and economic benefits of its nanomedicine technologies for Canadians, including the development of a skilled interdisciplinary workforce focused on nanomedicine. With expertise from a wide range of disciplines applied toward the development of nanomedicine therapeutics for high-burden human diseases and new diagnostics to detect and monitor the effects of therapy, NMIN brings together 60 principal investigators from 17 institutions across Canada together with 15 companies and eight not-for-profit research and granting bodies to expand and improve Canada's position as a leader in nanomedicine research and development.

### May



Dr. Anna Tinker, medical oncologist at BC Cancer–Vancouver, was appointed Provincial Gynecology Tumour Group Leader in British Columbia. She brings her tremendous experience in the care of women with gynecologic cancers and as a

leader of clinical trials into this role.

Dr. Gerry Krystal, distinguished scientist with the Terry Fox Laboratory, was awarded the Editor's Choice Award from the journal *Carcinogenesis* for his 2019 paper, "The effect of diet and exercise on tobacco carcinogen-induced lung cancer". The results

of this study suggest that a low carbohydrate diet supplemented with soy protein and fish oil, coupled with exercise, may dramatically reduce the incidence of lung cancer.



Drs. Christian Steidl and Katsuyoshi Takata, distinguished scientist and director and post-doctoral fellow, respectively, with the Centre for Lymphoid Cancer, received an operating grant of \$200,000 from the



Leukemia and Lymphoma Society of Canada (LLSC) to support their research on PRAME mutations in Diffuse Large B-cell Lymphoma (DLBCL).

Dr. Aly Karsan, distinguished scientist with Canada's

Michael Smith Genome Sciences Centre, was awarded a \$200,000 **Operating Grant from LLSC** to determine if targeting the IGF1R pathway will exploit del(5q) dependencies in lenalidomide resistant myelodysplastic syndrome.

Dr. Joanne Johnson, head of project management with Canada's Michael Smith Genome Sciences Centre, won the Canadian Association of Research Administrators (CARA) Research Project Management Excellence Award at CARA's 2019 Annual Conference in Montréal. The award is presented



to an exceptional research manager who has made outstanding contributions to the profession through innovation, creativity, hard work and dedication, determined based on voting and nominations from fellow CARA members.

#### June

**Dr. Steven Jones**, distinguished scientist, co-director and head of Bioinformatics with Canada's Michael Smith Genome Sciences Centre and professor of Medical

Genetics at the University of British Columbia (UBC), was named **the first Tier 1 Canada Research Chair in Computational Genomics** at UBC. Dr. Jones' research focus is the analysis of genomic and transcriptomic data in cancer, applying next-generation DNA sequencing technology to determine the mutations and rearrangements driving many tumour types. A key goal of his work is to develop bioinformatic approaches to help guide clinical decisionmaking by predicting efficacious cancer therapies from molecular analyses of tumour samples. In 2010, he was the first author of the world's first study to use whole-genome sequencing to inform the treatment plan of a cancer patient. He is a principal investigator and co-applicant on grants



The BC Cancer Lloyd Skarsgard Research Excellence Awards recognize outstanding graduate students in their final year of training at BC Cancer.

- Dr. Daiana Becker dos Santos (First Prize)
  Dr. Becker dos Santos, a Vanier Canada Scholar from
  Dr. Wan Lam's laboratory, received her PhD in Interdisciplinary Oncology from UBC this year. The title of her thesis research is: "Discovery of Oncofetal Micro RNA-Gene
  Networks Associated with Lung Cancer Aggressiveness."
  Dr. Becker dos Santos discovered that essential genes for human fetal lung development are being reactivated in lung cancer. By exploring the downstream consequences of such reactivation, she identified a novel biomarker for lung cancer aggressiveness and patient outcome.
- Dr. Shaun Jackman (Second Prize)
  Dr. Jackman received his PhD in
  Bioinformatics from UBC under the
  supervision of Dr. Inanc Birol and Dr.
  Jörg Bohlmann. The title of his thesis is:
  "Efficient Assembly of Large Genomes."



He developed the ABySS assembler software that is one of the enabling technologies used in the Personalized OncoGenomics program.

#### • Dr. Allen W. Zhang (Third Prize)



Dr. Zhang, Vanier Canada Scholar and MD/PhD student, received his PhD in Bioinformatics from UBC under the supervision of Dr. Sohrab Shah and Dr. Wyeth Wasserman. The title of his thesis is: "Evolutionary Dynamics of Ovarian

Cancer Microenvironments and Tumour Cells." His thesis research addresses the nature of immune-malignant cell interaction in ovarian cancer.

Dr. Martin Hirst, distinguished scientist with Canada's Michael Smith Genome Sciences Centre, as leader of the Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) Network, received a \$1 million funding renewal from





CIHR for CEEHRC — a network linking a variety of Canadian laboratories focused on epigenomic research that also provides epigenomic training opportunities and knowledge translation resources for researchers, clinicians and the public.

## July

Dr. Andrew Roth received a MSFHR Scholar Award to support promising early career researchers through salary support. Dr. Roth has recently started a group at BC Cancer focused on developing computational and statistical methods analyzing high throughput biological data.

#### CIHR Spring 2019 Project Grants

- Dr. Ryan Morin was awarded \$784,126 over five years to investigate the effect of regulatory mutations in the most prevalent form of non-Hodgkin lymphoma, known as diffuse large B-cell lymphoma.
- Dr. Andrew Minchinton was awarded \$573,750 over five years to investigate hypoxia-activated DNA repair inhibitors to improve cancer therapy.
- Dr. Haishan Zeng was awarded \$711,451 over four years with Drs. Harvey Lui, Joanne Matsubara and Sonia Yeung to study multiphoton photothermolysis based laser therapy for precision treatment of neovascular eye diseases.

## August

The MSFHR Health Professional-Investigator (HP-I) Program is designed to develop B.C.'s research talent, and decrease the gap between health research and its implementation. The awards support health professionals who are actively involved in patient care to conduct and apply research relevant to health and/or the health system. BC Cancer recipients in 2019 included:

• Dr. Jonathan Loree—a gastrointestinal medical oncologist, co-chair of the BC Cancer Gastrointestinal Cancers Clinical Outcomes Unit and co-chair of the Canadian Cancer Trials Group Colon Cancer Disease Group. His

research interests are focused on biomarker development, genomics and liquid biopsies to guide therapy selection.

- Dr. Janice Kwon, Gynecology Surgical Tumour Group Chair and a scientist with the OVCARE research program at BC Cancer. The award will allow Dr. Kwon to focus her time on evaluating tumour testing in ovarian cancer as a strategy to improve survival in women with ovarian cancer by increasing the identification of patients eligible for life-prolonging treatment with PARP inhibitors, as well as improve the efficiency and reduce the costs associated with conventional genetic testing in ovarian cancer patients.
- Dr. David Scott—a clinician scientist, clinical director of the BC Cancer Centre for Lymphoid Cancer and deputy head of the BC Cancer Research Centre's Department of Lymphoid Cancer Research. In collaboration with the



Lymphoma/Leukemia Molecular Profiling Project consortium this award will help support Dr. Scott's ongoing research to unveil the biology of aggressive B-cell lymphoma subgroups, including ABC subtype of diffuse large B cell lymphoma

(DLBCL), high-grade lymphoma harboring the MYC translocation and lymphomas involving extra-nodal sites.

Dr. Inanc Birol, distinguished scientist with Canada's Michael Smith Genome Sciences Centre, was awarded \$6.9 million from Genome Canada for a Large-scale Applied Research Project that will employ genomics research to discover and develop antimicrobial peptides (AMPs) as alternatives to

traditional antibiotics. AMPs are produced by some plant and animal species and have activity against a range of bacterial pathogens, showing great potential for use in the clinic and in agriculture. Using a genomics approach will accelerate the traditionally labour-intensive process of discovering novel AMPs. Dr. Birol's team will build on their previous proof-ofconcept research to scale-up their AMP discovery process. The discovery and characterization of novel AMPs by Dr. Birol's group has the potential to mitigate antimicrobial resistance in clinical settings, including within cancer hospitals. AMPs have also shown promise as anti-cancer agents. Dr. Kevin Bennewith, seniorscientist with Integrative Oncology and co-investigator Dr. Kelly McNagny (UBC), were awarded a Cancer Research Society Operating Grant of \$120,000 for their research into the role of eosinophils and B cells in the development and growth of metastatic tumours in the lungs.

#### September



Dr. Poul Sorensen, distinguished scientist with Molecular Oncology, was awarded a Distinguished Achievement Award for Overall Excellence, Senior Faculty from the UBC Faculty of Medicine, as well as the 2019 Bloom Burton Award–Bloom Burton & Co. is a medical healthcare investment firm and

the Bloom Burton Award is bestowed annually to honour an individual who has made the greatest contribution to Canada's innovative healthcare industry in the previous year.

Dr. Marcel Bally, head of Experimental Therapeutics, was awarded two grants by Networks of Centres of Excellence, NanoMedicines Innovation Network 2019-2021 Competition, with Drs. Brad Nelson, distinguished scientist with the Deeley Research Centre, Shyh Dar Li (UBC) and Cuprous Pharmaceuticals Inc. (CPI).

Dr. Andrew Minchinton, distinguished scientist with Integrative Oncology, received \$2.1 million from LifeArc and \$1.2 million from adMare, in support of an ongoing drug development program seeded with \$5 million from the Wellcome Trust which



previously funded development of promising small molecule inhibitors for DNA-PK —a key DNA repair protein involved in non-homologous end-joining. The medicinal chemistry will be performed in the U.K. and India, as well as Vancouver. The biological and radiobiological studies will be performed at BC Cancer. Dr. Samuel Aparicio, distinguished scientist and Head of Molecular Oncology at BC Cancer, with Dr. Joan Brugge



from Harvard Medical Centre, received a \$3 million collaborative Basser Initiative grant from the Gray Foundation to develop strategies to track and prevent breast cancer development in BRCA mutation carriers. Initial research has led to the

characterization of two specific subtypes of cells that accumulate significantly in breast tissues from BRCA1/2 carriers (and that are rare in breast tissues without BRCA1/2 mutations). Dr. Aparicio's team will build on these exciting new findings to decipher in detail why BRCA mutations cause these cells to accumulate and to expose vulnerabilities that could lead to new strategies for their elimination. The proposed work could transform both understanding of breast carcinogenesis in BRCA1/2 mutation carriers and the ability to predict and prevent it.

The Research Challenge Advisory Council announced funding for five teams in The Practice-based Research Challenge, an initiative to bridge the gap between clinical practice and research by empowering point-of-care interprofessional clinical teams to identify challenging clinical issues and find evidence-based answers through research. The five teams selected for funding will continue working with their mentors and developing their research skills as they conduct their research projects:

Team: Nikita Ivanov, Naureen Mukhi, Emma Hoag, Nicole Dyregrov, Jen Rosychuk

Mentor: Dr. Antony Porcino (Supportive Cancer Care) and Dr. Sally Thorne (UBC)

Unit: Systemic Therapy (Vancouver)

Title: Nurse-Patient Interactions in the Genitourinary (GU) Oncology Ambulatory Clinic Setting

Team: Dustin Mackay, Heather George, Ava Hatcher, Grace Cole

Mentor: Dr. Shannon Freeman (UNBC)

Unit: Staff Nurse (Prince George)

Title: Examining the experience of persons undergoing cancer treatment who observe other patients ring the milestone bell

# 2019

Team: Jenny Chang, Krisdeep Lally, Jacquie Wong Mentor: Dr. Fred Hsu (Medical Oncology) Unit: Radiation Therapy (Abbotsford) Title: Standardizing bladder filling protocol and patient education material at BC Cancer

Team: Ellie Heo, Cecilia Kim Mentor: Dr. Nafisha Lalani (Radiation Oncology) Unit: Radiation Therapy (Abbotsford and Surrey) Title: Pregnancy Associated Breast Cancer in British Columbia: Patterns of Care and Outcomes

Team: Caroline Pollock, Amber Brown-Dahl Mentor: Cheri Van Patten, RD (Oncology Nutrition) Unit: Oncology Nutrition (Vancouver) Title: Evaluating patient practices of home-based cleaning techniques of enteral feeding equipment

### October

Dr. Cheryl Duzenli and colleagues were awarded the CARO Supportive Care Award at the CARO Annual Scientific Meeting for the B-Skip pilot, completed in September 2019. which evaluated a patient reported outcome tool for patients to self-report serious skin reactions with high sensitivity and specificity, for women undergoing radiation treatment for breast cancer. The pilot was

completed at multiple BC Cancer centres, including Dr. Duzenli and Sheri Lomas in Vancouver, Dr. Robert Olson and David Morris in Prince George and Dr. Theodora Koulis in Kelowna.

Dr. Nadine Caron received an Honourary Doctor of Science

degree from Simon Fraser University. Dr. Caron is Anishnawbe from Sagamok First Nation, a surgeon, scientist, associate professor, an internationally renowned health advocate passionate about improving health outcomes for Indigenous peoples and an associate researcher at the



Canada's Michael Smith Genome Sciences Centre at BC Cancer. Dr. Caron's main research focus involves access to equal health status, health care services and the factors that lead to these for marginalized populations, including Aboriginal, northern and rural. The convocation ceremony took place October 2019.

Dr. Samuel Aparicio successfully renewed a Breast Cancer Research Foundation grant for a total of US\$500,000 to develop predictive biomarkers for genome targeting agents in triple-negative breast cancer at single cell resolution.

### November

Fifteen scientists from various BC Cancer Research departments were listed by Clarivate Analytics as among the most Highly Cited Researchers in the world in 2019 in their respective fields. Every year, scientists and scholars worldwide publish their findings in academic journals and proceedings, producing papers estimated in the range of more than two million. How does the research community determine the papers with the most value? Citations are one way and a paper that other scientific authors have frequently cited has arguably proved itself to be highly significant. This is the approach taken by Clarivate Analytics, which quantifies the number of citations for specific scientists in various disciplines and generates a list of Highly Cited Researchersthose who produce multiple papers ranking in the top one per cent by citations for their field. The select few that make it onto this list represent just 0.1 per cent of researchers worldwide. Researchers are selected for their exceptional performance in one or more of 21 fields. In 2019, 6,216 researchers were named as Highly Cited Researchers-3,725 in specific fields and 2,491 for cross-field performance. The 15 scientists from BC Cancer on the 2019 list include:

- Dr. Marco Marra
- Dr. Steven Jones
- Dr. David Huntsman
- Dr. Robert Holt
- Dr. Martin Hirst
- Dr. Inanc Birol
- Dr. Andy Mungall
- Dr. Richard Moore
- Dr. Yongjun Zhao
- Dr. Erin Pleasance
- Angela Tam
- Dr. Joseph Connors (former distinguished scientist)
- Dr. Randy Gascoyne (former distinguished scientist)
- Jacqueline Schein (former staff scientist)
- Dr. Nina Thiessen

Dr. Cyril Blake Gilks, consultant pathologist at BC Cancer and pathologist at Vancouver General Hospital, was recognized with the 2019 Terry Fox Medal presented by Doctors of BC at the **BC Cancer Summit** in November 2019. The Terry Fox Medal recognizes individuals conducting clinical practice, research or teaching/education who have achieved national or international recognition based on a distinguished career of achievement in their area of focus, a seminal advance through the conduct of their endeavours and promotion and achievement of advance in the conduct of cancer medicine and cancer control.

Drs. Poul Sorensen and David Huntsman were named Fellows of the Royal Society of Canada, the highest honour an academic can achieve in Canada. Dr. Sorensen is a distinguished scientist at BC Cancer and a professor in the Department of Pathology and Laboratory Medicine at UBC. In 1998, Dr. Sorensen's lab discovered a gene mutation, ETV6-NTRK3 that launched an entirely new field in cancer biology and which led to the development and 2018 FDA approval of a tumour-agnostic therapy called larotrectinib. The drug was subsequently approved by Health Canada on July 30, 2019. Larotrectinib, marketed by Bayer Pharmaceuticals as Vitravki®, targets at least 22 different cancers in both children and adults.



Dr. Huntsman has used pathology and genetic tools to redefine our understanding of ovarian and several rare cancers including hereditary stomach cancer. He proposed, developed and promulgated the current subtype-specific and biologically informed approach to ovarian cancer research, prevention and treatment.

Scientists from BC Cancer's Ovarian Cancer Research (OVCARE) program (past and present) were listed by the World Health Organization's International Agency for Research on Cancer (IARC) as among the world's top 15 most impactful ovarian cancer pathology researchers for the past five-year period:

- Dr. David Huntsman (#2)
- Dr. Martin Kobel (#4; former trainee)
- Dr. Blake Gilks (#5)
- Dr. Anthony Karnezis (#10; former trainee)

OVCARE scientists were also listed by IARC as among the world's top 15 most impactful endometrial cancer pathology researchers for the past five-year period:

- Dr. Blake Gilks (#2)
- Dr. Martin Koebel (#3; former trainee)
- Dr. Lien Hoang (#4)
- Dr. Cheng-Han Lee (#6)
- Dr. David Huntsman (#8)
- Dr. Aline Talhouk (#9)
- Dr. Frieder Kommoss (#10; former visiting scientist)
- Samuel Leung (#12)
- Dr. Melissa McConechy (#13)
- Dr. Anthony Karnezis (#14)

Dr. Marcel Bally was accepted as a Board Member of the newly established Canadian Pharmaceutical Sciences Foundation. This organization aims to help the pharmaceutical sciences in Canada through the support of quality of research, training skilled scientists in the field, continuing and professional education and early career pharmaceutical researchers.

Dr. Parveen Bhatti received funding to create a Virtual Tumour Tissue Bank that will identify available samples and include standard operating procedures for tumour specimen retrieval that can be used on a projectby-project basis for cancer cases arising in the BC Generations Project (BCGP) cohort.



The BCGP, which is based at BC Cancer, consists of 30,000 people that provided extensive lifestyle and health history data as well as urine and blood samples to support cancer research. Since it would be impractical to establish a physical tumour repository for such a large number of cases, they will create a Virtual Tumour Tissue Bank.

### December

Drs. Jenny Ko and Anna Tinker, medical oncologists at BC Cancer–Vancouver, were selected for Gynecologic Cancer Initiative-Clinical Trials Group 2019 Accelerating Grant for Clinical Studies for a trial proposal for a pragmatic trial comparing two standard doses of bevacizumab in combination with chemotherapy in epithelial ovarian cancer.

Dr. Jessica McAlpine's publication

"The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses", published in the Journal of Pathology, was recognized as one of the journal's most downloaded papers of 2019.



# Celebrating 20 years of Canada's Michael Smith Genome Science Centre at BC Cancer



2019 marked a significant milestone for Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer: its 20th anniversary.

In 1999, Drs. Don Carlow, Victor Ling and Simon Sutcliffe, leaders from BC Cancer, working with Nobel Laureate Dr. Michael Smith—with critical support from the BC Cancer Foundation, National Institutes of Health, Canadian Foundation for Innovation and BC Knowledge Development Fund—created the world's first genome centre embedded within a cancer clinic, garnering fast support from important partners including the Canadian Institutes of Health Research, Genome Canada and Genome BC.

Over the last 20 years the GSC has trained more than 2,000 highly-qualified personnel and published more than 1,400 peer-reviewed papers, which have attracted more than 170,000 citations. It has been part of nearly 900 research projects and have contributed to thousands of national and international research collaborations. Its 13 Principal Investigators have been leaders on projects awarded more than \$1.1 billion from more than 160 funders. Last year alone, the GSC sequenced 391,012,881,130,938 bases of DNA, bringing its total to more than 2.74 petabases (2,740,000,000,000,000) roughly equivalent to the number of base-pairs in nearly 900,000 human genomes.

Today, the GSC is working to help BC Cancer change outcomes for people affected by cancer in British Columbia and beyond, by harnessing the power of genome analysis to make fundamental research discoveries and promote patient-centred care, in cancer contexts and in other important health research areas.

The GSC celebrated its 20th anniversary with an Open House at its Echelon Technology Platform on November 15. More than 500 people attended to learn about genomics and bioinformatics science and technology. On November 21, the first day of the 2019 BC Cancer Summit, a scientific symposium was held featuring 16 speakers researchers, partners, former trainees and leaders in genomics—highlighting the technology advances, scientific investigations and ground breaking discoveries that have helped advance genome science. The event brought together current GSC scientists and staff, former colleagues, alumni, collaborators and friends, all sharing a passion for employing genomics to improve human lives.

Much has happened in the last twenty years and we are proud that the GSC has had a constant presence at the forefront of genomics and bioinformatics research. We can't wait to see what the next twenty years will bring.



#### The Honourable Premier Horgan visits the GSC for its 20th anniversary

On September 20, 2019 the GSC had the pleasure of hosting the Premier of British Columbia. The Honourable John Horgan received a hands-on, personal tour of its





From left to right: The family of the late Dr. Michael Smith and other GSC founders, including former BC Cancer President, Dr. Don Carlow and former BC Cancer Vice President of Research, Dr. Victor Ling, with GSC Director, Dr. Marco Marra.

DNA sequencing and bioinformatics technology platform from Director and Distinguished Scientist, Dr. Marco Marra.

The Premier prepared DNA for extraction in a liquid handling robot, experienced different types of DNA sequencing technology, saw live normal and cancerous pancreas cells in culture, explored single-cell extraction and sequencing, toured through the GSC's computer server room and learned of the different types data with which the GSC's bioinformaticians work.

"Cancer touches us all. About half of us can expect to receive a cancer diagnosis in our lifetime. That's why the work of [the GSC] is so important" said the Premier in a tweet following the tour. "What I saw yesterday and the people I met, gives me confidence that we can beat this disease. Thank you for having me."

# New recruits 2019

#### **Dr. Kevin Hay**

Dr. Kevin Hay joined the Terry Fox Laboratory as a Clinician Scientist with the Leukemia/Bone Marrow Transplant Program of BC in Vancouver. He is Director of the Clinical Cell Therapy Laboratory and Medical Director of the Conconi Family Immunotherapy Laboratory. Dr. Hay's clinical research with the Leukemia/BMT Program of BC focuses on the development of a CAR-T program in B.C. and clinical trials of CAR-T cell therapy. His laboratory aims to develop CAR-T cells targeting other cancer types, such as myeloma and to modify CAR-T cells to improve efficacy and decrease toxicity. Dr. Hay's lab is currently exploring novel multi-antigen targeting approaches, modifications to the CAR construct and different approaches to T cell manufacturing.



#### Food for thought: Dr. Rachel Murphy dissects diet and disease

Dr. Rachel Murphy is incredibly knowledgeable when it comes to nutrition and diet for cancer prevention. According to the BC Cancer scientist, approximately 40 per cent of cancers can be prevented through healthy living which includes eating well. Her population-based approach to research focuses on identifying key biomarkers of diet and lifestyle and its impact on cancer. Using the latest technologies including metabolomics and metagenome sequencing, she studies large populations of Canadians and works to inform new strategies to help Canadians reduce their risk of cancer by making healthy lifestyle choices. Her goal is to support people to make healthy lifestyle choices and reduce their risk of developing cancer.

In 2019 Dr. Murphy received one of only nine operating grants from the Canadian Institutes of Health Research to lead a national team which will provide evidence on modifiable risk factors, beyond smoking cessation, that contribute to lung cancer. 2019 also saw Dr. Murphy step into a scientist role with Cancer Control Research at BC Cancer after four years in an affiliate scientist role. And the icing on the cake? She contributed to nine peer-reviewed publications this year—five of which were led by her trainees.

Looking forward, Dr. Murphy serves up her thoughts on the future of cancer research in her field.

#### What are your thoughts on the future of oncology?

We know that one in two people will receive a cancer diagnosis in their lifetime. A greater emphasis on preventative policies and programs is needed to address this statistic and stop cancer before it starts. Precision medicine is offering promising treatment options for some patients but it also holds great potential to revolutionize preventative approaches by considering an individual's biological, epidemiological, behavioural and socioeconomic characteristics.

# Where have you seen the most significant progress in cancer research since the beginning of your career?

When I first started my training, technologies like metabolomics and genomic sequencing were just starting to be more widely applied to study cancer. This area has really expanded in the past decade and has transformed the field of nutrition and cancer, as well as cancer research more broadly. It has been exciting to see some of the discoveries from the application of these technologies such as the identification of new metabolic biomarkers for cancer risk and the emergence of the microbiome as an important mediator for many aspects of cancer including cancer incidence and response to therapy.

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

The growing number of Canadians who will develop cancer over the coming decades emphasizes the need for resources to be focused on cancer prevention research. It is critical to improve our understanding of risk factors for cancer and particularly factors that can be changed. There is also the need to focus efforts on cancers where little progress has been made with respect to survival rates, e.g. pancreatic, liver and lung cancer.

#### What advice would you offer to young scientists?

Don't be afraid to stretch the boundaries of your discipline—this will be how you can establish your niche. Seek out like-minded colleagues who see the added value you bring to research and recruit talented people to your team.

#### Down to the roots: Dr. Ly Vu looks for leads in acute myeloid leukemia

**Dr. Ly Vu** is in the thick of it when it comes to understanding the pathways of acute myeloid leukemia (AML). According to the BC Cancer scientist, approximately 30 per cent of patients with this diagnosis will relapse from the disease, which, at that point, has a poor survival rate. Her research takes aim at leukemia stem cells, particularly their self-renewal properties and how she can leverage their characteristics to stir up new treatment and improve outcomes.

2019 was a remarkable and challenging year for Dr. Vu. She forged ahead on a journey from New York City to Vancouver and within six months had grown her own independent research group from one person (herself) to a team of five.

As she steps up to the summit, Dr. Vu shares her predictions on the future of cancer research in her field.

#### What are your thoughts on the future of oncology?

There have been significant advancements in the last decade that further our understanding of cancer; however, these learnings have mostly been limited to understanding cancer cells in isolation. In the future, I believe we'll look deeper into how cancer cells interact within the tumour environment and within the body as a whole. I think there will also be a lot of focus placed on how and why a same set of cellular mutations turn into cancerous tumours for some people and not for others.

## Where have you seen the most significant progress in cancer research since the beginning of your career?

I would say the arrival of precision medicine, which allows clinicians to personalize cancer treatment for patients, has been the most significant advancement. When I started my PhD more than 10 years ago, patients were classified into broad cancer categories which had a corresponding standard treatment protocol as we had just started to look into mutations in cancer. Now we can routinely look into the genetics of a tumour and better identify treatments tailored specifically to a patient's unique cancer type. As sequencing technologies improve and become more cost-effective, we can provide it to more patients allowing for customized cancer care. In addition, the data we are able to collect from sequencing has been widely shared among the scientific and clinical communities allowing all researchers to access and build upon this data. This open and collaborative effort can lead to more discoveries that can have an impact on patient outcomes.



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

Patient relapse after responding to initial treatments is a big concern. Overcoming this resistance is critical to improving patient outcomes. To this front, we have started to identify cancer stem cells as one the main drivers for resistance to therapy and relapse in patients. A major focus in the field and of my research program is to understand the foundational features of cancer stem cells. The goal is to be able to single them out and target them specifically to get to the root of the diseases to hopefully eradicate it.

#### What advice would you offer to young scientists?

I think now is a very exciting time to be in oncology research. With all the advancements in technologies and development of new tools, we are more equipped than before to address many pressing questions in the field. What really makes me excited is that those questions are not only scientifically fascinating but also highly relevant and have immediate impacts in cancer treatments. As an experimental scientist, my advice to young scientists is to work to strengthen connections with our clinicians and clinician-scientists who are at the front line providing patient care. I think the combination of our backgrounds and perspectives will enable us to more effectivity translate discoveries from the bench side to bed sides.

# Service spotlight: the graduate student & post-doctorate society at BC Cancer

The graduate student and post-doctorate society, known as GrasPods, is the BC Cancer student organization that provides extra learning and social opportunities for those continuing their education at BC Cancer. Although it formed in 2005, 2019 marks its 10 year anniversary after being officially adopted and endorsed as a student society by BC Cancer. Their official mission is "to facilitate scientific and social networks among graduate students and post-doctoral fellows of the BC Cancer Research Centre and affiliated institutions," says 2020 GrasPods president Ann Sun. The group facilitates a host of events for its 291 members including research days, sports leagues and fitness challenges and social nights.

Top among their 2019 events included the BC Cancer Research Day which presents members with an opportunity to learn from keynote speakers, present posters and network with their peers and mentors. The event included prizes and sponsorships and was the most popular event of the year, seeing approximately 130 attendees. In 2019 GrasPods also hosted its first career fair, exposing attendees to potential careers outside of the typical tenure track. Both trainees and professional participants enjoyed the career panel and networking roundtables which consisted of leaders in the fields of science, education, communication and more.

"When looking for a graduate program there's a lot of things to consider," says Ann Sun. "While labs, atmosphere and resources are important, the one thing BC Cancer also offers is seminars, talks and workshops for students. GrasPods also helps students feel connected to our other student communities." GrasPods works closely with the UBC Graduate Student Society and other student associations across B.C.

For more information on GrasPods, visit their website at graspods.com and follow them on Twitter and Instagram at @GrasPods.



# Service spotlight: BC Cancer Libraries & **Cancer Information Centres**

The BC Cancer Libraries and Cancer Information Centres are a system of specialized libraries that provide a diverse array of tools and resources, offering knowledge-bridging services and knowledge translation. In addition to providing a valuable service for patients and the public, the library team also supports BC Cancer staff, researchers and clinicians to provide up-to-date and evidence-based resources to help inform patient care and advance cancer knowledge. The BC Cancer library system consists of one central library located inside the BC Cancer Research Centre and branches in Victoria, Surrey, Abbotsford, Kelowna and Prince George. Initially opened as a physician collection in 1954, the library expanded its resources and services to the public in 1977 and became the first patient information library of its kind in Canada.

"The Library is excited to collaborate on existing and new BC Cancer initiatives and work towards enhancing our services and resource collections in support of continued research excellence," says Chantalle Jack, Provincial Library Leader. "As users become more proficient with online searching, they are frequently contacting the library



for assistance with more complex inquiries. Librarians are knowledgeable of and skilled in using tools and strategies to find, access and search databases, grey literature, clinical trials and other sources required for research and data sharing."

In 2019, librarians spent more than one thousand hours answering 1,618 reference and literature search questions from BC Cancer staff, clinicians and researchers, including one inquiry that took 25 hours to complete. At the same time, 1,031 items were borrowed by BC Cancer staff, researchers and clinicians. The library also participated in the inaugural Research Challenge program and presented at the 2019 BC Cancer Summit.

Beyond books, the library and information centres team offers individual and group training, document delivery and access to a host of online material ranging from databases and journals to e-books and AV materials. Highly regarded and authoritative databases such as Medline, EMBASE, Cinahl, UpToDate and the Cochrane Library can be accessed through the library as well.

For more information on the BC Cancer Research Library and Cancer Information Centres, visit bccancer.bc.ca/

# Dr. Leah Lambert pushes to improve the circle of care

Dr. Leah Lambert knows cancer care doesn't always follow a straight line. The registered nurse with a PhD in nursing is focused on improving the patient journey and is working to erase barriers as breast cancer patients transition through their cancer care from diagnosis through to follow-up care with their primary physicians. Working as part of an interdisciplinary team on research and health systems, she has helped outline improvements in care which has led to better patient outcomes and system performance. Her studies aim to determine how to effectively provide quality and efficient health services and illustrates how exceptional person-centred care is possible throughout the cancer journey.

> In 2019, Dr. Lambert completed her PhD and began her postdoctoral fellowship with BC Cancer, highlighting the important work nurses provide in recognizing and responding to individual needs and circumstances—an example of BC Cancer's commitment to person-centred care.

> > With the next chapter still left to be written, Dr. Lambert pencils down her predictions for the future of research.

#### What are your thoughts on the future of cancer care?

So many opportunities exist for nursing to make meaningful contributions in shaping cancer care from a health systems and policy perspective. To prepare for the challenges ahead, it is critical that we work collaboratively. Nurses have always played an important role in improving both experiential and illness outcomes for people affected by cancer. Evidence indicates that patient safety throughout the cancer care system is significantly improved by the frequency with which patients have a positive connection with nurses. Nurses are attuned to patient wellbeing and can proactively intervene with information, support and assistance navigating health systems before concerns cause patient distress.

# Where have you seen the most significant progress in cancer research since the beginning of your career?

BC Cancer has been at the forefront of innovative research that has led to major advances not just in cancer treatment but across the full spectrum of a cancer journey. From genomic discoveries to improving end-of-life care, it is hard to single out just one area of significant progress. Even the smallest new learning can lead to exponential advancements; it's what we do with these learnings within our cancer system that will be critical to improving care and enacting change.

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

One of the most pressing challenges for cancer research is translating research discoveries into clinical practice. The transition from bench to bedside is critical to ensuring research advancements are directly relevant to the patients we work hard to support. Patients are at the heart of everything we do and we cannot lose sight of who is on the receiving end of these advancements in cancer research.

20

From a health systems perspective, optimizing health services and delivery of care using a multidisciplinary approach that is responsive to patient needs is critically important. Increasingly complex and personalized treatments pose a challenge in understanding what the long-term effects are for survivors. I believe this will continue to be a significant focus of future research efforts.

#### What advice would you offer to young scientists?

Choose to engage in work that you are passionate about and is personally meaningful to you. Maintain a spirit of curiosity that will carry you through the inevitable challenges of conducting research within complex healthcare and academic environments. Establish relationships not only with those in your field, but also with people outside your inner circle. The future success of our healthcare system will depend on the strength of multidisciplinary teams and breaking down the historic silos.

# Medical resident spotlight: Dr. Erica Tsang searches for solutions for pancreatic cancer

Dr. Erica Tsang is taking a deep dive into one of the most lethal types of cancer. Some of her work has included exploring the genetics of patients with early-onset pancreatic cancer to better understand how the disease begins and examining outcomes for advanced pancreatic cancer patients who are taking on new treatments after first-line therapies fail. This work, conducted with BC Cancer medical oncologist and clinical researcher Dr. Daniel Renouf, is critically important to putting the pieces together on a cancer that is still considered a puzzle to researchers and clinicians. It is estimated that in 2019, 785 British Columbians were newly diagnosed with pancreatic cancer.

In 2019, during her medical oncology residency training, Dr. Tsang published four first author papers. She worked collaboratively with BC Cancer oncologists on projects focused on characterizing the treatments and outcomes of patients receiving second-line, or alternative, treatments for pancreatic cancer. She also worked with the Personalized OncoGenomics (POG) program and examined the prevalence of actionable targets, treatments and outcomes in patients with lung cancer.

As the window into the future gets clearer for her, Dr. Tsang paints a picture of what is yet to come.

What are your thoughts on the future of oncology? One of the most exciting aspects of oncology is the pace of advancement of our treatments. All our work is devoted towards the common goal of improving outcomes for our patients, including enhancing their quality of life and prolonging survival with cancer. Importantly, there has been a movement towards incorporating patientreported outcomes, which is important to understanding how cancer treatments impact our patients' quality of life. There is also a tremendous amount of excitement in unlocking the potential of genomics and targeted cancer therapies.



Where have you seen the most significant progress in cancer research since the beginning of your career? Although I am still in training, there has been remarkable progress in genomics and targeted cancer therapies in recent years. Here at BC Cancer, the POG program represents an impressive collaboration between clinicians, researchers and bioinformaticians, in working to better understand cancer genomics and identify potential treatment targets.

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

In Canada, we are privileged to have a public health care system with equitable access to care. At the same time the financial cost of cancer care is rising. New and targeted therapies have the potential to be more effective but also more expensive. As a health system, we must find a way to balance the increasing benefits of novel therapies with their costs.

What advice would you offer to young researchers? The most important advice I can give is to find great mentors. I have been very fortunate to be supported by incredible mentors and supervisors throughout my clinical and research training and am forever indebted to them.



# Scientist spotlight: 2019 highlights of distinguished scientist Dr. Connie Eaves



2019 was a year of multiple milestones for Dr. Connie Eaves, co-founder of BC Cancer's Terry Fox Laboratory. In February she was recognized with a BC Cancer Long Service Award for her 45 years of service, believed to be the longest-serving BC Cancer employee of all time and in May she was inducted into the Canadian Medical Hall of Fame. In October Dr. Eaves received the Gairdner Wightman Award, which is awarded to a Canadian health researcher whose career has demonstrates extraordinary leadership and exceptional science. To cap the year, she was listed as one of Chatelaine Magazine's Women of the Year for her award-winning research on stem cells, leukemia and breast cancer. Dr. Eaves' work over the past 50 years has been a team effort carried out jointly with her husband, Dr. Allen Eaves, now emeritus. Their research has led to meaningful insights into the cells that produce leukemia and breast cancer in people, including uncovering chemotherapy resistant cancer stem cells and the presence in some types of leukemic patients of normal blood stem cells where these cells had not been previously detectable. Such discoveries have spurred the development of new treatments for these cancers. Many of the pioneering research methodologies generated they have developed have also become "gold standards" globally, facilitating research around the world.

Dr. Connie Eaves has been described by The Globe and Mail as "a stem-cell trailblazer and mentor", who has supported the development of over 100 trainee researchers, many of them women, in the fields of stem-cell and cancer biology. As the incoming President of the National Cancer Institute 25 years ago, she played a leadership role in establishing breast cancer research as a national priority in Canada. She has also worked tirelessly to advocate for more women in the fields of science, technology, engineering and mathematics (STEM)—an area that has also been a focus of her attention for several decades. Her passion in this regard is to endow young researchers with confidence and curiosity so that they can fulfill their dreams.



# Outstanding trainee publications 2019

The office of the vice president, 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. The papers were evaluated in three categories: Clinical, Basic and Health Services and Population Health Research. The Program Evaluation Committee reviewed 35 applications and granted four awards.

## Congratulations to the following recipients:



#### **Clinical Research (one award):**

**Dr. Lucia Nappi (Medical Oncology)** titled: "Developing a Highly Specific Biomarker for Germ Cell Malignancies: Plasma miR371 Expression Across the Germ Cell Malignancy Spectrum". \$1000.00 Award



#### **Basic Research (two awards):**

**1st – Patrick Coulombe (GSC**) titled: "Endothelial Sash1 is required for Lung Maturation through Nitric Oxide Signaling". \$1000.00 Award



**2nd – Dr. Tomohiro Aoki (LCR)** titled: "Single cell transcriptome analysis reveals disease-defining T cell subsets in the tumor microenvironment of classic Hodgkin lymphoma". \$500.00 Award



#### Health Services/Population Health Research (one award):

**Dr. Adam Raymakers (CCR)** titled: "Health-related quality of life data in oncology drug reimbursement submissions in Canada: a review of submissions to the pan-Canadian Oncology Drug Review". \$1000.00 Award

# Biology and genetics

## Scientists identify a possible treatment strategy for a deadly childhood cancer

Rhabdoid tumours (RTs) are rare and highly aggressive pediatric cancers typically diagnosed before the age of two. These invasive tumours spread rapidly throughout the infant's body and even with surgical interventions and aggressive chemotherapy, the outcome is often devastating. With a four-year survival rate of just over 20 per cent, novel therapies are urgently needed to help save the lives of children with RTs.

Using the power of genomics to decode the biology of RTs, scientists at the Canada's Michael Smith Genome Sciences Centre at BC Cancer (GSC) have potentially identified a novel therapeutic strategy. In a study published in Cell Reports, researchers conducted an extensive analysis of RTs from different anatomical locations, allowing them to classify all RTs into five distinct subgroups. And some patients falling into one of these groups may be candidates for a new treatment method.

While nearly all RTs are caused by loss of a protein called SMARCB1, they often show diverse clinical and biological characteristics, including multiple organ sites in which they occur. So far, RTs have been broadly classified into brain and non-brain types. In 2016, scientists at the GSC employed genomics technologies to extensively study non-brain RTs from the Children's Oncology Group in the U.S., while researchers at the German Cancer Research Center (DKFZ) in Heidelberg carried out a similar study of brain RTs. The two groups independently showed that RTs, even within one anatomical location, are diverse, implying that classifying RTs based on anatomical location alone was likely not accurate or useful.

To better understand biological relationships among RTs from multiple anatomical locations, researchers at the GSC and the DKFZ joined forces, working together to combine and analyze their data, studying the largest cohort of RTs to date. The study was co-led by Dr. Marco Marra, distinguished scientist and director of the GSC and by Dr. Marcel Kool, a senior researcher at DKFZ. Their collaboration proved to be a fruitful one, leading to discoveries with direct implications for a novel treatment strategy.



#### **Biology and genetics continued**

By profiling the genomes, epigenomes and transcriptomes from 301 RTs from multiple anatomical locations, their work revealed that not only were tumours from the same anatomical location diverse, but in some cases, brain RTs were actually more similar to tumours in distant locations than they were to other RTs in the brain. Digging deeper, the team identified five distinct subgroups. Being able to classify tumours into distinct subgroups is important—the more we learn about each subgroup, the better we can tailor cancer treatment based on key tumour characteristics.

Upon further examination of the RT subgroups, the team discovered that some RTs appeared to be interacting extensively with the immune system. Within the tumour tissues, they observed the presence of immune cells, called cytotoxic T cells, which play an important role in eliminating cancer cells. The team further corroborated their findings based on genomic data with extensive validation experiments. Because these traits have been seen in other cancer types that respond well to a particular type of immune-based treatments called immune checkpoint inhibitors, this discovery has raised a hypothesis that immune checkpoint inhibitors may be of utility for a subset of RT patients.

The unique setting of the GSC embedded within a cancer clinic allows for meaningful collaborations between scientists and clinicians. The hypothesis raised in this study needs to be tested through such collaborations. And the search for improved cancer therapeutics is already underway. The work has been presented to oncologists in the Children's Oncology Group in the US and at the Terry Fox PROFYLE (PRecision Oncology For Young peopLE) Initiative.

While this study provides the groundwork for further validation, research and identification of potential therapeutics for different RT subgroups, there are many remaining questions that dedicated researchers are striving to solve.

#### A genetic explanation for lymphoma patients that can't be cured by standard treatment

The most common form of non-Hodgkin lymphoma, known as Diffuse Large B-cell Lymphoma (DLBCL), is considered a curable disease with the exception of a subset of patients for whom the standard treatment is not effective. But scientists at the GSC have uncovered a genetic explanation for why some patients have poor prognosis.

Like all forms of cancer, DLBCL is the result of DNA mutations. And these patients have particularly damaging ones termed "double hit". Unfortunately, some patients test negative for double hit mutations using a standard laboratory test called fluorescent in-situ hybridization (or FISH) yet still respond poorly to standard treatment. This means they may not receive the intensive treatment they require.

In a study published in Blood, Dr. Ryan Morin, senior scientist at the GSC and associate professor at SFU with Dr. David Scott from the Centre for Lymphoid Cancer, with their team employed DNA sequencing to shed light on these discrepancies. Their results revealed the presence of double hit mutations in samples that had tested negative by FISH. The study demonstrated that testing by FISH may miss up to 19 per cent of patients with double hit mutations.

"We are systematically under-identifying patients that have the genetic event that predicts poor outcomes," said Dr. Laura Hilton, a post-doctoral fellow in Dr. Morin's group and lead author on the study. "Our findings reveal why."

The group found that these patients can more reliably be identified by looking for a particular cellular signature. Fortunately, there is a laboratory test called a NanoString that can be used to identify the signature, allowing clinicians to more accurately determine which patients may need more aggressive treatments.

Exactly what those treatments should be remains a current area of research, but clinical trials show that a

more intensive drug regimen may be effective. By identifying more of these cases, further clinical trials will be made possible.

# EZH2: genetic and molecular mechanism for immune escape in DLBCL

The BC Cancer research team led by Drs. Steidl and Scott at the Centre for Lymphoid Cancer (CLC) has recently unraveled a genetic mechanism underlying immune evasion in the most common subtype of lymphoma and published their results in Cancer Discovery. Major histocompatibility complex (MHC) molecules are proteins on the cell surface that function to present antigens derived from pathogens or tumour cells to T cells, thus important in inducing immune activity. MHC expression is frequently lost in DLBCL; however, the mechanism of MHC expression loss remains to be delineated. In their study, the team performed genomic, transcriptomic and immunophenotyping analyses using a populationbased cohort of DLBCL. From these analyses, the team has discovered that loss of MHC II is observed in cancers originating from the centroblast-rich dark zone of the



germinal center and is associated with inferior outcome. In MHC negative tumours, significant reduction in tumour infiltrating T cells was observed compared to MHC positive tumours in GCB-DLBCL, indicating that MHC expression impacts the composition of the tumour microenvironment (TME) and immune reactivity. The team further showed that EZH2 mutations were highly enriched in MHC negative tumours. To investigate the effects of EZH2 mutations on MHC expression, a functional in vitro assay was performed. The results showed that treatment with EZH2 inhibitors restored MHC expression in EZH2-mutated DLCBL cell lines. In collaboration with Weill Cornell Medicine, which developed an EZH2-mutant mouse model, the team showed significant reduction in MHC expression as well as T cell infiltrates in the tumours of the mutant mice compared to wild type mice, suggesting an important regulatory function of EZH2 in MHC expression and TME immune cell composition. Their data provide mechanistic insights into immune escape in GCB-DLBCL and suggest potential novel complementary therapeutic approaches combining immunotherapy and epigenetic reprogramming.

# Genome sequencing helps prioritize cancer treatment options

Every tumour is as unique as the patient from which it came. Everyone carries genes inherited from their parents—the "normal" or inherited genome. Mutations to the inherited genome can influence cancer development, progression and response to treatment. Cancer cells in turn develop additional mutations, with implications for the prognosis and treatment of the disease. Cancer genomics aims to decode each patient's normal and cancer genomes to enable clinicians to determine the best course of treatment for each individual.

This is the approach taken by the Personalized OncoGenomics (POG) program at BC Cancer, led by medical oncologist Dr. Janessa Laskin and GSC director Dr. Marco Marra. POG employs whole genome sequencing to analyze both the inherited and the cancer genomes of individual patients. In a study published in Cold Spring Harbor Molecular Case Studies, the POG team has again demonstrated the power of this approach to inform personalized cancer treatment planning.

This study demonstrates the immense potential of integrating whole genome sequencing into cancer treatment planning. Standard genetic testing, which involves sequencing only a subset of genes within a tumour, would not have detected a specific DPYD mutation. Whole genome sequencing allowed for the identification of a mutation that could be exploited, allowing the team to prioritize treatment with 5-FU over other treatment strategies.

## Improving a crucial research tool for deadliest form of brain cancer

Despite decades of research and countless clinical trials, a diagnosis with glioblastoma multiforme (GBM) essentially remains a death sentence. Even with surgical removal of tumours followed by radiation and chemotherapy, 90 per cent of patients succumb to the disease within five years.

Compiled by GSC scientists and published in the Proceedings of the National Academy of Science, an extensive catalogue is now available of genome and transcriptome data comparing GBM tumours from humans as well as those from tumour model systems. This will ultimately enable improved approaches for drug screening, contributing to the search for effective treatments for people with this devastating disease.

The group also identified a potential mechanism that allows GBM tumours to evade drug treatment. Previously, the ability of GBM to become drug resistant has been attributed to the tumours acquiring a hypermutated phenotype following treatment with the drug temozolomide (TMZ). But in this study, the group found that five out of the 14 TMZ-resistant GBM samples did not show this hypermutated phenotype, leading them to hypothesize that another mechanism of resistance was at play, revealed by genome and transcriptome analyses: increased expression of a gene encoding a DNA repair protein (MGMT). These findings may help guide treatment strategies in patients with recurrent GBM.

The wealth of information provided by this research is extremely valuable for the future study of GBM, particularly in the accurate interpretation of studies relying on this disease model and understanding its limitations. The in-depth comparison of human, laboratory and mouse GBM cells will enable researchers to avoid biases introduced by the experimental conditions.

## Biology and genetics continued

#### Progress in single cell sequencing Breast cancer—groundbreaking study for large-scale population analysis over thousands of cells

Dr. Samuel Aparicio and colleagues published a new ground breaking high-throughput method for amplication-free single-cell whole genome sequencing in the high impact journal Cell. The method can be scaled up to analyze tens of thousands of cells from different tissues and clinical sample types. A central problem in cancer control is the capacity of tumour cell populations to evolve over time, contributing to cancer cells spreading to other locations, treatment resistance, evasion of the cancer patient's immunity and differences found within the tumour tissue itself due to single cells evolving and changing over time in different manners from each other. This new approach allows researchers to decode cell population dynamics from genomes, transcriptomes and proteomes of single cells, ultimately translating these findings into better combinations of treatment and identifying factors causing treatment resistance.

In a second study, Dr. Aparicio and colleagues examined the effect of tissue dissociation on gene expression, cell stress and death. They published a study in the journal Genome Biology showing stress-related and heat shock genes are induced during dissociation with standard tissue digestion methods, which may confound single cell RNAseq analysis. In addition, they showed cell type-specific response to tissue dissociation by certain enzymes, which may further affect interpretation of single cell RNAseq data. They detailed an alternate dissociation method active at low temperatures, which preserves the transcriptome and can enhance capture of normal cells in a tissue-dependent manner. The stress responses and capture bias identified has far-reaching significance for researchers studying not just cancers but also any solid tissue types.

# Single cell approach to decipher the hodgkin lymphoma (HL) ecosystem

Hodgkin lymphoma (HL) is the most common lymphoma subtype in children, adolescents and young adults. HL tumours present unique morphology, which is dominated by normal immune cells within the tumour microenvironment (TME) with only a minor (~1 per cent) population of malignant Hodgkin and Reed-Sternberg (HRS) cells. While there is some evidence that rare HRS cells recruit immune inhibitory cells in their vicinity to create a tumour-favourable niche, comprehensive profiling of TME components or complex interactions between HRS cells and TME are yet to be explored. The recent study led by Dr. Steidl at the BC Cancer Centre for Lymphoid Cancers (CLC) included single-cell RNA sequencing (scRNAseq) using 22 HL specimens donated by patients and five reactive lymph nodes (RLN) from healthy donors. Application of a single cell sequencing approach led to the identification of a novel subset of T cells with substantial immunosuppressive functions, contributing to immune escape in HL. Knowledge about functional and spatial characteristics of the HL TME will be critical in development of novel immunotherapies and biomarkers which will guide treatment decisions to achieve precision medicine. This is the first study comprehensively profiling the HL ecosystem at single cell resolution and the results were published in Cancer Discovery.

#### **Biology and genetics continued**

## Probabilistic cell-type assignment of single-cell RNA-seq for tumour microenvironment profiling

Dr. Sohrab Shah and colleagues developed a new tool called CellAssign that leverages prior knowledge of cell-type marker genes to annotate single-cell RNA sequencing data into predefined or *de novo* cell types, which was published in Nature Methods.

CellAssign fills an important role in the sequencing analysis toolbox for researchers. Dr. Shah's group anticipates the CellAssign approach will help unlock the potential for large-scale population-wide studies of cell composition of human disease and other complex tissues through encoding biological prior knowledge in a robust probabilistic framework.

This work was funded by CIHR, BC Children's Hospital, Canadian Statistical Sciences Institute, UBC Data Science Institute, Susan G. Komen, BC Cancer Foundation, Terry Fox Research Institute, Canadian Cancer Society, Cancer Research UK, Memorial Sloan Kettering and the Allen Frontiers Group

# A high-throughput protocol for isolating cell-free circulating tumour DNA from peripheral blood

The advent of next-generation DNA sequencing has enabled researchers to develop assays for diagnosing and managing a variety of diseases, including cancer. Liquid biopsies are one such technique that can assay for circulating cell-free tumour DNA (ctDNA). It is non-invasive and can help clinicians in assessing disease progression and monitor treatment response. Standard isolation of ctDNA involves the separation of plasma by centrifugation followed by column or magnetic bead-based purification of nucleic acids. While magnetic beads are more amenable to automation on liquid handlers, the upstream centrifugation remains largely manual and limits scalability. Researchers at Canada's Michael Smith Genome Sciences Centre at BC Cancer developed a magnetic bead-based ctDNA isolation method that eliminates centrifugation steps to

allow ctDNA purification directly from whole blood in 96-well plate format. Furthermore, this automated method minimizes manual handling of patient blood, lowering the risk of sample swaps and exposure to staff of blood borne infections.



# Health economics & cancer control

#### Tenth anniversary of the Canadian Centre for Applied Research in Cancer Control (ARCC)

2019 marked the 10th anniversary of the Canadian Centre for Applied Research in Cancer Control (ARCC). ARCC is a world first research centre in health economics, services, ethics and policy research in cancer. It is national in scope—a hybrid model of a geographically distributed research centres linked by a strong pan-Canadian network. Generously funded by the Canadian Cancer Society since 2009, ARCC's mission is to improve cancer control and the delivery of cancer care through interdisciplinary, pan-Canadian leadership in health economics, services, policy and ethics research, education and knowledge translation. Over the last decade, ARCC has evolved to become a network of over 1200 researchers, clinicians, decision makers and trainees involved in applied cancer control work. ARCC supports its network through knowledge translation activities (annual conferences,

webinar series and cc-arcc.ca) and providing financial support such as travel awards, studentships and seed grants. During 2019, ARCC undertook a large range of pan-Canadian research projects examining: economic and ethics issues relating to precision medicine, gene therapies and incidental genomic findings; methods for patient and public engagement in cancer system decision-making; pan-Canadian analyses of cancer care costs; methods for using real world effectiveness data for funding decisions; and using big data to inform optimal models of care for cancer survivors.

ARCC is a pan-Canadian organization directed by Dr. Stuart Peacock and includes BC Cancer researchers Drs. Dean Regier and Mary McBride; their work includes researchers from cancer agencies and universities across the country.



# Screening & diagnosis



#### Using artificial intelligence and whole genome sequencing to make accurate cancer diagnoses.

Cancers are diseases of the genome. Imagine if, armed with the genetic data from the genes of tens of thousands of other consenting cancer patients, we could train computers to provide fast and accurate diagnoses?

A study led by scientists at Canada's Michael Smith Genome Sciences Centre at BC Cancer (GSC) and published in the Journal of the American Medical Association (JAMA) Network Open demonstrates that, yes, computers can provide cancer diagnosis with precision, including for cases that had previously failed human assessment.

This paper shows a novel use of whole-genome sequencing and machine learning techniques-specifically, measuring expression of all of the genes in the genometo provide a cancer diagnosis with guantifiable confidence.

"Our analysis highlights the progress machine learning approaches have made in fields previously considered to be the domain of highly skilled human expertise," says Dr. Steven Jones, co-director and head of Bioinformatics at the GSC and principal investigator for the study. "It also demonstrates where computational approaches can not only augment but improve upon clinical decision making."

In this study, scientists trained computers to look across 17,688 genes in the human genome and generate a diagnosis, with a confidence score, out of a set of 40 different cancer types. They found that the method had approximately 99 per cent accuracy in identifying cancers with mixed tissue types and had a success rate of 80 to 86 per cent in the most challenging cases-cancers of unknown origin and advanced cancers—that had already failed human assessment or were extremely difficult to diagnose by a human expert.

#### **Screening and diagnosis continued**

Machine learning methods are only as good as the data they have to train on. Efforts are needed to properly curate and sequence rare and advanced cancers so that scientists can better incorporate and improve pathologist's ability to diagnose them. Future research will examine the ability to leverage genomic data for other manually-driven cancer analysis tasks, such as alignment with appropriate therapies.

#### A new genetic link discovered in familial pancreatic cancer

Dr. Kasmintan Schrader and colleagues published the report "Base excision repair deficiency signatures implicate germline and somatic MUTYH gene aberrations in pancreatic ductal adenocarcinoma and breast cancer oncogenesis" in Cold Spring Harbor Molecular Case Studies, showing that individuals can carry inherited genetic changes that can sometimes impact the pattern of mutations that can arise in their tumour. This report highlights the potential utility in understanding carrier status for cancer susceptibility genes that may impact the mutational signatures identified in a person's cancer and also draws a link between pancreatic cancer and germline mutations in the MUTYH gene. Funding for this work was generously provided by the BC Cancer Foundation, Genome BC and CIHR.

## Development of a prototype low-cost early melanoma detector

Melanoma is the deadliest form of skin cancer; however, it is often difficult to differentiate from a benign mole. This year, a BC Cancer team led by Dr. Tim Lee has revealed their work on a handheld melanoma detection device that could allow for efficient, low-cost and widely accessible melanoma screening. The device's design and construction were carried out by a team of BC Cancer researchers and it was tested in collaboration with the UBC Dermatology Skin Care Centre. The device is an optical probe that shines laser light onto the skin and measures the changes in the light as it scatters away. The probe reads an aspect of light called optical polarization, the orientation of light waves, using new technology that could be refined for other kinds of cancer imaging.

This is the first prototype of a low-cost melanoma detection device that could allow for widely accessible melanoma screening, especially important for rural areas. The initial findings published in the journal SPIE indicate a strong ability to separate melanoma from benign lesions, which could improve the speed and efficiency of the melanoma screening process in our healthcare system. This is an important development that provides proof of feasibility for a low-cost device for this purpose. It is also the realization of innovative optical polarization technology that could be refined for other kinds of cancer imaging. This work was funded by the Natural Sciences and Engineering Research Council of Canada and the Canadian Dermatology Foundation.

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# Treatment

#### A new therapeutic approach for pancreatic cancer

Dr. Shoukat Dedhar and colleagues published a seminal paper in the high impact journal Gastroenterology demonstrating a key role of KRAS oncogene hypoxia driven Carbonic Anhydrase IX in the growth and metastatic dissemination of pancreatic cancer. Dr. Dedhar's study indicates a new potential therapeutic strategy for the treatment of pancreatic cancer, which is very difficult to treat and has very poor outcomes. This work is the foundation for the launch of a new Phase 1b clinical trial in pancreatic cancer patients currently being carried out at BC Cancer and Princess Margaret Cancer Centre in Toronto.

# First reported trial of single-agent monalizumab (IPH2201) in solid human cancers

Cancer immune evasion is largely regulated by immune checkpoint proteins. Cancers exploit immune checkpoint pathways as important mechanisms of immune resistance. Some cancers upregulate the expression of inhibitory ligands, resulting in a state of immune tolerance/immune exhaustion and several immune suppressive pathways have been identified. Epithelial ovarian, endometrial and cervical cancers can upregulate immune checkpoints within the tumour microenvironment, abrogating an effective host immune response. As many of the immune checkpoints are initiated by ligand-receptor interactions, they can be blocked by antibodies or modulated by recombinant forms of ligands or receptors. Monalizumab can restore the function of NK cells by blocking the transduction of inhibitory signals. As monalizumab was of interest to test in patients with advanced/metastatic/ recurrent gynecologic cancers including high-grade serous ovary/fallopian tube or peritoneal carcinoma (OVA-S and OVA-R; platinum-sensitive and platinumresistant, respectively) and endometrial (END) and cervical (CX) cancers, Dr. Anna Tinker and colleagues undertook a multicenter Phase I dose-ranging trial of single-agent monalizumab, testing three prespecified dose levels. The results of this study were published in Clinical

Cancer Research and showed that Monalizumab is well tolerated in patients with pretreated gynecologic cancers. Short-term disease stabilization was observed. Future studies should assess combinations with other agents, including immunotherapeutics.

#### Advances in prostate cancer treatment

Dr. Kim Chi and colleagues demonstrated that the sequence of abiraterone followed by enzalutamide was superior to enzalutamide followed by abiraterone. Furthermore, patients reported quality of life was better on abiraterone than enzalutamide particularly for elderly patients. In addition, they demonstrated that patients could be genomically characterized by a "liquid biopsy" through circulating tumour DNA, which had implications on patients outcomes with treatment. This "made in B.C.", investigator sponsored, grant funded study addressed an important clinical question, where they directly compared, in the context of a randomized study, two therapies for prostate cancer and their sequence. This study was funded by Canadian Cancer Society Research Institute, Prostate Cancer Canada and unrestricted grants from Astellas and Janssen and was published in The Lancet.

In a second study led by Dr. Kim Chi, apalutamide was shown to improve overall survival in men with advanced prostate cancer when added to standard androgen deprivation therapy with a tolerable safety profile and no detriment to patients reported quality of life. Dr. Chi was the leading principal investigator for this international Phase III trial which demonstrated improved overall survival and radiographic progression free survival with the addition of the Apalutamide, a novel androgen receptor antagonist, to standard androgen deprivation therapy for men with advanced prostate cancer. Apalutamide was approved by the FDA for this use in the summer and has just been approved by Health Canada for this use. This study was published in the New England Journal of Medicine in July 2019 and was funded by Janssen.

#### **Treatment continued**

## BC Cancer scientists develop specialized laser microscope to diagnose and treat disease, without cutting skin

Dr. Haishan Zeng and colleagues developed a precision laser microsurgery treatment for cancer and other diseases. The study results were published in the high impact journal Science Advances. They utilized ultrafast laser pulses that are tightly focused to a micron-size volume of a target, such as a vessel, inside eye diseases. Because of the locally high instantaneous light power density, multiple photons will be simultaneously absorbed at the focal point (and only there) to generate heat to destroy the target. Compared to conventional laser therapy, it will be able to destroy the targets much more precisely, while leave surrounding tissues intact. In conventional laser therapy light absorption could occur along the whole light pathway, which could cause collateral damage to normal eye tissues and affect vision. This unique technology will enable visualization, selection and destruction of the treatment target. It is a true "see and treat" approach that brings personalized precision therapy. It can be used to treat skin cancer and other skin diseases. It is especially appealing to ophthalmology applications to treat melanoma in the eye and vascular eye diseases such as corneal neovascularization, diabetic retinopathy and macular degeneration. The Canadian Institutes of Health Research, National Key Basic Research Program of China, National Natural Science Foundation of China, Canadian Dermatology Foundation, VGH & UBC Hospital Foundation and BC Hydro Employees Community Services Fund funded this work.

# Molecular classification defines outcomes and opportunities in young women with endometrial carcinoma

Dr. Jessica McAlpine's study of 257 young women with endometrial cancer paves the way for a potential paradigm shift away from the use of histologic classification and clinical data alone to guide treatment recommendations and towards a molecular classification system for more accurate stratification of risk and outcomes in this patient population.





With 15 per cent of endometrial cancers arising in women less than 50 years of age in North America and two-fold higher incidence recorded in other countries, traditional treatment strategies with consequences of loss of fertility and surgical menopause may be undesired or unacceptable to young women who may not have completed childbearing or wish to avoid surgical menopause. Dr. McAlpine's research will assess the utility of the ProMisE molecular classifier developed in her lab in predicting which patients are the safest candidates for conservative treatment. This work was published in the journal Gynecologic Oncology.

# Clinical trials: evaluation of brentuximab vedotin as frontline therapy in lymphoma

The clinical investigators at the Centre for Lymphoid Cancer (CLC) have been involved in several global clinical trials and contributed significantly to outcomes research. The clinical team led by Dr. Savage at the BC CLC has contributed to the ECHELON-1 clinical trial which is a large global, randomized phase III study to compare safety and efficacy of doxorubicin, vinblastine and decarbazine in combination with brentuximab vedotin (A+AVD) with that of standard of care ABVD (AVD+bleomycin) as frontline therapy for stage III or IV classical Hodgkin lymphoma (cHL). A total of 497 patients were recruited for this study and were randomized to A+AVD (n=250) and ABVD (n=247). The results showed manageable safety and improved progression-free survival in the group of patients treated with A+AVD. This supports the introduction of this new immuno-chemotherapy as frontline therapy in treatment of advanced stage cHL patients. Dr. Savage and her team were also involved in the ECHELON-2 trial, which is another large world-wide Phase II trial evaluating safety and efficacy of brentuximab vedotin in combination with cyclophosphamide, doxorobucin and prednisone (A+CHP) in CD30+peripheral T-cell lymphomas. This global study recruited 452 patients diagnosed with CD30+ peripheral T-cell lymphomas at 132 participating sites in 17 countries over three years. The patients were

#### **Treatment continued**

assigned randomly to the A+CHP arm or the standard therapy cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) arm. Superior efficacy was observed in the patients receiving A+CHP, supporting its usage as frontline therapy for treatment of CD30+ peripheral T-cell lymphoma patients. The results from these international trials demonstrated safety and efficacy of brentuximab vedotin in lymphomas, highlighting its potential to be used as frontline therapy across various subtypes of lymphoma.

# Defining outcomes of follicular lymphoma in the modern era

Here in B.C., a population-based retrospective study was conducted by the CLC clinical team led by Drs. Sehn and Freeman. 296 patients diagnosed with advanced-stage follicular lymphoma (FL) who were treated with frontline bendamustine and rituximab (BR) and maintenance rituximab were identified using the BC Cancer CLC



database. The results of the analysis showed excellent outcome estimated at 85 per cent and 92 per cent for two year event-free survival and two year overall survival, respectively. However, progression was observed in 13 per cent of the patients. The majority of the patients who had disease progression within 24 months harboured transformation to aggressive lymphoma. It can be implied from the data that occurrence of early transformation is an indication of disease progression and poor outcome, suggesting the need for identification of biomarkers to help manage this disease and further improve outcomes for these patients. To this end, the clinical and research teams at the BC Cancer CLC are currently leading a large national multi-centre genomic study, which is funded by Genome Canada, CIHR and BCCF to identify targetable biomarkers associated with progression and relapse.

#### **Treatment continued**

#### Re-evaluation of clinical outcome of ALK-negative Anaplastic large-cell lymphoma

Anaplastic large-cell lymphoma (ALCL) comprises a small proportion of adult lymphomas. Two chromosomal translocations involving DUSP22 and TP63 genes, which are mutually exclusive and often observed in Anaplastic lymphoma kinase (ALK)-negative ALCL are known to have clinical significance. The BC Cancer clinical team led by Dr. Savage conducted another population-based study which investigated the clinical features and outcome of ALCL. This is one of the largest studies evaluating the prognostic impact of DUSP22 gene rearrangements in ALK-negative ALCL and included 62 ALK-negative ALCL cases which were identified in the BC Cancer CLC database. The results of this comprehensive analysis showed the DUSP22 rearrangement in 19 per cent of cases, the TP63 rearrangement in only two per cent and triple negative, which lack any known rearrangements in the rest of 79 per cent. In contrary to the previous reports of favourable outcome in ALK-negative ALCL with the DUSP22 rearrangement, they observed that some cases with the DUSP22 rearrangement displayed high-risk clinical features and had an aggressive course, highlighting the need to identify this subset of high-risk patients and develop novel biomarkers. Dr. Savage and the research team at the BC Cancer CLC are currently conducting RNAseq analysis to determine if there is a biological difference in those with an aggressive course.

The data generated from the clinical research team at the CLC will continue to have significant impact on clinical practice and management of lymphoma.

## Promising findings in pancreatic cancer study highlight importance of whole genome, transcriptome sequencing

A study led by BC Cancer researchers identified an effective treatment of advanced pancreatic cancer with a drug often used for lung cancer. Published in Clinical Cancer Research, the study found a small group of patients whose pancreatic cancer carried a rare trait that was potentially treatable with a targeted therapy often used to treat lung cancer. After receiving treatment, those patients' health improved.

"Pancreatic cancer often comes with a poor prognosis. With this insight we have reason to be optimistic," said BC Cancer medical oncologist and clinician-scientist Dr. Daniel Renouf. "After looking into the genetic structure of the pancreatic tumours, in several cases we identified a unique trait that we had seen before in other cancer types that was potentially treatable. In these relatively rare instances, we have seen rapid and remarkable results. This is a breakthrough in terms of the potential of precision medicine for pancreatic cancer."

As part of this study, 47 British Columbians with pancreatic ductal adenocarcinoma received comprehensive whole genome and transcriptome sequencing and analysis. Three were identified to have a KRAS wild-type mutations and were positive for gene fusions involving ERBB3 ligand NRG1. Two patients with gene fusions involving NRG1 received afatinib treatment and demonstrated a significant and rapid response while on therapy.

Support for this research came from the BC Cancer Foundation, BC Cancer's Personalized OncoGenomics (POG) program and the Terry Fox Research Institute's Enhanced Pancreatic Cancer Profiling for Individualized Care (EPPIC) National research program, as well as Pancreatic Cancer Canada.

POG sarcoma- therapeutic implications of the genomic landscape of adult metastatic sarcoma

A team led by Dr. Xiaolan Feng published a systematic analysis of whole genomes and transcriptomes in 43 patients with 19 distinct types of advanced metastatic sarcoma in the journal JCOÆ Precision Oncology. The study was conducted as part of the POG program at BC Cancer, demonstrating the clinical utility of Personalized OncoGenomics in metastatic sarcomas. This research helps to identify molecular aberrations that are potentially suitable for clinically approved targeted therapy or theoretical targeted therapy under investigation in clinical trials. Research showed that large-scale structural variant aberration is the primary mechanism of mutagenesis in metastatic sarcoma. 17p11-12 was found to be the most frequent/recurrent amplification that is specific to sarcoma and further speculated potential oncogenic targets within this amplicon. Their research was also able to report on several novel mutational signatures in metastatic sarcomas, one of which is homologous recombination deficiency signature that may be associated with superior sensitivity to double-stand DNA-damaging agents in several sarcoma subtypes. This supports the use of genomic data in precision medicine and clinical trial design to improve care for patients with metastatic sarcoma.

## Advances in radiation therapy development of new PET imaging methods

Dr. François Bénard published a report on the development and evaluation of new 18F-Labeled radioisotope for PET imaging in a clinically relevant xenograft model of melanoma in the Nature journal Scientific Reports. Dr. Bénard's research group has been recognized nationally and internationally for their work developing and evaluating radiopharmaceuticals. In 2019 his group also published two important studies on the development and clinical evaluation of 18F imaging isotopes for use in prostate cancer in the Journal of Nuclear Medicine from Kuo et al. "One-step 18F-labeling and preclinical evaluation of prostate specific membrane antigen trifluoroborate probes for cancer imaging" and Rousseau et al. "A prospective study on [18F]-DCFPyL PSMA PET/CT imaging in biochemical recurrence of prostate cancer".

#### **Treatment continued**



#### BC Cancer Excellence Award for Kelowna brachytherapy

Dr. Juanita Crook was presented with a BC Cancer Excellence Award at the BC Cancer Summit. These awards highlight the incredible individuals and teams who work to ensure that British Columbians receive world-class, patient-centred cancer screening, treatment and support, or benefit from new discoveries that are helping change the face of cancer.

Brachytherapy is important in a number of cancer treatments. Dr. Crook's team is recognized provincially and internationally for their contributions to the field. Examples of the importance of this technique include breast brachytherapy, which can provide post-lumpectomy partial breast radiation to women living at a distance from BC Cancer in a single procedure completed in less than a day, saving them the cost and inconvenience of being away from home for several weeks. Penile brachytherapy can spare men from having a surgical penectomy to treat their penile cancer. High-dose rate brachytherapy for prostate cancer uses a reusable source rather than permanently implanted seeds and allows faster recovery from treatment.

#### CARA pilot study: first 20 breast cancer patients treated using novel BC Cancer technology to reduce side effects in Radiation Therapy

The treatment pilot study of the novel carbon fibre breastpositioning device (CARA) was completed in October 2019, with the first 20 patients successfully treated with this technology in both Vancouver and Kelowna. The unique carbon-fibre CARA device was engineered designed and manufactured at BC Cancer – Vancouver and has been patented by BC Cancer. This device is designed to reduce heart, lung, skin and normal tissue dose for patients undergoing radiotherapy for breast cancer in the supine position, without perturbing the dose to the target volume. The device enables treatment in a comfortable position and reproducible targeting of the treatment volume. CARA has now been demonstrated to be safe for treatment and to effectively reduce the volume of lung and normal tissue irradiated during treatment without compromising target coverage. The device also removes skin folds that can lead to severe skin reactions in some patients. The team led by Dr. Cheryl Duzenli believes that CARA will set a new standard of care in breast positioning for radiation therapy. This work was funded by the Canadian Cancer Society and represents a tri-disciplinary achievement between medical physics, radiation therapy and radiation oncology at BC Cancer – Vancouver and Kelowna.

Dr. Alanah Bergman—first "Dynamic Wave Arc" radiation therapy treatment in Canada delivered at BC Cancer – Vancouver

Radiation therapy has seen exciting forward leaps in treatment delivery technology over the last 10 years. In 2017, BC Cancer – Vancouver acquired a Vero 4DRT radiotherapy platform with generously donated funds secured by the BC Cancer Foundation. One of the features of this radiotherapy unit is that it is capable of delivering complex dynamic radiation therapy beam trajectories to patients to reduce the dose to nearby healthy tissues. This technology involves the simultaneous rotation of the beam around the patient around two axes (gantry and floor-ring) plus beam shaping while the beam is turned on. This clinical mode is called "Dynamic Wave Arc". In October 2019, the first patient (pelvic bone) was treated with this type of technology in Canada. This is an important milestone for BC Cancer, for the Canadian radiotherapy community and most importantly, for patients whose curative treatment options would otherwise be very limited due to proximity of sensitive organs to the tumour. Funding for equipment, software and operational funding for five years was provided by the BC Cancer Foundation.

#### Dr. Fatimah Alfaraj—Radiation Oncology BC Cancer – Prince George

Dr. Fatimah Alfaraj from Radiation Oncology at BC Cancer – Centre for the North published two studies in collaboration with colleagues from Toronto on treatment outcomes in oropharynx cancer patients who did not complete planned curative radiotherapy, the first published in the journal Oral Oncology and the second study published on the development and validation of a prediction-score model for distant metastases in major salivary gland carcinoma; the study data for the prediction-score model was international, including B.C. provincial data, with the analysis done in Toronto. Dr. Alfaraj is the second author of the study published in the Journal of Clinical Oncology.

#### Dr. Robert Olson—Radiation Oncology, BC Cancer – Prince George

Results of an international SABR-COMET Phase II trial were published in The Lancet. This randomized study demonstrated that stereotactic radiotherapy resulted in patients living longer without a recurrence of their cancer and gave an early signal that patients may actually live longer if they receive this new type of radiotherapy. The results pave the way for a larger, more definitive trial, which is being led from B.C. Multiple Radiation Oncologists internationally contributed to this study; B.C. co-authors were Drs. Robert Olson (second author), Devin Schellenberg and Mitchell Liu. The lead centre for the study was London Health Science Centre (Ontario).

# Cancer immunology and immunotherapy

#### Cancer "stemness" and immune responses against cancer

Many cancers show characteristics of stem cell populations, such as the capacity for self-renewal. Dr. Brad Nelson, with postdoctoral fellows Dr. Alex Miranda Rodriguez and Dr. Finn Hamilton, hypothesized that some cancers may therefore adopt immunosuppressive qualities that have been previously uncovered in normal stem cell populations. By interrogating large genomic and gene expression databases encompassing thousands of patients, they found that when cancer cells are more similar to stem cells, tumours are more likely to be immunologically "cold"-or hidden from the immune system-and have poorer prognosis. Their research, published in the April 2019 issue of Proceedings of the National Academy of Science, suggests that molecular pathways involved in regulating stem cells may be targetable in order to reawaken the patient immune system to cancer and to increase the effectiveness of immunotherapies against the disease.

#### New immunotherapy CLIC-01 clinical trial opens

The BC Cancer Immunotherapy group has developed domestic capacity for CAR-T therapy as a public health effort and launched the first clinical trial of a made-in-Canada CAR-T therapy.

Patients accrued to the CLIC-01 trial are treated at Leukemia/Bone Marrow Transplant clinics in Ottawa and Vancouver with specialized manufacturing of personalized cell therapy products occurring at the Conconi Family Immunotherapy Lab in Victoria. Under the direction of Dr. Brad Nelson, Dr. Robert Holt and Dr. Kevin Hay, researchers at the Deeley Research Centre, Canada's Michael Smith Genome Sciences Centre at BC Cancer and the Terry Fox Lab, BC Cancer have established the first of its kind manufacturing facility within our public health system where, allowing access to CAR-T therapies for Canadian within the Canadian Health service, developing Canadian expertise and capacity combine for innovation in the promising CAR-T field. Establishment of this research program should facilitate development of better CAR-T therapies that work for additional kinds of cancer as well as innovative approaches for providing cellular therapy in the Canadian system. Immunotherapy researchers at BC Cancer are transforming the future of cancer research.

#### Targeting hypoxia induced carbonic anhydrase IX enhances immune checkpoint blockade locally and systemically cancer immunology research

Dr. Shoukat Dedhar and colleagues published a seminal paper showing for the first time that the effectiveness of immunotherapy with immune checkpoint blockade can be improved by altering the local microenvironment of the tumour. The work points to novel combination therapeutic approaches utilizing a potential new drug, discovered in Dr. Dedhar's lab, for the treatment of solid cancers. The paper was published in the July issue of Cancer Immunology Research and featured on the cover.



Targeting myeloid-derived suppressor cells in combination with primary mammary tumour resection reduces metastatic growth in the lungs

Myeloid-derived suppressor cells (MDSCs) are an important component of a healthy immune system and normally function to suppress the activity of immune cells after an immune response is complete. MDSCs can also respond to proteins produced by tumours, causing these cells to build-up in various tissues where they can create localized environments that protect tumour cells from attack by the immune system. Dr. Kevin Bennewith's group has found that breast tumours can cause MDSCs to accumulate in the lungs, which is a common site of breast cancer spread (metastasis). Importantly, their recently published research shows that MDSCs persist in the lungs even after surgical resection of the primary tumour. They found the MDSCs that remain in the



lungs can support the survival and growth of metastatic tumours and therefore may represent an important contributor to metastatic recurrence. Their research went on to show that MDSCs are remarkably sensitive to the chemotherapy drug gemcitabine and that treatment with a low dose of gemcitabine after surgery disrupted the pro-metastatic lung environment by decreasing MDSCs in the lungs. Overall, Dr. Bennewith's research supports the development of strategies to monitor MDSC levels in patients during therapy and to target MDSCs as a complimentary therapeutic strategy to decrease the growth of metastatic tumours.

This work was published in the journal Breast Cancer Research and concludes a substantial (seven year) pre-clinical study by Dr. Bennewith's group. Their study was funded by the Canadian Institutes of Health Research and the Terry Fox Foundation.

#### **Cancer immunology and immunotherapy continued**

#### Real world efficacy and toxicity of immunotherapy for advanced non-small cell lung cancer

Dr. Doran Ksienski and colleagues, in a collaboration between BC Cancer – Victoria, BC Cancer – Surrey and the University of Victoria, have created a database on patients treated with immunotherapy for advanced non-small cell lung cancer at BC Cancer and based on information from this database they have been able to determine the safety of immunotherapy and how long these patients live.

Programmed death-1 (PD-1) receptor inhibitors have a key role in the treatment of patients with advanced non-small cell lung cancer (NSCLC). Pembrolizumab, a humanized antibody to PD-1, has been demonstrated to increase survival compared to chemotherapy in the first line and second line setting for patients with NSCLC. Nivolumab, a fully human antibody to PD-1, increases survival in the second line setting for patients with NSCLC.

Benefits and harms reported in clinical trials do not always mirror real life. Clinical trial patients tend to be younger and have fewer comorbidities compared to the general patient population. Although well tolerated, PD-1 inhibitors are associated with a unique spectrum of toxicities called immune-related adverse events.

Dr. Ksienski's team is working to better understand the incidence of adverse events with PD-1 inhibitors in the everyday clinical setting to provide informed consent, especially when multiple treatment options exist, to minimize harm to patients, facilitate early recognition and treatment of irAE and avoid early discontinuation of potentially lifesaving therapies.

This work has been published the journals Lung Cancer and Clinical Lung Cancer. The BC Cancer Foundation and AstraZeneca Canada provided funding for this study.

#### Scientists develop a new method for finding cancer-killing cells

Lying in wait within our immune systems are specialized cells called cytotoxic T cells (CTLs), searching for and eliminating diseased cells. Scientists have shown that we can harness the search-and-destroy functions of CTLs to help our bodies fight off cancer, but it's like searching for a needle in a haystack. A new method published in Nature Communications developed in the laboratory of Dr. Robert Holt, distinguished scientist at the GSC, has made it a lot easier.

"The method we developed allows us to rapidly and comprehensively survey the interactions between CTLs and their targets," said Dr. Holt. "This is a major improvement over the conventional methods we had to work with previously; we can now screen hundreds to thousands of times more potential antigens in parallel."

The method takes advantage of the CTLs' granzymemediated cell killing to identify disease antigens. To do this, the scientists generate a library of cells, each displaying a different antigen. Only a small fraction of these antigens will signal disease and the goal is to find them. They mix the cell library together with CTLs and wait. Within a couple of hours, the CTLs will have found their targets and will have released their arsenal of perforin and granzymes. Once the target cells have been invaded by granzymes, they light up in a way that can be detected by specialized laboratory instruments. Then, using DNA sequencing, the team can determine precisely which antigens signaled the presence of disease.

CTL-mediated immunotherapy is a promising avenue for novel cancer treatment. But it is not without risk. It is possible that the disease signals being displayed by cancer cells may also be present elsewhere in the body. Injecting an army of CTLs all searching for these antigens can lead to unintended consequences. But the method developed by Dr. Holt and Dr. Sharma can help prevent these undesired effects.

# Personalized OncoGenomics



The Personalized OncoGenomics (POG) Program, co-led by Dr. Marco Marra, director of Canada's Michael Smith Genome Sciences Centre at BC Cancer and BC Cancer medical oncologist Dr. Janessa Laskin, is a patient-centric research initiative, consisting of oncologists, pathologists and other clinical, research and technical personnel that aims to study the impact of embedding whole genome and transcriptome analysis into treatment planning for British Columbian cancer patients with otherwise incurable metastatic cancers.

## **POG FAST FACTS**



#### New signs in the health precinct of Vancouver designed using POG data

There are some new shapes on the streets of Vancouver. The DNA on 10th way-finding signs, designed by GSC staff scientist Martin Krzywinski, mark the entrance to the city's Health Care corridor and their intricate details are based on sequence data from POG. Here's a Q&A with the artist.

Where are the signs? On the east side of the intersection of 10th Avenue and Oak Street in Vancouver.

What do they show? Each shape on the signs represents a nucleotide base and each row represents a gene sequence. The shapes of complementary bases are vertical (A/T) or horizontal (C/G) reflections. Circles inside the shape indicate where a base repeats twice (small circle) or three times (large circle).



These shapes are part of the DNA ON 10TH font designed for the sign. Bright bases signal a gene mutation and form a double helix—the three-dimensional shape of DNA. The sequence along the helix is part of the TP53 gene an important tumour suppressor and regulator of cell division. There are several puzzles and "Easter eggs" built into the signs.

#### Where did the data come

**from?** The data represents DNA from cancer patients sequenced at the GSC at BC Cancer. Each unique row of shapes is a real gene sequence implicated in cancer. Modern breakthroughs in cancer treatment have been made possible by genomics, the study of DNA and its role in heredity, health and disease. I n our POG program, we compare patients' tumour and normal DNA to find the best targeted therapies.

**How are they different?** Sequences in rows that intersect with the 5' helix (the one that starts on the bottom row) are oriented in the direction of the sign. The helix shape on the north sign is as the helix on the south sign would appear if you were to look at it from the back.

How are they different in the day compared to at night? The signs are dimly backlit, giving them different day and night personalities. As the night ascends, the mysteries of the cell are revealed — the background sequence forming the double helix becomes distinguishable.

Learn more: http://mkweb.bcgsc.ca/dnaon10th/

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