2020 BC CANCER RESEARCH REPORT

BC CANCER RESEARCH INSTITUTE

Provincial Health Services Authority

UBC

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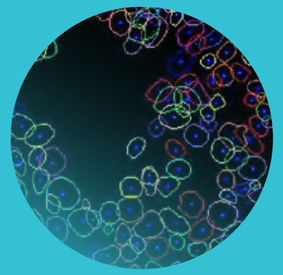


On the cover:
This image shows the application of deep learning for the automatic segmentation of a lung cancer tissue sample, where the different colour oval like boundaries are the outlines of individual nuclei. The Deep Learning AI segmentation is an advance in that it can correctly recognize the boundary of the nuclei with an accuracy equal to human observers, even in the challenging situations where many nuclei are piled up on top of each other

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

2020 has been an unprecedented year. The world was rocked by the COVID-19 pandemic which has, and continues to, significantly impact health care globally. BC Cancer was not immune to the consequences of COVID-19 and while patient care continued, new restrictions and guidelines impacted how we conducted our important work. But in the face of adversity springs new opportunity for innovation and I am proud that as a group BC Cancer continued to live up to our reputation as an international leader in research excellence. This year has been heavy, undoubtedly, but cancer does not stop in the wake of a deadly virus and neither do we. Our clinicians, nurses, researchers, administrators, leaders and trainees all stepped up and went above and beyond, facing challenges that no one could have predicted. As we continue to navigate the repercussions of COVID-19, there is also time to reflect on the successes of the year and incredible achievements we've made to deliver a positive impact for people affected by cancer.

The beginning of the year brought news of a formal partnership between BC Cancer Research, the Provincial Health Services Authority (PHSA), and the University of British Columbia (UBC). In February we formally announced the BC Cancer Research Institute (BCCRI); a UBC and PHSA-approved hub for cancer activity across the province. The move to a research institute enhances British Columbia's leadership position as a cancer research innovator allowing PHSA and UBC to come together behind a common cause to accelerate cancer research. The move allows the BCCRI to leverage existing infrastructure and resources to deliver bold new solutions and training opportunities that will help transform health care; at a time when it is now more important than ever.

This year also saw BC Cancer become the first in Canada to launch a lung cancer screening program for high risk individuals. In 1955, we were the first cancer program in the world to introduce cervical screening and the first in Canada to implement breast screening in 1988. Both screening programs have improved survival rates for cervical and breast cancer and now the same will be true for lung cancer which continues to be B.C. and Canada's deadliest cancer. In a tribute to the significant impact BC Cancer researchers have made to improving outcomes in lung cancer; our 2020 research report celebrates the achievements made in this field. We have entered a new era not just with screening but also in diagnostics, in better understanding cell biology and in identifying new treatment methods. These breakthroughs will help steer better outcomes for generations.

I'd also like to acknowledge and congratulate the researchers and trainees who continue to publish their work in the world's most prestigious journals and receive a remarkable number of awards, especially during these extraordinary times when much of our work has been conducted remotely under new work from home guidelines and adjusted lab practices.

While there is still much work to do, what sets BC Cancer apart is our strong sense of community and a common purpose, the spirit of collaboration and our ability to come together in the face of uncertainty and press forward to achieving our vision of a world free of cancer.

Dr. François Bénard
Senior Executive Director
Research

Message from BC Cancer Foundation President & CEO, Sarah Roth

In 2020 we saw our community deeply impacted by the COVID-19 pandemic. It caused a fundamental shift in how health care is delivered, in B.C., and across the world. It also impacted many funding streams to the BC Cancer Research Institute.

In response, we rallied BC Cancer Foundation donors to ensure the game-changing work did not stop. $2 million was raised to support critical research programs at risk of funding gaps. Our donors recognize that cancer is the greatest health issue facing our generation and we must advance innovation to improve outcomes for British Columbians and their families.

Last year nearly 30,000 British Columbians heard the words, "you have cancer."

4,000 of those people faced lung cancer – the leading cause of cancer death across the nation. Far too many people have died from this devastating disease. It's been in the shadows for too long, it's been underfunded and stigmatized. It's time for us to change this story.

Kelowna residents Shannon and Clayton Gall raised an incredible $1 million by rallying a group of their fellow PH&N colleagues, helping us reach our $1.75 million goal to launch the first lung cancer screening program in Canada.

Shannon is a lung cancer patient receiving treatment at BC Cancer – Kelowna. She is living life to the fullest because of an innovative therapy found through state-of-the-art genetic sequencing and clinical research. Shannon knows the life-saving value of funding innovation and she believed wholeheartedly that screening and early detection would change the outcome for thousands of people.

This support from a passionate community of donors has propelled BC Cancer's leadership in early detection and it will save countless lives.

At the BC Cancer Foundation, we know that cancer is relentless, and our donors are 100 per cent committed to breaking down this disease, across every lab and centre in B.C.

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.

Sarah Roth
President & CEO
BC Cancer Foundation

Portrait credit: BC Cancer Foundation.

Fast Facts

15 researchers named among the world's most Highly Cited

367 active clinical trials

11 patents filed

615 journal articles

8,270 total cumulative subject enrollment in clinical trials

21 patents issued

744 total publications

13 active spin-off companies (2 new)

41 active licenses

301 **Researchers** excluding affiliate investigators

732 **Trainees** increase of 120 from previous year

Funding: Total Grants Awarded: $76 million

By Sector

38% government

45% non-profit

17% industry & other sources

By Award Type

86% operating grants

4% salary awards

5% other infrastructure awards

5%

Awards & Funding

2020

January

Dr. Dean Regier was awarded a grant titled "Canadian Network for Learning Healthcare Systems and Cost-effective 'Omics Innovation'" from the Genome Canada, Genomics in Society Interdisciplinary Research Teams (GiSIRT) competition. The Canadian Network for Learning Healthcare Systems and Cost-effective 'Omics Innovation (CLEO Network) will: (1) inform the design of learning healthcare systems that turns genomic knowledge into sustainable cancer care; (2) advance research; (3) build capacity to deliver this research and its benefits into the future; and (4) produce research that yields individual, social, and economic benefits for all Canadians. The total funding for this award is $2.6M for 4-years.

A US Department of Defense (DoD) sub-award was given to BC Cancer and **Dr. Sam Aparicio** from a grant awarded to Dr. Sohrab Shah at Memorial Sloan Kettering Cancer Centre in New York, titled "Dissecting the impact of mutational processes on therapeutic response in ovarian cancer". This project will investigate the evolutionary, phenotypic and drug response impacts of mutational processes in high grade serous ovarian cancer (HGSOC).

Dr. Rachel Murphy was selected to participate in the International Agency for Research on Cancer (IARC), International Cancer Benchmarking Partnership Expertise Transfer Scheme. The scheme provides funds to collaborate with IARC and lead a study to understand lung cancer survival deficits across 21 jurisdictions in 7 countries.

CIHR Fall 2019 Competition

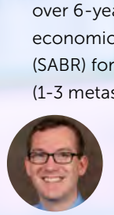
- **Drs. Ryan Brinkman** and **Andrew Weng** were awarded $317,475 for 1-year to study machine learning for flow cytometry data and trial analysis.

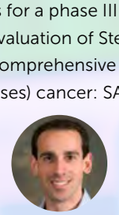
- **Dr. Xiaoyan Jiang** was awarded $902,700 for 5-years to study targeting a novel miR-185/PAK6 axis to overcome drug-resistance in human leukemia.

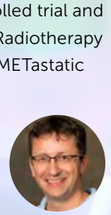
- **Dr. William Lockwood** was awarded $688,500 for 3-years to study the effects of smoking marijuana on lung cancer development: implications for screening and early detection.

- **Dr. Brad Nelson** was awarded $1.19M over five years to study mechanisms of B cell-mediated immunity in human cancer.

- **Drs. Robert Olson, Alison Allan, David Palma, Stuart Peacock,** and **Scott Tyldesley** were awarded $699,380 over 6-years for a phase III randomized controlled trial and economic evaluation of Stereotactic Ablative Radiotherapy (SABR) for Comprehensive treatment of OligoMETastatic (1-3 metastases) cancer: SABR-COMET-3.







February

Dr. Poul Sorensen received the 2020 Aubrey J. Tingle Prize which is awarded annually to a B.C.-based clinician scientist whose work in health research is internationally recognized and has had a significant impact on advancing research and its implementation to improve health and the health system in B.C. and globally. Among his many contributions to cancer research and treatment, Dr. Sorensen discovered the major gene fusion in Ewing sarcoma, a rare type of bone cancer often affecting children and teenagers. This became an instant diagnostic and therapeutic target and led to the discovery of many other gene fusions that drive and define other pediatric cancers. He later discovered the gene fusion in a type of soft tissue cancer most often affecting children under age one (infantile fibrosarcoma) and made the discovery that the same fusion was present in a type of breast cancer, a revelation which has had a direct impact on the development of new treatments. These were discoveries of historic significance, as this gene fusion has become one of the most exciting therapeutic targets in oncology today. Located at the BC Cancer Research Institute, Dr. Sorensen's lab is now focusing on how tumour cells adapt to stress.

Dr. Peter Stirling was awarded a Canadian Cancer Society Research Institute (CCSRI) Impact Grant with Dr. Philip Hieter (lead investigator) from UBC for their project "Setting a trap for cancer cells: high throughput screening for protein trapping synthetic lethal targets for cancer therapy". The total funding is $1.25M for 5-years.

Drs. Nhu Le (B.C. site PI), **Linda Cook** and **Martin Koebel** (Alberta site PI) were awarded a NIH/NCI1 grant for their project titled "Population-Based Study of Ketorolac and Ovarian Cancer Survival". The goal of the project is to address the potential use of ketorolac to improve epithelial ovarian cancer survival. The total funding awarded is $1.15M for 4-years.

April

Dr. Maxwell Gillatt, project preceptor Adeline Markarian, and the research team which includes Drs. Diego Villa, Mario de Lemos, and Lynne Nakashima along with Stephanie Woo, Kimberly Schaff, and Connie Son, were awarded the Canadian Association of Pharmacy in Oncology (CAPhO) Conference 2020 - Best Research Poster (Clinical) for project titled "Use, Response, and Outcomes of Brentuximab Vedotin in Transplant- ineligible Patients for Relapsed Hodgkin Lymphoma". They concluded Brentuximab Vedotin is a valid treatment option in this patient population which would otherwise have a poor prognosis.

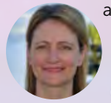
Dr. Shoukat Dedhar was awarded a new National Research Council of Canada (NRC) Collaborative grant titled: "AI for drug design". Dr. Dedhar's team will work on the identification and evaluation of new inhibitors of Carbonic Anhydrase IX (CAIX). The grant is $160,000 for 2-years.

Dr. Steven Jones and his research team together with Michael Brudno (Nominated Principal Investigator) from the Hospital for Sick Children, and Guillaume Bourque (Principal Investigator) from McGill were awarded funding from the national non-profit organization CANARIE (Canadian Network for the Advancement of Research Industry and Education) to build ClinDIG, a distributed system for clinical and genomics data. ClinDIG is a federated data environment that will combine diverse data sources into a single framework and will allow for federation of clinical and genomic data across Canada's National Education and Research Network.

Drs. Gregg Morin and **Torsten Nielsen** (UBC) were awarded a Canadian Cancer Society Innovation to Impact (i2I) grant for their project "Clinical application of a targeted proteomic classifier for triple negative breast cancer". The i2I grant will build on Drs. Morin and Nielsen's previous award with Canadian Breast Cancer Foundation (CBCF) and Canadian Cancer Society (CCS).

May

Dr. Sara Taylor was awarded the 2020 Canadian Cancer Trials Group award "Dr. Elizabeth Eisenhauer Early Drug Development Young Investigator Award". Dr. Sara Taylor is the medical director of the Clinical Trials Unit at BC Cancer - Kelowna. Dr. Taylor was presented with the award which is given to a young investigator within seven years of their MD, PhD or fellowship who has contributed significantly to an Investigational New Drug (IND) trial. She received the award for "IND238- A Phase II Study of Durvalumab Treatment in Patients Who Discontinued Prior Checkpoint Therapy Due to Immune Related Toxicity". Dr. Taylor is actively involved in phase I, II, and III clinical trials in Kelowna with research interest in breast cancer, survivorship, genomics, and patient-reported outcomes.



Awards & Funding

2020

Dr. Ryan Stubbins was awarded the Leukemia & Lymphoma Society of Canada (LLSC) Fellow Award as part of the UBC Clinician Investigator Program Scholarship. The award was presented to Dr. Stubbins on behalf of Leukemia & Lymphoma Society of Canada, in partnership with the Canadian Institutes of Health Research (CIHR).

Iris Lin, a PhD student from the Cancer Control Research department at the BC Cancer Research Institute (BCCRI) and the Craniofacial Science Program at UBC, was awarded a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award. Iris is supervised by **Dr. Denise Laronde**; the duration of the award is for 3-years.

June

The American Association for Cancer Research (AACR) has awarded teams associated with The Cancer Genome Atlas (TCGA), including three researchers from Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer with a 2020 AACR team science award. **Dr. Marco Marra** was awarded the 2020 AACR Team Science Award together with **Drs. Steven Jones** and **Gordon Robertson.**

July

Drs. Florian Kuchenbauer and **François Bénard,** together with lead investigator **Robert Britton** from Simon Fraser University (SFU), were awarded a Cancer Research Society Operating Grant for their project "18F Fluorinated Amino Acid as PET Radiotracers for Multiple Myeloma Funding". The award is $120,000 for 2-years.

Dr. Peter Stirling was awarded the Natural Sciences and Engineering Research Council of Canada (NSERC), Discovery Grant, "Nuclear protein quality control mechanisms during genotoxic stress". Total funding is $410,000 for 5-years.

Dr. Maryam Soleimani - The Kidney Cancer Research Network of Canada (KCRNC), Kidney Cancer Canada (KCC), and Canadian Urological Association Scholarship Fund (CUASF) awarded Dr. Maryam Soleimani with the 2020 Kidney Cancer Research Grant. This research grant is awarded annually to two applicants in Canada for novel research proposals related to advancements in kidney cancer. Dr. Soleimani's project aims to identify microRNA in the blood of patients with kidney cancer in order to best predict which treatment options they are most likely to respond to.

CIHR Spring Competition Operating Grants

- **Dr. Arman Rahmim** was awarded $898,876 for 5-years to study improved assessment of disease in lymphoma patients using quantitative PET imaging.

- **Dr. Fumio Takei** was awarded $784,126 for 5-years to study tissue resident and migratory group 2 innate lymphoid cells in health and disease.

- **Dr. Yuzhuo Wang** was awarded $765,000 for 4-years to study the role of PRDM16 in neuroendocrine prostate cancer development and aggressiveness.

August

Dr. Kevin Hay was awarded a Canada Research Society Operating Grant for research that will provide a broad characterization of all proteins expressed on the surface of myeloma cells. Dr. Hay's work will allow researchers to identify and validate optimal myeloma surface protein targets, as a crucial step towards advancing new cellular therapies for improving myeloma patient outcomes.

September

Dr. David Huntsman was elected into the Canadian Academy of Health Sciences (CAHS). He was elected for his demonstrated leadership, creativity, distinctive competencies and background, and a commitment to advance academic health science. The CAHS brings together Canada's top-ranked health and biomedical scientists and scholars to make a positive impact on the urgent health concerns of Canadians. CAHS Fellows, drawn from all disciplines across our nation's universities, health care and research institutes, evaluate Canada's most complex health challenges and recommend strategic, actionable solutions.

Dr. Poul Sorensen was awarded funding from Stand Up To Cancer-Kate McGarrigle Fund-Steve Golin Prize, Phillip A. Sharp Award for Innovation in Collaboration with Dr. Elizabeth Lawlor of Seattle Children's Research Institute. "Enhancing ferroptosis to block Ewing sarcoma metastatic capacity". Despite intensive treatments, outcomes for patients with metastatic Ewing sarcoma (EwS) are low and have not improved in over 30 years. There is urgent need to better understand why EwS spreads and to develop therapies to stop it. The group proposes that these effects depend in part on a novel axis and that inhibition of this axis will block metastasis. The award is $250,000 USD for 2-years.

Dr. Aly Karsan was awarded the Genome BC Award for Scientific Excellence. His efforts have made significant inroads for the application of genomics in a clinical setting.

October

Drs. François Bénard, Kuo-Shyan Lin, David Perrin and **Florian Kuchenbauer** were awarded a 2-year grant by the Cancer Research Society. The grant, titled "Development of CXCR4- targeting fluorescent radiotheranostic agents via a novel cross-linking macrocyclization strategy" will provide funding to develop radiopharmaceuticals targeting C-X-C chemokine receptor 4 (CXCR4) for detection and radiotherapy of cancer.

Dr. Sam Aparicio's Breast Cancer Research Foundation (BCRF) grant was successfully renewed. Originally funded for 1 year and renewed in 2019, the BCRF grant "Developing predictive biomarkers for genome targeting agents in TNBC, to single cell resolution" was funded again in 2020 for a third year. Total funding for 3-years is $675,000 USD.

Dr. Rob Holt was awarded a BioCanRx/BC Cancer Foundation KRAS Immunotherapy research grant titled "Recombinant T Cell Receptors to Target KRAS Hotspot Mutations in Pancreatic Cancer" for $950,000. Recent clinical research has shown that it is possible to engineer an effective T-cell response in patients unable to initiate/sustain anti-tumour immunity. This project will lay the groundwork for potential benefit to Canadian cancer patients - if it is eventually shown to be safe, feasible and efficacious.

Dr. Kevin Hay was awarded funding to study novel multiple myeloma target identification by cell surface proteomics for chimeric antigen receptor T-cell (CAR T-cell) immunotherapy. The award is in partnership with the Herbert James Davies Memorial Fund. The total funding is $120,000 for 2-years.

Dr. Shoukat Dedhar was awarded a Cancer Research Society Operating Grant funding for his project titled "Overcoming cancer recurrence and metastatic progression by targeting 'anastasis'". The total funding for the grant is $120,000 for 2-years.

Dr. Cheng-Han Lee was awarded funding in partnership with the Ann Matyas Memorial Fund for therapeutic screening of patient tumour-derived malignant mixed Müllerian tumour (MMMT) disease models. The total funding is $120,000 for 2-years.

Awards & Funding

2020

November

Dr. Florian Kuchenbauer together with lead investigator Robert Britton (SFU) were awarded a Canadian Cancer Society Research Institute, Innovation Grant titled "Small molecule inhibitors of O-GlcNAc transferase: validation of a new anticancer target" at $200,000 for 2-years. Dr. Kuchenbauer was also awarded the Canada Foundation for Innovation & BC Knowledge Development Fund, JELF for "Exploring mitochondrial function as therapeutic target in acute myeloid leukemia and multiple myeloma" with funding of $246,584 for 1-year. Additionally, Dr. Kuchenbauer was appointed Head of the Research Super Team for Blood Cancer Research with the Leukemia & Lymphoma Society of Canada in 2020.

Dr. Stephen Lam was awarded the Doctors of BC award Terry Fox Medal. The Terry Fox Medal recognizes individuals who have attained a distinguished career of achievement in their area of focus or a ground-breaking advancement in their field. Dr. Lam is an internationally recognized expert in lung cancer screening, prevention and treatment. His work has led to B.C. becoming the first province in Canada to announce a lung cancer screening program and has had a profound impact on patient outcomes.

BC Cancer researchers and clinicians included on Clarivate's Highly Cited Researchers 2020 list

Fifteen BC Cancer clinicians and scientists were named in Clarivate's Highly Cited Researchers 2020 list. Each has been ranked in the top one per cent in their fields using a method of data and analysis performed by bibliometric experts and data scientists at the Institute for Scientific Information at Clarivate.

For BC Cancer, those fields include clinical medicine, molecular biology and genetics, and cross-field a category which recognizes influence across several fields.

The list includes:

- **Dr. Inanc Birol** (Cross-Field), distinguished scientist, Genome Sciences Centre

- **Dr. Joseph M. Connors** (Clinical Medicine), retired clinician scientist, BC Cancer

- **Dr. Randy D. Gascoyne** (Clinical Medicine), distinguished scientist, BC Cancer Research Institute

- **Dr. Martin Hirst** (Cross-Field), senior scientist, Genome Sciences Centre

- **Dr. Robert A. Holt** (Molecular Biology and Genetics), distinguished scientist, Genome Sciences Centre

- **Dr. David G. Huntsman** (Cross-Field), distinguished scientist, molecular oncologist and Director of OVCARE, BC Cancer Research Institute

- **Dr. Steven J. M. Jones** (Molecular Biology and Genetics), director, Genome Sciences Centre

- **Dr. Marco A. Marra** (Molecular Biology and Genetics), director, Genome Sciences Centre

- **Dr. Richard A. Moore** (Molecular Biology and Genetics), group leader, sequencing , Genome Sciences Centre

- **Dr. Andrew J. Mungall** (Cross-Field), group leader, biospecimen and library cores, Genome Sciences Centre

- **Dr. Kerry J. Savage** (Clinical Medicine), medical oncologist, BC Cancer

- **Jacqueline E. Schein** (Molecular Biology and Genetics), former staff scientist, Genome Sciences Centre

- **Dr. Sohrab P. Shah** (Cross-Field), former distinguished scientist, current affiliated scientist, BC Cancer Research Institute

- **Angela Tam** (Cross-Field), staff scientist, Genome Sciences Centre

- **Dr. Yongjun Zhao** (Cross-Field), group leader, library technology development, Genome Sciences Centre

Researchers from more than 60 countries were included on the list. This year 195 Canadians landed in the Top 10 of researchers by country, accounting for 3.1 per cent of those who made the prestigious list.

December

Drs. Robert Holt and **Govinda Sharma** were awarded a Michael Smith Foundation for Health Research (MSFHR) Innovation to Commercialization (I2C) grant. The funding will support the commercialization of a new platform technology used to identify functional T-cell receptor epitopes. This platform will continue Dr. Sharma's research on further developing a rapid high-throughput discovery assay for finding and characterizing T cell receptor (TCR) proteins with potential to become next-generation cell-based immunotherapies. These funds will be used to perform advanced proof-of-concept work and continue to reduce the technology to routine practice.

A formalized partnership & a new name:

Announcing the BC Cancer Research Institute

2020 was a formative year for the BC Cancer Research Institute. In March, BC Cancer Research formally became a research institute in partnership with the University of British Columbia (UBC) and the Provincial Health Services Authority (PHSA) – a move that enhances British Columbia's leadership position in cancer research innovation. With a formalized partnership, the BC Cancer Research Institute (BCCRI) increases its strength as a hub for cancer research activity across the province, advancing cancer research discoveries and transformational technologies and treatments.

The BCCRI is led by Dr. François Bénard, senior executive director, research, BC Cancer, and professor in the Department of Radiology and associate dean, research, UBC Faculty of Medicine.

"BC Cancer Research has always had close ties with UBC and the Faculty of Medicine," said Dr. Bénard. "The designation as an institute is a signal of our strong interest and willingness to reinforce our ties and connections with the greater UBC community, expand our collaborations across disciplines, faculties and health authorities, and work with the university to scale and grow our capabilities to tackle all aspects of cancer research."

The move will also allow BCCRI to leverage existing resources and infrastructure to improve the health and wellbeing of British Columbians and beyond.

"We are accelerating research and innovation to help address one of the most challenging health issues facing Canadians," said Dermot Kelleher, dean of the UBC Faculty of Medicine and vice-president of Health. "By recognizing the BCCRI as a UBC-approved institute, it will enable us to work together to deliver bold new solutions and training opportunities that will help transform health for everyone."

The BCCRI has academic and research programs spanning across BC Cancer's many provincial locations and across several UBC faculties and departments. With more than 800 trainees at any given time, the Institute attracts a vibrant student, medical resident and postdoctoral fellow community. It is also home to enhanced postgraduate training programs in oncology and bioinformatics, helping equip scientists and health professionals with the tools they need to support patients and families affected by cancer.

The BCCRI is also home to many leading research programs, from genomics at the Michael Smith Genome Sciences Centre, cancer and stem cell biology at the Terry Fox Laboratory, to translational research, clinical trials and population-level cancer control research. BCCRI continues to maintain strong academic relationships with Simon Fraser University, the University of Victoria and the University of Northern British Columbia.

Expanding on our understanding of lung cancer:

Research advancements for British Columbia's deadliest cancer

Lung cancer is the leading cause of cancer related deaths in B.C. and across Canada. In 2020, an estimated 3,855 people in B.C. were diagnosed with lung cancer with almost half diagnosed at Stage 4, where the cancer has spread beyond the lungs and five-year survival rates are extremely low. It is the most deadly cancer accounting for six deaths every day in the province. Advancing research insights into the disease is critical to help save lives.

From improving diagnostic tools to implementing a screening program for high-risk individuals to better insight on cell biology and identifying novel treatment methods, 2020 was a year that expanded our understanding of lung cancer and will help change outcomes for generations.

L to R: Drs Wan Lam, Stephen Lam, Calum MacAulay, & William Lockwood

Stage One: Launch the first lung screening program in Canada

In September 2020, the province announced the first provincial lung screening program in Canada. The first-of-its-kind program comes from years of hard work and dedicated research by clinicians and researchers, spearheaded by Dr. Stephen Lam, distinguished scientist, Leon Judah Blackmore Chair in lung cancer research, and director of the MDS/Rix Early Lung Detection Program at BC Cancer. BC Cancer is a pioneer in developing population-based cancer screening. It was the first cancer program in the world to introduce cervical screening in 1955 and the first in Canada to implement breast screening in 1988. Both programs have improved survival rates for cervical and breast cancer.

"Implementing the first-in-Canada organized lung cancer screening program provides the platform to achieve a quantum jump to improve the survival and quality of life of lung cancer patients," said Dr. Lam. "By detecting and treating lung cancer in its early stage, survival outcomes for those who are diagnosed can be significantly improved."

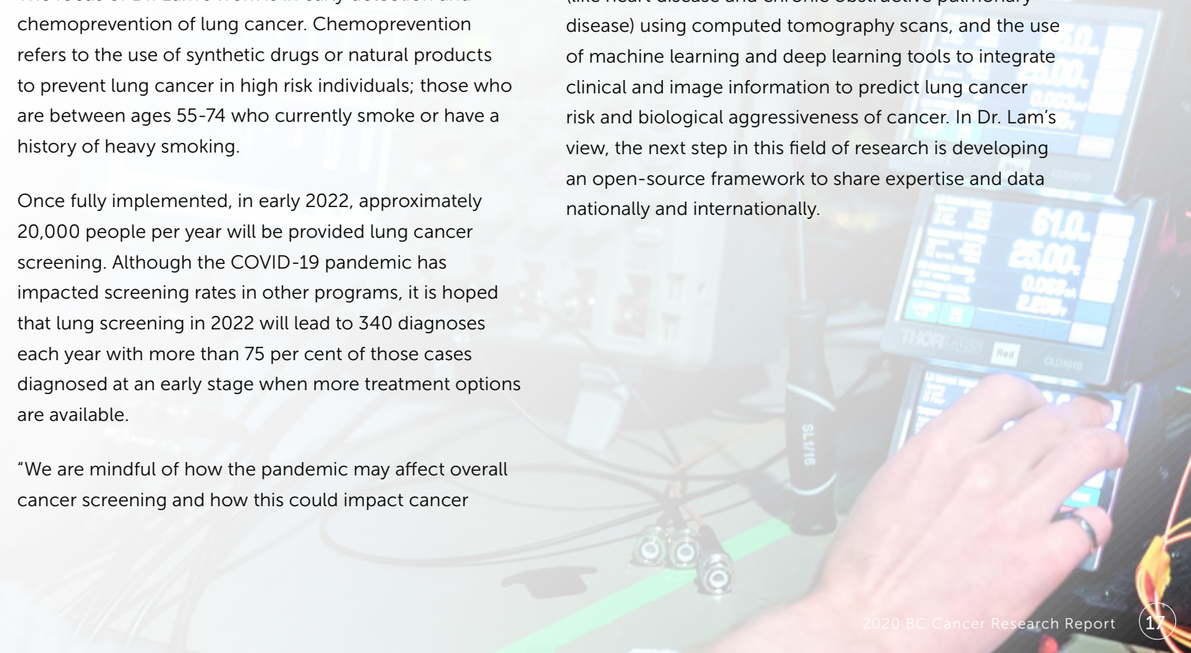
The focus of Dr. Lam's work is in early detection and chemoprevention of lung cancer. Chemoprevention refers to the use of synthetic drugs or natural products to prevent lung cancer in high risk individuals; those who are between ages 55-74 who currently smoke or have a history of heavy smoking.

Once fully implemented, in early 2022, approximately 20,000 people per year will be provided lung cancer screening. Although the COVID-19 pandemic has impacted screening rates in other programs, it is hoped that lung screening in 2022 will lead to 340 diagnoses each year with more than 75 per cent of those cases diagnosed at an early stage when more treatment options are available.

"We are mindful of how the pandemic may affect overall cancer screening and how this could impact cancer outcomes in the future. The advantage we have in lung cancer screening is that screening is based on cancer risk. The use of a lung cancer risk prediction tool allows us to prioritize screening starting from those with the highest risk and work down the list depending on the available screening capacity."

Following an initial lung screen, clinicians can further personalize surveillance screening interval or necessity for referral to specialty centres for diagnosis based on lung cancer risk using a deep learning approach. Research in the effect of cumulative exposure to outdoor air pollution on lung cancer risk at the individual level in relation to sex and ethnicity/race and biomarkers research using blood or breath samples are promising approaches to identify high risk non-smokers and light smokers who would benefit from lung cancer screening and chemoprevention.

In his years of research, the most significant progress Dr. Lam has witnessed in lung cancer screening stem from advances in computer vision technology used to detect early lung cancer and non-lung cancer diseases (like heart disease and chronic obstructive pulmonary disease) using computed tomography scans, and the use of machine learning and deep learning tools to integrate clinical and image information to predict lung cancer risk and biological aggressiveness of cancer. In Dr. Lam's view, the next step in this field of research is developing an open-source framework to share expertise and data nationally and internationally.



Stage Two:
Refine the tools used to definitively diagnose lung cancer

"Deep learning research is data-hungry; it requires large data sets with carefully collected ground-truth determinations of cancer status, disease stage, and treatment outcome. We must eliminate barriers from intellectual property ownership to move the field forward as quickly as possible so that the patients can benefit from the research."

Following a lung cancer screening or referral from a primary care physician, further testing may be required for a definitive diagnosis. The increased need for diagnostic confirmation then requires efficient and accurate methods to locate these nodules in the lung so clinicians can collect a sample for evaluation by a pathologist. These tests can include the use of imaging tools inside the airways. Dr. Pierre Lane, senior scientist at the BC Cancer Research Institute, is formally trained in engineering physics, and is one of the pioneers at BC Cancer noted for inventing and adapting to clinical practice the use of autofluorescence imaging (AFI) for the early detection of cancer.

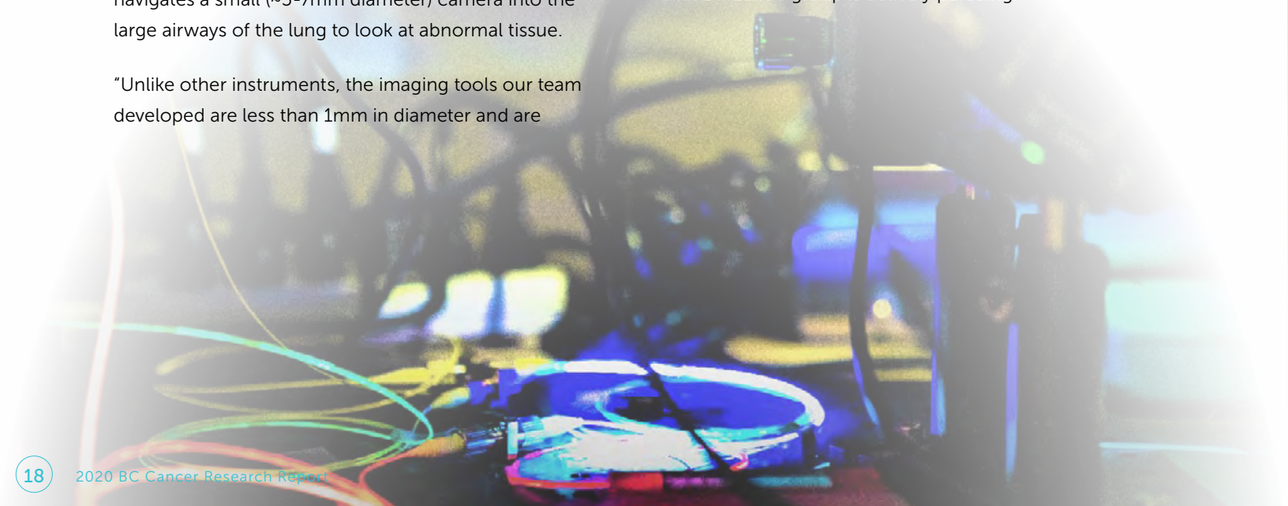
In 2020, Dr. Lane and team developed optical tools that clinicians can use to take a closer look at suspicious areas in the lung that appear abnormal during a lung cancer screening. These optical imaging tools are deployed during a bronchoscopy, a procedure where a clinician navigates a small (~5-7mm diameter) camera into the large airways of the lung to look at abnormal tissue.

"Unlike other instruments, the imaging tools our team developed are less than 1mm in diameter and are deployed through the instrument channel of the bronchoscope and out into the smaller airways which cannot be seen using conventional bronchoscopes," said Dr. Lane. "These small imaging devices provide volumetric images of the airway walls, with almost cellular resolution, in the very small peripheral airways where many cancers are believed to originate."

It is important to be able to visualize the size and shape of individual cells for the accurate detection of early cancers. One promising state-of-the-art optical imaging technique, called optical coherence tomography (OCT), has sufficient resolution to see cancerous tumour tissue, but isn't yet able to capture the cells that make up the layers of tissue.

In recent years, technological advances in other fields including light-emitting diodes (LEDs) and fiber optics have allowed for the improvement of optical fiber-based imaging systems for disease detection. "My group pays close attention to new technology developments, which are often driven by consumer demand for smaller and faster consumer electronic devices, to see if these advancements can be used to solve problems in medical imaging."

The development of high-resolution combined OCT and AFI system for early cancer detection is something that Dr. Lane's group is actively pursuing.



Stage Three: A new way of looking at tissue and cell composition

Once the tumour tissues have been removed from the patient, it is the work of a pathologist to make final assessment on the tissue and determine conclusively if the tissue is cancerous. Dr. Calum MacAulay is a distinguished scientist at the BC Cancer Research Institute. With a background in physics and engineering, his work on lung cancer is predominantly focused on novel early cancer detection methods and optimizing the existing process for early lung cancer detection.

While his work touches on many lung cancer projects at BC Cancer, one of his focuses is on multi-parameter measurements on tissue sections, which includes identifying various biomarkers and cell composition. Cell composition can highlight how a type of immune cell, called 'killer T-cells', recognize foreign cells like cancer within a person's body and work to destroy the foreign cells.

"My team and I have been evaluating how to quantify the interaction of specific immune cells with specific tumour cells at a cell by cell level. In particular we have been reviewing the frequency that a killer or helper T-cell is located next to a tumour cell across a whole section," said Dr. MacAulay. "In order to do that, we have to find every individual cell, decide what type it is and then look at all of its neighbours and quantify how many times this specific cell has that specific neighbour. We have discovered that placement of neighbouring cells offers a better indication of what's likely to happen to the patient. The placement of the cells is a better predictor of how aggressive a tumour is or whether the tumour is going to have recurrence than just the frequency of type of cell within a sample."

According to MacAulay, the way many T-cells work is that the cells must have surface contact with tumour cells and recognize it as a foreign invader in order for it to work against a cancer. If a patient has a lot of killer T-cells but they are not adjacent to a tumour cell that may not help a patient's prognosis. Dr. MacAulay and team are working on tools to help analyze staging and methods that allow for more efficient and holistic analysis of many cell types in tissue – conducting these cell by cell evaluations on thousands of people.

"Right now there are several systems that take multiple hours just to do a small part of one section. Assessing multiple sections or multiple samples could take weeks or months to do; however, you could potentially do it with a mass spec imaging system using modified conventional chemistry. Using approaches like this you could do it in days and you could do many cases at a time." Identifying nuclei and their boundaries (segmenting nuclei) out of tissue images has historically been extremely challenging. As artificial intelligence (AI) becomes more refined, machine learning is being applied to cell segmentation with results close to those achievable by researchers.

"If you'd asked me five years ago if we could do that, I'd have said no. But now we can. We've got some really recent data that suggests we can train a machine to segment out the nuclei of cell even from a cluster of overlapping cells. I'm excited about that because now we're able to build multiple molecular dimensions for every cell with a tissue." What comes next will be how to manage the significant amount of data that comes from this advancement.

"How to analyze this massive data meaningfully – that's going to be an interesting challenge. A challenge we at BC Cancer and other around the world are working to meet."

Stage Four: Novel treatment and thinking outside of the box

Even if something doesn't appear to have clinical relevance at the beginning, it doesn't mean it isn't worth understanding. Many of the most impactful discoveries influencing lung cancer care have started from a researcher trying to understand a basic and fundamental aspect pertaining to how cancer cells work.

Dr. William Lockwood, senior scientist at the BC Cancer Research Institute, investigates not only how lung cancer initiates and progresses, but also its response to treatment. He and his team seek to understand the basic biology of lung cancer cells, including which mutations drive the process of cell growth; particularly in people who have never smoked. In doing this research, he and his team at the Lockwood Lab in the department of Integrative Oncology at the BCCRI have made exceptional progress in better understanding the genetic basis of lung cancer and have uncovered novel compounds that can kill lung cancer.

"I am excited for the future of this work," said Dr. Lockwood. "Targeted and immune therapy have been game changing in lung cancer management, drastically improving the outcomes and quality of life for patients. In terms of my own work, my team and I have continued our novel pursuit of killing lung cancers through 'hyperactivation'. We liken this to putting on the gas pedal in tumours as opposed to the breaks, which traditional therapies try to achieve. We think this will offer an avenue to treat lung tumours that do not respond to targeted and immune therapies and may circumvent issues of resistance that remains a limitation of traditional treatment approaches"

Dr. Lockwood and team have discovered a target to achieve this through pharmacological inhibition and are now working to develop novel inhibitors for clinical use. This unique and outside of the box approach is a paradigm shifting strategy for lung cancer patient care and will be refined in the coming years.

One of the most pressing problems facing all cancer treatments is the issue of drug resistance. There are many effective therapies for the clinical treatment of lung cancer and more in the trials stage, however patients eventually develop drug resistance and the treatment becomes less effective and impacts long-term survival rates.

To that end, Dr. Lockwood and team have characterized a new compound which selectively kills lung cancer cells and not normal lung tissue. Using an innovative approach, they found that this drug inhibits the metabolic function of lung cancer cells, depriving them of essential molecules they need to survive. This novel vulnerability in lung cancer cells is present in the vast majority of patient tumours.

He and his team have also worked on two approaches to treat lung cancer caused by EGFR (epidermal growth factor receptor) mutant genes. In the first approach they found a protein, termed GGA2, that EGFR-mutant lung cancers need to survive. By targeting this protein, new treatment methods could kill both drug sensitive and resistant EGFR mutant tumours. In his second approach, the team uncovered how some EGFR-mutant lung cancers 'change their skin' to become resistant to targeted therapies. By understanding how the tumours are able to adapt, the team can work to develop new ways to prevent this form of resistance from occurring.

Lastly, and perhaps most exciting of all, in a year that has been dominated by COVID-19, Dr. Lockwood and his team have discovered a different type of virus, one that typically causes hand, foot and mouth disease but can be engineered to selectively kill lung cancer cells caused by a specific type of mutated gene called KRAS. Mutated KRAS genes cause the majority of lung adenocarcinomas and currently have no approved treatment.

"We now hope to translate these findings towards patient care, aiming to assess gene status in individuals and correlating this with lung cancer risk and developing more suitable formulations of compounds for treatment."

Conclusion

2020 was a monumental year for lung cancer research. As lung cancer rates continue to climb, the research breakthroughs being led by BC Cancer researchers, scientists, clinicians and trainees will help improve methods of early diagnosis, deliver less invasive care for patients and improve outcomes.

Lung cancer is the deadliest cancer in B.C. and Canada. Advancing our understanding of this complex disease and developing ways to more effectively and efficiently manage care continues to transform the lives of patients in British Columbia. Through world-class cancer research we are achieving our greater goal of a world free from the devastating impact of cancer.

New Hire Focus:

Dr. Laura Evgin – using immunotherapy to combat cancer

Dr. Laura Evgin began her role as a scientist at Canada's Michael Smith Genome Sciences Centre at BC Cancer in November 2020. With a focus on cancer immuno-therapy, her work explores two approaches to combating cancer; chimeric antigen receptor (CAR) modified T cells and oncolytic viruses. Oncolytic viruses are viruses that have been specially engineered to purposely infect and kill cancer cells. CAR-T cells are immune cells that have been engineered in the laboratory to detect and eliminate cancer cells, and they have shown great promise in the clinic.

"While CAR-T and oncolytic viruses have both gained regulatory approvals and achieved clinical success in some areas, their combined use can help to overcome some of their respective limitations. Using these agents together, we hope to develop a robust innate and adaptive immune response that will target cancer cells," says Dr. Evgin.

Combination therapy is not only additive; it makes each treatment option more effective. Even though an artificial CAR can be introduced into a T cell to allow it recognize tumour cells, the T cell still possesses its native T cell receptor (TCR). T cells, as part of a person's immune system, are trained to recognize and eliminate cells infected with invading pathogens, such as oncolytic viruses. Dr. Evgin has been able to generate T cells that have tumour specificity through their CAR and oncolytic virus specificity through their TCR. Leveraging this dual specificity represents a promising way to boost CAR-T cell therapy and potentially target OV infected tumour cells.

"Using engineered viruses provides the opportunity to shape CAR-T cell functionality and fate, " says Dr. Evgin. "I am very optimistic about the future of cancer treatment because a new molecular toolkit is available to scientists and oncologists."

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

Cancer immunotherapy is a fast-paced field that was in its early stages when I started training. Checkpoint inhibitors and CAR-T cells have now radically changed the way that many cancers are treated and provide a new hope for patients. This is both extremely encouraging and informative. Patient immune profiling has helped to understand the reasons why some treatments fail for some people and has spurred the development of more representative pre-clinical models. New predictive biomarkers are helping to identify which patients are most likely to experience long lasting responses.

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

Despite tremendous clinical success, there are still many patients who do not respond favourably to immuno-therapy or whose cancer returns. In order to combat immune suppressive factors and prevent relapse, we need to better understand how these mechanisms work in patients and integrate these findings into pre-clinical models that can account for a person's individual immune response.

What advice would you offer to young researchers just starting out?

Be creative, be open minded, and be willing to follow the science wherever it takes you; regardless of your initial hypothesis. When we first set out to combine CAR-T cells with oncolytic viruses, we ran into significant roadblocks that made us question the utility of the approach. These findings were surprising, and dissecting the underlying biology was not my initial intention. Moving forward, however, these findings will us to help design more effective strategies in the future.

New Hire Focus:

Dr. Yongjin Park – ushering in a new era of understanding

This year, Dr. Yongjin Park joined the BC Cancer Research Institute as a scientist in the molecular oncology department and assistant professor in the department of Pathology and Laboratory Medicine at UBC. His work focusses primarily on designing machine learning technology which will help researchers uncover patterns and better understand information hidden within large scale genomic data.

In recent years a significant amount of data has been collected from patients, especially from within their DNA and their tumours' DNA. Combining this information with clinical outcomes and increasing refinements around precision medicine, leveraging machine learning will result in more efficient and successful treatment outcomes for patients – as long as the technology can be developed and harnessed properly. This is where Dr. Park's expertise comes in.

In 2020, Dr. Park submitted several papers on the subject including one that will be published in February 2021 in Nature. This study, titled "Integrative analysis of 10,000 epigenomic maps across 800 samples for regulatory genomics and disease dissection" systematically demonstrates that epigenetic signatures can identify distinctive blocks of genomic modules. These modules differentially enrich genome-wide association studies (GWAS) signals. Dr. Park and the other collaborators provide a novel perspective that disease genetics are complex and polygenic (involving lots of genes) but still modular and hierarchically-organized. In this study Dr. Park helped to develop a statistical tool that highlights disease-specific hierarchical structures.

This year he also began analyzing over 2.3 million single-cell RNA sequences associated with neurodegenerative disorders like Alzheimer's disease. Causal inference and machine learning methods developed for this analysis will be applied to cancer research, improving our understanding of cancer progression in the context of multiple cell types and other relevant disorders.

"Human disease is polygenic, meaning that it involves hundreds of genes. These disease-causing genes frequently interact with environmental factors, such as aging. I have learned that the accumulated effect of a small set of changes made on the disease genes can explain a large proportion of disease variation. Cancer is also a genetic disorder, although a slightly different aspect is that genetic variants that occurred during a lifetime can also play a critical role. Interestingly, recent progress made with UK biobank data shows that cancer genetics primarily work similarly to other complex diseases."

Dr. Park provides his personal thoughts on the future of cancer research in the exciting world of machine learning for cancer research.

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

Single-cell technology is one of the most significant breakthroughs in cancer biology. Although the technology is still in its early days, tracking molecular changes at a cell resolution is gradually changing the field. Moreover, the size of data is no longer considered small in the advent of a biobank database.

Single-cell sequencing data allow researchers to infer how many copies of a particular genomic region are present and how many genes are activated

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

Cancer is extremely personal. Each individual carries a unique set of genetic information and has been exposed to different environments over the course of their lives. The data is so complex that research should strive to capture the mechanisms that cause cancer in a simplified experiment. Knowing the subtypes of patients and diseases, followed by multi-omics (including genomics, transcriptomics, proteomics, and metabolomics) analysis, will become a significant step toward creating treatments tailored to the patient.

What advice would you offer to young researchers just starting out?

With cancer cases expected to increase significantly, machine learning is becoming increasingly popular to can help clinicians more efficiently and effectively manage patients. Developing computational thinking can truly help understand how machine learning engineers evaluate problems. I believe it is important to harness machine learning to work for your clinical or research needs.

What are your thoughts on the future of research in machine learning?

I think applied machine learning and artificial intelligence will become even more powerful and popular, especially in research settings and in clinical and biomedical industry settings. As designers develop and refine algorithms, scientists and clinicians will have to establish a way to double check the work to prevent errors. We are on a new frontier of research. However, I also agree with Judea Pearl, who is a Turing Award recipient in 2011 and a strong advocate of causal inference, that we are on the verge of advancing ML to a next level beyond a sophisticated function estimation.

Linking cancer care data for Canadians with the Marathon of Hope Cancer Centres Network

The Marathon of Hope Cancer Centres Network is a bold vision, inspired by Terry Fox's cross-country marathon to bridge all of Canada together to benefit people living with cancer in every province. The network, first officially announced in 2019, will link cancer centres across Canada in ways that allow them to share data, information, technology and knowledge with the goal of gaining much deeper insights into individual cancers that will accelerate the implementation of precision medicine for cancer.

2020 saw a big step forward for one of the network's major projects – building a network of cancer data collected from 15,000 past, present, and future Canadian patients. This project, known as the "15K gold standard cohort" will include: clinical information, genomic information, imaging details, cancer pathology and outcome information on those 15,000 cases across the country. The 15K Cohort aims to be a demographically representative set of cancer cases with BC Cancer, and the BC Cancer Research Institute, sharing data representative of British Columbians and people from the Yukon.

"No other resource of this size exists within Canada at this point in time so it is pretty unique," says Mr. Stephen Herst, chief operating officer for the Terry Fox Research Institute. "The utility of the cohort will become clear when it's able to predict successful treatment outcomes for an individual cancer patient. It will allow cancer and data scientists to 'look under the hood' using molecular and artificial intelligence (AI) approaches to identify patterns and discover genomic changes that may inform successful combinations of treatment options based on the molecular analysis of the patient's tumour.

The goal is that in five years the 15K gold standard cohort will be completed with the assistance of five regional cancer hubs across Canada, which includes BC Cancer.

In preparation to launch the 15K gold standard cohort project, working groups have been working to align on key issues and reach consensus on how the Marathon of Hope Cancer Centres Network will deal with specific issues including: patient engagement, data, technology, platform, agreements, and scientific questions. "Institutions across Canada have different approaches to key issues, but through working together – we will find ways to bring all participants in the network together for this to be a success. BC Cancer's participation and leadership has been evident from day one." says Herst.

"This is a continuation of the journey Terry started with his Marathon of Hope run in 1980 to eradicate cancer. We are continuing his legacy with this, our roadmap to cure cancer."

Cascadia Data Alliance Competition – A new era of international collaboration & innovation

The Cascadia Data Alliance is a program without borders. Formalized in 2017, the alliance includes the BC Cancer Research Institute, the University of British Columbia (UBC), the Knight Cancer Institute at Oregon Health & Science University (OHSU), the University of Washington eScience Institute (UW), the Fred Hutchinson Cancer Research Center (Fred Hutch), and Microsoft. The regionally cohesive international consortium is aimed at promoting excellence in science and breaking down data silos.

In May 2020, the Cascadia Data Alliance took their partnership to the next level by introducing the Cascadia Data Alliance Competition. With a multidimensional funding model, a steering committee was engaged to determine how the alliance could encourage new partnerships between collaborating organizations and decided to run an open competition between them; thus the Cascadia Data Alliance Competition was born.

"The principal investigators had to be from different institutions. If they were only from one institution, they would not be eligible – you had to prove there was a collaborative aspect," said Dr. Christian Steidl, Executive Director of Research at the BC Cancer Research Institute, and member of the Cascadia Data Discovery Initiative Steering Committee. "We reviewed not only the scientific excellence, but how each organization would collaborate together and leverage available data and infrastructure. The committee reviewed and rated the highest-ranking projects submitted through the open competition."

The projects were required to have at least on principal investigator (PI) from one of the primary participating institutions and collaborative projects between junior and senior investigators were encouraged.

In the end, three proposals were selected to receive funding through the inaugural competition:

Project Title: Functional Capabilities of the Gut Microbiome in Immune Checkpoint Inhibitor-Associated Responses

Principal Investigators: Dr. Kerry Savage (BC Cancer) in partnership with members from Fred Hutch and OHSU.

About the Project: Immune checkpoint inhibitors (ICIs) are a powerful new treatment option for a variety of tumours, but efficacy varies between patients and mild to life-threatening side-effects can occur. The bacteria that reside in a patient's gut have been shown to impact ICI efficacy and to predict the development of colitis side-effects, but it is not clear specifically which bacteria impact ICI response or toxicity. The group proposes to create a large, multi-institution repository of oral and stool samples from cancer patients undergoing ICI therapy. They will then use cutting-edge technology and data analysis tools, and the power of 'cloud' computing, to detail the genetic content of gut-localized bacteria (microbiome) in individual patients and how they are associated with clinical outcomes. The group expects to accomplish fast and accurate data analysis and visualization at each study site, allowing them to identify potential mechanistic drivers of ICI efficacy and toxicity, and thereby advance promising strategies to improve clinical outcomes for patients.

Project Title: Pathology AI for a Federated Quality Assurance Program: Ovarian Cancer Pilot

Principal Investigators: Dr. David Huntsman (BC Cancer) in partnership with members from Fred Hutch, OHSU and UBC.

About the Project: As type-specific treatments are being developed for patients with epithelial ovarian cancer (EOC), it has become important to accurately diagnose the distinct cancer types. The group's vision is to establish an international network for artificial intelligence (AI)-based, privacy-protected pathology quality assurance. As a proof of concept, the team is proposing to develop and deploy a machine learning-based ovarian cancer histopathology classifier. They plan to use privacy-preserving synthetic data generation to train an ovarian cancer classifier, using pathology images collected at their three institutions. They will specifically identify the privacy threats associated with the necessary data-sharing, and then develop technical and socio-ethical guidelines that can be deployed around the world. Their long-term vision is to establish a learning systems network with point-of-care diagnostic applications that could also inform similar advances in other cancers.

Project Title: Monitoring breast cancer: Bringing single-cell and liquid biopsy analysis to the cloud

Principal Investigators: Drs. Samuel Aparicio and Andrew Roth (BC Cancer) in partnership with members from Fred Hutch and UW.

About the Project: Breast tumour genetics can change during disease progression, leading to distinct tumour cell populations that often contribute to therapeutic resistance. The group proposed to perform state-of-the-art single-cell genomic sequencing on breast cancer biopsies and circulating tumour DNA (a.k.a.: liquid biopsies) to evaluate genetic changes during the course of a patient's therapy. They will develop novel methods to integrate these data to monitor dynamic shifts in tumour composition. They also propose to create a harmonized database to store, access, and share abstracted clinical data. The group will implement these solutions in the Azure cloud environment to support the cross-institutional study of tumour evolution and clinical outcomes in breast cancer. Their developments will facilitate future cross-institutional collaborations, and likely produce significant opportunities for clinical translation, including biomarker discovery for improved disease surveillance.

As these research projects continue through 2020 and beyond, Dr. Steidl is looking forward to the new opportunities this competition will bring to the future of cancer research. "I strongly believe in our collective ability to break down the silos that once kept our organizations apart. We are moving forward into a new era of strengthened scientific excellence in our regional area and are breaking down barriers to fully utilize our data structure and having the maximum output of our data sets."

The Cascadia Data Alliance Competition will continue to support science and research excellence and advance cancer understanding and outcomes for years to come.

Researcher Focus:

Dr. Dean Regier – defining research that benefits patients

BC Cancer senior scientist Dr. Dean Regier focuses on real-world evidence to support precision medicine implementation. In his role as the director of the Health Economics Support and Research Unit (HESRU) at BC Cancer and through his lab at the BC Cancer Research Institute, his work aims to improve methods of evaluating the benefit of health care by incorporating person-centred evidence into economic models that answer questions of equity and value for money.

He works with researchers and health care professionals, patients and the general public to define benefit according to patients' values and health care system priorities. His work aims to answer two important questions about cancer treatments: does it work? And can our health care system afford it? As the incidence of cancer is only expected to rise, these questions become increasingly important.

For Dr. Regier, 2020 was a formative year. His lab, PACER, which stands for patient-centred, accessible, and efficient applications of precision medicine, was the sole successful health stream applicant to Genome Canada's 'Genomics in Society Interdisciplinary Research Teams (GiSIRT)' competition. His application, called the Canadian Network for Learning Healthcare Systems and Cost-Effective 'Omics Innovation (CLEO), received $2.6 million dollars in funding over four years to deliver on four important goals related to advancing research, building capacity to deliver on this research, producing research that yields social and economic benefits for all Canadians, and informing the design of learning healthcare systems the turns genomic knowledge into sustainable cancer care.

Thinking about the future, Dr. Regier gives his thoughts on the potential of cancer research in his field.

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

I've noticed there has been more of an emphasis placed on the importance of mapping out resource allocation as it relates to both the expected patient benefit and overall population benefit. This paradigm shift has led to advances in the sciences that generate experimental and real-world evidence of clinical effectiveness and cost-effectiveness.

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

There will always be a balance between maximizing individual patient health and maximizing population health, especially given constrained budgets. I believe one of the most significant concerns facing cancer research is around how to most efficiently allocate spending. There are inherent challenges in how we configure our systems toward a learning health care system that generates the types of data we need to make real-world decisions.

What advice would you offer to young researchers just starting out?

I think success in research and academics comes down to patience, resilience, and the pursuit of excellence.

After my post-doctorate I wanted a tenure track faculty position at a leading university. Once I achieved this goal, my personal circumstances changed and I moved back to Canada. During that time and in the following years, it became clear that I had a lot to learn before I could be successful as an independent investigator. I am a lifelong learner and I feel that my work as a researcher at BC Cancer followed by becoming an independent investigator has allowed me the experiences and skills to realize sustained success in academics.

What are your thoughts on the future of research in health economics?

I think the future of my field is moving into interdisciplinary research endeavours that connect the dots between genomic, clinical, health services, and all patient-level data to support sustainable and patient-centred learning healthcare systems. This will require a system-wide change in how we think about capturing, harnessing, and using data that comes from everyday patient care with a broader move toward open science.

Service spotlight: BC Cancer Research Ethics

BC Cancer's research ethics team is responsible for overseeing the ethical conduct and decision making in research projects across BC Cancer. This powerhouse group ensures the ethical principles and regulatory guidelines of research are followed, promotes education into research ethics and integrity, undertakes research relating to research ethics, and develops policies that ensure alignment to research practices when new challenges emerge.

The team's primary responsibility is to protect the safety, wellbeing and rights of research participants. During 2020 as health care systems across the globe shifted to minimize the impact of COVID-19, research ethics worked with the BC Cancer research community on modifications to study enrollment, testing, drug delivery, and data monitoring in order to ensure patient safety and study integrity. Since March 2020, the research ethics team has had input into several local and national COVID-19 related projects, including studies on: genome sequencing in patients with COVID-19, the effects of COVID-19 as a co-morbidity to cancer on patient care and prognosis, the impact of screening and surgical delays due to COVID-19, and a questionnaire study which seeks to understand how the pandemic has affected people across Canada.

In addition to the work on COVID-19, the team continued their focus on streamlining processes. As the complexity of science advances, the effect has created a significant administrative load for researchers. The research ethics team has developed key initiatives to streamline processes.

One of the ways they have done this is by positioning the BC Cancer Research Ethics Board (REB), which the team manages, as the disease-specific expert board province-wide. This means that BC Cancer researchers who undertake adult oncology research spanning different regional health authorities or institutions only need to submit their project to BC Cancer's REB for ethical review for a single review rather than multiple reviews.

In addition, a single privacy review is undertaken by the PHSA privacy office. The single review model is more effective and allows for a more timely review process. This is a direct benefit to patients as they can be assured that their project has been expertly reviewed and has ongoing oversight from oncology specialists. Another benefit is that they gain access to research projects in a timely manner, which is critical for many cancer patients in terms of being able to intervene with novel treatment options before further disease progression, which could lead to improved outcomes.

Looking towards the future, the research ethics team is working on the assessment of risks and benefits and ethical implications around genomic research, including biobanking, genetic discrimination, and balancing the rights and privacy of individuals who may have hereditary testing done with the rights of relatives to be made aware of findings that could have implications on their health. The team is also looking at artificial intelligence and big data, and impacts on privacy and confidentiality as material is shared across borders or in partnership with commercial collaborators. These issues are paramount for patient safety as research becomes more complex and globalized.

COVID-19 and cancer research

How BCCRI's epidemiology and public health research made a pivot during the pandemic

The COVID-19 pandemic caused a shift in health care systems around the world. Before the pandemic, Drs. Parveen Bhatti and Stuart Peacock were conducting population-based studies of cancer and evaluating how to improve patient outcomes. COVID-19 caused a pivot as both Dr. Bhatti, senior scientist and scientific director of Cancer Prevention and Dr. Peacock, distinguished scientist and co-director of Applied Research in Cancer Control (ARCC), began examining how COVID-19 now fits into the equation as they conduct research in real-time in an effort to collect data and address the challenges that the pandemic brought to cancer patients and the public.

Adding COVID-19 data to biospecimen collection

Dr. Bhatti's work at BC Cancer aims to better understand how risk factors cause cancer in an effort to develop more successful intervention strategies and prevent the occurrence of cancer. In addition to this work, Dr. Bhatti is the scientific director of the BC Generations Project (BCGP); B.C.'s largest-ever health study. This provincial project feeds into a national research initiative called the Canadian Partnership for Tomorrow's Health (CanPath); a study comprised of data and biospecimens from people in B.C. and across Canada which is used to help researchers learn more about how environment, lifestyle, and genes contribute to cancer and other chronic diseases. Before the pandemic, the team was gearing up to initiate collection of a second series of biospecimens from BCGP participants. The data would have allowed researchers to examine how biomarker measurements change over time and potentially identify much more accurate predictors of future cancer occurrence.

Leveraging the existing infrastructure available through BCGP and CanPath when the pandemic began, Dr. Bhatti and the other CanPath scientific directors were able to successfully apply for funding which allowed them to add COVID-19 data to information they were already collecting from participants for cancer research. In addition to questionnaire data focused on the pandemic, blood samples would be collected to measure COVID-19 antibody levels. Originally, blood collection required participants to go into a medical laboratory to provide samples. However, due to COVID-19 restrictions, this would not be possible or safe. Thanks to quick thinking, the BCGP and CanPath teams found an alternative method that allowed them to send fingerstick blood sample kits directly to participants for in-home collection. This pivot was only one example of the research ingenuity that was addressed in response to COVID-19.

"This experience has allowed me to witness firsthand the incredible resilience, dedication, and resourcefulness of the BCGP team and BC Cancer Research Institute staff. Despite the unprecedented challenges and uncertainties that have arisen from the pandemic, our team has worked tirelessly to minimize disruptions to critical, lifesaving research," says Dr. Bhatti.

When the research is complete, Dr. Bhatti and his team will have a far better understanding of infection dynamics of COVID-19 and identify the biological, societal, and behavioural factors that affect susceptibility to the virus. This important data will enable public health officials and clinicians to be more targeted with prevention and treatment strategies. BCGP will gather data and track health outcomes from participants until the year 2058. The totality of this information, collected over many years among a large study group, will provide a rich source of information for answering important questions about the origins of cancer and chronic diseases – now including COVID-19.

COVID-19 impact on health services

Reducing health inequalities and ensuring more effective health services are the cornerstones of Dr. Peacock's work. The impact of COVID-19 on his work was clear and undeniable. Very early on, it became evident that people were postponing cancer screening visits, introducing delays which could influence the number and severity of cancer diagnoses in the future. Visitor restrictions at hospitals and cancer centres would also have an impact on wellbeing, especially for patients and their families. Dr. Peacock began collaborating quickly with national and international colleagues to address these issues.

While the pandemic had an immediate and significant negative impact on health services, there was also a degree of innovation that sprang from COVID-19. One key example is a renewed focus on virtual health care, which grew exponentially in 2020, and allows people living in remote and rural communities access to health care without traveling into larger towns or cities.

"The weekend we went into lockdown in March, I was incredibly impressed by the pivot that the health system and my colleagues in the research side of the health system made, all in the period of 48 hours. It was remarkable to see researchers modifying some of their work to provide extra service to the health system if they needed it. I've been doing this almost thirty years now and I've never seen the health system dramatically change overnight and reorient with the genuine notion of the common public good at the center of it," says Dr. Peacock.

Dr. Peacock and ARCC have been working on a study examining patient reported experiences and psycho-social outcomes in the era of COVID-19 – both good and bad. In the coming years, Dr. Peacock and the ARCC team will be monitoring patients who started their cancer journey in the first wave of COVID-19. They will be assessing patients who received their diagnosis by virtual health appointments rather than during an in-person visit, and those coming in to get chemotherapy under the visitor restrictions that often require them to attend chemotherapy appointments alone.

A second study will be reviewing the overall cost of COVID-19 itself and its impact on the entire health system. ARCC and Dr. Peacock are leading the Canadian part of a global consortium to model the impact of COVID-19 on cancer screening programs, treatments, and patient outcomes. This effort, spearheaded by the Union for International Cancer Control, will provide global health services research leadership for cancer systems both during the COVID-19 pandemic and in the years that follow.

It is undeniable that COVID-19 has brought about real challenges. For researchers like Drs. Bhatti and Peacock, the key to their work moving forward is paying attention how this virus has impacted populations and conducting research that will give everyone better access to cancer programs and services and improving the overall wellbeing of patients, survivors, and their families.

Resiliency in research: the COVID-19 pandemic

How the Covid-19 pandemic impacted clinical trials

The COVID-19 pandemic caused a major shift in all areas of health care. Over the period of just a few days, following a declaration from the Provincial Health Officer and Minister of Health, some non-essential cancer services had to be temporarily suspended. Research activities including clinical trials at BC Cancer were impacted during what has been referred to as "the first wave" in March 2020. New patient recruitment for clinical trials was deferred and patients already on clinical trials were triaged into categories of who could be seen virtually and who had to continue receiving care inside the centres. Clinical trials staff worked behind the scenes to maintain patient safety first and foremost and then to maintain the integrity of clinical trials that were already in progress.

"The impact was significant at the time," said Dr. Bernie Eigl, medical oncologist and director of provincial clinical trials at BC Cancer. "I have to say things went much more smoothly than they potentially could have. The clinical trials team moved quickly and efficiently and functioned incredibly well. I think that allowed us to minimize the amount of time we were on hold and get going again quickly. I'm incredibly proud of B.C. for being able to do that."

After three weeks clinical trials slowly began to resume. "We were writing the rule book as we went along but coming out of the first wave we knew it was important to develop a standard operating procedure for pandemics. Not just for clinical trials but also labs, diagnostics, patient care – everything." When re-opening, significant considerations included ensuring patients were not going to be exposed to any risk and on prioritizing which of the many clinical trials were most critical to maintain. For example, patients who would not have otherwise had a standard of care option or the trials that used the least resources but had the potential to make the biggest clinical impact. "There was a lot to consider in the early days when we were trying to open as much as we could without burdening the larger health care system."

The shut down and re-opening process provided an invaluable opportunity to rethink long established processes. "A challenge like this gives you the opportunity or the necessity to think about who does what and why and so luckily we can get some efficiencies out of that. The pandemic made us think about every test or report or process that we put a patient through and asking ourselves, 'is this really necessary?' Already we've adopted remote monitoring for both patients and trial evaluators, which we didn't have before. It's a work in progress but I think that's a big positive." Remote monitoring would be most impactful for patients who live in more remote or rural areas who could now be monitored either directly from home or at a smaller centre or lab closer to their home. This initiative will continue to be a priority over the coming years.

While remote monitoring will be helpful for patient care, Dr. Eigl was quick to add that it will be important to continue to see patients in person to support emotional well-being. "Holding a hand, giving a hug, examining a patient hands-on; not being able to do those things probably doesn't necessarily have a huge impact on the patient's care but it could possibly have a big impact on their emotional care and I think that's a huge part too."

Although there are negative consequences to clinical trials shutting down, including patient well-being and the financial implications of lost revenue from philanthropy, Dr. Eigl also noted how the adversity brought people together. "We're resilient. The people we work with, the organizations we partner with, everyone that's doing clinical trials were as accommodating as they could be. There's a morale piece – and this isn't specific to clinical trials – but in our cancer world our patients are at higher risk for bad outcomes if they do get COVID-19 and we're still managing this within the population. It has really required people to step out of their comfort zones and do things that maybe aren't in their job description just to keep things moving. I've learned that I'm lucky to be working in a highly functional organization because we really did come together and I'm super grateful for it."

A bioinformatics method may help uncover link between immune system variability and COVID-19 susceptibility

COVID-19 can have symptoms that range from mild to life-threatening. This is due to several factors including age, pre-existing health conditions, and differences in genetics and immune responses. As researchers around the world work to better understand the factors that impact COVID-19 severity, novel tools that enable scientists to mine large datasets are needed.

In a study published in the journal Bioinformatics, GSC distinguished scientist Dr. Inanc Birol and group leader René Warren demonstrated the feasibility and utility of their bioinformatics tool, HLAminer, to investigate the role a person's unique immune system plays in COVID-19 susceptibility.

Human leukocyte antigen (HLA) proteins are essential components of a person's immune response to infectious disease. HLA proteins are present on the surface of cells and are responsible for telling the immune system whether or not an infection is present.

There are two classes of HLA proteins. If a cell engulfs a virus or becomes infected by one, HLA class II or HLA class I proteins, respectively, will display viral peptides on the cell surface. Specialized immune cells, called T cells, will then detect these viral peptides and activate an immune response.

In humans, there is a large degree of variability in both classes of HLA and different HLA alleles have been shown to impact disease outcomes. To enable researchers to explore the link between HLA alleles and disease, Warren developed a bioinformatics tool called HLAminer in 2012. The tool mines high-throughput next-generation sequencing data.

"Because of the central role HLA plays in a person's immunity and its association with disease susceptibility, knowledge about the HLA profiles of COVID-19 patients and asymptomatic COVID-19 positive individuals could help inform public health response strategies," says Warren.

In their study, Warren demonstrated that HLAminer can be used to determine HLA types from samples taken from patients with COVID-19. RNA was extracted from eight patient samples and HLAminer was used to analyze RNA-sequencing data, successfully identifying HLA alleles for all samples.

While the analysis of HLA types in this study uncovered some intriguing findings, the number of patients studied was small and further analyses are needed. This study provides an effective method that will enable researchers to enhance their understanding of the interplay between a person's immune factors and infectious diseases, including COVID-19.

"We hope that our report will sensitize scientists and clinicians to the importance of HLA determination and the practicality of deriving this information from COVID-19 clinical samples using RNA-sequencing, likely readily available and from sizeable cohorts," says Warren.

Pearls to pivoting a multi- disciplinary prostate cancer survivorship program during COVID-19

The COVID-19 global pandemic has had profound implications on health care delivery. In an effort to slow the transmission of the virus, some non-essential health services were temporarily suspended or pivoted to provide virtual health services for patients. The Prostate Cancer Supportive Care (PCSC) program, which provides multidisciplinary care for prostate cancer patients and their partners across B.C., was impacted by these temporary closures. To adhere to safety guidelines, the program went through a complete transformation of its in-person clinic services to delivery via virtual health. Health care providers and most patients adapted well to the change from in-person visits to virtual health appointments. Education sessions are now delivered exclusively through WebEx, Zoom, or pre-recorded videos posted to the program website and the full range of patient handouts and educational resources were converted to digital files and emailed to patients. While some limitations exist with virtual health, the PCSC is finding ways to overcome them. Virtual health care platforms and digital resources will continue to benefit PCSC patients who are geographically distanced from health care facilities even beyond the COVID-19 pandemic. The shift of the PCSC program to digital health started at the Vancouver site and was subsequently implemented across all BC Cancer PCSC sites.

How B.C. scientists are addressing the COVID-19 testing challenge

As the COVID-19 pandemic continues, public health authorities around the world are facing a significant challenge: ensuring a large enough supply of reagents to scale-up diagnostic testing. Researchers at Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer, the University of British Columbia (UBC) and the BC Centre for Disease Control (BCCDC) are working to develop new non-proprietary reagents to support current and future testing in British Columbia. Dr. Martin Hirst, senior scientist at the GSC and associate director of UBC's Michael Smith Laboratory (MSL), is leading this project with support from Genome BC through its Rapid Response Funding for COVID-19 Research program. The project is a collaborative effort between six B.C. labs, including, at the GSC, Drs. Robert Holt, Gregg Morin and Martin Hirst; at MSL, Dr. Thibault Mayor; and at LSI, Drs. Sheila Teves and Ivan Sadowski. They are using the infrastructure at the GSC, UBC and BCCDC to develop scalable and automated non-proprietary workflows for the development of stable reagent supply chains.

They are producing reagent formulas and automated workflows, shared initially between the UBC and BCCDC sites and, following qualification, to testing sites in B.C. and across Canada. They are working with private sector partners to formulate and produce reagents at scale and documenting automated workflows under Quality Management Systems to provide as turn-key solutions to testing sites in B.C. and beyond.

This work will be carried out at MSL and the Life Sciences Centre (LSC) at UBC, the GSC at BC Cancer and Public Health Lab at BCCDC. This research is ensuring a secure supply of laboratory reagents needed in B.C. to maintain and expand its capacity for COVID-19 testing. These reagents will undergo further validation and production will be scaled-up to meet increased testing demands in the province. The establishment of molecular resources, protocols and formulations to support large scale viral testing will also ensure that Canada is prepared to meet future pandemics, particularly in the case of any disrupted global supply chains. Ultimately, a stable supply of reagents, produced locally, will ensure testing can meet demands, resulting in enhanced contact tracing and isolation that will limit transmission and help to manage the spread of COVID-19.

B.C. scientists to begin genetic sequencing on Canadians with COVID-19

As part of a federal funding announcement in April 2020, Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer was selected as one of four Canadian institutions on the forefront of using genome science to understand how different people respond to COVID-19 infection.

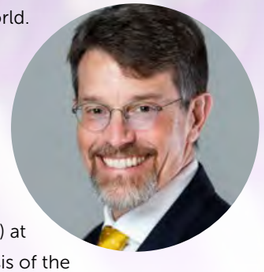
Researchers at the GSC will use cutting-edge genomic technology to sequence the DNA of thousands of Canadians who have tested positive for COVID-19. They expect to identify how the disease is transmitted and which people may be more vulnerable to the disease. These findings will help better inform public health policy to help keep Canadians safe by helping to better assess, triage and treat the most vulnerable COVID-19 patients.

"Scientists at the GSC were among the first in the world to sequence the SARS coronavirus genome in 2003. This funding will further Canada's contributions to our collective understanding of COVID-19 infection and disease prognosis," said Dr. Steven Jones, director & head of Bioinformatics at the GSC.

Biology & Genetics

An in-depth analysis of cervical cancers in Ugandan women

Cervical cancer disproportionately affects women in sub-Saharan Africa where it is the most common cause of cancer-related death and has disease rates higher than any other region in the world. Yet worldwide studies of the disease have predominantly focused on non-African populations. An international team of researchers, in work led by Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer, published an analysis of the genomic characteristics of cervical cancers in Ugandan women in the journal Nature Genetics. In the study led by Dr. Marco Marra, director of the GSC, researchers analyzed the genomes, transcriptomes and epigenomes of cervical tumours from 118 patients being treated at the Uganda Cancer Institute. Cervical cancer is the fourth most common cancer worldwide with 80 per cent of cases occurring in low- and middle-income countries. The disease is caused by infection with human papillomavirus (HPV), a sexually transmitted virus capable of causing cancer. While screening and vaccination are effective preventative measures, vaccination rates in low- and middle-income countries remain low. Resource limitations further complicate prevention and treatment strategies, leading to a predicted 50 per cent increase in cervical cancer mortality by 2040.



HPV type impacts cervical cancer characteristics and disease prognosis

HPV viruses are divided into categories called clades. HPV-16 and HPV-18, belonging to clades A9 and A7, respectively, are the most common causes of cervical cancer, detected in at least 70 per cent of cases. By comparing tumours caused by these two HPV clades, the research team identified previously uncharacterized differences and were able to correlate these findings to disease prognosis.

"High-risk HPVs are often grouped together, and they're not really investigated separately," says Vanessa Porter, a PhD candidate in Dr. Marra's laboratory and co-first author on the study. "This study is unique in that it looks at how different high-risk HPV types belonging to distinct clades impact cervical cancer tumour characteristics."

"This study not only highlights stark differences in biological profiles between high-risk HPV clades, but it also demonstrates the utility of looking in populations beyond North America or Europe where large-scale cancer studies have been traditionally conducted," says Emma Titmuss, research programmer at the GSC and co-first author on the study. "Understanding the biological differences between HPV clades is of great interest as this will hopefully lead to improved therapeutics."

By comparing data from tumours caused by different HPV clades, the researchers detected more than 100,000 differences in epigenomic DNA modifications that impact distinct genomic regions and more than 700 genes that were differentially expressed, uncovering a molecular explanation for differences in prognosis. Tumours caused by clade A7 HPVs had higher expression of genes that were indicative of a more aggressive cancer, consistent with disease outcome.

"HPV has been documented to interact with epigenomic modifiers in tumour cells, and many of the viral proteins have a direct effect on the host epigenome. But the clade specificity of this had not yet been explored," says Porter. "These findings indicate that there are clear differences in the epigenomes and transcriptomes of tumours affected by different clades and that these differences may impact disease prognosis."

Hypothesis generating research

"This project is a collaboration with many different institutions and people in Uganda. It has been an incredible experience to be part of something so big," says Dr. Alessia Gagliardi, staff scientist in Dr. Marra's group and lead author on the study.

The project was part of the National Cancer Institute's HIV+ Tumour Molecular Characterization Project and was a collaboration between researchers at the GSC and at research institutions across the USA. The study would not have been possible without the Fred Hutchinson Cancer Research Center and the Uganda Cancer Institute who oversaw sample and data collection in Uganda.

This study is a rich analysis of the genomic characteristics of cervical cancers and will provide researchers around the world with insight into cervical cancer and particularly the influences HPV can exert on tumour genomes.

This study highlights the importance of diversity and inclusivity in study cohorts and suggests that further studies such as this are needed to provide a truly global genomic perspective on cancers and their various causes.

Age is a factor in the onset of breast cancer and in physiological changes of breast tissue

Dr. Sam Aparicio published a paper in Nature Cancer titled "Age-correlated protein and transcript expression in breast cancer and normal breast tissues is dominated by host endocrine effects". The incidence of breast cancer increases with age, particularly after 50. Interestingly, levels of circulating estrogen in women decrease significantly after menopause, which is roughly around the age of 50. Dr. Aparicio and team investigated large breast cancer datasets to identify how age affects the development of breast cancer. They observed that a large fraction of the genes from breast cancer datasets show age-correlation while in other cancer types, such as lung, thyroid, kidney and prostate, this trend was much smaller. The strongest age-related gene in breast cancer was that of estrogen receptor along with other estrogen regulated genes. They also found that while breast tissues are the most sensitive to age-related changes, a small number of estrogen regulated genes in lung cancers were identified, indicating that estrogen may play a role in some lung cancers. Their data shows most age-correlated gene expression in breast cancers are likely due to gradual changes in age-related levels of physiological estrogen signaling.

Aging-associated inflammation as a driver of myeloid malignancies

In a study published in the journal Blood, led by Dr. Aly Karsan, distinguished scientist at Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer, researchers used various single cell sequencing and functional technologies to study the cells of patients with myeloid cancers. These findings provide evidence that inflammation plays a key role in aging- associated myeloid malignancies and shed light on a novel treatment strategy-using anti- inflammatory therapies-for elderly patients with reduced expression of a certain microRNA miR-146a.

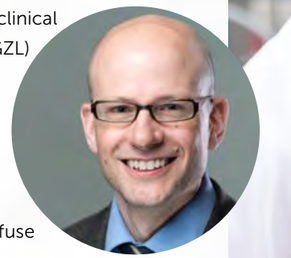
Using existing blood pressure medication to make cancer tumours more sensitive to radiation therapy

Dr. Kevin Bennewith published a study in Cancer Letters "Angiotensin II type 1 receptor blocker telmisartan inhibits the development of transient hypoxia and improves tumour response to radiation" demonstrating how a medication normally given to individuals with high blood pressure can be repurposed to stabilize tumour blood flow and improve oxygen delivery to hypoxic, or poorly oxygenated, tumour cells. This study, published by first-author graduate student Brennan Wadsworth showed that hypoxia can develop in solid tumours by several mechanisms, including unstable blood flow that limits the delivery of oxygen to regions of the tumour. This so-called "transient" hypoxia exposes cells to oxygen tensions that change over time and is thought to create tumour cells that are particularly resistant to radiation therapy and are more aggressively metastatic. Drugs have been developed to try and normalize tumour blood flow and reduce transient hypoxia, although they only work for short periods of time and have not been overly successful in the clinic. Research has found that the angiotensin II type 1 receptor blocker telmisartan decreases the deposition of collagen in the tumour by cancer- associated fibroblasts, increases net tumour blood flow to the tumour, and stabilizes microregional fluctuations in tumour blood flow. This blood flow stabilization decreases the development of transient tumour hypoxia and makes the tumour more sensitive to radiation therapy, providing a novel strategy to manipulate the solid tumour microenvironment for therapeutic benefit.

New combination treatment targets "cancer stem cells"

Dr. Xiaoyan Jiang, in collaboration with Dr. Shoukat Dedhar, published a high-impact paper in Cell Stem Cell "Integrin-linked kinase mediates therapeutic resistance of quiescent CML stem cells to Tyrosine Kinase Inhibitors". This landmark study paves the way for new combination therapeutic strategy for the treatment of CML with a novel ILK inhibitor developed in Dr. Dedhar's lab at the BC Cancer Research Institute.

Better classification for rare grey zone lymphoma subgroups



Dr. Christian Steidl and researchers at the BC Cancer Centre for Lymphoid Cancer (CLC) completed the Grey Zone Lymphoma Project. Lymphomas have more than 60 subtypes that are classified based on morphology, immunophenotype, genetic and clinical features. Grey zone lymphoma (GZL) is a rare lymphoma that cannot be accurately classified into the recognized subtypes and shares common morphologic and phenotypic features with classic Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL), in particular primary mediastinal B-cell lymphoma (PMBCL). Dr. Steidl and his team at the CLC in collaboration with the French LYSA group identified 2 GZL subgroups that have distinct biological and clinical features; PMBCL-like and DLBCL-like. The former is associated with a thymic clinical presentation. The results were recently published in Blood Advances and Blood.

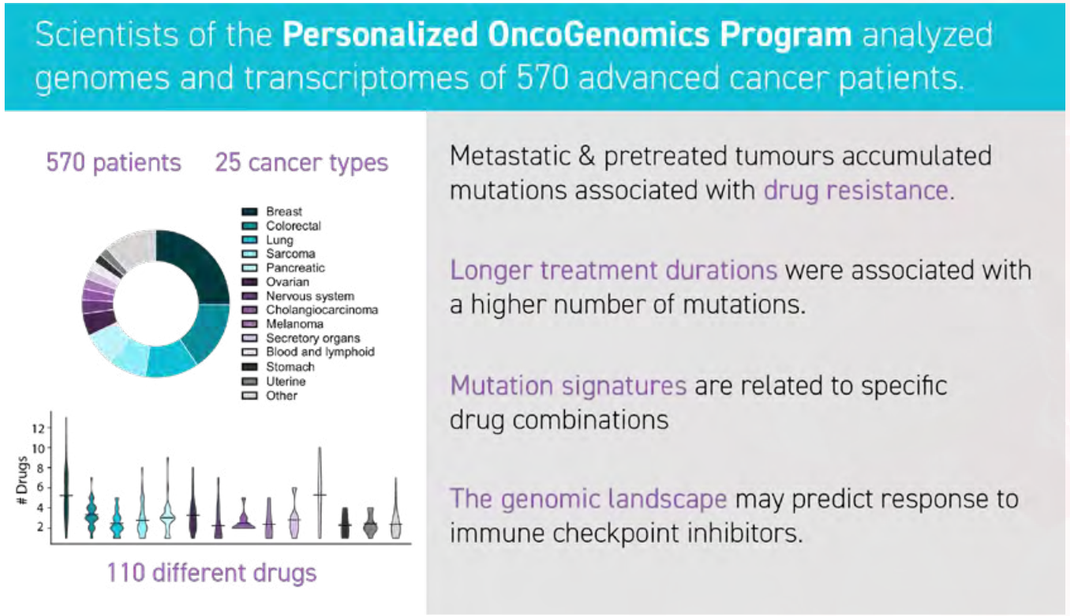
Clinical Research & Clinical Trials

DNA sequencing reveals the scars of cancer treatment

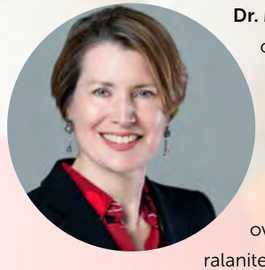
Dr. Marra and colleagues published a pan-cancer analysis of the POG570 cohort in Nature Cancer. The study focused on DNA mutations that occur in advanced-stage cancers to shed light on the genetic alterations that can happen following cancer treatment and tumour spread. Notable findings include evidence of prior cancer treatment written within the patients' DNA and the presence of a pattern of alterations that may predict a patient's response to future therapy.

Analyses revealed that tumours which had been treated with chemotherapy in the past had an increased number of mutations. Furthermore, the longer a patient received chemotherapy the more mutations they had, which was associated with chemotherapy resistance. These findings provide important insight into how genetic alterations may cause treatment resistance.

Analyses also identified patterns of genomic alterations that are associated with the immune system. These patterns correlated with patient survival and response to a type of chemotherapy called immune checkpoint inhibitors. These findings may enable clinicians to predict which patients will respond well these therapies and which patients will not.



New clinical trial for metastatic castration-resistant prostate cancer



Dr. Marianne Sadar co-discovered a drug that entered phase I clinical trials in patients with metastatic castration-resistant prostate cancer. Dr. Sadar's group tested over 250 analogs of the drug ralaniten to help select EPI-7386 as the clinical candidate for the treatment of advanced prostate cancer. This is the first study of Oral EPI-7386 in humans, and could lead to new treatment options for patients with metastatic castration-resistant prostate cancer. This work was completed in collaboration with ESSA Pharma Inc.

DNA sequencing reveals mechanisms of treatment resistance in patients with diffuse large B cell lymphoma

In a study published in the journal Blood Advances, led by **Dr. Ryan Morin**, senior scientist at Canada's Michael Smith Genome Sciences Centre (GSC) at BC Cancer, researchers used targeted DNA sequencing to identify mutations arising in diffuse large B-cell lymphoma (DLBCL) patients with relapsed disease.

The study used liquid biopsies, where tumour DNA is collected from a blood sample rather than from a more invasive tumour biopsy, to monitor disease progression following treatment with R-CHOP chemotherapy. Researchers identified six genes in which mutations could contribute to R-CHOP failure and resistance.

This study not only uncovers mechanisms of treatment resistance, but also provides insight into the importance of genetic testing for DLBCL patients and demonstrates how this could be accomplished using blood samples. Screening for mutations in key genes at the time of diagnosis and throughout treatment with R-CHOP may help clinicians better manage treatment strategies for DLBCL patients.

New clinical trial for PET neuroendocrine tumour imaging agent

The clinical trial of a PET imaging agent developed by **Drs. François Bénard, Kuo-Shyan Lin** and **David Perrin** was started at BC Cancer in June, 2020. The new imaging agent can be produced more effectively and in larger quantities using medical cyclotrons and results in higher resolution images for neuroendocrine tumours than what is currently being used by the Functional Imaging department.

Research discovery may offer new treatment options for people diagnosed with rare form of ovarian cancer

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a particularly devastating cancer that has no effective treatments. In a study published in Clinical Cancer Research, **Dr. David Huntsman** and colleagues have found a way to eliminate a compound within the SCCOHT tumour environment that essentially starves the cancer to death while having minimal effect on normal cells. This discovery has been validated in pre-clinical studies and is another step closer to better understanding a very aggressive form of ovarian cancer and providing better treatment outcomes for women diagnosed with this disease.

Molecular characterization of central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma found in the central nervous system. The low incidence rate and lack of tissue/biopsy materials have led to a poor understanding of this disease. Using the BC Cancer Centre Lymphoid Cancer (CLC) database, the CLC clinical team has been able to gather tissue samples of 115 patients diagnosed with PCNSL to evaluate molecular features of this entity. Similarly, the BC Cancer team led by **Dr. Savage** has examined primary testicular DLBCL and its biomarker association with clinical outcomes. The study showed that cases with either BCL6 and/or PDL rearrangements had an increased risk of CNS relapse. To further investigate molecular biomarkers of CNS relapse, the BC Cancer team collaborated with Princess Margaret Cancer Centre to comprehensively characterize CNS relapse. The results demonstrated that tumours leading to relapse are molecularly and genetically distinct from primary/diagnostic tumours, and also revealed that intra-tumoural heterogeneity gave rise to subclones in CNS, providing support for the clonal divergent mechanism underlying CNS relapse .

Evaluation of bendamustine and rituximab as induction therapy in mantle cell lymphoma

Mantle cell lymphoma (MCL) is an aggressive, incurable type of B-cell lymphoma, with a median survival rate of 38 months. Using retrospective data, the clinical team at the BC Cancer Centre for Lymphoid Cancer (CLC) evaluated a preferred chemotherapy mixture of bendamustine and rituximab (BR) used to treat MCL patients. The team discovered a significant improvement in survival rate in patients treated with BR. Randomized clinical trials evaluating combination treatments including BR are ongoing.

Technology Development & Commercialization

GSC spinoff Coastal Genomics takes the next step

GSC spinoff company Coastal Genomics was formed in 2013 to commercialize high throughput DNA size selection technology for genomics projects. The technology was developed initially for The Cancer Genome Atlas project, and has recently been used in cell free DNA purification. Cell free DNA (cfDNA) is DNA that circulates in a patient's bloodstream and the characterization of cfDNA can provide diagnostic insights for cancer.

Coastal Genomics was recently acquired by UK-based Yourgene Health, which will significantly strengthen Coastal's ability to distribute instruments for DNA size selection, including LightBench and the fully automated NIMBUS Select. For Dr. Robin Coope and his team, having Coastal Genomics achieve this success paves the way for future technology development projects.

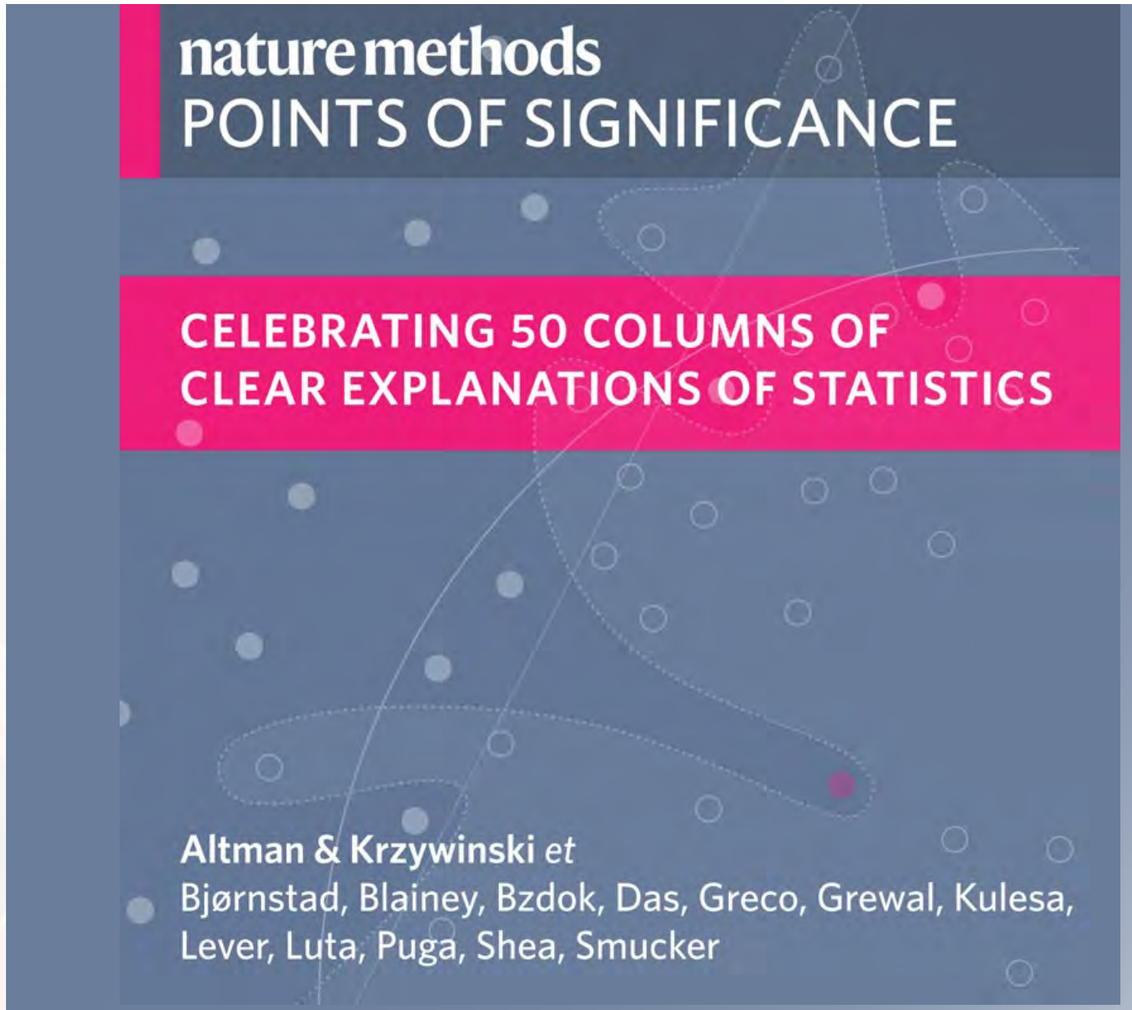
BC Cancer start-up Cytapex Bioinformatics Inc. acquired by Insightful Science, LLC

In 2016 Dr. Ryan Brinkman founded Cytapex, a bioinformatics contract research organization to commercialize cytometry informatics software he developed at BC Cancer. Cytapex partners with leading pharmaceutical, biotechnology, and medical device companies to improve and automate high-throughput and high-dimensional cytometry informatics for basic and clinical research, biomarker discovery, and clinical trials. On May 20th, 2020 Cytapex was acquired by Insightful Science.

50th Points of Significance column published in Nature Methods

In August 2020, GSC staff scientist Martin Krzyinski published his 50th article in Points of Significance, a popular column in the journal Nature Methods. The column, launched in 2013, is devoted to enhancing statistical literacy among life scientists. The 50th article was titled "Uncertainty and the management of epidemics" and was co-authored by Dr. Naomi Altman, professor of Statistics and Bioinformatics at Pennsylvania State University and co-founder of the column with Mr. Krzyinski. Since starting seven years ago, these 50 articles have been accessed 471,000 times.

Many articles focus on statistical methods that are widely used, or misused, in biological sciences or are inspired by current events such as modeling epidemics.



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