The Terry Fox Research Institute (TFRI) BC Node Research Day offers an informative and engaging program of research knowledge translation and exchange. The focus this year was the TFRI Marathon of Hope Cancer Centres Network (MoHCCN) and BC Cancer’s projects and activities in the MoHCCN. Presentations were delivered from each of the seven projects that comprise the launch of MoHCCN at BC Cancer, a presentation from Dr. Jim Woodgett, President of TFRI, and a panel discussion moderated by Stuart McNish, Host of Conversations That Matter.

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Speakers

In order of appearance.

Dr. Marco Marra, PhD, FRS(C), FCAHS, OBC, Director, Canada’s Michael Smith Genome Sciences Centre (GSC); Distinguished Scientist, BC Cancer Research Institute; Canada Research Chair in Genome Science, Professor, Department of Medical Genetics, Faculty of Medicine, University of British Columbia (UBC); and TFRI, British Columbia Node Leader

Dr. Francois Benard, MD, Senior Executive Director, Research & Distinguished Scientist, BC Cancer Research Institute; BC Leadership Chair in Functional Cancer Imaging, and Professor, Radiology, UBC

Dr. Jim Woodget, PhD, President & Scientific Director, Terry Fox Research Institute; and Senior Scientist, Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital

Dr. Daniel Renouf, MPH, MD, FRCPC, Medical Oncologist, BC Cancer; Assistant Professor of Medicine, UBC; Co-Director of Pancreas Centre BC; and Co-Chair, National Cancer Information Centre, Pancreatic Cancer Disease Group

Dr. Rod Rassekh, MHSc, MD, Investigator, Michael Cuccione Childhood Cancer Research Program, BC Children’s Hospital and Research Institute; and Clinical Assistant Professor, Division of Hematology, Oncology & BMT, Department of Pediatrics, Faculty of Medicine, UBC

Dr. Rebecca Deyel, MHSc, MD, Pediatric Oncologist and Clinician Investigator, BC Children’s Hospital and Research Institute; Co-Lead, Pediatric Precision Oncology Program in B.C.; and Co-Lead, Therapeutics Node, PRecision Oncology For Young peopLE (PROFYLE) program

Dr. Aly Karsan, MD, Distinguished Scientist, GSC, BC Cancer Research Institute; and Professor of Pathology and Laboratory Medicine, UBC

Dr. David Sanford, MD, FRCPC, Clinical Assistant Professor, Vancouver General Hospital (VGH), Leukemia/BMT Program of BC, Division of Hematology, Department of Medicine, UBC

Dr. Janessa Laskin, MD, Medical Oncologist, BC Cancer; Associate Professor, Department of Medicine, UBC; and Clinical Lead of the Personalized OncoGenomics (POG) program

Dr. David Scott, MBChB PhD, Hematologist, Clinician-Scientist, and Clinical Director of the Centre for Lymphoid Cancer, BC Cancer Research Institute

Dr. David Schaffer, MD, FRCPC, Associate Professor, Department of Pathology & Laboratory Medicine, UBC, Head, Department of Pathology and Laboratory Medicine, VGH, and Co-Director of Pancreas Centre BC

Dr. Torsten Nielsen, MD/PhD FRCPC, Clinician-Scientist Pathologist, VGH and BC Cancer; Director, MD/PhD Program, UBC; and former Chair of the CCTG Sarcoma Disease Site Committee

Dr. Martin Hirst, PhD, Distinguished Scientist, Head of Epigenomics, GSC, BC Cancer Research Institute; Professor, Department of Microbiology & Immunology, and Associate Director, Michael Smith Laboratory, UBC

Dr. Stephen Chia, MD, Medical Oncologist, BC Cancer; and Professor & Head, UBC Division of Medical Oncology

Dr. Samuel Aparicio, BM, BCh, PhD, FRCPath, FRSC, Nan & Lorraine Robertson Chair in Breast Cancer Research; Head, Department of Breast Cancer & Molecular Oncology, BC Cancer Research Institute; and Canada Research Chair in Molecular Oncology & Professor in the Department of Pathology & Laboratory Medicine at UBC

Dr. Nadine Caron, MD, MPH, FRCSC, General & Endocrine Surgeon, University Hospital of Northern BC; First Nations Health Authority (FNHA) Chair in Cancer and Wellness, & Professor of Surgery, UBC; Co-Director, UBC Centre for Excellence in Indigenous Health; and Senior Scientist, GSC
Dr. François Bénard, MD provided a historical summary about the Terry Fox Research Institute’s (TFRI) Marathon of Hope (MoH) from the perspective of British Columbia (BC). TFRI Marathon of Hope Cancer Centres Network (MoHCCN) is a $150 million national initiative. The primary goal of the MoH is to link cancer centres across Canada to share data and research, and enhance precision cancer opportunities for all Canadians. This talk was concluded with a discussion of future goals, current activities, challenges, and opportunities.

An open call was issued for proposals in B.C. Of the 19 proposals submitted, seven projects were selected (discussed through the Day):

1. Personalized OncoGenomics (POG)
2. PANGEN—Pancreatic cancer precision medicine
3. Biomarker-driven clinical management of relapsed lymphoid cancers in the era of genomic medicine
4. PRception Oncology For Young peopLE (PROFYLE)
5. Genomic and epigenomic sequencing to understand resistance and relapse in AML
6. Enabling Precision Oncology of Sarcomas in Canada
7. B-Precise: Biology of Breast Cancer and Triple Negative Breast Cancer
Dr. Woodgett talked about major TFRI programs supported in the 2021-2022 fiscal year. COVID-19 had a major impact on funding (e.g., less funding, programs not offered, etc.), though the situation is improving.

He also went over Marathon of Hope Cancer Centres Network (MoHCCN) and why it is needed, risks, benefits, etc., before finishing with current ongoing developments at TFRI.

**Terry Fox New Frontiers Program Project Grants**
- In this year’s competition, 13 letters of intent were received: three renewals of previous projects, plus 10 new project proposals. Out of the 13, seven were invited to submit a full application: all three renewals, plus four new project proposals.

**Terry Fox Translational Research Program**

**Terry Fox New Investigator Award**
- Nomination criteria have changed.
Marathon of Hope
Cancer Centres Network

Pilots
- Two-year pilot projects that began in 2017 between cancer centres: first was between BC Cancer and Princess Margaret Hospital.
- In 2018, Montreal Cancer Consortium joined, then Prairie Cancer Research Consortium.
- Most recently, the Atlantic Cancer Consortium was formed, which TFRI is hoping to onboard next year.

The Digital Health and Discovery Platform
- DHDP is a national digital platform that allows different cancer centres to build, collect and share data securely for the MoHCCN. The idea is to have a DHDP appliance (like a mini supercomputer) at every site/hospital.

Why MoHCCN is needed
- Currently, cancer centres are making their own individual investments into precision medicine; this is very expensive, not sustainable, there is also redundancy, etc. Individual cancer centres are not large enough to do everything, thus coordinated data-sharing and collaboration are necessary.

MoHCCN goals
- Save lives via precision cancer medicine.
- Provide an improved paradigm for cancer research (generating “big data” knowledge).
- Genomic profiles for 15,000 cancer patients (whole genome; immune, epigenetic, proteomic, etc.), to start.
- Create globally competitive cancer research and development centres in precision medicine.
- Grow the next generation of leaders in precision cancer research.

In March of this year, TFRI and Health Canada reached an agreement for MoHCCN where Health Canada contributes $150-million over five years, matched with funds raised by the participating cancer centres. TFRI is entrusted with designating cancer centres to be part of the network and is responsible for allocating funding for the different projects.

The idea behind MoHCCN is not to have a collection of parts (individual cancer centres, or nodes, only capable of specific tasks), but rather to have harmonization across all nodes (alignment of principles and practices across the network).

An important aspect of research projects across different cancer centres is that, collectively, they cover almost all cancer types. Cancers are not characterized by their site, but rather molecular lesions; hence, drugs made for a specific cancer may be applicable to others, so it's important to research all cancer types.

Dr. Woodgett also emphasized the importance in recognizing healthcare disparities (potentially exacerbated by precision medicine; a major concern of the Canadian government) in terms of population demographics, as well as the need to be able to get representative genomic profiles from multiple populations, cultures, and ethnicities.

TFRI is currently expanding membership for the DHDP, undergoing the Prairie Cancer Consortium designation, evaluating the Atlantic Cancer Consortium, integrating/supporting PROFYLE 2.0, looking to support the Northern BC Biobank in Prince George, recruiting a new Executive Director for the Network and will launch a new MoHCCN website in December.
Dr. Dan Renour, a clinical oncologist, described the collaborative effort that goes into BC Cancer patient care, including the integration between genomic and clinical research. He also detailed the seven approved projects for BC2C and highlighted their significance by pointing out that each project will be discussed in-depth during TFRI Research Day. He concluded with the vision for the TFRI BC node: to transform care pathways such that they incorporate genomic analysis and precision medicine as a part of standard clinical care for all cancer patients in British Columbia.
PROFYLE—PRecision Oncology For Young people—is a national program that enrolls pediatric cancer patients and young adults up to age 29 with poor prognoses. PROFYLE’s overall objective is to transform the care of patients across Canada using next generation molecular tools and cancer model systems to identify disease- and patient-specific biomarkers that are actionable targets for therapy.

Dr. Deyell introduced PROFYLE, and Dr. Rassekh explained how they prioritize Molecular Tumor Board (MTB) recommendations based on the genetic information from sequencing by implementing a Level of Evidence system: Level 1 is considered a “slam dunk” prediction of response/resistance to FDA/Health Canada approved therapies; Level 5, novel biomarkers, less studied data/territory. Most therapeutically actionable variants are classified as Level of Evidence 3.

Dr. Deyell also went through the latest program results, including most frequently identified actionable alterations. Overall, ~40% of cases had therapeutically actionable oncogenic mutations or fusions, and the team discussed how transcriptome data is being used to inform drug therapy. Actionable findings are discussed at an MTB where recommendations are made regarding treatment strategies; 56% of clinicians involved to date have indicated that such profiling was useful in clinical management.
**Genomic and epigenomic sequencing to understand resistance and relapse in AML**

*Dr. Aly Karsan, MD, PhD & Dr. David Sanford, MD*

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Dr. Sanford introduced and gave background (including prognosis, genetics, poor survival rate, etc.) on acute myeloid leukemia (AML), which is generally a disease of older adults.

Historically, treatment options have not changed much for AML, though this has changed recently (in the last 5-6 years). For some novel therapies of AML, Dr. Sanford went over different molecular mechanisms of resistance & relapse.

Dr. Karsan explained that the aim of his research is to use genomic and epigenomic sequencing approaches, plus RNA-seq, to understand why AML patients are relapsing after going into remission following treatment.

Dr. Karsan believes that using single-cell approaches of study will be critical in the future to studying AML relapse cases, and also detailed an innovative approach to identifying individual clones using mitochondrial DNA mutation tracking.
Personalized OncoGenomics (POG): Our use case for the integration of genomics into clinical oncology

Dr. Janessa Laskin, MD

Dr. Laskin, medical oncologist, described her job as essentially deciding what chemotherapy to give a cancer patient, and how she hoped for a more targeted approach to cancer diagnosis and treatment. In light of this, she highlighted the collaborative and multidisciplinary Personalized OncoGenomics (POG) project as one such effort to make precision medicine a reality.

In POG, a patient’s tumour tissue is biopsied, and then undergoes sequencing (including the whole genome and transcriptome) as does the patient’s normal DNA and RNA. After sequencing, a Targeted Gene Report is produced (i.e., a detailed and annotated panel of all sequencing data) along with a genomic report (more detailed); both are shared with a Molecular Tumour Board.

Dr. Laskin gave specific case examples, including how pathway analysis can be applied and used to treat downstream effects of mutated proteins. She also touched on predictive biomarkers/indicators (e.g., tumour mutation burden) and how combinations of markers were better than an individual marker.
Dr. Scott broadly discussed diffuse large B-cell lymphoma (DLBCL) and the clinical problem of relapse (experienced by 30-40% of DLBCL patients; outcome is very poor). He then went over the different subtypes of DLBCL—including recurrent translocations, gene expression, and genetics-based subtyping—whether this biology is “hardwired” into the tumours as patients go through disease, as well as tumour evolution patterns and their implications for patient treatment.

What are the molecular mechanisms of treatment resistance? Are there different types of relapses? Should they all be treated the same (e.g., using salvage chemotherapy and autologous stem cell transplant, or CAR-T cell therapy treatment)? The aim is to answer these questions by interrogating paired, diagnostic/relapse biopsies using sequencing to track tumour evolution, noting that CAR T-cell therapy does not work for everyone and that the costs are significant.

Dr. Scott went over his group’s results and technical findings (e.g., in late relapses, different mutations are occurring at relapse but in the same driver genes where initially other mutations were observed at diagnosis), before focusing on patterns of tumour evolution (e.g., direct/linear, branched, convergent), indicating that evolutionary trajectory of tumours seems to be an important consideration to studying relapse occurrence.
The goal of this program is to translate genomic information into clinical practice. Multiple studies have been designed (including PanGen—Prospectively Defining Metastatic Pancreatic Ductal Adenocarcinoma Subtypes by Comprehensive Genomic Analysis—in Vancouver) where pancreatic cancer patients are enrolled and undergo whole genome sequencing and whole transcriptome analysis in addition to clinical-grade follow-up (PanGen follows the POG pipeline).

Dr. Schaeffer started by giving background about pancreatic cancer, indicating that pancreatic ductal adenocarcinomas (PDAC) account for 95% of all pancreatic cancers, the rest being pancreatic neuroendocrine tumours (PNETs).

- 5-year survival rate of PDAC is 10%, and 80% of patients are diagnosed at late stage.
- 5-year survival rate of PNET approaching 50%, with a better outlook than PDAC.

Dr. Schaeffer went over the genomic and transcriptomic landscape of PDAC (90% of tumours have KRAS driver gene mutations). Historically, the majority of pancreatic cancer transcriptome analyses had been described in primary lesions; however, the majority of pancreatic cancer patients actually suffer from more advanced and metastatic cancer.
To address this, Drs. Schaeffer & Dr. Renouf formed Enhanced Pancreatic Cancer Profiling for Individualized Care (EPPIC), that focuses on metastatic pancreatic cancer.

Dr. Renouf went over some of the findings they and others have seen by looking at whole genome sequencing (WGS) data of pancreatic cancer; highlighted how treatment has changed with the use of WGS data to inform potential targets for therapy (e.g., a lung cancer inhibitor drug was able to effectively treat pancreatic cancer). Dr. Schaeffer also briefly mentioned metabolic subtypes of PDAC (e.g., tumour cells that increase glycolysis even in the presence of oxygen so that cells are hardwired to feed the tumour and cancerous growth).

Dr. Renouf concluded by touching on diabetes & PDAC, mentioning that glucose management has not really been properly explored as a way to treat tumours.

**Sarcomas & epigenomics**

*Dr. Torsten Neilsen, MD, PhD & Dr. Martin Hirst, PhD*

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**Dr.** Neilson talked about sarcomas—a large group of tumours that do not grow within a specific organ—and why it’s important to study the epigenome in this context. For MoHCCN, Dr. Neilson and Dr. Hirst want to focus on specific types of sarcomas, and listed their goals for Phase 1 of the program.
Sarcomas can impact people of all ages, and are commonly seen in animals. Surprisingly, sarcomas only account for 1-2% of all human cancers; humans are somewhat resistant to sarcoma development. (Terry Fox suffered from osteosarcoma—cancer of the bone; during his time, amputation was the typical intervention.) About half of sarcomas can be neatly classified based on gene expression. For many sarcomas, it’s essential to study the epigenome; many sarcoma mutations occur in genes coding for histones, histone-modifying enzymes, chromatin-remodelling complexes, and proteins mediating liquid-liquid phase transitions.

For the MoHCCN, Dr. Neilsen and Dr. Hirst want to profile (e.g., tumour/normal whole genome sequencing, RNA sequencing, and epigenomic analysis):

- **Chondrosarcoma**—the second most common of primary solid tumours of bone that do not respond well to conventional drug therapies or radiation; slow-growing tumours that occur in “nasty” locations on the body. Phase 1 of the program proposes profiling 50 chondrosarcomas.

- **Chordomas**—occur high in the spinal cord up against the brain stem, but also also in bone. Phase 1 of the program proposes profiling 120 chordomas.

- **Synovial sarcomas**—mainly occur in young adults and older adolescents, and do not currently have effective chemotherapy options. Unlike other cancers, synovial sarcomas have a very low mutational burden; instead, a small or single genetic change, usually a fusion mutation occurring in a transcription factor, causes wide-spread epigenomic changes that drive oncogenesis. Phase 1 proposes profiling 80 synovial sarcomas.

Dr. Hirst also mentioned the key objective of the International Human Epigenome Consortium (IHEC) is to develop reference epigenomes for accessible human cell types. The contribution of Canada to IHEC is the Canadian Epigenetics, Environment and Health Research Consortium (CEERC) network, which he leads.
Dr. Aparicio introduced the main pillars of the B-precise (precision medicine for breast cancer) programs. He discussed the past 30 years of breast cancer genomics research, variation between breast cancer patients, and then focused on triple negative breast cancer (TNBC), which is characterized by the absence of three common hormone receptors that are usually found in breast cancers: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Dr. Aparicio discussed the questions they hope to answer regarding TNBC through B-precise before discussing the next steps. Dr. Chia concluded by sharing some clinical data and patient cases.

B-Precise has 5 main pillars:
1. Precision medicine for young and high-risk patients
2. Increasing TNBC long term survivorship
3. Understanding why non-TNBC breast cancers recur
4. Enabling patient participation in research across BC
5. Training the next generation of researchers

Dr. Aparicio mentioned that one of the efforts in Vancouver involving his team, is to develop single-cell technology to dissect breast cancer heterogeneity; the single-cell approach of study is especially valuable in terms of identifying cancer cell clones that are resistant to chemotherapy. Dr. Chia closed with clinical data and case examples on residual disease.
**How can we make “hope” universal**

*Dr. Nadine Caron, MD*

Dr. Caron highlighted the disparities in access to research for Indigenous communities specifically located in Northern B.C. and talked about the Northern Biobank Initiative (NBI). NBI was created to address the genomic divide in Northern B.C. where no biobank or research enrollment efforts initially existed for cancer patients. She talked about the creation of a First Nations Biobank and why this is important for equity and inclusion, and to fulfil promises made by Canada to First Nations peoples.

“It’s become clear that those who have access to research, will simply benefit more. Or you could flip the coin and say, those who stand to benefit the most, those who endure the greatest health disparities, will actually benefit the least. And unless access to research, and the research opportunities—and the choice to be part of these research opportunities—are added to the list of disparities we need to address in Canada’s healthcare system, this unfortunately will not change.”
Panel discussion: The future of precision medicine

Drs. Jim Woodgett, Daniel Renouf, Rebecca Deyell, Janessa Laskin, Samuel Aparicio, Nadine Caron

Moderated by Stuart McNish

Each of the panelists introduced themselves then each gave their highlights about the 2021 TFRI Research Day. Next, Stuart McNish asked each individual panelist broad questions based on the topic of their presentations (e.g., he asked Dr. Rebecca Deyell about the future of research with young cancer patients; Dr. Sam Aparicio about where we will be five years from now in terms of breast cancer treatment, etc.).

Dr. Janessa Laskin raised the point (which was brought up again a few times) that “curing” cancer is a lofty goal, but that improving the quality of life and managing it (making it into a chronic, tolerable disease) is something that is achievable and attainable for many patients.

Dr. Daniel Renouf talked about the problem of translating research done in academic centres to the community; there is a widening divide in terms of analysis/treatment done in large academic centres vs. smaller ones (this is seen in Europe, the U.S., and Canada). He gave a pancreatic-specific example: the importance of testing for BRCA mutations.
Dr. Renouf also touched on the current disparity of equal distribution of expertise in Canada.

Dr. Nadine Caron shared a story on how a funder for the Centre for Excellence in Indigenous Health once offered $1-million to fund Indigenous PhD students and post-doctoral students, which she declined (to the shock of the Dean) because it would not solve underlying systemic issues. Instead, she indicated that it would be better to put the money into high school science programs, or bursaries for students not eligible for top scholarships, etc. The shared money, for whatever purposes, were best suited to Indigenous people rather than what universities want.

Within the next five years, Dr. Rebecca Deyell said she would like to see all children diagnosed with cancer to be included in cancer research programs. She also emphasized the importance of studying long-term side effects from cytotoxic cancer treatments:
- reduction in treatment toxicity;
- enhanced targeted therapy;
- more investigation in pharmacogenomics.

Dr. Deyell later touched on the problem with Health Canada’s limitations for pediatric patients to participate in research (i.e., as an issue of “protecting the children from research”, rather “protecting children with research”). She also said she would like to see some of the costs associated with sequencing shifted to the health care system.

Dr. Samuel Aparicio expressed that breast cancer science is far ahead of the ability to implement the research (Dr. Janessa Laskin later seconded this thought: the science/technology is ahead of clinical practice), though he believes that innovation is coming and will save the health care system millions of dollars by screening for disease much earlier and, in so doing, keep people out of hospital.

Stuart McNish asked Dr. Daniel Renouf and Dr. Jim Woodget about the existence of legal/ethical barriers to the implementation of precision cancer medicine. One perceived ethics risk that was expressed was public sentiment around privacy and sharing genomic data; Dr. Renouf said that most of his patients are keen to do whatever they can for their own sake, and for the sake of research. Dr. Jim Woodget seconded the idea that patients act as allies to research efforts. Dr. Woodget also said the main barriers are not technical but actually bureaucratic (e.g., believing we’re a single-payer country when every province/hospital can be different; Canadian health care is very fragmented); privacy/breaches of confidentiality are used a means to say “no, we can’t be sharing this information.” Dr. Woodget said the public is a true asset (they are the voters), and that they need to be engaged in order to gain their support.

Dr. Janessa Laskin talked about the importance of incorporating health economics early on (she mentioned it has been included from the beginning in POG and MoHCCN); to get better technology into care, the value of it needs to be demonstrated continually.

Dr. Deyell also touched on “the elephant in the room”: costs associated with cancer therapies.

Dr. Aparicio said that he has noticed that there is a tendency for the ability of expert leadership to be diluted. When the experts don’t have a sufficient voice, you end up with no progress. Dr. Woodget commented on the need for quality data and evidence in order to
make significant changes to health care. The COVID-19 pandemic was discussed as having illuminated problems with the status quo in health care, and how it needs to change.

The speakers also discouraged comparisons with the United States health care system; instead, Canada should experiment with different models of care and pick the best practices.

Stuart asked each panelist to share their thoughts about the future of precision medicine.

Dr. Jim Woodget: though there’s a lot of work to do, there’s some bright minds working on it; to the trainees in the audience, “you’ve picked the right career”.

Dr. Rebecca Deyell marveled at how far we’ve come: we’re right at the edge of another major shift in cancer treatment, with genomically-informed therapies.

Dr. Dan Renouf: the concept of multidisciplinary team-based medicine, inclusive of engineers, physicists, bioinformaticians, etc., will be key in moving forward; knowledge translation is critical in order to facilitate this.

Dr. Samuel Aparicio: learning is an ongoing process (from patients, colleagues, students, etc.) and the injection of fresh ideas is unstoppable and important.

Dr. Nadine Caron: “What’s possible should simply be done right away. What’s impossible will just take slightly longer.”

Dr. Janessa Laskin: what’s required is collaboration, data sharing, working together, learning from each other, and promoting each other’s excellence.

Dr. Marco Marra gave concluding remarks: The future we seek is rooted in the research we do today; he emphasized the importance of data, and “sober, thoughtful research”.

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