BIOLOGY & GENETICS

Spatial heterogeneity in medulloblastoma

Tumour heterogeneity poses a major challenge for the development of targeted therapies that will be effective against an entire tumour. A research team led by Dr. Michael Taylor at the Hospital for Sick Children and **Dr. Marco Marra** at BC Cancer analyzed spatial heterogeneity of genomic profiles, showing medulloblastomas, but not high-grade gliomas, have spatially homogeneous transcriptomes, which allowed for accurate subgrouping of tumours from a single biopsy. Conversely, suitable mutant candidate genes for targeted therapy showed high levels of spatial heterogeneity in medulloblastoma, malignant glioma and renal cell carcinoma, which brings the efficacy of monotherapies against a single target into question. Clinical trials of targeted therapies for medulloblastoma should first ensure the spatially ubiquitous nature of the target mutation.

A review of the MYC family of cancer genes and the protective effects of gene eEF2K

Distinguished Scientist, **Dr. Poul Sorensen** and colleagues summarized a review of research on the MYC family of cancer genes in *Cell Cycle*, which contributes to more than 50 per cent of all human cancer types. Sorensen's team has found that inhibition of the gene eEF2K can significantly decrease survival of pediatric neuroblastoma tumours that have amplified expression of the gene MYCN under caloric restriction. In their review, they suggest that eEF2K may also have relevance for other tumour types that overexpress MYC genes.

Translational control of aberrant stress responses as a novel hallmark of cancer

Under stress, cells block global protein synthesis to preserve energy while maintaining selective synthesis of proteins that support cell survival. One highly conserved mechanism to regulate protein synthesis under cell stress is to sequester messenger RNA (mRNAs) into stress granules, where their translation is silenced. Stress granules confer survival advantages and chemotherapy resistance to tumour cells under stress. Recently, it has been shown that genetically blocking stress granule formation dramatically reduces tumour invasive and metastatic capacity *in vivo*. In a review prepared for *The Journal of Pathology*, **Drs. Poul Sorensen** and **Amal M. El-Naggar** explain how deciphering mechanisms of selective mRNA translation under cell stress holds great promise for the identification of new targets in the treatment of cancer.

New Developments in Single Cell Genomics

Single-cell genomics is critical for understanding cellular heterogeneity in cancer. To enhance single cell whole genome sequencing, the labs of **Drs. Sohrab Shah, Samuel Aparicio** and **Carl Hansen** (UBC) collaborated to develop and patent a new technique to prepare Illumina libraries for sequencing. The results were published in *Nature Methods*. This technique has the capacity to routinely sequence 3000 cells at a time and represents the highest throughput and most unbiased method of whole genome sequencing of single cells in the field to date.

In 2017, **Dr. Sohrab Shah's** lab made several advances in computational methods for single-cell genomics. Published in *Genome Biology*, his team developed and released software, called ddClone – they showed this approach improves detection accuracy of cell populations present in a tumour, providing a tool for richer insight into how cancers evolve and ultimately acquire resistance to treatment. Also published in Genome Biology, Dr. Shah's team also developed a novel whole genome sequencing analysis method called ReMixt that can infer structural variations from cancer genomes, and developed a new data visualization software framework (E-scape tool suite) tailored for interactive browser-based data visualization of cancer evolution data, published in *Nature Methods*.

Installation of a new **Single Cell Genomics Suite** at BC Cancer was completed in December last year. This suite houses cutting edge sequencing and ancillary equipment in a clean environment. It is accessible to all researchers throughout the Centre. The Department of Lymphoid Cancer Research, in collaboration with the Genome Sciences Centre at BC Cancer, aims to define comprehensive mutational landscapes of refractory and relapsed lymphoid cancers at the single cell level. The fully characterized genomic information extracted from clinically relevant cell populations will give insights into treatment resistance and lead to identification of potential therapeutic targets.

FUNCTIONAL IMAGING

Development of a novel tracer for imaging tumour perfusion with positron emission tomography

Solid tumour perfusion is a proven variable of interest for predicting cancer aggression and response to therapy. Current methods for noninvasively imaging tumour perfusion with positron emission tomography (PET) are limited by restricted accessibility and short half-lives of perfusion radiotracers. As published in the *Journal of Nuclear Medicine*, a team led by BC Cancer's **Drs. Kuo-Shyan Lin, François Bénard**, and **Kevin Bennewith** has developed and verified the compound 2-18F-fluoroethanol (2-18F-FEtOH) can act as a "perfusion reporter" that can now help investigators distinguish between tumours of varying perfusion, and screen the efficacy of blood flow-modifying drugs for use as enhancements to existing cancer therapies.

POPULATION ONCOLOGY

Anne (Syexwaliya) Whonnock, Squamish Elder

Comparison of cancer incidence and survival between First Nations and non-First Nations people in BC

The first study ever to compare cancer development and survival between First Nations and non-First Nations people in BC shows an overall lower incidence of the disease for First Nations people, but also indicates lower survival rates for most cancers. The study was conducted jointly by BC Cancer and First Nations Health Authority and published in the journal *Cancer Causes & Control*. The 1993 to 2010 data set includes "Status Indian" peoples only and is not inclusive of all First Nations, Métis or Inuit peoples in BC.

The results indicate that both First Nations men and women in BC experience a higher incidence of colorectal cancer, with a 22 per cent higher age-standardized incidence rate for women and 39 per cent for men. There also appears to be a trend towards increasing incidence of colorectal cancer for both sexes. A 92 per cent higher incidence rate of cervical cancer was observed among BC First Nations women. Incidence rates of almost all other cancers were generally similar or lower in First Nations populations compared to non-First Nation populations. Trends in incidence rates over time were also similar, with the exception of lung cancer, which is increasing at a rate among First Nations people that may soon overtake declining rates in non-First Nations people. More research is needed to understand the specific reasons for these cancer rates among BC First Nations people.

First Nations people are also less likely to survive a cancer diagnosis compared to non-First Nations people in BC. Overall, poorer survival was seen in the First Nation population in 10 of the 15 cancer types examined in women and 10 of the 12 cancer sites examined in men. Lower survival rates could be influenced by a number of factors including challenges in access to high quality, timely, appropriate and effective cancer treatment, especially in rural and remote areas. Lower diagnosis may be impacted by limited access to screening programs.

The findings in this study suggest a complex basis for these disparities in cancer incidence and survival, and further studies along the entire spectrum of cancer care are required. It also affirms the need for a system-wide response to improve cancer diagnosis and care for First Nations people in BC. For many First Nations peoples, their cancer journey is negatively impacted through the experience of racism in health and social support settings. Culturally safe health and social services reduce barriers to accessing care and detecting cancer early. First Nations people are more likely to access care that is appropriate to their wellness beliefs, goals and needs.

To address these disparities in cancer incidence and survival, BC Cancer, First Nations Health Authority, BC Association of Aboriginal Friendship Centres and Métis Nation BC developed an Indigenous Cancer Strategy for the province that was launched in December, informed by research and extensive engagement with BC Indigenous communities, patients, survivors and their families.

Improving quality of community care for women with breast cancer across the care continuum

BC Cancer is committed to quality care for cancer patients throughout British Columbia. This involves not only treatment, but also community care for early diagnosis, patient support and care of comorbidities during treatment, and post-treatment care to minimize ongoing and late-occurring impacts of cancer. A research team led by **Mary McBride** identified factors leading to a higher (pre-existing disease) or lower (living in remote locations, or neighbourhoods with many immigrants) chance of being diagnosed through screening, and subgroups (immigrants) with longer time to diagnosis. They found that those living in different health regions or in lower income neighbourhoods had variable access to chemotherapy and a significant level of non-compliance with breast cancer follow-up guidelines, pointing to gaps in care that can affect survival. This research was part of a multi-province initiative — Canadian Team to Improve community-based cancer care coordination along the continuum of care (CanIMPACT) — to identify gaps in community care for breast cancer patients across Canada, funded by the Canadian Institutes of Health Research. As well as generating several publications in 2017, including in the *Journal of Family Practice Oncology, Current Oncology, International Journal of Population Data* and *Osteoporosis International*, the results from these studies have been shared with oncology practitioners, family physicians and screening programs throughout BC and Canada.

The cost and cost-trajectory of whole-genome analysis guiding treatment of patients with advanced cancers

Research exploring costs and benefits of whole-genome analysis-guided cancer care are crucial to guide health policy, yet limited data exist on the real-world costs of applying whole-genome analysis in a clinical setting. BC Cancer research led by economist **Dr. Dean Regier** and published in the journal of *Molecular Genetics & Genome Medicine* estimated the costs of applying whole-genome analysis to guide treatments for patients with advanced cancers. It characterized how costs would evolve over time, using the Personalized OncoGenomics program as a case study. Over time, the total costs decreased, driven by a reduction in costs of sequencing, though costs of some of the other components increased; expenditures needed to truly realize whole-genome analysis-guided cancer care remain significant. Dr. Dean Regier was invited to give a talk on a value framework approach to disclosing secondary findings from colorectal cancer screening based on his research into cost and cost-trajectory of whole-genome analysis at The Roundtable on Genomics and Precision Health of the National Academies of Sciences, Engineering and Medicine in Washington DC.