Ovarian Cancer Canada Tissue Banking Network
Annual Progress Report 2017

The Ovarian Cancer Canada (OCC) Tissue Banking Network is a virtual network of tissue banks located in Vancouver, Ottawa and Montreal, with Montreal being a hub for four cities in the province of Quebec. A recent grant from the Elizabeth Ann Quinton Memorial Fund at the Calgary Foundation has enabled the network to expand to include Edmonton's tissue bank. The OCC Research Committee is responsible for developing mechanisms to facilitate communication and cohesion among the banks and avoid duplication of studies. The generosity demonstrated by all the women who have donated their cancer tissues has been the foundation for many discoveries that continue to improve ovarian cancer care.

What is banked?

The OCC Tissue Banking Network collects samples from 800 to 1,000 women with ovarian cancer each year. There is considerable overlap in the types of samples collected by each bank, but each site has unique features that enable a wide range of research studies. Collectively, the types of samples that are banked include blood (serum, plasma, buffy coat), saliva, cells from normal ovaries, tissues from benign, borderline and malignant ovarian tumours of all subtypes, and the cells and fluid contained in ascites. The Vancouver bank has recently expanded its collection to include women with other types of gynecological cancers.

Collections from July 2016 to June 2017

In the past year, **a total of 1,409 women with gynecological cancers** gave consent for the collection of samples, resulting in **more than 7,000 samples being collected**, processed and banked by the OCC Tissue Banking Network. The banks also maintain databases of information about the patients and the samples, including the histologic subtype, stage and grade of tumour, and the dates of surgery and other treatments. Keeping these databases updated is very time-consuming, but is a unique and critical aspect of this banking network, as it allows more in-depth studies than simple access to samples normally permits. Most of the banks use the ATiM (Advanced Tissue Management) database created by the Canadian Tissue Repository Network.

Sample Distribution

The primary value of the OCC Tissue Banking Network is its ability to provide samples for ovarian cancer research. Tissues collected by the OCC Tissue Banking Network have proven useful for more than 450 research projects and have had a substantial impact on promoting ovarian cancer research not only in Canada, but around the world. In addition to supporting local research, the banking network has contributed to two large national collaborative projects. The TFRI-funded COEUR national resource is a pan-Canadian project that has compiled 2,000 ovarian cancer tissue samples and associated patient data, with the goal to validate biomarkers that can be used for stratification of ovarian cancer patients for improved diagnosis and clinical management, including access to appropriate clinical trials. The partnership has resulted in "an immunohistochemical algorithm", a new process for pathologists to use to ensure that they identify the correct subtype of ovarian cancer.

In 2016, the COEUR partnership helped to launch another exciting initiative – a national cancer immunotherapy project. The immune response to ovarian cancer has emerged as one of the most powerful prognostic biomarkers. In many cases, the immune cells in the tumour fail to recognize the cancer, and the tumour is allowed to grow. Importantly, we now know that certain immune cells can be "trained" to recognize the tumour. This new initiative will explore various forms of immunotherapy to identify strategies that will work best on ovarian cancer patients.

In addition to local and national initiatives, the Tissue Banking Network provides samples to several international ovarian cancer research consortia and global ovarian cancer initiatives including the Ovarian Tumor Tissue Analysis (OTTA) consortium, the Multidisciplinary Ovarian Cancer Outcomes Group (MOCOG) and Ovarian Cancer Association Consortium (OCAC).

Tissues from the banks currently support the following ongoing and new research:
- study of intratumoural heterogeneity of high-grade serous ovarian cancer
- detection of circulating tumour DNA in blood from women with cancer
- identifying genomic changes leading to endometriosis-associated ovarian cancer
- identification of new diagnostic markers to differentiate tumour "look-alikes"
- assessment of the immune microenvironment of ovarian cancers
- study of novel biomarkers of response to PARP inhibitors
- determining the cell of origin for small cell carcinomas of the ovary, hypercalcemic type
- investigating a targeting strategy for ovarian cancer harboring dysfunctional BRCA1
- identification of biomarkers that predict response to chemotherapy
- development and testing of small molecule inhibitors as ovarian cancer treatment

Impact

The greatest value of the tissue banks is that researchers are able to perform *translational research* - taking findings from basic research in the laboratory and extending those observations to ovarian cancers in women. At this moment, there are an estimated 50 ovarian cancer research projects in progress in Canada that utilize samples from the ovarian cancer tissue banks. The following are two of the **innovative new studies launched in the past year:**

A New Model of How Endometriosis-Associated Ovarian Carcinomas Develop

Drs. David Huntsman and Dawn Cochrane of the OVCARE team have begun to study the cellular origins of clear cell and endometrioid ovarian cancers. To date, it is unclear how these two histologically and clinically different tumours arise from the same tissue: endometrial epithelium of ovarian endometriosis. In their proposed model, clear cell tumours arise from cells sharing features with ciliated cells, whereas endometrioid tumours arise from secretory cells or their precursors. Using an organoid culture system, the team can study the interplay between mutations, microenvironmental factors and other modifiable risk factors, such as hormonal manipulation, to determine their role in cancer development. Gaining further insight into the cell(s) of origin of these cancers will be key to developing biologically-informed prevention strategies for these cancers, which are the second and third most common ovarian cancers.

Using Tampons for Cancer Detection Study

Building on a small proof of principle study from the United States, Dr. Anna Tinker has launched a study to find out whether tampons can be used as a reliable method to collect cancer cells that may shed through the cervix into the vagina – the DNA from the cancer cells can then be sequenced or analyzed for the presence of cancer mutations. Dr. Tinker's two-year study (Advanced Methods for Cancer Detection by Vaginal Screening – ADVISE) is enrolling 120 women, both healthy and others newly diagnosed with ovarian and endometrial cancer. Participants wear tampons for several hours and self-collect a sample of vaginal fluid using a swab prior to them having surgery or begin chemotherapy and other treatment – this home-based test kit is then sent to the OVCARE gynecological tissue bank where the team then processes the samples for analysis.

Highlights of Recent Research Discoveries

In the past year, there have been 29 publications in internationally recognized scientific journals that have reported the results from studies using tissue bank samples. The research has also been presented and discussed at national and international conferences. Some of the recent discoveries are described here:

Predicting patient responsiveness to PARP inhibitors

Patients suffering from ovarian cancer, whose cancers are known to have mutated BRCA genes, can be treated with drugs known as PARP inhibitors. Unfortunately, not every patient responds to this treatment. Researchers compared different ovarian cancer cell lines to study the variances in cells that did and did not respond to treatment. It was already known that BRCA and PARP expression are associated with the cell's mechanisms to repair damaged DNA. Repairing DNA in a cell is a complicated process that involves BRCA, PARP, and many other different components and pathways. After studying the cell lines, researchers found that the cell lines with defects in more than one DNA repair pathway were most susceptible to PARP inhibitors. In the future, cancer patients could be screened for DNA repair pathway deficiencies which could indicate how well they will respond to treatment with PARP inhibitors.

Micro-dissected tumour tissues on chip

Although oncology drugs are effective in treating cancers, clinical trials have shown that the rates of success can differ wildly from patient to patient. To improve treatment success rates, researchers developed a culture system capable of keeping small section of tumours alive. They were able to administer multiple drugs to the micro-dissected tissues within the culture system and analyse the tissue response over time. This method has been successfully applied to eight different types of tissues, showing that it will likely be usable for tumours from various sites. In the future, this technology has the potential to provide personalized medicine for patients by identifying the most effective course of treatment to increase patient survival and quality of life.

Better diagnosing high-grade serous ovarian cancers through imaging and gene sequencing

The TP53 gene is known to be a predictive marker that differentiates between types of ovarian cancers; high-grade serous ovarian carcinomas almost always show mutated TP53 whereas low-grade serous tumours do not. We currently use a microscopy technique (immunohistochemistry staining) to look for the protein that TP53 produces (p53) and these results are used to infer the gene status, however this technique is not always accurate. To improve this accuracy, researchers developed a new staining system that they tested alongside next-generation sequencing which reveals the exact genetic sequence of the TP53 gene. The improved staining system combined with the ability to look at the gene's sequence allowed the researchers to identify 99% of high-grade serous cases in their study, but also to differentiate between types of TP53 mutations, indicating p53's functional status. In clinical practice, next-generation sequencing may not always be possible, but p53 staining still holds a significant negative predictive value, virtually excluding all low-grade serous tumour cases. The ability to differentiate these cancers is crucial to selecting appropriate treatments and for interpreting p53 functional status for clinical trials.

Imaging fallopian tubes for ovarian cancer diagnosis

The fallopian tubes are believed to be where many high grade serous ovarian cancers originate. These lesions in the fallopian tubes are, however, difficult to diagnose and are frequently diagnosed by pathologists who painstakingly examine sections of the fallopian tube that have been removed surgically. Searching for lesions in this way is not only time consuming but can also easily miss a lesion which can be extremely small in size. To increase screening capabilities,

researchers have developed a system based on optical coherence tomography (OCT). The OCT probe was mounted on an endoscope and used to acquire images from fresh, intact fallopian tubes that had been surgically removed. The images were comparable to histological images, although they could not fully replace microscopic evaluation by a pathologist. The images were however clear enough to be able to guide a pathologist to a lesion they may have otherwise missed. This OCT system is in its infancy but may represent a non-invasive and practical way to screen women for lesions and increase the early detection of high-grade serous ovarian cancers.

Development of the "SP3-CTP" technology for proteome profiling
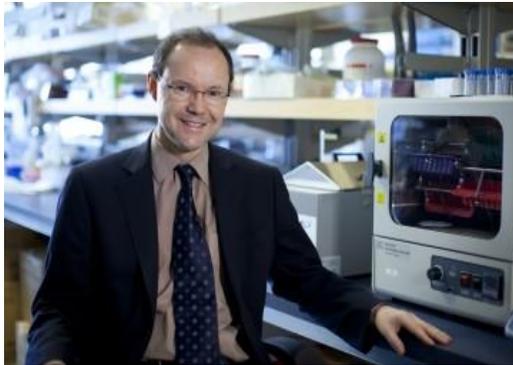
David Huntsman, OVCARE Scientific Director and co-Founder

Diagnosis is key to effective patient management and it is unlikely that any scientific advance will ever supplant the need for a correct diagnosis. However, different tumour types can look histologically similar, making accurate diagnosis challenging or even impossible. Consequently, diagnosis of tumour look-alikes is commonly incorrect, which in turn leads to improper patient treatment. Resolving this challenge would dramatically improve personalized patient management. The ground breaking technology, "SP3-Clinical Tissue Proteomic', developed by Dr. Gregg Morin's lab at the BC Cancer Research Centre, enables the analysis of single tumour tissue sections at unprecedented depth and sensitivity. The first validation of this technology was performed on ovarian cancer samples. Drs. Huntsman and Morin have recently been awarded a BCCF Strategic Priorities grant to identify markers that can be used to overcome several diagnostic challenges.

Proof that synchronous ovarian and uterine cancers are metastases and development of the concept of pseudo metastasis

This research, published in the *Journal of the National Cancer Institute*, is a breakthrough in understanding the origin and development of cancer that occurs in the uterus and ovary simultaneously, substantiating an approach to managing the disease practiced by doctors in BC. While usual metastasis involves cancer spreading through the blood stream and changing along the way, synchronous ovarian and uterine cancers spread through the fallopian tubes from the uterus to the ovary, and vice versa, without undergoing any changes. This shows that some metastases may be curable by surgery because the tumours have not had to change in ways that would allow it to grow in other parts of the body – this concept has been coined 'pseudo metastasis'. This study will have an immediate impact on the management of ovarian and endometrial cancers and should influence treatment of the disease around the world so women do not undergo needlessly aggressive treatment.

Uncovering seven new subtypes of ovarian cancer

A study published in *Nature Genetics* deciphered the entire DNA code from more than 100 ovarian cancer patients to uncover genetic abnormalities in the DNA of cells from the cancer. Led by Dr. Sohrab Shah, the team uncovered seven new subtypes of ovarian cancer. It is anticipated that these structural changes in the cancer may help identify patients who respond and won't respond to current chemotherapy.
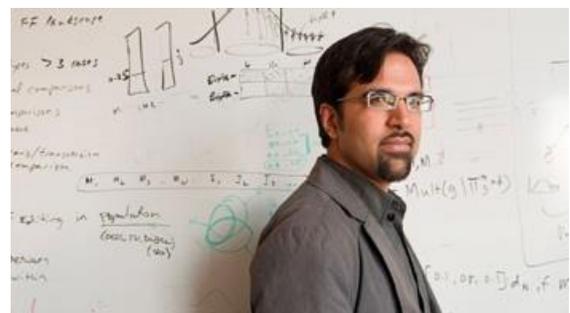
Sohrab Shah, Canada Research Chair in Computational Cancer Genomics