OUTSTANDING TRAINEE PUBLICATIONS

The Office of the VP, Research held a Publication Awards competition for papers of outstanding scientific merit first-authored by BC Cancer Students, Residents, Post-doctoral Fellows or Graduate Students. Awards were given in the categories of Basic and Translational, Clinical and Translational and Cancer Control and Health Services Research.

In the category of **Basic and Translational** research, **first place** was awarded to **Dr. Yikan Wang**, a Post-doctoral Fellow supervised by Dr. Sohrab Shah in the Department of Molecular Oncology, for the paper "Genomic consequences of aberrant DNA repair mechanisms stratify ovarian cancer histotypes" published in *Nature Genetics*. Dr. Wang and colleagues examined the global genomic patterns of 133 ovarian cancer patients and identified different patient subgroups.

Second place in the category of **Basic and Translational** research was awarded to Graduate Student **Dr. Alberto Delaidelli**, supervised by Dr. Poul Sorensen in the Department of Molecular Oncology, for the paper "MYCN amplified neuroblastoma requires the mRNA translation regulator eEF2 kinase to adapt to nutrient deprivation" published in *Cell Death & Differentiation*. Dr. Delaidelli and colleagues identified eEF2K as a pivotal mediator of the adaptive response of tumour cells to nutrient deprivation in childhood neuroblastoma with MYCN amplification, a pediatric cancer associated with aggressive disease and high mortality.

The award for the best **Clinical and Translational** paper was given to **Hanna McGregor**, a PhD student supervised by Dr. Haishan Zeng from the department of Integrative Oncology for the paper "Real-time endoscopic Raman spectroscopy for in vivo early lung cancer detection" published in the *Journal of Biophotonics*. McGregor and colleagues present the use of a real-time endoscopy Raman spectroscopy as an improvement over standard imaging techniques, to improve the specificity for localizing lung cancers in central airways.

In the category of **Cancer Control Research and Health Services Research** related to cancer (including Health Economics), the award was presented to **Deirdre Weymann**, a health economist with Dr. Dean Regier in the department of Cancer Control Research for the paper "The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers" published in *Molecular Genetics & Genomic Medicine*. Dr. Weymann and colleagues estimated the costs of applying whole-genome analysis to guide treatments for patients with advanced cancers, and characterized how costs evolve over time for BC Cancer's Personalized OncoGenomics program.

SCREENING & DIAGNOSIS

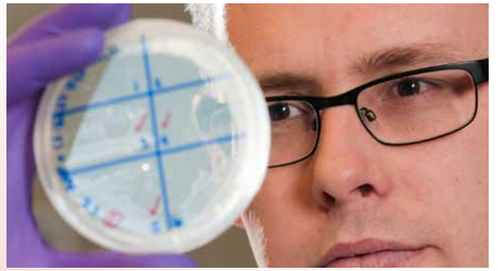
International collaboration leads to new genetic markers for breast-cancer risk

An international research project involving BC Cancer scientists, **Drs. John Spinelli** and **Angela Brooks-Wilson**, has identified new genetic markers associated with the risk of breast cancer. The findings, published in two separate studies in the journals *Nature* and *Nature Genetics*, reveal 72 new genetic variants that predispose women to breast cancer. Previously about 107 were known, including well-known mutations of the BRCA1 and BRCA2 genes, which occur in less than one per cent of women. Some of the newly identified genetic markers are much more common and, although each variant only increases the risk of cancer modestly, when combined the risks are multiplied. The project involved about 550 scientists around the world and was carried out by the OncoArray Consortium. The two studies, funded primarily by Genome Canada and the Canadian Institutes of Health Research, involved analyzing the genetic data of about 275,000 women, including 146,000 who had been diagnosed with breast cancer. BC Cancer provided data and DNA samples from approximately 1,200 breast cancer cases and an equal number of cancer-free controls identified through its breast screening program.

Advances in lymphoma and leukemia screening and diagnosis

A research team led by **Dr. Christian Steidl** in the Lymphoid Cancer Research (LCR) department has developed a novel prognostic model for classical Hodgkin lymphoma (cHL), called RHL30. Currently cHL patients with refractory or relapsed lymphoma receive salvage chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation (ASCT), which has a success rate of about 50 per cent. Dr. Steidl and his team used the NanoString digital gene expression profiling platform to develop RHL 30, a more reproducible biomarker assay for post ASCT outcome prediction, which can guide treatment decisions at the time of relapse. The results of the study have been reported in the *Journal of Clinical Oncology*.

Dr. Christian Steidl



Dr. David Scott

Dr. David Scott of the LCR department led the development of the MCL35 assay through a Lymphoma/Leukemia Molecular Profiling Project (LLMPP) consortium collaboration. This assay translates a previously described gene expression-based signature for proliferation in mantle cell lymphoma into an assay that can be applied to routine biopsies using the NanoString technology platform. The assay will allow the development of trials that will match treatment regimens to the risk of relapse of the patient. A patent has been filed on this assay, which was described in a paper published in the *Journal of Clinical Oncology* this year. In collaboration with several European groups, the assay has been applied to four clinical trials, demonstrating that it is prognostic for outcome and that intensive treatments improve outcomes in selected risk groups, suggesting that the assay will be useful in treatment planning.

Using MicroRNA to identify pediatric patients at risk of treatment failure or relapse

Children with acute myeloid leukemia (AML) whose disease is unresponsive to standard chemotherapy therapy or who experience relapse after initial response have dismal outcomes. A Canadian and American research team led by **Dr. Marco Marra**, Distinguished Scientist and Co-Director of the Genome Sciences Centre at BC Cancer, sought to comprehensively profile pediatric AML microRNA (miRNA) samples to identify dysregulated genes and assess the utility of miRNAs for improved outcome prediction. In a study published in the *Journal of Clinical Oncology* they identified 36 miRNAs where expression levels at diagnosis were highly associated with event-free survival. They then used the combined expression of these 36 miRNAs to create a novel miRNA-based risk classification scheme called AMLmiR36 to help identify patients who are at high risk of experiencing treatment failure.

Implementation of a novel molecular barcoding strategy for ctDNA sequencing

Genetic material from tumours is commonly present at low levels in the bloodstream of cancer patients. The use of this circulating tumour DNA (ctDNA) as a source of genetic material from tumours is rapidly being adopted as a non-invasive approach for studying changes in a tumour over time. **Dr. Ryan Morin**, Senior Scientist with BC Cancer's Genome Sciences Centre, has implemented a new molecular barcoding technique that allows for unprecedented sensitivity in the detection of mutations from ctDNA. This research, published in *Scientific Reports*, demonstrates the method can reveal changes in tumour burden over time, and that these changes are relevant to a patient's clinical response and have the ability to provide a signal for a possible relapse. The research team has developed customized assays for a variety of cancer types including some paediatric cancers.

New test identifies the risk of breast cancer reoccurrence

Molecular research has identified several distinct types of breast cancer, which have different risks of spreading and therefore warrant different treatment. Research performed by **Dr. Torsten Nielsen** at BC Cancer in collaboration with colleagues from the USA generated a test originally called PAM50 that identifies the major molecular types of breast cancer and assigns a risk score. Through BC Cancer's Technology Development Office, this new test has been commercialized in partnership with Seattle-based NanoString technologies and renamed Prosigna. Prosigna is used to identify a patients' 10-year risk of distant breast cancer recurrence and provides guidance as to the benefit of hormonal therapy and chemotherapy for an individual patient. The test was approved by FDA and Health Canada, and is now recommended in several independent international guidelines and health care assessments. In 2017, Prosigna became available as a test run in Vancouver for the benefit of women in British Columbia, while also being used in 13 countries around the world.

Origins of endometriosis and of clear cell and endometrioid carcinomas of the ovary and uterus

Dr. David Huntsman, and researchers at UBC and Johns Hopkins University, published a study in the *New England Journal of Medicine* that examined tissues from women with endometriosis and found non-hereditary gene changes. They discovered that endometriosis, until now viewed mostly as a hormonal and inflammatory disorder, contains genetic changes found in some cancers that likely cause the gynecological condition and could lead to more personalized treatments. Although these mutations are also found in some cancers, they do not indicate risk of developing cancer in most cases of endometriosis.

Endometrial epithelium is also the presumed tissue of origin for both eutopic and endometriosis-derived clear cell and endometrioid carcinomas; however, no single class of mutations has been found exclusively in either histotype. Dr. David Huntsman and his team identified the protein cystathionine γ-lyase (CTH) as a lineage-specific marker for clear cell carcinoma, as it is expressed at high levels in clear cell carcinomas of the ovary and endometrium. The results of this study were published in the *Journal of Pathology*.

Dr. David Huntsman

TREATMENT

Seven new subtypes of ovarian cancer identified

BC Cancer research led by **Drs. Sohrab Shah** and **David Huntsman** has uncovered seven new subtypes of ovarian cancer, which could result in new treatment strategies for some ovarian cancer patients including those that do not respond well to chemotherapy. The discovery, published in *Nature Genetics*, analyzed the genetic information of more than 100 ovarian cancer patients in order to identify abnormalities in the DNA of ovarian cancer cells. Two of the new genetic subtypes uncovered belong to a very common and deadly form of ovarian cancer called high grade serous carcinoma (HGSC). Scientists believe they have found a structural change in the DNA of one subtype that can identify HGSC patients that will not respond to chemotherapy and who may instead benefit from new classes of treatments. The other five subtypes uncovered were found by analyzing clear cell, endometrioid and adult granulosa cell ovarian cancers. The results from this work suggest that some of these subtypes may be susceptible to existing treatments, but clinical trials are needed to test and confirm this hypothesis. This information may be used to develop tests that can direct patients toward new investigational treatments.

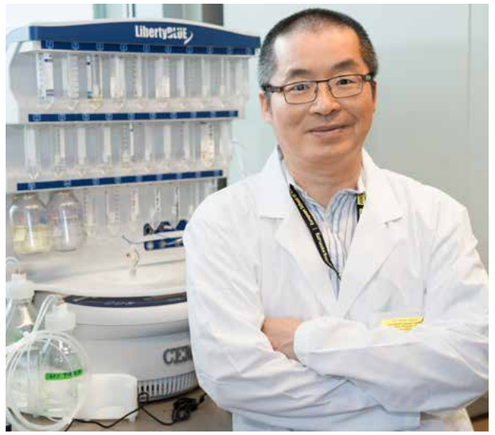
Approach to treatment for small cell carcinomas of the ovary, hypercalcaemic type

Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT), is a rare but aggressive and untreatable malignancy affecting young women. **Dr. David Huntsman's** research group, in collaboration with the Translational Genomics Research Institute (TGen) at the University of North Carolina recently discovered that SMARCA4 is the only gene recurrently mutated in the majority of SCCOHT cases. As recently published in the *Journal of Pathology*, they discovered that loss of SMARCA4/SMARCA2 caused a dependency of SCCOHT cells to the enzymatic activity of a protein called EZH2. Based on this discovery and a similar independent discovery by Epizyme Pharmaceutics, clinical trials are now underway to evaluate the efficacy of EZH2 inhibitors in SCCOHT patients.

Dr. Sohrab Shah

New radio-ligands ready for clinical trials

The bradykinin B1 receptor is overexpressed in many cancers. A team led by **Drs. François Bénard** and **Kuo-Shyan Lin** have developed a large number of improved radioactive ligands (molecules that bind to proteins in the body) targeting the bradykinin B1 receptor. Starting in 2015, using relatively unstable compounds, they have now developed, studied and identified many candidate compounds to be tested in clinical trials. As published in the journals *Molecular Pharmaceutics* and *Bioorganic and Medicinal Chemistry,* these new radiopharmaceuticals are very potent and stable and show very high accumulation in cancer cells, and also atherosclerotic plaques, that express the bradykinin B1 protein. This opens up the possibility for new therapeutic and cancer imaging options, using radiation that specifically targets cancer cells while reducing the amount of radiation exposure in healthy tissue.

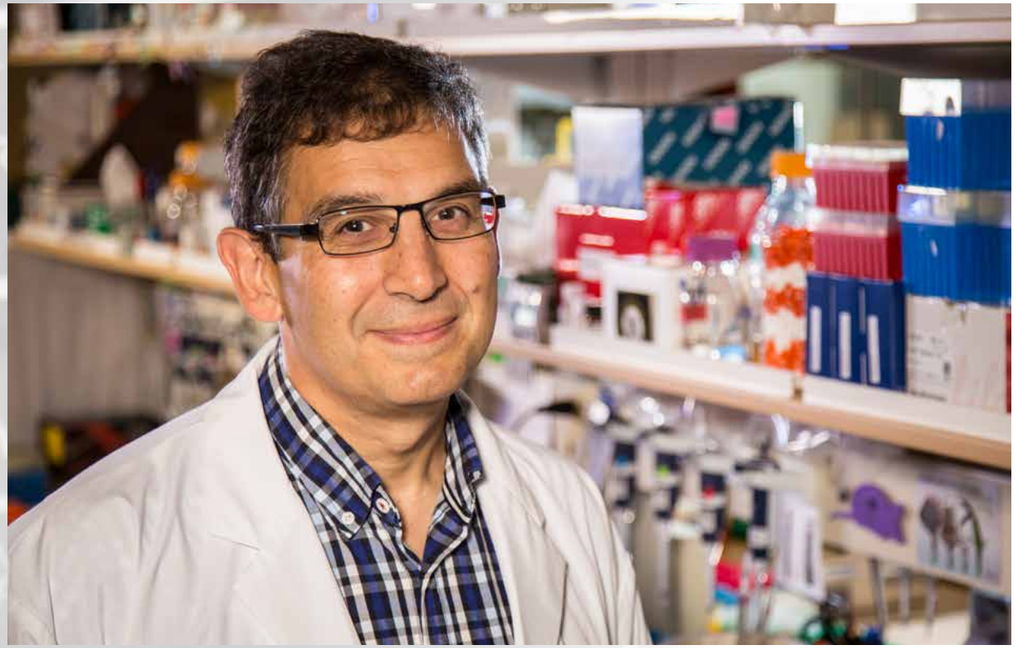


Dr. Kuo-Shyan Lin

Radiopharmaceuticals are also promising for imaging and the treatment of metastatic melanoma.
A research team led by Dr. Bénard has developed highly promising radiopharmaceuticals for melanoma imaging and radionuclide therapy. This was based on a known molecule that binds to a receptor known as melanocortin 1 that is overexpressed in melanoma. By modifying a link between the radioactive tag and the molecule, they were able to significantly enhance tumour retention and decrease the accumulation of the compound in the kidneys. These new radiopharmaceuticals have high potential to improve the imaging and treatment of metastatic melanoma.

Caspase protein helps cancer cells resist treatment by proteasome inhibitors

The maintenance of protein homeostasis is important for normal physiology and good health. There are two main degradative pathways in cells that contribute to this process, known as proteostasis. How these two pathways are coordinated is not well understood. In a study using the fruit fly model organism published in the journal *Autophagy,* **Dr. Sharon Gorski** and colleagues identified a molecule called a caspase that links the two pathways under conditions of cell stress. They showed that when one of the degradative pathways (called the proteasome) is inhibited, the caspase is essential for activating the other pathway to enable cell survival. As the proteasome is a target for cancer treatment, this discovery reveals a potential way that cancer cells may avoid being killed by the effects of proteasome inhibitor drugs, such as bortezomib in the treatment of multiple myeloma and mantle cell lymphoma.



Dr. Samuel Aparicio

Two new breast cancer drug discoveries

As published in *Nature Communications*, **Dr. Samuel Aparicio** has discovered that the drug CX-5461, originally developed for cancers of the blood and lymph system, can be repurposed as a treatment for breast cancer. Still early in development, Dr. Aparicio has shown that CX-5461 can bind to the DNA of certain regions of the genome causing it to fold up and interrupt the DNA copying process. The compound is selectively active in tumours from patients with mutations in the BRCA1/2 genes, known to cause a strong familial predisposition to breast cancer, and account for approximately 15 per cent of the population with the disease. The study is currently in Phase I of a multi-centre clinical trial that began in June 2016. Phase II will accept even more patients, to determine whether the activity found through preclinical studies is reflected in responses in patients.

In addition, a second paper also published in *Nature Communications* by Dr. Aparicio highlights the discovery of a different prototype drug, called 'T3', engineered to alter the way that cells translate DNA through splicing of RNA into proteins. This small yet highly-potent drug-like molecule is currently in lab-testing and is being used to understand how different breast cancer cells might be susceptible to having RNA splicing interrupted. The drug molecule interferes with the molecular machinery that stiches gene sequences together to make fully functional proteins. Mutations in RNA splicing genes and defects in splicing have been found in diverse cancers, including breast cancer. The prototype drug molecules are allowing Dr. Aparicio and his team to seek out situations where cancer cells are uniquely susceptible to interference with RNA splicing.