October 2020 (Spark-21) Awarded Spark Grants: Novel Technology Applications in Cancer Prevention and Early Detection

Listed in alphabetical order

Arrandale, Victoria
University of Toronto

Combining contact lens sensors, metabolomics and artificial intelligence to characterize exposure and breast cancer biomarkers

Background: Breast cancer is the most commonly diagnosed cancer among Canadian women and rates are increasing among Canadian women below age 50, in contrast to the decreasing trend for women above 50. Genetic predisposition accounts for less than 10% of breast cancers. Most cases are related to factors that impact hormonal levels, and modifiable factors including diet and exposure to infections, radiation, and chemicals.
Breast cancer can be prevented through exposure reduction; early diagnosis can improve prognosis. Current methods for exposure assessment and early detection are oftentimes expensive and/or invasive and inaccessible in remote locations. For example, traditional chemical-by-chemical methods of exposure assessment are expensive and burdensome. Mammography and MRI screening are expensive and invasive.
Efforts are being made to characterize exposure to multiple chemicals using novel high-throughput methods. Some proteins in blood and tear fluid are being evaluated as biomarkers for early detection of breast cancer. The nature of breast cancer as a metabolic disease suggests that metabolites may be more reliable biomarkers than proteins. This suggests that metabolomics may be a preferable method for identifying novel metabolite markers of breast cancer.
Goal: We aim to develop a non-invasive method that combines contact lenses (wearable technology), metabolomics and artificial intelligence (AI) for identifying and quantifying reliable exposures biomarkers and potential breast cancer biomarkers. The study will answer the following questions:

1.Can contact lenses, metabolomics and AI be used to measure exposure to endogenous and exogenous biomarkers?

2.Can contact lenses, metabolomics and AI be used to identify women who have breast cancer?

Contact lenses are commercially available and user-friendly. About 21% of Canadians between 18-55 years already use contact lenses and two-thirds of US users are women. The most common prescribed and cosmetic contact lenses are made from silicone rubber, a highly permeable polymer with a large capacity for retaining chemicals. Contact lenses collects time-weighted samples, overcoming time-dependent variability of measurements associated with spot sampling of biofluids. Silicone rubber strips have been used to measure exposure to environmental chemicals in many other studies.
Methods: Study participants: The study will recruit a total of 60 women (ages 19-50) from CanPath Ontario cohort who wear contact lenses: 30 who have been diagnosed with breast cancer in the previous two years and 30 who are cancer free.
Sample collection: There will be no physical interaction between the study participants and the research team. We will ship prescribed contact lenses (ACUVUE, Canada) to the participants along with sample containers and prepaid return shipping labels, and provide instruction on how to handle the samples. The participants will ship three pairs of contact lenses worn over three days (plus blanks) to our lab.
Extraction and chemical analysis: We will extract all contact lenses and use gas chromatography and high resolution mass spectrometry to perform untargeted metabolomics and quantify environmental chemicals such a flame retardants and plasticizers and their metabolites as well as known and suspected carcinogens (e.g., estrogen, progestogen, ethylene oxide, and relevant organochlorines) in the extracts.
Data analyses: We will use feedforward networks deep learning and random forest machine learning (ML) methods to compare and categorize the study groups and identify novel biomarkers of breast cancer. We will use BioTransformer, an ML implementation, to predict and identify unannotated compounds from the untargeted analysis.
Potential for disruption: This project will repurpose commercially available contact lenses (as wearable technology), metabolomics and AI to: (1) assess exposure to carcinogens, and (2) identify novel diagnostic biomarkers for breast cancer. If successful, a large proportion of the Canadian population could be easily screened for breast cancer and associated risk factors from their homes using this novel method.

Bentley, James
Nova Scotia Health Authority (NSHA)

Spectroscopy and artificial intelligence to disrupt the status quo in cervical cancer screening

Background

Cervical cancer kills one woman every two minutes, 90% of these women are from low- and middle-income countries. The WHO has challenged nations to eliminate this preventable disease and Canada has committed to do so by 2040. These targets can only be achieved globally by adapting novel strategies.
It is envisaged that the urine HPV testing has similar diagnostic accuracy as cervical specimens and vaginal self-sampling for cervical cancer screening. Urine testing may also be more acceptable to women, is easier to procure and may help overcome cultural barriers and improve compliance to screening globally.
Spectroscopy of biofluids is relatively a new technology, being evaluated for clinical applications. This technology facilitates unique finger-prints on biofluids, yielding specific signatures for disease biomarkers. To date, Infrared spectroscopy of biofluids in large cross-sectional studies have shown high sensitivity and specificity in dementia, brain cancers and endometrial cancers. Early proof of concept studies have demonstrated similar potential in urine testing for gynaecological cancers and other diseases. We have shown IR-S to differentiate between microbes based on the signatures of their chemical properties. A proof-of-concept study by us is evaluating concordance between spectroscopy and validated HPV tests to detect HPV genotypes in urine samples stored in bio-repository.

Hypotheses

Spectroscopy has the potential to detect high-risk HPV in urine samples and be a disruptive technology to detect cervical intraepithelial neoplasia 2 or worse disease (CIN 2+). Spectroscopy platforms have the capacity to be miniaturized to be used as a point-of-care device. Signals can be more efficiently analyzed with artificial neural networks (ANN).

Objectives

Primary:
Investigate the ability of spectroscopy to detect CIN 2+ by detecting high risk HPV in urine.
Study the concordance between HPV detection by IR-S and a validated HPV test
Secondary:
Develop ANN to analyse the spectroscopy signals to recognise the presence of HPV in urine samples.

Study Design

Two groups of women, 1. 144 with abnormal cytologic abnormality seen in colposcopy clinic, QE2 Health Sciences Centre, Halifax, and 2. 48 women >30 years, who have had a negative cervical cytology in the last 3 years, will be enrolled from IWK gynecology clinic. Cervical and urine specimens will be obtained from those enrolled, and both specimen types tested for high-risk HPV by HPV DNA test and by spectroscopy. Test results will be compared to determine concordance between specimen types and between the testing technologies. Biopsy confirmed CIN2+ will serve as the clinical endpoint to determine the sensitivity of spectroscopy for urine testing in comparison with HPV DNA testing. The spectroscopy outputs linked to histology will be used to develop ANN to improve diagnostic accuracy and remove the subjectivity.

Methods

Samples will be obtained after informed consenting. Aliquots of urine and cervical samples will be tested for HPV DNA at the NL Public Health Laboratory, St. John's. A blinded second set of aliquots will be independently tested by Raman spectroscopy available at the Department of Physics, Dalhousie University, Halifax. After analysis signals will be shared with evaluated to develop ANN.

Significance

This is a proof-of-concept study. Spectroscopy is a robust, portable and relatively simple technology; the results are instant, reproducible and reliable. Spectroscopic based urine screening could overcome the barriers and shortfalls of the currently used screening methods. Once we confirm that this has the ability to identify CIN 2+ by detecting HPV in urine, the test can be miniaturised and adapted to a point of care test. This will be significantly more economical and logistically simpler than currently available screening methods as no consumables and pre-processing of samples are required. We believe spectroscopy as a simple, affordable and acceptable test will disrupt the status quo of 'no screening' in the LMICs, accelerate elimination of cervical cancer, and thus avert 15 million deaths in next 50 years.

Campbell, Clinton
McMaster University

Evaluating the YOLO real-time object detection artificial intelligence algorithm for bone marrow cytology

Problem to be investigated

A bone marrow study is a requisite part of making a hematological diagnosis. It consists of an aspirate (liquid tissue) for cytology, a trephine core biopsy (solid tissue) for histopathology and numerous ancillary tests. Bone marrow aspirate review includes a nucleated differential cell count (NDC), where up to 500 bone marrow cells are counted manually and placed into one of 11 or more unique categories by an experienced human operator. The NDC allows for identification of abnormal cell populations, triggering additional testing and influencing critical clinical decision points such as initiating chemotherapy in acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS). Performing an NDC on every aspirate specimen is a tedious, time-consuming process limited to experienced tertiary reference centres and is associated with high inter-observer variability. This may lead to delayed or incorrect diagnosis, leaving an unmet need for innovative tools to support the aspirate review process.

A type of artificial intelligence (AI) algorithm called deep learning has shown considerable success in image classification in several histopathology domains using digital whole slide images (WSI). While highly impressive, most of these studies do not capture the unique problems and complexity inherent in bone marrow aspirate cytology. The NDC count represents a more complex deep learning problem that includes both object (cell) detection and non-binary probabilistic classification into one of many categories. Therefore, unique AI solutions tailored specifically to image classification problems in bone marrow aspirate cytology are needed.

You **O**nly **L**ook **O**nce (YOLO) is a recently developed deep learning algorithm that combines object detection and classification tasks into a single step. YOLO detects all objects in an image simultaneously and assigns class probabilities to each object virtually in real-time. YOLO has found real-world applications in self-driving cars, where all objects on the road are instantaneously detected and classified. Such a task is conceptually similar to detecting and classifying cells in a bone marrow aspirate digital WSI, where many distinct and often overlapping objects (cells) with complex features must be rapidly detected and assigned a class probability. We therefore propose designing and training a YOLO scheme with bone marrow aspirate digital WSI as a novel solution to support the bone marrow NDC toward improved diagnosis of hematological disorders.

Objectives of investigation

The objective of our study is to evaluate the ability of the YOLO AI algorithm to accurately perform an NDC on bone marrow aspirate specimens.

Methodology to be used

Cells in bone marrow aspirate digital WSI from normal, AML and MDS bone marrow specimens will be labelled by expert hematopathologists and used to train version 4 of YOLO AI algorithm, optimized for small object detection. Performance metrics including sensitivity and specificity will be evaluated.

Significance of research

This study will yield proof-of-concept data on the feasibility of applying state-of-the-art AI technology to object detection and classification in bone marrow cytology. This may eventually lead to commercial-grade technology that can support the NDC, which would have high impact on the field of hematopathology.

Potential to disrupt status quo

This work has potential to revolutionize the way diagnostic hematopathology is practiced. The ability to automatically and rapidly detect, identify and count thousands of bone marrow cells in using AI would streamline the hematopathology diagnostic workflow and increase diagnostic sensitivity and specificity of hematological cancers. It may also provide a feasible and cost-effective means to detect rare leukemic blast populations called measurable residual disease (MRD) which are believed to cause leukemic relapse / recurrence.

Chaurand, Pierre
Université de Montréal

Cancer steroidomics by tag-enhanced imaging mass spectrometry

Steroids control growth, differentiation, reproduction and metabolism in plants and animals. In cancer, steroid biosynthesis goes out of control. Synthetic steroids are often used to treat cancer, related symptoms and chemotherapeutic side effects. Although spaciotemporal mapping of the distribution of steroids would enable unique potential for early diagnosis and therapeutic management of cancer and other diseases, no imaging tools exist for effective detection of steroids in biopsied tissue.
Imaging Mass Spectrometry (IMS) is a discerning tool for molecular histology, but except for abundant cholesterol, low *in vivo* concentrations inhibit steroid analysis in biopsied tissue. Our steroid-tagging agents enhance sensitivity in IMS and mitigate problems of low concentration and poor ionization. With goals of using steroid histology to diagnose early and monitor cancer, we propose to validate full-spectrum steroid-tagged IMS in biopsied tissue from five different kinds of cancers.
Our steroid-tagging agents enhance detection by IMS to effectively image a full spectrum of steroids within tissues. Best tags will be validated in human cancer tissue biopsies. The spatiotemporal levels of steroids known to be up- and down-regulated in cancer will be studied to detect early and itemize hallmarks of different stages of cancer. Sensitive full-spectrum steroid profiling in biopsied tissue would have major socioeconomic and healthcare benefits for enhancing diagnosis and treatment of this insidious disease.
Our expertise in medicinal chemistry, IMS analysis, and biomolecular and clinical research is well positioned to make a leap in cancer imaging. Our reagents and methods are designed to enable routine steroid-tagged IMS for accurate and early cancer diagnosis. Validation in cancer tissue will have major ramifications for studying dysregulated steroid signaling in a range of diseases and after exposure to cancer-causing contaminants in the environment.

Diamandis, Eleftherios
Mount Sinai Hospital

Early diagnosis of gliomas by using a novel multiplexed serum proteomic technology

Gliomas are highly malignant tumors. Failures with gliomas include absence of effective treatments and late diagnosis. At diagnosis, most patients have large, metastatic tumors which are difficult to eradicate. Glioma patients will benefit from earlier diagnosis. There is convincing literature that early diagnosis of cancer leads to better outcomes (Etzioni et al. Nat Rev Cancer. 2003; 3:243-252). Our goal, a collaboration between Toronto, London (ON) and Sherbrooke, is to apply novel technology, developed by the company OLINK, to screen serum samples of patients with glioma, vs. controls, to identify diagnostic biomarkers that can be used for non-invasively diagnosing glioma, in combination with imaging/MRI, and artificial intelligence. One applicant, Dr. Richer, is a Neuropathologist with access to sera collected at glioma diagnosis and before therapy. For this preliminary study, we will use 50 glioma sera and 50 sera from age and sex-matched controls, as a proof of principle. These samples will be available from Dr. Richer. Calculations support >90% discriminatory power but an independent set of patients must await this outcome. Novel technology: Borrowing from the principles of immuno-polymerase chain reaction, OLINK developed the proximity extension assay which runs 92 plex immunoassays in parallel, measuring over 1,000 proteins in just 14 µl of sample. Immuno-PCR leverages the extreme sensitivity of PCR and the specificity of immunoassays to measure proteins at very low abundance. The principle of immune-PCR consists of first allowing protein targets to bind capture antibodies and then introducing a secondary antibody that is conjugated to an oligonucleotide sequence. The formed immunocomplex is detected by primers that are complementary to the DNA sequence on antibodies, to allow for amplification via PCR. The signal from the immune-complex is amplified, delivering a 1,000-fold greater depth compared to traditional ELISAs. In the case of the 92-plate reaction, 1 µl of sample (serum or plasma) is channeled into a micro well and incubated with 92 pairs of matched single stranded DNA conjugated antibodies along with DNA detection probes and internal controls for the hybridization, extension and amplification steps. The recognition feature via matched pairwise antibodies and selected hybridization of the complementary single stranded DNA sequences are key in reducing background signal and ensure specificity. OLINK offers 14 different 92 plex panels with biological relevance, including oncology. Since this entire process is automated and 1 µl of the sample is channeled per 92 plex reaction, 14 multiplex panels can be run in parallel using a total sample volume of 14 µl to measure 1,288 proteins. This is an astonishing feature since no other technology can deliver comparable results. This technology will be instrumental in quantitatively mining the serum from glioma patients and controls to identify a few biomarkers of the disease. We have already used extensively OLINK to identify biomarkers for other diseases. We found this technology to be highly reproducible (< 15% CV) and highly specific and sensitive (pg/ml range). This technology has unique advantages over mass spectrometry (MS) which suffers interference from high-abundance proteins of serum such as albumin. This technology is much more reproducible than MS quantification of proteins in serum. If our initial efforts are successful, we will expand this investigation by using additional and independent sets of patients to validate our algorithm. We recognize two major limitations:(a). The protein coverage is only approx. 1,200 proteins, which is 5% of all human proteins. (b). The

technology is expensive, costing approx. $1,000 per sample, even if the cost per analyte result is <$1. Our long-term goal is to limit the number or proteins measured in subsequent samples by developing custom panels of 10, 20 or 30 proteins. OLINK technology allows for custom panel development after the initial screening is completed. We conclude that this is a highly comprehensive and innovative approach to identify non-invasive serum biomarkers of glioma.

Easson, Alexandra
Princess Margaret Cancer Centre - UHN

Multispectral needle endoscopy: improving the patient breast cancer diagnostic experience

Idea: Best practice recommendations for breast cancer include biannual mammography for women age 50-74 years. While screening reduces breast cancer death by 20-48%, 8-12% are called back for a false positive result for more imaging, and in 1.5%, the radiologist may do a core tissue biopsy with a large needle, an invasive procedure causing tissue destruction, bleeding and pain. Repeat biopsies may be needed, and several areas may need biopsy in the same patient. This process takes time, is costly, can cause significant psychological distress and may lower future compliance, especially since most biopsies are benign. Our team of clinicians and physicists ***propose:*** to develop a Needle Endoscope with multispectral optical imaging capability (White light/Autofluorescence (AF)/Raman spectroscopy (WAR)) to allow ***direct real time*** diagnostic optical imaging of breast tissue during screening. We are the first to publish that an image produced by an AF-coupled microendoscope (0.7 mm outer diameter (OD), 3000 pixels (P) can distinguish cancer and normal breast tissue in a breast duct and a 2nd-generation AF-endoscope (OD 0.55 mm, 6000 P) can do the same when placed directly into breast tissue. We believe that a tri-modal optical imaging system will optimize the clinical diagnostic accuracy: white light to confirm location, AF has diagnostic accuracy of 70-80%, and Raman spectroscopy (accuracy 90-99%) will maximize diagnostic accuracy. These optical imaging principles are already used in glioma surgery. At the scale of a national screening program, the development of ***this first of its kind*** minimally invasive technology could provide the radiologist with a reliable tool to guide the biopsy needle to ensure that the appropriate tissue is sampled and avoid the need for biopsy if benign, resulting in ***significant clinical impact*** by minimizing tissue destruction, and improving the diagnostic screening experience.
Proposal: To know if this biopsy assist device is worth developing, we need to address 2 key questions: 1. **Can our multispectral WAR system diagnose breast cancer?** We will collect WAR data from matched annotated slides of frozen breast cancer (invasive ductal and lobular cancer) and normal tissue obtained from the University Health Network Research Biobank using a custom confocal microscope. Stained slides will be marked by pathology to generate annotated digital mark-ups denoting the regions of cancer, normal, and other. Each unstained slide would be placed under the confocal microscope and co-registered WAR data will be collected and interrogated to create images of diseased states. Supervised ***machine learning (ML)*** and ***deep-learning (AI)*** will interrogate this data to create a diagnostic WAR library (expected sensitivity/specificity > 90%). Spectral data collected using the confocal setup when spatially averaged is necessary to train new models for prediction for the creation of the portable endoscopy needle. **2. Does the need for biopsy and the biopsy needle size impact the patient?** We begin a pilot study to prospectively collect patient experience data from screened women undergoing breast biopsy where different size needles are routinely used. We correlate patient factors such as distress and pain with technical factors such as number and size of biopsy, and we gain a better understanding of the psychological and physical effects of false positives associated with breast screening.
This ***high-risk, high-yield*** project can: minimize the negative impact of false positive rates associated with screening mammography, offer a minimally invasive, direct access to breast tissue (potentially reduce the number of biopsies required), provide an open-source digitally annotated dataset for the research community to develop better tools for cancer diagnosis, and improve the patient cancer diagnostic experience by increasing adherence to screening programs to reduce breast cancer deaths.

Forghani, Reza
McGill University

Radiomics and machine learning based non-invasive biomarkers for prediction of peritumoral invasion in brain Metastases

Background: Brain metastasis (BrM) is an emerging complication of advanced cancer, affecting 20-40% of patients with solid tumors. We recently discovered peritumoral invasion as a driver of local treatment failure and shortened overall survival in patients with surgically resected BrM. Invasion status can only be determined by examination of the surgical resection specimen by a neuropathologist. Knowing this information prior to surgery would optimize surgical planning, enhance the accuracy of stereotactic radiosurgery (SRS) in non-surgical patients and allow for the implementation of targeted systemic therapeutic strategies based upon invasion status. ***We will develop tools and methodologies using computerized image analysis and artificial intelligence for the determination of invasion status in BrM non-invasively. Hypothesis/Objective:*** We intend to use computerized image analysis and machine learning of pre-operative MRI scans to develop image-based biomarkers of peritumoral invasion that can be used in surgical and SRS planning, using known invasion status in resected BrM as ground truth. We hypothesize that quantitative features extracted from MRI images can be used as biomarkers for predicting peritumoral invasion in BrM to achieve sufficiently high sensitivity and specificity to alter treatment planning.
Data and methodology: We will use supervised machine learning and radiomics approaches to identify image features associated with invasive cancer cells, as determined by the ground truth obtained through the assessment of surgical resection specimens. Our cohort will include over 300 retrospectively resected BrM specimens that have already been annotated for tissue invasion by a neuropathologist.
Aims: **Aim 1**: Use computerized image analysis and machine learning to identify imaging-based biomarkers in MRI scans to predict peritumoral invasion in patients with BrM. **Aim 2**: Determine the ability of the identified biomarkers for non-invasive prediction of patient outcomes such as local disease control and overall survival in an independent retrospective external dataset
Significance: This study has the potential to transform the care of patients with BrM by noninvasively detecting invasive cancer cells. This will allow for paradigm changing improvements in the following aspects of clinical management of BrM: surgical and post-operative SRS planning to eliminate invasive cancer cells, non-surgical SRS planning to detect invasive cancer cells outside of the contrast enhancing lesion, and application of systemic treatments that incorporate invasion status as a predictive biomarker.

Goodarzi, Aaron
University of Calgary

Using novel bio-dosimetry to measure personalized, lifetime radon gas exposure and transform the prevention and early detection of lung cancer

The PROBLEM. Lung cancer caused ~40% of cancer-related deaths but only attracted ~0.1% of cancer fundraising reported in 2019. This inequity is attributed to <u>false</u> stereotypes that tobacco causes all lung cancers, is therefore the patient's fault and that they must suffer the consequences quietly. 1 in 5 lung cancers in Canada actually occur in never-smokers, who experience the unjust stigmatization that smokers encounter, whilst also experiencing anxiety related to their inability to pinpoint their disease's origins. At a population level, radioactive radon gas inhalation is established as the 2nd leading cause of all lung cancers globally. It is generated geologically but normally dilutes to non-hazardous levels as it reaches the earth's surface. Unfortunately, modern buildings can concentrate radon to abnormally high levels, creating a dangerous and, in Canada, worsening carcinogen exposure issue. Radon exposure drives up cancer risk, synergizes with tobacco effects, and is important to consider for light smokers, whose tobacco-related cancer risk might be low, but if combined with radon can become as high as a heavy smoker. Essentially no-one has reliable radon data useful to measure lifetime exposure, and in the absence this and derive personalized radon-induced lung cancer risk, providing harm reduction advice, making a diagnosis at an earlier (and less lethal) stage, and conferring eligibility for lung cancer screening programs are less likely or simply just not possible for never- or light-smokers.
OBJECTIVE. There is an <u>unmet need</u> to determine lifetime radon exposure at an individual level. We will meet this challenge by bringing together population health, radiation biology and atomic physics to develop practical ways of measuring personalized lifetime radon exposure retroactively, from easily accessible, disposable tissues and in manner that can inform health decision making. We ***HYPOTHESIZE*** that modern isotope dilution mass spectrometry (IDMS) can serve as 'biodosimeter' to measure absorbed radon decay products in disposable, keratinizing human tissues (i.e. toenails), and is capable of informing lifetime radon exposure as an index test to stratify individuals into lung cancer risk brackets. We suggest that this is essential to widen lung cancer screening inclusivity to embrace never- and light-smokers, and improve radon-induced lung cancer prevention strategies.
METHODOLOGY. We will take advantage of a universal event in radon inhalation: solid metallic radioisotope accumulation. Specifically, as 222Rn (radon) undergoes radioactive decay it precipitates as solid 218Po that eventually

decays to 210Pb isotopes (t½ = 22 years) that are sequestered in bone as well as keratinizing tissues (lungs, hair, nails), with only ~25% being eliminated. The key question is whether they can be measured in a sufficiently sensitive manner to inform lifetime radon exposure. To address this, it is essential to have the atomic physics skill to measure radon-decay products in tissue, merged with long term, reliable population health data for a large number of people with known low and high radon exposure. Working together with the Evict Radon national study, the CanPATH longitudinal health study and other partners, our team now has ALL necessary tools and resources at our disposal to assess the viability of IDMS to measure 210Pb radon-decay products in toenails from people with highly detailed, long-term and known radon exposures.
SIGNIFICANCE. Success of this pilot project will ultimately enable: (i) people to gain knowledge of potentially unknown early-life radon exposure so that they can take informed, preventative action earlier and at a lower action threshold, (ii) lung cancer screening program referral methods that, for the first time, could include radon-exposed never-smokers and light-smokers and, (iii) improved lung cancer vigilance based on verified radon exposure, leading to diagnosis at earlier cancer stages with higher net survival rates. ***This will transform the currently inadequate status quo of radon-induced lung cancer prevention and diagnosis***.

Khalvati, Farzad
The Hospital for Sick Children

Early detection and novel stratification of pediatric low-grade gliomas by MRI-based artificial intelligence

Pediatric low-grade glioma (pLGG) is the most common brain tumour in children, accounting for approximately 40% of central nervous system tumours in childhood. With surgical excision as the main treatment, and chemotherapy and radiation as additional treatment options, death from these tumours is relatively rare, but the 10-year progression-free survival is less than 50%. Thus, many affected children will suffer multiple recurrences requiring multi-modal therapy leading to considerable morbidity. Recent progress in our understanding of the molecular and genetic markers for different types of pLGG has had a significant impact on patient outcome with improved precision of early diagnosis, surveillance, prognostication, and individualized treatment strategies for these patients.
Currently, the molecular landscape of pLGG is assessed through analysis of the tumour tissue. Patients with unresectable tumours usually undergo biopsy to obtain a tissue specimen for a molecular diagnosis. However, biopsies are invasive, have an inherent sampling error and cannot be performed in certain tumour locations. In addition, there is a significant time delay to perform brain tumour biopsy and genetic profiling to determine the molecular subtype of the tumour. Thus, biopsies are not only unable to represent the full set of potential mutations present in a particular tumour, they also harbor inherent risks such as infection, hemorrhage, and metastatic seeding. Moreover, the delay in biopsy procedures and the assessment of the genetic profile of pLGG afterward makes it impractical to use these genetic markers for early detection of unfavorable outcomes (e.g., tumour progression).
As a noninvasive method, recent advances in magnetic resonance imaging (MRI)-based artificial intelligence (AI) solutions have shown potential in early prediction of pLGG molecular markers. AI models, however, face challenges. Currently, the AI models for pLGGs are based on predefined radiomic features, which may not fully capture latent predictive information in the images. In addition, radiomics-based models require radiologists to manually segment tumours of hundreds of patients who have undergone biopsy. This labeling process is a tedious and costly task and often suffers from low inter- and intrareader reliability. Moreover, inaccurate and inconsistent manual annotations of tumour regions in MRI negatively impacts the performance of AI models. Tumour annotation may not be precise due to different factors including MRI quality, radiologist's experience, and the inherent complexity of tumour structure. Finally, for an AI model to be deployed in a clinical setting, a rigorous quality control system must be in place to provide confidence for clinical decision-making.
In this research, we aim to develop novel MRI-based AI solutions to determine molecular markers of pLGG with high accuracy. We will design and develop deep learning models to predict the genetic markers of pLGG with no need for manual annotations of the tumour regions in MRI. We also aim to design a method to provide the necessary confidence for AI results to be used in clinical decision-making. We will test the potential of our proposed AI algorithms to be deployed in clinical settings by evaluating their efficacy in predicting the genetic markers of pLGG based on initial MRI scans (e.g., two years before surgery) as well as predicting response to therapy and hence, enabling translational AI in pediatric medicine.
The successful completion of the proposed research will lead to AI solutions for the characterization, early stratification, and prognostication of pLGG patients. With improved accuracy and confidence in the MRI-based AI results, this research will have a significant impact on the quality of cancer care for pediatric

brain cancer patients and an important effect on the successful integration of AI models into clinical practice in general.

Krajinovic, Maja
CHU Sainte-Justine Research Centre

MicroDNA signature for prognosis of childhood acute lymphoblastic leukemia

Summary: The vast majority of cellular DNA in eukaryotes is contained in long linear strands. However, some exceptions in the form of extrachromosomal circular DNAs (eccDNAs) have been long recognized. Recent work has discovered eccDNAs deriving from unique (nonrepetitive) DNA, which due to its short size (<2kb), have been named microDNA. Our knowledge of this novel eccDNA is limited. There are only few reports including our own, that raised the questions about their biogenesis, function and clinical utility. Several studies reported typical size pattern of microDNA and preferential origin form transcriptionally active genes.
Given non-random positioning within the genome, microDNAs may reflect a specific status of the cells suggesting their potential utility as a new type of biomarker for disease detection, treatment assessment and progress surveillance. This is further supported by our experiments conducted in a panel of lymphoblastoid cell lines, treated or not with anti-cancer drugs. The number of microDNAs derived from the same gene exceeded largely the number expected by chance when comparison between individuals of same drug group was performed. MicroDNA may thus reflect changes that are specific for a given condition induced either by the treatment, or by tissue and cancer specific chromatin dynamics. Moreover, preliminary observations showed that microDNA are present in plasma/urine specimens with similar characteristics in term of length pattern and preferential origin from active genes. While microDNA may retain favorable features of cell free DNA, it offers a major advantage that is circular DNA form, resistant to the exonuclease cleavage and easily amenable to amplification.
Objectives: To analyze microDNA signature in samples from childhood acute lymphoblastic leukemia (ALL) patients, obtained at different points during disease evolution. **Specific aims** are to **1.** Identify microDNA signature from tissue and body fluids (bone marrow, urine, plasma) at different time points of disease progression; **2.** Develop microDNA-based assay adapted for clinical use. **3.** Design a microfluidic device that will facilitate the analyses of microDNA from various body fluids. We will analyze microDNA content in matched tumor and liquid biopsy samples from childhood ALL patients obtained at diagnosis, remission and relapse, as well as in samples from healthy controls.
Methodology: The circular DNA will be extracted and enriched through rolling circle amplification and subjected to high throughput sequencing. Bioinformatics pipeline will be used to identify circular microDNA clusters and to map them to the human genome. MicroDNA signature in term of size and abundance and set of genes from which microDNAs is produced will be identified and compared between tissue and body fluids and between different conditions (diagnosis, remission, relapse) to identify microDNAs with diagnostic and prognostic potential. We will also test different liquid biopsy volumes that are sufficient to capture microDNA diversity. Once the set of microDNAs with prognostic value is identified, diagnostic assay that will target only microDNAs present in these signatures will be developed. This will open the opportunity to design, validate and manufacture a microfluidic device that will automate all steps of microDNA assays from minute amounts of body fluids.
Significance: Refractory and relapsed ALL are still the leading cause of disease-related mortality among children. Identifying easily assessable predictive biomarker has a huge potential for early cancer diagnosis and prognosis giving clinicians tools to be able to intervene as soon as possible in the disease's development, thus greatly improving disease outcomes. Moreover, this project will open a possibility for subsequent fast transition to clinics by providing a microfluidic-based strategy to analyze circulating microDNA in a time, sensitive and cost-effective manner. If shown promising, this approach can be extended to other malignancies and can thus have wider application in oncology.

Liang, Jinyang
Institut national de la recherche scientifique

Towards a fast and high-resolution thermal imaging dermatoscope for early-stage detection of small-size melanoma

Melanoma, as the most aggressive type of skin cancer, has a worldwide incidence rate increasing faster than any other cancer. Detection of early-stage melanoma is key for reducing the number of unnecessary biopsies, the costs of care, and the mortality rate. Thermometry is an attractive method for melanoma screening. However, existing thermal imagers can reliably diagnose only melanoma with ≥15 mm in diameter, beyond the 6-mm-diameter warning size defined in the “ABCDE” rule of skin cancer. The overall goal of the proposed project is to explore the implementation of optical imaging thermometry based on luminescent temperature indicators as fast and high-resolution thermal imaging dermatoscopy for melanoma detection at the earliest possible stage. We aim to develop a new platform that will allow examining the transient temperature dynamics of the lesion under thermostimulation for directly discerning the malignant melanoma from the benign lesions and the healthy tissue. To achieve these goals, we propose a new approach that interfaces nanomaterials, microtechnology, ultrafast imaging, and pharmaceutical sciences. We will load temperature-sensitive upconverting nanoparticles (UCNPs)—acting as thermometers on the nanometer scale—within the matrix of dissolving polymeric microneedle arrays, which will deliver these nanothermometers in clinically relevant melanoma mouse models. We will also adopt an ultrafast imaging thermometer to record skin temperature dynamics. The proposed project will significantly improve thermal imaging-based melanoma detection, allowing for an earlier-stage diagnosis and thus drastically improving the overall welfare of patients. As a self-calibrated method, the proposed diagnosis will be finished in minutes. Importantly, the dose, depth, density, and location of the delivery will be customized for each patient. Furthermore, painless injection and cooling stimulation can be easily performed by medical professionals. Finally, the proposed methods feature an economical system perfectly compatible with existing digital dermatoscopes, showing great potential for future clinical use.

Lozano, Andres
The Toronto Hospital (Western Division) - UHN

Safety and feasibility of focused ultrasound-enabled liquid biopsy in patients with brain tumours

Background:
Glioblastomas have a poor prognosis despite maximal therapy. Accessing brain tumor material for pathological diagnosis of glioblastomas requires invasive procedures that carry risk to patients including brain hemorrhages and death. Liquid biopsies are emerging non-invasive alternatives to direct tumour biopsies but the abundance of circulating tumor DNA (ctDNA) is relatively low and this limits our ability to accurately make the molecular diagnosis of brain tumors. We now want to couple liquid biopsies with high intensity focused ultrasound (HIFU) to enhance the release of tumor DNA into the circulation and increase the sensitivity/and specificity of liquid biopsies for brain tumors.
Objective:
To increase plasma ctDNA and thereby improve the identification of ctDNA-based genomic and epigenomic biomarkers, magnetic resonance-guided focused ultrasound (MRgFUS) will be utilized in glioblastoma patients to enhance the release of tumour DNA into circulation.
Study type:
Single-center, prospective, single-blinded, single arm, controlled clinical trial.
Experimental Approach:
Aim 1: To assess the utility of MRgFUS in enhancing the abundance of glioblastoma ctDNA. Non-invasive glioblastoma diagnosis and treatment has the potential to transform patient care. It has been shown that MRgFUS can enhance circulating biomarker presence in animal models and that it can be safely utilized intracranially in humans. Accordingly, this Aim is to utilize MRgFUS to improve the abundance of circulating tumour DNA in 20 glioblastoma patients as the first step in the transformation to non-invasive glioblastoma diagnosis and monitoring. The results of this aim will inform on the optimal timepoint of plasma sampling after MRgFUS to obtain the highest quantity of ctDNA for use in molecular analyses.
Aim 2: To evaluate the utility of MRgFUS in enhancing the non-invasive detection of glioblastoma methylation signatures. Published work from our lab has shown that gliomas can be distinguished from other brain tumours with liquid biopsies but the identification of glioma subtype is more limited. . Given that glioblastomas have a distinct biology and are typically managed differently than lower grade gliomas, the ability to non-invasively determine glioma subtype is clinically very important. The use of MRgFUS to improve the sensitivity of non-invasive plasma methylation signature detection of presumed high grade glia tumors is AIM 2.
Aim 3: To improve the non-invasive detection of glioblastoma genomic alterations using MRgFUS. Attempts to identify tumour genomic alterations non-invasively through blood samples has largely been ineffective due to the low ctDNA abundance and its short half-life. The identification of glioblastoma mutations is important for prognostication at the time of diagnosis and to identify alterations with available targeted treatments. This aim utilizes MRgFUS to improve ctDNA abundance in order to allow for non-invasive detection of clinically-relevant genomic alterations in glioblastoma including IDH1/2, TERT promoter, CDKN2A/B, PTEN, EGFR, TP53, BRAF, and PDGFRA which are assessed in

glioma diagnostic panels for routine pathology practice.

Significance:

Overall, this work will support the use of a MRgFUS-enhanced liquid biopsy approach that avoids the risks of intracranial biopsy and identifies genomic and epigenomic alterations of presumed high grade glial tumors with higher sensitivities and specificities than can be achieved with current plasma-based approaches which approach the accuracy of tissue-based approaches.

Mahshid, Sara
McGill University

Physical fingerprints of single extracellular vesicles for liquid biopsy in brain cancer

Challenge: Some cancers remain incurable because treatments only attack a fraction of cancer cells leaving the rest unharmed. Moreover, tumour cells can change and adapt to drugs, evolving drug resistance. If there was a way to track these changes drugs could be applied in sequence, each optimized to target the vulnerabilities presented by the tumor cells at any given time. Periodical sampling of tumour tissue for analysis (biopsy) is not feasible in brain cancers such as glioblastoma because of the location and dispersal of tumour cells throughout the brain. However, it is feasible to collect blood or brain fluid (cerebrospinal fluid, CSF) and isolate 'remotely' the 'fingerprints' of cancer cells from myriads of small particles (extracellular vesicles - EVs) that the cells constantly shed into their surroundings. The problem is how to efficiently extract the information packaged in the EVs, which is made up of complex assembles of molecules (oncogenes) that 'drive' the different cancer cells from which the EVs originate.

Problem: Extracellular vesicles (EVs) are million times smaller than a cell and yet each can carry up to 200 different molecules from the cells that produce them. Therefore, to reconstruct the cancer cell diversity from a collection of EVs, the EVs need to be individually analysed. Presently, EVs are either measured in 'bulk,' thereby masking the differences between their producing cells, or only a handful of molecules can be measured per EV using laborious and slow biochemical methods that detect one molecule at a time.

SPARK solution: We have developed new technologies based on physical science approaches to measure properties of single EVs that can be applied over a collection (ensemble) of many EVs. In one approach, we have used the dynamics of single EVs in arrays of tiny holes (nanocavities) to extract the size and charge of EVs. In another, we have observed that molecular differences between EVs translates into changes in the EV Rama spectra. Together, this suggests that the biological complexity present in a single EV might translate into a distinct physical fingerprint (size, charge, Raman spectra) that can be used to efficiently characterize molecular level differences between EVs. This fingerprint, in turn reflecting changes in the underlying state of the originating cancer cells, can then be used to diagnose cancer type and patient response to specific drugs.

Methodology: Our proposed device confines single EVs in tiny holes (nanocavities) that can be induced to generate SERS spectra. In one operation mode, we allow the EVs to jump between the holes; this mode can be used to deduce EV size and charge. In a second mode, we completely confine the EVs in the holes and obtain single EV Raman spectra. Special cancer cell lines with known molecular properties will be used to establish how the fingerprint varies for different cancer sub-types with different drug resistance properties.

Team and Long-term Plan: This project brings together teams of bioengineers (Mahshid and Wachsmann-Hogiu), neurosurgeons/oncologists (Petrecca), physicists (Reisner), and tumour/EV biologists (Rak) who will share their perspectives in developing new diagnostic technology in presently incurable brain cancer. The present application will cement this team and allow a larger scale application aimed to further develop and translate the physics of oncogenic transformation into the clinic.

Significance: Physical representation of oncogenic and cancer driving molecular traits represents a novel approach to EV-based liquid biopsy that may enable treating each patient individually according to the molecular profile and biologically malignant state of the tumour. This non-invasive method will enable changing drugs as needed to optimize the therapy and will propel development of new therapies with our physical fingerprint serving as a measure of therapeutic response.

Mammo, Zaid
University of British Columbia

Advanced multi-functional in vivo retinal imaging for ocular oncology

Summary: Choroidal tumors present with a wide clinical spectrum including life-threatening malignant melanoma and choroidal metastasis. Ophthalmic examination and imaging are paramount in reaching a correct diagnosis. Significant overlap exists in the clinical and imaging findings of benign and malignant choroidal tumors, resulting in diagnostic dilemmas and anxiety for patients. This is compounded by the difficulty in obtaining in-vivo tissue diagnosis and the risk of extra-ocular seeding. Despite advances in ocular imaging, there continues to be a need for high-resolution choroidal structural assessment to aid in tumor differentiation. Our underlying hypothesis is that alterations in the melanin pigment in the RPE and choroid provide specific biomarkers for differentiation between malignant and benign tumors. These changes can be detected using multi-functional polarization-sensitive optical coherence tomography (PS-OCT). Such findings could provide diagnostic clues that may not be amenable to current ocular imaging tools.
Aims:1.To establish robust and repeatable in vivo measurements of the potential tumor-specific effects on the melanin pigment within the RPE and choroid in patients with choroidal tumors2.To demonstrate the ability of a novel non-invasive PS-OCT tool to measure quantitative and qualitative alterations in the RPE and choroid3.To investigate the potential role of PS-OCT as an adjunct screening tool to standard-of-care imaging modalities in choroidal tumor assessment
Methods: OCT measures the magnitude of backscattered light to build up two- and three-dimensional images of the retinal layers, RPE, and choroid. Recent advances in OCT technology allowed the expansion of its applications. OCT-Angiography (OCTA) allows the non-invasive visualization of the retinal and choroidal microvasculature. Also, PS-OCT draws advantage from the fact that ocular tissues, especially the melanin-rich RPE and choroid, can change the light's polarization state. In the proposed project, we will develop a prototype Jones matrix tomography system, a subtype of PS-OCT, along with an image classification approach for enhanced delineation and differentiation of choroidal tumors. Our prototype combines both conventional OCT, OCTA, and PS-OCT capabilities that would allow simultaneous in-depth structural and functional insight into the health of the RPE and choroidal melanocytes in patients with choroidal tumors.

Significance: Choroidal tumors constitute an important subset of intraocular cancers, yet frequently present ocular oncologists with diagnostic and therapeutic dilemmas. A number of decision-making tools have been developed to aid in the identification of high-risk features for suspicious melanotic choroidal lesions with malignant potential. Universally, such tools require long-term serial follow-up and extended diagnostic testing sessions that place a significant burden on patients and providers. These tools rely mainly on clinical findings and are difficult to broadly apply as they mostly relate to melanotic lesions. Hence, diagnostic uncertainty is especially prevalent in the setting of amelanotic tumors, which may include life threatening malignant and metastatic disease. There is currently no well-defined diagnostic evaluation system in place for these lesions. Hence, novel imaging tools allowing non-invasive early diagnosis and differentiation of choroidal tumors would facilitate choosing the appropriate local and systemic treatment options as well as informing long-term prognosis and follow-up plans. This innovation has the potential to optimize patient-related morbidity, ocular and systemic complications, as well as survival rates. It has the potential to revolutionize the diagnosis of choroidal lesions by improving diagnostic accuracy. Our project will aim to develop an advanced OCT-based imaging system to identify novel biomarkers of tumor-specific changes to the melanin and the microvasculature. This will enable identification of malignant and benign tumor characteristics and help identify malignant transformation of choroidal tumors and better tailor the treatment options available.

Marra, Marco
BC Cancer, part of the Provincial Health Services Authority

Long read DNA methylation sequencing for early detection of pancreatic adenocarcinoma

Pancreatic cancer has a dismal prognosis, with a 5 year survival of 10%. Early detection and improved survival as a result of screening of high-risk individuals illustrates the benefits of expanded surveillance for a broader population (PMID:31558858). Immune evasion and immunosuppression are fundamental to pancreatic cancer development. Immunosuppressive immune cells are elevated in the circulating blood of patients with precancerous and advanced pancreatic ductal adenocarcinoma (PDAC) (PMC6594197), and peripheral blood assays of cytokines that typify cancer cell immunomodulation are being studied for detection of pancreatic cancer (PMC1866873). Epigenomic profiles confer identity and function of various immune cell types. DNA methylation in peripheral blood distinguish colorectal cancer patients from healthy controls and predict cancer risk, suggesting surveillance of blood cell DNA methylation may represent a minimally invasive screening method utilizing an accessible input DNA source (PMID:27453436, PMID:32711505). DNA methylation profiling of circulating blood cells from patients with PDAC supports the potential utility of blood-based epigenomic surveillance for early detection (PMID:21455317).

The BC Generations Project (BCGP) is a prospectively collected cohort of 30,000 healthy British Columbians with detailed health, diet, lifestyle, medical and family history data, collected along with baseline blood samples. 42 BCGP participants subsequently developed metastatic PDAC, a number of which have post-diagnosis tissue and blood stored at BC Gastrointestinal Biobank, or were enrolled in the PanGen and/or Personalized OncoGenomics (POG) Program at BC Cancer and have undergone next generation whole-genome (NGS) and transcriptome sequencing of peripheral blood and metastatic tumour samples.
Long-read sequencing using Oxford Nanopore Technology (ONT) is an emerging powerful tool for analysing DNA modifications without the need for destructive base conversion or amplification. Nanopolish and DeepSignal use hidden Markov modeling and neural networks to detect DNA methylation from ONT sequencing data (PMID:30994904,PMID:28218898). Analysis of multiple DNA modifications from a single run, phasing of SNPs and DNA methylation and improved structural variant calling, particularly in regions associated with poor read mapping, are among the inherent benefits of ONT sequencing data demonstrated using analysis methods established at BC Cancer (PMID: 32624572, Akbari et al., submitted).
We propose to perform ONT sequencing of DNA prepared from baseline and advanced disease peripheral blood leukocytes from this cohort and matched healthy controls. DNA methylation will be detected from these data using machine learning approaches, and correlated with advanced PDAC and cancer risk from pre-diagnosis samples. Clinical, health and lifestyle data from BCGP combined with POG/PanGen derived NGS sequencing data will enable identification of DNA methylation correlates of PDAC risk and molecular subtypes, and reveal the impact of lifestyle factors on the immunophenotypes of PDAC patients. Phasing of DNA modifications and incorporation into methylation-based cellular decomposition techniques (PMID:30104673)will be employed to infer the cellular composition of heterogenous peripheral blood samples, and correlates with cancer risk such as immunosuppressive MDSCs will be assessed. In addition to analysis of DNA modifications, ONT-based SV detection affecting known PDAC predisposition genes may further reveal genomic rearrangements potentially associated with PDAC risk (PMID: 32624572).
Application of the novel technology proposed here to richly annotated pre-and post-diagnosis BCGP patients with POG/PanGen whole genome and transcriptome NGS data and ONT data for the generation of highly detailed molecular, clinical and lifestyle datasets will support discovery of cancer risk associated biomarkers that can be further explored using cost effective targeted

adaptive sequencing approaches amenable to multiplexing, and will provide crucial insight into the immunomodulatory mechanisms that occur during development of pancreas cancer.

Mason, Andrew
University of Alberta

Does Human Betaretrovirus (HBRV) infection predate the development of breast cancer?

Our ***Objectives*** are to (i) investigate breast cancer patients for evidence of infection with a human betaretrovirus (HBRV) and (ii) determine whether infection is present prior to the development of cancer.
An appreciation of the role of viruses in human cancer has led to the development of successful preventive vaccines against HBV and HPV. The mouse mammary tumor virus (MMTV) has been established as the causative agent for breast cancer in mice. This murine betaretrovirus has a variable 90% nucleotide similarity with HBRV. Betaretrovirus nucleotide sequences have been detected in human sporadic breast cancers in a worldwide distribution, and the complete proviral genome has been cloned from two separate breast cancer samples. However, the role of a human betaretrovirus (HBRV) in the development of breast cancer has been difficult to establish. The main stumbling block has been the lack of good diagnostic assays because betaretroviruses have low levels of expression and avoid immune recognition.
My lab first characterized HBRV in patients with the autoimmune liver disease, primary biliary cholangitis (PBC) in 2003. Since then we have

1. Isolated and cloned HBRV and demonstrated Koch's postulates for a PBC phenotype *in vitro*.
2. Identified proviral integrations in patients with PBC with ligation mediated PCR and next generation sequencing.
3. Shown that breast cancer and PBC patients make immune responses to HBRV using an HBRV Env ELISA and T lymphocyte interferon-γ release assay using HBRV peptides.
4. Characterized a mouse model with MMTV infection and autoimmune biliary disease.
5. Developed combination antiretroviral therapy (CART) to abrogate disease in this mouse model.
6. Used CART to improve histological and biochemical disease in PBC patients.

Specific Aims

1.Do patients with breast cancer have evidence of HBRV infection prior to diagnosis? Our HBRV Env ELISA showed that that significantly more breast cancer patients had serological reactivity (10%) as compared to 2% of age/sex matched controls. Therefore, we plan to analyze serum reactivity for anti-HBRV gp52 Env in breast cancer patients prior to diagnosis using prospectively followed participants in the Alberta Tomorrow Project (ATP). In this cohort, over 350 patients have developed breast cancer within a mean of ~2.5 years between sample donation and diagnosis. Once we have determined the seroprevalence of HBRV in patients prior to the development of breast cancer, we will perform a nested case control study to assess the association between HBRV and breast cancer risk using the extensive datasets available within the ATP. These include detailed, validated lifestyle questionnaires that accompanied the blood samples at the time of study entry.

2.Do patients with breast cancer make cellular immune responses to HBRV? We have established that breast cancer patients' PBMC produce interferon-γ using our HBRV Quantiferon assay. Therefore, we will determine the prevalence of infection in patients with breast cancer and relevant age matched controls.

3.Do patients with breast cancer have evidence of HBRV proviral integrations in breast cancer samples? Using our validated ligation mediated PCR and next generation sequencing and informatics protocol for evidence of HBRV proviral integrations (considered the gold standard for diagnosis). We will test our tumor bank of collected samples: breast cancer tissue, metastatic lymph node and relevant breast tissue controls. Further analysis of insertion sites for integration proximal to oncogenes will be performed to assess the oncogenic potential of HBRV.
Knowledge of cellular immunity, proviral integrations and the independent association of HBRV serology adjusted for risk factors will enable us to determine whether HBRV seropositivity is truly associated with the subsequent development of breast cancer. Data produced from this study will be of great public health relevance regarding the potential role of HBRV in breast cancer etiology and provide an impetus to develop strategies for early diagnosis and intervention with vaccine or antiviral suppression.

Mirkovic, Jelena
University of Toronto

Quantum opportunities in pathology

Problem to be Investigated Current methods in pathology diagnosis, which are based on visual cues using light microscopy and other adjunct test, have number of limitations. Subjective interpretation of light microscopy images leads to inter- and intraobserver disagreement in pathology diagnosis. Furthermore, certain pathologic processes may not be visible under light microscopy and most common ancillary testing, or could not be detected in real-time but require days to weeks for diagnosis. Thus, we aim to use the power of quantum technologies to improve diagnostic methods in pathology by developing novel ways to extract and quantify biochemical, structural, and molecular features of tissues and cells and to provide accurate quantitative assessment of disease state. *Objectives of the Proposed Investigation* Our goal is to bring the most sensitive tools of nature, quantum control and engineering provided by quantum information science to pathology. Pathologists examine tissues, cells, body fluids, and organs and use visual cues under the microscope and other adjunct tests to provide disease diagnosis necessary for appropriate patient treatment. Pathology strives to advance knowledge of pathways that lead to disease, which translates into improved treatment, diagnostic, and prevention methods. Till now, quantum information science based tools in the pathology were inaccessible.
Our first objective is to design and construct programmable structured light microscopes, and use them in the pathology laboratory in a large academic hospital to explore the power of quantum states for studying pathology samples. We envision that this microscope will be capable of extracting novel quantum biomarkers of disease, which will provide for accurate quantitative assessment of pathology samples. Our second objective is to develop disease specific algorithms based on the novel quantum biomarkers to address clinical problems and answer questions in pathology diagnosis that are not amenable to solving by existing methods. *Brief Indication of Methodology to be Used* Recent advances in QIS allow us to create tools that are tailored to be a sensitive test for the presence of specific structures and arrangements in matter. Such quantum measurements can be tuned to be selective for specific pathologies. For example, we envision tailoring spatial profiles of light's polarization to match a biological feature of interest (e.g. DNA, nuclei, cells, tissue structures) to provide simultaneous maps of polarization, optical activity, index of refraction, and absorption of pathology samples to allow for comparative assessment of samples by pathologies and clinicians. In order to achieve this goal we will need to develop novel methods and techniques at the interface of quantum information and pathology. One such method will be to design/construct programmable structured light microscope to use at the pathology laboratory in the large academic hospital. We want to take advantage of our unique team to develop disease specific algorithms based on the novel quantum biomarkers to address clinical problems and answer questions in pathology diagnosis, which are not amenable to solving by existing methods. For example, we will first focus on determining the extent of vulvar squamous cell carcinoma and vulvar intraepithelial neoplasia in the field of background lichen sclerosus with an ultimate goal to eventually guide a precise surgical removal. *Potential Benefits and Outcomes* We envision that this technique can be developed into a quantitative, real-time, non-invasive diagnostic tool for pathology. Potential applications may include determining the extent of cancer invisible to the eye/undetectable by existing clinical technology, in real-time tumor quantification of ex-vivo tissue core biopsies/fine needle aspirations to assure adequacy for molecular testing, and improvement of intraoperative assessment. We envision that our approach may also help advance knowledge of pathways that lead to disease, which will translate into improved treatment, diagnostic, and prevention methods.

Myers, Renelle
BC Cancer, part of the Provincial Health Services Authority

Early detection of lung cancer using VOC from breath and sweat

Background. Globally, lung cancer is the leading cause of cancer mortality in both men and women. When lung cancer is detected and treated early, the five-year survival rate of Stage 1A lung cancer is ≥80% versus 19% without screening. Two large sufficiently powered randomized trials showed a significant mortality reduction benefit (>20%) of lung cancer screening in ever smokers using low dose computed tomography (LDCT). Despite the benefits seen with LDCT screening, uncertainty remains around identifying high risk individuals who do not meet current screening criteria that miss a significant proportion of people who develops lung cancer. LDCT is a sensitive screening tool but the majority of screen detected lung nodules ≤15 mm is not malignant. Appropriate management of screen-detected lung nodules has significant implications for health care resource utilization and harm reduction from radiation exposure related to multiple imaging studies, invasive biopsy procedures, and clinically significant distress. A non-invasive, point of care biomarker that can identify individuals who are at high risk of developing lung cancer, or to predict malignancy risk of small screen detected indeterminate pulmonary nodules is needed. Volatile Organic Compounds (VOCs) in exhaled breath is a promising tool to identify individuals harboring early lung cancer. However, the VOC profiles have not been consistent in different studies. The microbiome in lung tumor tissue has been recently found to be different than non-tumor tissue and that the microbiome profile changes with cancer development and progression. We hypothesize that the VOC signals in exhaled breath is significantly influenced by the lung microbiome. If we understand

the relationship between VOCs generated by the lung microbiome and the phase of lung cancer development, we are much more likely to be successful in developing a robust test that can identify individuals at risk of developing lung on the one hand and differentiate malignant from benign lung nodules as well. Since dogs are known to be able to identify people not only with lung cancer but other cancers such as breast cancer, we seek to determine the role of sweat VOCs versus exhaled breath for early lung cancer detection.
Objective. The aim of this discovery study is to identify VOC biomarkers in exhaled breath and sweat from patients with or without early lung cancer and compare the VOCs in exhaled breath with headspace air of bronchial brush specimens that reflects the lung microbiome.
Study design: 30 former smokers between 55 to 80 years of age with newly diagnosed Stage I lung cancer and 30 former smokers at high risk of lung cancer, defined as >1.5% risk of lung cancer over 6 years based on the PLCOm2012 model who are currently enrolled in our ongoing BC lung cancer screening trial. All participants will undergo paired exhaled breath and sweat sampling, as well as collecting bronchial brushings using a standard research bronchoscopy protocol we have used in multiple NIH sponsored chemoprevention trials. Bronchial brush and sweat samples will be divided for head space gas analysis of VOCs and sequencing of 16S RNA. VOC profiles will be compared between cancer and non-cancer participants. Univariate analysis will be applied to individual VOCs. A P-value of <0.05 after correction for multiple comparisons will be considered evidence of association. Additional hypothesis generating exploratory analyses will include (i) Principal components analysis of the whole dataset – examining for any clustering apparent in the data and (ii) Discriminant analysis performed on a subset of the principal components representing a large portion of the total variance.

Significance: Developing a noninvasive biomarker that identifies high risk individuals who would not be eligible for screening with current selection criteria and can differentiate patients with malignant versus benign lung nodules would significantly improve the efficiency and safety of a screening program. The study will also further our understanding of the underlying biology driving the differences in VOCs between cancer and non-cancer individuals.

Narain, Ravin
University of Alberta

Safe galactose based nanoconstructs for early detection and therapy of liver cancer

Nanomedicine technologies have opened exciting opportunities in improving and enhancing diagnostic and therapeutic efficacy. Recent studies strongly suggest that nanoparticles could be used as diagnostic tools as well as carriers for drug, gene and radioisotope delivery. Nanocarriers can be designed in customized sizes and be equipped with the properties to facilitate easy endosomal uptake and enhanced permeation and retention (EPR) effect that enhance their accumulation in cancer cells. Our proposal pursues development of unique and versatile carbohydrate (galactose) -based nanoconstructs for early detection and treatment of liver cancer. Due to the presence of overexpressed asialoglycoprotein cell surface receptors, our technology will promote the selective uptake of the nanogels in primarily liver cancer cells that have high affinity to galactose residues. The beauty of the technology is that we will use same nanoconstruct for both therapy and diagnosis, i.e. theranosis. Depending on the modality, only the radioisotope will alter between Ga-68 (imaging) and Lu-177 (therapy). This nanoplatform is built on temperature responsive nanogels containing a permanent hydrophilic dense galactose based shell. The nanogel of selected size can be easily synthesized to facilitate delivery of drug doses in optimal but effective and non-toxic amounts. We will evaluate our nanogels containing radionuclides (lutetium-177 for therapy and gallium-68 for clinical imaging) using liver cancer cell culture technique and a liver tumor-bearing animal model study. The nanoconstruct will be tested in vitro in cell cultures to verify the specificity of the radinanocarriers to bind to cancer and normal liver cells as well as its localization in tumor and other tissues after administration in in BalBc NUDE mice with xenograft liver tumors. This will inform us about pharmacokinetic pattern of the nanogels containing radioisotopes in normal mice, followed by in vivo localization of the nanogels. A team of experienced investigators with long history of developments and collaboration in this field will lead this project. Results of this project will lead to scientific publications, intellectual property, and to the development of potentially a a safe and biocompatible nanotechnology for early cancer detection and therapy that can move quickly from bench to bedside.

Pawliszyn, Janusz
University of Waterloo

Screening of glioblastoma oncometabolite by ultrafast solid phase microextraction approach

Glioblastoma (GBM) is a brain cancer that manifests in the primary neuroepithelial cells of the central nervous system, and one of the most aggressive cancer diseases to afflict humans with very poor survival rate. The most efficient treatment for GBM is complete resection; however, the prospect of surgery is strongly contingent on the tumor's localization and dimensions [1]. In this sense, early diagnosis is crucial for effective treatment. Several low molecular weight compounds have been identified to date as possible biomarkers of GBM. Particularly, dysregulation of the oncometabolites: 2-hydroxyglutarate (2-HG) [2-4], N-acetylaspartate (NAA) [5], glutamate (Glu), and α-Ketoglutarate (αKG) [6] has been shown to be connected with alternated enzymatic pathways that occur within cancerous cells. Solid-phase microextraction (SPME), invented in 1990, has been recently applied to a range of bioanalytical applications. The principle of this extraction methodology lies in the equilibrium state established between the concentration of target analyte(s) in the sample and the fiber's coating [7]. During the extraction step only of low molecular weight compounds (<1500 Da) are enriched from the sample to the coating sorbent. A typical SPME protocol would be performed as follows: 1) preconditioning of SPME fiber in organic solution; 2) quick rinse of fiber with water; 3) immersion of SPME device within sample for a given period of time; 4) second rinse with water; 5) immersion of SPME device within organic solvent; 6) instrumental analysis. Additionally, SPME devices can be directly hyphenated to mass spectrometers (MS), thus combining the desorption and ionization steps for ultrafast quantification of compounds of interest. To date, various methods, such as direct analysis in real-time (DART), desorption electrospray (DESI), coated blade spray (CBS) microfluidic open interface (MOI), and probe electrospray ionization (PESI), have been reported by Prof. Pawliszyn's Group for direct SPME coupling to MS. In this application, we propose to optimize and validate a screening method for the detection of known oncometabolites: NAA, 2-HG, Glu, and αKG, in plasma, serum, and blood of donors affected by GBM. The final method will be based on one of the listed direct-to-mass-spectrometry SPME approaches: CBS, microfluidic open interface, and probe electrospray ionization. The matrix will be chosen (blood, serum, plasma) based on preliminary results. Non-tumor bearing volunteers will serve as a negative control. The final protocol will be simplified in such a way that non-trained medical personnel will be able to conduct on-site sampling, e.g. nurse at point-of-care, walk-in clinic, family clinic, etc. Briefly, the SPME-kit will contain a sampling device immersed within a preconditioning solution, with further materials, such as washing solution and storage containers, also included in the ready-to-use kit. Following the collection of sample and extraction, the SPME device will be transferred into an empty vial for transportation to an analytical facility equipped with a mass spectrometer. In the laboratory, SPME device will be analyzed by ambient mass spectrometry technique. This approach, with one hub responsible for the distribution of SPME ready-to-use kits as well as analysis, but with sampling carried out on-site in various health facilities, will significantly reduce the cost of population screening using one drop of blood. By enabling early screening tests, a large segment of the population can be routinely screened, and individuals presenting a profile associated with dysregulation of said metabolites can be directed to further testing such as magnetic resonance imaging (MRI) for confirmation. References1 Szopa. *BioMed research international*, 2017 Article ID 80135752 An. *Magnetic resonance in medicine*, 2017 *78*(1), 40-483 Sciacovelli. *Free Radical Biology and Medicine*, 2016 *100*, 175-1814 Yang. *The Journal of clinical investigation*, 2013 *123*(9), 3652-36585 Zand. *Journal of the National Cancer Institute*, 2016 *108*(6), djv4266 Maus. *Amino Acids*, 2017 *49*(1), 21-327 Reyes-Garcés. *Analytical Chemistry*, 2017 *90*(1), 302-360

Poh, Catherine
BC Cancer, part of the Provincial Health Services Authority

Cytology-based DNA measurement for oral cancer screening

Oral cancer (OC) is a significant global health burden with poor 5-year survival rates among the worst of all cancer types. Despite being easily accessible, OC remains to be detected at an advanced stage when radical interventions are required with devastating consequences on patients' quality of life and mortality. The key to improving this deadly outcome is the early detection of at-risk oral lesions. The current screening approach relies solely on the clinician's knowledge and experiences in recognizing and differentiating the majority of benign reactive lesions from early cancers. The subjectivity and required training have always hindered the interests of community clinicians and induced patient anxiety. Invasive biopsy, the current gold standard of diagnosis of a suspicious lesion, may not be readily accessible.

The success of pap smear in cervical cancer screening is inspirational. Spearheaded by our group, OralGetafics, a cytometry-based in-house cell classification platform, has shown its potential in non-invasively detecting OC from normal/reactive lesions; however, the current model relies heavily on human expertise, limiting its robustness. Deep learning and machine learning algorithms are promising avenues with the same or better ability to recognize objects compared to human eyes.

We **hypothesize** that the new algorithm, O-plus, can accurately classify cells into normal and abnormal (precancer- or cancer-like). **Specific Aims**: 1. To process and acquire data from existing 400 oral brushings (~500,000 cells); 2. To develop O-plus Cell Classifier using ~50,000 cells from 50 samples; 3. To develop O-plus Sample Classifier using 300 samples to detect normal, abnormal, and equivocal samples, the O-plus test; 4. To verify the sensitivity and specificity of the test on the remaining 100 samples.

Significance: After the validation from large-scale, multicentre studies, the test can provide a robust, non-invasive screening device. This can be implemented in the community to empower clinicians in the early screening for at-risk oral lesions and subsequently improve outcomes and reduce disease burdens.

Methodology: From our longitudinal study, we have banked >12,000 oral brushings of which 400 will be used for this study including 260 abnormal (75 OC, 45 severe dysplasia/carcinoma in situ, 140 mild/moderate dysplasia) and 140 normal (70 reactive and 70 normal) samples. Among these, 220 samples have been stained with Feulgen-Thionin and scanned using a whole slide scanner MoticEasyScan© (MOTIC Microscopes, Canada). The remaining 180 samples will be stained and scanned. We will first use ~50,000 cells from randomly selected 25 normal and 25 OC samples for the development of O-plus Cell Classifier. We will use OralGetafics with human input by our expert cytotechnician to separate ~50,000 cells into normal, abnormal (i.e. scorable cells) and junk. We will apply pixel-based UNet to detect cells' geometric centers, cUNet++, and boundaries, bUNet++, followed by Jaccard similarity coefficient (JSC) to normalize the intersection of the two segmentations by their union, SUNet++. In addition, we will use Random Forests (RF), a tree-based object classification to automate the collection of in-focus, intact epithelial cells from cell clusters based on a majority vote from a set of regression trees generated from random subsets of data. Several binary RF classifiers will be trained using ~50,000 objects and arranged in a hierarchical classification scheme designed to the maximum number of epithelial cells. In summary, we will integrate Deep Learning-based cell segmentation with a Machine Learning-based cell classification binary tree to develop a novel O-plus Cell Classifier. In Aim 3, using the O-plus Cell Classifier, a panel of DNA features will be captured for each cell of 300 samples. These features will be entered into stepwise linear analysis to separate cells into normal and OC-like to generate an O-plus sample score. We will then define cut-off values to classify samples into positive, negative, and equivocal. Lastly, we will verify the O-plus test on the remaining 100 samples against histology diagnosis for model accuracy.

Sanati-Nezhad, Amir
University of Calgary

Exosomal-based digital electronic health system for remotely and longitudinal monitoring of bladder cancer recurrence

Problem. Bladder cancer is common and has a high rate of recurrence. The standard of care for surveillance of bladder cancer involves repeated surveillance cystoscopy and urine cytology as frequently as every three months. These techniques are either invasive or have limited sensitivity for detecting recurrent disease. In this project, we will use cancer-specific nanoparticles, called cancer exosomes, present in the urine of bladder cancer patients for the rapid monitoring of bladder cancer patients.

Hypothesis. We hypothesize that digital and longitudinal monitoring of **1)** urine-based cancer exosome biomarkers of bladder cancer patients at their home using the XoTech platform, **2)** a web-based in-home communication with patients, and with **3)** a machine learning approach, once correlated and validated against the gold standard cystoscopy, will yield a predictive method for monitoring the trajectory of bladder cancer recurrence or recovery. These data can be interpreted as novel indices to expedite early diagnosis of cancer recurrence and facilitate quantitative monitoring of cancer recovery.

Aims. We will test this hypothesis through the following three Specific Aims (SA).
SA1: Developing and validating the testing platform for reliable isolation and detection of cancer exosomes in urine samples of bladder cancer patients.
SA2: Pilot in-home testing of the testing platform for in-home use.
SA3: Clinical evaluation of the testing platform.
Significance and Impact. The proposed home-based digital health monitoring technology is a novel technology and can be used to transform how cancer care is implemented. Patients can be monitored at home and early diagnosis of cancer recurrence risk can be detected by predictive cancer exosome biomarkers. This study will be evaluated which exosome measurement(s) provide the best indicators of bladder cancer recurrence and if these can be accurately followed over time, to enable early detection and intervention. If successful, the proposed digital biosensing technology has the potential to help bladder cancer patients with non-invasive treatment monitoring and developing new strategies for personalized therapy.

Tabori, Uri
The Hospital for Sick Children

Detection and prevention of hypermutant glioma in children and young adults

Glioma is the most common CNS tumour in children, adolescents and young adults (CAYA) and is the major cause of morbidity and mortality in this population. While driver mutations have been described in many of these tumours, a previously unrecognized subgroup of gliomas arise from a mechanism termed replication repair deficiency (RRD). Early recognition of RRD can allow for prevention and novel immune based therapeutics to improve outcome. RRD is caused by mutations in the mismatch repair proteins (MLH-1, PMS-2, MSH-2 and MSH-6) and/or DNA polymerase genes (PolE or PolD). It occurs either as a germline cancer predisposition syndrome or due to secondary DNA damage as a result of genotoxic therapies such as radiation or alkylating agents. In patients with RRD, glioma is the most common cancer and was previously universally lethal as these do not respond to chemo-radiation approaches. Strikingly, patients with RRD gliomas respond to immune checkpoint inhibition (ICI) and for the first time, up to a third are long term survivors. Additionally, recognition of RRD can lead to a surveillance regimen which has been proven to increase survival due to early recognition of glioma. Here we plan to utilize our national and international resources, genomic and imaging machine learning to uncover tools for detection of RRD in CAYA gliomas and develop a tumour vaccine. Early detection will permit early implementation of immune based therapies and surveillance protocols, both of which will improve survival in this cohort. To do this, we will exploit the inherent characteristic of RRD tumours which accumulate mistakes in repeated sequences, termed microsatellite instability (MSI). We developed a novel tool called microsatellite signatures (MS-sigs), diagnosing RRD with 100% sensitivity and specificity in tumour and germline tissue. This test uses low coverage (0.5X) whole genome sequencing (WGS) to sequence all microsatellite regions. Using MS-sigs, we can accurately identify which tumours were a result of an inherited germline cancer predisposition syndrome. In parallel, our group will use machine learning to diagnose RRD glioma based on specific physical sequences in the brain using MRI. Using our large repository, we are comparing the genomic data with imaging machine learning to diagnose RRD in CAYA gliomas radiographically. This proposal is comprised of 3 major aims: **Aim 1:** We will use MS-sigs to determine the prevalence and clinical characteristics of RRD in CAYA gliomas using a large cohort of (>2000) well annotated CAYA patients from 3 provinces including Ontario and the Maritimes, where a higher

prevalence of RRD has been found due to founder effect. CAYA were selected based on preliminary data that revealed enrichment of germline RRD in these young individuals. Using MS-sigs we will distinguish if RRD is inherited or acquired, and whether RRD has impact on survival and potential response to immunotherapy. We will then this data for aims 2 and 3. **Aim 2:** We will perform machine learning analysis on >2000 CAYA gliomas to uncover the radiomic RRD signature by imaging. Validation will be done using >200 fully characterized RRD gliomas from our international consortium. Finally, this data will be compared with aim 1 to determine whether artificial intelligence can serve as a diagnostic and early detection tool for RRD gliomas. **Aim 3:** We will use the MSI data on >30,000,000 genomic microsatellites from aim 1 to find common MSI loci for vaccine development. Using our already established collaboration with groups which are developing vaccines for specific MSI epitopes, we will search for the 10 most common immunogenic neoepitopes using genomic and transcriptomic data to be used for RRD glioma vaccine development. This will be used for both patients with active tumour and for RRD patients to prevent glioma formation. Uncovering the impact of RRD on CAYA gliomas will lead to increased awareness, wide-spread testing and early use of surveillance as well as immune based therapies for patients and relatives with RRD. This “game changing” approach will enable new treatment strategies and improve overall outcomes for CAYA patients with glioma.

Tsang, Benjamin
Ottawa Hospital Research Institute

Ovarian cancer early detection and chemosensitivity assessment by nanophotonics and artificial intelligence

Background and Rationale. Ovarian Cancer (OVCA) ranks third in the number of new cases and is the leading cause of death in gynecologic cancer. Although combined surgical debulking and chemotherapy is an accepted treatment modality, late diagnosis and chemoresistance remains major challenges to long term therapeutic success. Late OVCA diagnosis is a major obstacle for successful therapy since OVCA detected at late stages has poor prognosis. Currently, there is no organized screening or early diagnostic testing for patients with OVCA. Only 14.9% of OVCA patients are diagnosed at stage 1 with 5-year survival rate of 92%.We have observed the presence of exosomes in the plasma of high grade serous OVCA patients. To date, there is no reliable biomarker for early OVCA detection and chemosensitivity. Although exosomes are involved in cell-cell communications, their role in chemoresistance is unclear. Whether they have pathological significance and could serve as biomarkers for early OVCA detection remained to be determined. Using state-of-the-art photonics and paired chemosensitive and chemoresistant OVCA cell lines, we have shown that chemoresistant OVCA cell-derived exosomes are significantly higher in amount compared with that of chemosensitive cells. Also, exosomes derived from chemoresistant and chemosensitive OVCA cells exhibit distinct Raman spectra. These findings suggest that the Raman spectra of cell-derived exosomes may be used in tandem with a machine learning algorithm to determine the chemosensitivity of OVCA patients. Whether the above observations on circulating exosomes are histological subtype-specific is unclear. Although these preliminary studies are encouraging, we have yet to investigate their mechanistic role in OVCA chemoresistance as well as their applicability to clinical diagnosis. The **overall objective** of the proposed study is to use photonics and artificial intelligence to determine if circulating exosomes represent as a less-invasive (plasma) biomarker for early stage OVCA and chemoresistance. We **hypothesize** that circulating exosomes in OVCA patients may be a potential histologic subtype-specific prognostic biomarker, predictive of early stage, chemoresistance and patient survival. Our **specific objectives** are: (1) Mechanistically investigate the difference between exosomes secreted by chemosensitive and their resistant phenotypes and how that contributes to chemoresponsiveness.(2) Determine if circulating exosomes in patient samples are predictive of chemosensitivity, early stage OVCA and patient survival in various histological subtypes of OVCA and to determine if subtype stratification improves its predictive value. (3) Miniaturize our in-house platform used in the detection of exosomes and its applicability to clinical diagnosis. **Significance:** Circulating exosomes may serve as an important biomarker for early OVCA detection, chemoresistance and poor long-term survival. The present study will provide guidance to physicians on individualized treatment strategies, so as to maximize the benefits while avoiding treatment side effects.

Van Houten, Elijah
Université de Sherbrooke

Wearable technology for early detection of breast cancer – continual stiffness measurement senses the hyper-contrast (10X) in breast cancer tumours

This project addresses three overarching problems in the early detection of breast cancer: the inferiority of x-ray radiodensity as a breast cancer detection contrast mechanism; the obstacles in using other contrasts as a screening method; the challenge of increasing screening frequency for early detection. In addition, each of these problems can be broken into several subproblems, e.g.: the use of compression and ionizing radiation in x-ray mammography; the impact of breast radiodensity; the limitations of ultrasound methods for screening and the high cost of MR imaging; the costs and risks of repeated screening versus the advantage of regular screening data for automated detection via AI and 'big data' methods. The proposed technology offers solution paths for all these issues, and many other opportunities for new development.
The overall objective of this project is the development of a working prototype capable of detecting the presence and location of tumors within the breast. This prototype can then be used as a proof of concept to secure industrial partners and additional funding for the clinical development and commercialization necessary to bring the technology to market. The specific objectives of the project are: (a) to integrate cutting edge sensor technology; (b) to record data in lifelike breast phantoms and human subjects; (c) to detect and localize a variety of different tumor sizes, contrasts and locations in a series of different experiments using the data obtained.
This technology is based on methods like those used existing scientific and medical imaging techniques. Lifelike silicone gel breast phantoms integrated into a mannequin torso will be used to test the system. The data recorded by this system will be treated by sophisticated algorithms to determine the size and contrast within the silicone breast phantoms, to explore the sensitivity and specificity of the technology across a range of breast tumor configurations. Function and wearability of the prototype will finally be verified for human subjects.
Data quality and user interface limitations of ultrasound and the high cost of MRI have hindered viable screening methods. This project promises a massive (not just significant) change to breast cancer screening. In addition to completely revising how we think about novel imaging methods (which would have major impacts across a wide range of clinical applications, including brain and liver cancer), this technology will completely disrupt the normal practice for breast cancer screening.

Wishart, David
University of Alberta

A novel rapid, liquid biopsy early stage lung cancer diagnostic test

Summary: Lung cancer screening is relatively new, but there is considerable debate about the efficacy of low-dose CT scanning (LDCT). While LDCT does save lives, it is expensive, increases radiation-induced cancer risk and leads to frequent over-diagnosis. This high level of over-diagnosis can lead to unnecessary biopsies, increased healthcare costs, and heightened anxiety for patients. Several protein-based, microRNA and DNA-methylation assays have been described in the literature or are under commercial development. In most cases, the tests use a panel of 4-20 biomarkers and detect later stage lung cancer. Several recent metabolomic studies have identified potential metabolite markers for diagnosing lung cancer (especially non-small-cell carcinoma) in several different biofuids (serum, sputum, bronchial fluid). However, the published performance of these tests are lower than the performance of the biomarkers we have identified. Further, a central advantage to our early stage lung cancer assay lies in the fact that it is a multi-component test meaning that its sensitivity/specificity profile can be adjusted so that it essentially generates very few false negatives, which is ideal for screening.
Objectives: Building from exciting discoveries in our lab, our long-term objective is to develop a lung cancer screening test that will be made available to at-risk individuals in Canada through centralized diagnostic laboratories. In the proposed work, we will aim to validate our early stage serum lung cancer biomarker panels in a larger cohort of biobanked samples. Upon successful validation, we will convert our LC-MS/MS assay into a prototype laboratory developed test (LDT), which will then be evaluated by a third-party laboratory. Our team, which consists of leaders in oncology, lung cancer, mass spectrometry and clinical translation, will work together to ensure the successful translation, implementation and regulatory approval. Upon completion of this project, we expect to have: 1) a novel, validated biomarker panel for early-stage lung cancer detection; 2) an LDT that is compatible and easily integrated on technology platforms already routinely used in diagnostic labs (i.e. mass spectrometry); and 3) a well-developed plan for translation and implementation of the test.
Methodologies: We will use an LC-MS/MS-based assay to quantitatively measure the biomarkers previously identified. Logistic regression combined with machine-learning-based feature selection will be used to refine and validate our early-stage lung cancer detection algorithm that uses the already-identified metabolites along with other clinical parameters. A prototype LDT will be developed using approaches we have previously demonstrated for colon cancer screening.

Significance: Despite the promise and potential patient benefits of LDCT-screening, there are challenges with the implementation and adoption of such a program, including radiation exposure, poor patient uptake due to the lengthy follow-up processes and the resources required to implement and successfully execute a national LDCT screening program. Furthermore, LDCT has a very high false positive rate contributing to further health care resource depletion through unnecessary follow up procedures and biopsies, increased health care costs, increased patient risk and patient anxiety. We project that the cost of our MS-based blood test will be much lower, versus an LDCT, which is $300/test. A simpler, cheaper, more accurate early detection lung cancer test would benefit Canadian patients by providing improved health and survival for high risk patients (due to tobacco and other environmental exposures). Such a test will also have the potential to disrupt the dynamics of patient triage, leading to streamlined physician/patient communication and improved healthcare across the country.

Zadeh, Gelareh
Princess Margaret Cancer Centre - UHN

Precision diagnosis and prognosis of primary and metastatic brain tumours using DNA methylation profiling in liquid Biopsy

The majority of tumors are diagnosed by imaging before surgery or under the microscope by a pathologist after the tumor is removed. These methods introduce some inaccuracy and bias in the diagnosis of the central nervous system tumors. In addition, these methods are unable to predict the course of the disease and whether the tumors will likely recur and respond to treatment. As such, more accurate alternative methods need to be developed to improve the outcome of brain tumors and reduce the cost of treatment for the healthcare system. We have recently adopted epigenetic (DNA methylome) analysis of brain tumors in solid tumor tissue and have shown that DNA methylome can improve the accuracy of tumor diagnosis, which in turn, affects the type of treatment and can predict whether the tumor is likely going to recur after standard treatment (surgery, adjuvant chemotherapy, and radiation). Using this approach, we have developed a computational tool that can be used by clinicians to input DNA methylome data and determine the accurate diagnosis and aggressiveness of a type of brain tumor called meningioma. More recently, we analyzed the DNA methylome of circulating DNA that is released from the tumors into the plasma (liquid biopsy) of patients with glioma tumors. We were able to identify the methylome pattern specific to gliomas and distinguish them from other brain tumor types. Our goal is to develop a computational method to using DNA methylome data to predict if a tumor from the breast, lung or melanoma is going to metastasize to the brain. We will also refine our approach to the analysis of tumor DNA methylome in plasma for gliomas in order to determine whether lower-grade gliomas are likely to progress to higher grades and develop a more sensitive approach for early detection of glioma recurrence that is superior to imaging. This study is the first to evaluate the accuracy and utility of DNA methylome in plasma as a less invasive and more sensitive approach for the refinement of patient care and prediction of the course of the disease. Our study will also lead to development of a tool that could predict metastasis to the brain and thereby, allow more appropriate treatment planning.