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ABSTRACTS

Fluorescence and Photoacoustic Spectroscopy Together with Machine Learning in Biomedical Applications

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Abstract:

Fluorescence and photoacoustic spectroscopy are two sensitive spectroscopy techniques to study the molecular properties of a sample and found applications in several fields of science, including biomedical sciences. Both the techniques use suitable light excitations to generate corresponding signals in a sample specimen. Fluorescence spectroscopy targets a particular fluorophore of a sample to detect corresponding autofluorescence and avoids using external dyes for biomedical applications. However, the signal is sensitive to its local environment, affecting the fluorescence quantum yield. In the case of photoacoustic spectroscopy, which measures the direct absorption of radiation by the sample molecules, is proportional to only the amount of radiation absorbed, irrespective of the total radiation incident on the sample. The signal can be increased considerably by increasing the intensity of the incident radiation. The losses due to scattering, reflection, etc., can be avoided even for highly scattering samples, making the technique suitable to study biological specimens. When these techniques are applied for biomedical investigations understanding conformational change in molecules due to the onset of a disease, the captured signals/information are not always distinguishable among pathological conditions for being weak/primary in nature. Therefore, suitable machine learning tools are desirable to detect minor variations and reveal hidden information in real-time data analysis. We have demonstrated the use of these techniques in protein fingerprinting and identifying different cancerous conditions compared to controls and achieved suitable classification analysis in machine learning combinations. Our recent findings on clinical samples using fluorescence and photoacoustic spectroscopy will be presented and discussed during the meeting.

Key words: Fluorescence spectroscopy, Photoacoustic spectroscopy, Protein fingerprinting, Pathological conditions, Machine learning, Bio-marker detection, Disease diagnosis

Medical Diagnostics with Surface Enhanced Raman Scattering

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Abstract:

There are many challenges facing modern medical diagnostics necessitating constant innovation in this field. These challenges include low sensitivity, specificity, and long turn-around times for existing diagnostic techniques and the absence of a technology in some other applications. Raman spectroscopy is a potentially very powerful tool that can meet some of these needs. It is a method of assaying the vibrational spectra of molecules in a sample by measuring photons that are inelastically scattered from molecular bonds. Since the vibrational energy of different bonds are unique, these spectra represent fingerprints that can be used to identify and quantify different molecules. When measuring Raman spectra from complex biological systems such as tissue or cells, the data represent a biochemical portrait whose information can be used to discriminate between disease states and quantify biomarkers. Extracting this information from these complex datasets involves employing machine learning techniques. Furthermore, Raman spectra are inherently weak signals which need amplification to meet diagnostic demands. This talk will provide an overview of ongoing research on Raman-based diagnostic systems which employ signal enhancement from the nano-scale light focusing properties of metal nanoparticles. For example, we will discuss the design of a Raman flow cytometer which measures spectra from bacteria flowing through a liquid-core optical fiber in order to diagnose infections. The cells in this system are decorated with silver nanoparticles which enhance inherent Raman scattering from their constituent molecules that can be used for pathogen identification, including differentiating between antibiotic susceptible and resistant strains.

Keywords: Medical Diagnostics, Sensors, Photonics, Raman Spectroscopy, Nanomaterials, Machine Learning

Detection of ovarian cancer chemoresistance using a novel sensor and artificial intelligence

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Abstract:

Ovarian cancer (OVCA) is the most fatal gynecological cancer with chemoresistance being one of the main obstacles of treatment success. Since there is no reliable approach to predict chemo-responsiveness, there is the urgent need to develop a diagnostic platform. Our objective is to predict OVCA chemoresponsiveness, histologic subtypes and early diagnosis using surface enhanced Raman spectroscopy and artificial intelligence. We have developed a novel sensor which utilizes cysteine functionalized gold nanoparticles to simultaneously bind to cisplatin (CDDP) and exosomes. Exosomes were isolated from OVCA cell lines with various histologic subtypes using ultra-centrifugation and characterized with nanoparticle tracking device, Western blot and electron microscopy. We determined that chemoresistant cells secrete significantly higher levels of exosomes as well as exosomal CDDP compared with their sensitive counterparts. Using our support vector machine (SVM) model we could differentiate between endometrial (EM) and high grade serous (HGS) OVCA cell-derived exosomes with ~75% accuracy. The test accuracy for HGS exosomes (~88%) was significantly higher compared to EM exosomes (~70%), implying that the biochemical differences related to chemosensitivity may be more pronounced in this subtype. However, a single factor was not sufficient to achieve a good diagnostic due to the high variance of tumor cells. Using CDDP concentration, exosome concentration, and SVM class, we developed a multi-factor diagnostic platform to overcome this issue, achieving AUROCs of 0.97 to 1. Silencing Plasma gelsolin (pGSN; an actin binding protein) decreased exosomal CDDP secretion in the resistant cells whereas its over-expression in sensitive cells upregulated exosomal CDDP suggesting the potential role of pGSN in exosomal CDDP secretion. We observed that pGSN interacts with cortactin (CTTN; exosome releasing protein) and both proteins were significantly expressed in chemoresistant patients compared to chemosensitive patients. Taking together, pGSN could be a potential transcription factor for CTTN leading to increased exosomal release of CDDP. This robust platform will inform clinicians to provide alternative treatments to patients that are likely not to respond to chemotherapy; an intervention that will positively impact patients' survival. (Supported by grants from Canadian Cancer Society, Brain Canada Foundation and the Canadian Institutes of Health Research).

Keywords: Ovarian cancer, chemosensitivity, biomarker, exosome, nanophotonic, machine learning

Label-free Nonlinear Optical Microscopy for Biomedical Research

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Abstract:

Non-linear optical (NLO) microscopy has proven to be a powerful tool especially for tissue imaging with sub-cellular resolution, high penetration depth, endogenous contrast specificity, pinhole-less optical sectioning capability. Here, we discuss NLO microscopes including the two-photon fluorescence (TPF), fluorescence lifetime imaging microscopy (FLIM), polarization-resolved second harmonic generation (SHG) and coherent anti-Stokes Raman scattering (CARS) techniques with various samples within the context of label-free non-invasive molecular imaging. A compact multimodal NLO microscope based on a laser scanning microscope, a femtosecond laser, a time-correlated single-photon counting system, and a photonic crystal fiber are introduced for biomedical applications. By integrating TPF, FLIM, SHG, and CARS microscopy, the proposed scheme provides profound insights into the physicochemical properties related to 3D molecular orientation distribution, inter- and intra-molecular interactions, and disease progression in biological systems and organs. The non-linear signals are generated from collagen in tissue (SHG), amylopectin from starch granules (SHG), sarcomere structure of fresh muscle (SHG), elastin in skin (TPF), nicotinamide adenine dinucleotide (NADH) in cells (TPF), and lipid droplets in cells (CARS). Again, the non-linear signals are very specific to the molecular structure of the sample and its relative orientation to the polarization of the incident light. Thus, polarization-sensitive NLO microscopy provides high image contrast and quantitative estimate of sample orientation. An overview of the advancements on polarization-sensitive SHG microscopy including Stokes vector based polarimetry, circular dichroism, and susceptibility are also presented. The working principles and corresponding implements of above-mentioned microscopy techniques are elucidated. The high peak power and the low average intensity of near-infrared laser pulses allow for deep-penetration imaging without compromising sample vitality. Linking nonlinear optical phenomena with time/spectral/polarization-resolved imaging also makes it possible to obtain multidimensional information to address complex biomedical questions.

Key words: Non-linear optical microscopy, Two-photon fluorescence microscopy, Second harmonic generation, Coherent anti-stokes Raman scattering, Fluorescence lifetime imaging, Nicotinamide adenine dinucleotide, Collagen.

Biophotonics and design Innovations

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Abstract:

Medical diagnostics is a field that requires a lot of collaboration between groups with diverse set of skills. In the Biophotonics lab at the University of Ottawa, we work closely with groups (e.g. Tsang lab for Ovarian Cancer) from the life science side to better understand the application side. However, biophotonics research often require equipment that is costly. This makes it difficult to pursue for young researchers and/or in developing countries. Moreover, as researchers, we often focus our effort on the scientific challenges and not pay enough attention to the design and commercialization aspects of medical diagnosis. This talk will focus on the untapped opportunities in using low-cost technologies such as 3D printing and microcontrollers to develop Biophotonics equipment such as Raman systems and femtosecond fiber lasers. We will also discuss the design challenges in taking such equipment beyond the lab. Finally, we will explore the commercialization challenges facing many of these medical diagnostics.

Keywords: Biophotonics, Spectroscopy, low-cost technologies, Design and commercialization.

Genetic and Epigenetics of Epithelial Tumors – Our findings and Opportunities

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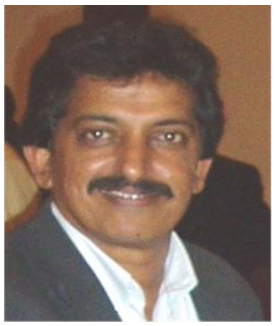
Abstract:



The multistep initiation, progression and dissemination of cancer is due to both genetic and epigenetic alterations in the genome. Accumulation of genetic mutations and alterations such as copy number variations (CNVs), deletions, insertions and translocations; and epigenetic changes such as in DNA methylation, non-coding RNAs and chromatin modifications are the key determinants of various phases of tumor progression. These changes can make tumor cells vulnerable or resilient to several modalities of treatment which are exploited as synthetic lethality or using target specific drugs. In the cellular context the driver gene mutation and the co-occurrence can be mutually exclusive. Besides there is an interplay between genetic and epigenetic alterations which are discreetly manifested and remains to be fully exploited clinically as diagnostic indicators or for therapy using RNAi or drugs. Our efforts, over the years, allowed us to examine several human sporadic epithelial cancers such as those originated from breast, cervix, oral and colon. Our genetic and epigenetic analysis coupled to understanding the underlying mechanistic underpinnings were significant in enabling us to structure the common and unique driver and passenger changes in different types of human tumors at distinct stages. In colon cancers, genetic changes with respect to mutations and CNVs were discernible (both known and novel) during progression from ulcerative colitis as well as in sporadic tumors. Cervical cancers were unique in a way that its aetiology is coupled to human papilloma virus infection and microbiome that causes disbiosis leading to epigenetic changes. Tumors accumulate mutations over the long latent period of progression to squamous cell carcinoma and metastasis. DNA methylation changes led us to not only identify several biomarkers but also potential tumor suppressors. These DNA methylation changes in the promoters reduced the gene expression profiles of protein-coding and non-coding genes. These included miRNAs which served as critical regulators of growth and signalling in cervical tumors. These results will be presented with examples to show how the analysis of genetic and epigenetic alterations will lead to discovery mechanisms, diagnostic markers and as potential therapeutic targets.

Key words: Cancers, mutations, DNA methylation, miRNA, cross-talk, diagnostics.

Organoids: An amenable experimental model for studying epigenetic aspects of endometriosis

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Abstract:

Endometriosis is defined by the presence of endometrial tissues outside of the uterus. It is a painful, sex hormone-dependent disease that affects 10%-15% of women worldwide. Around 30%–50% of affected women may be asymptomatic or suffer from dysmenorrhea, dyspareunia, or infertility. Current treatments for endometriosis are not effective in all cases and there is no definitive cure for this disease. This limitation is mainly due to our limited knowledge about cellular and molecular mechanisms involved in the pathogenesis of endometriosis. Epigenetic causes have been hypothesized for endometriosis based on correlative evidence. However, limited access to a reliable experimental model inhibited advances in this field. Recently developed endometriotic organoids opened a new window in endometriosis research; we provided the first insight into epigenetics of endometriosis organoids as a novel *in vitro* platforms for studying endometriosis. Our study revealed a conserved pattern of methylation alteration in endometriosis tissue biopsies and organoids for most of the investigated genes (56 out of 84). Moreover, we have shown endometriosis organoids as suitable preclinical models for demystifying epigenetic mechanisms underlying disturbed progesterone signaling and attenuated response to progesterone. This platform allows for genetic manipulation by loss- and gain-in- function studies. Moreover, organoids could serve as "avatars" of an individual patients for drug testing in personalized medicine.

Keywords: Endometriosis, Infertility, Organoid, Epigenetics, Experimental model

Microfluidic 3D Tumor Model for Breast Cancer

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Abstract:

Ex vivo assays with 2D and 3D tumor cell culture, as well as patient-derived xenografts (PDX) have the drawback that they do not capture all subtleties of the original tumor microenvironment. Therefore, they are often not sufficiently predictive for drug screening and personalized medicine. Among the alternative preclinical models for cancer drug screening are organoid spheroids and tumor tissue slice cultures. Tumor tissue slice cultures can in principle be developed into a diagnostic tool to select the optimal treatment for each individual tumor. They have been recently employed in drug sensitivity screening and functional studies, with the advantage of relatively easy processing of tissue and maintaining the original morphology and cellular composition of tumors for several days up to weeks in culture. We have developed a microfluidic "Cancer-on-chip" (CoC) device with tumor tissue slices grown *in vitro* under precisely controlled condition to evaluate and predict individual tumor response to therapy. Histopathological analysis, EdU and TUNEL staining for morphology, proliferation, and apoptosis, as well as gene expression analysis of RNA derived from tissue slice and extracellular vesicles from the culture media collected from the outflow showed that breast tumor tissue slices (breast PDX and primary tumor tissue) can be maintained without any gross histopathological changes and cell viability in our CoC device. Our CoC prototype enables real time monitoring of tumor growth and response to individual patient therapy by direct microscopic observation of cellular responses and time course liquid sampling from the outflow for DNA and RNA analysis.

Key words: Breast Cancer, 3D tumor model, Microfluidics, Cancer-on-Chip, Drug response

Type 2 Diabetes associated changes in immuno-metabolic axis: Influence on neutrophil functions and consequences in infections and thrombosis

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Abstract:

Neutrophils, major component of innate immune system eliminates pathogens through degranulation, phagocytosis and NETosis. Terminally differentiated neutrophils upon stimulation by pathogens, cytokines and metabolic intermediates, expel their DNA along with histones and granular proteins to produce neutrophil extracellular traps (NETs). These DNA lattices serve as a platform to activate pro-inflammatory mediators, immobilize and kill the pathogens, and simultaneously clear the infection. However, besides the active role in eliminating acute infections, externalized chromatin and components of NETs contribute to the pathogenesis of diseases associated with sterile inflammation including Type 2 diabetes (T2D), vascular disorders, autoimmune diseases, digestive disorders and cancers. Our team using preclinical/clinical models and proteomics/metabolomics approaches aims to understand underlying mechanisms responsible for neutrophil dysfunctions in T2D and associated pathologies such as recurrent infections and thrombosis. We show that during T2D, hyperglycemia reprograms metabolism in neutrophils leading to insufficient pools of NADPH and facilitates formation of constitutive NETs, leading to reduced response to infections. On the other hand, elevated metabolic intermediates such as homocysteine in T2D induce bidirectional activation of platelets and neutrophils leading to thrombosis in stroke. In this presentation we discuss paradoxical effects of neutrophils in T2D.

Keywords: Neutrophil extracellular traps, Host-pathogen interactions, Immuno-metabolism, Type 2 Diabetes

Plasma gelsolin and the immune system: Lessons learnt from cancer to fight COVID-19

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Abstract:

Ovarian Cancer (OVCA) is the leading cause of death in gynecologic cancer. Although combined surgical debulking and chemotherapy is an important treatment strategy, chemoresistance remains a major challenge. We have shown that pGSN secreted and transported via exosomes, up-regulates HIF-1α–mediated pGSN expression in chemoresistant OVCA cells in an autocrine manner and confers cisplatin resistance in otherwise chemosensitive OVCA cells. Elevated pGSN down-regulates the functions of immune cells (T cells, NK cells, macrophages and dendritic cells) in the tumor microenvironment as well as outperforms CA-125 as a favorable biomarker for early stage detection, residual disease and patients' prognostication. Interestingly, pGSN regulates the production of pro-inflammatory cytokines; a phenomenon that is also implicated in the pathogenesis of COVID-19, a respiratory infectious disease caused by SARS-CoV-2. pGSN depletion significantly reduces its organ-protective function, leading to multi-organ dysfunction syndrome (MODS), the "cytokine storm", increased mortality and long-term morbidity in survivors, complications that are commonly seen in COVID-19 patients. Whether this is of pathological significance and a potential biomarker for COVID-19 severity and treatment response remains to be determined. With >403 million reported cases and >5.5 million deaths worldwide, identifying novel biomarkers such as pGSN will enable physicians to predict/assess the progress of COVID-19 patients and inform decision-making for available therapeutic intervention.

Blood samples were longitudinally collected from COVID-19+ and negative patients and the levels of pGSN, cytokines and anti-spike protein antibodies assayed. Their mean values were correlated with clinical parameters of the patients to develop a diagnostic platform. pGSN levels were significantly downregulated in COVID-19 patients compared with the healthy cohorts. Additionally, pGSN's combination with IL-6, IP-10 and M-CSF significantly discriminated COVID-19 patients from healthy cohorts. Although the combination of pGSN and IgG presented as a strong predictor of COVID-19 severity and death, its combination with IL-6 was a significant predictor of mild cases and favorable outcomes. Taken together these suggest that multi-analyte panel of pGSN with cytokines and antibodies present as a significant predictor of COVID-19 hospitalization outcomes compared with conventional clinical laboratory markers such as CRP and ferritin. This research will revolutionize clinical management and health system interventions in response to SARS-CoV-2 infection. (Supported CIHR)

Keywords: ovarian cancer, COVID-19, plasma gelsolin, cytokines, chemoresistance, biomarkers, disease progression, clinical outcome.

Polycystic Ovarian Syndrome and Bisphenol A: What do we know?

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Abstract
Endocrine-disrupting chemicals are the exogenous elements that interfere, disrupt the actions of hormones, and subsequently cause adverse health effects on the living system due to persistent exposure. Bisphenol A (BPA) is one of the widely explored endocrine disruptors utilized in the synthesis of plastics. It has structural homology to estrogen, thereby interacting with estrogen receptors by interceding in hormones biosynthesis. Therefore, BPA is suspected to be detrimental by affecting the female reproductive system. Biomonitoring confirms the burden of BPA in body fluids, which leads to reduced fertility, endometriosis, and polycystic ovarian syndrome (PCOS). PCOS is a complex condition with undetermined etiopathology that affects childbearing-aged women and is frequently attributed to female infertility. Extensive data revealed that PCOS was associated with genetic differences and environmental effects. Due to the obvious intricacies of the hormonal pathway, it is challenging to ascertain BPA actions that cause endocrine disruption. As the precise molecular pathomechanisms of BPA in PCOS are not completely understood, this study aimed to undertake case-control, cross-sectional, and animal model studies to elucidate underlying mechanisms of BPA-induced PCOS leading to reduced fertility. The current study provides insights on molecular, reproductive, and endocrine perceptions of BPA-exposed PCOS that benefit in understanding the multifaceted nature of PCOS endocrinopathy induced by BPA exposure and in predicting disease strategies.

Key words: Endocrine-disrupting chemicals, Polycystic ovarian syndrome, Bisphenol A, Infertility, Estrogen

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