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2021 Connecting Young Minds (CYM) Undergraduate Research Conference: 5-Minute Research Presentations

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Abstract
Connecting Young Minds (CYM) is an annual bilingual student-led research conference held at the University of Ottawa. Our mission is to encourage undergraduate students to network with professors, present their research, and gain experience drafting scientific literature. The conference engages the interests of students in the sciences through presentations held by keynote speakers, interactive breakout rooms with graduate level students, and a research-based competition. Each year, CYM hosts a 5-minute research presentation competition in which ten candidates are selected by a panel of judges based on the submission of an abstract pertaining to their research. The competition provides an opportunity for undergraduate students to highlight their research findings to an audience and series of judges in a concise and engaging manner. Abstracts in this booklet were submitted by participants on a volunteer basis.

Keywords: undergraduate research conference; science; abstract competition; undergraduate studies; bilingual conference; Connecting Young Minds

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Conference Abstracts
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Connecting Young Minds 5-Minute Research Presentation Abstracts

Effects of age-related macrophage dysfunctions on atherosclerosis regression

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Atherosclerosis is defined by the buildup of plaque in the artery wall, causing the narrowing of arteries. Studies revealed the causative role of monocytes in the development of plaques as they infiltrate the subendothelial layer of the vessel, differentiate into macrophages and engulf excess lipids. These events contribute to atherosclerosis progression, a process by which early lipid-rich lesions gradually develop into rupture-prone plaques. In contrast, atherosclerosis regression is defined as the reduction of one or more standard plaque parameters, including size, lipid content and inflammation. In response to excess lipids, aged macrophages showed an impaired energy metabolism, dysfunctional autophagy and an altered capacity to transition from M1 to M2 phenotype. While these processes were shown to contribute to plaque regression, the effects of age-related macrophage dysfunctions and their impact on plaque regression remain unknown. We hypothesize that aged macrophages impair regression through age-related dysfunctions of autophagy and M1 phenotypic presentation. To test this, we compared the capacity of autophagy in non-loaded and aggregated-LDL (agLDL)-loaded aged and young macrophages collected from peritoneal and bone marrow of 3-months and 2-years old mice. RT-qPCR and western blot revealed that autophagy is more activated in aged macrophages as compared to young. However, agLDL-loaded aged macrophages exhibited impaired cell metabolism. Together, our results identify differential autophagy gene expression, autophagy flux and cell metabolism in aged

as compared to young macrophage foam cells, highlighting the need to better understand atherosclerosis regression in the aged environment, to guide the development of therapies targeted towards our aging population.

Towards ambiphilic chemistry with phosphonium ylides

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While catalysis is considered one of the pillars of green chemistry, it often relies on naturally scarce elements, notably from the transition metal family. Because of the toxicity, price, and extraction issues associated with these precious elements, the development of green catalysts based on earth-abundant elements has become increasingly attractive. Towards this goal, we studied a family of phosphorus-containing complexes for the activation of organic molecules, taking steps towards the development of new metal-free catalytic processes. Computational chemistry was used to screen for promising systems which were targeted for synthesis in the laboratory. The ambiphilic nature of phosphonium ylides was found to be key in the reactivity and the addition of electron withdrawing groups in particular made them very effective. There is strong potential for reactions with multiple-bonded functional groups in two- and three-molecule systems.

Correcting the R506Q mutation of Factor V Leiden in model derived iPSCs by employing CRISPR Cas9 as a novel preventative strategy

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Factor V Leiden (FVL), is an autosomal dominant genetic disorder characterized by a defective anticoagulant response, increasing one's susceptibility to venous thromboembolism by 50%. FVL patients exhibit increased rates of ischemic stroke and myocardial infarction because of a point mutation (R506Q) on the factor V (FV) gene G1691A in exon 10, which alters the coagulation system by inactivating the recognition and cleavage abilities of activated protein C (APC). This causes the clots to remain longer than usual, increasing the possibility of an embolism. Generally, FVL patients are subject to debilitating cerebrovascular conditions that permanently damage vascular tissue. Diagnosis typically occurs after damage and treatment options are limited to blood thinners. Employing CRISPR and iPSCs as a preventative gene therapeutic measure could reverse effects of FVL at a molecular level. Peripheral blood mononuclear cells are extracted from mice and reprogrammed into iPSCs. To remove R506Q on G1691A, SpCas9 and sgRNA expression vectors are created, coupled with homology arms containing exon 10 with the corrected FV gene, and Cas9/gRNA ribonucleoprotein (RNP) to cleave the strand. The targeting construct is knocked in using homology directed repair and its incorporation is verified by PCR/sequencing. Electroporation transfects the targeting vector and RNP complex into iPSCs. These gene edited iPSCs are differentiated into hepatocyte like cells (HLCs) and tested for FV antigen levels before and after knock in. Recovered clotting activity of FV with gene corrected HLCs is expected. Ultimately, current pharmacological interventions are temporary; however, this novel preventative strategy reverses effects of FVL, providing a permanent treatment to allow the normal functioning of FV.

Adverse events and length of stay following laparoscopic paraesophageal hernia repair

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Objective reporting of postoperative adverse events (AEs) following laparoscopic paraesophageal hernia repair (LPEHR) is limited and essential for quality assessment of surgical care, as well as the impact (if any) of antireflux technique (Dor vs. Nissen) and use of mesh cruroplasty. All patients undergoing LPEHR (January 2008 to April 2020) underwent prospective monitoring of AE incidence and severity, categorized by the Thoracic Morbidity & Mortality Classification System (based on Clavien-Dindo schema) during postoperative recovery. Of the 99 patients included, 28 (28.3%) experienced at least one AE, comprising Grades I (17%), II (50%), IIIa (21%), and IIIb (11%); there were no Grades IV or V AEs. Atrial arrhythmias (n = 6), myocardial ischemia (n = 3), and infections (n = 3) were the most frequent complications. 9.1% of patients had a prolonged LOS (PLOS), and 1% required readmission. The choice of fundoplication or mesh cruroplasty had no effect on AE rates. 94 subjects underwent fundoplication where Dor (71.3%) had a trend towards reduced median LOS (median [interquartile range]) 2 [2–4] as compared to Nissen (28.7%) 3 [3–4] days (P = 0.15). 94 subjects underwent crural repair with mesh (31.9%) or no mesh (68.1%), with a LOS of 3 [2–4] and 2 [2–4] days (P = 0.5). This study highlights that a third of patients undergoing LPEHR will experience a postoperative AE, one tenth will have a PLOS, and 1% require re-admission, with no significant impact based on type of fundoplication or mesh cruroplasty.

Development of selective irreversible peptidomimetic Factor XIIIa inhibitors through systematic variation of linker chain length & warhead functionality

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Current anticoagulants employed for the management of venous thrombosis and coronary artery disease inhibit thrombin or Factor Xa, key enzymes in the blood clotting cascade. Though effective, these treatments preclude soft clot formation, increasing bleeding risks. There exists a need to develop anticoagulants which permit soft clot formation; Factor XIIIa (FXIIIa), a transglutaminase enzyme responsible for solidifying clots in the cascade's final step, is a promising inhibition target. Previously reported FXIIIa inhibitors function by trapping the active site's Cys thiolate with an electrophilic warhead carried by a peptidomimetic scaffold; these compounds lack selectivity over human tissue transglutaminase (hTG2), a ubiquitously expressed isozyme. The present work aims to design irreversible peptidomimetic FXIIIa inhibitors with higher selectivities over hTG2. Differences in the isozymes' binding pocket depths suggest that shortening the linker length between the warhead and peptide could increase selectivity for FXIIIa. A series of 8 inhibitors with linkers of 1-4 methylene units leading to either acrylamide or α-chloroacetamide warheads were designed based on previous scaffolds. Compounds were produced through solution-phase organic synthesis and solid-phase peptide synthesis, and subsequently evaluated for activities against both isozymes through fluorescence-quenching and colorimetric assays. Preliminary kinetic results indicate reactivity differences as linker length is altered, displaying the importance of this structural consideration in inhibitor design. Warhead comparisons are underway, and will be reported in due course. These findings will aid in the development of the next generation of FXIIIa inhibitors, and in the design of fluorescent probes for the further study of the structure and function of FXIIIa.

Investigating the role of LAG3 expression in natural killer cells

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Natural killer (NK) cells are effector lymphocytes that protect the body from infections and tumors by secreting inflammatory mediators and cytotoxic molecules. Under chronic stimulation in cancer and viral infections, NK cells experience a decrease in these functions, a phenomenon called exhaustion. Exhausted NK cells often upregulate immune checkpoint receptors, including LAG3. LAG3 is known to inhibit T cell function, but its role in NK cells is unknown. We hypothesize that LAG3 is

a driving force of NK cell exhaustion, and we are interested in discovering the underlying mechanisms. Using flow cytometry, we analyze the differences in functionality, signaling pathways, and metabolism between NK cells expressing or not LAG3 in murine models of infection and cancer. As expected, LAG3+ NK cells were less functional. However, when we performed the mechanistic studies, surprisingly, we observed that LAG3+ NK cells displayed increased activity of the MAPK, mTOR, and metabolic pathways. This may suggest that LAG3+ NK cells are not undergoing exhaustion, but, instead, the cells are shifting their efforts away from their host defensive functions to perform other cellular functions. Our next steps are to replicate these experiments and test the effects of deleting the LAG3 gene from NK cells. The discovery of the role of LAG3 in NK cell exhaustion can ultimately contribute to immune checkpoint blockade therapies that are currently undergoing clinical trials for the treatment of cancer.

Evaluation of fluorescent properties in an organometallic dual-lanthanide compound

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Fluorescence imaging is a widely employed tool in clinical and pre-clinical research. From imaging subcellular structures to organs and organ systems, fluorescent probes are vital for the progression of science and medicine. Lanthanide-organic complexes have favourable luminescent characteristics, namely strong emissions over narrow wavelength ranges, and excitation over a range of wavelengths. The organic ligand is thought to act as an antenna, absorbing incident light and subsequently exciting the lanthanide ions through energy transfer. The lanthanide ion then undergoes emission, producing the desired luminescent qualities. Here we focus on determining the luminescent properties of an organometallic complex comprised of an organic ligand chelating two lanthanide ions. Four water-soluble compounds were synthesized and characterized by mass spectrometry (MS), and nuclear magnetic resonance spectroscopy (NMR) methods. These compounds are composed of a conserved organic ligand, with two lanthanide ions each. The four lanthanide ion pairs are Eu(III)-Gd(III), Eu(III)-Yb(III), Eu(III)-Lu(III), and Lu(III)-Lu(III). Eu(III) complexed with organic ligands is typically luminescent, and most of the luminescence is hypothesized to come from that lanthanide ion. Lu(III) is optically inactive, thus the Lu(III)-Lu(III) compound will be used to determine the luminescent properties of the organic molecule without emission from a lanthanide, while maintaining the overall charge and retaining many organometallic properties of the molecule. Fluorescence excitation and emission spectra will be taken and used to evaluate the luminescent properties of the compounds. These compounds will be followed up with in vitro and in vivo studies to evaluate their use as probes for molecular imaging.

Assessing individual and collective effects of inhibiting E6/E7 HPV proteins and additionally induced DNA damage on p53-induced apoptosis in HeLa cells

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The p53 tumor suppressor is a well-studied transcription factor that becomes activated in cells with DNA damage, playing a crucial role in suppressing tumorigenesis. In healthy cells, the MDM2 ubiquitin ligase mediates p53 degradation to prevent apoptosis. However, in HPV-induced cervical cancer cells, the HPV virus will induce the expression of an ubiquitin ligase called E6 to accelerate p53 degradation and allow for continuous cancer development. Previous studies on the inhibition of the E6 protein alone claimed it insufficient in achieving proper p53 activation. Here, we compared individual and collective effects of inhibiting the E6 protein, as well as the introduction of additional DNA damage in Hela cells. We hypothesized the introduction of DNA damage or the inhibition of E6 alone will have similar effects on p53 activation, but will lead to increased levels in the combined treatment. Through indirect immunoblotting, quantitative PCR using GAPDH as a control gene, and immunofluorescence microscopy using γ-H2AX and C-CASP3 as molecular markers for early stages of apoptosis, the assessments of p53 activation and expression reveal that the introduction of additional DNA damage alone is a more significant contributor to p53-induced apoptosis than the inhibition of the E6 ubiquitin ligase, while the combination of additional DNA damage and E6 inhibition led to a significantly increased level of p53 expression and activation in HeLa cells. The quantification of p53 activation in this project provides insight to a more beneficial treatment method for HPV-induced cervical cancer, and should be further experimented in clinical settings.

Scriptomic evaluation of the translatability of new treatments in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is a highly metastatic type of breast cancer and one of the largest contributors to cancer mortality in women. Many TNBC treatments that successfully produce general anti-tumor effects preclinical studies fail to display significant impact at the clinical level. This is partially because they do not inhibit the growth of cancer stem cells (CSCs) which have increased ability to evolve into metastatic tumors as well as metabolic pathways commonly associated with increased metastasis. This study will evaluate the potential of four recently proposed TNBC treatments which all successfully reduced tumor viability *in vitro* and/or *in vivo* to inhibit genes involved in CSC survival, metastatic metabolomic signature, and immunosuppression. TNBC cell lines and/or patient-derived xenografts were treated with four different treatments: DCC-2036, 9Gy proton irradiation, miR302b+cisplatin combination, and DFX+doxorubicin combination. Genome-wide mRNA profiling was performed on control and treated groups. We assessed the differential expression of genes associated with CSC growth, metastatic metabolomic signature, and immunosuppression in TNBC tumors. DCC-2036 treatment significantly induced the expression of CSC markers and genes associated with the metastatic metabolomic signature and immunosuppression. 9Gy proton irradiation has mixed effects on the expression of our candidate genes, yet mostly induced the expression of stemness and metastasis markers. Both miR302b and DFX dual therapy both failed to inhibit the candidate genes, yet without significantly inducing their expression. GSEA analysis confirmed the results obtained for all four treatments. We concluded that all four treatments failed to significantly impact the expression of protein pathways involved in CSC growth and in metastasis. Therefore, we hypothesize that these treatments will likely not show positive effects in clinical studies. We encourage the researchers to perform more rigorous assays evaluating the impact of their proposed treatments on CSC growth and metastasis in order to more accurately assess the translatable potential of their treatments.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

SB: President of the Connecting Young Minds (CYM) Undergraduate Research Conference, reviewed abstract submissions to ensure proper formatting standard, assisted undergraduate authors with their submissions, drafted the CYM abstract, drafted and formatted the abstract booklet, and gave final approval of the abstract booklet to be published.
ZS: Co-VP of External Communications of the Connecting Young Minds (CYM) Undergraduate Research Conference, reviewed abstract submissions to ensure proper formatting standard, assisted undergraduate authors with their submissions, contributed to the drafting of the CYM abstract, and gave final approval of the abstract booklet to be published.
MG: Co-VP of Logistics of the Connecting Young Minds (CYM) Undergraduate Research Conference, reviewed abstract submissions to ensure proper formatting standard, assisted undergraduate authors with their submissions, contributed to the drafting of the CYM abstract, and gave final approval of the abstract booklet to be published.

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