Research Day Abstracts

2024

4th Year Honours Specialization Students

Presenter's Name: Barboza, Rachel
Additional Authors: Lin A, Liu E, Le Q, Ling C, Castellani CA, Zhang Q
Abstract Title: The Molecular Characteristics of Granular Mitosis in Glioblastomas

Abstract:
Introduction: Glioblastoma is the most common malignant neoplasm of the central nervous system and has a poor prognosis with an average survival of 6 months. A high proliferative index, such as an increased mitotic rate, is a key feature of these high-grade tumors. "Granular mitosis" (GM) is a unique type of atypical mitotic figure observed exclusively in glioblastoma, but not other tumors. The molecular etiology of GM formation in glioblastoma is largely unknown.

Methods: To understand GM's pathogenesis, we used The Cancer Genome Atlas (TCGA) Glioblastoma Multiforme dataset (N=619). First, we identified patients who exhibited granular mitosis through the annotation of diagnostic tumor histology whole slide images. Using the patient's corresponding transcriptomic, epigenomic, and genomic data, we conducted differential gene expression, methylation, mitochondrial (mt) DNA, and copy number variation (CNV) analyses via linear mixed model regression after data cleaning and preprocessing. Where relevant, potential confounding factors such as sex and ethnicity were accounted for. Downstream in silico overrepresentation analysis will be performed to identify pathways and features of interest. Multi-Omics Factor Analysis (MOFA) will also be conducted to detect patterns by integrating these datasets to gain an in-depth understanding of the factors associated with GM. Genes that show differential methylation, gene expression, CNV, and mtDNA will be prioritized for further follow-up. Finally, clinical information will be correlated for associations with identified outcomes.

Results: There were 82 glioblastoma slides reviewed, and 53 glioblastoma cases were included for analysis (35 GM positive, 18 GM negative). The transcriptomic analysis results show that 60 genes are differentially expressed between glioblastoma patients who exhibit granular mitosis and patients who do not (FDR < 0.05; fold change >2). Functional enrichment through Gene Ontology (GO) analysis has identified associations with nucleosome assembly and organization ($p = 3.19e-10$), as well as chromatin structure ($p = 1.18e-11$).

Discussion: These preliminary findings demonstrate a molecular difference between patients who exhibit GM and those who do not. As additional diagnostic slides are annotated, more patient data will be included in our findings. Additionally, they provide a basis for further analysis of differential expression for patients with high and low concentrations of granular mitosis.

MEDICAL BIOINFORMATICS

Presenter's Name: Feng, Kevin
Additional Authors: Hallett M, Bjazevic J
Abstract Title: Predictive Modeling of Kidney Stone Composition Using Machine Learning and Clinical Data

Abstract:
Introduction: Kidney stones are a common urological condition that occurs when mineral and organic deposits form solid formations within the renal system. About one in ten individuals is affected by this condition, and it often causes severe pain when the stones pass through the urinary tract. Understanding the composition of kidney stones is essential for developing effective treatment and prevention methods, given the variety of stone types and corresponding treatment options available. Currently, clinicians can only determine the composition of kidney stones after removing them from patients. Therefore, we aim to use machine learning methods to build predictive models to analyze clinical data and identify kidney stone composition without invasive procedures.

Methods: A group of 661 individuals with kidney stones were studied to collect data on stone composition, 24-hour urine profiles, serum biochemistry, and patient demographic and medical history. Using this clinical data, we trained a binary classification random forest machine learning model to determine if patients would have stones containing calcium monohydrate, calcium dihydrate, calcium phosphate, apatite/brushite, uric acid, struvite, and cysteine. The sensitivity, specificity and F1 score were used to evaluate the model's performance.

Results: Using the F1 score to evaluate the performance of the classification model using a threshold of greater than 0.75 as a good model, the binary classification random forest machine learning model was able to determine whether a stone would contain calcium monohydrate or calcium dihydrate. Both calcium monohydrate and calcium dihydrate models could determine true positive cases with a sensitivity of 0.933 and 0.808, respectively. However, they cannot determine true negative models with specificity values of 0.136 and 0.4, respectively. The binary classification random forest machine learning could not determine whether kidney stones contain calcium phosphate, apatite/brushite, uric acid, struvite, and cysteine.

Discussion: Preliminary findings indicate that a basic binary classification random forest model struggles to accurately predict the composition of kidney stones. However, as this model serves as a benchmark for comparison, more advanced deep learning techniques will be explored in the project's progression to address the limitations observed in the random forest model.

Presenter's Name: Liang, Derick
Additional Authors: Shooshtari P
Abstract Title: Application of Machine Learning in Predicting Gene Expression Profiles of Individual Cells Using Their Chromatin Accessibility Activities

Abstract:
Introduction: Multi-omic profiling integrates diverse 'omics' data to understand biological systems, crucial for elucidating disease mechanisms and advancing personalized medicine. However, experiments to find multi-omics data can be extremely expensive and when produced, variations in sample preparation, data acquisition, and processing can lead to inconsistent and non-comparable results across different studies or platforms. To address the challenges in extracting multiple modalities from a single cell, recent research has focused on computational methods that can infer these modalities. BABEL, developed by Wu et al., represents a computational solution, predicting single-cell RNA or ATAC sequences from one another. Despite its capability, BABEL's prediction accuracy diminishes when applied to untrained cell types or species. This research evaluates BABEL's performance on expanded datasets across various cell types and species, aiming to enhance its predictive accuracy for broader applications in biomedical research.

Methods: To accomplish this aim, we will utilize four models developed using BABEL's machine learning algorithm: the original Wu et al. model (control), a second model incorporating additional human cell types, a third substituting human cells with mouse cells to maintain dataset size but introduce species diversity, and a fourth model combining the approaches of models two and three, using more datasets and cell types from both species. The impact of expanding training datasets and integrating diverse species on BABEL's performance will be assessed through density plots and correlation coefficients between predicted and experimental results.

Discussion: Improving BABEL's predictive accuracy with diverse cell types and species could make advancements in multi-omic studies, enabling easier, efficient comparative analyses. This advancement accelerates research through computational efficiency, reducing traditional sequencing costs and time. It could also enhance disease research and large-scale screenings, providing insights into population genetics and treatment responses, marking a significant step forward in utilizing computational models for complex biological data analysis.

Presenter's Name: Tran, Michael
Additional Authors: Poon AFY
Abstract Title: Investigating the role of surface-exposed proteins in virus evolution

Abstract:
This project aims to investigate the evolutionary dynamics of human viruses, with a focus on the role of surface-exposed proteins and their encoding genes in viral adaptability and immune system interactions. Viral diseases, such as the COVID-19 pandemic, highlight the importance of understanding viral evolution due to their significant impact on global health and economies. Surface-exposed proteins in particular are crucial for virus-host cell interactions and immune evasion. The study aims to determine if genes encoding surface-exposed proteins experience higher rates of adaptation compared to other viral regions due to the intense selection pressure from immune system interactions. A dataset of over 4000 Hepatitis C Virus (HCV) RNA sequences was collected from Genbank and analyzed to assess selection pressures, with a focus on synonymous versus non-synonymous mutation rates. After alignment with MAFFT, the sequences are organized into their genotypes and subtypes and further into protein-coding genes. FUBAR analysis with hyphy produces heatmap fingerprints to visualize the selection pressures across the HCV genome, highlighting areas and trends of evolutionary change and especially differences between genes and genotypes. The research also incorporates machine learning, using image recognition to classify and label gene fingerprints based on their encoding of surface-exposed proteins. This innovative approach aims to bypass the complexity of high-dimensional data analysis typically associated with such studies. The significance of this research lies in its potential to enhance our understanding of HCV's evolutionary mechanisms and immune evasion strategies. The findings can inform vaccine and antiviral drug development, providing insights into the adaptability of HCV and possibly other rapidly mutating viruses, and improving preparedness for future viral threats.

MEDICAL BIOINFORMATICS

Presenter's Name: Weng, David
Additional Authors: Hu P
Abstract Title: Synthetic lethality and single-cell transcriptomic signature driven drug repurposing for ER+/HER2+ breast cancer

Abstract:
Introduction: Breast cancer heterogeneity poses challenges in determining effective treatment strategies. Current clinical subtyping based on receptors fails to fully capture the heterogeneity found in the disease. Highly heterogeneous subtypes — such as estrogen receptor positive and human epidermal growth factor receptor 2 positive (ER+/HER2+) breast cancers — show high variability in patient outcomes. Differences in gene expression have been used to delineate subgroups with worse prognoses within the ER+/HER2+ subtype using single-cell RNA sequencing (scRNA-seq). This technology can also identify synthetic lethality (SL), a genetic interaction where only simultaneous loss of function in both genes leads to cell death, uncovering targets for cancer-specific treatments. We aim to leverage scRNA-seq to identify potential repurposed drugs to target subgroups in ER+/HER2+ breast cancer through two avenues — SL and reversal of disease transcriptomic signatures.

Methods: SL genes are uncovered using the tool Synthetic Lethal Identification in R (SLIdR) using viability scores predicted from DepMap and mutation data from cBioPortal across 1201 breast cancer patients in The Cancer Genome Atlas (TCGA) samples with oncogenes defined with COSMIC cancer gene census' Tier 1 breast cancer genes. Reversal of transcriptomic signature uses the tool A Single-cell Guided Pipeline to Aid Repurposing of Drugs (ASGARD) with a treated and untreated ER+/HER2+ breast cancer sample and three healthy references. ASGARD generates predicted repurposed drugs and SL genes are used as targets in DrugBank drug searches. Validation of repurposed drugs uses computational prediction of binding, literature review, and ADMET models.

Results: SLIdR analysis found two SL gene pairs sharing a driver gene — FOXA1-MUC16 and FOXA1-CHST11. Repurposed mono-drug and drug combinations will be identified by ASGARD. Drugs targeting MUC16 and CHST11 will be searched for using DrugBank. All potential drugs will be assessed using computational tools and literature review.

Discussion: We attempt to find potential therapeutic approaches for ER+/HER2+ breast cancer, addressing blind spots in current treatment strategies due to ill-defined diagnostic criteria. Leveraging scRNA-seq technology through SL, transcriptomic signature-driven drug repurposing and computational validation allows for more personalized treatment options while reducing laboratory costs in development of new treatment strategies.

Presenter's Name: Daniel, Maria
Additional Authors: Kawa DT, Jackson-Boeters L, Betts D, Kiser P
Abstract Title: Exploring the Role of the Adaptor Protein p66Shc on Murine Embryonic Stem Cell Differentiation and Maturation

Abstract:
Embryogenesis is a complex developmental process that relies on mechanisms of cell proliferation, signaling, and differentiation mediated by molecules such as adaptor proteins. When these mechanisms are interrupted, embryo pathologies occur. The general developmental role of the p66Shc adaptor protein on cell fate and maturation of the neuroectoderm germ layer has been explored. However, more research is required to expand on that role for different stages of maturity within a germ layer. To address this knowledge gap, I conducted a research project that aims to determine if p66Shc knockout (KO) causes maturation arrest in cells, and if it plays a role on maturation of ectoderm lineage derivatives other than the neuroectoderm. The methodology of this experiment built on previous research. We used Cell Lineage Identification RT^2 Profiler PCR Arrays to quantitatively analyze teratomas that were previously generated in vivo with wild type and p66Shc KO mouse embryonic stem cell injection in immunodeficient mice (Betts). Immunohistochemistry, hematoxylin staining, and in vitro qualitative analysis were also performed. By correlating immunohistochemistry with observed cellular morphological changes in the KOs, we hypothesize that the maturation state of the observed cell sets can be identified and are affected by p66Shc KO. This research is currently in progress, but its results will be available prior to the research poster submission deadline. It is expected that hematoxylin and eosin analysis will result in the WT teratomas characterized by well differentiated cells and the p66Shc KO teratomas characterized by poorly or undifferentiated cells. For immunohistochemical analysis, it is expected that the undifferentiated p66Shc KO cells will not be pluripotent but rather have committed to a germ lineage. After immunohistochemical analysis of the neuroectoderm-excluding ectoderm maker, it is possible for the p66Shc KO cells to be committed to the neuroectoderm or another ectoderm derivative. These results will expand on p66Shc's known role on cell differentiation and maturation. This can help understand how embryo pathologies arise. To enhance our understanding of both embryogenesis and its pathologies and explore improved knowledge translation in future approaches, the One Health approach will be applied to the results to address stakeholders outside academia and the influence of the animal, human, and environmental health pillars on this topic.

Presenter's Name: Han, Seungwon
Additional Authors: Olea-Popelka FJ, Leseni T
Abstract Title: Tuberculosis in an Urbanizing Kenya: Investigating the link between urbanization in the 21st century and human, bovine, and zoonotic tuberculosis

Abstract:
Introduction: Kenya is experiencing population growth and urbanization, where more people are moving to cities from rural communities. Urban areas are hotbeds for aerial tuberculosis (TB) amongst humans, and urban and peri-urban agriculture in poorly ventilated settings increase opportunities for bovine TB (BTB) and zoonotic TB (ZTB) transmission. A burgeoning urban population and increasing demands for milk and beef will exacerbate pre-existing challenges with human TB, BTB, and ZTB. Thus, the main goal of this research is to investigate how urbanization is linked to TB in Kenya in the 21st century. However, the current discourse about TB in Kenya is focused mainly on human TB.

Methods: To address the research gap, a scoping review was conducted to investigate the link between urbanization and human TB, BTB, and ZTB in 21st century Kenya. Scientific peer-reviewed articles were sourced from the databases MEDLINE (Ovid), PubMed, Scopus, and Web of Science. Literature was selected using the software Covidence following PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

Results: Most articles reported findings on human TB and identified risk factors for human TB associated with urbanization such as overcrowding and poverty. Urban slums were identified as being vulnerable to multidrug-resistant human TB. Fewer sources were found for BTB and ZTB, but slaughterhouses were cited as a risk factor for both. Furthermore, rural agricultural communities with limited knowledge on BTB and zoonoses were identified as being at risk for BTB and ZTB.

Discussion: These findings demonstrate urban and rural challenges in the management of human TB, BTB, and ZTB in Kenya. Both urban and rural challenges are heightened by socioeconomic factors, comorbidities, and lack of resources for diagnoses and surveillance. This research showcases the current lack of discourse and need for more research on BTB and ZTB in Kenya in relation to urbanization. The challenges of TB, BTB, and ZTB in an urbanizing 21st century Kenya necessitates a One Health (OH) approach especially since urbanization will continue to impact the environmental circumstances of animal and human interactions. TB in an urbanizing Kenya is a great challenge, but a successful approach against human TB, BTB, and ZTB in Kenya in collaboration with multisectoral OH stakeholders will set an example for similar challenges in other urbanizing countries.

Presenter's Name: Hazeema
Additional Authors: Frisbee SJ
Abstract Title: Bridging the Gap: Insights from a Scoping Review on Reducing Hypertension Control Disparities in Primary Care Settings

Abstract:
Introduction: In the last decade, stakeholders overseeing hypertension (HT) control guidelines at national and international levels have underscored the significance of prioritizing marginalized communities. Recommendations for addressing HT control disparities and enhancing primary care have been published. Despite these efforts, the persistent low rate of controlled HT in these populations prompts an inquiry into the implementation, components, and effectiveness of targeted interventions in primary care settings.

Methods: A scoping review following the PRISMA-ScR Checklist is currently underway. Using a comprehensive search string, 1012 relevant empirical studies were identified from Scopus, PubMed, CINAHL, and Embase. As of now, 607 studies have undergone screening, with 25 meeting the eligibility criteria. Eligible studies are primary full-text research papers, published in the past 5 years, detailing interventions for adults diagnosed with HT from underserved or marginalized communities seeking care in primary care settings. These interventions focus on improving HT control, with reported outcomes comprising mean changes in blood pressure and/or shifts in the proportion of patients achieving controlled HT.

Results: Data from 17 of 25 eligible studies, with participant counts ranging from 16 to 3658, reveal the use of various intervention components such as home blood pressure monitoring (HBPM), web-based HT education applications, patient-centered lifestyle coaching by Community Health Workers, and medication prescription and adjustment by pharmacists using predetermined algorithms. The majority of these studies highlight a significant and immediate decrease in systolic blood pressure among hypertensive patients after the intervention, with sustained positive effects in subsequent follow-ups.

Discussion: Complex multi-component interventions, limited in feasibility and acceptability, may not be imperative for improving HT in marginalized populations. Focusing on cost-effective intervention elements, such as web-based HT education applications and HBPM directly integrated with the patient's electronic health record, appears sufficient for effective HT control. A stakeholder analysis will be conducted to identify the major stakeholders involved in environmental and animal topics relevant to this research project. Subsequently, an effective One Health approach aimed at mitigating HT control disparities at a population level will be discussed.

ONE HEALTH

Presenter's Name: Jose, Pious
Additional Authors: Olea-Popelka FJ, Castellani CA, Cameron L
Abstract Title: Exploring Epigenetic Age Acceleration and Mitochondrial Dysfunction in Asthma

Abstract:
Introduction: Asthma is a respiratory condition with a substantial global health burden. asthma development involves predisposing genetics and environmental exposures such as animal allergens from pets, cigarette smoke, and air pollution. Therefore, a One Health approach considering environmental, animal, and human health is vital to understanding asthma. Although asthma mediated by type 2 (T2) inflammation is well understood, less is known about the often more severe non-T2 asthma. The field of epigenetics and mitochondriomics are tied to the values of One Health since they explore how our bodies adapt to these environmental effects. Thus, studying environmental effects through epigenetic regulation of gene expression, mitochondrial DNA (mtDNA), and epigenetic aging is vital to finding the pathogenesis of non-T2 asthma.

Methods: We examined the relationships between epigenetic age and mitochondrial (mt) dysfunction in asthma. Epigenetic age was calculated using Horvath, Hannum, SkinHorvath, PhenoAge, GrimAge and DunedinPACE clocks on publicly available datasets of two independent Asthma studies looking at bronchial (N=130) and upper airway epithelial (N=104) cells of 234 individuals. We also assessed the CpG sites related to mt hub genes associated with non-T2 asthma to find potential epigenetic markers for this subtype. We also plan to measure mt function and mtDNA copy number of immune cells involved in non-T2 asthma to assess whether mt dysfunction affects asthma severity.

Results: Preliminary data show that asthmatics have a greater epigenetic age acceleration (EAA) than non-asthmatics. In asthmatic patients, the SkinHorvath clock had an EAA of 3.60 years (p = 1.71e-3). The Horvath clock showed an EAA of 2.51 years (p = 7.00e-3). Hannum showed an EAA of 2.01 years (p = 3.50e-2). PhenoAge showed an EAA of 2.76 years (p = 4.14e-3). GrimAge showed an EAA of 1.08 years (p= 2.85e-2). DunedinPACE did not show a significant difference between patients and controls (p=9.10e-2). All clocks show a positive direction of effect. Expected results for future work include the identification of potential epigenetic markers for Asthma susceptibility and observations of mt dysfunction in immune cells associated with non-T2 asthma.

Discussion: Exploring connections between epigenetic age, mt dysfunction, and asthma subtypes through a One Health lens will increase our understanding of the development of asthma and uncover new therapeutic approaches.

Presenter's Name: Mattekatt, Juhi
Additional Authors: Elsayed S
Abstract Title: Investigation of Antimicrobial Stewardship in North American Indigenous Communities

Abstract:
Introduction: Antimicrobial resistance is a growing threat that requires stewardship strategies to limit the growth and spread of resistant pathogens. Indigenous communities in North America have historically been underserved, and this has likely resulted in a lack of adequate antimicrobial stewardship in these communities. In the present review, we aim to explore the quality of antimicrobial stewardship practices in North American Indigenous communities. This has been done by determining the appropriateness of antimicrobial prescribing practices in Indigenous communities; and by determining what antimicrobial stewardship strategies are currently present at health centres within Indigenous communities.

Methods: A narrative review was performed using literature found from Scopus, Embase, PubMed, Cochrane, CINAHL, and Web of Science. Search strings using key words were used to search these databases. Only English-language articles published between January 2000 and June 2023 were included. Critical appraisals of the included articles were conducted using CASP checklists.

Results: This review is currently in process and completed results will be presented on April 4th. This project is expected to find that there is excessive and inappropriate prescription of antibiotics by health centres targeted at Indigenous communities. A lack of appropriate stewardship strategies, and increased rates of antimicrobial resistant infections compared to non-Indigenous communities are also expected.

Discussion: This review expects to find gaps in the current approach to antimicrobial stewardship in North American Indigenous communities. Improper dispensation of antimicrobials due to a lack of stewardship practices contributes to the rise of resistant pathogens within these communities. Proper antimicrobial stewardship must be practiced by all communities that use antimicrobials. Thus, this project may emphasize the need for increased support to Indigenous communities so that antimicrobial stewardship practices can be integrated into routine clinical care for this patient population. Stewardship strategies can be implemented by increasing surveillance through a One Health approach, as well as by properly educating stakeholders, which can include both healthcare providers and patients.

ONE HEALTH

Presenter's Name: Sharma, Shreya
Additional Authors: McKinley G
Abstract Title: Investigation of the Environmental Impacts of the Cryptocurrency Industry

Abstract:
Introduction: Cryptocurrencies are digital currencies, used as alternative forms of payment or investment, and secured by cryptography. Concerns about resource usage and environmental impact have emerged as the industry grows and becomes more computationally intensive. Despite these concerns, there is still a gap in understanding the full extent of the industry's environmental impact. Therefore, this scoping review aims to describe the environmental impact associated with the cryptocurrency industry. To achieve this goal, the specific objective of this research is to review and synthesize existing scientific and non-scientific literature to better understand the environmental effects of cryptocurrency activities.

Methods: The scoping review methodology was adapted from the PRISMA Extension for Scoping Reviews (PRISMA-ScR) framework. Open-access scholarly and non-scholarly sources published in English between 2020 and 2023 from North America, China, and India were collected from Scopus, ProQuest, PubMed, and the Bielefeld Academic Search Engine.

Results: Of the 299 sources retrieved, 26 sources were selected for inclusion in this review based on eligibility criteria and access to full-text versions. Five of the 26 studies discussed cryptocurrency data centers' environmental consequences. Ten studies considered the environmental impact of cryptocurrency mining hardware. Sixteen sources discussed the electricity and energy needs of the cryptocurrency industry, emphasizing its role in greenhouse gas and carbon emissions. Eleven sources discussed mitigating the environmental impact of the cryptocurrency industry through regulatory recommendations, modifications to the cryptocurrency blockchain or energy sources, and changes in investment trends.

Discussion: The findings show the considerable environmental impacts of the cryptocurrency industry. The research highlights the multifaceted nature of environmental degradation caused by cryptocurrency activities and identifies opportunities for future research and action to promote sustainability within the industry.

One Health Relevance: This research is significant to the One Health approach as it underscores the interconnectedness between technological innovation, environmental sustainability, and social well-being. It highlights the need for collaborative efforts across animal, human, and environmental health sectors to holistically address the environmental impacts of emerging industries like cryptocurrency.

Presenter's Name: Sun, Gracie
Abstract Title: The LinkUp Study – Evaluating the Outcomes of the 519Pursuit's LinkUp Mentorship Program & the Role of Mentorship in Social Inclusion for People Experiencing Homelessness in London, Ontario

Abstract:
In Canada, 35,000 Canadians experience homelessness on any given night, with at least 235,000 people experiencing homelessness in a year. This is a concern as people experiencing homelessness experience worsened health outcomes alongside greater barriers to accessing healthcare. This is exacerbated by social exclusion which drives individuals to physically exclude themselves further through encampments; thus, subjecting individuals to greater health risks and increasing inaccessibility to support. 519Pursuit is a non-profit organization in London, Ontario which seeks to improve the social inclusion of the homeless community in London through the launch of the LinkUp program, a mentorship program to pair participants experiencing homelessness to a mentor. The purpose of the study is to understand the outcomes of the LinkUp program, the association of mentorship and social inclusion, and understand best practices for 519Pursuit to expand the program. Through a community-based participatory research approach in collaboration with the 519Pursuit, a qualitative narrative-phenomenological semi-structured interview study will be conducted with up to 15 mentor pairs. Interviews will be transcribed and undergo Braun & Clarke 2018 thematic analysis. The anticipated results of the study are to uncover the individual and group benefits of the program through building friendship and also broader implications on improving individuals' quality of life and aim to be revealed by April. In addition, the participants' experiences are valuable in understanding best-practices for the LinkUp program. These findings alongside discussing homelessness and mapping relevant stakeholders through a One Health approach will be used to broaden our understanding of the association between homelessness, mentorship, and social inclusion, and provide valuable opportunities for knowledge translation.

ONE HEALTH

Presenter's Name: Suthakaran, Karshana
Additional Authors: Schmid S
Abstract Title: Examining the Impact of Environmental Enrichment on Autism Spectrum Disorder Through the Use of Cntnap2 Knockout Model Rats

Abstract:
Introduction: Autism Spectrum Disorder (ASD) is a prevalent neurodevelopmental disorder in Canada. One of the primary behavioural symptoms of ASD is an exaggerated startle response to sensory stimuli. While pioneering research has explored the benefits of environmental enrichment on neural plasticity and startle response in various neurodevelopmental disorders, there remains a significant gap in ASD research. Therefore, employing the Cntnap2 homozygous knockout rat model, which effectively mimics autism-like symptoms, this study aims to investigate the effects of environmental enrichment (EE) in laboratory settings. The study will assess how housing the rats in EE cages can change autism-related phenotypes, specifically startle responses, behaviour, exploration, and social interactions. It is hypothesized that the EE cages will modify acoustic startle response (ASR) and augment prepulse inhibition (PPI), simultaneously enhancing exploratory and social behaviours.

Methods: In order to test the hypothesis, knockout and wild-type rats were housed in EE cages from birth to the end of juvenile period and compared to rats raised in standard cages. Using a pressure-sensitive platform, the ASR and PPI were measured at the juvenile and adult stages to investigate auditory processing. Open field tests using open-top chambers and sociability tests were also performed to examine exploratory behaviours and social interactions, respectively. A One Health approach will be utilized to identify relevant stakeholders that are pertinent to this study.

Results: The results of the data analysis from the testing phase are anticipated to be available in March. It is expected that EE will lead to a decrease in startle reactivity and an increase in PPI. Moreover, EE rats are likely to exhibit elevated levels of exploratory behaviour and sociability. These outcomes are consistent with the improvements observed in studies examining the effects of EE in the context of schizophrenia and other autism rat models.

Discussion: The findings from this research and subsequent One Health integration will advance our understanding of the impact of EE on sensory processing within the ASD framework. It could facilitate translational research between Cntnap2 knockout rat models and humans with autism, focusing on the potential of EE to alleviate symptoms. Furthermore, it could inform effective interventions and influence public health policies and environmental management strategies.

ONE HEALTH

Presenter's Name: Volcko, Lauren
Additional Authors: Frisbee SJ
Abstract Title: Facilitators and Barriers of Implementing Digital Interventions for **Diabetes:** A Scoping Review

Abstract:
Introduction: Diabetes mellitus, a significant global health challenge, affects millions worldwide and imposes substantial costs on healthcare systems. Despite advancements in treatment, many individuals fail to meet treatment targets, leading to secondary complications with associated additional costs. Although not widely implemented, the effectiveness of digital interventions to support diabetes self-management has been shown. This scoping review aims to investigate the utilization of these digital interventions in clinical settings and identify barriers and facilitators to their implementation.

Methods: This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for Scoping Reviews (PRISMA-ScR). Relevant articles published between January 2010, and November 2023 were identified through Scopus, EMBASE, PsychInfo, ProQuest, CINAHL and PubMed. Included studies were peer-reviewed, primary studies, describing type 1 and type 2 diabetic or pre-diabetic patients over 18 years old. Qualitative analysis will be used to identify themes surrounding barriers and facilitators for implementation based on the perceptions of both providers and patients in selected articles.

Results: In total, 1038 were screened and 22 articles were included in the final review. Extraction and synthesis of the results remain ongoing. Preliminary results indicate that barriers for providers include concerns of integration into clinical workflow, and a lack of organizational framework for implementation of digital interventions. Similarly, patient barriers centre around a lack of motivation and participation with "faceless" advice. Relevant findings from data extraction of the thematic analysis will also be included in the results.

Discussion: The results from this scoping review can provide a foundation for digital health implementation and identify priorities to achieve broader adoption addressing the challenge that diabetes poses globally. A One Health approach will be used to identify relevant key stakeholders to highlight the need for collaboration between disciplines to holistically address diabetes.

Presenter's Name: Wang, Judy
Additional Authors: Sposato L, Wang N, Baranchuk A, Ayan D, Chan D
Abstract Title: Investigating electrocardiographic abnormalities as predictors for Post-Stroke Major Adverse Cardiovascular Events

Abstract:
Introduction: Ischemic stroke (IS) in humans is linked to an increased risk of major adverse cardiovascular events (MACE). Electrocardiograms (ECGs) and troponin (cTnT) tests are conducted as part of standard stroke workup to detect concurrent myocardial infarctions (MI), but subtler indications of cardiovascular damage on these tests are often overlooked. Thus, this study hypothesized that certain ECG abnormalities and increased cTnT levels are associated with a higher post-stroke MACE risk. Specifically, the objective was to investigate if ECG abnormalities can predict PS-MACE alone or in combination with high cTnT levels, at 90 days and 12 months after the ischemic stroke.

Methods: This retrospective study drew from a cohort of 2000 patients, including those over 18 years old treated for stroke at the London Health Sciences Centre from 2019-2020. ECGs were collected, de-identified, and stored in the London Ontario Stroke Registry, then analyzed by the Kingston Health Sciences Center based on waveform morphology and time-series metrics. Next, this data was matched to patient outcomes such as MACE during follow-up.

Results: This study is currently ongoing, and final results will be presented by April 4th. However, it is expected that indicators of cardiac injury like elevated cTnT levels, and ECG characteristics such as ST depressions, negative T waves, and prolonged QRS intervals will be linked to PS-MACE outcomes.

Discussion: Following IS as a multidisciplinary disease, this study aims to bridge the neuro-cardiology awareness gap in cerebrovascular events. Pre-existing studies separately focus on ECG indicators of first-stroke risk, or target MACE following cardiovascular procedures. Yet, they neglect investigating ECGs as predictive of MACE post-stroke. Recognition of high-risk populations can improve stroke monitoring in racial groups more susceptible to IS or socioeconomically less able to access treatment, relating to social determinants of health and identification of relevant stakeholders as a component of a One Health approach to the disease. Therefore, the goal is to help develop a quick and inexpensive point-of-care tool for identifying patients at high risk of severe cardiovascular outcomes after a stroke.

Presenter's Name: Bari, Amaan
Additional Authors: Chang N, Madahey H, Hardy DB, Dhanvantari S
Abstract Title: Phytocannabinoid-induced Reprogramming of Mouse αTC1-6 cells

Abstract:
Introduction: In North America, the prevalence of maternal cannabis use and its potential consequences are concerning. Previous studies have demonstrated that gestational cannabis exposure increases the risk of pancreatic dysfunction for the exposed offspring later in life. The current belief is that the main phytocannabinoids (PCs) found in marijuana, cannabidiol (CBD) and fj9-tetrahydrocannabinol (fj9-THC), exert their effects on pancreatic islets through the endocannabinoid system (ECS). While this signaling pathway is well characterized as a regulator of insulin secretion in β-cells, its regulatory role in α-cells is less understood. Preliminary data from our lab suggests that both the ECS itself and the spatial distribution of glucagon are modified in α-cells exposed to CBD and fj9-THC, contributing to the overall outcome of cannabinoid-induced α-cell dysfunction. Based on these observations, we hypothesize that PC exposure results in alterations to ECS signaling and glucagon trafficking within pancreatic α-cells.

Methods: Mouse αTC1-6 cells were treated with 30 μM of either CBD or fj9-THC to simulate PC exposure and to assess potential cannabinoid-induced alterations. Gene expression of key components of the α-cell ECS was determined using qRT-PCR, and intracellular localization of glucagon was assessed using immunocytochemistry and confocal fluorescence microscopy, where the colocalization of glucagon with different cellular compartment identifiers was analyzed.

Results: Both CBD and fj9-THC treatments are expected to lead to an upregulation of ECS target genes, highlighting this pathway as an important regulator of cannabinoid-induced cellular alterations. Spatial distribution of glucagon is expected to be altered, with glucagon being observed away from the cell periphery and instead being colocalized with lysosomal markers, suggesting that glucagon secretion is disrupted by ECS signaling.

Discussion: Through these experiments, we aim to identify how CBD and fj9-THC induce changes in pancreatic alpha cells by exploring how critical components of the ECS and glucagon trafficking may be altered upon exposure to these PCs. These findings will lead to a better mechanistic understanding of cannabinoid-induced α-cell dysfunction, and they will contribute to ongoing efforts to elucidate the connections between cannabis consumption and long-term metabolic dysfunction.

Presenter's Name: Burley, Leina
Additional Authors: Al Jawhri MW, Yu M, French A, Cameron L
Abstract Title: Investigation of Metabolic Pathway Use by Th2 vs Th2-Th17 Cells

Abstract:
Introduction: Asthma is a chronic inflammatory disease of the airways that is typically considered to be mediated by either Th2 or Th17 cells. Recently, asthma severity was found to be associated with a dual-positive population of Th2-Th17 cells, indicating that a mixed inflammatory profile plays a role in severe asthma. Th2 cells are known to utilize glycolysis, fatty acid synthesis (FAS) and fatty acid oxidation (FAO) through the mitochondria. Th17 cells utilize glycolysis and glutaminolysis but downregulate FAO, leading to lipid accumulation. We examined whether Th2-Th17 cell metabolism aligns more with Th2 or Th17 cells and how this relates to pathogenicity. We hypothesized that Th2 cells differentiating to Th2-Th17 undergo metabolic rewiring involving the attenuation of FAO and mitochondrial function. As this would lead to fatty acid accumulation, we modeled this condition by treating cells with saturated fatty acids (SFA) and assessed if this influenced pathogenicity by increasing or decreasing IL-10 and/or increasing IL-17 production.

Methods: Th2 cells (IL2) and Th2-Th17 cells (IL2/TGFb/IL-21) were examined for differences in glycolysis (GLUT1), oxidative phosphorylation (CYCS), glutaminolysis (GLS, GLUD1), fatty acid synthesis (ACACA, FASN, FADS1) and fatty acid oxidation (SLC22A5) using qRT-PCR. How IL1b treatment of Th2-Th17 cells influenced metabolism and pathogenicity was also examined. Th2-Th17 cells will also be cultured with media enriched with saturated fatty acid (SFA) and compared to a control media enriched with polyunsaturated fatty acid (PUFA) to analyse if this influences pathogenicity by increasing IL-17 production.

Results: Our results demonstrate that Th2-Th17 cells showed an increase in GLUT1 and a decrease in CYCS, compared to Th2 cells, while no statistically significant differences were observed between Th2 and Th2-Th17 cells for genes associated with glutaminolysis, FAS or FAO. IL-1b treatment may reduce IL-10, more experiments are being performed. The results for the impact of SFA versus PUFA treatment on Th2-Th17 cell IL-17 production is forthcoming.

Discussion: Th2-Th17 cells may be upregulating glycolysis and have lower mitochondrial function, suggesting metabolic rewiring plays a role in increased IL-17 production and pathogenicity. These results highlight the potential for metabolism as a therapeutic target for severe asthma.

Presenter's Name: Cheung, Tiffany
Additional Authors: Gholami H, Maleki S
Abstract Title: Changes in Systemic Cytokine Levels from Gut Microbiota Modulation with Antibiotics and Immunotherapy

Abstract:
Introduction: Success of immune checkpoint inhibitors (ICIs) as a cancer therapy is limited by tumour immunogenicity and gut microbiota composition, whose roles are currently unclear in ICI response. Neuroblastomas are characterized by their low immunogenicity and poor response to ICIs. The Maleki lab has previously sensitized neuroblastomas to ICIs by inducing mismatch repair (MMR) deficiency, rendering the tumour immunogenic as evidenced by reduced tumour volumes in induced-deficient MMR (idMMR) neuroblastoma-bearing mice after anti-CTLA-4 treatment. However, the effects of antibiotics on gut microbiota modulation on immunotherapy response have not been investigated in an idMMR neuroblastoma model regarding their influence on systemic cytokine levels during gut bacteria modulation and immunotherapy. IL-2 shows potential as a combination therapeutic with ICIs, and elevated IL-6 levels are linked to ICI-related toxicities. Therefore, I hypothesize that systemic IL-2 and IL-6 levels in idMMR neuroblastoma-bearing mice given antibiotic treatment can be used as predictive markers for anti-CTLA-4 response.

Methods: Mice will be given an antibiotic cocktail consisting of 1mg/mL ampicillin, 1mg/mL neomycin, 0.5mg/mL vancomycin, and 1mg/mL metronidazole to deplete their gut microbiota. Mice will be subcutaneously injected with idMMR neuroblastoma cells and administered 3 doses of anti-CTLA-4 once tumours are palpable. Serum will be collected between antibiotic administration, tumour injection, anti-CTLA-4 treatment, and at the endpoint for cytokine analysis. IL-2 and IL-6 will be quantified using enzyme-linked immunosorbent assays (ELISA) from collected serum to compare changes in cytokine levels between treatments.

Results: Decreased levels of IL-2 and increased levels of IL-6 are expected following antibiotic treatment and tumour injection, whereas increased levels of IL-2 and decreased levels of IL-6 are expected following anti-CTLA-4 treatment.

Discussion: This project will enhance our understanding of changes in cytokine levels in response to antibiotics and immunotherapy, providing insight into the factors influencing immunotherapy response that are currently hindering strategies to improve ICI success in intractable cold tumours. Investigating IL-2 and IL-6 further elucidates their roles in influencing immune responses in antibiotic treatment and immunotherapy, contributing to our understanding of the complex dynamics involved in cancer immunotherapy.

PATHOLOGY

Presenter's Name: Chharawala, Victoria
Additional Authors: Chharawala V, Zhang R, Armstrong JJ, Hutnik CML
Abstract Title: A Geographical Needs Analysis of Ophthalmologists in Ontario: Current Assessment of Specialist Distribution and Patient Demand

Abstract:
Introduction: Ophthalmologists are few relative to the population of Ontario and tend to practice in large population centres with secondary and tertiary care hospitals. More broadly, Ontario's population is growing and aging, placing additional demands on the short supply of ophthalmologists. The purpose of this study is to determine the geographic distribution of practicing ophthalmologists in relation to patients seeking ophthalmologic care in Ontario. It is hypothesized that differences in geographic distributions of patients and ophthalmologists will be associated with health inequalities in access to specialized eye care services in Ontario. In addition, temporal trends in population-level characteristics, such as median age and population size, will confirm an increasing need for ophthalmologists in Ontario.

Methods: A retrospective analysis of ophthalmic service billing claims data from the Ontario Ministry of Health and Long-Term Care between January 2016 and October 2023 was performed. This included counts of service claims for each pair of physician and patient forward sortation areas (FSA), the nature of the service provided, and a patient age range. A similar retrospective analysis, between September 11th and September 30th, 2023, was undertaken utilizing ophthalmology patients' electronic health records from the Ivey Urgent Eye Clinic at St. Joseph's Hospital in London, Ontario. Here, data collection included patient postal code, diagnosis, date and time of visit, number of follow-ups, patient age, speciality of the referring physician, and the referring complaint. Population-level data for age, growth distributions, and FSA boundaries were obtained from the 2021 Canadian census. Altogether, patient and physician distributions, patient characteristics, and population characteristics were visualized using ArcGIS Online mapping software and analyzed statistically in R.

Results: Analyses to date suggest disparities between physician and patient distributions, which may contribute to longer distances travelled for patients to access ophthalmic care. Mapped temporal shifts in patient distributions appear to correlate with the aging and growing population of Ontario.

Discussion: Identifying unknown factors such as patient-to-physician distance, local specialist density, and areas in need of increased ophthalmologist supply in Ontario is key to improving healthcare accessibility and informing future human resource allocation in ophthalmology.

Presenter's Name: Chou, Michael
Additional Authors: Steriopoulos J, Lu H, Zhang Z
Abstract Title: Determining the Molecular Mechanism of Signaling Between the Necrosome and Mitochondria During TLR-3-Mediated Necroptosis

Abstract:
Introduction: Organ rejection continues to be a major challenge in the field of transplant medicine. Cell death pathways such as necroptosis contribute to this rejection, but the mechanism of necroptosis is not well understood. More specifically, the molecular mechanism of the pathway between the mitochondria and necrosome is currently unknown during toll-like receptor 3 (TLR-3)-mediated necroptosis. We hypothesize that phosphoglycerate mutase 5 (PGAM5) and dynamin-related protein 1 (Drp1) are used by the necrosome to signal to the mitochondria during TLR-3-mediated necroptosis. We also hypothesize that PGAM5 and Drp1 are directly recruited by the necrosome during TLR-3-mediated necroptosis, rather than through an intermediate signaling molecule.

Methods: PGAM5 and Drp1 in microvascular endothelial cells (MVECs) will be silenced by PGAM5 or Drp1 siRNAs and necroptosis will be induced to determine if there is a significant decrease in cell death. Co-immunoprecipitation will then be done in control MVECs to determine if PGAM5 and Drp1 are directly recruited and bound to the necrosome.

Results: We expect PGAM5 and Drp1-silenced MVECs to exhibit significantly less necroptosis than control cells. This means that when compared to control cells, PGAM5 and Drp1 silenced MVECs should exhibit a significantly lower level of cell death. In addition, through co-immunoprecipitation, we expect to find that PGAM5, Drp1, and the necrosome directly interact by binding to each other.

Discussion: These expected findings would provide evidence for the involvement of PGAM5 and Drp1 in the TLR-3 necroptosis pathway, as well as the potential pathway in which PGAM5 and Drp1 are involved. Given that organ rejection is one of the leading causes of death after an organ transplant, defining the TLR-3 necroptosis pathway will help future researchers develop new therapeutic strategies to target necroptosis in the cells of newly transplanted organs. This can help overcome the challenge of organ transplant rejection and further advance the knowledge in the field of transplant medicine.

PATHOLOGY

Presenter's Name: Halka, Felobater
Additional Authors: Jackson-Boeters L, Darling M
Abstract Title: S100A7 Levels as a Marker for Predicting Malignant Transformation in Actinic Cheilitis

Abstract:
Introduction: Actinic cheilitis (AC) is an oral potentially malignant disorder (OPMD) that has the potential to transform into lip squamous cell carcinoma (LSCC). S100A7, a calcium-binding protein that is predominantly expressed in skin, is typically found at high levels in hyperproliferative skin diseases, such as AC. We have previously shown S100A7 to be a potentially useful biomarker for identifying OPMDs at risk of malignant transformation. Based on this background information, we hypothesize that high levels of S100A7 in AC are a positive predictor of malignant transformation.

Methods: Formalin fixed paraffin embedded tissue samples were immunohistochemically stained for S100A7. QuPath image analysis software was used to quantitate the levels of S100A7 in samples of normal controls, high-risk controls, low-risk controls, AC, and LSCC. The 5-year risk of malignant transformation was analyzed using an S100A7 immunohistochemistry-based signature algorithm (S100A7 ARS). Appropriate statistical analysis will be used to determine any correlation between S100A7 levels and malignant transformation.

Results: It is expected that S100A7 levels will be significantly increased in AC compared to normal and low-risk controls. A positive correlation between S100A7 levels in AC and malignant transformation is expected. AC cases which have transformed are expected to have higher S100A7 levels and S100A7 ARS risk than control tissues.

Discussion: These results should provide an insight into the association between S100A7 levels in AC and the risk of malignant transformation. The S100A7 ARS has been shown to have a role for risk stratification in malignant transformation of OPMDs. This study, along with future studies, may lead to S100A7 being established as an important biomarker in OPMDs and identify lesions which require early treatment prior to malignant transformation. In conclusion, it is expected that the findings of this study would support the hypothesis that S100A7 levels serve as a positive predictor of malignant transformation of AC.

Presenter's Name: Harris, Cole
Additional Authors: Wang E, Chakrabarti S, Feng B
Abstract Title: The Role of miR-9 in Alzheimer's Disease

Abstract:
Introduction: Alzheimer's disease is a progressive neurodegenerative disorder that affects the brain and causes a gradual decline in cognitive and functional abilities. Epidemiological studies have shown that diabetic patients have an increased risk of developing Alzheimer's disease. Excessive and pathological vascular remodeling that is a hallmark of diabetes could underlie the increased risk of developing Alzheimer's. A microRNA, miR-9, shows altered expression in experimental models of diabetes, and might mediate glucose-induced endothelial changes. However, the effects of miR-9 on the hippocampus in diabetes are still not clear. We hypothesize that diabetes-mediated changes in vascular miR-9 generate Alzheimer's-associated alterations in the brain.

Methods: To test this hypothesis, we created an miR-9 transgenic mouse model with endothelial-specific overexpression of miR-9. C57BL/6 wild type and miR-9 transgenic mice were injected with streptozotocin to induce diabetes, and then hippocampus tissues were collected. We then analyzed the expression of genes related to Alzheimer's using SanPrep Column microRNA Miniprep kits and RT-qPCR, specifically caspase 3, bcl-xl, amyloid beta, and tau proteins. We will use ELISA to determine the related protein levels, and staining to observe histological changes associated with Alzheimer's disease.

Results: Our results show higher expression of caspase 3 and lower expression of bcl-xl in B6 wild type diabetic mice than in B6 wild type control mice. We expect to see similar expressions of caspase 3 and bcl-xl to the B6 control mice in both diabetic and control miR-9 transgenic mice. We also expect to see a similar pattern with amyloid beta and tau, similar expression in the B6 control, miR-9 control, and miR-9 diabetic mice, with higher expression in B6 diabetic mice. Finally, we expect to observe more frequent histological changes associated with Alzheimer's disease in the diabetic B6 mice compared to the other groups.

Discussion: These findings show that diabetes increases the expression of Alzheimer's associated changes in the hippocampus. We also expect these findings to demonstrate the protective role of miR-9 in diabetes-mediated alterations in the brain associated with Alzheimer's, providing a novel mechanism and possible future therapy for Alzheimer's disease.

PATHOLOGY

Presenter's Name: Khanderooy, Parsa
Additional Authors: Lalonde E, Mohseni Meybodi A
Abstract Title: Evaluation of Targeted Next-Gen Sequencing and Chromosomal Microarray Analysis for detection of Copy Number Variants in Solid Tissue samples of Gliomas

Abstract:
Introduction: The detection of copy number variants (CNVs) plays a pivotal role in the diagnosis, subtyping, and treatment of gliomas. While Fluorescent In Situ Hybridization (FISH) remains the clinical gold standard for CNV diagnosis, its utility is limited by lengthy processing times, the necessity for manual analysis, and the need for experienced personnel. Emerging technologies such as Next-Generation Sequencing (NGS) and Chromosomal Microarray Analysis (CMA) have shown promise for CNV detection. Our study seeks to evaluate the accuracy of NGS and CMA in identifying key glioma CNVs, including EGFR amplification, 1p19q Co-deletion, Monosomy 10, Trisomy 7, and the homozygous deletion of CDKN2A/B genes compared to FISH in FFPE glioma tissues.

Methods: This study involved a retrospective review of patient charts and test results to select appropriate FFPE specimens. We assessed CMA accuracy using 16 glioma specimens previously analyzed by FISH and microarray between 2021 and 2023. For NGS accuracy, we examined 21 specimens analyzed by FISH and NGS from 2021 to 2023, with 10 samples having undergone all three analyses. FISH served as the reference standard. We utilized the Oncomine Comprehensive Assay v3 (OCA v3) (Thermo Fisher Scientific, USA) for targeted NGS, complemented by Ion Reporter for software analysis, and developed a custom pipeline for additional CNV detection.

Results: Preliminary CMA results demonstrated variable accuracy across different CNVs. Detection of 1p deletion yielded concordant results in 13 of 14 cases (92.86%). Detection of CDKN2A/B homozygous deletion, EGFR amplification, Trisomy 7, and Monosomy 10 was 100% concordant. However, only one of seven positive cases for 19q deletion was identified. Analysis from targeted NGS is in progress, with expectations for high accuracy in identifying the relevant CNVs.

Discussion: This study underscores the potential of integrating high-throughput technologies like NGS and CMA into clinical practice, potentially replacing FISH. Such advancements could significantly reduce diagnostic turnaround times for glioma CNVs from months to weeks, especially critical in regions facing shortages of medical laboratory technologists. However, the adoption of these methods requires standardization and the establishment of custom reference baselines for comparison. Our findings will contribute to the standardization efforts for CNV detection in FFPE samples using targeted NGS and CMA.

Presenter's Name: Khandwala, Zoya
Additional Authors: Khandwala ZF, Zakirova K, Dick F
Abstract Title: The role of the WNT signalling cascade on Epithelial-Mesenchymal Transition in High-Grade Serous Ovarian Cancer

Abstract:
Introduction: High-grade serous Ovarian Cancer (HGSOC) is an aggressive form of Epithelial Ovarian Cancer (EOC) characterized by atypia and pleomorphic nuclei. A defining characteristic of HGSOC is the cellular aggregates known as spheroids that form in the peritoneum during metastasis. These aggregates enter a dormant state wherein they are growth-arrested and unresponsive to therapy. Spheroid cells are suspected to possess qualities of both epithelial and mesenchymal cells. The formation of the hybrid cluster is attributable to Epithelial-Mesenchymal Transition (EMT). Some evidence suggests that EMT, a component of metastasis, is regulated by the WNT signalling pathway. The WNT pathway is thus far known to modulate other metastatic cell behaviours such as adhesion, proliferation, and fate in various cancers, EOC included. Given the existing and unknown information on WNT and EMT, we hypothesize that the WNT genes will promote epithelial-mesenchymal transition, spheroid survival, and ultimately metastasis.

Methods: The OvCar8 cell line will be used to establish an in vitro model for serous ovarian cancer, where control cells and WNT 8B/9B double-knockout cells will be followed. Initially, a primary tumor model will be created by allowing cells to adhere to tissue culture plates. Fixed numbers of cells will then be plated to ultra-low attachment plates to form spheroids that will incubate for seven days. EMT status will be analyzed by comparing RNA and protein expression of epithelial and mesenchymal cell markers such as cytokeratin and vimentin, respectively, through RT-qPCR and Western Blots of the adherent cells and 7-day spheroids. Furthermore, RT-qPCR will be used to examine RNA expression of EMT-regulating transcription factors Twist, SNAI1, and SNAI2.

Results: We expect that the WNT 8B and 9B double knock-out cells will show a shift in Epithelial and Mesenchymal balance. The double-knockout adherent and spheroid cells should be more epithelial, and thus should express more cytokeratin and less vimentin compared to the healthy control cells. Furthermore, the double-knockout cells should have lower expression of EMT-promoting transcription factors Twist, SNAI1 and SNAI2.

Discussion: Currently, the lack of existing research on spheroid dormancy and EMT in HGSOC contributes to high morbidity and mortality. This study attempts to identify the role of WNT 8B and 9B in Ovarian Cancer to develop therapies to improve patient prognosis.

PATHOLOGY

Presenter's Name: Kim, Sewon
Additional Authors: Jackson-Boeters L, McCord C
Abstract Title: The utility of p16 and p53 immunohistochemistry staining to determine the prevalence of HPV in Oropharyngeal squamous cell carcinomas submitted by Ontario dentists

Abstract:
Introduction: The human papillomavirus (HPV) is a group of viruses that infects the genital and oral areas of the human body. The high-risk strains of this virus can cause oropharyngeal squamous cell carcinomas (OPSCC) and the incidence of HPV-related OPSCC is on the rise. This increasing trend is worrisome and the problem is compounded by insufficient discussion with patients about HPV-related oral cancers and inadequate screening of the oropharynx for this virus by dentists. In HPV related carcinomas p16, a tumour suppressor protein, is overexpressed and is often used as a surrogate marker of HPV. HPV infection can also cause degradation of p53, another tumour suppressor protein, and is a newly emerging surrogate marker for HPV infection. The aim of this study is to assess the prevalence of HPV-related OPSCC in a sample of biopsies submitted by dentists and dental specialists using p16 and p53 immunohistochemistry (IHC) staining.

Methods: Cases of OPSCC were collected from oral pathology archives from 2002-2020. p16 and p53 IHC staining was performed on all 55 of the selected specimens of OPSCC. p16 IHC staining was performed using CINtec histology kit which included mouse anti-Human p16INK4a antibody Cases were stained for p53 using the Dako Omnis automated slide stainer. A 3 point grading system was used to assess p16 staining. Cases were categorized into 5 groups according to the pattern of p53 expression. Statistical analysis is ongoing.

Results: Our cohort was predominantly male and the median age was 63. 14.5% of the cases included in our study are p16-positive and have an HPV-related p53 IHC. Approximately 12.7% of the samples were p16-positive but showed an HPV-unrelated p53 IHC pattern. These samples were classified as HPV-. Interestingly, one out of 55 cases were p16-negative but had a p53 IHC pattern associated with HPV which is not observed frequently in literature.

Discussion: Our results provide insight into the prevalence of p16 positive OPSCC that are submitted by Ontario dentists and dental specialists. The prevalence of p16-positive HPV associated OPSCC in our study was lower than that reported in the literature. This study has the potential to be educational material for dental providers on the importance of screening for HPV. This study could also have implications on the current standard of HPV assessment in biopsies which is the sole use of p16 staining, by assessing the complementarity between p16 and p53 immunostaining.

Presenter's Name: Monaghan Chow, Isabella
Abstract Title: Identification and Characterization of circCRIM1 expression profile in Cardiomyocytes

Abstract:
Cardiovascular disease (CVD) is the leading cause of death globally and affects approximately 2.4 million Canadians. Circular RNA, a group of covalently closed single stranded RNAs, have been found to be implicated in a variety of cardiac pathologies such as ischemia reperfusion injury and coronary artery disease. Circular CRIM1 (circCRIM1) has been shown to increase its expression following ischemia reperfusion injury (IRI), however its exact role in CVD has yet to be discovered and it has multiple isoforms reported. Based on our preliminary data that a novel circCRIM1 isoform consisting of exons 2-4 and 13 is up-regulated in IR injured heart cells in vitro, I hypothesize that this novel circCRIM1 isoform is expressed predominantly in cardiomyocytes. Here I will characterize circCRIM1 in human and mouse cardiomyocytes. I will also determine the expression of both isoforms across a variety of mouse tissues and observe expression levels in response to cardiomyocyte injury. Junction specific primers will be used to amplify circCRIM1 isoforms in HL-1 and AC16 cell lines. The stability and half-life of circCRIM1 will be determined by treating cells with RNaseR and actinomycin D. Mouse tissue will then be isolated and harvested to examine the expression of isoforms across tissues. In addition, I will detect circCRIM1 expression in cell lines with cellular injury induced by IRI, H2O2 and CoCl2. We expect to determine the expression profiles of circCRIM1 in cardiac tissue and observe changes of circCRIM1 expression following cellular injury. Discovering a potential gene regulator-circCRIM1-in the pathogenesis of cardiac diseases will expand the knowledge of the role circular RNAs have in IRI. A better understanding of this process will be helpful in the future development of effective biomarkers for diagnosis or treatment of CVD.

PATHOLOGY

Presenter's Name: Orsava, Jenna
Additional Authors: Diao H, Taray-Matheson D, Vytlingam K, Min W
Abstract Title: The Interplay of Piezo1 and DLC1β in Cardiac-Ischemia Reperfusion Injury During Heart Transplantation

Abstract:
Introduction: Cardiac ischemia-reperfusion injury (IRI) occurs intraoperatively during heart transplantation and threatens the survival of the graft within the recipient. Previous experimentation in our lab has implicated DLC1β overexpression as one potential method of preventing the injurious effects of IRI. Another protein, Piezo1, may also be involved in cardiac IRI, as indicated by studies that have demonstrated its upregulation during myocardial injury; thus, manipulating its expression may be cardioprotective. It remains unknown however if this is true, and if it is, whether or not controlling Piezo1 can work synergistically with DLC1β to provide cardioprotective effects. Based on the literature review as well as previous data collected in our lab, we hypothesize that Piezo1 expression will increase in the context of cardiac IRI but can be counteracted by DLC1β, and that Piezo1 inhibition will lead to reduced cell death during IRI.

Methods: We will test this by culturing rat cardiomyocytes and exposing them to hypoxia-oxygenation reperfusion (H/OR) to determine how this may alter Piezo1 expression through changes in mRNA transcript and protein levels. We will also treat cardiomyocytes with either a mechanosensitive channel inhibitor (GSMTx4) or a Piezo1-specific activator (Yoda1), subject them to H/OR, and assess the effect of Piezo1 on cell death. Finally, we will also test the effect that DLC1β overexpression has on Piezo1 expression in cardiac grafts after heart transplantation.

Results: Our results show that in both rat cardiomyocytes and mice hearts, Piezo1 is upregulated after IRI. Treating rat cardiomyocytes with Yoda1 upregulated Piezo1 expression and increased the percentage of PI+ dead cells under IRI. Treatment with GsMTx4 however, decreases the expression of Piezo1 in cardiomyocytes and results in a decreased percentage of PI+ dead cells. Finally, treatment of cardiac grafts with DLC1β has demonstrated cardiac injury in IRI, which is related to the repressed expression of Piezo.

Discussion: These findings indicate that the increased expression of Piezo1 seen during IRI plays a role in the development of the injury, and inhibition of this molecule is cardioprotective, providing a potential pharmacological target for preventing graft rejection. Piezo1 inhibition and DLC1β overexpression may act synergistically together to reduce cell death during IRI, which needs further study.

Presenter's Name: Osei-Owusu, Cornelius
Additional Authors: Osei-Owusu C, Abud A, Nawal J, Wong C, Armas Machado M, Ryeed R, Sekar V, Guga S, Frisbee SJ
Abstract Title: Microcirculation and Critical Limb Ischemia

Abstract:
Introduction: Critical limb ischemia (CLI) is the end-stage manifestation of Peripheral Artery Disease and is characterized by pain at rest and tissue ischemia, with subsequent risk for necrosis and limb loss, and studies have reported a 1-year mortality rate ranging from 15-40%. The standard of care for CLI is revascularization by surgical or endovascular techniques. However, the outcomes of revascularization are poor, with reported risk of 1-year major adverse limb events (amputation, reintervention) as high as 37%. Reasons for poor outcomes are not well understood. One hypothesis is that revascularization restores bulk blood flow but there is unknown impact on the restoration of microcirculatory function, which is needed to restore tissue perfusion and function. Therefore, the purpose of this scoping review is to investigate the relationship between microcirculatory function and clinical outcomes in CLI patients.

Methods: A systematic search was conducted on MEDLINE, EMBASE, Scopus and CINAHL to identify articles related to "microcirculation" and "critical limb ischemia", using a specific search strategy for each database. Study screening, for both title/abstract and then full-text, was conducted through Covidence based on a pre-determined inclusion and exclusion criteria. Data extraction is also being completed in Covidence, where information about study participants, microcirculation assessment technique, study design and key details relevant to the review question are being recorded.

Results: The search yielded 3551 studies across the four databases and 299 studies remained after title/abstract screening. Full-text screening, data extraction and synthesis remain ongoing. Thus far, 22 studies have undergone data extraction. Among these studies, there is a mix of experimental studies and observational studies, both longitudinal and cross-sectional. The two microcirculation measurement techniques used in these studies were transcutaneous oxygen pressure (TCPO2) and skin perfusion pressure. Amputation-free survival, major adverse limb events and wound healing were clinical outcomes commonly assessed.

Discussion: This study highlights the value of assessing the microcirculation as a tool for prognosis in CLI patients. Measuring the microcirculation could indicate which patients will benefit from revascularization and other interventions, which could guide clinical decisions and improve the cost-effectiveness and morbidity of treating CLI.

PATHOLOGY

Presenter's Name: Potter, Maya
Additional Authors: Donavan J, Arts E, Quiñones-Mateu M
Abstract Title: Early detection of SARS-CoV-2 variants of concern using a wastewater surveillance model

Abstract:
Introduction: Severe acute respiratory syndrome 2 (SARS-CoV-2) is the instigator of the coronavirus disease 19 (COVID-19) global pandemic that led to a dramatic loss of human life worldwide. The emergence of variants of concern that pose an increased risk to global public health exemplifies the necessity for timely epidemiological surveillance. Wastewater surveillance of SARS-CoV-2 has been an immensely valuable tool domestically in London, Ontario throughout the pandemic and provides a means of tracking disease prevalence and dynamics on a broad geographic scale. We have previously shown that London wastewater can be used to monitor the emergence and proportions of circulating SARS-CoV-2 variants of concern over time. While it is known that wastewater surveillance is an effective tool for epidemiological surveillance, whether it provides an effective means of detecting new viral variants earlier than traditional clinical testing remains uncertain.

Methods: To answer this question, wastewater was collected from five treatment facilities across London, Ontario between June 2021, and January 2023. We focused on samples collected between August and December of 2021 to explore the potential for early detection of the Omicron BA.1 variant. RNA was purified from the wastewater, reversed transcribed into cDNA, and nested PCR based on the SARS-CoV-2 spike gene was performed. Deep sequencing using the Illumina miSeq platform was employed to identify the emergence of Omicron BA.1 in the London population.

Results: Our results show that by using nested PCR with high sensitivity, wastewater surveillance can detect new viral variants up to two months before traditional clinical testing. We detected Omicron BA.1 in London wastewater samples in September of 2021, yet clinical surveillance methods did not detect this variant until November of 2021.

Discussion: These results highlight the effectiveness of wastewater surveillance as a method for epidemiological surveillance. Early detection of variants of concern permits the development of strategies to contain epidemic outbreaks. These data can ultimately be used to guide and inform public health decision-making in the future.

Presenter's Name: Quan, Trinity
Additional Authors: Kum J
Abstract Title: Developing a Histopathological Atlas of Laboratory Mouse Tissues as an Open Educational Resource

Abstract:
The COVID-19 pandemic has exponentially accelerated a change in the methods by which education is delivered. With almost 1.2 billion students out of the classroom during the pandemic, there was a global shift toward virtual learning with increased use of online resources, including open educational resources (OERs). OERs are learning, teaching, and research materials available in the public domain, allowing for no-cost access and use.

Mouse models play a pivotal role in research as they offer insights into disease mechanisms and help to predict therapeutic actions. Currently, virtual microscopy and mouse atlas resources that are open access are quite limited, creating barriers for researchers and trainees in accessing these educational resources. Therefore, our study aims to create a histopathological atlas of laboratory mouse tissues as an OER.

To develop the histopathological atlas of the mouse tissues, we explored the use of Movat pentachrome stain for the histological visualization of collagen, elastin, muscle, mucin, and fibrin. As the pentachrome stain remains less explored compared with the widely used hematoxylin and eosin (H&E) stain, we will also include a comparison of the structures seen in both of these stains. Our comparative analysis of the two stains will help to determine if the pentachrome stain reveals additional key elements that may be undetected in the H&E stain. Specifically, we will explore the tissues from the eye, lung, liver, kidney, heart, tibia and femur of C57BL/6 mice. These stained tissue slides will be digitally scanned and analyzed to describe the tissue histology, anatomy, and physiology observed with the pentachrome stain compared to the H&E stain. We will then summarize these observations and will provide high-quality histological images of the various mouse tissues as an OER.

The goal of this project is to develop a histopathological atlas of laboratory mouse tissues available in the public domain in collaboration with other researchers exploring various disease models and staining techniques. By creating this OER, our study will contribute to the global shift towards accessible education, foster collaborative research, and provide a histopathological atlas for open science research and educational use.

PATHOLOGY

Presenter's Name: Resendes Torrado, Maya
Additional Authors: Khan ZA
Abstract Title: Assessing Hyperglycemic Memory Duration via ECM Gene Expression

Abstract:
Introduction: Diabetes mellitus is a prevalent chronic metabolic disease characterized by hyperglycemia and classified into type 1 (T1DM) and type 2 diabetes (T2DM). Conventional treatments focus on controlling blood glucose levels. Cohort studies have demonstrated the value of long-term intensive treatment in offsetting the onset of diabetic complications. As well as proposing the phenomenon known as hyperglycemic memory (HGM). HGM is when high glucose-induced cellular dysfunction continues after glucose normalization. Yet, the sustained duration of hyperglycemic memory remains unclear. Previous research has proposed that even short-term exposure followed by glucose normalization can elicit memory formation. However, the genome is highly dynamic, and these modifications may not persist following the normalization of glucose. Therefore, the research aim is to assess hyperglycemic memory duration using extracellular matrix (ECM) gene expressions as markers.

Methods: In experiment 1, high-glucose (at 30mM) exposure for 7 days, following glucose normalization (at 5.5mM) for 7 days on human microvascular endothelial cells (HMEC) will be assessed. The affected cells will be prepared for RNA isolation on days 2, 7, 9, 11, and 14 post-seeding. Isolated RNA will be measured, and cDNA will be synthesized. Real-time qRT-PCR will be conducted on 4 ECM (Fibronectin (FN) and 3 collagen variants) primers and 2 housekeeping primers, followed by statistical analysis. In experiment 2, HMEC harvested from patients with T1DM and T2DM will be assessed and compared to statistical analyses from experiment 1. Direct RNA isolation will be conducted and measured, and cDNA will be synthesized. Real-time qRT-PCR will be performed using the primers referenced in experiment 1, followed by statistical analysis.

Results: An expected outcome may be elevated expression of ECM during high-glucose exposure, peaking at 7 days and returning to normal levels during glucose normalization. The expression levels of the collagens and FN may also vary, suggesting the complexity of ECM gene regulation and the potential for reversibility of memory formation with proper glucose control.

Discussion: This study will demonstrate the duration of hyperglycemic memory and the potential of reversibility of altered gene expression, contributing to our understanding of memory formation and its impacts on diabetic complication development.

PATHOLOGY

Presenter's Name: Sreeram, Aparna
Additional Authors: Khan ZA
Abstract Title: Association Between Enhanced Adipogenesis and Diabetic Neuropathy in Bone Marrow

Abstract:
Introduction: Diabetes mellitus is a prevalent disease that causes significant morbidity due to its induction of numerous secondary vascular complications. The bone marrow is a major target of diabetic complications, exhibiting osteopenia, neuropathy, and accelerated adipogenesis. Studies have identified a correlation between nerve fibre neuropathy and bone loss, and our laboratory has reported heightened adiposity in the bone marrow of diabetic rodent models. However, a comprehensive understanding of the relationship between neuropathy and adipogenesis remains unknown. Based on these findings, I hypothesize that decreased innervation of bone marrow is causally linked to elevated bone adiposity in diabetic mice compared to non-diabetic counterparts.

Methods: Previously, our laboratory induced type-1 diabetes in C57BL/6 mice and acquired histological samples of bone tissue. To test this hypothesis, Nissl staining with cresyl violet dye and immunofluorescence staining for the neuron-specific Rbfox3 protein was employed alongside DAPI counterstaining to visualize neuronal density and distribution within the tibia and femur bone tissue of diabetic and non-diabetic mice. PLIN-1 immunostaining will be used to identify adipocytes and assess their density and spatial arrangement in relation to neurons within bone tissue. Image analysis will be performed using QuPath.

Results: Cresyl violet staining was positive in the cytoplasm of all cells within bone and retina tissues, demonstrating a lack of specificity for neurons. However, immunofluorescence staining for Rbfox3 showed potential for specifically detecting neurons. The ganglion cell layer of mouse retinal tissues exhibited positive staining for Rbfox3 in nuclei and perinuclear cytoplasm. Contrastingly, photoreceptor cells were negative for Rbfox3, suggesting specificity for neurons. Rbfox3-positive cells were also found to be dispersed throughout the bone tissue of the femur and tibiae, exhibiting staining in nuclei and cytoplasm. I expect that Rbfox3-positive cells will be localized proximal to PLIN1-positive cells within the tibia and femur bone marrow, and that diabetic bone tissue will show diminished neuronal staining coupled with elevated PLIN1 staining in comparison to non-diabetic bone tissue.

Discussion: These results optimize methods for identifying post-mitotic neurons in bone marrow and offer insights into the mechanisms underlying diabetes-induced alterations in bone microarchitecture.

Presenter's Name: Sulman, Muhammad
Additional Authors: Sulman M, Agbar SA, Sidahmed A
Abstract Title: Quantitative analysis of eplet load in heart transplant success: Evaluating the significance of mismatches across different HLA loci

Abstract:
Introduction: HLA antigen mismatches are known to be a contributor to the failure of transplanted hearts by increasing the likelihood of immune rejection. Polymorphic residues on the surface of HLA molecules, known as eplets, are the key elements recognized by the recipient's immune system, leading to transplant rejection. This study aims to find associations between the number of eplet mismatches at different loci, and time to the first incidences of rejection and failure.

Methods: To evaluate the effect of mismatches, over 100 donor-recipient pairs were HLA-typed at high resolution. Heart biopsies collected at regular intervals, were graded for acute cellular rejection by pathologists. A survival analysis was conducted, controlling for clinical factors (Age, BMI, etc.) to obtain significance of the associations between eplet mismatches and adverse outcomes including rejection and failure.

Results: Eplet mismatches in HLA-DQ significantly increase the incidence of Grade 2R (moderate) rejection. Increased participants may be required to better understand the role of eplet mismatches in adverse outcomes at other HLA loci.

Discussion: Eplet mismatches at HLA-DQ significantly increase the risk of moderate rejection. This highlights the potential of eplet matching to guide personalized immunosuppressant dosing and effective patient-recipient matching for heart transplantation.

Presenter's Name: Truong, Ivy
Abstract Title: Optimizing the digital quantification of PD-L1 as a predictive marker for immunotherapy response

Abstract:
Introduction: PD-L1 is an established biomarker for predicting anti-PD-L1/PD-1 immunotherapy response in various cancers. Measuring PD-L1 expression can help with predicting patient response and prognosis, assessing whether immunotherapy is the most optimal treatment. Traditionally, the quantification by pathologists is a laborious and imprecise process of manual counting using a conventional microscope. Furthermore, biases and interpretations between pathologists result in varying reproducibility and accuracy with quantification, leading to an increased risk of inappropriate treatment. Integrating digital image analysis (DIA) can support pathologists in various diagnostic techniques and has shown promise in improving accuracy and reliability. We hypotheszie that DIA would improve the accuracy of biomarker quantification, specifically PD-L1, across various tumours for predicting immunotherapy response.

Methods: QuPath, an open-source digital image analysis software, was used for the analysis of whole slide images of gastric, and head and neck squamous cell tumors obtained from Canadian Biomarker Quality Assurance. A random-trees classifier will be trained on regions of interest, categorizing cells into tumour, immune, and stromal cell types, and applied to the whole tumour sample. Quantifying PD-L1 expression amongst the cell types allows calculation of combined positive score (CPS) and tumour proportion score (TPS), the standard scoring system for PD-L1 expression. Concurrent validity was assessed by comparing DIA and manual scores with ground truth data, determining accuracy of digital scoring.

Results: DIA was capable of detecting PD-L1-positive cells while also classifying them based on cell types. Furthermore, quantification yielded more reliable results, demonstrating greater agreement amongst intraclass scoring than manual assessment. Quantification using DIA demonstrated greater accuracy compared to visual scoring.

Discussion: DIA scoring demonstrated higher intraclass agreement, higher accuracy and precision, compared to visual scoring. Analysis using DIA provided insight into the barriers of scoring, such as staining patterns. Integrating DIA as a supportive tool for pathology lays the groundwork for creating a fully automatic machine-learning system capable of multiple diagnostic tasks across various whole slide images. DIA can potentially standardize biomarker quantification due to improved reproducibility in scoring amongst pathologists

PATHOLOGY

Presenter's Name: Wang, Kelli
Additional Authors: Li G, Vinokurtseva A, Teplitsky JE, Liu H, Hutnik CML
Abstract Title: Targeting Fibrotic Pathways: The Anti-Scarring Potential of Losartan Following Glaucoma Surgery

Abstract:
Introduction: Glaucoma is the leading cause of irreversible blindness, affecting over 80 million individuals worldwide. It refers to a spectrum of optic neuropathies of which the only modifiable risk factor is intraocular pressure, and surgery is the most definitive way to lower it. The surgery creates an alternative drainage pathway for fluid, thereby reducing the risk of glaucomatous progression. Unfortunately, excessive post-surgical subconjunctival scarring driven by Human Tenon's capsule fibroblasts (HTCFs) results in surgical failure by blocking the newly created drainage pathway. Mitomycin C is the current gold-standard treatment for postoperative scarring, but it exhibits unreliable effectiveness and causes many adverse effects. Safer, more effective, and more predictable ways to modulate post-surgical wound healing would be a major advancement. Exploring the off-target effects of therapeutic agents that are already used represents a novel approach to drug discovery. Angiotensin receptor blockers (ARBs) are oral medications widely used to treat systemic blood pressure. This research explores the potential of ARBs when administered in the eye, to downregulate TGFβ1 induced HTCF myofibroblast transdifferentiation through modulation of the renin-angiotensin system. The aim of this study is to assess the anti-fibrotic effects of losartan (LS), an ARB, on HTCFs in an in vitro model.

Methods: Optimal concentrations of both LS and Angiotensin I (AngI) were determined by creating a dose-response curve using assays of cellular metabolic activity (MTT) and cell death (LDH). Primary cultures of HTCFs generated from glaucoma patients were pre-treated with 2, 20, or 40 μM of LS for 24h, then 0.1 or 100 μM of AngI for 48h. When the appropriate treatment concentrations are determined, Western blot and immunofluorescence assays will be performed to examine the anti-fibrotic effects of LS.

Results: The optimized LS concentration of 20 μM decreased cell metabolism, while having minimal effect on cytotoxicity. Meanwhile, the optimal AngI concentration was 0.1μM and caused an increase in cellular metabolic activity with little effect on cytotoxicity.

Discussion: The behaviour of HTCFs when exposed to LS and AngI supports the potential for LS to be further explored as a wound modulating agent. Further experiments aimed at investigating the effects on pro-fibrotic proteins such as αSMA and MMP-9 will provide premise to explore this novel off-target effect of LS.

Presenter's Name: Whittier, Abigail
Additional Authors: Rutledge A, Knauer M, Stevic I
Abstract Title: Validation of the Roche Epstein-Barr virus serology assays

Abstract:
Introduction: Epstein-Barr virus (EBV) is associated with several diseases, including infectious mononucleosis and Hodgkin lymphoma. EBV serology testing can be used to characterize infection status and to assess the risk of EBV-associated diseases. At London Health Sciences Centre, EBV viral capsid antigen (VCA) IgG and IgM antibodies are tested on a Diasorin Liaison XL analyzer in-house, and serum samples for anti-EBV nuclear antigen (EBNA) IgG antibody testing are sent out to the Public Health Ontario Laboratory (PHOL). The aim of this study was to evaluate the performance (precision and method comparison) of EBV VCA IgG and IgM and EBNA IgG assays on the Roche e801 analyzer to consolidate and standardize these assays with a large panel of other infectious disease serology tests.

Methods: Precision was assessed using negative and positive quality control (QC) materials in the 5x5 manner. Instrument comparison involved analyzing both leftover patient serum samples which had been tested on the Diasorin Liaison XL, and anonymized PHOL serum samples tested on Bio-Rad Bioplex 2200, on the Roche e801. The Roche e801 was then compared qualitatively against the comparator methods for equivalency using predefined acceptable performance criteria.

Results: For precision, the negative and positive QC for EBV VCA IgG and IgM, and EBNA IgG Roche assays had total coefficients of variation of 2.8% and 3.6%, 1.6% and 1.5%, and 1.7% and 3.2%, respectively. The EBV IgM comparison had overall, positive, and negative agreements of 77.9%, 55.9%, and 100.0%, respectively and a Cohen's kappa coefficient of 55.9%, n=68. The EBV VCA IgG comparison between the Roche assay and the Diasorin Liaison XL assay had overall, positive, and negative agreements of 89.7%, 100.0%, and 75.6% respectively, and a Cohen's kappa coefficient of 78.2%, n=97. The Roche EBV VCA IgG assay was also compared to the Bioplex 2200 assay and had overall, positive, and negative agreements of 91.3%, 82.5%, and 100.0%, respectively and a Cohen's kappa coefficient of 82.5% n=80. The EBNA IgG comparison between the Roche assay and the Bioplex 2200 assay had overall, positive, and negative agreements of 97.5%, 95.0%, 100.0%, respectively and a Cohen's kappa coefficient of 95.0%, n=80.

Discussion: The precision and method comparison results for all three Roche assays were clinically acceptable. Variation in data observed, particularly for IgM assays, may be due to variation in assay formulation.

PATHOLOGY

Presenter's Name: Zhang, Richard
Additional Authors: Hosseini N, Shooshtari P
Abstract Title: Identifying shared and distinct gene regulatory mechanisms across 8 different psychiatric disorders

Abstract:
Introduction: The pathophysiology underlying psychiatric disorders and the shared/distinct mechanisms between them are not well understood. To date, several genome-wide association studies (GWASs) have found tens to hundreds of genomic loci associated with psychiatric disorders. Most of the disease risk variants (i.e., SNPs) found by these GWASs lie in regulatory regions, specifically open chromatin sites in brain cell types. To investigate the gene regulatory effects of these SNPs, an integrative analysis of GWAS and single cell ATAC-seq (scATAC-seq) data can be performed. Previous data integration studies mainly focus on one disease, and a comprehensive comparison across multiple diseases is lacking. We aimed to integrate 11 psychiatric GWAS datasets, encompassing 8 disorders, with 3 brain scATAC-seq datasets, to test the hypothesis that shared/distinct cell type-specific gene regulatory mechanisms across psychiatric disorders can be found through a data integration approach.

Methods: We obtained GWAS results for 8 psychiatric diseases from the Psychiatric Genomics Consortium, GWAS Catalog, and PubMed. We used 3 scATAC-seq datasets containing cell types from the developing human and mouse brain, and adult human brain. A data integration pipeline developed at the Shooshtari lab, incorporating standard R packages and command line tools, was used to integrate GWAS and scATAC-seq data. Our pipeline prioritized SNPs, cell type and developmental stage-specific open chromatin peaks, transcription factors, and genes relevant to each disease. We identified pertinent pathways using common pathway analysis tools, GREAT and EnrichR. Finally, we compared results across the 8 disorders.

Results: Our analysis found a median of 340 SNPs influencing TF binding, 46 open chromatin peaks, 54.5 TFs, and 14 genes associated with each psychiatric disease. A total of 52 biological pathways were linked with at least one disorder. Notably, the TFs ETV3 and DLX6 were each prioritized in 4 different psychiatric disorders. The gene TMEM106B was linked to Alzheimer's disease, depression, and anxiety. Additionally, three genes (SMG6, FAM53C, and CDC25C) were found relevant to both schizophrenia and bipolar disorder.

Discussion: Our findings support the results of previous studies which proposed relationships between groups of psychiatric disorders, and the roles of specific genes, TFs, and pathways in different disorders, while providing novel insights into disease mechanisms.