THE UNIVERSITY OF BRITISH COLUMBIA

School of Biomedical Engineering

Faculties of Applied Science and Medicine

SYNERGY RESEARCH DAY

Trainee Talks

10:30AM | Gordon B Shrum; B1001

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Using Single-Cell Metabolomics to Study Heterogeneity in Stem Cell-Derived Pancreatic Beta Cells

Aria Donthineni

Dr. Francis Lynn's Lab

Type 1 Diabetes (T1D) is an autoimmune disease characterized by the destruction of pancreatic beta cells, disrupting glucose homeostasis. While islet transplantation can restore normoglycemia without relying on insulin injections, its use is limited by donor scarcity. Stem cell-derived beta cells (SC-β) offer a promising alternative, but current in vitro differentiation protocols yield immature SC-β cells with reduced glucose-stimulated insulin secretion. Single-cell transcriptomic and epigenomic studies reveal metabolic immaturity and heterogeneity during SC-β differentiation. Prior bulk metabolomic methods lack the resolution to assess this at the single-cell level. This project aims to characterize the metabolic heterogeneity of SC-β using single-cell energetic metabolism by profiling translation inhibition (SCINETH), a flow cytometry-based technique for analyzing single-cell metabolism to discern the metabolic capacities and dependencies. We hypothesized that understanding the metabolic heterogeneity during SC-β differentiation, and if it can be altered by metabolites and small molecules, is key to further improve differentiation protocols. Our previous research has shown that Compound A, a glucokinase activator that enhances the first step of glycolysis, increased expression of Neurogenin 3 (NGN3), a key transcription factor in endocrine lineage specification. [f1] We aimed to understand how Compound A influences the metabolism of NGN3-expressing cells by SCENITH. Preliminary findings suggest the presence of a metabolic shift from glycolysis to oxidative phosphorylation between day 12 and day 14 of differentiation. For samples without Compound A treatment, oxidative phosphorylation increased in capacity from day 12 to day 14 while glycolysis decreased in dependency. Samples exposed Compound A maintained a higher glycolysis dependency.

Quantifying Seated Pregnant Occupant Anthropometry Using 3D Imaging

Dean Harris

Dr. Peter Cripton's Lab

Background: There is an inefficient amount of research done on the safety of pregnant vehicle occupants, although motor vehicle crashes are the leading cause of death for pregnant people and fetuses in the United States and Canada . Seatbelts have been primarily evaluated with male anthropomorphic test devices (ATDs), but females and males have large differences in body size and shape. The differences are even greater when comparing pregnant vehicle occupants to males. This research study aims to quantify the seatbelt fit of a large (eventually 500) cohort of pregnant people by analyzing belt fit relative to external anatomy.
Methods: Each participant is seated in a simulated vehicle seat and 3D scanned with a LiDAR scanner. Markers are placed on the left and right Anterior Superior Iliac Spine (ASIS) and on the sternoclavicular (SC) joint . Each participant's scan is analyzed using 3D Slicer and Meshmixer. Specifically, the distance from the belt to key bony anatomy is measured to quantify belt fit.
Results: An initial analysis of the scans has shown that the seatbelt is offset from the ASIS bilaterally and being shifted away from the sternum in the axial plane. The enlarged pregnant abdomen pushes the seatbelt away from the desired path and prevents the seatbelt from engaging with the ASIS. The markers representing the ASIS usually sit higher than where the seatbelt lays along the waist. Additionally, the seatbelt tends to engage more with soft tissue like the breasts instead of the sternum.
Discussion: Our goal is to improve the understanding of seatbelt fit for pregnant occupants, quantify anthropometry, and educate the public on how seatbelts should fit during pregnancy. This study also provides insight on how to quantify seatbelt fit for pregnant occupants, supporting the advancement of injury prevention in motor vehicles.

Developing In-Vitro Functional Assays to Investigate the Efficacy of iPSC-derived CAR T cells with Engineered Intracellular Domains

Victoria Chong

Dr. Peter Zandstra's Lab

Chimeric Antigen Receptor (CAR)-T cell therapy involves harnessing T cells with engineered receptors to precisely kill cancer cells and has shown remarkable efficacy against hematologic malignancies. However, as a patient-specific process, it faces barriers in accessibility due to high cost, long manufacturing time, and variability in patient-derived T cell quality. Induced pluripotent stem cell (iPSC) derived CAR-T cells present a promising alternative due to their unlimited self-renewal, ease of genetic engineering and controlled differentiation into T cells, giving rise to "off the shelf" T cell therapies. A major pitfall of the iPSC-to-T cell pipeline, however, is CAR tonic signaling, where differentiation becomes skewed toward undesired innate-like phenotypes. To address this, we are engineering CAR intracellular domains (ICDs) to modulate tonic signaling and guide differentiation toward functional T cells. Results have demonstrated that a novel ICD can reduce tonic signaling and increase progenitor T cell output by 5-fold. A significant challenge in cell therapy development is that promising preclinical research often fails to improve patient outcomes in clinical trials. Therefore, it is critical to develop robust in-vitro and in-vivo functional assays to characterize iPSC-derived CAR-T cells and predict clinical performance. This work aims to develop in-vitro functional assays consisting of (1) cytotoxicity assays to quantify tumor cell killing, (2) cytokine production assays to assess activation and potency, and (3) rechallenge assays to determine long-term therapeutic function. This research advances our understanding of how iPSC-derived CAR-T cells compare to conventional PBMC-derived cells and contributes to the development of universal CAR-T cell therapies.

Structural MRI changes and neurocognitive correlates in adults with moderate-severe complexity congenital heart disease

Yundi Wang

Dr. Thalia Field's Lab

Background: Research on neurocognitive outcomes and structural brain findings in adults with congenital heart disease (ACHD) remains limited with the majority of studies focusing on infants and youth. Here in this study, we investigated differences in neurocognition, quality of life and MRI volumetric data in an older cohort of adults with moderate and highly complex CHD compared to controls. We also examined sociodemographic, medical and educational determinates of neurcognition and quality of life (QoL) in ACHD.

Methods: As part of the SEARCH study, participants aged ⩾18 years with a history of moderate or severe CHD were recruited from the Pacific Adult Congenital Heart Disease clinic (n=99). Participants underwent brain MRI, neurocognitive assessment using MoCA and the NIH Toolbox Cognitive Battery; and mood and QoL assessment using the PHQ-9 and EQ-5D-5L, respectively. Neuroimaging, cognition and QoL results from ACHD were compared with established control cohorts (Rebchuk et al., 2022)(n=53), and UBC's Healthy Volunteer MRI Registry (n=25)).

Results: A total of 96 ACHD (76 moderate and 20 severe CHD) participants were included in analysis. Adults with severe, but not moderate, CHD had worse PHQ-9 scores when compared to control. EQ-5D-5L scores were not different between participant groups. NIHTB-CB detected cognitive impairments in ACHD not evident on MoCA. ACHD exhibited reduced total brain volumes, as well as decreases across multiple cortical, subcortical, and hippocampal regions of interest, with the extent of reduction increasing with CHD severity. Notable cortical and hippocampal regions significantly associated with NIHTB-CB scores include the supramarginal gyrus, CA1 head and subiculum head. History of hypertension and recreational drug use were associated with worse MoCA and NIHTB-CB scores, respectively. Alcohol consumption was associated with worse MoCA, NIHTB-CB and EQ-5D-5L scores.

Conclusion: In this older ACHD cohort, cognitive impairments and brain volume reductions were evident, particularly with increasing CHD severity. Modifiable lifestyle factors such as hypertension and risky health behaviors are potential targets for intervention to improve cognition and QoL. Our findings support routine neuroimaging and cognitive screening in this patient population, especially for those with severe CHD.

Modeling Atrial Fibrillation Using Patient-Derived hiPSC Cardiomyocytes

Raj Dhillon

Dr. Zachary Laksman's Lab

Atrial fibrillation (AF) represents the most common cardiac arrhythmia globally, significantly increasing risks for stroke and heart failure. Despite its clinical importance, the specific genetic and cellular mechanisms underlying AF are not fully clear. AF is a complex polygenetic disease influenced by over 100 genetic loci identified through genome-wide association studies (GWAS). Most of AF-associated single nucleotide polymorphisms (SNPs) are located within non-coding, regulatory regions of the genome, suggesting that they impact disease risk by altering transcriptional factor binding. This project aims to address this critical knowledge gap by investigating how genetic variations contribute to AF pathology in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). Our lab is using a high-throughput approach called Massively Parallel Reporter Assay (MPRA). This assay will allow us to systematically identify genetic variants associated with AF that functionally influence gene expression. In our MPRA, we have included approximately 11,317 candidate SNPs associated with AF and other cardiac traits identified through GWAS. We are currently working on optimizing our hiPSC- CMs differentiation protocol as this will help support reliable downstream experiments. we are refining the differentiation protocol by optimizing parameters such as cell seeding density, media composition, and culture conditions. Next, we will test both 2D and 3D cell culturing to assess changes in scalability, electrophysiological activity, and contractility resulting due to different culture conditions. Finally, we will also test a novel 'cell village pooling' approach, in which multiple genetically diverse hiPSC lines are differentiated together to evaluate how genetic context influences cardiomyocyte development and function.

Deep Learning on PPG Signals for Sleep Apnea Detection in Children

Corliss Chu

Dr. Calvin Kuo's Lab

Sleep apnea is characterized by complete pauses in breathing lasting at least 10 seconds during sleep. Currently, polysomnography (PSG) is the standard diagnostic method. However, this laboratory-based method is costly, limited in accessibility and reliant on sleep specialists' expertise. To address the above limitations, wearable devices utilizing artificial intelligence (AI) have been increasingly explored as tools for automated detection and pre-screening for symptomatic individuals.

Apnea episodes often result in changes in blood oxygen saturation (SpO_2). While SpO_2 is readily available from a pulse oximeter, it is a derived metric calculated from the underlying photoplethysmography (PPG) waveform. Because SpO_2 values are averaged over a period of time, they can mask subtle pulsatile and respiratory changes. As a result, AI algorithms developed solely with SpO_2 may fail to identify certain apnea events. This project, therefore, investigates the use of raw PPG signals as input to a deep learning model for apnea detection.

A convolutional neural network was designed to directly learn the spatial and temporal patterns from the time-frequency representations of the PPG signal. The model uses templates that span the entire frequency range while sliding along the time axis, aiming to identify when and where key signal features are most prominent. The current model achieves a sensitivity of 67% for detecting apnea events. While further improvement is needed, combining physiology-driven data processing with a CNN architecture forms the basis for creating an accessible and reliable apnea detection tool for children.

Evaluating a Novel Bile Acid for Treating Steroid-Insensitive, Type 2-Low Asthma

Jessica Xin

Dr. Kelly McNagny's Lab

Type 2-low asthma is a severe endotype of asthma that affects over 100 million people worldwide. These patients respond poorly to conventional corticosteroid treatments and have severe neutrophilic inflammation and airway remodelling. It is driven predominantly by Type 3 immune responses involving IL-17-producing T helper 17 (Th17) cells and group 3 innate lymphoid cells (ILC3s), both expressing the transcription factor RORγt. Isolithocholic acid (isoLCA) is a secondary bile acid metabolized in the human gut and has emerged as a potent and specific inhibitor of RORγt, which can suppress pathogenic Th17 and ILC3 activity and subsequent neutrophil recruitment. We assessed the potential of isoLCA to inhibit RORγt-expressing cells in a Type 2-low asthma mouse model both at the time of exacerbation and after immune memory is established. Through histological analysis and spectral flow cytometry of fresh bronchoalveolar lavage fluids (BALF) and lungs, our results indicate that oral administration of isoLCA significantly reduces neutrophil inflammation in the airways. Intracellular staining for transcription factors and cytokine secretion shows that isoLCA suppresses RORγt-expression (Th17 and ILC3 cells) and IL-17A cytokine-producing cells in the lungs. These findings demonstrate isoLCA's therapeutic potential in treating Type 2-low and steroid-insensitive asthma. Future directions involve determining the therapeutic duration and kinetics of isoLCA in vitro and in vivo through the development of an RORγt suppression assay and quantifying bulk proteomics via Olink analysis of BALF supernatants.

The role of Inflammatory bowel disease in the neurological immune response to the development of Alzheimer's disease pathology in mice

Leo J. Chung

Dr. Annie Ciernia's Lab

People with inflammatory bowel disease (IBD) are six times more likely to develop Alzheimer's disease (AD), but the mechanisms connecting them are unknown. IBD is characterized by changes in the intestinal microbiota, which result in intestinal and systemic inflammation, altered microbiota metabolite production, and microglia dysregulation. Short chain fatty acid (SCFA) producing bacteria are decreased in mouse models of IBD, which can lead to inflammation. Microglia – the resident immune cells of the brain – respond to changes in gut inflammation and SCFA levels, maturing abnormally in IBD mice models. Interestingly, inflammation, decreased SCFA levels, and microglial dysfunction are associated with development of Alzheimer's disease (AD). Specifically, microglia are important in regulating amyloid-beta plaque content, and alterations to microglial regulation contribute to plaque accumulation. We hypothesize that the IBD microbiome both induces IBD-associated inflammation and decreases SCFA levels, disrupting microglial function and linking gut dysbiosis to AD pathology through increased amyloid-beta deposition and impaired immune responses. This study includes four cohorts of mice; 1) healthy-control (HC) mice, 2) IBD mice (germ-free mice with human IBD microbiota), 3) AD mice (5xFAD mutation causing AD pathology), and 4) IBD-AD mice. Immunohistochemistry was performed on brain sections of adult mice to determine amyloid-beta plaque concentration and microglial activity. We hypothesize that IBD-AD mice will exhibit the most severe AD pathology, and the lowest amount of plaque-associated microglia. This study will help us better understand the connection between IBD, AD, and the role of microglia. Examining the microglial and plaque-associated pathologies will provide a better understanding of the mechanisms behind IBD and AD, and future studies will build towards therapeutics to reduce the risk of AD in IBD patients.

Developing a Dendritic Cell-Targeting Cancer Vaccine

Jae-Yoon Kim

Dr. Yanpu He's Lab

The immune system plays a critical role in controlling tumour development and metastasis. Cancer immunotherapies aim to eliminate tumours by activating certain immune signalling pathways that drive potent anti-tumour responses. Among these pathways, stimulator of interferon genes (STING) has recently emerged as a promising therapeutic target. Our lab has been developing protein-based STING signalling complexes for cancer treatment; however, current designs lack selectivity for immune cells where activation is most effective. To address this limitation, we designed a new STING fusion protein to target dendritic cells (DC), a key antigen-presenting immune cell population.

Producing this recombinant protein in E. coli presented two major challenges: endotoxin contamination and low protein purity. We addressed these issues by creating a new E. coli strain that combines an endotoxin-free background with rare codon tRNAs, enabling cleaner, higher-yield production of the STING fusion protein. This advancement reduces toxicity concerns and provides a platform to evaluate its function rigorously. We will assess DC targeting and antigen-presentation efficiency ex vivo using a DC cell line, and validate its therapeutic potential by testing its efficacy in eliciting anti-tumoral immunity in mouse cancer models.

Characterization of Structural Variants in Key Metastatic Prostate Cancer Driver Genes

Tiffany Xie

Dr. Alexander Wyatt's Lab

Genetic testing is recommended for metastatic prostate cancer (mPCa), as genomic alterations in the patient and their cancer can impact prognosis and treatment selection. Structural variants (SVs) are a class of large genomic alterations that can modulate mPCa driver genes. However, they remain poorly characterized, as most SVs occur in noncoding regions not evaluated by clinical assays. Here, we aim to establish the frequency and distribution of SVs within mPCa driver genes, including DNA damage repair (DDR) and tumour suppressor genes.

We analyzed 3971 blood plasma cell-free DNA (cfDNA) samples from a unique meta-cohort of 2279 mPCa patients. To facilitate SV detection, samples were sequenced on a panel covering coding and non-coding regions of mPCa genes. Mutations, copy number alterations, and SVs were identified using a custom bioinformatics pipeline.

Among 1647 patients with detected tumour DNA, 479 had a pathogenic SV in at least one DDR or tumour suppressor gene. PTEN, TP53, RB1, and BRCA2 were the most frequently impacted genes with SVs detected in 219, 127, 90, and 50 patients respectively. Within these genes, 82.3% (533/648) of SVs had breakpoints exclusively in intronic or intergenic regions. Therapy-actionable BRCA2 gene alterations were found in 163 patients, of which 25 were attributed solely to SVs and in 25 patients, SVs contributed to biallelic BRCA2 inactivation. Overall, SVs impacting clinically relevant genes are frequent in mPCa and may be missed with current clinical assays. Future work analyzing the association between SVs and patient outcomes will clarify the clinical relevance of SVs.