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2022-2023 IgNITE Medical Case Competition: CardioRespiratory Medicine

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Abstract
The IgNITE Medical Case Competition is an annual research case competition organized by students across North America. Our mission is to provide high school and university students the opportunity to gain valuable research experience while networking with industry professionals. Each year, students in teams of 1-4 are paired with an experienced mentor to develop and present a novel research proposal within a specified theme of the competition. Students are taught the fundamental scientific principles underlying three lab techniques which can be applied in their proposal for the competition or used in their future research career. This year's theme was CardioRespiratory Medicine, and competitors learned about RNA Sequencing, Model Organisms, and *In vivo* imaging systems. Furthermore, the IgNITE community grew internationally this year with over 550 high school and university students participating in the competition. Presented in this booklet are the Top 40 teams' abstracts and we invite you to visit our website (www.ignitecompetition.org) to watch their associated elevator pitch videos. We hope you enjoy reading through some of this year's top proposals and encourage you to join our ever-growing community.

Keywords: IgNITE Medical Case Competition; Cardiorespiratory; RNA Sequencing; Model Organisms; *In vivo* imaging systems; Undergraduate; High School; Case Competition; Medicine

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Conference Abstracts

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IgNITE Abstracts

Comment l'édition du gène ITPKC peut empêcher la régulation négative de l'activation des lymphocytes T via la voie Ca2+/NFAT, associée à la maladie de Kawasaki

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La maladie de Kawasaki (KD) est une vascularite systémique pédiatrique d'étiologie inconnue pour laquelle une influence génétique est suspectée. L'allèle C du gène ITPKC, ce qui code l'enzyme inositol-trisphosphate 3-kinase, a une relation imminente avec l'inactivité des cellules T dans la vascularite. Ce dernier entraîne un risque accru de lésions coronariennes, qui est un symptôme principal de la maladie de Kawasaki. De plus, un polymorphisme nucléotidique (PSN) dans le gène ITPKC appeler rs28493229 a été associé à la pathogenèse de KD. L'ITPKC réduit l'activation des cellules T dans la vasculopathie et des observations confirment que l'activation restreinte de ces cellules déclenche une réaction dans laquelle les lésions coronaires et le KD vont progresser. Notre objectif avec cette proposition de recherche est d'utiliser l'édition de gêne pour réguler l'utilisation de cellules nuisibles qui ont un impact sur le cours de cette maladie. L'édition de gènes est une méthode très efficace pour empêcher un gène de se coder dans des parties ciblées de notre ADN pour le remplacer ensuite par une séquence mutée. Les cellules immunitaires seront incubées et récoltées in vitro afin de subir un test de cytométrie en flux (FCM) pour analyser le nombre de lymphocytes T dans divers groupes de traitement et un groupe témoin. En utilisant CRISPR (Lanese & Vidyasagar, 2022), une technologie d'édition de gènes fréquemment utilisée en laboratoire, on peut programmer une enzyme Cas9 attachée à un ARN de guidage, pour cibler notre gène ITPKC dans les groupes de traitement. Les résultats attendus sont que le gène ITPKC favorise la régulation négative des lymphocytes T, qui est très étroitement liée à la maladie de Kawasaki. Cela va alors améliorer nos connaissances sur la maladie ainsi que sur le traitement recommandé pour lutter contre cette dernière.

Investigating NF-kB inhibition as potential epithelial-mesenchymal transition and NSCLC treatment

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Lung cancer is the third most common cancer among humans. With a survival rate of 18.6%, it has a lower survival rate than colon, prostate, and ovarian cancer combined. Recently, various studies have demonstrated the role of inflammation and epithelial-mesenchymal transition (EMT) in non-small cell lung cancer (NSCLC). However, a lack of research exploring potential therapeutic targets for NSCLC in this field remains. Moreover, in tumors, nuclear factor-kappa B (NF-kB) was found to be constitutively activated by growth factors and current anti-cancer therapeutics. Therefore, this study aims to (i) investigate the viability of the highly selective allosteric NF-kB inhibitor, BMS-345541, for NSCLC, and (ii) to explore the correlation between NF-kB, inflammation, and EMT. Given its pro-apoptotic role in research for asthma and prostate cancer, we propose administering BMS-345541 by oral gavage to murine NSCLC models. To confirm viability, we will examine metastatic properties, apoptotic index, and transforming growth factors beta 1 (TGFB1) levels via cell invasion assay, TUNEL assay, BALF collection, and ELISA assessment. Furthermore, we will quantify pathological changes and track EMT regulator levels via immunohistochemical staining and imaging of lung tissue, mRNA reverse transcription, polymerase chain reaction analysis, and western blot analysis. A downregulated expression of TGFB1 and vimentin, as well as an increased apoptotic index and expression of E-cadherin, will indicate treatment efficiency and prove NF-kB and EMT correlation. Succinctly, this study may provide novel therapeutic targets, insight into anti-cancer drug resistance, and contribute to current scientific knowledge on inflammatory diseases.

Preventing atrial fibrillation in hypertrophic cardiomyopathy using ACEIs and ARBs

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Hypertrophic cardiomyopathy (HCM), a genetic cardiovascular disease, is the leading cause of cardiac death in young people, often due to atrial fibrillation (AF). AF is generally treated using antiarrhythmics and anticoagulants, which have adverse side effects after long-term use, and are therefore unsuitable for HCM patients. AF is characterized by a rapid and irregular atrial heartbeat, marked by a short action potential (AP) and atrial effective refractory period (AERP) in atrial cardiomyocytes. Prior studies have indicated that the renin-angiotensin system is involved in lowering AP duration and AERP. It has been hypothesized that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which block the renin-angiotensin system, could prevent AF. Therefore, in this study, we seek to examine the viability of ACEIs and ARBs as prophylactic measures against the development of AF in HCM patients. To test this, we will extract atrial cardiomyocytes from HCM patients by performing enzyme dissociation on myocardial tissue. We will then treat the isolated cardiomyocytes in vitro with an ACEI, an ARB, a combination of both, or a control saline solution, and use the patch-clamp technique to determine the frequency and duration of their APs. We expect AP duration and AERP to be longer in treated cells, while neither medication will provide a greater advantage, and, as prior research suggests, the combination will not yield significant benefits. The results of this study will present a new preventative measure against AF for HCM patients which would be safe for long-term use.

Development of non-invasive RNA therapy for drug-resistant cystic fibrosis mutations

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Cystic fibrosis (CF) involves mutations in the trans-membrane conductance regulator gene (CFTR), causing faulty chloride channel activity. Consequently, chloride and bicarbonate transport are impaired, which reduces mucus transport and clearance at the cell surface epithelium, leading to the development of lung infections. The R553X mutation is the 4th most common disease genotype, in which premature mRNA termination occurs. Due to the complete absence of CFTR protein, mutant R553X is unresponsive to standard drug treatments, unlike other CF genotypes. Therefore, this study proposes a non-invasive form of RNA therapy, delivered through nebulization, as an alternative treatment for this population. Nebulization delivers aerosolized RNA products directly to lung epithelial cells, while minimizing systemic exposure. We will deliver lipid nanoparticles containing CFTR mRNA or a placebo to CFTR1m1HGU mice, which have diminished CFTR protein levels, through nebulization. The lipid nanoparticles will be tagged with epithelial sodium channel (ENaC) antibodies to

target epithelial cells. Miniaturized bronchoscopy and patch-clamping will be performed to assess chloride and sodium channel activity of the CFTR protein. Additionally, bronchoalveolar lavage and immunohistochemistry will be performed to measure mucus viscosity. We expect that the mice treated with CFTR mRNA should have significantly higher chloride channel activity, lower sodium channel activity, and decreased mucus viscosity, resembling healthy lung epithelial cells. Long-term lung function will be assessed through spirometry and methacholine tests. These results could provide insight into a novel treatment for CF patients, particularly for drug-resistant cohorts. Non-invasive RNA therapy could enhance the quality of life for thousands worldwide.

Butyrylcholinesterase in the pathogenesis of sudden infant death syndrome

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Butyrylcholinesterase (BChE), an enzyme associated with the autonomic nervous system, catalyzes the degradation of the choline family of neurotransmitters and is involved in neurodevelopment. BChE supports the role of acetylcholinesterase, a cholinergic enzyme in postsynaptic neuromuscular junctions, which terminates nerve relay functions by hydrolyzing the neurotransmitter acetylcholine. Sudden infant death syndrome (SIDS) affects 1 in 2000 healthy newborns and is manifested by cardiorespiratory failure and autonomic defects. Low serum levels of BChE have been correlated with SIDS, indicating it may contribute to cardiorespiratory arrest. We hypothesize that reduced expression of the BChE enzyme will cause respiratory neuron dysfunction and result in SIDS. We will perform single-cell RNA sequencing on different respiratory neuron groups, including the dorsal, ventral, and pontine respiratory groups extracted from C57BL/6 mice (n=3) according to the protocol established by Johnson et al. on knockout of BChE and wild-type mice. In addition, we will perform in-vivo high-speed fluorescent imaging of the respiratory motor neuron groups in the knockout of BChE and wild-type C57BL/6 mice (n=5) following the injection of a Ca 2+ sensitive dye, allowing us to visualize the neural activity of these neuronal groups in real-time. The single-cell RNA sequencing data may show differences in ion channel expression in generating the neuronal activity of respiratory neurons. These findings may provide mechanistic insights into the role of the BChE enzyme and the pathogenesis of SIDS to provide a foundation for developing therapeutics against SIDS in newborns.

The characterization of Kawasaki disease-specific genes using CRISPR-Cas9

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Kawasaki disease (KD) is a systemic vasculitis and the leading cause of acquired heart disease for children across several continents. KD is triggered in genetically predisposed patients by environmental stimuli resulting in abnormal inflammatory reactions. Current research focuses on upregulated genes, however, the characterization of genes specific to KD is largely absent. We aim to identify genes specific to KD that could serve as diagnostic biomarkers and therapeutic targets. First, we will conduct whole genome-sequencing of patient samples. Readouts of mutated and differentially expressed genes will be investigated as candidate genes. Candidates will be investigated in vitro, using CRISPR-Cas9 knockout assays, and will be targeted in patient peripheral blood mononuclear cells (PBMCs). The candidates in healthy and patient PBMCs will be assessed through inflammatory assays, notably enzyme-linked immunosorbent assays (ELISA), to determine the severity of inflammation through cytokine concentration. Finally, we will create an in vivo system using the L. casei wall extract mouse model that mimics KD. In this model, CRISPR-Cas9 will be used to knockout the candidates that provided the most significant effects from our in vitro screen. We will then conduct assays to determine the effect of genes on KD and off-target effects. We expect specific genes to show a reduced inflammatory response when knocked out by CRISPR-Cas9. Though it has been over 50 years since KD was first described, there is still no formal diagnostic test. The characterization of specific genes is crucial to the early diagnosis and treatment of KD.

Sonic machine learning evaluation system for interstitial lung disease diagnosis

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Interstitial lung disease (ILD) comprises many parenchymal lung disorders characterized by clinical phenotypes displaying inflammation and fibrosis. ILD has a prevalence of approximately 256 per 100,000 people, and the estimated median global

burden of ILD equates to 51% of a country's GDP per capita, ranging between 14 - 180% in Western nations. Medical professionals misdiagnose ILD cases 40% of the time on average leading to delayed diagnosis. Of individuals diagnosed with ILD, 55% receive at least one misdiagnosis, and 38% receive more than one before final diagnosis. The median time before the onset of initial symptoms and initial misdiagnosis to the final diagnosis was 7 months and 11 months, respectively. Of these individuals, almost 1 in 5 reported a delay greater than 3 years. Several machine-learning techniques have been applied for auscultation of the lungs, outperforming doctors' classification success rates with F1 scores ranging between 85% and 85.7%, with area under curve (AUC) values between 80.5% to 92%. To enhance diagnostic speed and accuracy, we propose the Sonic Machine Learning Evaluation System (SMLES). SMLES will convert wav files to fast Fourier transformations (FFTs) to create sound frequency magnitude spectra. Collected FFTs will be inputted into an algorithm leveraging linear discriminant, linear support vector machine (L-SVM), quadratic SVM, and k-nearest neighbor. SMLES reports if a condition is present and if so, which condition with a predicted F1 score and AUC over 90%. This tool can be leveraged to improve diagnosis and outcomes associated with ILD.

Potential of MenSCs to recover damaged myocardium in cardiac disease

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Cardiac disease, primarily myocardial infarction (MI), is the second leading cause of death in Canada, affecting 2.6 million Canadians. With annual cardiomyocyte turnover being only 1-2%, the damage caused by cardiomyocyte loss becomes irreversible. With no treatment available to recover damaged tissue, mesenchymal stem cells (MSC) have shown promising results in cardiomyocyte proliferation and improving cardiac function. However, bone marrow derived MSC are more difficult and invasive to procure, limiting further research. We propose to use explore the possibility of cardiac muscle regeneration by using menstrual blood-derived stem cells (MenSC), a novel type of mesenchymal stem cell with higher abundance and superior proliferative capacities. We propose to investigate this by increasing expression of FGF2, PDGF, IL6, neuregulin-1 and periostin in MenSCs to activate cardiomyocyte differentiation in vitro. These cells, along with undifferentiated MenSCs will then be injected into cardiac tissue to promote angiogenesis via the paracrine effect as well as reduce cardiac fibrosis. We hypothesize that a dual approach through immunomodulation and regeneration will be most effective to recover damaged cardiac tissue and improve cardiac function long term. This will be studied by transplanting transdifferentiated cardiomyocytes grown in vitro using cardiomyocyte rodent cultures and undifferentiated MenSC into MI-induced rat models. Echocardiography and positron emission tomography would be used to assess cardiac function. We expect increases in viable myocardium due to the pro-angiogenesis properties of transdifferentiated cells and immunomodulation of lymphocytes by undifferentiated MenSCs. If found to be effective, this treatment holds the potential to save millions of lives globally.

Direct diagnosis of LTBI using Rv0081 lateral flow assays

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Latent tuberculosis (TB) infection (LTBI), caused by Mycobacterium tuberculosis, is a chronic asymptomatic respiratory infection. In Canada, LTBI prevalence in adult Indigenous populations is 14-30%, which is disproportionately greater than the 7% in Canadian-born non-Indigenous populations. Distrust in healthcare systems and traumatic historical TB practices deters engagement in testing and treatment, allowing LTBI to persist at overwhelming rates. Although non-contagious, 5-15% of LTBI cases will progress to the active disease state, risking transmission and ultimately fatal if left untreated. Research suggests that with current LTBI preventative therapies, the rates of LTBI activation can be decreased by 90% with diagnosis. However, no test to exclusively detect LTBI in affected individuals exists. The purpose of our project is to create and test a lateral flow assay using monoclonal anti-Rv0081 antibodies, derived from Rv0081, a latent-specific antigen. We hypothesize the lateral flow test will detect, with high sensitivity, LTBI in guinea pig blood samples. To assess the sensitivity of the lateral flow assay, we will test samples of 0.02 mL of blood in extraction buffer from two guinea pig groups: 1) asymptomatic TB-inoculated (LTBI) group and 2) TB-negative control group. With monoclonal antibody use, we expect to detect, using gold tagged antibodies, the presence of Rv0081 only in the LTBI group with high sensitivity. In providing a rapid, diagnostic resource, we hope to reduce cases of active TB, combat easily preventable death in rural and Indigenous communities, and work towards the elimination of TB altogether.

Reducing post-ischemic stroke injury by silencing FasL, TNFR-1, and calpain

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Stroke is the third leading cause of death in Canada. Ischemic stroke involves the occlusion of arteries through plaque buildup, reducing blood flow to critical areas of the brain and promoting apoptosis of neuronal cells. Past literature shows that individual silencing of Fas Ligand (FasL) and tumour necrosis factor receptor-1 (TNFR-1) in the intrinsic apoptosis pathway and calpain (Cal) in the extrinsic apoptosis pathway decreases ischemic-stroke-induced brain injury in animal models. We hypothesize that silencing all three proteins to block both pathways will lead to decreased cerebral injury in mice following MCAO-induced cerebral ischemia. siRNAs targeting FasL, TNFR-1, and Cal will be injected intravenously with the RVG-9R cell-penetrating peptide system into 3-month, male C57BL/6J mice for individual and combination silencing. FITC tagged with each siRNA-RVG-9R system will be used to confirm siRNA entry into neurons. The expression of each protein will be quantified in brain tissue using qPCR and western blotting. Infarct volume, neurological assessments examining motor, sensory and cognitive deficit, and a TUNEL assay quantifying apoptotic cells in cerebral tissue will evaluate the effectiveness of the apoptosis-silencing treatments. The mice treated with the siRNA-RVG-9R combination system are expected to have lower mortality rates, smaller infarct volumes, fewer apoptotic neuronal cells, and lower neurological deficit scores than mice injected with individual protein siRNA-RVG-9R systems. This study will provide insight into non-invasive, intravenous treatment to block extrinsic and intrinsic apoptosis pathways to treat post-ischemic stroke mice, leading to future treatments in stroke patients.

Inhibition of TGF-β to prevent cell proliferation in Marfan's syndrome

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Marfan syndrome (MFS) is an autosomal dominant genetic disorder caused by mutations in the FBN1 gene encoding fibrillin-1. MFS patients present with weak structural support in connective tissues, increasing the risk of life-threatening aortic dissections and aneurysms. It has been suggested that fibrillin-1 is unable to bind to and sequester TGF-β in MFS patients, leading to the over-proliferation of connective tissue cells. Current MFS treatments include symptomatic therapy and invasive surgical interventions; they do not address the disease pathophysiology. We hypothesize that inhibition of TGF-β will restore connective tissue homeostasis in MFS patients. To test this, we first identified three small molecules with high predicted affinity for the TGF-β active site using Structure-Based Virtual Screening with the Mcule software and low toxicity under SwissADME. To determine the K_D values of these small molecules for TGF-β, we will perform Fluorescence Energy Resonance Transfer. Second, we will measure cell proliferation on fibrillin-1 knockdown fibroblasts upon small molecule exposure to establish a therapeutic concentration. Finally, we will test our inhibitors on MFS mice ($FBN1^{C1039G/+}$ genotype) by intravenously administering our inhibitors at a constant dosage for a twelve-week period. Following sacrifice, we will measure aortic dimensions and histology, and compare them to non-MFS mice. We expect that the most potent TGF-β inhibitor will restore connective tissue homeostasis as aortic characteristics dictate. These findings are expected to validate the theory that TGF-β signalling leads to cardiovascular complications in MFS patients and lay the groundwork for novel targeted MFS treatments.

Inhaled liposome-packaged oncolytic viruses for treatment of lung cancer

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Lung cancer is the deadliest and second most common cancer, with adenocarcinoma—cancer of mucus-secreting gland cells—as the most widespread subtype. Viral oncotherapy is a cancer therapy that employs viruses that specifically target cancer cells, usually due to reduced antiviral defenses in cancer compared to normal cells. They can attack cancer cells either by direct lysis or by enhancing immune targeting of cancer cells. One of the main challenges in viral oncotherapy is delivery—while oncolytic viruses can be directly injected into tumours, it is often invasive. There are attempts to achieve systemic bloodstream delivery, but innate viral defenses in the blood pose a difficult barrier against it. This study aims to test the efficacy of inhaled viral vectors in targeting lung tumours in mouse models with induced adenocarcinoma through the

LSL-KrasG12D mutation. First, a myxomavirus oncolytic virus will be prepared with a reporter gene that codes for green fluorescent protein (GFP) and packaged into liposome nanoparticles. These particles will be delivered intranasally to the mice using a nebulizer, compared to injection into the bloodstream. In vivo fluorescence imaging for GFP will determine the location and degree of viral replication. Biopsy/histology will determine the tumour progression post-infection. We expect that the inhaled nanoparticle-packaged myxoma virus would effectively localize to lung adenocarcinoma cells and reduce tumour size and progression. This would help in working towards the goal of developing oncolytic therapies for humans, given that there is only one FDA-approved viral oncotherapy (talimogene laherparepvec a.k.a. T-VEC).

Nano-encapsulated mycobacteriophages as an anti-tuberculosis therapy

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Tuberculosis (TB) is a leading cause of death attributed to a bacterial infection by Mycobacterium tuberculosis. The mycobacterial infection is often characterized as either latent or active, with the former being able to be activated over time. TB is an airborne disease activated by the mycobacterial damage to the alveolar macrophages engulfing the pathogen and infection of other tissues. Untreated active TB infection can lead to fibrotic changes in many tissues and ultimately organ failure. The broad anti-biotic resistance of M. tuberculosis hinders disease treatment and stresses the need for alternative therapies. Mycobacteriophages are non-virulent viruses that infect and lyse mycobacteria, thereby shedding the light on a potential treatment for TB. However, the intracellular growth of M. tuberculosis limits mycobacteriophages due to their inability to cross mammalian cell membranes. Therefore, we hypothesize that using mannosylated nanoparticles, a cocktail of mycobacteriophages will enter alveolar macrophages, killing the mycobacterial hosts and terminating TB infection. PLGA nanoparticles containing a cocktail of DS6A, TM4, and D29 mycobacteriophages will be mannosylated to selectively deliver the viruses to alveolar macrophages with mannose receptors. Mannosylated and non-mannosylated empty and loaded nanoparticles will be infused in four guinea pigs' cohorts with latent TB due to the pathogenesis similarity to humans. We expect higher mycobacteriophages load and absence of M. tuberculosis in the sputum and urine of guinea pigs treated with loaded mannosylated nanoparticles compared to the control cohorts, indicating the efficiency of nano-encapsulated mycobacteriophages as an anti-TB therapy in-vivo. This novel therapy proposes a potential treatment for TB-positive patients.

Reprograming the immune system to fight lung cancer

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Due to a lack of effective treatment, non-small cell lung cancer (NSCLC) has a high mortality rate. CAR-T therapy can be used to target specific cancer cells, however, proliferative exhaustion of antigen-specific T-cells presents a major challenge in CAR-T therapy. We hypothesized this can be combated through induced pluripotent stem cells (iPSCs). To derive iPSCs from T-cells, CD3+ cells are infected with Sendai-virus containing Yamanaka factors along with SV40 T-antigen. T-cells used for CAR-T therapy must be HLA-matched to ensure immunocompatibility. To bypass this restriction, we applied a CRISPR/Cas9 system to render hypoimmunogenic pluripotent stem cells by deleting HLA-genes and introducing immunomodulatory factors (PD-L1, HLA-G, CD47). To differentiate the iPSCs into T-cells, they are cocultured with OP9/DLL1 stromal cells, which is confirmed with flow cytometry using CD3, CD4 and CD8 as markers. Lung-specific X (LunX) protein is highly expressed in NSCLC cells but not in normal tissues. Lentivirus is used to introduce LunX-specific CAR and costimulatory signaling domain into T-cells (CAR LunX T-cells). CAR LunX T-cells in the presence of NSCLC cell lines are expected to release of cytokines, detected through indirect-ELISA, and death of NSCLC cells. No significant response is expected when cocultured with other cancer or normal cell lines, signifying the specificity of CAR LunX T-cells. To test for immunogenicity, CAR LunX T-cells are transplanted in humanized mice models, and no significant immune response is anticipated. Our research shows that iPSC-derived CAR LunX T-cells are effective against lung cancer without the need for HLA-matching, implying the use of CAR-T therapy could help millions.

Novel methods for reduction of stent thrombosis using 3D-bioprinted drug eluting stents

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Coronary Artery Disease (CAD) is a leading cause of death worldwide. Current interventions with the highest rate of success include Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG). PCI utilizes new second-generation (G2) Drug Eluting Stents (DES), which are alloy-based and coated with a synthetic biodegradable polymer. These second-generation DES secrete immunosuppressive and anti-proliferation drugs. While PCI is more effective and has better success rates in the short term, the risk of Stent Thrombosis (ST) in the long run is significantly increased. ST is often the result of inflammation at the site of stent deployment. PCI has many advantages such as reduced hospital stay and its ability to be conducted laparoscopically. Thus, a novel method for reducing the significantly increased risk of ST is indicated to improve surgical outcomes. We propose utilizing 3D-Bioprinting techniques to develop and manufacture a fully biodegradable DES, which would not only elute previously mentioned immunosuppressive and anti-proliferation drugs but also anti-inflammatory drugs (G3-DES). Proof of concept would be obtained in-silico by utilizing benchtop tests such as a 3-point bending, conformability, and wall apposition. Pigs would be split into two groups, CAD and Healthy, with each group receiving G2-DES or G3-DES. ST prevalence would be monitored over 18 months. Analysis will include comparison of ST prevalence in G3-DES treated CAD and G2-DES treated CAD pigs. Application of positive results include better surgical outcomes and reduced need for revascularization for patients treated with PCI.

Optimal control of MOG1 drug gene therapy in Brugada syndrome

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Brugada syndrome is an inherited subtype of channelopathy caused by the inability of cardiac sodium ion channels in the heart muscle to function properly due to SCN5A. The mutation in the SCN5A gene leads to uncoordinated heart muscle function and fatal arrhythmias. Currently, the existing treatment methods, beta-blocker and ICD, primarily aim to prevent and alleviate the symptoms of Brugada syndrome instead of fully curing the disease, and these may also lead to severe complications that will stay with the patient for life. The present experiment was designed to use zebrafish as a model organism to combine with gene therapy to test an optimal amount of genetic drug involving the MOG1 protein that can increase the expression of SCN5A and allow the thorough transportation of sodium ions in the heart. There is over 70% homology of human cardiac proteins to zebrafish, so zebrafish can be considered a significantly advantageous model organism. In the experiment, the SCN5A gene from mammals will be implanted after PCR sequencing into healthy zebrafish eggs to model the development of mutated heart internal structure. Then, subcloning the MOG1 protein into an adeno-associated viral vector (AAV) and injecting it into mature zebrafish with gradually increasing units over time while monitoring changes in the sodium ion channel's activity via muti-lead electrocardiogram and observing the structural changes of the ventricular cavity via micromanipulation. Ideally, we will find a constantly increased density of cardiac sodium current and increased expression of sodium ion channels at a specific amount of drug, which can reverse cardiac arrhythmias.

Reducing myocardial reperfusion injury via SERCA stimulation and NKA inhibition

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Current standard treatment for myocardial infarction are reperfusion strategies—however, while reperfusion salvages ischemic myocardium, it can exacerbate damage; a paradoxical phenomenon known as myocardial ischemia-reperfusion injury (MIRI) for which there is no effective therapy. While the pathophysiological mechanisms of MIRI are not fully understood, intracellular Ca 2+ overload and oxidative stress have been identified as two key mechanisms that initiate apoptosis, a significant indicator of reperfusion injury. Previous studies demonstrate that stimulating Sarco(endo)plasmic reticulum Ca 2+ -ATPase (SERCA) activity after reperfusion mitigates Ca 2+ overload while the inhibition of Na+ /K+ -ATPase (NKA) exhibits cardioprotective effects against oxidative stress by attenuating reactive oxygen species (ROS) amplification. Istaroxime is a novel agent used to treat heart failure (HF) by (i) accelerating Ca 2+ re-uptake by increasing the activity of SERCA isoform 2a and (ii) inhibiting NKA; effectively targeting two key mechanisms underlying reperfusion injury. Therefore, this study will evaluate whether istaroxime's proven effect on ameliorating HF will translate in MIRI. To investigate the efficacy of istaroxime as a therapeutic agent, MIRI will be induced in mice models via ligation of the left

anterior descending artery. The experimental models will be subjected to istaroxime infusions prior to reperfusion via removal of the ligation. Finally, myocardial infarct size will be measured after slicing and staining the heart for delineation of the ischemic zones. I expect that the administration of istaroxime in the experimental models will significantly reduce myocardial infarct size, further emphasizing the cardioprotective potential of targeted SERCA activation and NKA inhibition by targeting the underlying mechanisms initiating apoptosis.

Investigating the correlation between vitamin-D3 and the progression of ATTR-CM

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, life-threatening cardiac disease caused by amyloid fibril accumulation in the left ventricle, the heart's main chamber. The most common form of ATTR-CM is a valine to isoleucine substitution at position 122 (V122I) on the TTR gene. Current therapies ease symptoms by delaying fibril development but have undesirable side effects, like sinusitis and cataracts, negatively impacting one's quality of life. Vitamin-D3 (VD3) has been found to reduce the formation rate of amyloid plaques in mice brains, which may have similar implications in the heart. Thus, we propose a VD3-supplemented diet that is innocuous and accessible. C57BL/6 mice will be used, where three groups containing eight mice will be fed anormal, deficient, or enriched VD3 diet, respectively. The TTR gene containing the V122I mutation will be inserted into the mouse metallothionein-I gene to form MT-hMet30 via restriction cloning. MT-hMet30 will then be microinjected into 12 fertilized eggs, and those that successfully integrate the gene will be inbred to produce 24 transgenic mice. Mice will be weaned from VD3 at 3-4 weeks of age and euthanized in 3-month intervals up until 24 months following birth. After euthanasia, amyloid deposits in heart tissue samples will be visualized under a polarization microscope. We predict the mice fed with an enriched diet will have 30% less of an amyloid buildup rate than mice with a normal diet. If effective, VD3 can be tested as a therapeutic agent to lower doses of current high-risk medications.

Exosome-based delivery of Pip4k2c modRNA to prevent cardiac fibrosis

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Cardiac fibrosis (CF) is a remodeling of the heart that occurs in various heart diseases. This leads to long-term heart failure due to myocardial scarring that reduces contractility of the heart. It is known that CF is controlled by TGF-β1, which can convert cardiac fibroblasts into pathological myofibroblasts that cause CF. Preventing this transformation by blocking TGF-β1 in cardiac fibroblasts may be crucial in stopping the development of CF. Research shows that upregulation of the Pip4k2c gene attenuates CF by inhibiting TGF-β1 activity, thereby reducing and even reversing the effects of CF. This project seeks to introduce a novel exosome-based therapy to deliver Pip4k2c modified mRNA (modRNA) specifically to activated cardiac fibroblasts by targeting the fibroblast activation protein-alpha (FAP-α). Following cellular uptake, recipient fibroblasts will translate the delivered Pip4k2c modRNA into proteins that suppress TGF-β1. To test our hypothesis, two groups of mice will undergo transverse aortic constriction to induce myocardial infarction and subsequent CF. One group of mice will receive a control FAP-targeted exosome with no transgene, while the experimental group will receive our therapeutic FAP-targeted exosome carrying Pip4k2c modRNA. Successful delivery of the modRNA-exosome system is expected to transiently increase Pip4k2c expression and reduce TGF-β1 activity in activated cardiac fibroblasts, which will be measured and quantified using RNA-sequencing technology. Overall, we expect to see improved heart function and reduced myocardial scarring in our experimental mouse model, which would characterize this strategy as a possible therapeutic to improve the lives of millions who suffer from cardiac fibrosis every day.

Novel decoy gene therapy for Marfan syndrome targeting AP-1

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Marfan Syndrome (MFS) is a genetic disease affecting connective tissue, with thoracic aortic root (TAR) aneurysm resulting from aortic elastolysis being a predominant complication. It is caused by matrix metalloproteinases (MMPs) -2 and -9 overexpression arising from increased transcription factor activating protein-1 (AP-1) levels. Existing therapies only delay

disease dissemination, thus research towards development of curative treatments especially in models more anatomically related to humans, is essential. To address aortic elastolysis, AP-1 function will be suppressed via binding to RNA transcription factor decoy oligonucleotides (TFDON) delivered through adeno-associated viruses. This study will treat MFS porcine models (Glu433AsnfsX98) because of their high cardiac anatomical similarities to humans. Aortic grafts will be extracted from porcine models and treated with AP-1 TFDON. Live-cell single-molecule RNA imaging will verify successful transduction and oligonucleotide expression after treatment. Treated grafts will be implanted into Marfan and wildtype pigs, and untreated grafts into pigs of control groups. Transesophageal echocardiogram scans of the aortic root will be performed weekly to assess relative TAR dilatation, a key indicator of elastolysis progression and aortic root structure integrity. Throughout the experiment, MMPs expression in aortic smooth muscle cells (ASMC) will be measured with Western Blotting while RNAseq analysis will monitor AP-1 mediated pathways and verify changes in MMPs pathways. AP-1 neutralization through TFDON is expected to reduce MMP-2 and -9 expression in ASMC and decrease TAR dilatation in Marfan pigs. This study paves the way for a novel, safe, and effective treatment that cures MFS without altering the host genome.

Inflammatory markers in subclinical exercise-induced arrhythmogenic right ventricular cardiomyopathy

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Exercise-induced arrhythmogenic right ventricular cardiomyopathy (EIARVC) is one of the leading causes of sudden cardiac arrest in otherwise healthy endurance athletes. This condition is characterized by the widespread death and subsequent replacement of cardiomyocytes with scar tissue in the right ventricle (RV). It is a result of additive hemodynamic stress on right ventricle endothelial cells due to intense exercise and progresses over several years before manifesting as palpitations and arrhythmia. During the subclinical phase of this condition, RV damage occurs with no clinical manifestations. Endothelial cell damage signals the release of pro-inflammatory proteins, essential for regulating the immune response during acute endothelial tissue injury. Hence, this study investigates the relatively unknown role of inflammatory markers interleukin-1β, interleukin-6, interleukin-10, C-reactive protein, tumour necrosis factor-α and transforming growth factor-β in subclinical EIARVC. Inflammatory marker plasma levels will be measured using quantitative ELISAs and ELISpots in a large sample of varsity athletes over several years. Plasma will be retrospectively analyzed to determine if specific inflammatory protein levels were elevated before clinical manifestations. We predict that higher levels of these inflammatory markers are present in the subclinical phase of EIARVC, during which athletes have no overtly detectable symptoms but are still at risk of sudden cardiac arrest. Thus, our study has the potential to bridge the gap between inflammation and subclinical EIARVC by updating the diagnostic criteria to include high levels of inflammatory markers in asymptomatic patients. This intervention could allow for early disease detection and contribute to risk management, preventing sudden cardiac death in young athletes.

Inhibition of miR-150-5p decreases cardiac fibrosis in diabetic rats

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Diabetic cardiomyopathy refers to the abnormal remodelling of the heart muscle in diabetic patients characterized by the presence of cardiac fibrosis. Individuals with cardiac fibrosis overproduce extracellular matrix proteins which accumulate in the heart, consequently leading to cardiac dysfunction. The role of MicroRNAs (miR) which are small noncoding RNA segments have been shown to regulate the rate of cardiac fibrosis. Specifically, in-vitro modelling revealed that overexpression of miR-150-5p in hyperglycemic conditions contributes to increased cardiac fibrosis. However, these findings have yet to be studied in-vivo and the impact on cardiac function is unknown. Therefore, this study aims to investigate the effect of miR-150-5p on cardiac fibrosis and cardiac function in diabetic rats using a knockdown and control group. First, Sprague Dawley rats will be injected with streptozocin to induce a diabetic state. Adenovirus (Ad)-shmiR-150-5p will be injected to knock down miR-150-5p. Over 16 weeks, the rats will be fed a high-glucose diet which would allow for the hyperglycemic overexpression of miR-150-5p in the control group. Cardiac function will be assessed using echocardiography to quantify left ventricular wall thickness, ejection fraction, and cardiac output. Histological staining will be used to examine the extent of fibrosis compared to the total myocardial area. It is hypothesized that the rats with knockdown expression will have decreased cardiac fibrosis and increased cardiac function compared to the control group. These results provide insight into the therapeutic potential of targeting miR-150-5p to treat diabetic cardiomyopathy.

LDL gene-specific variation on increased atherosclerotic risk in South Asians

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Atherosclerosis (AS) is a cardiovascular disease resulting in the thickening and blockage of blood vessels due to increased low-density lipoproteins (LDL). The 2014 South Asian Genome project identified eight genetic variants associated with a hypothesized increase in disposition to LDL: APOH, IGF1, IGF2, LYN, LDLR, NEUROD1, PNPLA2, and VLDLR. As the atherogenicity of these eight genetic LDL-producing variants have yet to be quantified, this study will investigate their variable expression through in vivo transgenic mouse models. To identify mutation nature and location, next-generation sequencing will be used. Each variant will then be injected into groups of 30 BALB/c mice, delivered through an adeno-associated virus vector along with one control group lacking genetic modifications. Purified water ad libitum and an atherogenic diet consisting of 15% fat, 5% cholesterol, and 2% cholic acid will be administered. AS progression will be measured at weeks 8, 16 and 24 via blood tests quantifying plasma LDL levels; nuclear magnetic resonance spectroscopy via NMR-MOUSE measuring LDL particle size; and an MRI detecting lipid-containing lesion development. After 24 weeks, mice will be euthanized and aortic root cross-sectional cut will be performed, followed by aortic root staining with Sudan IV to reveal lipid-laden plaques. In SA-gene variants exhibiting a positive correlation with AS risk, higher plasma LDL levels, smaller and denser LDL particles, and more significant lesion growth is expected. Implicated gene variants could better illustrate global population risk and potential therapeutic targets for underrepresented South Asians in cardiovascular research.

Evaluating the utility of tenecteplase-coated magnetic nanoparticles in treating ischemic stroke

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Ischemic strokes account for over 60% of all strokes, a leading cause of death worldwide. Thrombolytic therapies remain the predominant treatment for ischemic stroke; however, poor delivery and biocompatibility hinder their efficacy. Nanoparticles offer improved target specificity and stability in drug delivery. We propose the use of magnetic nanoparticles (MNPs) together with tenecteplase, a promising yet understudied thrombolytic drug. Our research aims to (i) increase target specificity of tenecteplase, (ii) improve drug delivery time, and (iii) improve the thrombus lytic rate. MNPs will be synthesized through: co-precipitation with iron(II) and iron(III); modification via addition of silicon to form SiO_2-MNPs; and surface functionalization to form tenecteplase-coated MNPs (T-MNPs). The effectiveness of the T-MNPs will be tested against an injection of fluorescence-tagged tenecteplase. A treatment and control group with 10 mice each will be pretreated with $FeCl_3$ to form clots, followed by injection with T-MNPs and tenecteplase respectively through the tail vein. After injection of the treatment group, magnetic targeting can direct the T-MNPs to the clot and low-intensity ultrasound will facilitate release of the drug. Magnetic resonance imaging (MRI) will be used to evaluate fibrin specificity of T- MNPs, residual thrombus size and lytic rate for both groups. Presence of fluorescence can be used to evaluate target specificity within the control. We expect T-MNPs to decrease residual thrombus size, increase lytic rate, and improve fibrin specificity. This study will offer insight into the efficacy of nanoparticles in improving drug-delivery and outcomes for ischemic stroke patients.

Identification of atherosclerosis-promoting genes in the CD36/JNK/AP1 pathway

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Atherosclerosis is a vastly prevalent cardiovascular disease characterized by the accumulation of lipid plaques and arterial hardening. It impacts 42% of adults globally and underlies severe comorbidities, including strokes and aneurysms. The leading cause of atherosclerosis is the increased uptake of oxidized low-density lipoproteins (oxLDL) by endothelial-associated macrophages. An exaggerated uptake of oxLDL can transform macrophages into foam cells, which have an integral role in disease pathogenesis. Specifically, oxLDL uptake is facilitated through scavenger receptors, with CD36 receptors being the principal candidate overexpressed in foam cells. Preliminary studies have shown a protective effect against atherosclerosis in CD36 knockout mice. However, given the receptor's ubiquity, numerous off-target effects were observed, such as markedly increased de novo lipogenesis. Thus, we will investigate downstream effectors following the CD36/JNK1/AP1 pathway to determine more effective methods of reducing oxLDL uptake. Upon oxLDL binding to CD36,

JNK dimerizes with AP1 to regulate genes containing the 5'-TGAG/CTCA-3 motif. We propose using DNA probes complementary to this motif to identify atherosclerosis-associated genes in macrophage cell lines. Once gene candidates are established, performing differential expression analyses of RNA-seq data between diseased and healthy plasma control samples, we expect to identify the genes most implicated in atherosclerosis. Following this, in vitro verification of the candidates will be performed, with the most promising candidate(s) advancing to knockdown experiments in animal models. As such, our identified gene(s) will provide a precise locus for therapeutic exploration, thus diminishing the various off-target effects evident in current therapies.

Sequencing the major histocompatibility complex to observe the genotypic correlation in primary vasculitis syndrome

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Primary vasculitis is a branch of autoimmune diseases in which the immune system attacks the vascular tissue, leading to compromised blood flow to other organ systems and possible death in severe cases. The condition has previously been linked to de novo mutations in the form of single nucleotide polymorphisms (SNPs) in the major histocompatibility region (MHC). However, there are over 200 genes within the MHC, making it difficult to localize and identify the responsible SNPs. For example, HLA-B*51 has been associated with the vasculitis syndrome Behcet's disease, but a cohort in Turkey did not show mutation here, indicating that there may be other mutations driving the disease. Our aim is to further localize and compare the genotypic backgrounds of cardiac versus systemic vasculitis; 3 groups of participants will be gathered and have their MHC regions sequenced through Next-Generation Sequencing (NGS). All groups will comprise 16 individuals each, one control group and two observed groups respectively. These observed groups will include individuals with localized cardiac vasculitis, and systemic vasculitis (involving multiple organ systems). Once sequenced, the MHC regions of each group will be assessed to determine if any consistencies exist in terms of regions and types of mutations. We hypothesize that cardiac and systemic vasculitis disease mechanisms would be driven by different SNPs, and this analysis would provide greater insight into the genetic mechanisms of the respective diseases. The data collected from this study may be used to inform future research and develop genetic therapies for vasculitis patients.

Inhibitory effects of opioids on hERG channels during pregnancy

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Globally, the prevalence of opioid usage was reported to be as high as 29%. Opioid usages risks unhealthy vaginal delivery, stillbirth, and worsened fetal growth. Opioid's methadone, l-α-acetylmethadol, and fentanyl are associated with the inhibition of cardiac channels, particularly hERG channels, inciting QT prolongation, and potentially, Torsades de Pointes. Given poor prospects in pregnancy with opioid use, no study has yet to evaluate the underlying mechanism associated with these outcomes. This study aims to evaluate the inhibitory effects of opioids on hERG channels in pregnant mice. 40 pregnant transgenic mice expressing hERG channels will be divided into four groups (methadone, l-α-acetylmethadol, fentanyl, and control) of ten. Incremental doses of opioids will be given to all experimental groups. Electrocardiograms will continuously monitor for QT prolongation and cardiac disorders, ultimately indicating hERG channels inhibition. Groups will be controlled for nutrition, exercise, blood pressure, weight, and pregnancy stage. Increased hERG blockade is expected in opioid-administered mice, worsening cardiac and pregnancy outcomes. Adverse fetal events observed in pregnant mice using opioids could be explained by partial hERG channels blockage, resulting in prolongation of the QT interval and even sudden cardiac death. This study will allow for a stronger understanding of the underlying mechanisms and risks of opioid use during pregnancy. Naloxone is an opioid antagonist associated with reversing QT prolongation initiated by opioids. If the suggested mechanism is validated, naloxone could be introduced for clinical treatment of opioid-induced cardiac disorders in pregnant women.

Investigating SHP and PCSK9 interactions in cholesterol-mediated cardiovascular diseases

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Improper cholesterol metabolism results in the accumulation of low-density lipoproteins (LDL), which transport cholesterol from the liver to body cells. High levels of LDL cholesterol can deposit in blood vessels, forming plaques and contributing to cardiovascular diseases like atherosclerosis. The farnesoid X receptor (FXR) is responsible for the transcription of genes involved in cholesterol metabolism. Studies demonstrate an inverse relationship between the FXR target gene SHP and the expression of PCSK9, an LDL receptor-degrading enzyme; however, an exact relationship has not been identified. SHP represses an enzyme that converts cholesterol to bile acid; thus, SHP upregulation promotes cholesterol absorption. We hypothesize that SHP and PCSK9 directly interact to regulate cholesterol metabolism. To test this, we would downregulate SHP and PCSK9 individually and simultaneously in three mouse models, with a fourth wild-type model as a control. As protein levels are a measure of gene expression, blood samples from each mouse would undergo Western blotting, the results of which would be corroborated by an ELISA assay. SHP- and PCSK9-specific antibodies would be used in the PCSK9- and SHP-downregulated mice respectively. The resulting SHP and PCSK9 levels would be compared to the control to determine the existence and direction of an SHP/PCSK9 interaction. Results are expected to indicate a direct SHP/PCSK9 relationship, which may occur in either direction, ultimately leading to elevated LDL. If successful, future research may explore potential therapeutic targets for managing atherosclerosis and downstream cholesterol-mediated cardiovascular diseases by blocking SHP/PCSK9 interactions.

The effects of raloxifene promoted angiogenesis on adaptive cardiac hypertrophy

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Heart failure (HF), a condition where the heart pumps insufficient amounts of blood, is significantly increasing in Canada. The thickening of heart tissues, hypertrophic cardiomyopathy (HCM), is a significant risk factor for the development of HF. Following an acute myocardial infarction (MI), commonly known as a heart attack, HCM often develops to compensate for damaged tissues and to maintain cardiac function. Angiogenesis is the development of new blood vessels and is required to support this adaptive HCM; we intend to study if the promotion of angiogenesis will improve heart function throughout HCM, thus delaying the development of HF. To induce angiogenesis, we will use the estrogen analogue drug raloxifene to activate the vascular endothelial growth factor (VEGF) signalling pathway. We will inject mice undergoing phenylephrine-induced HCM with raloxifene. New muscle growth will be measured using an echocardiogram. We will monitor the mice for HF by measuring ejection fraction and systolic and diastolic pressure. We hypothesize that providing raloxifene after induced HCM will delay the progression of HF by relieving over-compensation from insufficient blood vessels. We predict the experimental group injected with raloxifene will show a greater ejection fraction and lower systolic and diastolic pressure than the control group. We suspect there will be a threshold of VEGF activation, at which the experimental group will begin to show decreased cardiac function which should be accounted for. This study would provide insight into a possible preventative measure to reduce the risk of HF post MI.

Using CRISPRi to downregulate TGFβ1 in COPD mouse models

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CRISPRi is a biotechnique that can repress gene expression by blocking transcriptional initiation and elongation of DNA. Chronic obstructive pulmonary disease (COPD) is a chronic lung condition characterized by inflammation of the airways. Scientific research has demonstrated that the TGFβ1 cytokine is elevated in COPD patients. However, the mechanisms underlying TGFβ1 are not well understood. To further explore the role of TGFβ1 in COPD, we are using CRISPRi with in vivo mouse modelling to downregulate the TGFβ1 gene. We will be measuring changes in the severity of COPD. As COPD is a common and severe disease that is poorly understood, exploring genes involved with COPD is crucial for therapeutic development. At eight weeks of age, eighty female mice will have COPD elicited by receiving 1.2 µg/g of elastase one day per week for four consecutive weeks. These mice will then be randomized equally between a control or intervention group. After COPD has been induced, the intervention group will receive CRISPRi, and ELISA assays on plasma samples will be

used periodically to confirm the downregulation of TGFB1 in the intervention group. To conclude the study, spirometry will be evaluated against COPD GOLD guidelines to assess the severity of COPD by the percentage of predicted FEV1 value. We expect that downregulation of TGFβ1 will reduce inflammation in COPD patients, improving symptoms. Understanding the role of TGFβ1 in COPD will allow for the development of treatments that can target an underlying genetic cause of COPD.

Using prime editing to correct cystic fibrosis mutations

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Cystic Fibrosis is the most common fatal genetic disease within Caucasians. It is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene and affects many organs, primarily the lungs. Normally, the CFTR protein functions as an ion pump that transports chloride ions outside the cell. Its defective form in CF patients causes intracellular chloride accumulation, where the chloride ions begin to absorb water from the mucus within the lungs. This in turn causes the dehydrated mucosal layer to thicken and promotes the adherence of bacteria and viruses on the surface. Current CF therapeutics aim to enhance chloride export by prolonging channel pore opening, but does not correct the defective gene. Thus, our research will focus on correcting CF mutations with a CRISPR-Cas9-derived prime editing system. With currently-established statistical data in global CF patients, we will identify the most prevalent CF mutations and the PAM sequences near these mutations to direct the Cas9 nickase to induce a single-stranded cleavage. Using a guide RNA as a template in the presence of a reverse transcriptase, the mutation will be transcribed back to the wild type sequence. This prime editing system will initially be tested in vitro in pig lung epithelial cells, followed by subsequent tests to deliver this prime editing system to their lungs in vivo using a lentivirus vehicle. Together, we aim to more effectively revert these mutations in CF individuals of all ages to correct this disease, without inducing unnecessary DNA damage in other sites of the genome.

SOCS family protein responsible for allergic asthma T cell differentiation

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Asthma is an obstructive airway disorder affecting over three million Canadians, with allergic asthma being the most prevalent phenotype. It is characterized by chronic inflammation of the lower respiratory tract, attributed to the activation of Th2 and Th9 cells. It was recently demonstrated that Cullin5 ubiquitin ligase complexes are critical in allergic asthma, as they dictate T cell fate choice by disfavouring Th2 and Th9 cells, thus reducing the risk of developing allergic asthma. An important component of this complex is the SOCS family protein that recruits the appropriate substrate for degradation. However, the identity of the SOCS protein involved in allergic asthma T cell differentiation remains unknown. To address this, we will use RNA interference to knock down SOCS family gene expression in human CD4+ T cells to identify the gene responsible for differentiation. We will then perform CRISPR/Cas9-mediated knock-out, and plasmid transfection-mediated overexpression of the identified SOCS gene, using a co-culture of CD4+ T cells with healthy or asthmatic human primary bronchial/tracheal epithelial cells, and measure the expression levels of pJAK1 and pSTAT6, two biomarkers of allergic asthma inflammation. We expect to see low levels of pJAK1 and pSTAT6 when the SOCS protein is overexpressed in the asthmatic cells, as the Cullin5 complex is known to decrease allergic asthma inflammation. Identification of the SOCS protein will allow future research to investigate this as a potential druggable target to expand treatment options for allergic asthma.

Investigating TGF-β and transient endothelial cell plasticity after myocardial infarction

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Ischemic Heart Disease (IHD), a leading cause of death worldwide, is estimated annually to cause nine million deaths. IHD is the obstruction of blood flow in the coronary arteries due to atherosclerosis, which can induce myocardial infarction (MI). Researchers have investigated the potential of endothelial cells acquiring a transient mesenchymal state for regeneration -

showing cell plasticity after MI. A factor influencing cell plasticity is the multifunctional cytokine protein TGF-β, which enables angiogenic sprouting and neovascularization by loosening endothelial junctions. However, despite mimicking mesenchymal stem cells (MSC), endothelial–mesenchymal transition (EndMT) activities are lost within fourteen days. Investigating the effect of increased doses of TGF-β on the time dependence of EndMT via the expression of the mesenchymal gene, will reveal whether this process results in accelerated angiogenesis, and thus enables faster recovery. MI will be induced in the TGF-β treatment and control groups of Mus musculus by coronary artery occlusion without ventilation prior to TGF-β injection treatment, which will occur after fourteen days. Single-cell RNA sequencing (scRNA-seq) and immunofluorescence staining with NG2 will be performed weekly post-MI for a period of twenty-eight days to identify mesenchymal activation and view the progression of pericyte formation. Between the two groups, it is expected that mesenchymal gene activity will persist or increase after TGF-β treatment beyond fourteen days post-MI, leading to greater pericyte proliferation. Therefore, this study will enable the development of a targeted treatment for those who cannot undergo revascularization procedures.

Exploring a stereolithography machine's ability to bio-print cardiac tissue

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Heart disease is the leading cause of death for nearly every person in the United States and the second leading cause of death in Canada. It is one of the largest medical problems we face as humans. However, there is a great deal of research ongoing to find solutions to these problems, with one of the most interesting and promising being bioprinting. This field is vast and there are many techniques used to great effect, with stereolithography being one of the most promising. This technique utilizes lasers to harden light sensitive media into solid structures. However, despite its promise, there is a lack of testing done with this technique. To correct this, the goal of this paper is to explore the possibilities of this untapped sector. More specifically, exploring the possibilities regarding the heart. To accomplish this task and build upon our understanding of this field in general, we will be utilizing a setup designed in a paper by Zongjie Wang et al. This setup was chosen for its impressive ability to negate the downsides of stereolithography in general. It minimizes the UV exposure to the actual tissue, it is cost effective, and it maintains many of the benefits of a more traditional stereolithography system. In the original paper this design was only used for relatively large-scale printing, the goal of this paper is to determine whether this design can print the small and intricate pieces of the human heart.

Hyaluronic acid and CRISPR-Cas 9 for alpha-1 antitrypsin deficiency

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Alpha-1 antitrypsin deficiency is a condition that causes floppy alveoli, and consequently induces emphysema. The alpha-1 antitrypsin protein is misfolded due to a mutation in its gene; SERPINA1. When alpha-1 antitrypsin isn't present in sufficient levels, elastin, the protein responsible for giving alveoli their shape, is degraded. In North America, the prevalence of this condition is 1 per 3000 to 5000 people. Yet, only 5% are diagnosed. Even when diagnosed, treatments are limited as lung transplants are highly reserved, and enzyme replacement involves frequent IV infusions. Contrastingly, Hyaluronic acid is accessible and has been effective in treating lung diseases due to its anti-inflammatory and water binding properties. Thus, this placebo-controlled study proposes a combination therapy that 1) uses CRISPR-Cas9 to remove and replace the mutated SERPINA1 gene and 2) administers hyaluronic acid to PiZ transgenic mice models mimicking the human condition. A lipid nanoparticle delivery system containing the cas9 system, guide RNAs, and the SERPINA1 gene will be injected into the mice. Accompanying this, a Hyaluronic acid inhalation solution will be administered twice a day for 2 weeks. Progression of lung function will be measured using arterial blood gas tests. Furthermore, desmosine and isodesmosine, amino acids uniquely involved in elastin breakdown, will be measured for in plasma using liquid chromatography mass spectrometry. It is expected that after this treatment PiZ mice models will show decreased levels of emphysema and improved lung function. Ultimately, this study could lead to significant strides in treating alpha-1 antitrypsin deficiency and save many lives.

Suppression of atherosclerosis by CRISPR-Cas9-mediated knockout of CD47

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Atherosclerosis is a buildup of arterial plaque that reduces blood flow to the heart and causes coronary artery disease, the third leading cause of death worldwide. Atherosclerosis in coronary arteries is initiated by damage to endothelial tissue caused by high levels of LDL cholesterol and results in the buildup of arterial plaque. Mature arterial plaque is composed of a complex of white blood cells, smooth muscle cells, and lipids surrounding a core of necrotic cells, which causes a chronic state of inflammation. Macrophages struggle to remove necrotic cells in the atherosclerotic plaque due to the upregulation of CD47, a cell-surface receptor protein that sends "don't eat me" signals to phagocytic cells. We hypothesized that CD47 knockout by CRISPR-Cas9 in the atherosclerotic tissue would facilitate the phagocytic clearance of the necrotic core. CRISPR-Cas9 was delivered to atherosclerotic tissue using targeted lipid nanoparticles (LNPs). To achieve cell-specific delivery, the LNPs' surfaces were decorated with antibodies targeting upregulated cell surface proteins in the necrotic core, specifically VCAM-1 (a common biomarker of atherosclerosis). The LNP/CRISPR-Cas9 system was tested in $ApoE^{-/-}$ mice, a mouse model for spontaneous atherosclerosis. The progression of atherosclerotic plaque was detected non-invasively by MRI and fluorescence imaging. This study combines several robust strategies, such as LNP delivery and CRISPR-Cas9 gene-editing to knock out CD47 expression in atherosclerotic plaque, and shows great promise as a treatment for heart disease.

Investigating the correlation of cor pulmonale in cystic fibrosis mutations

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Cystic fibrosis (CF) affects 1 in 3,600 Canadians, with 8.3% of affected patients at risk of developing Chronic Cor Pulmonale (CCP). CCP is the failure of the right side of the heart caused by prolonged pressure. Six classes of mutations cause CF due to defects in the Cystic Fibrosis Transduction conductance Regulator (CFTR); our primary focus will be class V, which reduces the quantity of proteins. While no known correlation between CFTR classes and CCP exists, current research suggests a connection between class V and reduced exercise capacity; this indicates decreased cardiac function, possibly due to chronic heart failure, and may indicate a connection to CCP. To investigate this, we will use forty rats for each class of CFTR mutation, which will serve as experimental groups, and forty rats in control. Electrocardiograms will be telemetrically recorded after rats reach appropriate weight levels. In addition, we will use echocardiograms to confirm the heart structures of all rats. In rats that develop CCP, heart structure will increase in muscle mass on the right side. We expect the experimental group's electrocardiograms will have taller R waves in the right precordial leads and deeper S waves in the left precordial leads. Additionally, we expect class V rats to develop CCP at greater rates. Using these methods to confirm the correlation between class V mutations and CCP would allow doctors to start early preventative care, increasing patient life expectancies and reducing instances of CCP within CF patients.

T reg cell therapy: a novel treatment for pulmonary arterial hypertension

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Pulmonary Arterial Hypertension (PAH) is a progressive cardiorespiratory disease impacting 1-3 million individuals globally. PAH is characterized by perivascular inflammation due to endothelial cell injury, which leads to right ventricular hypertrophy and heart failure. $CD4 + CD25^{high}$ and $CD4 + CD25^{-}$ Regulatory T cells, regulate the immune response to inflammation caused by CD8 + cytotoxic T cells and prevent endothelial injury. Deficiency in these T reg cells is correlated with the progression of PAH. This study examines whether T reg cell therapy effectively reduces the symptoms of PAH in rats, as the therapeutic potential of T reg cells against PAH has not yet been investigated. We hypothesize that rats undergone T reg therapy have less severe post-PAH endothelial injury compared to the control group. We will inject both groups with SU5416, a vascular-endothelial-growth factor-receptor-blocking agent, to trigger endothelial cell apoptosis. The treatment group will be injected with supplemental $CD4 + CD25^{high}$ and $CD4 + CD25^{-}$ reg cells, and the mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) will be measured by direct right heart catheterization in both groups. We expect T reg therapy to relieve the symptoms, which is to be observed through mPAP and PVR measurements under the disease threshold; mPAP < 20 mmHg at rest and PVR 3 Wood units. The T reg cell therapy's effectiveness in alleviating PAH symptoms in rats will enable further exploration of PAH treatment through clinical trials, which is essential due to the lack of effective treatments for PAH.

GRK mediated β2 desensitization

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Long-term treatment of chronic obstructive pulmonary disease (COPD) with β2 agonist (short/long-acting) may cause lung receptor mediated tachyphylaxis. In turn, this will limit the efficacy of the agonist treatment in patients with COPD. β2 receptor desensitization is mediated by G protein-coupled receptor kinase (GRK), resulting in receptor internalization. Our team proposes to study which type of GRK acts on β2 receptor and then examine the GRKs present in lung smooth muscle tissue. We will perform an in-vitro analysis using various immortalized cell cultures (i.e. HEK293) where GRK subtypes, GRK1 through 7, are examined to observe which of them partake a role in receptor internalization. Each cell culture would also have a β2 receptor, which is, in turn, activated by isoproterenol. Stimulated β2 activates Gαs leading to elevated levels of cAMP that can be measured with a GloSensor. Each culture group would be transfected with a plasmid containing a siRNA to knockdown a specific GRK. The cAMP of the control and siRNA GRK knockdown groups will also be recorded in response to isoproterenol pretreatment and rechallenge. In our research, we expect GRK2, 3, 5, and 6 to be found in the lung tissue smooth muscle, with GRK 2 and 6 having the highest levels in the pulmonary tissue, and hence being the most likely culprit in desensitizing β2 adrenergic receptors. Once determined, the GRK subtype can be targeted to improve the β2 receptor sensitization and prolong the duration patients can remain on pulmonary treatments mediated by β2 receptors.

Congenital heart disease: maternal ADIPOQ polymorphism and high nitrite diet

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Congenital heart disease (CHD), characterized by structural or functional cardiovascular anomalies at birth, is the most prevalent congenital defect and a leading cause of mortality and morbidity in newborns. Maternal genetics and diet influence CHD incidence. A single nucleotide polymorphism (SNP) at rs2241766 of the gene ADIPOQ decreases adiponectin levels, which is linked with maternal diabetes, a risk factor for CHD. Furthermore, high nitrite diets have increased nitric oxide signalling and the likelihood of neonatal heart abnormalities. Currently, neither ADIPOQ variation nor high nitrite diets are screened as health risks in prenatal care. This study aims to determine causality between the maternal ADIPOQ variant, maternal nitrite consumption and CHD prevalence by using a zebrafish (Danio rerio) model system. CRISPR-Cas9 will be used to obtain ADIPOQ variant positive and negative female zebrafish, which will be confirmed by SNP genotyping. These groups will be further divided based on high and baseline sodium nitrite incubation. Female species will mate with male species lacking the ADIPOQ variant and high nitrite incubation. We will conduct histological staining of offspring tissue with hematoxylin and eosin, and photomicrographs will be taken under a polarizing microscope. We expect offspring with both experimental conditions (positive maternal ADIPOQ variant at rs2241766 and high nitrite incubation) to have the highest severity of CHD, with one of two experimental conditions to have mild-to-moderate CHD severity, and with neither experimental condition to have no apparent CHD. Findings from this study can provide insight into preventative measures for CHD during prenatal care.

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

DB: Co-President and founder of the IgNITE Medical Case Competition, assisted authors with their abstract submissions, drafted the conference abstract booklet, and gave final approval of the version to be published.
BB: Co-President and founder of the IgNITE Medical Case Competition, assisted authors with their abstract submissions, reviewed the abstract submissions and ensured that they adhered to correct formatting standards, and gave final approval of the version to be published.
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