Research Project Title: EMEPO- A novel therapeutic approach for heart disease

Student Presenter: Eaman Abay

Faculty Mentor: Mark Ziolo

Faculty Mentor Department: Physiology and Cell Biology

Research Abstract: Heart disease is the leading cause of death in the US and around the world. Consequently, there is a high demand for novel therapeutics to treat the myriad of cardiomyopathies. These diseased hearts generally have high oxidative stress, which is an increase in reactive oxygen species (ROS) levels. Unfortunately, clinical trials using only antioxidants failed. In addition to the oxidative stress, there are also reduced nitric oxide (NO) levels. This suggests that one mechanism of heart disease is through the nitroso-redox imbalance (increased ROS, decreased NO) in the heart. We synthesized a novel drug 2-(2-ethoxy-2-oxoethyl)-2-(ethoxycarbonyl)-3,4-dihydro-2H-pyrrole 1-oxide (EMEPO), which restores the nitroso-redox balance by decreasing ROS while releasing NO. In this study, we tested EMEPO’s potential therapeutic effect on heart function in a murine model of heart disease. To test this, wild type mice were given myocardial infarction (MI) at 3 months which is a common ischemic model for heart disease. Three days post MI they were injected with either EMEPO, Allopurinol (an anti-oxidant), or left untreated. Pressure-volume (PV) loop analysis was used to measure heart function under electrical stimulation (rates of pressure development) and under induced stress with adrenergic stimulation (Dobutamine). Compared to the other groups, mice injected with EMEPO had significantly better functional response during stimulation as measured by maximum (dP/dtmax) and minimum (dP/dtmin) pressure at various heart rates, and ventricular relaxation (Tau). Similarly, the mice also had a higher beta-adrenergic response when stimulated (as shown by the significantly higher dP/dtmax and Tau values), meaning the mice had an improved response to stress through contractile force. The infarcted mice showed notably increased heart function in vivo when treated with EMEPO. Restoring nitroso-redox balance via this treatment is significantly better than just the use of anti-oxidants. Thus, EMEPO may provide a comprehensive strategy for treating patients with heart disease.
Research Project Title: Associations among post-operative pain, narcotic administration, and maternal anxiety in infants with congenital heart disease

Student Presenter: Jacob Bailey

Faculty Mentor: Tondi Harrison

Faculty Mentor Department: College of Nursing

Research Abstract: Introduction/Background

Infants with complex congenital heart disease (CCHD) undergo surgical interventions in the first weeks of life and may experience significant post-operative pain. Parental anxiety may affect infant pain, and mothers of infants with CCHD have increased anxiety. Our purpose was to examine relationships among infant postoperative pain, narcotic administration, and maternal anxiety.

Methods

This study examined a secondary aim of a two-group randomized controlled trial testing a 30-minute massage intervention in 60 infants undergoing their first cardiac surgery before age 12 months. Measures included pain (Face, Legs, Activity, Cry, Consolability), maternal anxiety (State-Trait Anxiety Inventory), average daily narcotic administration, disease severity (Risk Adjustment for Cardiac Surgery), and infant sex. Data were analyzed with group-based trajectory modeling for pain scores and narcotics administration. Resultant classifications were outcome variables in logistic regression models with predictor variables maternal anxiety, group, disease severity, and infant sex.

Results

The 2-class pain trajectory model revealed 83.21% of infants had stable low pain scores (Class 1), and 16.79% had initial high scores that gradually dropped (Class 2). Infants likely to be in Class 2 had mothers with higher anxiety (OR=5.34, CI=0.96,29.72), received massages (3.25, CI=0.53,20.08), and were male (OR=0.70, CI=0.14,3.55). The 2-class narcotic model revealed 85.00% sample had a low, stable trajectory (Class 1) and 15.00% had an inverted-U trajectory (Class 2). Infants likely to be in Class 2 had mothers with higher maternal anxiety (OR=1.59, CI=0.48,5.32), received massages (OR=3.82, CI=0.67,21.57), and had more severe disease (OR=3.80, CI=1.09,13.31).

Conclusions

Although firm conclusions cannot be drawn due to large confidence intervals, findings suggest that maternal anxiety may be associated with both pain and narcotic administration. Interventions to reduce parental anxiety are a potential approach to reducing infant post-operative pain. Additional research is needed to examine associations of infant pain with maternal anxiety as well as massage, disease severity, and infant characteristics.
Research Project Title: GlcNAc conjugated atorvastatin with enhanced water solubility and cellular internalization

Student Presenter: Justin Jiang

Faculty Mentor: Yizhou Dong

Faculty Mentor Department: College of Pharmacy

Research Abstract: Atorvastatin, also known by its trade name Lipitor, is a drug used to treat high lipid levels and prevent certain cardiovascular diseases. Although atorvastatin is still widely prescribed today, its bioavailability is rather low, which can be contributed to its poor water solubility, dissolution rate, and membrane permeability. Therefore, to improve the effectiveness of atorvastatin, we conjugated it with a targeting ligand, N-acetylglucosamine, that previous studies identified as having strong affinity for hepatic receptors. We synthesized two ligand-drug conjugates with differing pH sensitivities and quantified both their solubility and membrane permeability via UV-Vis spectra. Furthermore, we performed a previously published method to measure the low-density lipoprotein receptor expression as an indication of atorvastatin’s mechanism of action. Through these studies, we concluded that both conjugates significantly improved cellular uptake and solubility of atorvastatin while maintaining comparable levels of biological activity. Therefore, our ligand-conjugates offer a promising model for improving the cell specificity of atorvastatin.
Research Project Title: A continued analysis of the cost-effectiveness regarding inhaled pulmonary vasodilator therapy in adults

Student Presenter: Andrea Gerstner

Faculty Mentor: Georgianna Sergakis

Faculty Mentor Department: Respiratory therapy

Research Abstract: ABSTRACT: In the adult population, the inhaled pulmonary vasodilator, epoprostenol (iEPO), is readily used in conjunction with other therapies to help treat several different clinical scenarios. The inhaled pulmonary vasodilator, epoprostenol, is FDA approved to treat pulmonary hypertension but is also used in other off label indications such as hypoxemia and ARDS. This agent improves oxygenation, inhibits platelet aggregation, reduces inflammation, and decreases pulmonary vascular resistance. Currently at our institution there is no criterion in place for the initiation, weaning and discontinuation of iEPO on patients for which this drug is used in patients, other than those with pulmonary hypertension. Currently, there are gaps in the literature that provide initiation, weaning and discontinuation criteria for hospitals that use iEPO for diagnoses such as hypoxemia. The purpose of this study is to examine retrospective charting on patients for which iEPO was initiated, to determine effectiveness of oxygenation and to determine the utility of a protocol for initiation, weaning and discontinuation of iEPO. Our aims were to answer:

1. What are the current practices for using iEPO for hypoxemia at our institution?
2. What is the average time it currently takes to wean iEPO at The Ohio State Wexner Medical Center?
3. What are the cost-savings when applying an evidence-based protocol to use of inhaled epoprostenol for hypoxemia?

METHODS: Following IRB approval, a retrospective chart review will be conducted for all patients who were started on inhaled epoprostenol at the Ohio State University Wexner Medical Center (OSUWMC) in the year 2015-2017. The review will be completed in order to create an evidence-based protocol for initiation, weaning and discontinuation of inhaled epoprostenol. The studied population will be restricted to adult patients, specifically patients who are receiving iEPO for hypoxemia. The primary data points that will be recorded are the PaO2/FIO2 ratio, the oxygen index, the MAP and the patient’s SPO2. These four primary data points will be measured to conclude improvement in the patient’s oxygenation. The data points will be observed before the administration of inhaled epoprostenol and will be compared to the most recent values recorded after the medication was administered. Ventilator settings will also be recorded, along with the patient’s PEEP, FIO2, the mode of ventilation, duration of time on the ventilator, significant changes in the patient’s care, if the patient was on nitric oxide simultaneously, if the patient was placed in the prone position, and the patient’s outcome (mortality). Weaning strategies will also be described (whether or not the patient was suddenly or slowly weaned from the medication). The evidence-based protocol will be produced by observing trends in the data for which iEPO was initiated on patient’s with hypoxemia, which can be defined as a PaO2 of 50-60mmHg on an FIO2 of greater than 60%. Along with initiation of an evidence-based protocol, potential cost savings will also be examined.
RESULTS: By developing an evidence-based protocol, it is found that money can be saved at the hospital for the initiation, weaning and discontinuation of iEPO. Currently at our institution there is no protocol in place for the initiation, weaning and discontinuation of iEPO.

CONCLUSION: An evidence-based protocol should be used in place of the current practices at The Ohio State Wexner Medical Center for the initiation, weaning and discontinuation of iEPO.
Research Project Title: PRMT5 inhibitors in the re-expression of fetal hemoglobin

Student Presenter: Kaylin Kavanaugh

Faculty Mentor: Rosa Lapalombella

Faculty Mentor Department: Internal Medicine

Research Abstract: Sickle Cell Disease is a chronic blood disorder caused by a missense mutation where the 6th amino acid, glutamic acid, is replaced by valine. Symptoms of the disorder include anemia due to shorter cell life, pain episodes (known as crises) that last anywhere from a couple of hours to a few weeks, frequent infection, and permanent organ damage. Protein arginine methyltransferase 5, also known as PRMT5, is an enzyme that methylates histone arginine residues such as H3R8 or H4R3. Studies have shown patients with Hereditary Persistence of Fetal Hemoglobin (HPFH) experience continuous production of fetal hemoglobin (HbF) into adulthood. Sickle cell patients with HPFH (although a less common phenotype of Sickle Cell) see large reductions in symptoms. The overall aim of our specific research is to pharmacologically re-express HbF in order to replicate the re-expression of HbF found in S/HPFH patients, and therapeutically alleviate symptoms of the disorder. Previous work from our lab showed small molecule inhibitors of PRMT5 to be effective in re-expressing HbF in human cells. We hypothesized the experimental compounds PRT220 and EPZ015666, known PRMT5 inhibitors, will re-express HbF in a similar fashion. We tested compounds PRT220 and EPZ015666 by dosing them on HEL92.1.7 cell lines within a 72 hour period. Viability of cells was checked daily via trypan blue. After the 72 hour period, whole cell lysates were collected and run on an immunoblot. Of the two PRMT5 inhibitors, PRT220 showed a reduction in PRMT5 activity at histone H3R8 without affecting cell viability. Ultimately, further development of these compounds will lead to the expansion of clinical treatments of therapeutic alleviation of patients with Sickle Cell Disease.
Research Project Title: Non-invasive preclinical porcine maxillofacial model to study excessive scarring of the face following burn injury

Student Presenter: Douglas Guzior

Faculty Mentor: Sashwati Roy

Faculty Mentor Department: Surgery

Research Abstract: Background: Following burn injury, facial scarring is excessive wherein it is not comparable to scarring on other parts of the body. Facial burn leads to marked functional deficits including oral incompetence and facial abnormalities, along with impacts such as increase social, emotional, and psychological stress of the subject. This study was aimed at developing a robust preclinical model for maxillofacial burn injury with emphasis on non-invasive techniques, such as laser speckle imaging (LSI) to monitor blood flow as well as utilizing harmonic ultrasound doppler imaging (HUSD) to monitor wound depth, elasticity, and scar formation. Methods: Burn wounds were made using a gauged, electrically-powered burner that continuously measured instrument temperature, which then automatically increased power to the instrument to maintain a constant desired temperature. Up to 50% of the face and four distinct regions of the back were affected by severe 200°C burn wounds. Wound healing progression was monitored via non-invasive imaging such as laser speckle microperfusion imaging and harmonic ultrasound with Doppler (n=7 pigs). Results: Application of burns resulted in fourth degree burns (verified by CT imaging) with bone involvement leading to deficits such as contracture and excessive scarring. Contracture and scarring were evident as early as 56 days post-burn. Ectropion, eversion of the lower lip, and oral incompetence were also observed. Conclusion: This DOD funded study constitutes the first preclinical model to study burn injury in the face and underlying mechanisms.
Research Project Title: Exploring the antimicrobial activity of novel bacterial topoisomerase inhibitors

Student Presenter: Jacob Harris

Faculty Mentor: Dan Wozniak

Faculty Mentor Department: Microbiology

Research Abstract: Fluoroquinolones are a class of broad-spectrum antibiotics commonly used to treat a variety of bacterial infections. Their antimicrobial activity is due to their ability to inhibit the function of bacterial DNA gyrase proteins. DNA gyrases, also known as DNA topoisomerases, are enzymes that regulate the over-winding of the DNA which occurs during DNA replication. These enzymes are essential for the integrity of the genetic material during replication. However, despite the potency of this class of antibiotics, fluoroquinolone resistant isolates have emerged at an alarming rate. These resistant mutants typically have acquired mutations in multiple genes which contribute to the organism’s ability to resist antibiotic treatment. Most commonly, resistant strains have modified the target protein or upregulated their multidrug efflux pump proteins. Moreover, this increasing amount of resistant strains has been met with limited development of new antimicrobials that can treat bacterial infections. Thus, it is imperative to continue to explore novel bacterial topoisomerase inhibitors (NBTI’s) for use against resistant strains.

In collaboration with a lab in the College of Pharmacy, we have acquired ~70 NBTI’s that are derivatives of fluoroquinolones. We have performed minimum inhibitory concentration (MIC) assays using these compounds against a lab standard strain of Staphylococcus aureus (ATCC 29213), as well as a methicillin resistant Staphylococcus aureus (MRSA) strain. We have preliminary evidence that suggest some of these compounds demonstrate similar antimicrobial activity as the currently available fluoroquinolones. Additionally, these NBTI’s will be assessed against other bacterial species, both Gram positive and Gram negative. Including, the Gram-negatives Pseudomonas aeruginosa and Acinetobacter baumannii, to determine if there is any antimicrobial activity.
Research Project Title: Long-acting formulations conjugated with known HIV drugs shows higher potency in vitro

Student Presenter: Austin Keller

Faculty Mentor: Jesse Kwiek

Faculty Mentor Department: Microbiology

Research Abstract: Introduction and Background:

Daily antiretroviral therapy (ART) is commonly prescribed to suppress Human Immunodeficiency Virus (HIV-1) replication among people living with HIV-1. In recent years many researchers have shown an interest in exploring ways to replace daily ART therapies with longer lasting regimens. One of the innovative approaches is the conjugation of antiretroviral drugs with the long-acting formulations (LAF). Based on the evidences of success with some of the HIV-1 drugs conjugated with LAF in treating HIV-1 infected patients, here we test the potency of two novel antiretroviral drug conjugates.

Methods:

Hela derived genetically engineered TZM-bl cells were infected with HIV-1 NL4-3 in the presence and absence of ten-fold dilutions of both LAF conjugates and unconjugated drugs for 48h at 37°C. Post infection, the tat-induced reporter gene expression was measured in infected and non-infected TZM-bl cells by luminescence produced using Bright-GloTM reagent (Promega, USA) quantified on Spectramax i3X (Molecular Devices, USA). Dose-response curves and the half maximal effective concentration value (EC50) for each drug was calculated using GraphPad Prism.

Results:

The LAF-conjugates maintained their antiviral activity, and when compared to the unconjugated drugs, the LAF-conjugates were almost 10-fold more potent.

Conclusion:

Upon conjugation, the antiretroviral efficacy of the novel drugs remains intact, however, the LAF-conjugates are more potent than their unconjugated counterparts. This shift in potency may be due to the fact that the LAF allows for better absorption of the drug, which in turn means a lower concentration is needed to act at the same level of inhibition as the unconjugated form. Better absorption and higher potency would allow HIV-1 infected patients to take ART medications less frequently. It is believed that with longer lasting regimens, prescription and adherence to ART would significantly increase leading to reduced transmission of HIV-1 as well as reduced numbers of patient deaths.
Research Project Title:

Student Presenter: Natalia Oliverira

Faculty Mentor:

Faculty Mentor Department:

Research Abstract: The effect of L-carnitine in contrast-induced nephropathy in diabetic rats
Research Project Title: Small molecule M4 disperses Salmonella biofilms

Student Presenter: Laura Kuo

Faculty Mentor: John Gunn

Faculty Mentor Department: Microbiology

Research Abstract: Typhoid fever continues to be a pressing global health concern affecting millions of people per year. Individuals contract the disease by consuming food and water contaminated with the etiologic agent, Salmonella Typhi (S. Typhi). Of those that resolve the systemic infection, 3-5% will go on to become chronic carriers with the primary reservoir of the bacteria being the gallbladder. The development of chronic carriage has been strongly correlated with the presence of gallstones. Furthermore, we have demonstrated that the ability of S. Typhi to form biofilms on gallstones provides tolerance to bile and antibiotics and facilitates typhoid carriage. Chronic carriers are crucial in the spread of the disease as there are no other biotic vectors for this human-specific pathogen. Due to the importance of biofilms in the development of chronic carriage, the identification of biofilm dispersal agents will provide new therapeutic strategies. We have evaluated the anti-biofilm properties of several small molecules against Salmonella and identified a promising 3,5-dichloro compound, M4. This compound inhibits and disperses Salmonella biofilms with an IC50 of 8.1 uM and 21.0 uM, respectively, but does not kill Salmonella and showed no significant toxicity to eukaryotic cells or Galleria mellonella larvae. Our findings demonstrate that M4 could provide a pharmaceutical alternative to eliminate the asymptomatic carriage state and thus limit the global spread of typhoid fever.
Research Project Title: MIR-21 in resolution of wound inflammation

Student Presenter: Carly Polcyn

Faculty Mentor: Amitava Das

Faculty Mentor Department: Surgery

Research Abstract: Wound inflammation is a part of the wound healing cascade that aims to restore normal physiological function of injured tissue. Persistent inflammatory response might be detrimental and cause loss of organ function. Diabetic wounds are characterized by increased burden of dead cells. Cleaning of dead cells by macrophages (efferocytosis) is important to resolve inflammation. miRNAs are small non-coding RNA molecules which regulate gene expression by binding to the 3' UTR of targeted mRNA and have a critical role in inflammation. Our lab has previously reported an increased expression of inducible miR-21 in post-efferocytotic peripheral blood monocyte-derived macrophages resulting in a net anti-inflammatory phenotype. However, wound macrophages are considerably different from cultured macrophages and there is no evidence on the role of miR-21 in wound macrophages in vivo. To elucidate the significance of wound macrophage miR-21 in wound inflammation, an animal model with myeloid specific knock down of miR-21 was developed by crossbreeding mice carrying floxed miR-21 allele (miR-21fl/fl) with LysM-Cre mice. The animals were characterized by genotyping with DNA from tail biopsies by PCR. Bone marrow-derived monocytes (BMDM) were isolated from the femurs of mice and followed by positive selection using magnetic beads conjugated with CD11b antibody. For wound macrophages, PVA sponges were isolated on day 7 by repeated compression followed by CD11b positive selection. RTPCR analysis revealed a significant knockdown of miR-21 in BMDM and wound macrophages. Current studies are ongoing to test the significance of the miR-21 in wound inflammation that would enable an understanding of the miR-21-dependent mechanisms which are impaired in chronic wounds.
Research Project Title: Integrating molecular and epidemiological data in models of HIV-1 transmitted integrase strand transfer inhibitor resistance

Student Presenter: Alexander Northrop

Faculty Mentor: Laura Pomeroy

Faculty Mentor Department: College of Public Health, Division of Environmental Health Sciences

Research Abstract: Introduction:

The human immunodeficiency virus (HIV-1) affects nearly 37 million individuals globally and causes acquired immunodeficiency syndrome (AIDS). No vaccine for HIV-1 nor cure for AIDS currently exists; however, with access and adherence to medicine known as antiretroviral therapy, those infected with HIV-1 can survive for many years. Guidelines for HIV-1 treatment consist of a regimen of different classes of drugs, which target various parts of the viral replication cycle. A recently developed class of antiretroviral drugs, Integrase Strand Transfer Inhibitors (INSTIs), is remarkably effective in treating HIV-1. Yet, there is a growing concern that the current widespread use of INSTI-class drugs will lead to an accumulation of INSTI-resistant HIV-1 mutants because drug resistance has occurred in all other antiretroviral drug classes developed to date. Due to the relatively low prevalence of INSTI-resistant mutants in drug-naïve populations and the recent introduction of INSTI drugs to the market, it is difficult to measure rates of HIV-1 drug resistance molecularly or epidemiologically. Nevertheless, it is important to determine these rates of both acquired and transmitted drug resistance in order to maintain effectiveness of the drugs.

Methods:

Toward this goal, we designed a mathematical model that estimates the rate of transmission of HIV-1 strains with primary INSTI-resistant mutants or transmitted drug resistance (TDR). We parameterized the model with estimates from molecular and epidemiological literature to represent HIV-1 transmission in Washington D.C.

Results:

We compared rates of TDR to rates of overall drug resistance and assumed that the difference quantifies acquired drug resistance conferred by selective pressure from the use of antiretrovirals. In this way, we quantified and predicted cumulative INSTI drug resistance.

Conclusions:

This work informs HIV-1 treatment. First, we estimated the rate of TDR versus acquired drug resistance, which has yet to be accomplished in epidemiological or biological studies. Secondly, we predict when it would be advisable for clinicians to screen patients of drug resistant strains of HIV-1 before prescribing INSTI-class drugs. Finally, by developing the model, we have established a method to evaluate the drug resistance for other cases of drug resistance.
Research Project Title: Evaluation of fetuin-A as a mediator of scar formation

Student Presenter: Nicholas Pappa

Faculty Mentor: Traci Wilgus

Faculty Mentor Department: Pathology

Research Abstract: There are major differences in wound healing between adult and fetal skin. It has been discovered that early gestation fetal skin heals by regeneration with no scarring, yet late gestation fetal skin and adult skin heal with the formation of scar tissue. The formation of scar tissue can have negative effects as scar tissue can hinder normal tissue growth and even affect patients psychologically. Fibroblasts are essential to wound healing and scar formation. These cells produce the excess collagen that forms a scar. Therefore, fibroblasts are a crucial factor in determining whether the wound healing process will result in scar formation or the damaged skin will regenerate. Research was performed comparing protein expression in fibroblasts from different stages of development. Proteomic analysis showed that expression of the protein fetuin-A (FetA) was significantly higher in fibroblasts of embryonic day 18 skin, which heals with a scar, compared to fibroblasts of embryonic day 15 skin, which heals by regeneration. Higher levels of FetA were also observed in whole E18 skin compared to E15 skin. Injection of recombinant FetA into E15 fetal wounds increased the amount of scarring compared to control wounds. Cultured fibroblasts treated with FetA showed an increase in collagen expression compared to control samples. The data suggest that FetA may promote scar formation. Very little research has been done on the effect of FetA on fibroblast function and scar formation, but the results suggest that inhibition of FetA may be a mechanism to reduce scar formation in wounds. Current studies are being performed to examine scar formation in FetA knockout mice to confirm the significance of FetA in scar formation.
Research Project Title: Identification of small molecules with curative and transmission blocking activities to the human malarial parasite, *Plasmodium falciparum*

Student Presenter: Abu Rogers

Faculty Mentor: Mark Drew

Faculty Mentor Department: Microbial Infection and Immunity, Ohio State University College of Medicine

Research Abstract: *Plasmodium falciparum*, the most pathogenic human malarial parasite, has multiple life stages within the human host: primarily the asexual blood stages that cause disease and the sexual blood stages, called gametocytes, which are infective to female *Anopheles* mosquitoes. In order to both treat and to eradicate the disease, novel anti-malarial therapeutics with curative and transmission-blocking properties are required. Transmission of the parasite to the mosquito can be blocked by killing the gametocytes present in the bloodstream (gametocidal) or by inhibiting the process of the sexual development (anti-gametogenic). For the first part of this study, several in vitro assays were utilized to investigate the activity of six compounds purified from *Cinnamosma fragrans*, a Madagascan plant used as an antimalarial in traditional medicine. All six compounds were found to be potent against the asexual stages, with the most potent displaying an IC50 in the sub-micromolar range. Current studies indicate two of these compounds inhibit the process of gametocyte exflagellation, suggesting dual curative-transmission blocking activity. For the second part of this study, we focus on central carbon metabolism of gametocytes. Our lab has identified several inhibitors of the *Plasmodium falciparum* enzyme hexokinase (PfHK) which block formation of glucose to glucose-6-phosphate. These compounds kill asexual parasites at sub-micromolar concentrations, and are not toxic to human cell-lines. Assays are currently underway to assess their transmission blocking activity on sexual gametocytes.
Research Project Title: Hypoxamirs in ischemic wound healing: Role of miR-210 and miR-101

Student Presenter: Erin Sheehan

Faculty Mentor: Subhadip Ghatak

Faculty Mentor Department: Department of Surgery

Research Abstract: Background: Hypoxia is the deprivation of oxygen in the wound and causes severe peripheral vasculopathies inducing the hypoxamiR miR-210. Elevated miR-210, persisting in wound edge tissue as ischemic memory suppresses oxidative metabolism and inhibits cell proliferation necessary for healing. Moderate hypoxia is important for angiogenesis that facilitates wound healing. miR-101 regulates angiogenesis. However, the significance of miR-101 expression in hypoxia is still elusive.

Methods: 8-10 weeks old male C57bl/6 mice were used for this study. A monopedicle flap measuring 3 cm long and 1 cm wide was developed on the dorsal skin of the mouse. A silicon sheet was planted underneath the flap to negate the possibility of probable perfusion under the flap. The flap edges were cauterized and sutured to adjacent skin. Laser speckle imaging was performed to evaluate the extent of perfusion in the flap. At day 3 after the surgery, the flap was collected and divided in three different region (1cm apart) named as proximal, intermediate and distal according to the extent of hypoxia. One part of each fraction was collected in OCT and the other portion was snap frozen for RNA isolation. Epithelial keratinocytes were collected using Laser Capture Microdissection (LCM). RNA isolation, cDNA synthesis and qRT-PCR were performed to measure the expression of miR-101 and miR-210 in each section. U6 was used as housekeeping control.

Results: Using mono-pedicle flap model, the extent of ischemia was categorically characterized by dividing the flap into three parts (proximal, intermediate and distal). Laser speckle imaging showed that the distal portion of the flap is more ischemic than the proximal part. Expression of miR-210 was found to be proportional to the extent of hypoxia. Unlike miR-201, the expression of miR-101 was found to be proportionally downregulated with the extent of ischemia. Laser Capture Microdissection of the keratinocytes showed that downregulation of miR-101 is more in the region of moderate hypoxia (proximal region) whereas in the distal region the expression of miR-101 is unaffected.

Conclusion: This data suggests that expression of miR-101 is downregulated in response to moderate hypoxia that may be attributed to induce the expression of angiogenic genes.
Research Project Title: Fish oil supplementation reduces high levels of circulating pro-inflammatory cytokines in older adults with chronic wounds

Student Presenter: Sarah Wood

Faculty Mentor: Jodi McDaniel

Faculty Mentor Department: The Ohio State University College of Nursing

Research Abstract: High levels of circulating pro-inflammatory cytokines are characteristic of chronic systemic inflammation, a condition that promotes many age-related disorders including chronic wounds, cardiovascular disease (CVD), and arthritis. Low-risk therapies to reduce chronically high levels of pro-inflammatory cytokines in aging are needed because by 2060 the U.S. population aged ≥ 65 years is projected to reach 23.5% (98 million). Some studies have shown that the bioactive components of fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), moderate pro-inflammatory cytokine synthesis, but their effects specifically in older adults remain unclear. This study’s purpose was to compare plasma levels of three major pro-inflammatory cytokines in older adults with chronic wounds receiving oral EPA+DHA therapy versus placebo therapy. This randomized, double-blind study evaluated 35 older adults with chronically inflamed leg wounds at a university research center. For 8 weeks, EPA+DHA Group participants (n=16) consumed EPA+DHA supplements (2.5 g/d) and Placebo Group participants (n=19) consumed a placebo. Fasting blood plasma samples were collected at Weeks 0, 4 and 8 to quantify levels of pro-inflammatory cytokines IL-6, IL-1β and TNF-α. Sociodemographic, comorbidity, and body mass index (BMI) data were also collected. On average, participants were 60.6 years (SD=11.96) with a BMI of 41.7 (SD=11.51). The majority were male (60%), Caucasian (74%) and had diagnoses of CVD (77%) and/or arthritis (51%) in addition to a chronic wound. There were no significant differences in age, BMI, or comorbidities between groups. After adjusting for baseline differences, the EPA+DHA Group demonstrated significantly lower levels of IL-6 (p = .008), IL-1β (p < .001), and TNF-α (p < .001) at Week 4 and at Week 8 [IL-6 (p = .007), IL-1β (p < .001), and TNF-α (p < .001)] than the Placebo Group. Additionally, there were no reported side effects. The findings suggest that low-risk EPA+DHA therapy may help prevent or reduce severity of common inflammation-driven disorders in aging. It is recommended that future studies test EPA+DHA therapy in larger, more diverse samples of older adults.
Research Project Title: The effect of protocol adherence and equipment type for blood pressure measurement

Student Presenter: John Mickley

Faculty Mentor: Kevin Evans

Faculty Mentor Department: Radiologic Sciences / Respiratory Therapy Division

Research Abstract: High blood pressure is found in 1 out of 3 U.S. adults and is increasing in prevalence. The screening of patients is accomplished by obtaining a patient’s blood pressure (BP) either manually or with an automated system. The manual technique for obtaining a BP was the original gold standard, but with technologic improvements, automated machines in clinics and at home has created an alternative. This study was devised to address providers concerns over the validity of automated BP measurements. This study was designed to compare how the readings of manual and automated BP were related and the changes induced with varied protocols for measuring BP. The goal was to determine whether the equipment or method could cause discrepancies in BP readings when transitioning from manual to automated apparatuses. All subjects (39) had their BP measured following protocol, utilizing three different measurement devices: manual (MA), automated Midmark IQ vitals (PR), and an automated Omron home unit (OM) as well as measured in a typical doctor’s office visits (TY). The results showed that the mean systolic BP (SYS) for TY (123.7mmHg) > OM (118.3mmHg) > PR (114.8mmHg) > MA (111.0mmHg), all statistically significant (p<0.01). The mean diastolic BP (DIA) for TY (79.6mmHg) > PR (71.5mmHg), OM (71.05mmHg) and MA (70.0mmHg), with TY significantly higher than the other 3 (p<0.01). Despite the significant difference, all the measurements had a high intraclass coefficient between them, SYS (0.87mmHg), DIA (0.81mmHg). When comparing the number of participants categorized in each hypertension stage, TY categorized 7 participants as stage 1 hypertensive while OM categorized 3, and both MA and PR only categorized 1. The results demonstrate that, in this cohort of participants, there was a significant difference between protocol adherence and the lack of protocol, which was more than the difference between manual and automated apparatuses. These study results would suggest that there is a potential for possible misclassification of patients based on BP protocol. This could have implications for treating patients based on improper BP protocol. It is imperative medical professionals revisit the process for measuring BP and properly treat hypertensive patients.
Research Project Title: Topically administered imiquimod induces systemic autoimmunity in humanized NSG mice

Student Presenter: Perry Blough

Faculty Mentor: Jarjour No

Faculty Mentor Department: Wael

Research Abstract: Introduction/Background

Imiquimod (IMQ), a TLR7 agonist, has been shown to induce a phenotype in mice that resembles Systemic Lupus Erythematosus (SLE) in humans. When applied topically, IMQ prompts systemic autoreactivity that mimics lupus-like manifestations such as autoantibodies, cutaneous lesions, and glomerulonephritis. However, the role of lymphocytes in this lupus model is not well understood. Moreover, the function of cutaneous lymphocytes in humans and lupus mouse models is relatively unknown. The aim of our project is to establish a humanized lupus mouse model that exhibits skin and kidney disease in order to explore the role of cutaneous lymphocytes in the development of lupus skin lesions in these mice.

Methods

Two cohorts of immunodeficient mice were injected with either human peripheral blood mononuclear cells or phosphate-buffered saline as a control. Additionally, each cohort was topically treated with IMQ on their shaved left dorsum and a control cream on their shaved right dorsum twice per week over the course of four weeks. Weights were recorded each week, and blood and urine samples collected throughout the duration of the experiment were analyzed using autoantibody ELISAs, Urine Albumin ELISAs, and BUN assays. At the conclusion of the study, all mice were sacrificed and various tissues were harvested for histopathologic assessment.

Results

At the conclusion of the project, the experimental cohort developed significantly worse cutaneous lesions than the control cohort on the side treated with IMQ. Additionally, the experimental cohort exhibited elevated levels of serum autoantibodies, and histopathologic analysis of kidney tissue indicated the development of glomerular IgG deposition in the experimental cohort. Immunohistochemistry also revealed elevated levels of IgG in the lesional skin of the experimental cohort.

Conclusion

Preliminary data suggests that lymphocytes play a key role in the development of lupus-like manifestations. Further experiments are necessary to resolve the specific cell-type mediating this disease, which may help determine therapeutic pathways regulating such manifestations that could be translated into impactful treatments for individuals suffering from SLE and other autoimmune diseases.
Research Project Title:

Student Presenter: ahmad shkoukani

Faculty Mentor: sergakis No

Faculty Mentor Department: georgianna

Research Abstract: Inhaled Epoprostenol for hypoxemia: Review of Current Utilization and development of an Evidence-Based Protocol