Mentor(s):
Joseph Benoit, PhD
Professor
Physiology & Pathology

Project Title:
Development and Assessment of a Computer Model of External Compressive Forces on Interstitial Fluid Dynamics

Project Abstract:
The formation and transport of lymph has been extensively studied in man and animals. As a result, the factors governing the exchange of fluid and macromolecules across the capillary are well understood. Less is known about interstitial fluid dynamics and the movement of interstitial fluid into and through the lymphatic system. One reason for this limited understanding of interstitial fluid dynamics is that most of the physiological measurement techniques are invasive and cause disruption of the normal capillary, interstitial fluid, and lymphatic interfaces. In a previous report, we developed a computer model that accurately simulated transcapillary fluid and macromolecular exchange in the small intestine. Using this modeling approach, we were able to systematically examine the dynamics of capillary exchange. The summer research project described in this abstract proposes to use a dynamic systems modeling approach to examine the effects of intrinsic lymphatic pumping and simulated lymphatic pumping techniques on transcapillary dynamics, interstitial fluid transport and lymph flow. Students working with the P.I. will use iSee Systems Stella Architect software to develop a three compartment physiological model capillary, interstitial, and lymphatic fluid dynamics. Stella uses object oriented programming and as such does not require any prior computer programming experience. The project will consist of three phases. In Phase I, students will learn the basics of compartmental analysis and dynamic simulation. Phase II of the project will involve reviewing the scientific literature and gathering information on baseline values for capillary, interstitial and lymphatic variables that have been obtained in previous physiological studies. Students will work with the P.I. to incorporate these values into mathematical relationships that describe the three compartments: capillary, interstitial, and lymphatic. The relationships will then be incorporated into a computer model using the Stella program. Phase III will center on establishing the baseline characteristics and evaluating the predictive capabilities of the model system. The first series of simulations will evaluate capillary filtration, interstitial fluid volume, and lymph formation during periods of increased capillary filtration with passive lymphatic drainage. The second series of simulations will evaluate the effects of intrinsic lymphatic pumping on removal of interstitial fluid during periods enhanced capillary filtration. The third series of simulations will examine the effects of rhythmic tissue movement on removal of interstitial fluid during periods of enhanced capillary filtration. Analysis and comparison of the various simulations will allow the researchers to better understand the physiology of lymph transport and the therapeutic implications of manipulative approaches that promote lymph drainage.

Mentor(s):
Debra Bramblett, PhD
Associate Professor
Biomedical Sciences

Michael Woods, PhD
Assistant Professor
Physiology and Pathology

Project Title:
Development of a Multiplexed Reverse Transcription-Loop-Mediated Isothermal Amplification (RT-LAMP) Assay for the detection of emerging arboviruses

Project Abstract:
The long-term goal of this proposal is to establish an institutional capability to conduct arbovirus surveillance in New Mexico and elsewhere, and to position BCOM to play a central role in responding to emerging infectious diseases that may one day impact the southwestern US. The explosive emergence of Zika, Dengue and Chikungunya into Central America and the Caribbean in recent years has raised concerns that these diseases may one day establish themselves in the United States just as West Nile virus did following its initial introduction into the US in 1999. Furthermore, a warming climate has expanded the range of the primary mosquito vector for these viruses, Aedes aegypti, to include most of the southern United States, including New Mexico. The US is no less immune to emerging infectious diseases than any other place in the world, and therefore it is essential that we prepare for the inevitability that these “foreign” diseases will one day be our diseases. To accomplish our goal, we propose to develop an isothermal nucleic acid amplification technique capable of detecting multiple emerging arboviruses in a rapid, “low-tech” format that can be performed in the field or at the bedside without the need for complex or expensive equipment. This assay will be based on a multiplexed reverse transcription-loop-mediated isothermal amplification (RT-LAMP) reaction targeting West Nile virus (WNV), Zika virus, Dengue virus (DENV) and Chikungunya virus (CHIKV). To demonstrate the utility of this assay we plan to test a large collection of mosquitoes collected from across New Mexico to determine the distribution and prevalence of WNV in the state. These data will help public health planners better identify the areas of potential concern for future arbovirus emergence, and help communities address existing disease threats by adopting stronger intervention and control strategies. Specific Aims for the 2018 summer student projects: • Specific Aim (Student) #1: Use bioinformatics tools to develop/Design Reverse-Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) primers specific to West Nile virus (WNV), Zika virus, Dengue virus (multiple serotypes) and Chikungunya virus. • Specific Aim (Student) #2: Optimize LAMP reaction conditions for each primer set using a colorimetric reaction indicator and standardized plasmid targets.

Mentor(s):
Kristin Gosselink, PhD
Associate Professor
Physiology & Pathology

Project Title:
Central Regulation of Energy Balance in Stress and Hypertension

Project Abstract:
Essential hypertension is a prevalent condition that increases the risk for serious cardiovascular, renal and neurological disorders. Genetic and environmental factors are implicated in the development of hypertension, which is often associated with stressful lifestyles and co-morbid with other conditions including obesity, diabetes, and dyslipidemia. Multiple animal models exist for the study of hypertension and, interestingly, an array of investigations has identified a link between hypertension and energy balance. Chronic calorie restriction prevents the development of hypertension in spontaneously hypertensive rats (SHR), and these animals demonstrate reductions in food intake and body weight even when fed a high fat diet. Other studies have identified an important role for the orexin system in the regulation of hypertension, but there is limited understanding of the role of ghrelin, another orexigenic peptide, in controlling blood pressure even though plasma ghrelin levels are elevated in SHR as well as normotensive rats exposed to stress. The purpose of this study is to evaluate and compare ghrelin receptor expression in brain regions activated by acute or repeated stress exposure in SHR and Wistar-Kyoto control rats. Our hypothesis is that stress-sensitive brain regions will have higher numbers of ghrelin receptor-expressing neurons, and that this effect will be exaggerated in SHR compared to normotensive animals. This study will identify a potential mechanism through which stress and energy balance may be integrated in the control of hypertension, and inform possible targets for behavioral or pharmacological intervention.

Mentor(s):
Samuel Kadavakollu, PhD
Assistant Professor
Biomedical Sciences

Project Title:
Risk Stratification Algorithm of Severe Sepsis Patients in the Desert Southwest

Project Abstract:
Context: Sepsis is caused when the body has an extreme response to an infection whether in the skin, lungs, urinary tract, or somewhere else. Sepsis is a chain reaction throughout the body. Without timely treatment, sepsis can rapidly lead to tissue damage, organ failure, and death. It is considered a life-threatening medical emergency which requires early identification and early treatment. Severe sepsis is a leading cause of death in hospitals and is increasingly prevalent in the United States. It represents one of the most common diagnoses leading to ICU admission, a major driver of cost in the U.S. healthcare system, approximately 20 billion dollars a year. Severe sepsis strikes more than a million Americans every year, approximately 30 percent of those people die. The number of sepsis cases per year has been on the rise in the United States. Thus, there is a clinical and economic imperative to optimize treatment among patients with severe sepsis. Objective: Administrative data is readily available for research and quality improvement in severe sepsis. However, there is not a sepsis-specific algorithm applicable to clinical data with which to adjust for illness severity and comorbidities. The objective is to develop a risk adjusted tool that can be utilized to predict risk for mortality in the severe sepsis population. Severe sepsis is a labyrinthine syndrome; therefore, severity adjustment tools are important for efforts seeking to improve patient care and outcomes. To date, there has not been a simple-to-use, publicly available, sepsis severity algorithm that can be applied using common clinical data already being collected. There is a gap in the repository of techniques relevant to sepsis research, quality improvement, and the treatment of patients. Developing a severe sepsis risk stratification tool, utilizing patient data upon identification of severe sepsis, will help guide important decisions being made by physicians, patients and family. By identifying factors before the patient declines, it is possible to develop targeted interventions to mitigate the impact of severe sepsis. Study Design/Setting/Participants: Retrospective review of electronic medical records for adults, 18 years and older, who were diagnosed with sepsis, at MountainView Regional Medical Center, will have data manually abstracted to collect defined data points. Patients with a discharge ICD-9 or ICD-10 code for sepsis, and identified with the data analytics platform PremierConnect, during the time period of October 2015 through May 2019 will be included in the sample size. Risk stratification is a process that helps determine detectable characteristics associated with an increased chance of unwanted outcomes, in this case-mortality. Thus, by creating an algorithm for risk stratification, predictive analytics can then guide the care rendered to the patient.

Mentor(s):
Adrienne Kania, DO
Associate Professor
Clinical Specialties

Pedro Del Corral, MD, PhD
Assistant Professor
Physiology & Pathology

Harald Stauss, MD, PhD
Assistant Professor
Biomedical Sciences

Project Title:
Effect of Osteopathic Manipulative Treatment on Autonomic Balance

Project Abstract:
Osteopathic manipulative treatment (OMT) has been demonstrated to shift autonomic balance from sympathetic to parasympathetic tone [1, 2], which has been implicated with reduced cardiovascular morbidity and mortality [3] and reduced systemic inflammation [4]. This may provide a mechanistic link between OMT and its effectiveness in inflammatory diseases such as Crohn's disease [5]. However, the temporal autonomic response to repeated OMT applications is not well understood. Specifically, it is not known how many OMT sessions are needed to achieve a maximal effect on autonomic balance. Therefore, we propose to test the hypothesis that repeated applications of OMT have additive effects and, thus, gradually improve autonomic balance. Furthermore, we hypothesize that the magnitude of the maximal effect of repeated OMT applications correlate with a decline in the pro-inflammatory marker C-reactive protein (CRP). To test these hypotheses, two groups of healthy subjects will receive six repeated applications (3-4 days apart) of either OMT (fourth ventricle compression, CV4) or sham OMT (palpation only). CV4, has been demonstrated to increase heart rate variability (a marker of parasympathetic tone) 10-15 min following a single OMT application [2] and to reduce muscle sympathetic nerve activity during a single OMT application [1]. At each visit autonomic parameters, including heart rate and its variability, blood pressure and its variability, baroreflex function, skin conductance, pupillary diameter) will be assessed before, during, and up to 15 min following OMT or sham OMT. Saliva samples will be collected before and 15 min following OMT for determination of CRP. To test if acute and chronic OMT applications reduce sympathetic responsiveness, the responses of blood pressure, heart rate, heart rate variability, and salivary cortisol concentrations to a cold pressor test will be assessed at baseline (at least 24 hours prior to the first OMT application) and after the first and last OMT application.

References
1. Cutler, M.J., et al., Cranial manipulation can alter sleep latency and sympathetic nerve activity in humans: a pilot study. J Altern Complement Med, 2005. 11(1):103-108.
2. Curi, A.C.C., A.S. Maior Alves, and J.G. Silva, Cardiac autonomic response after cranial technique of the fourth ventricle (cv4) compression in systemic hypertensive subjects. J Bodyw Mov Ther, 2018. 22(3):666-672.
3. Kleiger, R.E., et al., Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol, 1987. 59(4):256-262.
4. Tracey, K.J., Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest, 2007. 117(2):289-296.
5. Piche, T., et al., Osteopathy decreases the severity of IBS-like symptoms associated with Crohn's disease in patients in remission. Eur J Gastroenterol Hepatol, 2014. 26(12):1392-1398.

Mentor(s):
Nancy Minugh-Purvis, PhD
Professor
Anatomy & Cell Biology

Kristopher Vaudrey, MA
Instructor
Anatomy & Cell Biology

Project Title:
Reassessing Microtia in New Mexico

Project Abstract:
The abstract was not included in this listing at the investigators request. If interested, please see Dr. Ontiveros or the PI for more information.

Mentor(s):
Nancy Minugh-Purvis, PhD
Professor
Anatomy & Cell Biology

Kristopher Vaudrey, MA
Instructor
Anatomy & Cell Biology

Adrienne Kania, DO
Associate Professor
Clinical Specialties

LeAnn Jons-Cox, DO
Associate Professor
Clinical Specialties

Project Title:
Enhancing Palpatory Skill Development in Entering Osteopathic Medical Students

Project Abstract:
The abstract was not included in this listing at the investigators request. If interested, please see Dr. Ontiveros or the PI for more information.

Mentor(s):
Steven J. Ontiveros, MBA, PhD
Assistant Professor
Anatomy & Cell Biology

Project Title:
Determining the Effects of Resveratrol on Hexokinase II Mitochondria Membrane Attachment in Cancer Cells

Project Abstract:
Worldwide, cancer is a major health concern that is generally classified under a broad group of diseases, but fundamentally it is a progressive disease of continuous cell proliferation, where malignant cells have lost their ability to properly regulate the progression of the cell cycle. Studies have shown that malignant cells bypass normal control measures by using altered cellular mechanisms that help drive continuous proliferation. Although, great advancements have been achieved in the development of therapies for treating cancers, the chief concern with the use of current strategies is that they are also harmful to normal cells. For this reason there is a desperate need for more target-based strategies that are highly selective, and are capable of exploiting the difference between normal and cancer cells.

Hexokinase (HK) proteins are glycolytic enzymes that bind mitochondrial membranes and are responsible for phosphorylating glucose within the first step of glycolysis during ATP production. Unlike normal cells, cancer cells secure ATP levels by utilizing mechanisms of altered sugar metabolism. Studies have shown that cancer cells consume more glucose than normal cells, and have a propensity to use glycolytic mechanisms. HK enzymes are highly expressed in malignant cells, and are known to facilitate the shift from normative state of oxidative phosphorylation for obtaining ATP, to an altered model in cancers where cells secure their energy needs through glycolytic mechanisms. Therefore, once cells have become malignant, glycolysis is a pivotal mechanism for the growth and maintenance of cancer cells. It is this differences observed between securing ATP in normal and malignant cells serves as potential target for therapies.

Resveratrol (2,5,4'-trihydroxy-trans-stilbene) is a natural occurring polyphenol that is generally found in berries, such as grapes, blueberries, and raspberries, peanuts, and many other sources. Resveratrol has been shown to possess intracellular antioxidant activity, and serves as a protective mechanism in response to injury against pathogens such as bacterial or fungi. Although, resveratrol has been shown to have minimal toxicity to normal cells, it demonstrates anticancer activity during tumor development. These anti-proliferative effects have been observed in a variety of cancer cell lines, including A549, HeLa, and MCF-7 cells. Studies have demonstrated that it binds to complex V (ATP synthase) and inhibits ATP synthesis.

Since resveratrol is capable of inhibiting glycolysis in cancer cells, we aim to determine if the mechanism of this naturally occurring phenol is achieved by targeting HKII and its attachment to mitochondrial membranes in MCF7 cells, and hypothesize that the inhibition of glycolysis by resveratrol is achieved by HKII membrane detachment.

Mentor(s):
Richard Selinfreund, PhD
Associate Professor
Physiology & Pathology

Marat Telipov, PhD
Assistant Professor
Chemistry & Biochemistry

Barbara Lyons, PhD
Associate Professor
Chemistry & Biochemistry

Erik Yukl, PhD
Assistant Professor
Chemistry & Biochemistry

Project Title:
Collaborative Study- BCOM-NMSU; Computer Modelling Guided Development of Complexes to Increase Bioactivity of Clinically-Important Compounds

Project Abstract:
On one hand there is a critical need to develop protecting molecules to extent the shelf-life and cellular half-life of clinically important pharmaceutical and bioactive co-factors. For example, extending the shelf live and increasing effective potency is a critical health need in the area of vaccines, protein based pharmaceuticals, and essential vitamins. On the other hand reducing the effective levels of circulating molecules in the blood stream that cause disease is equally as important. For example the use of cyclodextrins (CD) to lower lipid composition. Early studies have shown that exposing cells to cyclodextrins lowers the levels circulating cholesterol. A number of life's key processes including cell growth, bone osteogenesis and the clotting cascade are dependent on vitamin K (Dowd P. et al., 1991 J. Am. Chem. Soc. 114: 7723; Vermeer, C. and Knapen H. H. Ann. Review Nutr. 1995. Vitamin K is not made by mammals and must be included in the diet. This essential vitamin is not stable. Saturation of the double bond of vitamin K considerably reduces biological activity (Suttie, J.W In the Handbook of Vitamins; Machlin, L. J. Ed; Marcel Dekker Inc. New York, 1991 p 145-194. There is a critical need to develop stabilizing molecules for vitamin K. In the present study we propose a Summer Intern program in collaboration with Drs. Talipov, Yukl and Lyons to develop a computer guided model to stabilize vitamin K. In Dr. Marat Talipov laboratory, a BCOM medical student will be awarded a Summer Internship to use computer guided modeling to guide the selection of CD analogs that will stabilized vitamin K. In a parallel internship a BCOM medical student will work with Dr. Barbara Lyons and Dr. Erik Yukl to develop a bioassay to insure bioactivity Vitamin K- CD complex.

Mentor(s):
Richard Selinfreund, PhD
Associate Professor
Physiology & Pathology

Adela Lente, MD
Professor
Clinical Specialties

Justin McHorse, MS
Office of the Dean

Project Title:
Pueblo of Jemez & Burrell College of Osteopathic Medicine Youth Health Empowerment – Career Pathway Program

Project Abstract:
Purpose: The purpose of the Pueblo of Jemez & Burrell College of Osteopathic Medicine Youth Health Empowerment - Career Pathway Program (PJBCOM YHE-CPP) is to address and improve social determinants of health through the development of social capital via mentorship for Jemez youth to broaden their knowledge base and skillset to be better equipped to maximize their secondary educational experience for entry into an allied health career or in pursuit of a higher education. Approach: I. Jemez Youth Health Empowerment Summer Program II. Integration of curriculum in the Walatowa High Charter School designed to develop knowledge of the allied health fields III. External Allied Health Internship Training Programs with Corporations IV. Internal Pueblo of Jemez Health and Human Services Allied Health Internship Programs, which transition into careers Goal: To establish a two-way bridge partnership between the Pueblo of Jemez and the Burrell College of Osteopathic Medicine that heightens social determinants of health for the Pueblo of Jemez and fosters a sense of cultural humility for BCOM medical students, faculty and staff that will promote a more engaged and committed delivery of healthcare. Focus and Sustainability: PJBCOM YHE-CPP will build a sustainable presence of Native American allied health professionals who will return to their communities and fill healthcare positions serving their people and improving social determinants of health.

Mentor(s):
Richard Selinfreund, PhD
Associate Professor
Physiology & Pathology

Paul Breslin, PhD
Professor
Monell Chemical Senses Center

Project Title:
Comparison of Metabolically Balanced versus High Fructose Corn Syrup based beverages on glucose & HbA1c levels.

Project Abstract:
There has been much made about how low- or non-caloric sweeteners may alter metabolism by acting on T1R ("sweet taste") receptors in major metabolic organs and tissues throughout the body. Similarly, much has been made about how anticipatory regulatory hormones are triggered orally by glucose but not by other sweeteners. Together, these illustrate that sugars convey two independent signals from the oral cavity and beyond. One is a T1R-based signal associated with sweetness and the other a metabolic signal triggered by the breakdown of glucose in oral cells to yield ATP. But there have not been any studies elucidating the relationship between these two oral signals, their inter-relationship and inter-dependence functionally, or the quantitative relationship between the two, that is, ratio of these two signals. We hypothesize that during the normal course of eating fruits and other mono and di-saccharide containing foods that there is an ideal ratio of the magnitude of the sweet taste signal and the magnitude of the metabolic signal generated from free glucose that maximizes liking, preference, and consumption of foods and beverages. Curiously, this ratio tends not to favor maximum metabolic signaling over sweet taste. Hence, we prefer sweet AND calorically dense foods over calorically dense non-sweet foods such as potatoes and rice. Furthermore, even when two foods or beverages are sweet and have calories, we tend to prefer the one that has less-than-full calories. Conversely, foods that are sweet but lack calories are enjoyed but are not preferred to ones that have calories. For example, sugared soda is highly preferred to "diet" soda in the market place. Whereas the sugars glucose, fructose and sucrose (a disaccharide of glucose and fructose) are concerned, we generate calories largely via glucose rather than fructose in the mouth because fructose transporters are less common except in the intestine and liver. Thus, it is not clear that free fructose in the oral cavity is favored metabolically. Rather, fructose is the most potent sugar gram for gram at eliciting sweet taste. Hence, fructose tends to be more responsible for sweet taste than calories and glucose tends to be more responsible for caloric signal than for sweet taste. Sucrose, interestingly, is purely a sweetener and carries no calories except in the instance that oral sucrase or other oral saccharidases cleave sucrose into its component monosaccharides, which happens in our mouths. This is because only monosaccharides are transported into cells to be metabolized. We propose to study this the proposed comparative study.

Mentor(s):
Harald Stauss, MD, PhD
Assistant Professor
Biomedical Sciences

Pedro Del Corral, MD, PhD
Assistant Professor
Physiology & Pathology

Project Title:
Clinical Physiology: Effects of Non-Invasive Transcutaneous Auricular Vagal Nerve Stimulation on Hemodynamic, Autonomic, Endocrine and Immune Function

Project Abstract:
Vagal nerve stimulation (VNS) has been considered a potential treatment option for patients with a variety of diseases, including obesity, heart failure, chronic pain, as well as inflammatory diseases, such as psoriasis, lupus erythematosus, rheumatoid arthritis and Crohn's disease. Most of the therapeutic effects of VNS are thought to be mediated through modulation of autonomic nervous system function and/or activation of the parasympathetic anti-inflammatory reflex. Currently, VNS requires surgical implantation of an electronic device similar to a cardiac pacemaker to stimulate the cervical vagus nerve. Recent studies suggest that transcutaneous stimulation of the auricular branch of the vagus nerve (taVNS) may allow to achieve similar therapeutic effects non-invasively. To investigate this possibility, we propose to test the hypothesis that taVNS causes modulation of autonomic nervous system function and activates the parasympathetic anti-inflammatory reflex. To test this hypothesis, we will assess autonomic function (heart rate and its variability, blood pressure and its variability, baroreflex function, skin conductance, pupillary diameter) as well as inflammatory markers (cortisol, cytokines TNF α, IL-1β, IL-6, IL-8, secretory IgA from sputum samples, ELISA kits from Salimetrics) in healthy subjects during resting baseline conditions (no taVNS 30 min), during taVNS (for 30 min), and during recovery (no taVNS, 30 min). In a control group, sham stimulation (with the stimulator turned off) will be performed instead of taVNS.

Mentor(s):
Michael Woods, PhD
Assistant Professor
Physiology & Pathology

Project Title:
Mechanisms of Zika Virus-Mediated Cell Cycle Blockade

Project Abstract:
Zika virus is a mosquito-borne virus associated with increased rates of microcephaly in neonates born to infected women. Previous research has shown that the Zika virus Envelope protein induces G2/M cell cycle arrest in PC12 neuroendocrine cells associated with upregulation of p53 and p21 and downregulation of cyclin B1 (Liu et al., 2018). Failure to proceed through the G2/M checkpoint results in caspase activation and apoptosis. Additional studies have described transcriptional perturbations in Zika-infected neural precursor cells (Tang et al., 2016). The goal of this work is to expand on our understanding of the molecular mechanisms responsible for inducing neural progenitor cell death, and subsequent defects in brain development. As a part of this study, students will measure changes in expression and activation of several proteins important in cell cycle regulation, specifically an initiator of the G2/M checkpoint Chk1 and several of its targets, including proliferating cell nuclear antigen (PCNA), the protein phosphatase CDC25c, and the DNA replication licensing factor MCM2. Additionally, students will test the effect of a Chk1 inhibitor on Zika-infected NPCs. Students will learn to measure quantitative and qualitative changes in protein expression and activation primarily using Western blotting and/or immunofluorescent microscopy. Furthermore, students will develop experience growing and sub-culturing neural progenitor cell lines. All work with infectious virus will be conducted by collaborating scientists at New Mexico State University, who have the training and experience necessary to safely handle the virus. We will not handle any infectious materials in the BCOM BioSciences Research Lab (BSRL).