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Behavioral Sciences and Psychology

Role of Gesture-Accompanied Speech in Boosting Children's Vocabulary Learning (iOS application)

Isabela Agi Maluli

Faculty Mentor: Makeba Wilbourn

Authors: Isabela Agi Maluli, Makeba Parramore Wilbourn, Sarah Gaither

Behavioral Sciences/Psychology

Abstract:
The study examines the impact of gesture-accompanied speech on enhancing children's vocabulary, crucial for academic success. Vocabulary size is highlighted as a primary indicator of school readiness and academic achievement. The research focuses on the racial and socioeconomic disparities in vocabulary development, emphasizing the importance of targeted interventions. Central to the research methodology is the "What's that Word" game, based on the Peabody Picture Vocabulary Test (PPVT-5), designed to measure the effectiveness of gesture-accompanied learning. The game serves as both a pre- and post-test tool, providing concrete evidence of the gains in vocabulary learning facilitated by gestures. The game was developed using a code in Swift applicable for iOS devices. The proposed study seeks to further validate these findings through a controlled experiment involving first and second-grade students, exploring the potential of gesture-accompanied speech as a powerful educational tool to bridge the vocabulary gap. By incorporating gesture into vocabulary instruction, this research advocates for a more effective and culturally sensitive approach to teaching, promising to transform educational practices and outcomes for children across diverse backgrounds.

Children's willingness to pay a cost to follow rules depends on context and gender

Hannah Auddino

Faculty Mentor: Tamar Kushnir

Authors: Hannah Auddino, Jessa Stegall, Meltem Yucel, Xin Yue, Michael Tomasello, Shaun Nichols, Tamar Kushnir

Behavioral Sciences/Psychology

Abstract:
Children are sensitive to the ways rules are presented and use contextual cues to infer whether to exert self-regulation skills to obey them. In this study, we aim to see how different contextual rules, (group normativity vs individual authority), may affect children's self-regulation of difficult rules, while also investigating the influence of gender on this behavior. At the Duke Child Studies labs and the Museum of Life and Science in Durham, NC, we aimed to see if 4.00-5.99 -year-old (N = 41, data collection ongoing), children were sensitive to the difference between group (associated with the school or museum) and individual (the experimenter's desires) rules, and if group rules better predicted children's rule following behaviors. We then asked exploratory questions about their intuitions regarding the scope of the rule. Children were asked to only play with a small "boring" run and resist the desire to play with a larger "fun" run. Children were randomly assigned a condition: 1) authority, in which the rule is "I don't know what others want, but I want you to…", 2) norm, in which the rule is "Here at our school/museum, we only…", and 3) control, in which no rule was given. In every condition, the experimenter left the room and children were left for 3 minutes. Their proportion of rule following was determined by number of marbles placed in the "boring" run over total number of marbles used. Children were then asked three questions: 1) teaching, where they were asked to teach a puppet what it should do with a marble, 2) desire, where children demonstrated what they wanted to do with the marble, and 3) rule generalization, where children were asked explicitly if there was a rule related to the marble runs. If children understand that group norms exert power beyond individual authority, then they should continue to pay a cost to follow the rule in the norm, but not in the authority condition after the experimenter leaves. Preliminary data shows that children in the authority and norm conditions were significantly more likely to pay a cost to follow a rule than those in the control ((F(2, 35) = 17.77, p < .01)). In addition, girls were somewhat less likely to break the rule than boys in the experimental conditions (X2(1, N = 19) = 1.10, p = .29) and when compared to chance (3/14 cases, Binomial test, p = .057). Overall, our data shows that children's self-regulation can be increased through contextual cues, and this may be mediated by gender.

Why Students Hate Group Work: Understanding and Addressing Barriers to Collaborative Learning

Jeslyn Brouwers

Faculty Mentor: Bridgette Hard

Authors: Jeslyn Brouwers, Alissa Rivero, Angela Vieth, Bridgette Hard

Behavioral Sciences/Psychology

Abstract:
While collaborative learning in college classrooms yields many rewards, including preparing students with the interpersonal skills necessary for the workplace and improving student learning outcomes, many students dislike group work and approach it in ways that undermine its benefits (Pfaff & Huddleston, 2003). Building on these observations, we conducted two studies to 1) examine student attitudes towards group work across a semester-long group project and 2) to create, implement, and assess the effectiveness of a pedagogical intervention aimed at improving student group work experiences. In Study 1, we surveyed two cohorts of students enrolled in an undergraduate Psychology methods and statistics course, collecting quantitative and qualitative data and gathering insights from focus groups. Our analyses identified accountability as a key ingredient to successful group work. Study 2 applied insights from Study 1 to create an intervention, tested on a new cohort of students enrolled in the same class. Our baseline data suggests that, overall, students held neutral initial attitudes towards group work, but participation in group projects can improve these attitudes. Study 2 provided mixed evidence on the efficacy of the proposed intervention compared to baseline. While we expected student attitudes toward group work to increase at a higher rate throughout the intervention semester, student attitudes generally started off and ended more positively. Through this research, we seek to provide a novel framework for evaluating and scaffolding student group work experiences to enhance collaborative learning opportunities for undergraduate students.

Motivation control beliefs and their impact on regulatory strategy use during goal pursuit

Maria Brown

Faculty Mentor: James Shah

Authors: Maria Brown, Carlie Scheer, Sunny Zhu, Zhuying Guo ,Skyler Wyly, James Shah

Behavioral Sciences/Psychology

Abstract:
Extending research on the significance of individuals' implicit beliefs for goal pursuit and self-regulation, we examine how individual's beliefs about the nature of motivation and the control they have over it impact self-regulation and overall well-being. More specifically, we examine how beliefs about the nature and controllability of motivation might relate to the motivational strategies one uses to increase or maintain motivation, as well as the longer-term benefits of controlling motivation for persistence and well-being. A pilot study suggests that a belief in the controllability of motivation does tend to promote positive self-regulatory behaviors and well-being. In the current study, three hundred participants were recruited through Prolific to complete three online surveys in Qualtrics across two months, following up after two weeks and again after two months. In the first session, we measured participants' beliefs about motivation, and after manipulating participants' beliefs about the controllability of their motivation, had them identify and characterize three goals they were pursuing. In both follow-up sessions, we assessed their progress toward each goal and the extent to which they used regulatory strategies during their goal pursuit, as well as their performance and persistence in two word puzzle tasks.

Does parenting style impact social interactions in lemur species?

Catherine Byun

Faculty Mentor: Leslie Digby

Authors: Catherine Byun, Leslie Digby

Behavioral Sciences/Psychology

Abstract:
Social interactions between offspring and their parents may be influenced by an offspring's relationship with their mother in the first few months of life. Parenting style may be a major determinant of how secure offspring feel in this relationship, with some species demonstrating intense attachment through the mother carrying an infant at all times while others display a more laissez-faire parenting style by parking infants in nests and other group members caring for it. Though it is unclear how variable levels of maternal contact early in life impact attachment security of offspring and how this in turn impacts social behavior. I conducted observations on two different lemur species, sifakas (Propithecus coquereli) and ruffed lemurs (Varecia), with differing levels of maternal presence in early infancy. I found partial support that the parenting style of ruffed lemurs, characterized by lower levels of maternal contact, results in more socially secure offspring. Ruffed lemurs displayed higher levels of overall affiliative behavior (Med = 0.519; Mean = 0.522; SD = 0.126 proportion of time spent social) and lower levels of aggression (Med = 2.62; Mean = 5.49; SD = 5.71 events/hour) towards non-maternal group members compared to sifakas. Although, age of juvenile offspring may have had a stronger influence on parent-offspring interactions as younger juveniles displayed significantly higher levels of sociality ($p = 0.009$; $p = 0.03$; $p = 0.06$) than older juveniles. Overall the laissez-faire parenting style may lead to greater sociality in offspring with sociality naturally advancing as an offspring ages. Understanding all the factors that influence juvenile behaviors may help explain individual social preferences of primates as adults and as well as the determinants of sociality in general.

Childhood Trauma and Memory: Exploring Time-Dependent Effects of Adverse Childhood Experiences

Carmel Falek

Faculty Mentor: Gregory Samanez-Larkin

Authors: Carmel Falek, Sarah Gaither, Gregory Samanez-Larkin

Behavioral Sciences

Abstract:
Episodic memory, unique from other memory systems, entails the reimagination of past experiences. Episodic memory and related neural structures become more complex as children develop, all the way through adulthood, specializing as encoding and attention skills come online. Neglect and abuse early in development negatively affect neural, cognitive, and behavioral outcomes in adulthood. Facing such adversity during childhood, a period crucial to neural development, has been found to correspond to structural and functional changes to the hippocampus, along with reduced episodic memory performance. However, these past studies were limited, only done with children or adults who have diagnosed psychopathologies or focused on episodic memories related to their trauma. This underlines the limited understanding we have of the impact of these adverse experiences on non-trauma-related episodic memory, unrelated to abnormal psychological conditions. Additionally, there is an incomplete model of how early adverse experiences shape cognition across adulthood, accounting for a developmental lens to the life-long effects of early experiences. In the current two-part study, we analyze an elderly population and college students, outlining how general episodic memory performance is impacted by trauma immediately after removal from the home setting to decades later. The overarching goal is to confirm the literature's understanding of how adversity in childhood affects memory unrelated to their personal experiences and hippocampal volume, while also underlining the manifestation of these effects throughout adulthood. We assess an elderly (65+) population using the Childhood Trauma Questionnaire and various episodic memory paradigms, and then compare results in a replicated study for college students (18-22), emphasizing the growth of either resilience or fragility of victims over time. We also analyze sociocultural differences in these effects, emphasizing if well-being, race, or socioeconomic status mediates the relationship. Our findings emphasize the time-dependent effects of adversity on memory and the importance of examining underlying psychological consequences on memory relating to distinct forms of trauma.

Understanding Motivation Control Beliefs Through AI-driven Qualitative Interviews

Zhuying Guo

Faculty Mentor: James Shah

Authors: Zhuying Guo, Sunny Zhu, Maria Brown, Carlie Scheer, Skyler Wyly and James Shah

Behavioral Sciences/Psychology

Abstract:
Extending research on the significance of individuals' implicit beliefs for goal pursuit and self-regulation, the present study examines how individual's beliefs about the nature of motivation and the control they have over it may impact self-regulation and overall well-being. More specifically, we examine how beliefs about the nature and controllability of motivation might relate to the motivational strategies one uses to increase or maintain motivation, as well as the longer-term benefits of controlling motivation for persistence and well-being. A pilot study suggests that a belief in the controllability of motivation does tend to promote positive self-regulatory behaviors and well-being. In the current study, participants are recruited through CloudResearch to complete an AI-driven qualitative interview and an online survey in Qualtrics measuring participants' beliefs about motivation. The Engage AI Analysis software summarizes interviews, highlights noteworthy responses, and quantifies themes that are related to participants' beliefs about the controllability of motivation and their ability to self-regulate during goal pursuit. The sample size is determined by theoretical saturation, where the range of themes that make up the theory is fully represented by the data. From an initial sample of 60 participants, we use AI to identify new themes in each increment, adding in increments of 10 until 90% theoretical saturation is achieved. This study is part of a set of ongoing studies exploring the effects of motivation control beliefs on goal progress, persistence, and regulatory strategy use.

Behavioral Compassion and Religiosity

Abby Li

Faculty Mentor: Patty Van Capellen

Authors: Abby Li, Patty Van Capellen, Cheryl Tan, Aiyanna Kimble

Behavioral Sciences/Psychology

Abstract:
Background: Empathy, or the capacity to understand and share someone else's emotions, is a widely known feeling amongst humans. Previous research has found that showing empathy involves cognitive costs. As a result, empathy is a regulated and motivated process driven by personal goals and cares. However, research has also shown that religiosity is associated with increased valuation of compassion, and (limited) prosociality. The purpose of this study is to examine whether compassion (i.e., caring about someone else's emotions), like empathy, is an effortful process and to determine whether religiosity is associated with having more compassion. Methods: Participants (N=352) were recruited online and randomly assigned to two groups. The Prayer priming group was reminded of the power of prayer and were given a chance to pray at the end of the survey, and the Control group was not given such instructions. Then participants engaged in an 18-trial task during which they saw images of war victims in Ukraine and were asked to choose to either describe or care for the person they saw. Their decisions to these trials were recorded and served as a measure of choice to engage in compassion. Participants also reported their religiosity. Results: Analyses will test whether 1) the prayer framing increased compassionate choice; 2) there are associations between the measures of religiousity and the number of times they chose to care. These findings will shed light on whether religion can be harnessed to build a more compassionate society.

Art therapy and emotion regulation: Investigating creative engagement's impact on mental health

Kayla Lihardo

Faculty Mentor: Kevin Labar

Authors: Kayla Lihardo, Lucas Bellaiche, Dr. Kevin LaBar

Behavioral Sciences/Psychology

Abstract:
Art therapy employs creative activities such as painting to facilitate the self-expression of emotion, a mechanism which can be harnessed into emotion regulation. Past art therapy interventions in clinical populations have yielded meaningful results demonstrating reductions in both stress and depression. However, these previous paradigms lack proper control measures and standardization, administering art-making activities without defining the properties of that intervention. To address multiple methodological concerns in cognitive art therapy research, we implemented a within-subjects paradigm to examine both the behavioral and physiological effects of creative engagement. Over the course of three days, participants (n=99) were randomly assigned to carry out a creative task and non-creative control task in separate sessions. Participants were instructed to paint a non-representational artwork for 20 minutes in the creative task, and to complete printed mazes for 20 minutes in the non-creative control task. Behavioral measures of state anxiety, emotional distress, and mood disturbance were measured before and after each condition and on the third day via validated questionnaires, while physiological measures of heart rate were measured during each condition via Fitbits. Engaging in the abstract painting task resulted in a significant but short-lived decrease in anxiety compared to the non-creative maze-completion task. Results also demonstrated greater average heart rate and peak-to-trough values in response to the abstract painting task than the maze-completion task, indicating higher physiological sensitivity to creative conditions. These physiological results suggest the act of creative art-making potentially elicits greater cognitive but not motor engagement as compared to a non-creative control task, while behavioral results point to the anxiety-reducing benefits of art therapy. However, the effect of condition on differences in anxiety was not shown to be mediated by heart rate. While the relationship between our behavioral and physiological findings remains unspecified, the current study emphasizes the promising therapeutic role of creative engagement as a mechanism for emotion regulation.

Behavioral characterization of compulsive fentanyl self-administration

Ellen Mi

Faculty Mentor: Kafui Dzirasa

Authors: Ellen Mi, Karim Abdelaal, Kafui Dzirasa

Behavioral Sciences/Psychology

Abstract:
Over 75% of drug overdose deaths in 2021 in the United States involved opioids. To better understand the nature of opioid addiction in humans, intravenous self-administration paradigms in rodents have become a standard model to allow for the behavioral investigation of addiction and the biological mechanisms of substance use disorders. Importantly, the criteria for addiction-like behaviors in rodents exhibit face validity in modeling human behavioral phenotypes in substance use disorder. Namely, key substance use disorder criteria outlined in the Diagnostic Statistical Manual - V (DSM-V) can be modeled in self-administration paradigms, including persistent drug-seeking, punishment resistance, and relapse. However, few studies have shown comprehensive modeling of fentanyl-addiction related phenotypes in mice despite the growing public health issues around fentanyl use. Here we show successful modeling of fentanyl-induced addiction-like behaviors in an intravenous self-administration paradigm in mice. We found that over a six-week fentanyl self-administration paradigm, mice displayed persistent drug-seeking, escalation in drug use, and reinstatement. Following operant conditioning training, mice also showed an escalation of fentanyl intake over two-weeks of intermittent access to the drug. Moreover, progressive ratio testing allowed us to identify mice with an unusually high motivation to seek fentanyl. We also observed significant punishment resistance across all mice tested. Lastly, following a one-week extinction period, we observed cue-induced reinstatement of drug seeking behavior. Together, these results demonstrate a useful model of addiction-relevant behaviors in mice self-administering fentanyl, empowering future work to begin to understand the neural bases of these behaviors. The ultimate goal of these studies is to lead towards the identification of brain regions or circuits to target in the treatment of substance use disorders. This could be through deep brain stimulation or other emerging technologies to target the brain in region- and circuit-specific ways to improve human health.

Characterizing sleep-wake cycles in dogs from activity levels, age, sex, and temperament

Emily Sandberg

Faculty Mentor: Brian Hare

Authors: Emily Sandberg, Morgan Ferrans, Brian Hare

Behavioral Sciences/Psychology

Abstract:
Across many species, sleep patterns are associated with variables such as age, sex, daytime activity levels, and temperament. Yet, current research lacks an in-depth characterization of dog sleep patterns and how they vary according to these variables during the critical developmental period of young puppyhood. Such studies are crucial in order to establish dogs as a model organism for studies of sleep and for additional applications in the realms of dog welfare and training. In the present study, we characterized how often and for how long young dogs wake, as well as their barking patterns during sleep. We evaluated sleep behaviors for dogs aged 8-18 weeks and determined longitudinal patterns using a sample of Canine Companions service-dogs-in-training (N=21). Video recordings of dogs were analyzed using a novel coding scheme to determine duration and frequency of awake bouts and barking. Mixed-effects logistic regression models reveal that awake-bout length (minutes) and frequency did not vary significantly by weeks of age, daytime activity levels, or temperament. However, we did find significant sex differences in awake bout length (p<0.009). These results suggest distinct daytime and nighttime temperaments, as well as the importance of this developmental period for developing adultlike sleep patterns. Further study is required to examine sleep behaviors in puppies beyond 18-weeks to better understand how adultlike patterns emerge and the stability of the patterns observed in this study.

Motivation control beliefs and their impact on persistence and performance

Carlie Scheer

Faculty Mentor: Jim Shah

Authors: Scheer, C., Brown, M., Zhu, S., Guo, Z., Wyly, S., & Shah, J. Y.

Behavioral Sciences/Psychology

Abstract:
Extending research on the significance of individuals' implicit beliefs for goal pursuit and self-regulation, the present study examines how individual's beliefs about the nature of motivation and the control they have over it may impact self-regulation and overall well-being. More specifically, we examine how beliefs about the nature and controllability of motivation might relate to the motivational strategies one uses to increase or maintain motivation, as well as the longer-term benefits of controlling motivation for persistence and well-being. A pilot study suggests that a belief in the controllability of motivation does tend to promote positive self-regulatory behaviors and well-being. In the current study, three hundred participants were recruited through the Duke University SONA System to complete an online survey in Qualtrics. We measured participants' beliefs about motivation, and after manipulating participants' beliefs about the controllability of their motivation, assessed performance and persistence in a word target task and remote associates task intended to measure motivation behaviorally in the moment. Participants completed an easy and hard version of both the word target task and the remote associates task, then were evaluated based on the amount of time spent persisting on the word target task and their performance on both tasks. We then analyzed how performance and persistence varied as a result of the changing task difficulties. This study is part of a set of ongoing studies exploring the effects of motivation control beliefs on goal progress, persistence, and regulatory strategy use.

The Effects of Perseverative Cognition on False Memory

Angie Xie

Faculty Mentor: Kevin LaBar

Authors: Angie Xie, Jane Rothrock, Kevin LaBar

Behavioral Sciences/Psychology

Abstract:
Depression is a prevalent mental disorder associated with cognitive impairments, including memory disturbances such as false memories and over-generalized memory. Despite depression's well-documented association with memory deficits, limited research examines how rumination influences recognition memory, particularly for neutral stimuli. This study aimed to investigate the relationship between rumination, a perseverative cognitive style characteristic of depression, and recognition memory, particularly false memory occurrence. Twenty healthy participants were assigned to either a perseverative or intermixed group and underwent memory encoding and recognition tasks. Results revealed no significant differences in recognition accuracy or false memory occurrence between the groups. However, individuals with higher trait rumination demonstrated increased susceptibility to false memories, irrespective of recognition accuracy. Depressive symptoms negatively correlated with both recognition accuracy and discriminability, mediating the relationship between rumination and false memory occurrence. These findings suggest that depressive symptoms may promote a familiarity-based recognition style, potentially enhancing the accessibility of distorted memories. Limitations include a small sample size and limited generalizability. Nonetheless, this study contributes to understanding the complex interplay between rumination, depressive symptoms, and memory processes, offering insights with clinical relevance.

Cognitive Accessibility of Prescription Drug Information

Flora Ye

Faculty Mentor: Ruth Day

Authors: Flora Ye & Dr. Ruth S, Day

Behavioral Sciences/Psychology

Abstract:
Patients receive printed information with their medications at the pharmacy. These leaflets provide key information so patients can take prescription drugs safely and effectively. However, prescription information leaflets are not very cognitively accessible – they are hard to understand, remember, and use. Therefore, it is critical to increase their cognitive accessibility in order to promote patient health and well-being. The Day Cognition Lab designed an Enhanced format for prescription information leaflets based on well-established cognitive principles and tested its efficacy in a series of experiments. Participants were 748 adults from the general population with a wide range in demographics (age, gender, ethnicity, and education level). Through random assignment, half of the participants read a prescription drug leaflet in the Original format currently proposed by the U.S. Food and Drug Administration (FDA). The other half read the same information in the format of our Enhanced design. Participants then completed a series of tasks that assessed their comprehension, memory, and other cognitive processes. These tasks covered key information contained in the leaflet, such as the medication's uses, side effects, warnings, and drug interactions. Performance of the Enhanced group was superior across the majority of the tasks (with p-values < .0001 for most). The Enhanced group understood and remembered more information than the Original group. These results suggest that adopting a more cognitively accessible format for prescription leaflets will not only enhance cognition but also enable patients to have better health outcomes. Adverse reactions may be minimized and drug effectiveness increased.

Motivation control beliefs affect differential regulatory strategy use and well-being

Sunny Zhu

Faculty Mentor: James Shah

Authors: Zhu, S., Brown, M., Scheer, C., Guo, Z., Wyly, S., & Shah, J. Y.

Behavioral Sciences/Psychology

Abstract:
Extending research on the significance of individuals' implicit beliefs for goal pursuit and self-regulation, the present study examines how individual's beliefs about the nature of motivation and the control they have over it may impact self-regulation and overall well-being. More specifically, we examine how beliefs about the nature and controllability of motivation might relate to the motivational strategies one uses to increase or maintain motivation, as well as the longer-term benefits of controlling motivation for persistence and well-being. Correlational pilot data suggests that a belief in the controllability of motivation does tend to promote positive self-regulatory behaviors. In the current study, three hundred participants were recruited through Prolific to complete an online survey in Qualtrics. We measured participants' capacity for self-control, and after manipulating participants' beliefs about the controllability of their motivation, assessed how likely they were to use certain regulatory strategies on a goal they were currently pursuing. We also conduct exploratory analyses measuring the differential usage of each self-regulation strategy as a function of participants' beliefs about the controllability of motivation. This first study in a set of studies aims to experimentally test the effect of motivation control beliefs on regulatory strategy use, with ongoing studies exploring effects on goal pursuit and persistence.

Biological Sciences

Development of Cold Elutable Resin of NanoBody Alfa-Tag System

Aadesh Anchaliya

Faculty Mentor: Seok-Young Lee

Authors: Aadesh Anchaliya, Justin Fedor, Seok-Yong Lee

Biological Sciences

Abstract:
Epitope tags are incredibly useful in protein expression and pulldown. There are many specialized version of such tags that can be used in a variety of instances, with some having particular advantages over others. One such tag is called the ALFA-tag which is a hydrophilic 15 amino acid sequence that has a high inclination to form an α-helix. With this tag there is also a high-affinity Nanobody that is able to detect ALFA-tagged proteins. The interaction between the ALFA-tag and NbALFA is very tight, and thus there is also a Peptide-Elution version of the Nanobody. My research will focus on engineering a cold-elutable version of the Nanobody, as the current one is elutable only at room temperature. This will include analysis of bonding interactions between the AlFA-Tag and Nanobody and mutating key amino acids so that the interaction between ALFA-tag and NbALFA is weakened. Through performing mutagenesis, protein expression, and elution tests of all the mutants, I hope to provide the lab with a tool of a cold-elutable peptide that can be used for endogenous protein pull downs and a wide variety of other applications.

Fiber-type phenotype changes in the jaw-muscles of developing capuchins

Olivia Ares

Faculty Mentor: Megan Holmes

Authors: Olivia Ares, Caitlin B. Yoakum, Mariana Dutra Fogaça, Andrea B. Taylor, Callum F. Ross, Janine Chalk-Wilayto, Myra F. Laird, Claire E. Terhune, Megan A. Holmes

Biological Sciences

Abstract:
Jaw muscle fiber-type myosin in primates is highly varied, providing flexibility across contractile properties. Further, primate jaw-muscle fiber-type phenotype has been consistently linked to variation in feeding behavior. Currently, the fiber phenotype of young primates is unknown. We predict that fiber phenotype will modify to match feeding requirements as primates transition from suckling to weaning to an adult diet. Additionally, ontogenetic changes in fiber phenotype will vary between primate species that demonstrate different feeding behaviors. Here, we report on a preliminary analysis using immunohistochemistry to determine fiber-type expression in the masseters of an ontogenetic sample of tufted (Sapajus, n=13) and untufted (Cebus, n=13) capuchins. Capuchins are an excellent model for these analyses; Sapajus are known to have a mechanically challenging diet as opposed to Cebus. Three antibodies were used to determine the presence/absence of Type-I (NOQ7.5.4), Type-I alpha-cardiac (MyH6) and Type-II (MY32) myosin fiber types. Age groups were divided into infant, juvenile, subadult and adult based on dental eruption. The majority of cells across age ranges and genera were hybrid cells (co-expressed multiple myosins). Fiber-types did vary between age groups, notably Sapajus increased Type-II expression by 25% while Cebus increased Type-I by 50%. Fiber phenotype was significantly different between Sapajus and Cebus within each age group (p<0.001, log-linear regression) and Sapajus consistently displayed a greater variety of hybrid-types across ontogeny. These results are novel as they’ve not been reported before, demonstrating that fiber-type is not stagnant across age groups and further highlighting the flexibility of primate jaw-muscles during ontogeny.

Safeguards of the Mitochondrial Genome: Novel Mitophagy Responses May Ensure mtDNA Integrity in the C. elegans Germline

Sasha Bacot

Faculty Mentor: Joel Meyer

Authors: Sasha Bacot, Siddharthan Balachandar Thendral, Ian Ryde, Joel Meyer

Biological Sciences

Abstract:
The mitochondrial genome appears to be surprisingly resilient to mutation accumulation despite its intrinsically high potential for mutagenesis; the mechanism of transgenerational mtDNA quality control has not been fully elucidated. We assessed whether the C. elegans fndc-1 mitophagy pathway could be involved in the maintenance of germline mtDNA integrity. We found that FNDC-1 activity increases in the germline with UVC-induced mtDNA damage, and that fndc-1 loss of function mutants are sensitive to such damage. Our findings pose fndc-1 mitophagy as a candidate mechanism of transgenerational mtDNA quality control.

Discovery and Characterization of Heat Shock Protein Inhibitors with Antimalarial Activity

Elizabeth Boger

Faculty Mentor: Emily Derbyshire

Authors: Elizabeth Boger

Biological Sciences

Abstract:
Malaria, a mosquito born disease, is responsible for over 200 million infections causing over 400,000 deaths each year. These infections are the result of the microscopic parasites Plasmodium, with the species Plasmodium falciparum being the primary cause of malaria death in young children. Certain proteins are essential to each step of the life cycle of Plasmodium, one of which is heat shock protein 70 (Hsp70), which acts as a protein co-chaperone and stabilizes the digestive vacuole (DV) membrane. Hsp70 is an attractive drug target for malaria treatment because of its involvement in all life stages of the parasite and its upregulation during drug resistance, yet no prior study has fully achieved species selective Hsp70 inhibition. Thus, all currently reported molecules that disrupt Plasmodium Hsp70 also inhibit human Hsp70. Over the past two years, I have worked to address this problem by first screening a library of 3400 drug-like compounds while selecting for those that bind to Hsp70 and impact its thermal stability. With this data, I then analyzed the compounds' species selectivity for Plasmodium over human protein. Finally, I determined the viability of Plasmodium-infected human blood and liver cells with addition of our selected Hsp70-targetting compounds. These experiments allow for a better understanding of Hsp70 as a druggable target and ultimately how to induce malaria parasite death.

A S100A8/9-TLR4 Signaling Axis Suppresses Dendritic Cell Expression of the CXCL9 Chemokine

Linda Cao

Faculty Mentor: Brent Hanks

Authors: Linda Cao, Bala Theivanthiran, Ph.D., Y-Van Nguyen, Nicholas DeVito, M.D., Michael Plebanek, Ph.D., Kaylee Howell, Mandy Wang, Brent Hanks, M.D., Ph.D.

Biological Sciences

Abstract:
Dendritic cells (DCs) play a vital role in facilitating anti-tumor immunity. Acting at the intersection between the innate and adaptive immune systems, DCs recruit cytotoxic CD8+ T cells to the tumor microenvironment (TME) by generating a CXCL9 chemokine gradient in response to Type I Interferon (IFN) signaling. Several prior studies have shown granulocytic myeloid-derived suppressor cells (PMN-MDSCs) to interfere with DC function and to inversely correlate with the quantity and activation state of CD8+ T cells within the TME. One candidate molecule thought to contribute to the immunosuppressive properties of PMN-MDSCs is S100A8/9, a Ca2+ binding protein. However, our mechanistic understanding of the impact of S100A8/9 protein on DCs has remained limited. Recent studies by our group have revealed that the S100A8/9 protein indirectly decreases DC-dependent expression of the CXCL9 chemokine. Prior work has shown the S100A8/9 protein to mediate signaling through toll-like receptor-4 (TLR4), which is a highly conserved DC-expressed pattern recognition receptor. I therefore hypothesized that genetically silencing DC TLR4 expression would diminish S100A8/9-mediated suppression of DC CXCL9 expression. Indeed, we found TLR4-targeted genetic silencing using homozygous TLR4 knockout mice to reverse S100A8/9-mediated suppression of CXCL9 expression by DCs. These findings suggest that the S100A8/9-TLR4 signaling axis regulates IFN-beta-dependent signaling in DCs and interferes with dendritic cell's ability to recruit CD8+ T cells to the TME. Future studies will investigate whether the RAGE receptor, may also contribute to the impact of S100A8/9 protein on DC CXCL9 expression in the TME. Characterization of the exact mechanisms involved in PMN-MDSCs-induced DC dysfunction in the TME promises to provide opportunities for developing novel therapeutic strategies capable of enhancing anti-tumor immunity and overcoming mechanisms of immunotherapy resistance.

Roles of the WASH complex in macrophage migration and mycobacterial pathogenesis

Carson Carranza

Faculty Mentor: David Tobin

Authors: Carson Carranza, Mollie Sweeney, Ana-María Xet-Mull, David Tobin

Biological Sciences

Abstract:
Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis, a disease with 10 million new cases and 1.5 million deaths per year. In most cases, Mtb is contained within the lungs and is transmitted through aerosolized respiratory droplets from infected individuals. Interestingly, some patients present with extrapulmonary disease, despite transmission only occurring from lung to lung. Mtb primarily replicates within infected macrophages, and we have shown in larval zebrafish that these cells are crucial for mediating dissemination via migration to distal tissues. However, the host genes regulating this process are currently unknown. Previously, we performed a yeast-two-hybrid screen and identified WASHC4 as a potential host target for a secreted dissemination-promoting mycobacterial effector EsxM. WASHC4 is a stabilizing subunit in the larger WASH complex. The WASH complex is an activator of Arp2/3, the central regulator of branched F-actin polymerization within cells. We hypothesize that the WASH complex has a previously undescribed role in macrophage migration and that this pathway is altered during mycobacterial infection. Here, we use the zebrafish-Mycobacterium marinum model to study these novel roles for the WASH complex. Due to its role in cytoskeleton remodeling and cell motility, the WASH complex likely plays a nuanced role in immune cell function and pathogenesis. Thus far, we have established knock-out WASHC4 zebrafish lines and assessed differences in cell migration, mycobacterial infection burden, and dissemination. Larval zebrafish infections with M. marinum have revealed that mutant WASH fish experience higher infection burden and dissemination. Additionally, we observed inherent differences in macrophage migration in the absence of infection using tail-wounding assays with zebrafish expressing a fluorescent macrophage reporter. Currently, we are investigating how interactions between the WASH complex and a dissemination-promoting mycobacterial effector affect mycobacterial pathogenesis. These experiments will increase our understanding of mycobacterial dissemination and provide new insights into the cell biology of macrophage migration.

Visualizing Yap activity in Zebrafish through a fluorescent protein knock-in in the ccn2a gene

Claudia Carugati

Faculty Mentor: Daniel Levic

Authors: Claudia Carugati, Daniel S. Levic

Biological Sciences

Abstract:
The Bagnat Lab wanted to create a gene knock-in that allows us to infer YAP (yes-associated protein) activity. YAP is a downstream regulatory protein in the Hippo signalling pathway. In particular, we wanted to create a tool to visualize Yap activation in live imaging. To do this, we followed a knock-in protocol developed by the Bagnat Lab at Duke University to create a Venus knock-in for the ccn2 gene. (Levic et al., 2021) ccn2, also known as ctgf, is ideal for this experiment because it has a yap binding site in its promoter sequence, meaning it can be used as a transcriptional reporter for YAP activity. The fluorescent protein tag is a destabilized form of GFP known as Venus-PEST, which would allow us to see dynamic changes in the expression of the reporter. We aim to make a functioning C terminal p2a Venus-PEST knock in the ccn2 sequence. With a successful knock-in, through live imaging, we could see when YAP is activated because it would translocate to the nucleus and turn on ccn2 expression, which would get translated together with the fluorescent protein. We would see this through a burst of Venus expression. The procedure we followed to make the knock-in started by finding CRISPR target sites to design oligos and synthesize gRNA for the target sites. Then, we created a donor plasmid containing the cloned fragment of the gene of interest with mutated gRNA sites. These components were part of the injection mix injected in zebrafish zygotes, specifically in the blastodisc formed within a few minutes of fertilization. Successful development of this knock-in line will provide a tool for precisely assaying YAP activity during zebrafish development, morphogenesis, and regeneration.

Determining transcription factors that influence X-linked gene expression during XCI

Kyra Chen

Faculty Mentor: Eda Yildirim

Authors: Kyra Chen, Semin Kim, Eda Yildirim

Biological Sciences

Abstract:
Xist, a noncoding RNA, is essential for the initiation of X chromosome inactivation (XCI) which results in transcriptional silencing of one of the two X chromosomes in female cells equalizing X-linked gene expression between female and male mammals. XCI is stably maintained with continuous Xist expression in epiblast cells and in adult tissues. Nevertheless, we have little understanding of the significance of Xist expression during the XCI maintenance. In mice, targeted deletion of Xist in hematopoietic stem cells (HSCs) results in 100% penetrant blood cancers in the form of mixed myeloproliferative and myelodysplastic syndrome (MPN/MDS). Towards understanding how Xist loss leads to female-specific cancer, the Yildirim lab recently showed that Xist loss leads to increased chromatin accessibility and upregulation of a set of genes. Notably, motif analyses of the increased chromatin accessibility sites revealed enrichment of several transcription factors (TF), including TEAD, Runx, and Klf, suggesting a potential role for specific transcription factors in controlling X-linked gene expression. Based on these findings, I hypothesize that Xist-mediated silencing of X-linked genes is critical in controlling the expression of X-linked genes through specific TFs. In my proposed project, I will set up a siRNA-based screen to target candidate TFs and determine how their knockdown and overexpression influence X-linked gene expression and cell proliferation. First, I will target each TF by siRNA in female mouse embryonic fibroblasts (MEFs), and validate the efficiency of knockdown by performing real-time RT-PCR. I will then investigate how KD of each TF changes X-linked gene expression by real-time RT-PCR in control and Xist deficient female MEF cell lines. These cell lines recapitulate the maintenance phase of XCI and are widely studied for mechanistic studies addressing factors that influence XCI maintenance. As read-out X-linked genes, I will utilize a panel of 12 X-linked genes. Lastly, I will focus on the TFs that influence X-linked gene expression and determine how their KD impacts cell proliferation. These studies will help narrow down TFs that likely crosstalk with Xist during XCI maintenance and help generate preliminary data for future projects in which the Yildirim lab will investigate TF-mediated regulation of X-linked genes in blood lineage using mouse models and in human cancers.

Investigating the role of ceramide transport protein (CERT) during the Plasmodium liver stage

Isabel Colon

Faculty Mentor: Emily Derbyshire

Authors: Isabel Colón, Erin Schroeder, Emily R. Derbyshire

Biological Sciences

Abstract:
Malaria is caused by Plasmodium parasites which are deposited into the host by a mosquito bite. The parasite first travels to and infects liver cells before egressing to the bloodstream. During the liver stage, the Plasmodium parasite resides in the parasitophorous vacuole (PV). The PV membrane increases in size to accommodate the replicating parasite organelles, membranes, and nuclei. For these events to transpire, the parasite needs an abundance of nutrients including sphingolipids. Previous research has demonstrated that sphingolipids are upregulated in Plasmodium berghei infected HuH7 cells and that they are trafficked to the Plasmodium parasite to aid in their development. Ceramide transport protein (CERT) could potentially play a role in sphingolipid trafficking to the PV. To study the role of CERT during the Plasmodium liver stage, we first generated a CERT CRISPR knockout cell line. We then compared parasite development between wildtype and CERT knockout cells by measuring parasite load with a plate reader assay. Immunofluorescent microscopy was also used to identify the infection rate, parasite size, and CERT localization. Lastly, the number of sphingolipids or ceramides trafficked to the PV were compared between wildtype and knockout cells to determine if CERT supports sphingolipid acquisition.

Investigating the RIOK2-NFkB Interaction in Prostate Cancer

Abby Cortez

Faculty Mentor: Everado Macias

Authors: Abby Cortez, Everardo Macias

Biological Sciences

Abstract:
Right Open Reading Frame Kinase (RIOK2) is critical in ribosome assembly, which is needed for proliferating cancer cells. Targeting RIOK2 is shown to decrease tumor growth, likely due to impairment of ribosome biogenesis. Recently, our group discovered that RIOK2 has novel DNA binding activity, but there are still unknowns such as the cofactors it binds. A published high-throughput mass spectroscopy study suggests that RIOK2 interacts with RELA, a subunit of Nuclear Factor Kappa-light-chain-enhancer (NF-kB). NF-kB is a transcription factor that regulates genes essential for cancer cells. We hypothesize the RIOK2-NF-kB interaction supports disease progression. A nuclear fractionation experiment showed RIOK2 in the nucleus and cytoplasm. A co-immunoprecipitation assay of 22RV1 and PC3 cell lysates showed that NF-kB was bound to RIOK2 when not part of a ribosome complex. A drug combination assay indicated an additive effect on proliferation when co-targeting both proteins. The results of preliminary studies validated the presence of an NF-kB -RIOK2 interaction in prostate cancer cells. Next, we will conduct a nuclear-fractionation assay targeting RIOK2 or NF-kB to understand where the interaction occurs and its regulation. Conversely, we will use NF-kB activating ligands to determine how activation of NF-kB affects RIOK2-NF-kB binding. An understanding of this interaction is important to understand basic cancer cell biology and for potential translational interventions.

Exploring the role of Draper in the glial induction of neuronal toxicity

Jayden Cyrus

Faculty Mentor: Nina Sherwood

Authors: Jayden Cyrus, Dr. Emily Ozdowski, Dr. Nina Tang Sherwood

Biological Sciences

Abstract:
The spastin gene encodes a microtubule severing protein, and when mutated in humans leads to Autosomal Dominant Hereditary Spastic Paraplegia (AD-HSP), a neurodegenerative disease that impairs motor function in the legs. In Drosophila, spastin null larval neuromuscular junctions (NMJ) are characterized by a high synaptic bouton count with a “bunched” phenotype. In addition to neuronal proteins, glial proteins are also known to regulate synapses. One such protein is Pak3, a kinase that regulates actin polymerization and filopodial projections. Studies have shown that when Pak3 is deleted in spastin null Drosophila, neuronal structure and function are restored. While it is known that Pak3 deletion rescues the neurons by acting in subperineurial glia (SPG), the exact mechanism remains unclear. We hypothesize that Draper, an engulfment receptor in glia, may participate in this mechanism. Preliminary results indicate that, like Pak3 deletion, deleting draper and spastin rescues the spastin null phenotype, further demonstrating a requirement for glia in the pathology caused by loss of spastin. Additionally, although it is known that Draper functions in glia, the specific subtype of glia - wrapping, perineurial, or SPG - remains unknown. Therefore, my aim was to identify the specific subtype of glia in which Draper acts to cause the neuronal defects seen when spastin is lost. To do this, I knocked down Draper in a glial-specific manner using the UAS-GAL4 system to express draper-RNAi in a spastin null background. My results indicate that Draper works in perineurial and wrapping glia, but not SPG. Interestingly, this implies that while Pak3 works in SPG, Draper acts in other glia, implicating four different cell types in this interaction: neurons, wrapping glia, perineurial glia, and SPG. Understanding the specific cell type(s) in which Draper acts will provide the first step in understanding how these proteins regulate neuronal structure and neuronal health, better our comprehension of how glia communicate with neurons and other glia, and shed light on the glial induction of neuronal toxicity.

B-arrestin spatial conformations and trafficking patterns induced by Ang II and biased analogs

Saisha Dhar

Faculty Mentor: Sudarshan Rajagopal

Authors: Saisha Dhar, Anand Chundi, Srikrishna Darbha, Uyen Pham, Sudarshan Rajagopal

Biological Sciences

Abstract:
G protein-coupled receptors (GPCRs) are the largest class of integral membrane proteins expressed in humans and the targets of nearly one-third of all FDA-approved drugs. While several GPCRs have been shown to signal through both G protein- and B-arrestin-mediated pathways, some ligands can preferentially activate signaling through either pathway, a paradigm termed 'biased agonism.' These ligands can result in different conformations at the receptor and at B-arrestin. The detailed structural and molecular features underlying biased signaling, and the responses downstream of GPCRs, remain unclear. To study this, we stimulated Angiotensin II type 1 Receptor (AT1R) by either Angiotensin II (Ang II), the endogenous ligand, or by TRV023, a B-arrestin-biased ligand. This resulted in different B-arrestin recruitment patterns at the receptor, plasma membrane, and endosomes. Using NanoBiT Fluorescein Arsenical Hairpin (FlAsH) biosensors with Ang II and TRV023 stimulation, we found that ligand-specific B-arrestin conformations resulted at the receptor and the endosomes. We expanded our ligand panel to include Angiotensin II and six other functionally diverse TRV ligands (some Gq-biased and some B-arrestin-biased), and found that these recruitment patterns are ligand- and location-specific as well. Our ongoing work includes assessing B-arrestin conformations using FlAsH biosensors for Ang II and the panel of TRV compounds. We hope to identify patterns between B-arrestin and AT1R conformations in response to the ligands in order to elucidate signaling pathways and develop more efficient therapeutics.

Exploring the Impact of UBE2A Mutations on Translation Control during Oxidative Stress in UBE2A

Rachel Field

Faculty Mentor: Gustavo Silva

Authors: Rachel Field, Gessica Barros, Gustavo Silva

Biological Sciences

Abstract:
UBE2A deficiency syndrome, also called X-linked intellectual disability type Nascimento, is a rare disease caused by variants in the E2 ubiquitin-conjugating enzyme UBE2A. Patients present with moderate to severe intellectual disability, speech impairment, facial dysmorphism, urogenital abnormalities, hirsutism, and other symptoms. Previous studies showed that Rad6, the yeast homolog of UBE2A, ubiquitinates ribosomes and regulates translation during oxidative stress. UBE2A could have similar function. Here, we explore the role of Nascimento-associated UBE2A mutations in translation control. Click-iT HPG protein synthesis assays, Western blots, auxin-inducible degron-mediated degradation, and additional techniques will be used to investigate the effect of these mutations on translation rate, ubiquitination, protein expression, and oxidative stress response. Results provide insight into UBE2A function and how it may be altered in UBE2A deficiency syndrome.

Analyzing Effects of ARF Gene Modification on Temperature Regulation in Arabidopsis thaliana

Jacob Frietze

Faculty Mentor: Lucia Strader

Authors: Jacob Frietze, Lucia C. Strader, Sunita Pathak

Biological Sciences

Abstract:
Recent years have featured a stark rise in global temperatures, and the coming years only point to the continuation of this trend. This has impacted the migration and habitat patterns of many animal species to maintain their optimal habitat climate. However, stationary plants bear the risk of reduced growth in these hotter temperatures. One possible solution is genetically modifying plants to grow better in temperature-stress conditions, and this involves the manipulation of genes involved in biomolecular condensate formation. Biomolecular condensates are membrane-less organelles composed of proteins and RNA, which control many cellular processes on a biochemical level including the responses to environmental changes like temperature. Previous studies have found that the Auxin Response Factors, (ARF7 and ARF19) form condensates that regulate auxin signaling in roots, a phytohormone critical for overall plant growth. Further analysis of gene structure has shown that the Intrinsically Disordered Region (IDR) in ARF19 is necessary for the formation of condensate. Research within the Strader Lab currently focuses on swapping the ARF19-IDR region with two different polypeptides: Resilin-like polypeptides (RLPs) and Elastin-like polypeptides (ELPs). These artificial peptide polymers have been previously shown to phase separate at different temperatures. In particular, RLP undergoes phase separation (condensate formation) at low temperatures, and ELP undergoes phase separation at high temperatures. The goal of this research is to analyze the effect of these peptide swaps on temperature regulation in Arabidopsis thaliana and create a functional temperature-sensing mechanism in the plant. Preliminary results through protoplast transfection show that some of these RLPs and ELPs respond to changes in temperature through phase separation. Further analysis in transgenic lines expressing the ARF19 with these polypeptide swaps will assist in generating thermosensor plants. Successful temperature regulation of these thermosensor plants would suggest a method of vegetation survival despite the growing stressors of the global climate.

Activity of Intracellular Mediators in Post-TBI Epilepsy and Inflammatory Response

Amy Fulton

Faculty Mentor: Brad Kolls

Authors: Amy Fulton, Brian Mace, Eduardo Chaparro, Bradley Kolls

Biological Sciences

Abstract:
Inflammatory response following TBI is implicated in post-traumatic epileptogenesis, although the exact pathway and mechanism remains unclear. The lifetime burden of both TBI and epilepsy are high, and especially when they are concurrent. Our study probed the expression of several proteins implicated in a proposed neural response pathway in groups of mice subjected to TBI, inflammation-causing agents, and both, across various time points. Ten mice were divided into four groups: sham (untreated), LPS-treated, TBI-injured, and LPS + TBI. Mice were first treated with LPS, if applicable, to induce inflammation. Mice were then injured with TBI at a 3mm displacement. Brain was fixed at time points of 3, 6, 9, and 24 hrs. Protein isolation and concentration assays were completed using these experimental animals at each time point. All results were compared to findings in control (sham/untreated) animals to account for the neurological effects of surgical anesthesia. Findings included high BDNF expression at 3 and 9 hours in LPS-treated groups, as well as slightly elevated levels at 9 hours in the TBI-only group. IL1-Ra expression lingered at high levels for much longer in TBI + LPS mice than in TBI-only or LPS-only mice. AIF1 peaked at 6 hours in both TBI groups, but not in the LPS-only group. IKBa expression was relatively similar across groups, but all treated groups (TBI, LPS, and TBI + LPS) showed very high levels of pIKBa at 6 hours compared to controls. NFKB showed increased expression at 24 hours in both LPS-treated groups, and pNFKB spiked at 6 hours in all groups, especially LPS and LPS + TBI. LRP showed relatively consistent expression across all groups and time points. Expression of most all proteins was highest at 6 hours, except BDNF which peaked at 9 hours. These results provide potential insight into the regulation of inflammatory response following TBI and inflammation, including potential overlap and divergence in pathways.

Establishing cell lines from fresh and frozen mouse lemur tissue

Maia Goel

Faculty Mentor: Anne Yoder

Authors: Maia L. Goel, J. Carolina Segami, Anne D. Yoder

Biological Sciences

Abstract:
Complete, high-quality genomes exist for few species due to the complexity of sequencing areas containing complex repeated elements like telomeres and centromeres. This deficit needs to be addressed. Precise reference genomes—ideally, telomere-to-telomere (T2T) genomes—have the potential to significantly advance our understanding of all biological phenomena and the evolutionary processes that shape them. Mouse lemurs, an endangered clade of primates, are an ideal system to study the evolutionary processes affecting the biological process of speciation, but a complete T2T reference genome for this or any other lemur clade does not yet exist. Creating a T2T reference genome requires a large amount of high-quality DNA, ideally from natural populations. Methods for collecting DNA from natural populations in Madagascar are enormously challenging for numerous reasons relating to the organisms and the challenges of working in the impoverished country of Madagascar. Thus, we must rely on lab-based technologies to overcome these challenges. In this study, we first adapted existing cell culture protocols to successfully culture mouse lemur cells and thereby amplify small amounts of available genetic material. Additionally, we are developing a protocol for tissue cryopreservation that can be reproduced under difficult field conditions. This protocol will allow us to obtain frozen tissue with viable cells for cell cultures. To our knowledge, these protocols have never been established for lemur cells. Once completed, however, they can be adapted for the study of other non-model organisms and endangered species. Our work will ultimately shed light on mouse lemur speciation, resulting in one of few complete T2T genomes for a non-model organism, and further enabling future studies of Earth's endangered biota.

EXAMINING DIETARY DIVERSITY IN A PALEOGENE HYRAX FAUNA FROM THE FAYUM DEPRESSION, EGYPT

Walter Kornfeld

Faculty Mentor: Matthew Borths

Authors: W.O. Kornfeld, E.M. Simpson, M.R. Borths

Biological Sciences

Abstract:
With most ungulates absent from Africa until the Miocene, the morphologically diverse hyraxes were a major component of the Eocene-Oligocene community at Quarry L-41 (~34 Ma) in the Fayum Depression, Egypt. However, their foraging strategies are poorly understood. This study focuses on four extinct hyraxes: Thyrohyrax meyeri, Thyrohyrax litholagus, and Megalohyrax eocaneus, all expected to be grazers; and Saghatherium bowni, previously described as a browser. Mesowear can place extinct herbivores on a spectrum from grazer to browser based on the abrasiveness of their lifetime diets. Crown height, tooth length, and cusp angle were measured for the first lower molars (M1) in these four hyrax species. Specimens were categorized into Wear Classes (WC), which correspond with developmental age. WC ranged from 1, first adult molar fully erupted, to 8, all molars extremely worn with significant dentin exposure. Change in mean crown height and cusp angle across different wear classes was not significantly different. Nonetheless, apparent trends suggest compositional differences in diet. Change in mean crown height for Saghertherium indicates that it incorporated more graze than browse because M1 wear occurred in earlier WCs and increased throughout life. In contrast, less wear for WC 1 through 4 in Thyrohyrax indicates that it incorporated more browse. This agrees with recently collected carbon isotope data, which suggests that Saghatherium's diet included more graze than Thyrohyrax's. These data are consistent with the description of Thyrohyrax as an arboreal browser. The change in mean crown height for Megalohyrax also suggests a less abrasive diet, although sample size for Megalohyrax was smaller. The browse-biased diet for Megalohyrax is surprising, as isotope values suggest a more open environment. Browsing in salt-stressed environments, forest canopies or forest edges could explain these combined data. Megalohyrax could have foraged in a wider variety of environments than the other taxa because its larger size enabled a wider range. By reconstructing the diets and niche partitioning among morphologically diverse hyraxes at L-41, we hope to gain insights about the ecosystem represented by L-41 near the Eocene-Oligocene Boundary (EOB). This locality represents a time of ecological dynamism when many

mammalian communities were dramatically restructured, though the impact of the EOB on African mammal communities remains poorly understood.

Targeting DNA Replication Stress in Glioblastoma Cells that Utilize the Alternative Lengthening

Marharyta Krylova

Faculty Mentor: Matthew Waitkus

Authors: Marharyta Krylova, Alexandrea Brown, Laura Strickland, Elise Erman, Matthew Waitkus

Biological Sciences

Abstract:
Gliomas are the most common primary malignant brain tumors in adults and children. Grade 4 gliomas, termed glioblastomas (GBM), are invariably lethal, with a median survival of approximately 15 months in spite of aggressive treatment with surgery, radiation, and chemotherapy. An improved understanding of therapeutic vulnerabilities and mechanisms underlying these vulnerabilities is needed to improve the outcomes of glioma patients. A significant subset of malignant gliomas utilize alternative lengthening of telomeres (ALT) for telomere maintenance, which contributes to cellular immortalization. ALT+ cells generally exhibit higher levels of DNA damage and DNA replication stress relative to telomerase+ cells. Based on this intrinsic difference, we aim to further exacerbate the levels of DNA damage in ALT+ cells for therapeutic effect. This study focuses on identifying the effects of depleting a specific replication fork reversal enzyme, SMARCAL1, in ALT+ cells to investigate the therapeutic potential of SMARCAL1 inhibition as a glioma therapy. Our fundamental hypothesis is that suppressing SMARCAL1 activity in ALT+ cells will increase the levels of DNA double-strand breaks and replication stress to levels that will lead to cell death via mitotic catastrophe. We find that SMARCAL1 invariably localizes to ALT-associated PML bodies in ALT+ glioma cells. Using an inducible RNA interference approach to deplete SMARCAL1 in ALT+ glioma cells, we found that SMARCAL1 depletion leads to DNA DSBs and nuclear abnormalities indicative of mitotic catastrophe. This study advances our understanding of SMARCAL1's role in glioma cell immortalization, opening avenues for future research and potential clinical applications.

Investigating differences between human and chimpanzee gene regulation and neurogenesis

Katie Lam

Faculty Mentor: Debby Silver

Authors: Katie Lam, Federica Mosti, Debra Silver

Biological Sciences

Abstract:
Human Accelerated Regions (HARs) are non-coding DNA segments that have been conserved throughout vertebrate evolution but exhibit substantial sequence divergence in humans. The Silver Lab previously generated a new human cell line that replaced the human sequences of HAR1984 with the respective chimpanzee sequence (Hs-HAR1984Pt/Pt) and made cortical organoids. The resulting Hs-HAR1984Pt/Pt cortical organoids revealed a reduced number of intermediate progenitors (IPs) and fewer mitotic cells than the control Hs-HAR1984Hs/Hs. The expression of the target genes TRA2B and ETV5 was decreased in the Hs-HAR1984Pt/Pt organoids. During neurodevelopment, ETV5 is crucial for neuronal differentiation of neuroprogenitor cells and TRA2B is essential for the proper development of the cerebral cortex. The Silver Lab subsequently generated a chimpanzee cell line with humanized HAR1984 (Pt-HAR1984Hs/Hs). 2D differentiations of chimpanzee-induced neuroprogenitor cells with both human and chimpanzee HAR1984 sequences were generated and maintained to analyze differences in morphology, cell composition, and RNA expression. Fluorescence imaging was used to analyze the cell composition and record the positions of different types of cells in the HAR1984 2D differentiations. Quantitative PCRs were analyzed with the primers for OCT4 and PAX6 to confirm differentiation, while ETV5 and TRA2B primers confirmed elevated levels of expression in Pt-HAR1984Hs/Hs. The results of this project revealed an increased number of mitotic cells in the humanized cell lines, indicating an increased number of progenitors as the radial glia goes through more mitotic divisions during differentiation, and the bigger pool of progenitors can ultimately make more neurons.

Lia Lapidot, Kevin Erning, Yana Al-Inaya, Brian Mace, Fernando Gonzalez, Tatiana Segura, David Hasan, Eduardo Chaparro

Lia Lapidot

Faculty Mentor: Eduardo Chaparro

Authors: Nanoparticle Biomaterials for the Treatment of Moyamoya Disease: an Initial Investigation

Biological Sciences

Abstract:
Cerebrovascular ischemia due to constriction of cerebral arteries poses a substantial neurological threat. Our study investigated a potential new treatment for moyamoya disease, one form of such ischemia, which is caused by a gradual occlusion of the carotid arteries. An occlusion-stenosis model was used to induce moyamoya-like pathophysiology in mice. We investigated the therapeutic properties of hydrogel biomaterials in this model. These biomaterials mimic the extracellular matrix and can induce controlled VEGF delivery, promoting angiogenesis and tissue repair, and can be implanted non-invasively. On this basis, we postulated that hyaluronic acid (HA) gels, with or without VEGF, can induce growth of endothelial cells and restore blood flow in mice with forebrain ischemia. Mice were divided into four groups: control, vehicle-only (chronic ICA occlusion and stenosis), HA gel treatment, and CLUVENA(Clustered VEGF Nanoparticle) hydrogel treatment. Biomaterials were implanted on top of the brain surface in treated mice. Two weeks post-treatment, brains were dissected, sectioned, and stained for CD31 and DAPI for endothelial and nucleic identification. We found ischemic (vehicle-only) animals to have significantly diminished levels of endothelial cells and nuclei in the forebrain, as compared to control animals. Treatment groups (both HA and CLUVENA) displayed a raised level of both cell types, near to control levels. This suggests these gels promoted angiogenesis, which restored functional vasculature capable of supporting new cell growth in these animals. Therefore, we concluded that these angiogenic biomaterials hold significant potential for treating ischemic conditions like moyamoya disease, especially given the potential for minimally-invasive use.

Respiratory pathology in the mdx/utrn dko mice: a murine model for Duchenne Muscular Dystrophy

Jane Lee

Faculty Mentor: Mai ElMallah

Authors: Jane Lee, Marán Y Hernández Rodríguez MD, Debolina D. Biswas PhD, Mai K. ElMallah MD

Biological Sciences

Abstract:
Duchenne muscular dystrophy (DMD) is an X-linked severe neuromuscular disorder caused by a lack of dystrophin. Patients develop respiratory insufficiency and hypoventilation as a result of the progressive muscular degeneration. Utrophin is a protein that is localized to the sarcolemma of skeletal muscle fibers. In humans, utrophin is present at the sarcolemma during the fetal period and is replaced by dystrophin at birth. In mdx mice, utrophin compensates for the lack of dystrophin causing a milder phenotype of muscular dystrophy compared to humans. The mdx/utrn-/- mice show an early onset of muscle dystrophy, severe muscle weakness, and premature death, so it may be a more representative model for human disease. To our knowledge, the mdx/utrn-/- respiratory pathology has not been characterized. This study aims to characterize respiratory insufficiency, neurobehavioral deficit, and survival of mdx/utrn-/-. We performed whole body plethysmography weekly starting at 6 weeks of age until 10 weeks of age to assess respiratory function at baseline during normoxia (FiO2: 0.21; N2 balance) and during a respiratory challenge with hypoxia and hypercapnia (FiCO2: 0.07, FiO2: 0.10; N2 balance). Metabolic response to hypoxia was recorded at 8 and 9 weeks of age. Strength tests were performed. Postmortem studies included histological analysis of the diaphragm, tongue, and tibialis anterior to assess for muscle fiber regeneration and fibrosis. We found that the mdx/utrn-/- mice exhibit a decline in weight compared to age-matched wild-type mice and die prematurely at approximately 7-14 weeks of age. During normoxia, breathing frequency was significantly higher in mdx/utrn-/- mice. Also, these mice experience significantly reduced tidal volume, minute ventilation, peak inspiratory flow, and peak expiratory flow during a respiratory challenge from 6 weeks of age. In addition, the ventilatory equivalent for oxygen and carbon dioxide is significantly reduced during the respiratory challenge as the disease progresses. Furthermore, the mdx/utrn-/- have significant kyphosis, with decreased grip strength from 6 weeks of age. Hematoxylin and eosin staining showed fibrosis and centralized nuclei in the diaphragm, tongue, and tibialis anterior. Overall, these results indicate that mdx/utrn-/- mice display respiratory dysfunction that mimics the DMD

phenotype. Thus, mdx/utrn-/- mice provide a useful model to study the impact of novel therapies on respiratory function for DMD.

Gut parasite identification in lemur taxa

Nicole Lee Heberling

Faculty Mentor: Christine Drea

Authors: Nicole Lee Heberling, Caroline Shearer, Marie Nathalie Rafanomezantsoa, Christine Drea

Biological Sciences

Abstract:
Madagascar is a biodiversity hotspot, having the fourth greatest primate diversity globally. Its endemic primates represent around a third of the world's species, with lemurs being the most endangered mammals on the planet. Better understanding of the health factors impacting these animals may help when considering conservation initiatives. There has been some past research on helminth presence and identification in various lemur species, yet, in many cases, there is little to no information available. We compared the helminth parasites infecting the gut of two closely related brown lemur species, the crowned lemur (Eulemur coronatus) and Sanford's lemur (E. sanfordi), for which wild groups are restricted to the same isolated forests of northern Madagascar. We collected 29 fecal samples from 19 individuals (N=6 crowned; N=13 Sanford's) in Amber Mountain National Park during the dry season of 2023. For initial survey and identification, we scanned the samples for adult worms under a dissection microscope; we will later use glycerine to protect or recover collapsed worms and potentially dissect worms to analyze them further. We then used standard fecal centrifugation and floatation techniques to count the eggs, identify the helminth species, and take diagnostic images of them through a microscope. To date, based on analysis of 6 samples, we have tentatively identified adult Lemuricola spp. and eggs from Callistoura sp., Trichuris sp., Strongyloides spp., and cyclophyllidean cestodes, with a distinctly higher prevalence of Callistoura sp.; every sample so far was infected to some degree. Ultimately, we seek to compare the helminth species of both brown lemur species in relation to their different socioecologies and behavioral endocrinology. This research can lead to a better understanding of the intrinsic and extrinsic factors affecting the gut health of these endangered, sympatric species.

The Impact of Age on Ozone Time Course Responses in Rodents

Kaitlyn Lewars

Faculty Mentor: Robert Tighe

Authors: Kaitlyn Lewars, Aaron T. Vose, Marissa A. Guttenberg, Michaela C. Albright, Anastasiya Birukova, Loretta G. Que, Jennifer Ingram, Kymberly M. Gowdy, and Robert M. Tighe

Biological Sciences

Abstract:
Ozone (O3) increases morbidity and mortality through increased lung inflammation. Age is a susceptibility factor in O3-induced inflammation but the mechanisms are poorly understood. Young (8-10 weeks) and aged (12-18 months) C57BL/6 male mice were exposed to O3 or filtered air (FA) for 3h. 12, 24, 48, and 72h following exposure, bronchoalveolar lavage fluid (BALF) and lung tissue were collected. BALF was assessed for airspace inflammation, total protein/albumin, and cytokines/chemokines. Lung tissue was assessed by real-time PCR for inflammation, epithelial integrity, and oxidant stress associated genes. BALF protein/albumin were elevated in both cohorts following O3 exposure with no difference based on age. BALF neutrophils increased at 12h in both groups, but were higher in young mice. Gene expression profiling revealed differences in O3 exposure responses between young and aged cohorts at 12h post-exposure with the aged cohort having higher gene expression. Given the differences in gene expression between the cohorts, we were interested to confirm if this was associated with evidence of O3-induced airspace cytokine responses. We observed peak cytokine levels principally at 12h post-exposure. Overall, there were less differences between the young and aged cohorts in protein cytokine responses than had been observed in the whole lung gene expression. In summary, we observed age related changes in O3-induced lung inflammation where there was suppression of airspace inflammation in aged mice. Furthermore, discordant findings between gene expression and BAL cytokines suggest potential impaired translation of proteins or impaired airspace secretion of cytokines in exposed aged mice.

Chicken Olfactory Receptors Respond to Pyrazines

Renee Li

Faculty Mentor: Hiroaki Matsunami

Authors: Renee Li, Robert Driver, and Hiroaki Matsunami

Biological Sciences

Abstract:
Olfaction, or a sense of smell, is crucial to animal survival and reproduction, aiding in foraging, danger avoidance, and kin recognition. Olfaction is facilitated by olfactory receptors (ORs), a class of G-protein coupled receptors expressed in the olfactory sensory neurons of the olfactory epithelium, through binding to odorant molecules. As the largest gene family in vertebrates, ORs allow animals to detect a wide variety of chemicals through olfaction. Though birds are among the most diverse of terrestrial vertebrates, it was long thought that they relied more heavily on visual and auditory cues and less on olfaction. However, recent behavioral work has suggested birds use olfaction for foraging and locating nesting sites, and OR counts in birds were found to be higher than expected. Testing chicken consensus ORs, a combination of multiple ORs used for laboratory experimentation but not naturally occuring, showed they responded to pyrazine, an aromatic odorant. In light of this, we hypothesized that natural “native” chicken ORs should also respond to pyrazines. We performed GloSensor cAMP assays, which fluoresce upon protein activation, on over 40 native chicken ORs to measure their response upon pyrazine exposure. We found two native chicken ORs responded to the pyrazines, strongly suggesting chickens are capable of detecting pyrazine odors with relevance to their behavior and ecology.

Identifying DAF-16/FOXO target genes governing oocyte provisioning responses to nutrient stress

Rebecca Liu

Faculty Mentor: Ryan Baugh

Authors: Rebecca Liu; Kinsey Fisher; Ryan Baugh, Ph.D.

Biological Sciences

Abstract:
Many studies have demonstrated that maternal environment can impact progeny growth and development, suggesting that intergenerational communication occurs in utero. In theory, this phenomenon can be beneficial to prepare progeny for stressful environments like nutrient deprivation. For example, reduced insulin/IGF1-like signaling (IIS) during dietary restriction increases vitellogenin lipoprotein (i.e., yolk) provisioning to the oocyte in the roundworm C. elegans via the FOXO transcription factor DAF-16 (Jordan et al., 2019). This increase in maternal provisioning increases progeny size and prepares offspring to withstand early life starvation by preserving reproductive success (Hibshman et al., 2016). However, the exact molecular mechanism(s) by which DAF-16 promotes increased vitellogenin provisioning is unclear. Strains genetically engineered to have daf-16 function in only specific tissues highlight the intestine as the main site of action for increased vitellogenin provisioning in dietary restriction. Therefore, the primary focus of this study is to identify DAF-16 intestinal target genes responsible for vitellogenin provisioning to the oocyte during nutrient stress. RNA sequencing was conducted on daf-16^(null) and daf-16^(intestine) strains to identify differentially expressed genes in the intestine during dietary restriction. 88 candidate genes were then screened via RNAi for their effect on embryo size and vitellogenin content using an automated image-based assay. Using a vitellogenin reporter gene (crg9070[vit-2::gfp]), I identified 36 intestinal DAF-16 target genes involved in vitellogenin provisioning under nutrient stress conditions. Gene Ontology (GO) annotations highlight three major functions of these target genes: hydrolase activity, transferase activity, and innate immunity. This work is significant for addressing molecular mechanisms by which IIS to the intestine regulates oocyte vitellogenin provisioning, providing a model to understand soma-to-germline communication and intergenerational adaptation to nutrient stress.

Interpretable Binding Affinity Prediction with Persistent Homology

Yuxi Long

Faculty Mentor: Bruce Donald

Authors: Yuxi Long, Bruce Donald

Biological Sciences

Abstract:
Accurate binding affinity prediction is crucial to structure-based drug design. Recent work used computational topology to obtain an effective representation of protein-ligand interactions. Although persistent homology encodes geometric features, previous works on binding affinity prediction using persistent homology employed uninterpretable machine learning models and failed to explain the underlying geometric and topological features that drive accurate binding affinity prediction. In this work, we propose a novel, interpretable algorithm for protein-ligand binding affinity prediction. Our algorithm achieves interpretability by an effective embedding of distances across bipartite matchings of the protein and ligand atoms into real-valued functions by summing Gaussians centered at features constructed by persistent homology. We name these functions \textit{internuclear persistent contours (IPCs)}. Next, we introduce \textit{persistence fingerprints}, a vector with 10 components that sketches the distances of different bipartite matching between protein and ligand atoms, refined from IPCs. Let the number of protein atoms in the protein-ligand complex be n, number of ligand atoms be m, and $\omega \approx 2.4$ be the matrix multiplication exponent. We show that for any $0 < \epsilon < 1$, after an $O(mn \log(mn))$ preprocessing procedure, we can compute an ϵ-accurate approximation to the persistence fingerprint in $O(m \log^{6\omega}(m/\epsilon))$ time, independent of protein size. This is an improvement in time complexity by a factor of $O((m+n)^3)$ over any previous binding affinity prediction that uses persistent homology. We show that the representational power of persistence fingerprint generalizes to protein-ligand binding datasets beyond the training dataset. Then, we introduce \textit{PATH}, Predicting Affinity Through Homology, an interpretable, small ensemble of shallow regression trees for binding affinity prediction from persistence fingerprints. We show that despite using 1,400-fold fewer features, PATH has comparable performance to a previous state-of-the-art binding affinity prediction algorithm that uses persistent homology features. Moreover, PATH has the advantage of being interpretable. Finally, we visualize the features captured by persistence fingerprint for variant HIV-1 protease complexes and show that persistence fingerprint captures binding-relevant structural mutations.

Regulation of Adult Body Plan Construction in a Sea Urchin with Non-feeding Larvae

Brennan McDonald

Faculty Mentor: Gregory Wray

Authors: Brennan D. McDonald, Abdull Jesus Massri, and Gregory A. Wray

Biological Sciences

Abstract:
Biphasic lifecycles, in which organisms have both larval and adult stages, are widespread among animals, but little is known about how the transition between the two phases is regulated. Sea urchins are a unique system for studying this phenomenon because of the stark differences between their bilateral larval and pentaradial adult body plans. In this study, we used single cell RNA-sequencing to analyze the development of Heliocidaris erythrogramma, a sea urchin species with an accelerated, non-feeding mode of larval development. The sequencing time course extends from early embryogenesis to roughly a day before the onset of metamorphosis in H. erythrogramma larvae, which is a period that has not been covered by previous datasets. We found that the non-feeding developmental strategy of H. erythrogramma led to several changes in the specification of larval cell types compared to sea urchins with feeding larvae, such as the loss of a larva-specific skeletal cell population. Furthermore, we identified that the morphogenesis of the larval and adult body plans in sea urchins appears to be controlled by distinct gene regulatory programs. These observations lay the groundwork for future work testing the regulation of metamorphosis in sea urchins and other species with biphasic life cycles.

Lgals3 Expression in KRT13+ Hillock Cells: An Immunomodulator in Squamous Cell Lung Cancer

Srijan Meesala

Faculty Mentor: Trudy Oliver

Authors: Srijan Meesala, Tony Reyes, Abbie Ireland, Luke Izzo, and Trudy G Oliver

Biological Sciences

Abstract:
Lung squamous cell carcinoma (LSCC) is a subtype of non-small-cell lung cancer (NSCLC) associated with poor survival outcomes due to a lack of targeted therapies. Our laboratory previously created a genetically engineered mouse model (GEMM) of LSCC driven by SOX2, a highly overexpressed oncogene in LSCC. Recently, we analyzed single-cell RNA sequencing data of mouse tumors and identified a distinct LSCC population marked by keratin-13 (KRT13) for patients. A previous study identified tumor-propagating cells (TPCs) in a squamous tumor, which resemble normal basal cells that allow for serial transplantation and proliferation of the disease. Interestingly, KRT13+ cells are found in unique “hillock” structures in the differentiating lung epithelium that express squamous-lineage markers and are immunomodulatory. We hypothesize that KRT13+ cells in LSCC are similarly important for squamous fate and immunomodulation. To identify the role of these KRT13-expressing cells, we analyzed scRNA-seq and publicly available human tissue microarray data for enriched genes and proteins. Our analysis revealed that this KRT13 population is highly enriched in Lgals3, a secreted protein that is known to regulate myeloid recruitment in multiple contexts. Since myeloid infiltration can be either pro-tumor or anti-tumor, this quickly becomes an interesting clinical avenue to explore. To test if Galectin-3 can alter myeloid infiltration in LSCC, we genetically deleted Lgals3 in tumor organoids that have KRT13+ populations, which secrete high levels of Galectin-3 by ELISA. Knocking out Lgals3 should decrease myeloid migration, which we will determine using transwell assays in vitro. In addition, we will knock out Lgals3 in GEMMs in vivo to validate the results from the tumor organoids. We expect that Lgals3 knockout will lead to a decrease in myeloid recruitment in tumors, which we will measure by immunohistochemistry (IHC) staining. To test if Galectin-3 is sufficient to alter myeloid migration, we overexpressed Lgals3 in a small-cell and adenocarcinoma GEMM that has low Galectin-3 expression and low myeloid infiltration. Here, we expect that IHC staining will reveal that Galectin-3 promotes myeloid recruitment. Together, these studies will determine if KRT13+ secretes Galectin-3 as a mechanism to alter immune populations in LSCC, which may be further developed as therapeutic strategies to improve patient outcomes.

Do lemurs have besties? Interspecies comparisons of social behavior and hormone concentrations

Kavya Menke

Faculty Mentor: Christine Drea

Authors: Kavya Menke, Caroline Shearer, Christine Drea

Biological Sciences

Abstract:
Androgens (e.g. testosterone) mediate aggression and social dominance, and concentrations are typically higher in males than females. Generally, higher androgen concentrations have negative health and reproductive consequences in female mammals (e.g. polycystic ovary syndrome). In lemurs, however, it is common for females to exhibit androgen-mediated, social dominance over males. We do not fully understand the consequences of androgen-mediated female dominance on social relationships. By comparing female-dominant (Eulemur coronatus) and codominant (E. sanfordi) species living in sympatry in Madagascar, this study aims to understand how hormonal differences may relate to differences in social networks. We examined social partnerships by recording nearest neighbors during focal observations and compared sex and species differences in androgens by quantifying the androgen metabolite concentrations in feces. Preliminary social networks based on nearest-neighbor data show that, across species, social bonds are strongest between mixed-sex pairs and weakest between males, suggesting that male lemurs tend to be more socially peripheral than females. Assay results to date show that female E. coronatus have greater fecal androgen concentrations, approaching male values, than do female E. sanfordi. These comparisons indicate that differences in social organization relate to differences in androgen concentrations, but more behavioral data are needed.

Our Insecticide Problem: Countering Pyrethroid Resistance in Knockdown Resistant Aedes aegypti

Ishaan Narsinghani

Faculty Mentor: Ke Dong

Authors: Ishaan Narsinghani, Funmilayo Egunjobi, Felipe Andreazza, Ke Dong

Biological Sciences

Abstract:
The pesticide treadmill is the ecological process by which mosquitoes and other organisms develop resistance to a vast array of insecticides through artificial selection. One such broad-spectrum class of insecticides, termed pyrethroids, have been widely applied across Sub-Saharan Africa, South America, and North America to control populations of Aedes aegypti—a known vector for dengue virus, yellow fever, and Zika, among others. Broadly, pyrethroids act as potent neurotoxicants by prying open the voltage-gated sodium channel and have therefore proven effective in controlling Ae. aegypti populations for decades. However, as per the pesticide treadmill, the growing use of pyrethroids has triggered significant rates of insecticide resistance—known as knockdown resistance (kdr)—in Ae. aegypti, accounting for a staggering 50 million cases of infection and 300,000 deaths annually. Such kdr strains of Ae. aegypti have been linked to mutations in the insects' voltage-gated sodium channels. A new mutation, L199F, was recently discovered in Ae. aegypti populations in Vietnam and Cambodia. However, whether L199F is involved in pyrethroid resistance in Ae. aegypti is unknown. We performed a previously established oocyte preparation procedure to maintain Xenopus cultures. Then, wild-type and mutant sodium channel genes were injected into Xenopus oocytes individually for protein expression using established protocols. Finally, two-electrode voltage clamp electrophysiology was used to assess (1) the functional properties of the mutant channel and (2) its sensitivity to the pyrethroids deltamethrin, transfluthrin, bifenthrin, and bioallethrin. Here, we provide compelling evidence that the L199F mutation is knockdown resistant to several widely-applied pyrethroids—most notably deltamethrin—but remains sensitive to transfluthrin, among others. In pinpointing which pyrethroids are effective in controlling select Ae. aegypti populations, this experimentation develops a new way to counter insecticide resistance in the future—minimizing mosquito-related deaths as a whole.

Novel Combination Therapy for MYC-Driven Medulloblastoma: Targeting BRD4 Dependency

Taylor Nguyen

Faculty Mentor: Scott Floyd

Authors: Taylor Nguyen, Scott R. Floyd

Biological Sciences

Abstract:
Medulloblastoma (MB) is a high-grade malignant pediatric brain tumor, accounting for 20% of childhood brain tumors; however, molecular diversity has rendered generalized treatment insufficient at improving patient prognosis. There is no clear etiology of MB, but four principal subgroups have been identified: Wnt, Shh, Group 3 (G3), and Group 4 (G4). The G3/G4 subgroups comprise 60-65% of all cases and are associated with greater metastasis and drug resistance incidences, but do not have a discrete molecular driver. Recent studies have shown overexpression of the MYC oncogene in G3/G4 tumors, suggesting MYC-driven etiologies. MYC is a transcription factor associated with the global upregulation of gene transcription, or hypertranscription, when overexpressed; however, it is considered pharmacologically "untargetable" due to a lack of druggable enzymatic function or interaction surface. Owing to its essential role in transcription elongation and as a transcriptional regulator of MYC, BRD4—a bromodomain and extra-terminal (BET) domain protein—has become an attractive therapeutic target in MYC-driven cancers. Inhibition of BRD4 has been shown to impact MYC-driven tumor progression; however, the mechanism is unclear. Known functions of BRD4 support two contradictory potential mechanisms: BRD4 inhibition (1) reduces MYC transcription and halts MYC-tumor progression or (2) hinders transcription elongation which induces DNA damage in the hypertranscriptional state, reducing tumor viability. The primary objective of this study was to determine which mechanism of BRD4 inhibition can be leveraged to treat MYC-driven medulloblastoma. Our data support MYC-driven tumor's dependency on BRD4 to support transcription and tumor viability. Combined pharmacologic BRD4 protein loss using BET inhibitor and degrader, dBET6, and genetic overexpression of MYC in HeLa cells decreased viability, increased apoptotic death, and increased DNA damage. Conversely, HeLa cells with genetic MYC protein loss treated with dBET6 did not exhibit viability loss, increased apoptotic death, or increased DNA damage. Combination treatment of dBET6 and kenpaullone (KPL), an inhibitor of GSK3B—a kinase that facilitates MYC proteolysis—induced lethality with strong synergy. Thus, leveraging MYC-driven hypertranscription's dependency on BRD4 for tumor viability is a potential avenue for developing novel combination therapies to treat G3/4 MYC-driven medulloblastoma.

G proteins modify ubiquitin-directed bias in Barr recruitment and internalization in GCGR

Preston Nibley

Faculty Mentor: Sudha Shenoy

Authors: Preston C. Nibley, Poonam Kumari, Annie Bao, Crista N. Vroman, Nora S. Madaras, Pavitra Murali, and Sudha K. Shenoy

Biological Sciences

Abstract:
Stimulation of the seven-transmembrane glucagon receptor (GCGR) by its ligand, glucagon, elevates blood glucose levels in response to hypoglycemia. Targeting GCGR activation presents an opportunity for crafting innovative treatments for managing blood glucose, obesity, and heart failure. GCGR activates stimulatory heterotrimeric G proteins (Gs), enhancing cAMP production and signaling through Protein Kinase A. Additionally, beta-arrestin1 (Barr1) and beta-arrestin2 (Barr2) are recruited to activated GCGRs, moderating G protein signaling. In the context of GPCR signal moderation, Barrs play a secondary role as scaffolds, facilitating signaling through GPCR-Barr megaplexes. We identified that polyubiquitin chains linked to lysine333 (K333) on GCGR serve as a foundation for efficient G protein association. Removing this ubiquitin marker from GCGR significantly decreases G protein association while boosting Barr1 engagement and p38 MAPK scaffolding, leading to a ubiquitination-dependent preference for Barr1 signaling. Employing GCGR-wildtype (WT) and ubiquitin-lacking GCGR-K333R (K333R) as models for unbiased and Barr-biased receptors, respectively, and utilizing bioluminescence resonance energy transfer (BRET) assays, we explored the impact of G protein expression on the agonist-driven Barr1 recruitment and GCGR internalization. In HEK-293 cells, Barr1's attraction to K333R was markedly higher in both agonist potency and efficacy than to WT. Conversely, in HEK-293 cells devoid of Gs/Gq/G12 (G6-KO cells), Barr1's attraction to WT reached levels seen with K333R. Moreover, reintroducing Gs-alpha in G6-KO cells restored the increased Barr1 connection with K333R. This result implies that G proteins might counteract the association between Barr and ubiquitinated GCGR, serving as mutual antagonists to Barr-induced steric occlusion of the G protein attachment site. These data provide insights into specific regulation of Barr1 in mediating glucagon signaling and might ultimately lead to testing and development of glucagon agonists biased toward specific GCGR transducers.

Describing Host Sphingolipids' Role in Plasmodium Invasion of Hepatocytes using Flow Cytometry

Porter Petruzziello

Faculty Mentor: Emily Derbyshire

Authors: Porter Petruzziello, Erin Schroeder, Emily Derbyshire

Biological Sciences

Abstract:
Transmitted to humans by female Anopheles mosquitoes, Plasmodium parasites cause the life-threatening disease malaria. After entering a host, parasitic sporozoites travel through the bloodstream to the liver, where they reside within a protective membrane called the parasitophorous vacuole membrane. This study investigates the role of host sphingolipids in the invasion of hepatocytes by Plasmodium berghei. Research has shown that cells infected with Plasmodium berghei have significantly higher levels of the sphingolipids sphingomyelin and ceramide compared to noninfected hepatoma cells. This increase in sphingomyelin and ceramide levels has been observed 25 to 35 hours post-infection (hpi), suggesting that Plasmodium requires these sphingolipids during the liver stage. To investigate the importance of sphingolipid composition in the host cell for pathogen invasion, a novel flow cytometry protocol has been developed. The impact of sphingomyelin depletion using bacterial sphingomyelinase and the importance of ceramides by the addition of exogenous C16-ceramide is explored by treating cells with the respective compounds at the time of infection and fixing them 3 hpi. Preliminary data from microscopy supports our hypothesis that invasion rates are impacted by altering the composition of these sphingolipids in the host cell. Employing our novel flow cytometry protocol, we aim to quantify the infection rate of Plasmodium under various conditions and describe the importance of host sphingolipid composition for pathogen survival. This investigation will elucidate the role of sphingolipids in the invasion of hepatocytes and help guide research into potential antimalarial targets.

Contribution of Nrg1/ErbB4 Signaling to the Homeostatic Effects of Seizures in Epilepsy Models

Emma Podol

Faculty Mentor: James McNamara

Authors: Emma Podol, Yangzhong Huang, Joshua Marek, James McNamara

Biological Sciences

Abstract:
Temporal lobe epilepsy (TLE) is known to be induced by a brief episode of seizures themselves (status epilepticus, SE), yet the mechanisms by which TLE develops and progresses ("epileptogenesis") remain elusive. Briefly inhibiting BDNF/TrkB signaling induces regression of epileptogenesis, yet this only occurs when introduced following a seizure. Thus, these findings led us to propose that seizures also activate signaling pathways that inhibit epileptogenesis. The receptor tyrosine kinase ErbB4 is expressed exclusively in the interneurons of the hippocampus where the activation and inhibition of ErbB4 signaling exerts anti- and pro- convulsant effects respectively in diverse seizure models. We hypothesize Nrg1 activates its receptor ErbB4 to be involved in this seizure-activated, anti-epileptogenic signaling pathway. SE mice cohorts were induced by intravenous infusion of kainic acid (KA) while control mice cohorts were infused with PBS. Animals were euthanized 24 hours following SE and mouse brain sections were prepared. We conducted in situ hybridization experiments using RNAscope technology to examine the expression levels of targeted Nrg1 mRNA in mouse hippocampus. The spatial profile of KA-SE induced Nrg1/ErbB4 signaling was determined using ImageJ software that produced image based, semi-quantitative analyses of the RNAscope data. We found that SE induced significant increase of Nrg1 mRNA expression in dentate gyrus (DG) but not in CA1 and CA3 of mouse hippocampus. Considering that ErbB4 receptors are expressed in hippocampal interneurons together with the requirement of parvalbumin (PV) interneurons for the anticonvulsant effects of Nrg1 suggested that seizures may enhance PV neuron mediated synaptic inhibition. Our results will provide insights into understanding the circuits and cells in which KA-SE activates Nrg1/ErbB4 signaling, which will facilitate elucidating its functional consequences.

FIRE-KRAB: Rapid, inducible CRISPRi to elucidate mesoderm specification in the green sea urchin

Zachary Pracher

Faculty Mentor: David McClay

Authors: Zachary Pracher, Carl Manner, Esther Miranda, and David McClay, Ph.D.

Biological Sciences

Abstract:
The developmental gene regulatory network (GRN) of the green sea urchin (Lytechinus variegatus) has been extensively investigated to illuminate the genetic interactions underlying embryogenesis and regeneration. Traditionally, functionally characterizing new GRN elements requires target knockdown using morpholino antisense oligonucleotides, which are costly, take a long time to synthesize, and can sometimes induce toxicity, thus confounding experimental results. To address these obstacles, we created the FIRE-KRAB system for gene-specific, inducible, and reversible transcriptional repression in the L. variegatus embryo utilizing a catalytically dead Cas9 fused to an inducible dimerizing pair and a KRAB repressor domain. In this investigation, we demonstrate that FIRE-KRAB successfully enables inducible and reversible transcriptional repression in the L. variegatus embryo. Subsequently, we deploy FIRE-KRAB to investigate the diversification of the mesoderm lineage into three functionally distinct subpopulations through epithelial-mesenchymal transitions (EMTs). Some cellular mechanics underlying these EMTs have been previously characterized, but the regulation and process by which these EMTs create three new mesodermal lineages in L. variegatus remains unknown. Using previously collected single-cell RNA-Seq data and in situ hybridization, we found novel GRN candidates for differentiating pigment and blastocoelar cell EMTs. Perturbing EMT GRN elements with FIRE-KRAB, we aim to deepen our understanding of how the regulation and mechanics of EMT contribute to the diverse mesodermal lineages necessary for a complete embryo. Furthermore, with FIRE-KRAB, we hope to create a new paradigm for elucidating GRN structure and function across diverse model organisms, providing insights into fundamental principles of development. These new insights, in turn, can begin to reveal how the early embryo utilizes EMT to generate diverse cell types, how this developmental process evolves, and how it can be dysregulated in disease.

Using Recombinant CuZnSod1 to Understand Its Metalation State and Activity in Candida albicans

RyAnn Pryor

Faculty Mentor: Kathy Franz

Authors: RyAnn A. Pryor, Francesca A. Vaccaro, Katherine J. Franz

Biological Sciences

Abstract:
Copper (Cu) is important for numerous biological processes. Despite its necessity, Cu is tightly regulated in cells due to its toxicity when in excess. In the opportunistic fungal pathogen Candida albicans, the complete mechanisms for copper homeostasis are not fully known. However, one known key player in Cu homeostasis in C. albicans is superoxide dismutase (Sod1). Sod1 requires copper and zinc to convert highly reactive superoxide radicals into the more manageable oxygen and hydrogen peroxide. The Franz lab has observed an increase of a population of Zn-only inactive Sod1 when C. albicans is in a copper-deficient state as a result of antifungal stress. We hypothesize that Sod1 may be directly involved in mechanisms of Cu homeostasis. My work is focused on development of a method for the recombinant overexpression, purification and reconstitution of CuZnSod1 from C. albicans. The goal is for this recombinant CuZnSod1 to serve as a standard for analysis of the metalation state and activity of native Sod1 from C. albicans subjected to various treatments which induce a stress response. An understanding of the activity of native Sod1 from C. albicans will contribute to a more complete picture of Cu homeostasis in C. albicans so that in the future, these mechanisms can be exploited in the design of better antifungals.

Effects of Hemarthrosis on Meniscus Repair and Post-Traumatic Osteoarthritis Development

Pranav Rastogi

Faculty Mentor: Amy McNulty

Authors: Pranav Rastogi, Allison Robinson, Kevin Betsch, Dawn Chasse, Dr. Jocelyn Wittstein, Dr. Samuel Adams, Dr. Amy McNulty

Biological Sciences

Abstract:
Menisci are crescent-shaped, fibrocartilaginous structures situated between the tibia and femur that provide shock absorption and stability for the knee joint. Commonly, tears in the meniscus result from abrupt cuts or pivots, especially in sports-related activities, and age-related degeneration. These tears can result in joint degeneration by altering both the biological and biomechanical environment of the knee, which leads to the development of post-traumatic osteoarthritis (PTOA). About two-thirds of meniscus-injured patients develop radiographic PTOA within 5-15 years of injury. Still, mechanisms that lead to PTOA development are unknown. Hemarthrosis, bleeding in the joint space, often accompanies traumatic knee injuries and occurs in conditions like hemophilia, which leads to hemophilic arthropathy with joint degeneration like PTOA. Our lab has previously shown that blood exposure can induce catabolism of meniscus explants ex vivo; however, little is known about its influence on meniscus healing and subsequent PTOA development following meniscus injury. We aim to elucidate the effect of blood on meniscus healing and PTOA development following meniscal injury. To accomplish this, our lab has generated a surgical model of meniscus injury and hemarthrosis in rabbits. A 5mm radial meniscus defect was surgically induced in the anterior horn of the medial meniscus and following joint closure, groups either received no treatment or 1mL of autologous blood was delivered intra-articularly. Controls (sham) underwent the same surgical procedures without the defect induction. In this pilot study, we are assessing gross and histological grading of joint tissues, including analysis of synovitis, meniscus repair, and PTOA development by cartilage grading. Understanding the effects of blood in the meniscus healing and PTOA development may provide avenues to improve meniscus repair strategies and reduce the physical and financial burden of traumatic knee injuries on patients.

The Role of CTRP4 in Modulating Inflammation due to Perinatal Hypoxic-Ischemic Encephalopathy

Jocelyn Reyes

Faculty Mentor: Jeffrey Russ

Authors: Jocelyn Reyes, Alkisti Capper, Donna M. Ferriero, Eric J. Huang, Jeffrey B. Russ

Biological Sciences

Abstract:
Perinatal hypoxic-ischemic encephalopathy (HIE) is caused by a lack of blood flow and oxygen to the term neonatal brain. This injury is thought to induce a chronic inflammatory response, oxidative stress, excitotoxicity, and cell death. The possible outcomes of this injury include neurological disabilities, seizures, and cerebral palsy. It is essential to understand how cells in the neocortex respond to injury to develop a therapy that may reduce these chronic responses. Based on unpublished single nucleus RNA sequencing from the Russ lab, a protein that showed the greatest changes in gene expression after HIE is CTRP4. This protein may help reduce inflammation as past research has shown CTRP4 exhibits anti-inflammatory activity in other disease models in vivo. We aim to quantify the degree CTRP4 exhibits anti-inflammatory activity after HIE through the use of a mouse model of perinatal HIE. We hypothesize that administration of CTRP4 after perinatal insult will lead to a decrease in injury compared to mice that do not receive exogenous CTRP4. In the experiment, we will compare four conditions: control mice, control mice treated with exogenous CTRP4, HIE mice, and HIE mice treated with exogenous CTRP4 after injury. All experimental mice will experience HIE via the Vannucci Method at P9 while controls will undergo sham surgery. Tissue harvesting will occur after injury, followed by histology and quantification. The degree of injury will be measured through analysis of lesion size, quantification of glial scarring, and staining and analysis of microglia and CD68. CTRP4 intensity levels will also be quantified. If CTRP4 does have an anti-inflammatory effect after HIE, this could lead to the development of a novel therapeutic strategy to reduce inflammation and treat the devastating symptoms of HIE in children.

Prenatal Environmental Toxin Exposure Alters the Adolescent Brain

Erika Rispoli

Faculty Mentor: Staci Bilbo

Authors: Erika Rispoli, Trisha Vaidyanathan, Dang Nguyen, Staci Bilbo

Biological Sciences

Abstract:
The prevalence of neurodevelopmental disorders (NDDs) has increased rapidly in recent decades and epidemiological studies indicate a correlation between prenatal toxin exposure and NDDs . Genetic mechanisms of these disorders have been studied extensively; however, environmental factors contributing to NDD development remain less understood. Current evidence suggests that alterations in synapse refinement underlie NDD pathology. Sleep, critical to this refinement, is disturbed in nearly 86% of NDD patients. This study used the Diesel Exhaust Particle and Maternal Stress (DEP/MS) paradigm to co-expose pregnant mice to DEP and a maternal stressor. While previous studies have revealed sex-specific social and behavioral changes in DEP/MS adults, we focused on adolescence. Adolescence is a critical developmental period when NDD sleep disturbances are particularly prevalent. This study aims to characterize NDD phenotype of DEP/MS offspring specifically during adolescence. Preliminary RNA sequencing data indicates upregulation of over 450 genes in microglia in DEP/MS adolescents compared to controls. No changes in astrocyte gene expression were observed. Preliminary analysis of sleep data does not suggest changes in overall time spent in REM/NREM and wake. However, analysis of spectral power reveals disrupted high-frequency network dynamics in DEP/MS female adolescents. Additionally, altered network dynamics were frontal-cortex dependent and sleep state independent. Because the frontal cortex undergoes significant development during adolescence, we hypothesize that changes in network dynamics may have functional consequences contributing to NDD development.

The association of forgiveness with physiological responses to memories of past wrongdoings

Daniel Robelo

Faculty Mentor: Felipe De Brigard

Authors: Daniel Robelo, Gabriela Fernandez-Miranda, Kaylee Miceli, Leonard Faul, Kevin Labar, Felipe De Brigard

Biological Sciences

Abstract:
Currently, there is a debate with regards to forgiveness and its relationship with memory. Some support the episodic fading (EF) account, which states that when forgiving one's episodic (sensory, contextual, temporal, and spatial details) and affective (emotional tone, valence, and intensity at retrieval) characteristics for memories of wrongdoings change. The other party posits the emotional reappraisal (ER) account, which holds that only the affective characteristics change. Previous data collected from our lab seems to align with the ER account, which would lead to forgiveness involving lower ratings of intensity and negative valence. This evidence was limited to self-report measures, however, so our current study utilizes physiological measures (electrodermal activity, corrugator supercilii and zygomaticus electromyography, heart rate, and respiration rhythm) using the BIOPAC system (in addition to a 16-item self-report questionnaire) to observe physiological patterns. This allowed us to analyze the phenomenological characteristics of memories of neutral events vs. wrongdoings through objective measures. We found that memories of wrongdoings produce stronger responses for electrodermal activity and corrugator supercilii amplitude than memories of neutral events. Furthermore, memories of wrongdoings high on forgiveness, when compared to those low in forgiveness, displayed lower emotional intensity and less negative valence in self-reported and physiological measures of emotional responses during recall. Our physiological responses matched our self-report measures in corroborating the emotional reappraisal account of forgiveness and hint at the potential use of emotional reappraisal techniques in facilitating forgiveness.

Insulin/IGF Signaling Pathway Modulation by ist-1/IRS: Implications for Starvation Resistance

Ainsley Scheiner

Faculty Mentor: Ryan Baugh

Authors: Ainsley Scheiner, Jingxian Chen, Ryan Baugh

Biological Sciences

Abstract:
The insulin/IGF signaling (IIS) pathway is a critical regulator of aging and metabolism throughout animals. The roundworm C. elegans is a powerful model system to study IIS, with extensive evolutionary conservation of molecular function. ist-1 is a homolog of human IRS-1 that facilitates the binding of phosphoinositide 3-kinase (PI3K) to insulin and insulin-like growth factor receptor (IGFR), but its function in C. elegans remains largely unexplored. In this study, a brood size assay was employed to investigate the potential involvement of ist-1 in starvation resistance and reproduction in C. elegans. Our investigation revealed a significant phenotype associated with ist-1. Specifically, ist-1 mutant worms exhibited significantly larger brood sizes compared to wild-type worms following starvation, suggesting a pivotal role for ist-1 in promoting growth at the expense of starvation resistance in C. elegans. These findings align with the expectation of the role of ist-1 based on the current understanding of the IIS model and shed light on the potential function of the ist-1 human ortholog IRS-1.

Contribution of IL34 signaling in microglial function in development and Alzheimer's disease

Ashka Shah

Faculty Mentor: Staci Bilbo

Authors: Ashka Shah, Ben Devlin, Staci Bilbo

Biological Sciences

Abstract:
A role of microglia in the brain is the removal of unwanted or damaged synaptic connections and neurons. During development microglia play an important role in the clearing of extra synapses and cells, so excessive activation of microglia in development could have consequences both during development and for neurodegenerative diseases like Alzheimer's Disease (AD). Microglia are regulated by signaling at the colony stimulating factor 1 receptor (CSF1r), which has two known ligands, colony stimulating factor 1 (CSF1) and Interleukin-34 (IL34). Because previous data in the lab has shown that IL34 signaling can decrease microglia synaptic pruning, we aimed to investigate whether disrupted or increased IL34 signaling contributes to microglial homeostasis and phagocytosis. Specifically, we blocked IL34 or CSF1 individually to determine if it has functional consequences on differential CSF1r signaling in microglia in the brain after the second week of postnatal development, and how this affects the maturity of the microglia in the anterior cingulate cortex (ACC), as it is a cortical region important for social cognition and has been implicated in AD. We hypothesized that mice with blocked IL34 would have an increased number of immature microglia that are more phagocytic compared with control and blocked CSF1 mice. We found that blocking IL34 at P15 decreased the percentage of homeostatic mature microglia and increased the percentage of immature, phagocytic microglia in P17 mice. Additionally, in another set of experiments we aimed to investigate whether virally overexpressing IL34 has consequences on synaptic numbers in the beginning of postnatal development. Because IL34 KO mice and blocked IL34 mice at P15 have been shown to have more phagocytic microglia, we hypothesized that the overexpression of IL34 between P1 and P8 would instead increase mature microglia, leading to microglia that are less phagocytic of synapses during postnatal maturation, and increasing the number of synapses. Our preliminary data shows a trend of increased number of synapses at P8 in mice that were infected with IL34 overexpression virus than mice that were infected with the control at P1. We are currently collecting more data to increase the power of statistical tests.

The Response of the Rete Ovarii to Estradiol

Vidita Shah

Faculty Mentor: Blanche Capel

Authors: Vidita Shah, Dilara Anbarci, Jennifer McKey, Blanche Capel

Biological Sciences

Abstract:
The Rete Ovarii (RO) is a tripartite epithelial structure connected to the ovary, thought to be the female homologue to the Rete Testis. Previously the RO was believed to be vestigial, however new evidence suggests that the RO plays a role in fertility and ovulation via hormone signaling. We previously found that the RO secretes proteins essential for ovarian function which are sent to the ovary. The RO also expresses estrogen receptor 1, suggesting that it can interpret circulating hormones. We also found that certain genes were upregulated or downregulated during estrus or diestrus, indicating that it is responding to estrogen. We hypothesize that the RO acts as an "antenna" for the ovary, responding to external cues such as hormones and secretes and sends proteins to the ovary that regulate ovarian function such as oocyte ovulation rate. To test this hypothesis we cultured Postnatal day 21 RO's with estradiol, fulvestrant (an estrogen receptor antagonist), or IGF1 for 5 days to determine the response of the RO to external cues.

Elucidating the role of Spastin in regulating lipid droplet (LD) morphology

Mingma Sherpa

Faculty Mentor: Nina Sherwood

Authors: Mingma Lucky Sherpa, Dr. Nina Sherwood

Biological Sciences

Abstract:
Autosomal Dominant Hereditary Spastic Paraplegia (AD-HSP) is a progressive neurodegenerative disease characterized by limb weakness and spasticity that affects 1.8 out of every 100,000 individuals globally. Prior genetic studies have shown that the loss of function of the SPAST gene, which codes for Spastin protein, is the most common mutation in AD-HSP. Spastin is a microtubule severing protein and recent studies have shown that spastin mutant also impacts lipid droplet (LD) biogenesis and lipid metabolism in Danio rerio (zebrafish), Caenorhabditis elegans, and Drosophila melanogaster. In these model organisms, spastin depletion resulted in morphological changes in LDs, including a higher number of smaller LDs compared to the wild type. Lipid droplets are organelles that store neutral lipids and have a single-layered hydrophilic membrane with proteins that can regulate LD function. Proteins, such as Spastin, that target the LD membrane have been found embedded in the endoplasmic reticulum (ER) which later accumulates on the LD membrane and regulates the dispersion of LDs. Spastin protein is 49% identical in humans and Drosophila, making it worth studying these newly mapped spastin mutants and their respective changes in LD morphology in Drosophila. We hypothesized that the LDs in Drosophila larvae are affected by the spastin mutant, and our goal was to visualize LDs in both wild type and spastin mutant fly lines to look for localization patterns as well as compare LD densities. To test this hypothesis, we used the newly identified 336/5.75 spastin mutant generated using the T32 line. The 336/5.75 larvae and white larvae, used as control, were dissected and immunostained using anti-HRP 568 (neurons), 660 phalloidin (muscles), and BODIPY 493/503 dye (lipid droplets). Results from confocal microscopy showed that LDs were localized primarily in the brain and also observed in the muscles. Consistent with the previous studies, LDs were more numerous in the control, whereas the mutant line had relatively fewer LDs. Furthermore, comparing these changes in LD morphology to the well-established synaptic bouton morphology in spastin mutants will contribute to the understanding of the relation between these spastin mutant phenotypes. These studies will give further insights into understanding AD-HSP disease pathogenesis in humans and elucidate underlying genetic mechanisms with the potential to provide targeted therapies.

Molecular Mechanisms of Toxicity of GenX and PFOA in C. elegans

Kate Silver

Faculty Mentor: Ryan Baugh

Authors: Kate Silver, Tess Leuthner, Ryan Baugh

Biological Sciences

Abstract:
Per- and polyfluoroalkyl substances (PFAS) are a class of over 14,5000 chemicals developed during the manufacturing of nonstick cookware, fire retardants, and other household materials. According to a report published by the Centers for Disease Control and Prevention, there are detectable levels of PFAS in the blood of over 97% of Americans. One PFAS in particular, PFOA, is suspected to cause cancer, preeclampsia, decreased vaccine response, and liver damage. However, it was phased out of intentional production in 2015 and replaced with an alternative PFAS called GenX. Despite the adverse health effects associated with both GenX and PFOA, little is known about how genetic variation alters biological responses to these chemical exposures. Thus, further investigation is necessary to fully comprehend the mechanisms of toxicity of these two compounds. In this study, we provide a proof of concept for using RNA interference in liquid to conduct genetic screens to investigate variation in response to PFAS exposure and the role certain gene pathways play in the mediation of toxicity in the powerful genetic model C. elegans. We hypothesize that two gene classes, Insulin-like signaling (ILS) genes and nuclear hormone receptors (NHRs), impact the survival outcome and growth of worms. We found that worms fed the E.coli strain, HT115, were nearly twice as resistant as worms fed the E. coli strain, HB101, when exposed to GenX (One-way ANOVA, $p = 0.0002$) and PFOA (One-way ANOVA, $p = 0.003$). Additionally, we found that two NHRs, nhr-8 and daf-12, may play a role in mediating the response to PFAS (Welch's t-test, p < 0.05). These results are crucial to developing a greater understanding of how PFAS physiologically alter health outcomes in not only C. elegans but humans and other mammals as well. Future studies could be conducted using this now well-established experimental paradigm with the remaining 270 NHRs and PFAS compounds to thoroughly understand the extent to which genetic variation mediates PFAS susceptibility.

Flaviviridae are Differentially Regulated During Infection by UFL1, the Ligase for UFMylation

Grace Sorensen

Faculty Mentor: Stacy Horner

Authors: Grace Sorensen, Hannah Schmidt, Stacy Horner

Biological Sciences

Abstract:
Flaviviridae such as dengue, Zika, and hepatitis C virus are human pathogens with a high disease burden worldwide. Understanding the proteins that regulate Flaviviridae replication is important for developing effective viral treatments and vaccines. The Horner Lab has previously shown that UFL1, a protein involved in regulating cellular stress and intracellular membrane dynamics, is recruited to antiviral innate immune signaling sites in the cell during viral infection. We examined the role of UFL1 in regulating Flaviviridae infection and found that depletion of UFL1 reduced infection by the orthoflaviviruses dengue, Zika, Yellow Fever- 17D, and West Nile. Interestingly, we found that hepatitis C, which is a hepacivirus, is not regulated by UFL1. Based on UFL1's described role in innate immune signaling, we then examined whether the observed regulation of infection by UFL1 was dependent on intact STAT1 signaling. Our results show that UFL1 depletion does not reduce dengue and Zika virus infection in STAT1-knockout cells, indicating that regulation of these viruses by UFL1 is dependent on a functional interferon response. Interestingly, yellow fever-17D and West Nile virus infection continue to be decreased by UFL1 depletion in STAT1-KO cells, indicating that the mechanism of regulation by UFL1 is independent of innate immune signaling for these viruses. In order to gain insight into potential mechanisms by which UFL1 regulates viral infection, we used a luciferase assay at early timepoints to demonstrate that UFL1 depletion does not affect Zika virus entry and initial translation. Future experiments will similarly test initial translation of yellow fever-17D with UFL1 depletion to test the hypothesis that viral translation may be differentially regulated by UFL1 between these two groups of viruses. Identifying pathways differentially regulated by UFL1 during infection will provide insight into novel mechanisms of viral regulation and inform the development of effective viral treatments.

Select mitochondrial toxicants induce an enhanced RNA interference response in C. elegans

Clare Sparling

Faculty Mentor: Joel Meyer

Authors: Clare Sparling, Dillon King, Joel Meyer

Biological Sciences

Abstract:
Mitochondrial dysfunction activates immune responses and plays a role in many immune diseases. Given that many environmental toxicants target mitochondria, we assessed whether mitochondrial toxicants could activate immune responses in Caenorhabditis elegans. Studying this question serves two purposes. One, it may identify environmental toxicants that modulate immune activity. Two, probing various aspects of mitochondrial dysfunction with mechanistically distinct toxicants may provide insight into the specific characteristics of mitochondrial dysfunction that induce immune activation. RNA interference (RNAi) is used by C. elegans to defend against viral pathogens. Thus, an enhanced RNAi ("eri") phenotype was used to screen for immune activation. Rotenone (Complex I inhibitor), antimycin A (Complex III inhibitor), sodium azide (Complex IV inhibitor), and paraquat (redox cycler) exposures induced an eri phenotype in C. elegans. Thenoyltrifluoroacetone (Complex II inhibitor), N,N'-dicyclohexylcarbodiimide (ATP synthase inhibitor), carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (uncoupler), and UVC (mtDNA damage) exposures failed to induce an eri phenotype. The eri phenotype induced by antimycin A and sodium azide was abrogated by treatment with the antioxidant N-acetylcysteine, and the eri-phenotype induced by rotenone and paraquat may partially depend on the DRH-1 pathway. Our findings indicate that select types of mitochondrial dysfunction induce an enhanced RNAi response in C. elegans.

Impact of Aged Tumor Microenvironment in Ovarian Cancer

Lila Taylor

Faculty Mentor: Zhiqing Huang

Authors: Lila Taylor, Ethan Nguyen, Lila Teitle, Bella Mendieta, Jihua Feng, Zhiqing Huang

Biological Sciences

Abstract:
Ovarian cancer (OC) is the deadliest cancer in the female reproductive system and the tumor microenvironment (TME) plays fundamental role for cancer development, progression, and chemotherapies. As a heterogeneous disease, cancer includes cancer cells and the stromal tissues in TME; both are influenced by epigenetic and genetic alterations in cellular pathways. Age poses a significant risk factor for OC and most OC patients are diagnosed in their 60s. The components in the TME, lipids and immune cells, are integral parts of the intricate landscape driving cancer pathogenesis and their impacts in an aged setting have not been well studied. This study aims to investigate the impact of aging, lipid levels, and immune cells in TME on ovarian cancer growth. We used cancer-associated fibroblasts (CAFs, from aged vs young Wi38), lymphocytes from aged or young mice, and lipids obtained from differentiated preadipocytes (3T3-L1) to model the TME's effects on OC proliferation as they all play the significant roles in TMEs in supporting and regulating tumor growth and progression. We analyzed OC cell proliferation when they were co-cultured under each TME condition. We found OC cells were less proliferated when cultured in aged WI-38 medium versus young WI-38 medium in both HEYA8 and CAOV2 OC cell lines. 3T3-L1 preadipocytes were differentiated and produced lipids in medium; co-cultured HEYA8 and CAOV2 cell lines showed a significant increase in HEYA8 cell growth when they were cultured under high fat conditions using the medium from the differentiated 3T3-L1 compared with the low-fat conditions using the medium from the undifferentiated 3T3-L1 cells. The co-culture of OC cells (HEYA8 and CAOV2) in aged lymphocytes showed significantly lower cell proliferation when compared to young lymphocyte co-culture. We were also able to see the more proliferative cell growth for the chemo-resistant OC cells (M41-cisR) than the chemo-sensitive OC cells (M41) when they were cultured under high fat conditions. Taken together, our data suggests that aged stromal cell and lymphocytic conditions reduced cancer cell proliferation, while the high fat environment can significantly increase the cell growth in OC cells. Additionally, the chemo-resistant OC cells are more aggressive than the chemo-sensitive OC cells when they are exposed in high lipid conditions. More studies in the future are needed to investigate the mechanisms for the influences of aged TME in cancer.

Attempting to Induce Insulin Sensitivity in Tissue Engineered Skeletal Muscle Models

Will Temme

Faculty Mentor: George Truskey

Authors: Will Temme, Mingzhi Xu, George Truskey

Biological Sciences

Abstract:
Tissue engineered microphysiological systems allow personalized simulation of physiological processes in a manner that is structurally and functionally comparable to tissues in vivo. Skeletal muscle is responsible for the majority of the body's insulin-mediated glucose uptake. Existing in vitro skeletal muscle tissue models tend to display sub-physiological insulin response characteristics. Furthermore, a 2022 in vitro study found that lowering concentrations of key nutrients and insulin in culture to physiological levels caused adipocytes to demonstrate potent insulin response. Given these findings in adipocytes, we hypothesized that physiologically accurate insulin response properties in tissue engineered myobundle models could be induced by culturing cells in serum-free media with low concentrations of key nutrients, such as amino acids. Serum-free media was selected because some constituents of serum may inhibit skeletal muscle differentiation and reduce insulin sensitivity. Extended culture in serum free media with relatively low amino acid concentrations resulted in elevated insulin-mediated glucose uptake in monolayer culture but produced low contractile and glucose uptake properties for myobundles.

Application of Digital PCR to Measure HIV-1 Latency and Reactivation in the CNS

Ariana Vaida

Faculty Mentor: Amanda Brown

Authors: Ariana Vaida, Amanda Brown PhD

Biological Sciences

Abstract:
Latent reservoirs are target cells for HIV at a resting state that are susceptible to reactivation upon treatment interruption. Historical data and accruing findings using innovative technologies and in vivo models support the role of macrophages and microglia function as cellular reservoirs of latent HIV-1. Our lab and others have shown that elevated proinflammatory response remains closely tied to HIV-associated neurocognitive disorders (NeuroHIV) despite the suppression of the replicating virus by antiretroviral therapy (ART). However, the literature of the molecular mechanisms contributing to NeuroHIV and latency remains limited. Sensitive methods are required to quantify HIV nucleic acid in the CNS. In comparison to tradition quantification technology, modern digital PCR provides absolute target quantification without reliance on a standard curve. To test this, we cultured and synthesized the cDNA of human peripheral blood mononuclear cells (PBMCs) derived from 2 donors over 14 days. The samples were divided amongst 4 groups, of which nearly half of the surviving cells were HIV-infected and the remaining served as a control, treated with the same concentration of ART, quantified the number of viral RNA copies by digital PCR (dPCR), and measured the p24 antigen with an ELISA-based titration protocol. We observed significant detection of viral RNA in the samples infected and untreated considering they experienced long-lived transcriptional activity. Our data indicates that dPCR is a promising method for viral load detection with greater efficiency and sensitivity than qPCR, suggesting that the application of digital PCR technology may be the next generation platform to overcome the challenges of quantification at low concentrations in the context of persistence. In future work, we plan to replicate these findings with human microglia and blood samples derived from in vivo humanized mice models to validate the protocol designed for further quantification of HIV-1 latent reservoirs.

Uncovering the Role of Two Related Mannoproteins in the Fungal Pathogen Cryptococcus neoformans

Jaqueline Villanueva Govea

Faculty Mentor: Jennifer Tenor

Authors: Jaqueline Villanueva Govea, Dena Toffaletti (Ph.D.), Jennifer Tenor (Ph.D.), John Perfect (M.D.)

Biological Sciences

Abstract:
Cryptococcus neoformans, an opportunistic fungal pathogen, primarily affects immunocompromised individuals by infecting the lungs and central nervous system. A defining characteristic of C. neoformans is its capsule comprised of polysaccharides, proteins, and other molecules, which shields this yeast from environmental stresses including the body's immune system. Glycoproteins associated with the capsule are comprised of protein and carbohydrate chains that are involved in many physiological functions and can be antigenic. An example of a glycoprotein found in that capsule are mannoproteins. Mannoproteins in C. neoformans can be immunogenic and can stimulate the immune protection of the host. Little is known about how mannoproteins contribute to the virulence and survival of C. neoformans in vivo. Our previous transcriptomic work on Cryptococcus gene expression in human cerebral spinal fluid has identified several mannoproteins with a high abundance of transcripts. This study focuses on two predicted glycosylphosphatidylinositol-anchored mannoproteins, CNAG_05424 and CNAG_01272, which are likely paralogs through genetic analysis. To identify the role(s) of these genes in C. neoformans, particularly in aiding the cell wall DNA encoding process and interaction with the host immune response, single and double gene deletions were constructed. First, plasmids were constructed to facilitate the deletion of the genes at their native site. Next, sgRNA was designed to allow us to use the CRISPR-CAS9 strategy for the construction of the deletion strain. Following strain validation, phenotypic characterization of the strains will be performed to identify the role(s) of these mannoproteins in cell wall integrity, antigenicity, interaction with immune cells such as macrophages, and effect on stress resistance. By identifying the impact that these genes have based on their absence in the cell, we can gain a better understanding of the roles of these uncharacterized mannoproteins to further our research on genes that contribute to the pathogenesis of Cryptococcus.

Synthesis of Daucane Anti-austerity Agents against PANC-1 Human Pancreatic Cancer Cell Line

Eric Wang

Faculty Mentor: Jiyong Hong

Authors: Eric Wang, Yiquan Zhao, Dr. Iljin Shin, Dr. Hyoungsu Kim, Dr. Jiyong Hong

Biological Sciences

Abstract:
Human pancreatic cancer is one of the most aggressive and lethal types of cancer. It is the seventh leading cause of cancer-related death worldwide, with over 400,000 people diagnosed annually across the globe. Despite improvements in treatment and detection, the five-year survival rate of pancreatic cancer remains at a dismal 12%. This is partially attributable to a hypovascular tumor microenvironment, which creates an immunosuppressive and chemotherapy-resistant environment for pancreatic cancer cells. Thus, antiausterity strategies, which target the ability of cancer cells to survive in these nutrient-starved conditions, have been targets for therapeutic research. Ferutinin and another novel secondary metabolic sesquiterpenoid, both isolated from the roots of Ferula hezarlalehzarica, were found to exhibit preferential antiausteric activity against the PANC-1 human pancreatic cancer cell line in nutrient-deprived media. Herein we report our progress toward the total synthesis of Ferutinin and the novel sesquiterpenoid, with the synthetic hallmark being a radical cyclization to introduce both ring junction stereocenters. Utilizing the established synthetic scaffold, syntheses and antiausteric activities of various analogs against PANC-1 cells will also be explored, ascertaining the properties of similar molecules not found in nature.

Factors Influencing Seed Dispersal - Variation in Functional Traits Across Lemur Species

Dedriek Whitaker

Faculty Mentor: Leslie Digby

Authors: Dedriek Whitaker - Student Presenter | Camille DeSisto - Graduate Student Mentor | Leslie Digby - Faculty Mentor

Biological Sciences

Abstract:
Since the late 1980s, researchers have recorded a massive decrease in biodiversity in Madagascar (Ralimanana et al. 2022). The island has undergone extensive deforestation and fragmentation in recent decades, leading to the loss of many species and their habitats (Vieilledent et al. 2018). Anthropogenic activities, such as agricultural expansion, logging, and charcoal production, result in severe ecological consequences (Ganzhorn et al. 1999). Effective conservation measures will almost certainly need to focus on changing human patterns, but one important aspect is maintaining animal mechanisms that help maintain forest growth and replenishment, including seed dispersal. Many vertebrates have an active role in seed dispersal, by which they are able to distribute seeds throughout their habitat ranges to aid in forest regeneration (Schupp et al. 2010). Lemurs have a particular importance, as most highly frugivorous species are known to be both effective and primary seed dispersers in Madagascar (Razafindratsima 2014). Understanding factors that affect certain processes of seed dispersal, such as the gut passage rate, is crucial to learning more about the effect that this conservation mechanism has on the environment. Gross and colleagues (1996) found that there are both body size and sex differences in gut passages rates in groups of Nubian ibex. There is limited knowledge on the potential relationship of certain functional traits, such as sex, age, and body size, on gut passage rates in lemurs. The relationship between social dominance and feeding ecology can also provide more information on seed dispersal in mammals, specifically lemurs, as this could affect food intake volume and access to favored resources (Overdorff et al. 2005). Through a study conducted at the Duke Lemur Center (DLC), I aim to answer the question: (1) Are there any correlations between lemur gut passage rates and their functional traits (sex, age, and body size)? The study will include Eulemur coronatus, Eulemur flavifrons, Eulemur mongoz, Lemur catta, Varecia variegata, and Varecia rubra. The Propithecus genus is not included due to their history of being seed predators (Razafindratsima 2014). Understanding the variability and factors influencing gut passage rates may enable better predicted patterns of seed dispersal by different lemur species.

Early Adolescent Genotoxic Stress Damage on Skeletal Muscle Stem Cells and Their Niche

Cathy Yang

Faculty Mentor: Joe Chakkalakal

Authors: Cathy Yang, Vijitha Puviindran, John Bachman, Danny Panken, Elena Torres Ponce, Joe V Chakkalakal

Biological Sciences

Abstract:
Genotoxic stress is a consequence of cancer treatments such as radiation whose persistence contributes to accelerated aging of tissues and organs. Immediately following radiation of growing adolescent skeletal muscle, extensive DNA damage is observed, the integrity of muscle stem cells is reduced, and regenerative capacity is inhibited. Most of this damage subsides within weeks. This study provides insights into the immediate and enduring impact of genotoxic stress on particular cell populations. Using single-cell RNA sequencing analysis and assessment of fate, we reveal that most muscle stem cells lost with adolescent radiation are non-quiescent. Furthermore, weeks after early adolescent radiation, remaining muscle stem cells demonstrated little, if any, signs of DNA damage. In contrast, persistent signs of genotoxic stress were observed in components of the muscle stem cell niche. This was associated with an increase in macrophage content and the expression of TGFbeta superfamily members and regulators, which based on Cell Chat analysis have the potential to impact multiple cellular processes during skeletal muscle growth and regeneration. Collectively, these observations indicate that the persistence of genotoxic stress after early adolescent radiation occurs primarily in the niche as opposed to muscle stem cells.

Behavioral Characterization and whole-brain activity mapping of psychedelics in zebrafish

Ruo Yan Elysia Ye

Faculty Mentor: Eva Naumann

Authors: Ruo Yan Elysia, Minel Arinel, Eva A. Naumann

Biological Sciences

Abstract:
Psychedelics are emerging as promising therapeutics for multiple mental health disorders. However, most of the current research on the underlying neurobiological mechanisms of psychedelics has been concentrated on rodents and is insufficient in illustrating how psychedelics affect sensory circuits as a whole system. The larval zebrafish is an ideal model organism as it provides optical access to the entire brain at a single-cell resolution. Their transparency allows for non-invasive, in vivo imaging, and provides an exceptional opportunity to visualize neural dynamics and circuitry in the organism. Therefore, using larval zebrafish, we investigated the sensorimotor behaviors and their underlying neural circuitry with acute exposure to the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI). Using high-resolution multi-camera array microscope and custom-built behavior rigs, we recorded zebrafish responses to a series of locomotor, photomotor, and optomotor behaviors, as well as responses to light, dark, and vibration startles before and after exposure to DOI or a vehicle control. Fish in the DOI condition exhibited a decrease in locomotor activity in a dose-dependent manner. However, under dark stimuli (i.e., dark epoch and dark flash), this motor response had an inverted “U-shaped” dose-effect relationship, whereas no difference was observed in light conditions or vibration startles. Interestingly, when fish were shown moving gratings to investigate their optomotor response behavior, the locomotor activity did not change throughout the experiment. Instead, they performed stronger turns in response to left and right visual gratings. Finally, we performed volumetric two-photon imaging in brain regions involved in sensorimotor transformations, such as the pretectum and the hindbrain, to uncover the specific neural circuits that DOI is activating or inhibiting. Future work will include determining changes in functional connectivity before and after exposure to DOI using a recurrent neural network model. Our findings demonstrate stimulatory and inhibitory functions of DOI that are concentration- and environment-dependent. These findings can propel the identification of neural circuits affected by exposure to psychedelics and understanding how psychedelics alter sensory processing.

Birth weight across Daasanach communities in Northern Kenya and the effect of multiparity

Katie Zhang

Faculty Mentor: Herman Pontzer

Authors: Kathryn Zhang, Elena Hinz, Srishti Sadhir, Leslie Ford, Amanda McGrosky, Rosemary Nzunza, David Braun, Emmanuel Ndiema, Asher Rosinger, Herman Pontzer

Biological Sciences

Abstract:
Pregnancy is physiologically demanding and may have long-term effects on mothers, yet the effects of prior pregnancies on pregnancy outcomes are not well understood, particularly among non-industrialized subsistence populations. Among Western populations, an increase in birth weight and decreased risk of low birth weight (LBW, <2500g) are typically found in mothers with low multiparity (2-4 births) compared to primiparous mothers. This is attributed to physiological changes positively impacting fetal nutrient flow following a first pregnancy. We tested the effects of multiparity on birth weight using data from Ileret Health Centre (IHC) delivery records (n=111), a clinic in Marsabit County, Kenya, providing maternal medical services to Daasanach pastoralist communities. IHC data provide a unique opportunity to investigate pregnancy outcomes in a population living an energetically demanding lifestyle in a resource-limited environment. Using data from primiparous and multiparous mothers (2-9 births), mean birth weight differences and LBW unadjusted odds ratios were calculated for these parity groups. Birth weight trended upward, with a mean increase of 60g for multiparous mothers (mean=3049g, SD=455g) compared to primiparous mothers (mean=2989g, SD=481g), but this difference was not statistically significant (p=0.58). Similarly, there was a non-significant trend of decreased risk of LBW (OR=0.58, 95% CI= 0.15-2.9) for multiparous mothers (7.95% LBW) compared to primiparous mothers (13.0% LBW). These results are consistent with studies of Western populations and highlight the importance of examining daily energetic demands and resource availability when evaluating maternal health and pregnancy outcomes.

Generating snoRNA-guided Programmable 2'-O-methylation

Justin Zhao

Faculty Mentor: Christopher Holley

Authors: Justin Zhao, Eric Cockman, Christopher Holle

Biological Sciences

Abstract:
Small nucleolar RNAs (snoRNAs) are critical in guiding post-transcriptional modifications like 2'-O-methylation (Nm) in RNA, which play crucial roles in downstream processes such as splicing and translation. This study provides a novel method for Nm validation, addressing a significant gap in modern Nm research, and offers insight into the intricacies of snoRNA-guided Nm. While mapping of Nm modifications has seen significant improvement within the past decade, no major techniques have been able to validate these potential sites. Additionally, many mapping techniques lack consensus among proposed Nm sites, especially on less abundant species such as mRNAs. Without a proper validation technique, Nm research lags compared to its peer post-transcriptional modifications. The RNaseH-based Nm-VAQ assay proposed here quantifies 2'-O-methylation at single nucleotide resolution across various RNA species including rRNA, snRNA, and mRNA. Its optimization for mRNA allows for an unprecedented way to study the effects of Nm modifications in low abundance transcripts. This allows researchers to validate proposed Nm sites and understand the stoichiometry of methylated versus unmethylated sites and its downstream effects on translation. This study also explores the use of synthetic snoRNAs in guiding Nm modifications. Utilizing the novel Nm-VAQ validation assay, exogenous snoRNAs are shown to rescue Nm in genetic knockout models. These exogenous snoRNAs can be modified to guide Nm at any location along the target RNA transcript. This method facilitates the study of how Nm modifications on different regions of an mRNA transcript, including but not limited to the start/stop codon, 5' or 3' UTR, exons, and splice donor/acceptor sites, impact downstream processes. Preliminary work indicates that synthetically modified snoRNAs demonstrate the ability to modify exogenous RNA transcripts such as luciferase, impacting translation efficiency and protein expression. The addition of a modification in the luciferase exon increases mRNA abundance but decreases protein expression, consistent with previous findings on other mRNAs. Future work is needed using the Nm-VAQ assay to fully elucidate the relationship between Nm modification levels and the corresponding changes in transcription and translation. These findings set the scene for novel understanding of the relationship

between snoRNA abundance, 2’-O-methylation efficiency, and Nm’s impact on gene expression.

Enhancement of translation in living cells through synthetic ribonucleoprotein granule

Miranda Zhong

Faculty Mentor: Ashutosh Chilkoti

Authors: Miranda Zhong, Daniel Shapiro, Ashutosh Chilkoti

Biological Sciences

Abstract:
Intrinsically disordered proteins (IDPs) are a diverse class of proteins that lack a well-defined three-dimensional structure and play crucial roles in various cellular processes. One subgroup of IDPs form membrane-less organelles called Ribonucleoprotein Granules (RNPGs) through liquid-liquid phase separation. RNPGs are involved in regulating protein expression and RNA processing, but the underlying mechanics of how RNPGs form, their structure, and how they are regulated remains poorly understood. In this study, we explored the potential of synthetic ribonucleoprotein granules (RNPGs) to exert external control over gene expression. To do so, we utilized Elastin-like polypeptides (ELPs), a class of synthetic IDPs that were developed by the Chilkoti lab, as a platform for creating synthetic RNPGs. We created ELPs fused with a variant of the Pumilio homology domain protein (Pum2), which binds specific mRNA targets via recognition of an 8 nucleotide (nt) sequence called the Pumilio recognition sequence (PRS). The Pum2-ELP fusions exhibited liquid-liquid phase separation like native IDPs, forming distinct granules in cells. To assess the functionality of the synthetic RNPGs, we appended the PRS at the 3'-end of an mRNA that encodes mCherry, a fluorescent reporter protein. We discovered that binding of the mCherry-PRS mRNA by the Pum2-ELP protein sequestered the mRNA into granules in cells, which led increased protein translation from the sequestered mRNA relative cells that do not form granules. This highlights the potential of synthetic RNPGs as a tool for externally regulating gene expression. Furthermore, our study provides insights into the mechanisms of RNPGs in cellular processes and expands our understanding of the functional roles of IDPs in cellular biochemistry.

Health/Clinical Research

Role of Artificial Intelligence and Bioinformatics to Investigate Survival, Differentially Expressed Genes, and Potential Therapeutic Targets in Patients with Heart Failure

Perisa Ashar

Faculty Mentor:

Authors: Perisa Ashar

Health/Clinical Research

Abstract:
Machine learning (ML) and deep learning can be employed to predict survival of patients with heart failure (HF) based on demographic factors and clinical parameters. Bioinformatics can be used to investigate differentially expressed genes (DEGs) in cardiac tissue of patients with and without HF. A dataset of 299 HF patients was analyzed (Chicco et al.; Ahmad et al.). Various ML models with different train-test split ratios were used to predict survival. A sequential model automated neural network (ANN) was also developed. An RNA-seq microarray dataset (GEO: GSE161472) was analyzed to investigate DEGs in LV free-wall tissue in patients with and without HF using the limma R package. Gene symbols corresponding to the top 200 entries of probe IDs with the most upregulated and downregulated genes ($p < 0.05$) were used for enrichment analysis. Protein-protein interactions (PPI) were used to identify overlapping hub genes from 6 algorithms. The logistic regression model (90:10 train-test split ratio) had the highest accuracy predicting survival of HF patients (F1-score = 93%). The ANN had a 99% accuracy on the last 300th epoch and an average F1-score = 88%. Analyses of the upregulated and downregulated genes each had a PPI p-value < 0.01. Upregulated genes were involved with keratan sulfate catabolic processes and collagen binding. Downregulated genes were associated with neutrophil aggregation and interleukin-2 production. PPI network of the combined DEGs identified the following 8 hub genes: STAT3, CXCL10, TLR2, TIMP1, CCL2, CYBB, SPP1, and CD68. STAT3 had the most target miRNAs (148) while CCL2 had the highest number of transcription factors (22). In conclusion, artificial intelligence can accurately and effectively predict mortality in HF patients. Bioinformatics analyses also identified potential candidate molecular markers for novel pharmaceutical interventions in HF.

Role of TRPV4/P2Y in Glial-Neuronal Dynamics on Migraines

Calvin Cho

Faculty Mentor: Carlene Moore

Authors: Calvin Cho, Malak Fouani, Christopher Wickware, Carlene Moore

Health/Clinical Research

Abstract:
Emerging research has elucidated the crucial role of TRPV4 ion channels, P2Y activation, and glial cells in the development and modulation of neuropathic pain. This study investigates the role of TRPV4 ion channels and p2Y activation in glial-neuronal dynamics, specifically focusing on their synergistic involvement in migraine pathophysiology. Emphasizing the role of TRPV4 in Satellite glial cells (SGCs), we hypothesize that TRPV4 interaction within these cells is critical for migraine onset and progression, particularly in the trigeminal ganglion. Our approach includes using cultured glial cells for assays to assess TRPV4 and P2Y activation. Techniques such as immunohistochemistry, dye coupling assay, qPCR, and imaging are employed to analyze responses to TRPV4 agonists and to visualize glial-neuronal interactions. A key aim is to understand how TRPV4 in SGCs contributes to migraine-related pain. We plan on utilizing co-localization studies, calcium imaging, and validation of TRPV4 expression in cultured SGCs. Additionally, we explore how inflammatory conditions alter TRPV4 function in SGCs, using treatments like inflammatory soup and subsequent examinations through protein-biochemistry, immunocytochemistry, and RT-qPCR.The study also investigates TRPV4's modulation of neuron excitability in SGCs through patch-clamp recordings and in-vitro Ca2+ imaging. Anticipated findings include changes in neuron firing frequency and response to agonists, providing insights into migraine mechanisms. Additionally, behavioral testing in specific mouse models will examine the role of TRPV4 in SGCs in migraine-like pain. This study aims to unravel new dimensions of the complex interplay between neuronal and glial elements in migraine and could unveil novel pathways for therapeutic intervention, offering significant potential in migraine management.

Impact of Age Related Adipokines in Lipid Metabolism in Ovarian Cancer

Santiago Garcia

Faculty Mentor: Zhiqing Huang

Authors: Santiago Garcia, Jihua Feng, Hannah Lee, Zhiqing Huang

Health/Clinical Research

Abstract:
Ovarian cancer (OC) ranks among the most prevalent gynecological malignancies, with persistently low survival rates compared to other types of cancer of the female reproductive system. Aging has not been well studied as a risk factor for OC development and poorer prognosis, especially the aging of the tumor microenvironment (TME). The differential gene expression (DEGs) arises in mid-life in gonadal adipose tissue organs before other organs and persists with advanced age. There is increasing evidence showing that adipose tissues, the main TME components in OC, play an important role in promoting cancer initiation and progression. However, the functional involvement of aged adipocytes in OC remains insufficiently understood. In this study, we conducted bulk RNA sequencing and lipidomics analysis of gonadal adipose tissues from young and aged rats before and after tumor formation. Our goal was to elucidate the genetic underpinnings of lipid alterations associated with OC progression. We have found that the aged adipose microenvironment is more susceptible to OC outgrowth, with significantly higher tumor formation rates observed in aged rat xenograft models than its young counterparts (p<0.05). We have revealed significant shifts in the gene expression of groups of young vs. aged rats before tumor formation, groups of young vs. aged rats when the tumor formed, and groups of aged rats before and after tumor formation. Additionally, we observed shifts in the lipid components of the gonadal adipose tissues between young and aged rat xenografts when a tumor was generated. The associated genes clustered in three groups that showed coherent biological functions, including cytokine-cytokine receptor interaction, lipid metabolism, and immune response. Gene and metabolomic profiling studies have revealed a close relationship between adipokines and lipid metabolism, highlighting the significance of factors such as the patatin-like phospholipase domain containing 3 (Pnpla3) and phosphatidylserine in glycerolipid metabolism. Collectively, this data highlights the impact of aging on the differential gene expression and lipid components in tumor adipose tissue, suggesting that targeting the adipose tissue microenvironment, particularly the balance of adipocyte-derived factors, holds promise as a therapeutic strategy for OC and warrants further investigation.

Provider Perspectives on Barriers to Healthcare Accessibility for Refugees in Durham, NC

Taylor Glatt

Faculty Mentor: Wesley Hogan

Authors: Taylor Glatt, Wesley Hogan

Health/Clinical Research

Abstract:
Barriers to healthcare exist for many people, especially those from more vulnerable populations. Refugees face unique challenges such as language barriers, acculturation challenges, and difficulties navigating an unfamiliar medical system. In addition, all have recently faced persecutory conditions in their countries of origin resulting in their refugee status. These barriers frequently compound, creating challenges for refugees trying to seek primary and specialty care. In the US, each clinic or hospital system has its own system for setting up interpretation and other existing systems to mitigate these barriers. An extraordinarily high number of these systems have flaws that leave many refugees struggling to navigate the healthcare system. As a result, they often do not receive necessary care. When individuals are sick, they should focus on healing, not on navigating a complex health system. Refugees have high levels of resilience, but they should not have to exercise it when seeking healthcare. In this study, I wanted to better understand common barriers and challenges that refugees face when accessing healthcare. I worked to identify specific barriers to accessible healthcare for refugees by interviewing and surveying healthcare providers in Durham County. This research defines "healthcare provider" as anyone involved in the care cascade, including physicians, nurses, administrators, and social workers. Under the best of circumstances, all these individuals collaborate to provide medical and social support for refugees so they can thrive. I surveyed 20 providers and interviewed an additional six. Through the surveys and semi-structured interviews, it became evident language, cultural differences, and a lack of health literacy relating to the US healthcare system form refugees' largest barriers to care. The current structure of the healthcare system does not accommodate for taking care of these populations due to time, resource, and financial constraints. Providers see many of these issues, but lack a sustainable, systemic solution to improve these barriers. Existing literature supports many of these findings. Comparing my research to this body of work, I also make a series of recommendations for areas of fruitful future research. For some of my findings, little research exists, highlighting the need for further research to improve the healthcare experience and outcomes for refugees.

Intervention to Improve Self-Management of Blood Pressure for Low-Income Black Patients

Camryn Johnson

Faculty Mentor: Bradi Granger

Authors: Camryn Johnson, Jada Allen, Devan Desai, B.A., Megan Gaines, Rohan Gupta, Anna Tharakan, Jennifer Nguyen, Ashna Sai, David Surzykiewicz, Aiyana Villanueva, Vivien Wambugu, Velda Wang, Elliot Yoon, Holly Biola, MD, MPH, Bradi Granger, RN, PhD

Health/Clinical Research

Abstract:
Hypertension is a leading cause of preventable mortality and morbidity and is disproportionately represented among minority populations. Despite proven interventions outlined in practice guidelines, only 48% of patients who are diagnosed with hypertension have their condition controlled. Additionally, health-related social needs (HSRN) are associated with hypertension incidence. In a southeastern US county, the prevalence of hypertension is 42%, with a strong association with race, suggesting opportunities to intervene at a neighborhood level to reduce hypertension disparities and improve overall population health. We aim to implement a novel intervention to understand the HSRN influence within this population, and how the identification of these needs can impact blood pressure. We used a pre-post single cohort design over 2-cycles of quality improvement evaluation. We identify Black low-income patients with uncontrolled hypertension (SBP > 160 mmHg and/or DBP > 100 mmHg) from a local federally qualified health center (FQHC). Trained student ambassadors provided health education via telephone outreach, BP cuffs, and HSRN identification, with follow-up at 7 months. Among Black participants (n=345), average age was 55.4 years (SD 8.7), and a majority were male (n=173, 50.1%) and uninsured (n=159, 46.1%). Engagement in calls occurred for 67.8% (n=234) of the cohort; cuff distribution was 22.9% (n=79); and goal setting occurred for 64 patients. BP improved for 40% of the cohort (mean pre: 168/98 mmHg, mean post: 150/89 mmHg; p<0.0001). Of the cohort reached, 33% expressed social needs including food insecurity, housing, and medication costs. This innovative, community-based, telephonic outreach intervention identifies HSRN that can negatively influence blood pressure in underserved patient populations. Goal setting, feedback follow-up on needs, and skills-teaching with didactic education content (i.e. AHA Essential 8 handouts) provide an affordable and individualized method to address HSRN. Findings can be feasibly scaled to other low-income, low-resource populations in community settings.

Sex and ethnic disparities in hepatitis B evaluation and treatment across the world

Sahith Kudaravalli

Faculty Mentor: Mindie Nguyen

Authors: Sahith Kudaravalli, Daniel Q. Huang, Ming-Lun Yeh, Lindsey Trinh, PC Tsai, Yao-Chun Hsu, Leslie Y. Kam, Vy H. Nguyen, Eiichi Ogawa, Dong Hyun Lee, Takanori Ito, Tsunamasa Watanabe, Masaru Enomoto, Carmen Monica Preda, Michael KL Ko, Rex Wan-Hin Hui, Masanori Atsukawa, Takanori Suzuki, Sebastian Marciano, Ana Barreira, Son Do, Haruki Uojima, Hirokazu Takahashi, Sabrina XZ Quek, Htet Htet Toe Wai Khine, Masatoshi Ishigami, Norio Itokawa, Min Seok Go, Ritsuzo Kozuka, Raluca Ioana Marin, Irina Sandra, Jiayi Li, Jian Q. Zhang, Christopher Wong, Yoko Yoshimaru, Dang KH Vo, Cheng-Hao Tseng, Chul-jin Lee, Kaori Inoue, Mayumi Maeda, Joseph K. Hoang, Angela Chau, Wan- Long Chuang, Chia-Yen Dai, Jee-Fu Huang, Chung-Feng Huang, Maria Buti, Yasuhito Tanaka, Adrian Carlos Gadano, Man-Fung Yuen, Ramsey Cheung, Seng Gee Lim, Huy N. Trinh, Hidenori Toyoda, Ming-Lung Yu, Mindie H. Nguyen

Health/Clinical Research

Abstract:
Background & Aims: Oral antiviral therapy with nucleos(t)ide analogs (NAs) for chronic hepatitis B (CHB) is well-tolerated and lifesaving, but real-world utilization data are limited. We examined the evaluation and treatment rates of patients from the REAL-B consortium. Methods: This was a cross-sectional study nested within our retrospective multinational clinical consortium (2000-2021). We determined the proportions of patients receiving adequate evaluation, meeting AASLD treatment criteria, and initiating treatment at any time during the study period. We also identified factors associated with receiving adequate evaluation and treatment using multivariable logistic regression analyses. Results: We analyzed 12566 adult treatment-naïve CHB patients from 25 centers and 9 countries (mean age 47.1 years, 41.7% female, 96.1% Asian, 49.6% Western region, 8.7% cirrhosis). Overall, 73.3% (9206 patients) received adequate evaluation. Among the adequately evaluated, 32.6% (3001 patients) were treatment-eligible by AASLD criteria, and 83.3% (2500 patients) of these initiated NAs, with consistent findings in analyses using EASL criteria. On multivariable logistic regression adjusting for age, sex, cirrhosis, and ethnicity plus region, female sex was associated with adequate evaluation (adjusted [a]OR=1.13, P=0.004), but female treatment-eligible patients were about 50% less likely to initiate NAs (aOR=0.54, P<0.001). Additionally, we found lowest evaluation and treatment rates among Asian patients from the West, but no difference between non-Asian and Asian patients from the East. Asian patients from the West (vs East) were about 40-50% less likely to undergo

adequate evaluation (aOR 0.60) and initiate NAs (aOR 0.54) (both P<0.001). Conclusions: Evaluation and treatment rates were suboptimal for patients with CHB in both East and West, with significant sex and ethnic disparities. Improved linkage to care with linguistically competent and culturally sensitive approaches is needed.

Arraigados Juntos: Lessons Learned from a Cross-Sectoral Food as Medicine Pilot

Elaijah Lapay

Faculty Mentor: Patrick Hemming

Authors: Elaijah Lapay, Linda Tang, Esko Brummel, Trevor Sytsma, Elliot Yoon, Natalie Wickenheisser, Hannah Malian, Willis Wong, Patrick Hemming

Health/Clinical Research

Abstract:
Medically tailored groceries show promise in addressing diet-related chronic diseases like hypertension. Despite growing engagement from student clinics and community organizations, research on their effectiveness remains scarce. The "Arraigados Juntos" or “Rooted Together” project, a collaboration between Root Causes Fresh Produce Program, El Centro Hispano, and NCCU’s Dietetic Internship Program, examined a student-run clinic's program combining tailored groceries, nutrition education, and community organization involvement to improve health outcomes in African American and Hispanic/Latinx adults with hypertension and food insecurity. Conducted as a randomized clinical trial in Durham County, NC, from April to July 2023, participants were identified from the EHR of a large medical center who were screened, consented, enrolled, and randomly assigned to either receive weekly medically tailored groceries following the DASH Diet, coupled with up to 6 nutrition education sessions led by a language-concordant dietician, or to a control group that attended up to 3 data collection sessions and received compensated DASH Diet-aligned produce bags. With 1577 eligible participants, 50 consented and were randomized, with 39 individuals (17 in the treatment group and 22 in the control group) participating for over two-thirds of the sessions across two months. The intervention group experienced a statistically significant decrease in systolic and diastolic blood pressure (-0.125 [-0.249, -0.001] and -0.081 [-0.151, -0.011] mmHg, respectively, per additional day in the study). However, the control group did not show significant changes in blood pressure. Self-reported food insecurity significantly decreased in the intervention group (-38.46% [-64.91%, -12.01%]) but not in the control group while the control group reported a significant increase in fruit and vegetable intake (2.63 servings [1.49, 3.76]) but not the intervention group. No BMI changes were noted in either group. Further research is needed to assess the combined impact of nutrition education sessions and medically tailored groceries, along with identifying the parameters necessary for significant health outcomes, especially among different racial and ethnic groups and for speakers of non-English languages and of diverse culinary cultures. As a feasibility pilot, this randomized

control trial shows promise for larger, more diverse studies addressing the intersection of food security and chronic disease.

Time-Restricted Eating Improves Antitumor Immunity via Insulin-Like Growth Factor 1

Kate Lee

Faculty Mentor: Shahla Bari

Authors: Kate Lee, Wanyu Zhang, Angie Huang, Mostafa Eysha, Shahla Bari

Health/Clinical Research

Abstract:
Background: Treatment of metastatic head and neck cancer remains an area of unmet need with a median survival of less than a year. We tested the efficacy of a novel circadian-aligned fasting intervention called “time-restricted eating” (TRE), to improve ICB response in tumor-bearing head and neck syngeneic mice models (MOC1), and showed a significant reduction in tumor growth, which we then recapitulated in a pilot, open-labeled, interventional clinical trial in 30 metastatic head and neck cancer patients. We noted significant improvement in median progression-free survival (5 months vs not reached (NR), HR-0.2, p-0.0008) and overall survival (8 months vs NR, HR-0.00000045) in patients observing TRE vs those who did not. The favorable effect of TRE was mediated via modulation of the gut microbiome, microbial tryptophan metabolome, and insulin signaling, specifically reduction in circulating insulin-like growth factor 1 (IGF1). We hypothesized that IGF1 mediates ICB resistance by protecting tumor cells from cytotoxic T-cell activity. Methods: We performed in vitro luciferase cytotoxicity assays using HLA-A2+NY-ESO+ squamous cell cancer 4 (SCC-4) human cancer cells as targets, and HLA-A2-restricted NY-ESO-1-specific T cell receptor (TCR) -transduced T cells. We co-cultured the tumor cells and the T cells for 24 hours under different conditions of IGF-1 concentration (100 ng, 50 ng, and 10 ng) and T cell-to-tumor cell ratio (1:5, 1:10, and 1:20). We also treated the tumor cells with IGF-1 alone to assess its direct cytotoxic effect. Results: We observed that IGF-1 impaired the ability of the T cells to kill the tumor cells in a dose-dependent manner, while IGF-1 had no cytotoxic effect on the tumor cells in the absence of T cells. Conclusion: While the role of IGF1 in treatment resistance has been described, its role and mechanism in antitumor immune response is largely unknown. We, for the first time, demonstrate the role of IGF1 in impairing T cell-mediated antitumor activity in a dose-dependent fashion, thus contributing to ICB resistance. Further work will help us develop alternative strategies to modulate IGF1 and improve ICB resistance, in patients who are unable to tolerate TRE.

Trends of Chronic Liver Diseases by Income Level and Socioeconomic Factors in the U.S. National

Eunice Lee

Faculty Mentor: Mindie Nguyen

Authors: Eunice Yewon Lee, Vy H. Nguyen, Ramsey C. Cheung, Mindie H. Nguyen

Health/Clinical Research

Abstract:
Background: With polarizing income disparities between the top 20% and remaining 80% of the U.S. population, quality of healthcare may be prone to risk. Investigating the prevalence of chronic liver disease (CLD) based on income to poverty ratio and trends over time, we studied the impact of socioeconomic status on liver health risks. Methods: We combined data from 10 survey cycles (1999-2018) in NHANES. To model the existing 20-80 national divide observed in income groups, we divided participants into high- and low-income groups by their income to poverty ratio using the cut-off point of 5 as it gave the closest proportion: 25-75. Results: Our study included 59,204 adult participants. 44,462 (75.1%) had an income to poverty ratio<5 (low-income) and 14,742 (24.9%) had ≥5 (high-income). The weighted prevalence of HCV, HBV, NAFLD, and ALD in low-income groups were 2.2% (n=876), 5.5% (n=2,200), 33.8% (n=4,345), and 4.7% (n=2,086), respectively compared to lower rates in high-income groups: 1.0% (n=82), 3.2% (n=263), 29.6% (n=798), and 3.9% (n=354). Low-income groups had higher odds of having any CLD history (odds ratio (OR), 1.22; 95% CI, 1.08—1.37; P=0.001), when adjusted for age, sex, race and ethnicity, education, and country of birth. Same trends were observed for history of HCV infection (OR, 2.03; 95% CI, 1.46—2.81, P<0.0001), HBV infection (OR, 1.47; 95% CI, 1.26—1.72; P<0.0001), and NAFLD (OR, 1.17; 95% CI, 1.02—1.35; P=0.030). From 1999 to 2018, low-income groups had higher rates of viremic HCV infection (P<0.0001), viremic HBV infection (P=0.016), NAFLD (P<0.0001), and AFLD (P<0.0001) than high-income groups. For CLD prevalence trends over time, we found higher rates of viremic HCV infection (HCV antibodies positive and HCV-RNA present) in low-income groups than higher-income groups (P<0.0001). For current HBV infection (HBsAg positive), no clear trend over time was observed, but low-income groups exhibited higher prevalence than high-income groups (P=0.016). Prevalence of NAFLD and AFLD increased over time (NAFLD low-income, P=0.001; AFLD high-income, P=0.04) with similar disparities between income groups. Conclusion: The prevalence of 4 major CLDs significantly differed between income groups from 1999 to 2018. Recently in 2017-2018, higher median liver stiffness also highlighted more advanced liver disease in low-income, demonstrating the impact of

socioeconomic factors on the prevalence and severity of liver diseases of various etiologies.

Frequency in Care-seeking Behaviors and Preferences Among Hispanics and across SES

Alejandra Mella-Velazquez

Faculty Mentor: Cheryl Lin

Authors: Alejandra Mella-Velazquez, Pikuei Tu, PhD, Cheryl Lin, PhD

Health/Clinical Research

Abstract:
Hispanics are the largest racial minority group in the U.S., yet many of their healthcare needs are not adequately addressed and health disparities persist. This study investigates the frequency of Hispanics visiting healthcare providers (HCP), importance of self-selecting a HCP, and difficulty of finding one, compared to other races and across socioeconomic status (SES). An online survey assessed 1,485 participants' health behaviors and preferences (Hispanic=314, Asian=313, Black=316, White=542). Five medical disciplines were examined: primary care physician (PCP), dentist, optometrist, gynecologist, and chronic disease specialist. Kruskal-Wallis tests indicated the significant effects of both race and SES. Whites had the highest percentages in regularly seeing each HCP. Mann-Whitney U tests found no significant difference between Whites and Hispanics in visiting a specialist and gynecologist. The three minorities' care-seeking behavior showed little discrepancies, except that Hispanics saw a specialist more frequently than Asians, and Asians compared to Blacks saw a dentist more and a gynecologist less regularly. Notable, Hispanics and Asians rated significantly lower importance in self-selecting a HCP while experienced more difficulty than both Whites and Blacks. Pair-wise comparisons across SES groups revealed that participants with lower income or education saw all HCPs less regularly but expressed the same choice importance; reported difficulty was associated with income but not education. Each racial group was further split by SES and found that regardless of income and education, Whites were more likely than minorities to regularly visit HCPs (except for gynecologist where the difference was only in the higher education group). Across all races, the lower income group had no frequency difference in seeing a dentist; participants rated importance the same within the lower education and higher income groups, respectively. Among minorities, minimal differences in both behavior and perceptions were observed regardless of SES. Results consistently showed lower rates of receiving care in minorities compared to Whites (though at varied extent), even when accounting for SES, which help explain disparities in health outcome and perpetuating inequities in the healthcare system. The findings demonstrated the joint impacts of the determinates on patients' behaviors and experience and the need to attend to minorities' challenges in accessing and obtaining care.

Analyzing Retinal Layer Structure in Individuals with Post-Traumatic Stress Disorder using OCT

Sejal Patel

Faculty Mentor: Sharon Fekrat

Authors: Sejal D. Patel; Naveen Karthik, MD; Grant A. Justin, MD; Stephanie J. Chiu, PhD; Dilraj S. Grewal, MD FASRS; Sharon Fekrat, MD FASRS

Health/Clinical Research

Abstract:
Changes in retinal structure can potentially serve as biomarkers for neurodegenerative diseases. This study aimed to investigate alterations in retinal layer thickness and volume in individuals with post-traumatic stress disorder (PTSD) compared to controls using optical coherence tomography (OCT). Patients diagnosed with PTSD between January 2018 and December 2021 were recruited, while excluding those with certain pre-existing conditions such as cognitive disorders, brain injury, and ocular diseases. Age- and sex-matched controls were also enrolled to ensure comparability. OCT images were obtained using Zeiss Cirrus HD-5000 Spectral-Domain OCT, and the Duke Reading Center Visualizer algorithm was employed for the segmentation of retinal layers. Mean thickness and volume were calculated for specified retinal layers within 1-, 3-, and 6-mm ETDRS rings, further divided into superior, temporal, inferior, and nasal quadrants. The results revealed significant differences between PTSD patients and controls. Specifically, PTSD patients exhibited lower mean thickness and volume of the retinal pigment epithelium (RPE) layer, along with increased thickness of the photoreceptor layer in perifoveal rings and quadrants. Additionally, decreased thickness was observed in the ganglion cell and inner plexiform layer (GC+IPL) and inner nuclear layer (INL) among PTSD patients compared to controls. These findings suggest potential alterations in retinal layers associated with PTSD, particularly in GC+IPL, INL, and RPE, which may serve as biomarkers for the disorder. Further research is warranted to elucidate the underlying mechanisms and clinical implications of these findings.

Postoperative changes in sustained attention and potential relationships with postop sleep

Nicole Pedicini

Faculty Mentor: Michael Devinney

Authors: Melissa Adams, Nicole Pedicini, Jack Fallon, Sophie Wu, Cina Sasannejad, Mona Hashemaghaie, Michael Devinney

Health/Clinical Research

Abstract:
Postoperative delirium is a disturbance in cognition that occurs in up to 40% of older Americans who undergo surgery each year. Delirium risk may be increased by poor postoperative sleep, since inattention, a delirium hallmark, occurs with sleep deprivation. A way to measure the effect of sleep deprivation on attention is the psychomotor vigilance test (PVT), which assesses basic reaction times to quantify decrements in attention over 5 minutes. Using pre- and postoperative PVT, and postoperative electroencephalography (EEG), we examined postoperative changes in sustained attention and their relationship with the prior night postoperative total electrographic sleep time. Data was collected in a single center randomized controlled trial (NCT05733286) of postoperative suvorexant administration to increase postoperative sleep and reduce delirium severity. Data was obtained from 28 patients (age≥65 years) undergoing non-cardiac surgery with planned postoperative inpatient overnight stay. Postoperative sleep was measured with the Dreem EEG Headband, and participants underwent PVT using the NASA PVT+ application, which reports mean response time, mean response speed, false starts, and # of lapses. A paired t-test was used to compare preoperative and postoperative day 1 performance in the above PVT metrics. Spearman correlation was performed between postoperative day 0 night total sleep time and postoperative day 1 change in mean response speed. From baseline to postoperative day 1, there was a significant increase in mean response time (mean difference = 239 ms, 95% CI [12.7, 465 ms], p = 0.039) and # of lapses (mean difference = 5.2, 95% CI [1.55, 8.85,], p = 0.008), as well as a significant decrease in mean response speed (mean difference = -0.441, 95% CI [-0.756, -0.125,], p = 0.008). There was no significant increase in false starts (mean difference = 3.13, 95% CI [-4.97, 11.2,], p = 0.43). We also explored relationships between total sleep time and the change in PVT performance on the subsequent day. In the sample with complete data (n = 24), total sleep time was not significantly correlated with mean response speed (Spearman ρ = -0.28, p = 0.18). Sustained attention is impaired in the immediate postoperative period, but its relationship with postoperative sleep requires further study. Subsequent analyses will

assess this relationship and further studies are needed to determine relationships between postoperative sleep, sustained attention, and delirium.

Hemipelvectomy and the Impact of Reconstruction on Load Transmission and Gait Symmetry

Rachel Poutre

Faculty Mentor: Daniel Schmitt

Authors: Rachel L. Poutre, Rebecca W. Cook, Sarah E. Little-Letsinger, Mayowa Adegboyega, Julia Visgauss, William Eward, Daniel Schmitt

Health/Clinical Research

Abstract:
A hemipelvectomy is the surgical removal of a portion of the hip. It is among the most rare and invasive procedures performed today and can have profound implications for the gait of a patient. Hemipelvectomy surgeries are used to treat bone or soft tissue tumors, ischemia, and severe infection that have developed or spread to the pelvis. The pelvis may be reconstructed with a prosthetic with reattachment of muscles, or the pelvis may be left "flail," where no prosthetic is used and/or the muscles are left unattached. Although gait asymmetry is a significant risk factor for hemipelvectomy patients, few studies examine the success of these procedures in terms of gait asymmetry. A direct comparison of non-pathological, non-prosthetic, and prosthetic symmetry can be used as a measure of success and may inform reconstruction methods. This study investigates impact on gait by examining load transmission in the pelvis of a patient who has undergone a hemipelvectomy in comparison to a non-pathological subject. Gait analysis data from the patient and a healthy individual were collected and applied to finite element models of the pelvis and proximal femur. These models illustrate how strain distribution and gait are affected by reconstruction technique.

Family caregiver perspectives on shared decision making in intensive care units

Astha Ray

Faculty Mentor: Deepshikha Ashana

Authors: Astha Ray, Kayla Thompson, Martha Lee, Kimberly Johnson, Christopher Cox, Brittany McDowell, Katelyn Dempsey, Tumi Akeke, Sharron Docherty, Deepshikha Ashana

Health/Clinical Research

Abstract:
Shared decision making (SDM) is a collaborative process among clinicians, patients, and their families to make medical decisions that align with patients' preferences. SDM in intensive care unit (ICU) settings is challenging. Patients are often seriously ill and lack decisional capacity; thus, urgent, cognitively complex, and highly emotional decisions pertaining to the use or withdrawal of life-prolonging therapies must be made by their families who lack established relationships with ICU clinicians. Our goal was to identify clinician-level facilitators of and barriers to effective SDM from the perspectives of racially diverse family caregivers who made major treatment decisions in ICU settings. In this study, we identified family members who self-identified as Black or White and who were the primary surrogate decision-maker for patients mechanically ventilated for ≥4 days in medical or surgical ICUs at Duke. We conducted virtual, semi-structured interviews with participants using narrative prompts about experiences of decision making and semi-structured prompts about trust, hope, and emotional support as related to decision making. A codebook comprising deductive and inductive codes was used by two coders to conduct concurrent open coding. Axial and selective coding to develop a theory of family-centered SDM among racially diverse caregivers in ICUs is ongoing. Among 30 interviewed family members, 60.0% identified as Black and 40.0% as White. 56.7% were the partner of the patient. Several clinician behaviors were viewed by families as directly fostering SDM: transparency (e.g., being forthcoming about medical details as well as uncertainty) and partnership (e.g., inviting family's unique expertise of patient). Other clinician behaviors facilitated SDM indirectly by strengthening the therapeutic alliance: validation (e.g., affirming caregiver's faith beliefs) and care for the caregiver (e.g., attending to caregiver's physical or socio-emotional needs). Family members also noted clinician behaviors that hindered SDM: pressure (e.g., rushing family to make decisions) and disregard (e.g., examining patient without acknowledging family in the room). This analysis identified clinician behaviors that can enhance or hinder SDM during critical illness. Our findings may provide targets for future clinician-facing interventions to promote effective and equitable SDM.

How to Stay Connected in the World of Research Dissemination

Kennedy Rouser

Faculty Mentor: Stephanie Ibemere

Authors: Kennedy Rouser, Taliyah Thomas, Stephanie Ibemere

Health/Clinical Research

Abstract:
Normal research dissemination involves publishing findings in academic journals, presenting at conferences, and sharing through online repositories, often inaccessible to those who are not members of academia. These methods ensure that research is accessible to other scholars, often facilitating collaboration, feedback, and the advancement of knowledge within the academic community. What about those beyond the academic community? The typical approach to research dissemination can create inequities by limiting access to research information, particularly for marginalized communities who may not have access to expensive journal subscriptions or attend conferences. To address this issue, our research team proposed ensuring broader accessibility to our findings, aiming to reduce disparities in access to valuable research information and promote health equity, through use of a website. Our goal is to share research conducted by our group not only with our scientific colleagues, but to also make it accessible to those affected by the research or those who otherwise may not have access to scientific journals. To address the issue of limited access to research information and promote health equity, our research team embarked on developing a website as a central hub for disseminating our findings. We employed a multidisciplinary approach, leveraging team science to combine expertise in public health, technology, and communication. The development of coding skills was crucial in developing the website infrastructure, ensuring user-friendly navigation and accessibility features. Logo development played a role in branding the website, making it visually appealing and recognizable. Collaborative teamwork was essential in overcoming technical hurdles and ensuring that the website met the needs of diverse users. Furthermore, we learned the significance of effective communication and outreach strategies in promoting the website and engaging with target audiences. Overall, the development of the website served as a learning experience, highlighting the power of collaboration, innovation, and inclusive practices in advancing research dissemination and promoting health equity.

Exploring the Mental Health Outcomes of Orphaned and Separated Children: Udayan Care

Akhilesh Shivaramakrishnan

Faculty Mentor: Sumedha Ariely

Authors: Akhilesh Shivaramakrishnan, Seth Liyanapathirana, Alekshyander Mishra, Sumedha Ariely

Health/Clinical Research

Abstract:
Orphaned and separated children (OSCs) are extremely vulnerable to negative health outcomes in life. India has the largest population of OSCs in the world, and childcare institutions (CCI) in the country continue to face structural barriers in providing adequate mental health support for these children. Udayan Care is a CCI and NGO based in New Delhi, India that employs the "ghar" model as opposed to foster care, placing orphaned and separated children in one of its small-group homes. Since 2013, Duke has been collaborating with Udayan through an undergraduate Student Research Training program to assess the mental health of Udayan OSCs. The data collected can then be used to inform future implementation of direct mental health support initiatives. As part of the project, the 2023 team conducted interviews with 120+ OSCs and delivered pilot life skills workshops. The findings are being utilized to develop further supports OSCs, including the recent implementation of counselors for all transitioning young adults. The team conducted interviews with OSCs served by Udayan Care, including those living in the residential care homes and ‘aftercare’ participants—young adults transitioning out of the homes. Aiming to assess participants' mental health status, the interviews included standardized measures of depression, anxiety, trauma, and stress, among others, while also qualitatively assessing knowledge of coping strategies. To build more confidence about the transition to independent life, life skills workshops were administered to aftercare participants. Qualitative interviews revealed that many young adults were not emotionally ready or equipped with the life skills needed to effectively make the transition out of residential care. However, participants did express the desire to have more workshops similar to those delivered in the pilot, and qualitatively mentioned that these helped them feel more confident about transitioning to independence. As such, the team will work with Udayan to develop a sustainable model for the continuation of these workshops. Results showed that not all Udayan OSCs felt prepared to live independently and many desired further mental health support. Based on these, Udayan implemented direct counseling for all transitioning adults. Future programs will utilize recommendations from counselors to better understand how to improve young adults’ transition.

Mental Health Parity in North Carolina: Current Challenges, Progress, and Policy Priorities

Annabel Tang

Faculty Mentor: Sandra Yankah

Authors: Annabel Tang, Sarah Muzzy, Sandra Yankah

Health/Clinical Research

Abstract:
Mental health parity is the equal coverage of mental health and substance use disorder treatments in insurance plans as compared to physical illnesses. While the 2008 passage of the Mental Health Parity and Addiction Equity Act (MHPAEA) greatly advanced parity in the United States through national legislation, many states, including North Carolina, still face numerous challenges with achieving and implementing parity due to enforcement issues, coverage gaps, and shortages of mental health providers. In addition to the legislative framework provided by MHPAEA, state-level legislation and initiatives informed by patient utilization patterns are needed to advance mental health parity. The present study evaluates the current landscape of mental health parity in North Carolina, seeking to identify opportunities for enhancing mental health parity and proposing evidence-based policy recommendations that address the identified challenges. Findings indicate that the most prominent issues with achieving mental health parity in North Carolina include the unavailability/lack of updated information of mental health providers and inability of consumers and regulators to identify violations of MHPAEA in insurance plans; the widespread distribution of oversight and enforcement of the federal law leaves room for unequal enforcement between states. To alleviate these challenges, we recommend increased communication and consistency between federal agencies, state agencies, and insurers, as well as further funding and use of psychiatric telemedicine programs, particularly in emergency rooms across North Carolina.

Intervention to Improve Self-Management of Blood Pressure for Low-Income Black Patients

Anna Tharakan

Faculty Mentor: Bradi Granger

Authors: Anna Tharakan, Jada Allen, Devan Desai, B.A., Megan Gaines, Rohan Gupta, Camryn Johnson, Jennifer Nguyen, Ashna Sai, David Surzykiewicz, Aiyana Villanueva, Vivien Wambugu, Velda Wang, Elliot Yoon, Holly Biola, MD, MPH, Bradi Granger, RN, PhD

Health/Clinical Research

Abstract:
Hypertension is a leading cause of preventable mortality and morbidity and is disproportionately represented among minority populations. Despite proven interventions outlined in practice guidelines, only 48% of patients who are diagnosed with hypertension have their condition controlled. Additionally, health-related social needs (HSRN) are associated with hypertension incidence. In a southeastern US county, the prevalence of hypertension is 42%, with a strong association with race, suggesting opportunities to intervene at a neighborhood level to reduce hypertension disparities and improve overall population health. We aim to implement a novel intervention to understand the HSRN influence within this population, and how the identification of these needs can impact blood pressure. We used a pre-post single cohort design over 2-cycles of quality improvement evaluation. We identify Black low-income patients with uncontrolled hypertension (SBP > 160 mmHg and/or DBP > 100 mmHg) from a local federally qualified health center (FQHC). Trained student ambassadors provided health education via telephone outreach, BP cuffs, and HSRN identification, with follow-up at 7 months. Among Black participants (n=345), average age was 55.4 years (SD 8.7), and a majority were male (n=173, 50.1%) and uninsured (n=159, 46.1%). Engagement in calls occurred for 67.8% (n=234) of the cohort; cuff distribution was 22.9% (n=79); and goal setting occurred for 64 patients. BP improved for 40% of the cohort (mean pre: 168/98 mmHg, mean post: 150/89 mmHg; p<0.0001). Of the cohort reached, 33% expressed social needs including food insecurity, housing, and medication costs. This innovative, community-based, telephonic outreach intervention identifies HSRN that can negatively influence blood pressure in underserved patient populations. Goal setting, feedback follow-up on needs, and skills-teaching with didactic education content (i.e. AHA Essential 8 handouts) provide an affordable and individualized method to address HSRN. Findings can be feasibly scaled to other low-income, low-resource populations in community settings.

Utilizing a Quality Improvement Method on Hypertension Management for Black Patients

Velda Wang

Faculty Mentor: Bradi Granger

Authors: Velda Wang, Jada Allen, Devan Desai, Megan Gaines, Rohan Gupta, Camryn Johnson, Jennifer Nguyen, Ashna Sai, David Surzykiewicz, Anna Tharakan, Aiyana Villanova, Vivien Wambugu, Elliot Yoon, Holly Biola, MD, MPH, Bradi Granger, RN, PhD

Health/Clinical Research

Abstract:
Hypertension is a leading cause of preventable mortality and morbidity and is disproportionately represented among minority populations. Despite proven interventions outlined in practice guidelines, only 48% of patients who are diagnosed with hypertension have their condition controlled. In a southeastern US county, the prevalence of hypertension is 42%, with a strong association with race, suggesting opportunities to intervene at a neighborhood level to reduce hypertension disparities and improve overall population health. Aims To improve access to care through targeted opportunities for self-management of blood pressure (BP). This quality initiative used a pre-post evaluation design. We identified Black low-income patients with uncontrolled hypertension (SBP > 160 mmHg and/or DBP > 100 mmHg) from a local federally qualified health center (FQHC). Trained student ambassadors provided telephone outreach, BP cuffs, and goal setting on AHA Essential 8 for 4 months. Follow-up occurred at 7 months. Among Black participants (n=345), average age was 55.4 years (SD 8.7), and a majority were male (n=173, 50.1%) and uninsured (n=159, 46.1%). Engagement in calls occurred for 67.8% (n=234) of the cohort; cuff distribution was 22.9% (n=79); and AHA Essential 8 goal setting occurred for 64 patients. BP improved for 40% of the cohort (mean pre: 168/98 mmHg, mean post: 150/89 mmHg; >0.0001). Of the cohort reached, 33% expressed social needs such as food insecurity, housing, and medication costs. Findings suggest that telephone outreach with student ambassadors successfully improves patient engagement and reduces blood pressure, on average.

Sickle Cell Disease Management in a Nigerian Context: Qualitative Analysis of Local Healthcare

Eric Zhao

Faculty Mentor: Stephanie Ibemere

Authors: Eric Zhao, Taliyah Thomas, Kennedy Rouser, Stephanie Ibemere

Health/Clinical Research

Abstract:
Sickle cell disease (SCD) remains a significant challenge, particularly in countries like Nigeria, where it disproportionately affects communities. Despite the availability of diagnostic and treatment protocols, numerous barriers impede their effective implementation among healthcare workers in Nigeria. These barriers include limited access to testing and lab workup, inconsistent protocols or knowledge of protocols, and local cultural understanding of SCD. To address these challenges and develop tailored protocols for Nigeria, a qualitative study was conducted involving interviews with 25 Nigerian healthcare workers, including nurses and doctors, focusing on SCD management and clinical decision tools. The study aimed to identify local factors influencing SCD management and inform the development of effective interventions. Interview questions covered topics such as existing guidelines, available toolboxes, and barriers to implementation. Rapid qualitative analysis involved the use of summary templates to code interview transcripts. Once these data were aggregated, our team used thematic analysis to identify overarching themes. Thematic analysis was conducted by reading through coded sections of interviews and identifying themes, which were then discussed and refined through group consensus meetings. Supporting quotes from participants were identified for each theme, and themes with good saturation were selected. The qualitative design was chosen for its flexibility in information acquisition, the opportunity to explore differing perspectives, and exposure to unique insights. To ensure trustworthiness, the study adhered to established criteria for qualitative research, which include credibility, transferability, dependability, confirmability, and audit trails. Preliminary findings have revealed several overarching themes, including "Conflicting awareness and use of SCD guidelines" and "Clinician and health system SCD management protocols." This research is critical in informing the development of successful clinical interventions for SCD in Nigeria, with implications for improving SCD management globally.

ATF4 regulates resistance to arginine deprivation in MYC-high small cell lung cancer

Lisa Zuo

Faculty Mentor: Trudy Oliver

Authors: Lisa Y. Zuo, Margaret C. Weber, Abbie S. Ireland, John Bomalaski, Ralph J. DeBerardinis, Trudy G. Oliver

Health/Clinical Research

Abstract:
Small cell lung cancer (SCLC) is a deadly and aggressive neuroendocrine cancer marked by a remarkable response to first-line chemotherapy, then rapid relapse and resistance to subsequent treatment. Treatment-resistant SCLC is often associated with overexpression of MYC. Previous research has demonstrated that in a genetically-engineered mouse model of MYC-high SCLC, arginine deprivation therapy with pegylated arginine deiminase (ADI-PEG20) leads to superior survival rates compared to chemotherapy. However, the eventual resistance that develops to ADI-PEG20 is not well understood. Single cell RNA sequencing of ADI-PEG20-resistant and control tumors revealed global transcriptional rewiring upon resistance and predicted transcription factor ATF4 as a top regulator. Indeed, ATF4 and ATF4 target genes are increased in both ADI-PEG20-resistant tumors and in vitro in human SCLC cell lines following arginine deprivation. Thus, we hypothesize that resistance to arginine deprivation may be driven by the integrated stress response as mediated by ATF4, allowing for transcriptional and metabolic rewiring. ADI-PEG20 resistance is marked by an initial persister-like state with decreased cycling and metabolic rewiring including changes in amino acid and antioxidant pathways. To test if ATF4 is sufficient to drive this persister-like state, we developed a tetracycline-inducible overexpression model of ATF4 in MYC-high human SCLC cell lines. Overexpression of ATF4 was sufficient to induce expression of many resistance-associated genes, including those involved in amino acid metabolism, as well as a G0/G1 cell cycle stalling, phenocopying the cell cycle changes seen after arginine deprivation. To test the necessity of ATF4 for persistence upon arginine deprivation, we used inducible hairpins to knockdown ATF4 in human SCLC cell lines. Preliminary data suggest that knockdown of ATF4 decreases cell survival with long-term arginine deprivation and prevents metabolic rewiring of amino acid and antioxidant pathways that may be critical in allowing cells to persist following arginine deprivation. Together these data suggest that ATF4 is a central driver of transcriptional and metabolic rewiring upon arginine deprivation. Additional studies are ongoing to determine if ATF4 is necessary for ADI-PEG20 resistance and if the integrated stress response or downstream pathways could be targeted to reduce resistance to ADI-PEG20 in vivo.

Humanities

Dictionary of Art Historians

Selom Bediako

Faculty Mentor: Lee Sorensen

Authors: Selom Bediako

Humanities

Abstract:
The Dictionary of Art Historians is a biographical database of historians of western art written and maintained by scholars for the benefit of the public. The current project focuses on uncovering and chronicling Black art historians, often unrecognized in a predominantly white art world. First, a list of names that warranted further research was compiled by combing through annotated bibliographies, research periodicals, books, and more. One such name that emerged was Henri Ghent, the first director of the Brooklyn Musuem's Community Gallery and founding member of Black Emergency Cultural Coalition. Through research spanning interviews, digital archives, magazines, and books, Ghent's contributions as a critic and activist for Black art were brought to light.

A Brief History of the Aeolian Organ In Duke University Chapel

Bradley Bowen

Faculty Mentor: Robert Parkins

Authors: Bradley Bowen, Dr. Robert Parkins

Humanities

Abstract:
Duke University Chapel is graced by unique and prestigious pipe organs that are heard by thousands of visitors each year. These organs have a rich history, earning their reputation as some of the finest instruments in the southeastern United States. Four pipe organs occupy the space: the Aeolian (1932), the Flentrop (1976), the Brombaugh (1997), and a movable Bennett and Giuttari continuo instrument (2014). All four pipe organs are distinctive and acclaimed, and each reflect the complexity of this sophisticated musical instrument in different ways. The Kathleen Upton Byrns McClendon Aeolian organ is the original instrument to Duke Chapel and symbolizes the significance of early 20th-century American pipe organs. The organ was built by the Aeolian Organ Company and installed in the chapel in the spring of 1932. Today, the Aeolian organ remains a world-class instrument. It has a wide range of dynamic levels and a broad palette of colors, from soft string sounds to loud tubas and trumpets, giving the organ remarkable versatility. Not only can it accompany the choir and lead the congregation in hymns for worship services, but it is also especially effective in accompanying silent films, playing orchestral transcriptions, and performing music of the late-Romantic organ repertoire. Following a restoration in the early 2000s, the Aeolian has reemerged as a spotlight instrument featured in Duke's annual organ recital series. Its appeal has grown since its origin and has become particularly prominent as one of only a few large orchestral organs in original condition that remain from the early 1900s. The Chapel's Aeolian organ is admired for this historical significance and enjoyed by many thousands of visitors and worshipers each year. The Aeolian legacy includes many organists, advocates, and supporters, but the public connection has proven to be the most powerful source of its longevity, historical significance, and sentimental acclaim. As Duke University celebrates its centennial in 2024, the Aeolian organ is also approaching its 100th anniversary in 2032. Its relevance and public affection continue to grow, while the resolve to preserve its character has maintained the Aeolian organ as an integral part of Duke Chapel and University culture, well positioned for the trajectory forward.

A Pilot Study: Incorporating Felt Sense Pedagogy in Writing Centers

Tomas Esber

Faculty Mentor: Eliana Schonberg

Authors: Tomas Esber, Eliana Schonberg

Humanities

Abstract:
This project proposes inaugurating a shared vocabulary for understanding writing processes that are guided by felt sense. This sense is the something "in mind" not yet harnessed by words or images. It is an internal embodiment of expression that, ultimately, tends to guide our writing. This project seeks to address the following: What would it look like to prioritize felt sense in a consultation? What would be some of the methods that can be used to cultivate felt sense in a session? How do tutors leave writers so that they are more likely to be able to engage their felt sense afterwards? In doing so, the project attempts to implement, refine, and challenge learnings on felt sense by introducing them into the pedagogy of writing center consultations. This is, at its core, a collective undertaking that attempts to transform the mystified and unrecognizable into a shared language and understanding of what it means for a writing process to be guided by felt sense. More succinctly, it is a call for a movement of felt sense epistemology from the personal to the collective.

Existing Among Ambiguity: Understanding Heritage Language and Identity

Charles Hester

Faculty Mentor: Yunchuan Chen

Authors: Mac Hester, Yunchuan Chen

Humanities

Abstract:
The present study seeks to contribute to the growing field of scope ambiguity research that focuses on heritage language speakers. The participants in this study are college-aged members of the Chaoxianzu ethnic minority group who reside in Northeast China. They generally speak both Korean and Mandarin Chinese at home, attended Chaoxianzu schools with dual-language instruction, and consider Chinese their socially dominant language. This study is concerned with heritage language grammar: specifically, whether Chaoxianzu can correctly interpret scope assignment in Korean and Chinese Q-Neg sentences like, "all teachers did not use Sandy's car." If interpreted correctly, participants should reject the inverse scope in Chinese and accept it in Korean. This study examines the state of heritage language research and what is predicted by Polinksy and Scontras's (2019) representational economy hypothesis, as well as subsequent studies testing this hypothesis. Based on this theory, the heritage participants' Chinese and Korean scores (denoting how frequently they accept the inverse scope in Q-Neg sentences) should fall somewhere in between the two poles of Chinese and Korean native speaker scores, representing inconsistent acceptance. Utilizing a sentence-picture matching truth value judgment task, this study replicates Chen & Huan's (2023) findings that heritage speakers can be categorized into three groups: rejecting IS in both languages, accepting IS in both languages, or accepting IS in Korean while rejecting in Chinese. With these results, this study suggests that heritage speaker's grammar follows a level of structural predictability, somewhere between native Korean and Chinese grammars, which can be further explored through future research in hopes of developing a more comprehensive understanding of heritage identities and language through methods like predictive modeling.

Even in Grief, We Remain Beautiful: Chin Refugees' Reflections and Lamentations on Grief

Thang Lian

Faculty Mentor: Calvin Cheung-Miaw

Authors: Thang Lian, Dr. Calvin Cheung-Miaw

Humanities

Abstract:
By examining the intimate transnational intersections between displacement and resettlement, this project (a) investigates and records how Chin refugees form(ed) communities in Michigan through oral history, (b) situates the Chin people's history within Myanmar's historical contexts "post-independence" (post-1948), (c) uses various archives to delineate the Chin people's history before and after 1948, and (d) interprets community history via frameworks of class, race, and religion. This project is both a reflection and a lamentation. By weaving together archived history, personal narratives, and oral histories conducted with two Chin refugees from Michigan, I reflect on and theorize about grief within the Chin diaspora and its role in community formation. How does grief speak about our relationships with the homeland? How does grief speak into the silence of our experiences as refugees? The process of writing this essay also emerges from my lamentations amidst the ongoing dispossession and killings of our land and people. Grief haunts but, as this essay demonstrates, it also creates hallowed spaces for communal mourning where we speak and act out our deepest love for one another. Thus, the soul of this project lies in collecting, narrating, and analyzing Asian American community history to orient us toward a different, more expansive understanding of what it means for communities like Chin refugees to exist and liv

Inside the Insane Asylum: The Intersection of Race, Patient Labor, and Incarceration

Glory Olowojoba

Faculty Mentor: Hannah Jacobs

Authors: Glory Olowojoba, Hannah Jacobs

Humanities

Abstract:
Goldsboro State Hospital in North Carolina was a segregated insane asylum for Black patients during the early 19th century and is known as Cherry Hospital today. Southern doctors held a general belief that the hard physical labor of chattel slavery improved the mental health of enslaved people. Further, asylum superintendents and physicians held a general belief that cases of insanity in Black individuals greatly increased due to emancipation. As the Black patient population in insane asylums of the American South increased substantially, superintendents created labor programs that they stated would restore Black patients to health. Scholars describe the similarities between prisons and insane asylums including their use of hard physical labor and harsh punishments. Kylie Smith discusses how the Central State Hospital in Georgia had prison-like dormitories and highlights Whitfield Hospital in Mississippi which is described as a prisoner of war camp in an inspection report. Additionally, Edward Baptiste explains how patients were often transferred between prisons and insane asylums, two forms of captivity. This research describes the similar functions of insane asylums and prisons to expose the contradictions within Goldsboro State Hospital's intended purpose and actual operations. Further, this research analyzes biennial reports, inspection reports, and the journals of Dr. Frank Whelpley, Goldsboro State Hospital's superintendent, to highlight the asylum's exploitation of patients through free labor for economic gain. Additionally, this research applies a critical lens to the shortcomings of mental health care for Black individuals in order to improve health equity efforts in the North Carolina healthcare system.

Sonic Curation and Blues Aesthetics in American Plays

Trisha Santanam

Faculty Mentor: Taylor Black

Authors: Trisha Santanam, Taylor Black

Humanities

Abstract:
Jeremy O. Harris's Slave Play (2018) interrogates how the legacy of slavery impacts sexuality, and labor for Black individuals in present-day America in a way that transgresses conventional literary form. Including pop-music, such as Rihanna's "Work," and The Universe's "Multi-Love," Slave Play extends the bounds of written language, transmitting information through both lyrics and also what can be intuitively felt and understood by way of musical attunement. Harris achieves this by invoking the concept of sonic curation, a method of arranging music that is informed by the afterlives of social, political, and geographical histories. Such musical refrains surround Slave Play, emerging from and engaging with concepts located within the blues tradition. Using Slave Play as a guide, I analyze how the idea of sonic curation is embedded in other American plays that reflect on Black lived experiences. Authors like Lorraine Hansberry, August Wilson, Adrienne Kennedy, and Suzan Lori-Parks include minstrel, jazz, modern-pop, and blues songs into their plays to make their writings transcend what can be understood by pure dialogue. These writers are indebted to traditional sonic curators—Ma Rainey, Big Mama Thornton, Nina Simone, Dinah Washington— who work within and beyond blues traditions. These singers know how to not only communicate knowledge through lyrics but also transmit the feeling of an experience through sound. The practice of sonic curation is one that is concerned not only with preservation but also re-membering. An audience viewing such plays is pushed to become "critically re-attuned" to feeling as a method of knowing.

Relationships between syphilis, mental hospitals, and social attitudes in 1920's North Carolina

Evelyn Shue

Faculty Mentor: Hannah Jacobs

Authors: Evelyn Shue, Hannah Jacobs

Humanities

Abstract:
During the 1920's, in the aftermath of World War I, sexually transmitted infections (STIs) like syphilis emerged as a significant public health concern in American urban centers and disproportionately affected the Black community. The implementation of public health measures and innovations in medical diagnosis and treatment aimed to mitigate the rapid spread of syphilis and neurosyphilis in North Carolina. Authorities and institutions regulated populations inequitably along racial and gendered boundaries, inevitably linking STI management to issues of race and sexuality. Heightened awareness in the medical community regarding general hygiene, diagnosis, and treatment was coupled with efforts to address perceived moral decline reflective of racist and sexist attitudes at the time. Although advancements including the Wassermann test, malaria-induced fevers, and arsenic and mercury-based drugs facilitated syphilis diagnosis and control, treatment options were painful and life-threatening. They were thus often turned down by individuals of higher social status while marginalized peoples had little choice in what treatment was administered to them. To explore the evolution of syphilis incidence among Black populations in post-World War I North Carolina mental hospitals in response to improved biomedical advancements and demographic and social shifts, this author scrutinizes extensive archival records and primary sources including newspapers, diaries, and nursing handbooks, alongside secondary literature. These sources reveal a peak in syphilis incidence following World War I, likely influenced by the destabilizing effects of the war in terms of population movement. Examining public health and clinical interventions against syphilis within North Carolinian mental hospitals, as well as the injustices committed against Black patients in the process, is crucial for fostering healing, building trust in modern medical systems, and informing equitable healthcare policies today.

Dictionary of Art Historians

Monet Shum

Faculty Mentor: Lee Sorensen

Authors: Monet Shum, Lee Sorensen

Humanities

Abstract:
The Dictionary of Art Historians was initially conceived as a methodological tool for English-language readers, and it seeks to compile the documented facts of an historian's life in order to serve as a background for understanding a specific text and the historiography of art. The DAH serves as a database of the major art historians in the Western world. The Fall 2023 and Spring 2024 editions of the Dictionary display the changing goals to prioritize research on art historians of color and women art historians, aiming to foster diversity and equity within the field of art history. This shift reflects a crucial commitment to inclusivity, acknowledging and rectifying historical imbalances in representation. By highlighting the contributions of marginalized voices, the dictionary seeks to enrich scholarly discourse, challenge entrenched biases, and promote a more comprehensive understanding of art history that reflects the diversity of human experiences and perspectives.

Networks of U.S. Art Historians of Color

Jerry Zou

Faculty Mentor: Lee Sorensen

Authors: Jerry Zou, Lee Sorensen

Humanities

Abstract:
The title "art historian" is a modern concept. Since the establishment of the United States in the mid-20th century, many scholars of art, especially scholars of color, did not enjoy this honor. Despite the setbacks, groups of African American art scholars thrived, boosted by social movements like the Harlem Renaissance and the establishment of the Department of Art at Howard University in 1921. This project studies African American scholars of art in U.S. history, identifying figures who contributed greatly to our understanding of art and art history yet received little acclaim. In addition to the lack of standardization over the usage of the term "art historians," we studied historical figures across many disciplines, including art production, curation, publishing, journalism, education, and many others. Through writing biographical dictionary articles and creating network visualization graphs, this project views African American art historiography not as a group of individual actors but as an interconnected, intergenerational, and supportive scholarly community.

Physical Sciences

A Kinetic Analysis of Prodrug Hydrolysis and Activation by β-Lactamase Enzymes

Andrew Dale

Faculty Mentor: Addison Duda

Authors: Andrew M. Dale, Addison M. Duda, Sophia A. Kuhn, Katherine J. Franz

Physical Sciences

Abstract:
Bacterial Resistance to conventionally prescribed antibiotics poses a serious threat to human health. A major cause of multi-drug resistant pathogens is the acquisition and expression of β-lactamase enzymes among bacteria. The development of β-lactam prodrugs is currently being investigated as a new method to combat ESBL derived drug resistant bacterial infections. Selective killing of ESBL producing bacteria has been achieved; however, the kinetic consequence on drug activation has yet to be understood. The indicated results compare hydrolysis rates of these ESBLs and being to understand the mechanism of ESBL inhibition achieved by drug activation. Understanding relative hydrolysis rates guides further direction regarding subsequent structural modification of prodrug structure to further enhance selective killing of ESBL positive infections.

Improving Lambda Signal Extraction with Domain Adaptation via Normalizing Flows

Rowan Kelleher

Faculty Mentor: Anselm Vossen

Authors: Rowan Kelleher, Matthew McEneaney, Anselm Vossen

Physical Sciences

Abstract:
The present study presents a novel application for normalizing flows for domain adaptation. The study investigates the ability of flow based neural networks to improve signal extraction of Lambda Hyperons at CLAS12. Normalizing Flows can help model complex probability density functions that describe physics processes, enabling uses such as event generation. Lambda signal extraction has been improved through the use of classifier networks, but differences in simulation and data domains limit classifier performance; this study utilizes the flows for domain adaptation between Monte Carlo simulation and data. We were successful in training a flow network to transform between the latent physics space and a normal distribution. We also found that applying the flows lessened the dependence of the figure of merit on the cut on the classifier output, meaning that there was a broader range where the cut results in a similar figure of merit.

Prodrug exploits beta-lactamase activity to selectively suppress drug-resistant bacteria

Sophia Kuhn

Faculty Mentor: Katherine Franz

Authors: Sophia A. Kuhn, Addison M. Duda, Andrew M. Dale, Katherine J. Franz

Physical Sciences

Abstract:
Antibiotic resistance has become a serious and growing global health threat as bacterial strains continue to evolve and acquire multimodal resistance against antibiotics, leading to treatment failures and increasing death tolls from bacterial infections. Among the various acquired antibiotic resistance mechanisms, the production of beta-lactamases (Bla) by bacteria has received considerable attention. Current treatments for infection from bacteria are insufficient, with most approaches being inadequate to target the Bla-producing population in mixed microbial environments. Specifically, Bla-producing bacteria evade growth suppression while non-Bla-producing bacteria belonging to the host's microbiota are collaterally damaged. Methods to selectively suppress resistant bacteria must be developed to address the growing complications surrounding bacterial infection treatment and establish an improved catalog of beta-lactam drugs. AcephPT is a cephalosporin prodrug that exploits Bla enzymatic activity to selectively suppress Bla-producing bacteria in a mixed microbial environment. Compared to previous generation prodrugs, AcephPT has enhanced selectivity for suppressing the growth of resistant bacteria. This activity was determined by developing a mixed microbial assay to quantify selective suppression of a clinically relevant Bla-producing strain. Time-course proton NMR experiments using an isolated Bla were performed to profile the hydrolytic activation of AcephPT. The enzymatic rate of AcephPT's activation was quantified and compared to other antimicrobial agents by defining kinetic parameters using UV/Vis spectroscopy. Given the enhanced selectivity of AcephPT as a suppressor of resistant bacteria, its activity proposes a new viable antibiotic for combating antibiotic resistance in mixed microbial environments.

Acoustic Signal Processing for Boundary Detection Between Materials

Humberto Lopez

Faculty Mentor: Patrick Codd

Authors: Andre Lopez, Ravi Prakash, Patrick Codd

Physical Sciences

Abstract:
This study explores the use of sound signals to discern material boundaries, with the goal of integrating this capability into a controller for a robotic tactile system. It seeks to identify features and methods that gauge the similarity of produced signal at the material transition boundary, to a signal produced on a homogenous material characteristic of the desired material. A variety of sound features have been studied including Short-time Fourier transform coefficients (STFTCs), Wavelet packet transform coefficients (WPTCs), Mel-frequency cepstrum coefficients (MFCCs), zero crossing rate, spectral centroid, and discrete Fourier transforms. Promising features include short-time Fourier transform coefficients and wavelet packet transform coefficients. Methods such as cross-correlation, cosine similarity, correlation coefficients, and convolution have been explored with no significant success due to the complexity of audio signals. In the future, the study aims to develop methods for utilizing these features in real time to stay within the desired material boundary.

An AdS/CFT Approach to Spherical Gluon Plasma Balls Under Hadronization Phase Transition

Danming Peng

Faculty Mentor: Berndt Mueller

Authors: Danming Peng, Berndt Mueller

Physical Sciences

Abstract:
In this study, we investigate gluon plasma balls under hadronization phase transition in large-N gauge theories via the AdS/CFT correspondence, where the unconfined gluon plasma is dual to an AdS black hole and the confined vacuum corresponds to an AdS soliton. In prior work, Aharony et al. proposed the existence of localized plasma balls by numerically constructing a planar domain wall solution that interpolates the plasma and the confining phases. Employing ADM formalism, asymptotic expansions, and numerical methods, our research extends this work by solving for an interpolating metric that represents a spherical plasma ball surrounded by a confined vacuum at the deconfinement temperature. We explore its degrees of freedom and determine the thermodynamically preferred states by minimizing the free energy numerically. These solutions will allow us to investigate the energy density, surface tension, curvature effects, and radius dependence of the plasma ball by analyzing the gravitational field data from a dual perspective.

A Critical Analysis of the Environmental Impact of Academic Travel in Astronomy Spheres

Shambhavi Sinha

Faculty Mentor: Arun Kannawadi

Authors: Shambhavi Sinha, Arun Kannawadi

Physical Sciences

Abstract:
Existing literature has demonstrated with quantitative data the significant contribution to greenhouse gas emissions from academic travel, particularly flights. Within the field of astronomy, by examining the emissions breakdown from various sources, including flights, supercomputing usage, observatories, and campus operations, existing research has given a detailed breakdown of the environmental impact of astronomers' activities on climate change. Various existing astronomy institutions have studied their carbon footprint impacts, noting travel done by astronomers as a significant portion. It is thus, critical to analyze and assess this impact on a global scale and reflect on how astronomers can help reduce their part of the burden to the earth. This project delves into the case study of the carbon footprint impact of academic travel within the astronomy community, particularly focusing on the General Assembly meeting of the International Astronomy Union (IAU) in 2022 held in Busan, South Korea. While existing research has arrived at conclusions based on per-capita carbon footprint, this project aims to explore the impact on the market demand on the flights to Busan (or Seoul) caused by holding the IAU 2022 General Assembly there through an analysis of flight data and emissions statistics. By augmenting the publicly available attendee information with the nearest airport information and, analyzing this data, we plan to use causal inference and probabilistic calculations then to see to what extent flight demands would be impacted if astronomers chose not to attend this conference. Through this, the research endeavors to assess the feasibility and implications of reducing academic travel for astronomers. Quantitative facts and comparative analyses from Australian and European contexts provide valuable insights into the scale of emissions and potential mitigation measures. Ultimately, the project seeks to inform policy discussions, academic practices, and individual choices within the astronomy community toward achieving substantial reductions in greenhouse gas emissions while fostering a culture of environmental stewardship and responsibility.

First-Principles Simulations of Rare-Earth Metal Chalcogenide Semiconductors

Chris Wu

Faculty Mentor: Volker Blum

Authors: Chris Wu, Max McWhorter, David Mitzi, Volker Blum

Physical Sciences

Abstract:
Recent work has identified bournonite (PbCuSbS3) as a semiconductor material with promising light-absorbing and spin-transport properties. In this work, we investigate the possibility of substituting Sb atoms in the bournonite structure with rare earth metals Y and La. We run first-principles density-functional theory simulations using Perdew-Burke-Ernzerhof (PBE), PBE with non-local many-body dispersion (PBE+MBD_nl), and hybrid (HSE06+TS2018) exchange-correlation functionals to compute crystal structures, total energies, band structures, and density of states of PbCuYS3 and PbCuLaS3 in bournonite structures. We compute direct spin-coupled bandgaps of 1.47 eV and 1.42 eV respectively, comparable to the experimentally determined 1.29 eV direct bandgap of naturally occurring bournonite. Initial synthesis attempts yielded copper lanthanum sulfide (CuLaS2) and PbCuYS3 in the aikinite (PbCuBiS3) structure. Naturally occurring aikinite (PbCuBiS3), in comparison, has an indirect bandgap of 0.91 eV estimated from optical measurements. To inform future synthesis attempts, we use the HSE06+TS2018 functional to compute and compare total energies for PbCuYS3, PbCuLaS3, PbCuSbS3, and PbCuBiS3 in the bournonite and aikinite structures

Electrocatalytic 1,3-Difunctionalization of Arylcyclopropanes for Heterocyclic Construction

Justin Zhang

Faculty Mentor: Qiu Wang

Authors: Justin Zhang, Qiu Wang

Physical Sciences

Abstract:
1,3-difunctionalized motifs are ubiquitous in biologically-relevant products such as pharmaceuticals and agrochemicals. These 1,3-difunctionalized motifs are difficult to access through alkene and diene reaction systems that have been extensively studied. Arylcyclopropanes represent a route for facile synthesis of these 1,3-motifs. Many existing arylcyclopropane functionalization reactions are known to occur through oxidation of the arylcyclopropane to a radical cation intermediate. In our reaction, we aim to conduct this oxidation through electrocatalysis, resulting in a modular reaction that avoids the use of toxic metal catalysts and harsh organic oxidants.

Feasibility of Repurposing Used Li-Ion Batteries

Bridget Zhu

Faculty Mentor: Josiah Knight

Authors: Bridget Zhu, Josiah Knight

Physical Sciences

Abstract:
Lithium-ion batteries are used for almost all modern-day portable consumer electronics and are the most promising energy storage technology on the market necessary to efficiently transition to renewable energy. Mining for the critical minerals (namely cobalt and lithium) required for manufacturing li-ion batteries is currently highly exploitative to people and the planet. Consumer li-ion batteries for many applications are also often disposed of improperly, long before the end of their lifespan, leading to toxic waste in landfills. The objective of this experiment is to demonstrate the feasibility of small-scale li-ion battery recycling and provide the means and incentive for more widespread battery recycling research in order to reduce toxic waste and unethical lithium/cobalt mining. A series of experiments is conducted using 25 li-ion batteries salvaged from discarded e-cigarettes (most of the batteries are 16350 batteries rated for 650 mAh and 3.7V). The batteries are tested, singly and in combinations, using load resistances to approximate actual charge/discharge cycles. The measurements allow calculation of internal resistance, power delivered and charge/discharge times to determine the battery health. Results show that all 25 batteries are fully operational and have potential for repurposing. Further research into recycling and applications of this and other categories of small li-ion batteries is thus justified.

Quantitative Sciences

Constructing Minimal Mod-3 Surfaces: A Solution to Plateau's Problem

Hiba Benjeddou

Faculty Mentor: Demetre Kazaras

Authors: Hiba Benjeddou, Demetre Kazaras

Quantitative Sciences

Abstract:
The Plateau problem is a fundamental challenge in geometric measure theory with the objective of finding minimal surfaces that have prescribed boundaries. Originating from Joseph Plateau's 19th-century soap film experiments, this problem seeks to identify surfaces that locally minimize surface area, with natural occurrences observed in membranes under equal opposing pressure, exemplified by soap films spanning wireframes. We focus on minimal surfaces within three-dimensional space, specifically exploring a unique subset called minimal mod-3 surfaces. These intriguing surfaces comprise oriented minimal surface pieces meeting in groups of three along "singular curves," with consistent 120-degree angles between intersecting faces. Importantly, they possess a unique characteristic: their orientations allow their boundaries to cancel out modulo 3. Our research adopts an innovative wireframe approach to address this problem, focusing on wireframes designed with hexagonal symmetry, allowing the extension of minimal-area surfaces across three-dimensional space through rotations and translations. This method yields non-trivial examples of minimal mod-3 surfaces characterized by their boundary cancellation modulo 3. Starting with a regular hexagon in two dimensions, we extrude it to create a hexagonal prism in three dimensions, carefully selecting edges to obtain wireframes with hexagonal symmetry that extend seamlessly across 3-space. This process is then repeated for three copies of wireframes, arranged to intersect at 120-degree angles, with orientations chosen strategically to facilitate boundary cancellation modulo 3. The result is the creation of a "hexaprism" surface featuring both hexagonal symmetry and minimal mod-3 characteristics. This study showcases how the wireframe method, coupled with principles of geometric measure theory, enables the creation of minimal surfaces with intricate geometries. The use of hexagonal symmetry in wireframe design provides a structured approach to extend minimal surfaces across 3-space, offering a unique solution to Plateau's problem.

Fusion Oncoprotein ESM model

Kseniia Kholina

Faculty Mentor: Pranam Chatterjee

Authors: Kseniia Kholina, Sophia Vincoff, Shrey Goel, Pranam Chatterjee

Quantitative Sciences

Abstract:
Oncofusion proteins are the key pathological hallmarks of various human cancers. Their unique structural biology—resulting from chromosomal translocations, a region representing the fusion of two distinct genes—results in highly disordered protein states. Fusion proteins combine domains from different proteins, creating hybrid proteins with altered or novel functions, contributing to cancer development. Fusion proteins pose significant challenges as therapeutic targets, as they can confer resistance to conventional cancer therapies. One of the key difficulties in targeting fusion proteins is their highly disordered nature: these proteins often lack a fixed three-dimensional structure and can adopt various conformations depending on their environment and interacting partners. Current deep neural networks have shown great potential in advancing cancer therapy development; models such as Google DeepMind's AlphaFold-2 and MetaAI's ESMFold can predict protein structure with remarkable accuracy. However, when tasked with structure prediction of highly disordered oncofusions, no model can accurately capture fusion protein nature, and therefore, cannot perform well on downstream tasks such as peptide binder design. Therefore, we aim to finetune the state-of-the-art ESM2 protein language model (pLM) in order to obtain information-rich embeddings to enhance our understanding of fusion protein nature, leading to the prediction of potential therapeutic binders for these proteins. The ESM2 pLM fine-tuned on oncofusion proteins will provide us with a powerful tool that can inform other sequence-based modules of the nature of these highly disordered proteins. Recently, we developed other sequence-based toolkits such as PepMLM and SaLT&PepPr that enable endogenous degradation of target proteins; thus, sequence-based peptide binder design is a promising avenue for targeting and degrading oncofusions. Through the identification of potential binding peptides using a model equipped with information-rich embeddings, we can advance the development of targeted therapies for cancer treatment. We are optimistic that ESM2 fine-tuned with robust oncofusion sequence data will accurately capture key information regarding the nature of highly disordered proteins and enable downstream fusion-specific binder design for cancer-related diseases.

An Artificial Intelligence Circuit to Detect Dark Matter at the LHC

Tanish Kumar

Faculty Mentor: Ashutosh Kotwal

Authors: Tanish Kumar, Zakk Heile, Nika Kiladze, Zesen Zhuang, Ashutosh Kotwal

Quantitative Sciences

Abstract:
At CERN's Large Hardon Collider, the world's highest-energy particle accelerator, physicists recreate the conditions of the early universe to discover the constituents of dark matter by experimentally observing the products of proton-proton collisions. However, with protons colliding every 25 nanoseconds, computationally processing all the detector data from every collision is an impractical task. Our work is focused on designing and implementing a filtering algorithm that processes collision data, within the significant time constraint, to assess whether each collision warrants further study. We have determined that the most efficient way to do this is to use an unsupervised machine learning technique spread across a custom-designed, massively parallel computer. This device will use a novel graph-computing architecture, very different from the traditional Von Neumann architecture. Our focus is on the data produced by the inner-most detectors, a set of five barrels made with silicon pixel sensors, with a resolution of ~15 microns. These detectors output a cloud of space points, representing the energy depositions of decay particles as they pass through the detector's layers. To determine if the collision is worth studying further, we implement a novel algorithm at the hardware-level by designing field programmable gate arrays (FPGAs) – which are configurable integrated circuits. The filtering algorithm has two main stages: 1) appropriately structuring the cloud of space points to feed into the massive parallel computer and 2) reconstructing particle tracks at each node of the graph computer, given a slice of space points. The first stage of the algorithm creates patches (contiguous subsets) of space points given geometrical slices of the incoming data; these patches are passed to nodes of the computer, ensuring that all possibilities for particle tracks are accounted for. The second stage of the algorithm treats the space points as a graph, eliminating links via the application of a graph operator until the remaining linkages represent particle trajectories. These tracks are used to decide if the collision produced decay particles that are consistent with dark matter candidates. If found to be consistent, our artificial intelligence circuit would lead to more careful study and analysis of the collision. We aim for this project to be implemented in the next upgrade of the LHC to enable a unique and unprecedented search for dark matter signatures.

Optical and Sensor-Based Tracking for Enhanced AR-Guided Neurosurgical Training

Tiffany Ma

Faculty Mentor: Maria Gorlatova

Authors: Tiffany Ma, Sarah Eom, Maria Gorlatova

Quantitative Sciences

Abstract:
This thesis details a series of enhancements to the NeuroLens augmented reality (AR) system for neurosurgical training, integrating advanced tracking technologies and contextual guidance tailored to user-specific behavior. These technologies include the incorporation of strain gauges for detailed tool deformation tracking, the deployment of stereo-camera sensors for improved spatial awareness, the development of AR-guided craniostomy procedures, and the utilization of IMU sensors for precise instrument orientation feedback. These enhancements are designed to provide more contextually relevant, real-time guidance and feedback based on the user's handling of instruments. Comprehensive user studies validate the improvements in the system's accuracy, user engagement, and educational impact. The culmination of this work offers a more intuitive, accessible, and effective platform for educating future neurosurgeons. Through detailed documentation of the development process, system evaluations, and reflections on published works, this thesis highlights the technical achievements and interdisciplinary approach essential for innovating medical training technologies.

Age and Sex Differences of Cerebral Hemodynamics in the Presence of Venous Hyperintense Signal

Aurea Michael

Faculty Mentor: Meher Juttukonda

Authors: Aurea S. Michael, Nikou L. Damestani, Shrikanth M. Yadav, John Jacoby, Meher R. Juttukonda

Quantitative Sciences

Abstract:
Brain white matter lesions (WML) are physiological irregularities linked to cerebral brain is associated with increased WML burden. Brain venous hyperintense signal (VHS) in perfusion-weighted arterial spin labeling (ASL) images may indicate irregular cerebral hemodynamics, namely capillary shunting and reduced oxygen extraction efficiency. VHS appears as a bright ASL signal in major brain veins. A recent study showed significant interaction between VHS presence and the relationship between maximum oxygen extraction fraction and WML burden. However, the study included a small sample (n=30) of elderly individuals (60-80 yrs). In this study, we aimed to investigate the prevalence of VHS in a larger sample that includes participants across the adult lifespan (40-100 yrs) and whether VHS is associated with differences in CBF and ATT in aging. We also aim to determine whether the effect of VHS presence on CBF and ATT is different between males and females. The study included 100 subjects of the Human Connectome Project in Aging (HCP-A) dataset. Each subject's perfusion-weighted ASL image (1200ms post-labeling delay, 1500ms labeling duration) was rated for VHS. Subjects were classified as VHS present (VHS+) or VHS absent (VHS-), and subjects with unclear VHS were excluded. Two raters independently rated each image to reduce bias. CBF and ATT were calculated from ASL. Forty-six subjects were classified as VHS+, thirty-two as VHS-, and twenty-two were excluded due to unclear VHS. VHS+ exhibited a higher average age (73.0 ± 15.8 yrs) than VHS- (56.0 ± 14.6 yrs). Consistent with previous studies, CBF declined with age, with a slower decline in VHS+ than VHS-. ATT in VHS+ was significantly lower ($p = 0.048$) and increased slower with age than VHS-. While VHS- males and females exhibited increasing ATT with age, in VHS+, the interaction of ATT with age was significantly different ($p = 0.05$) between males and females. Our results suggest that VHS may be an important indicator of age-related vascular physiology. Additionally, cerebral autoregulatory mechanisms that elongate ATTs in typical aging may be impaired in individuals with VHS. Finally, male versus

female ATT differences further suggest that age-related diseases may manifest differently between the two sexes.

Can you feel the shape of a heat conductor? How a single bend affects the rate of heat transfer

Zachary Robers

Faculty Mentor: Roberto Camassa

Authors: Zachary Robers, Dylan Bruney, Roberto Camassa

Quantitative Sciences

Abstract:
Reshaping a rectangular metal conductor into an L-shape, while maintaining its original area and perimeter, significantly alters its temperature diffusion. Our experimental investigation involves placing a local RTD probe at the end tip of various conductor geometries to explore the influence of the L-bend on temperature diffusion. Numerical studies support our experimental findings, revealing noteworthy global changes in the conductor's temperature distribution. Additionally, through a perturbation analysis, we gain valuable insights into the underlying reasons behind this phenomenon. This research sheds light on an effective method to control thermal behavior in metal conductors, with potential implications in controlling heat exchange in electronics applications.

Fast Sparse Constrained MCMC Sampling Algorithms over Polytopes

Benny Sun

Faculty Mentor: Yuansi Chen

Authors: Benny Sun, Yuansi Chen

Quantitative Sciences

Abstract:
We propose novel formulations of various MCMC sampling algorithms (Dikin, Vaidya, John Walk) for generating samples from a uniform distribution over a polytope in a sparse constrained setting. We prove that our new formulation of these walks in a sparse constrained setting is identical to its full-dimensional counterparts. However, by preserving sparsity, our implementation improves its scalability across dimensions. Here, we developed an optimized C++ package with Python wrapper code. We demonstrate these improvements by showing its ability to sample up to 10^5 dimensions with near linear growth in per-iteration cost in polytopes like the simplex, hypercube, and Birkhoff polytopes. These improved runtimes reflect similar performances from the Kook et al 2022 paper for Hamiltonian Monte Carlo algorithms. The Dikin, Vaidya, and John Walk are from the same class of MCMC sampling algorithms derived from interior point methods. Each calculates a proposal distribution which bends itself to local geometry while doing an accept-reject step to ensure a uniform stationary distribution. They are known for improved mixing times. While previous literature focuses on the full-dimensional formulation (Ax <= b), we provide an alternate formulation in a sparse constrained setting (Ax = b, x_{i}>= 0 for some i). Using our facial reduction algorithm, we show that any full-dimensional form can be translated into a simplified constrained setting. This is especially important for scalability, as constrained settings, unlike full-dimensional, preserves sparsity. By allowing the preservation of sparsity, our algorithms under this alternative formulation thus scale better in higher dimensions.

Social Sciences

The Acquisition of the English Plural Form by Native Japanese Speakers: An Investigation

Layla Arty

Faculty Mentor: Yunchuan Chen

Authors: Layla Arty, Yunchuan Chen

Social Sciences

Abstract:
Native Japanese speakers learning English are unlikely to receive any input that unlike the plural form -tachi in Japanese, the plural form -s has a constraint that disallows it to have an associative meaning. Previous researchers have argued that because of this poverty of the stimulus issue, native Japanese- English learners are unlikely to acquire the knowledge of the constraint on -s. This study explored this hypothesis and investigated the role that proficiency plays in the acquisition of -s. Participants completed a truth value judgment task where they evaluated whether the displayed sentence matched the image shown to them. Their responses were recorded and analyzed as percentages of "yes" answers. We found that the majority correctly rejected the associative reading of the items and that the level of proficiency did not correlate with their ability to acquire the constraint. We concluded that L1 Japanese L2 English learners can acquire the constraint of the plural morpheme -s. These findings provide support for Schwartz and Sprouse's Full Access theory and suggests that poverty of the stimulus issues can be overcome through the learner's access to UG, though further research is needed to support this conclusion.

The relation between navigational self-efficacy and use of university resources

Emma Chun

Faculty Mentor: Molly Weeks

Authors: Emma Chun, Marina Wagemaker, Sarah R. Eisensmith, Molly S. Weeks

Social Sciences

Abstract:
Adaptive help- and support-seeking are crucial to student success in college (Fong et al., 2023; Parnes et al., 2020). At the same time, the college support landscape can be complex and challenging to navigate (Winograd & Rust, 2014). Although orientations toward and expectancies of help-seeking have been examined extensively (see Fong et al., 2023), researchers have not yet focused on students' confidence that they can effectively navigate university resources and support systems, or navigational self-efficacy. The goal of the current study was to develop a measure of navigational self-efficacy and examine its association with the use of university programs and services and broader measures of student adjustment. As part of a larger study, undergraduate students (n = 1,515) responded to 8 items asking about the degree to which they can find the information and resources they need on campus (e.g., "I can navigate the resource landscape at [university]"; "I can find resources at [university] that will help me explore my interests"), as well as two single-item measures designed to assess students' confidence in navigating opportunities and the support landscape on campus. In addition, participants also reported on their use of university programs and services, their sense of enthusiasm and gusto for their academic work (i.e., academic engagement, Asher & Weeks, 2012), connections to faculty (adapted from Asher & Weeks, 2012), feelings of belonging on campus (Asher & Weeks, 2014), and institutional trust. Confirmatory factor analyses supported a two-factor model [chi-square (8) = 41.30, p < .001; CFI = .993, TLI = .987, RMSEA = .052 [.037–.069], SRMR = .017], with one factor assessing general navigational self-efficacy (alpha = .83) and a second assessing efficacy for finding specific resources (alpha = .85). Strong measurement invariance across a variety of student identities was supported for both factors. Navigational self-efficacy measures were associated with student self-report of accessing campus programs and resources, such that participants who reported higher efficacy also reported accessing more programs and services. Further supporting the validity of the measures, navigational self-efficacy was associated with students' connections to faculty, sense of enthusiasm for their academic work, feelings of belonging, and institutional trust. Future directions for research and application will be discussed.

COVID-19's Impact on Undergraduate Students' Priorities, Major Decisions, and Career Aspiration

Annie Cui

Faculty Mentor: Nicholas Carnes

Authors: Yaxuan (Annie) Cui, Nicholas Carnes

Social Sciences

Abstract:
How has the COVID-19 pandemic changed higher education? In this paper, I develop a theory for how the pandemic affected undergraduate students' priorities, majors, and career choices using qualitative interviews with 27 Duke undergraduate students and 21 advisors. I find that the pandemic has affected students in a variety of ways: some students describe no impact, but more students indicated that the pandemic influenced their concerns about financial security, parental influence, and the importance attached to in-person classes, and ultimately their major and career choices. These findings indicate that exogenous shocks like COVID-19 can intensify important trends in higher education in ways that scholars of higher education have not fully grasped.

The Impact of Harsh Parenting and Maternal Depression on Executive Function in Early Childhood

Julia Davis

Faculty Mentor: Ken Dodge

Authors: Julia O. Davis, W. Benjamin Goodman, Kenneth A. Dodge

Social Sciences

Abstract:
The environment that a child grows up in has an important impact on neurodevelopment. Specifically, previous research has demonstrated that parenting behaviors and parent-child interactions influence the development of executive function (EF). EF is associated with a wide variety of positive outcomes in childhood and beyond, including academic achievement and social and emotional stability. In the present research we focused on two fundamental EF skills: attention, and inhibitory control (IC). We investigated the relation of harsh parenting and maternal depression at 30 months with EF (attention and IC) at 30 and 42 months using a combination of parent self-report and research observation data from the Family Connects (FC) early childhood intervention. FC is a short-term, postnatal universal nurse home-visiting program that identifies family-specific needs and connects families with community resources to address their needs. Harsh parenting and maternal depression at 30 months are significantly associated with poorer IC and attention at both 30 and 42 months, after controlling for medical risk at birth, child gender, child race/ethnicity, socioeconomic status, maternal age, and maternal education. These results shed light on the relation between parenting behaviors and EF, suggesting that harsh parenting behaviors and parent mental health challenges may negatively impact neurodevelopment. Further, these results may be a foundation for the design of early childhood interventions or policies aimed at promoting healthy parent-child interactions and early cognitive development.

Pursuing Equitable Sustainable Development

Durga Sreenivasan

Faculty Mentor:

Authors: Durga Sreenivasan

Social Sciences

Abstract:
This summer, I researched equitable sustainable development for India's marginalized communities. Thanks to the Robertson Scholarship Program, the Dean's Summer Research Fellowship, and the Human Rights Summer Research Grant, I got to deepen my understanding of the impact of colonialism on marginalized communities, and the linkages between these historical/anthropological issues with the action-oriented Sustainable Development Goals. This summer, I learned the importance of pursuing social equity in sustainable development in a hands-on way. By working in a poverty-alleviating organization funded by a South Indian who left corporate America, I better understood how the private sector can play a key role in achieving the Sustainable Development Goals.

Between the Binaries of Mauritian Creole: Through the Lens of Primary School Educators

Katheryn Turner

Faculty Mentor: Dominika Baran

Authors: Katy Turner, Deonte Harris, Dominika Baran

Social Sciences

Abstract:
Mauritian Creole was formed by enslaved people in settlement colonies on the island of Mauritius. It is the language spoken by the majority of Mauritians, although it is frequently met with negative language attitudes. The education system reflects these negative attitudes and favors English and French, colonial languages. Few language guidelines for education exist in Mauritius, leaving teachers to make decisions on how language will be used in their classrooms. Teachers make decisions knowing that the children must learn material in English, as the final exams that permit education beyond primary school are in English. I interviewed five primary school teachers in two English medium schools to explore their language ideologies towards Mauritian Creole and how that impacts language use within the classroom. The teachers sit between the binaries of Mauritian Creole being either 'good' or 'bad' for students in education. They used the discourse of modernity to mask the underlying, complex reasons why they believed Mauritian Creole should not be used in the classroom. However, these teachers also honor the language and how it is tied to Mauritian culture and history by using it as a tool for connection and learning. These teachers are imparting the complex way they experience Mauritian Creole unto their students through the hidden curriculum. In a landscape defined by colonialism, I argue that actual people's lives don't align with the binary of the rejection of colonialism or under its purview. To live between these binaries shapes the way they think and hold Mauritian Creole.

What Do Americans Think Democracy Means?

Christina Wang

Faculty Mentor: Nicholas Carnes

Authors: Christina Wang, Nicholas Carnes

Social Sciences

Abstract:
Research on how Americans think about democracy primarily uses surveys and quantitative methods. However, these studies rely on researchers' assumptions about democracy and do not ask about how people understand democracy on their own terms. In this study, I apply an interpretive method to investigate what Americans think democracy means and how they make sense of it in their everyday lives. I conducted semi-structured conversations among 11 self-forming groups across four regions in Virginia in June and July of 2023. I did not observe a consensus or clear typology of democratic meanings across the 11 conversations. Participants discussed diverse and complex meanings of democracy which the current literature does not document. I also observed that participants' democratic meanings were not isolated or readily retrievable. Rather, participants constructed democratic meanings using conceptual tools that allowed them to talk about democracy in relation to their broader values and worldviews. My findings suggest that existing quantitative methods on this topic may not accurately capture how people understand democracy. Future research on how people think about democracy should use methods that center on people's own experiences and understandings, rather than scholars' definitions of democracy.

Children's Collaboration with Robots

Sarah Yoon

Faculty Mentor: Tamar Kushnir

Authors: Sarah Yoon, Teresa Flanagan, Tamar Kushnir

Social Sciences

Abstract:
Children growing up in the digital age are expected to interact with new, innovative technnologies, such as robots, in their daily lives (e.g., for education or entertainment). Increasingly, robots are being used as partners in collaborative settings with children, such as peer tutoring or reading (Kanda et al., 2004; Chen et al., 2020; Michaelis & Mutlu, 2018). Yet, the effectiveness of these collaborative robots depends on how well they are able to maintain trust throughout collaboration, even when they make mistakes. The present study, therefore, aims to adress how children collaborate with a robot when it fails, and whether this depends on the robot's response to the failure. We focus on participants in early childhood as this is the time period during which children are most likely to glean the educational benefits of collaborative robots. In this study, 27 4-7 year old children (Mage = 5.89, SDage = 1.70, 44% Female) played a collaborative game with a robot in which both partners had to press a button to successfully move a frog across lily pads. The robot partner initially played the game successfully for the first 3 times but then stopped pressing the button. The robot's failure was marked as either a remorseful mistake (e.g. "Oops, I missed the button. I am so sorry.") or an intentional transgression (e.g. "Haha, I did not press the button."). We measured children's persistence in the collaborative activity as their willingness to continue playing the game with the robot after it fails. We found that children initially persisted longer when the robot apologized for its mistake (87%, N = 13/15, SD = 0.35) than when the robot intentionally failed (50%, N = 6/12, SD = 0.52), $X^2(1) = 4.40$, $p = .036$. This work is relevant to developmental research and the future of robot designs, as we are already seeing the importance of incorporating recovery strategies to maintain trust and engagement during child-robot collaborations. Data collection for this study is ongoing and next steps include behavioral coding for children's protest behaviors.

Investigating Data Sandbox Experiments in Asia

Elaine Zhang

Faculty Mentor: Chad Routh

Authors: Elaine Zhang

Social Sciences

Abstract:
The rapid technological developments call for innovative ways of data regulation. Data sandboxes are one of these ways. Commonly categorized into operational and regulatory sandboxes, data sandboxes allow innovators and regulators to test innovative technology and data practices in a secure environment. Originally popularized in the fintech space, they have been used to improve regulatory and technical collaboration for over a decade and have been tested in over 70 countries and on the municipal, state, and national levels worldwide. They have facilitated interagency efforts and coordination within governments, and have helped actors in the private sector, public sector, and civil society build trust and find avenues to work together. As one of the most economically vibrant and culturally diverse regions in the world, Asia presents a rich tapestry of societal, political, and economic intricacies that demand nuanced exploration. With rapid globalization and technological advancements shaping the region's trajectory, there is an urgent need to delve into the nuances of its sandboxes and understand how sandboxes in Asia contribute to and shape the global data governance landscape. As an active actor in data governance, Asia is no stranger to sandboxes. Singapore, for example, was an early and highly motivated adopter of regulatory sandboxes in fintech. Other Asian countries, such as China, Malaysia, Japan, Thailand, and Philippines, have also either designed or implemented sandboxes. Previous research on sandboxes in Asia either focused on a specific region such as Southeast Asia or only touched upon specific case studies. A holistic view that encompasses the diverse range of sandbox initiatives across the continent is lacking. This gap presents an opportunity for my research project to contribute to the body of knowledge by providing a more nuanced and in-depth exploration of sandbox experimentation in Asia. The project researches the landscape of regulatory sandboxes across key Asian states, using desk research and semi-structured interviews to understand the structure, operation, and impact of sandboxes across financial services, health, artificial intelligence, and other cross-cutting topics. These insights can then be compared and contrasted with sandbox experiments from other regions, drawing upon lessons learned to build a fair and inclusive data future collaboratively.