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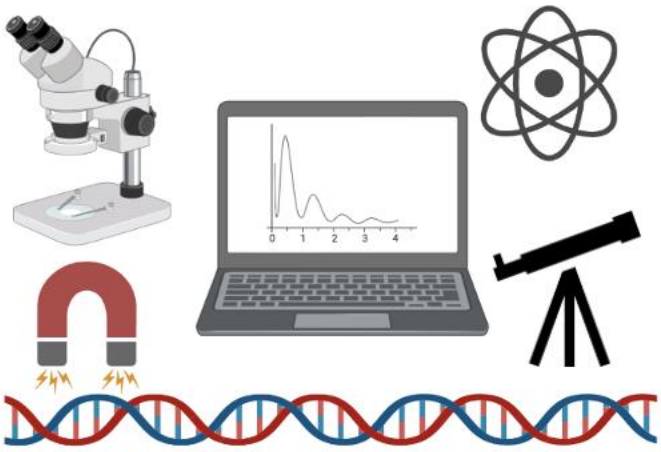

STARS2 Annual Symposium

April 15, 2024

5PM - 8PM

Marsh Auditorium
260 Whitney Ave

Schedule of Presentations

5-5:15	Dr. Alexia Belperron *Director of STEM Fellowships*	Welcoming Remarks
5:15-5:25	Jennifer Wang *Dept. of Molecular, Cellular, and Developmental Biology*	Estimating the effect size of cancer mutations in epistatic contexts with mutation timing information
5:25-5:35	Matt Midy *Dept. of Molecular Biophysics and Biochemistry*	Engineering RNA Aptamers by Directed Evolution from a Natural TPP Riboswitch Scaffold
5:35-5:45	Barkotel Zemenu *Dept. of Physics*	Characterizing the Outgassing of Electronegative Impurities in nEXO
5:45-5:55	Harper Lowrey *Dept. of Molecular, Cellular, and Developmental Biology*	CFH1 Conservation Sheds Light on Functionally Essential Amino Acids
5:55-6:15	William An *Dept. of Ecology and Evolutionary Biology*	Investigating the effect of bacterial diversity on the evolution of *Pseudomonas aeruginosa* virulence in response to phage H6
6:15-6:30	Alyse Olcott *Dept. of Earth and Planetary Sciences*	Investigating the Effect of Titan's Hydrologic Cycle on its Surface Environment
6:30-8:00	STARS2 Students	Poster Presentations

Poster Presentations

Daena Rodriguez Rueda *Dept. of Molecular, Cellular, and Developmental Biology*	Investigating the role of histone deacetylation in critical periods of vertebrate neurodevelopment
Noemi Guerra *Dept. of Molecular, Cellular, and Developmental Biology*	Chimeric Parasites: A Novel Approach for Studying the Role of Cysteine-Rich Protective Antigen (CyRPA) across *Plasmodium* Species
Jackson Roberts *Dept. of Ecology and Evolutionary Biology*	Deciphering the relationship between PRDE-1 and transcriptional regulators in piRNA biogenesis in *C. elegans*
Andy Tang *Dept. of Molecular, Cellular, and Developmental Biology*	Comparative Analysis of TP53 Alleles in Pancreatic Ductal Adenocarcinoma
Eric Stevens *Dept. of Molecular, Cellular, and Developmental Biology*	Tracking Splicing Mutations in Leukemia
Angelica Lorenzo *Dept. of Biomedical Engineering*	Microvessel-on-a-Chip Model to Investigate the Role of TNF-α on Fibrotic Pericyte Signaling

Mikayla Labissiere *Dept. of Biomedical Engineering*	Endothelial Targeting with Improved Nanoparticles for Specific and Localized Use
Lydia Tarekegn *Dept. of Molecular Biophysics and Biochemistry*	Insulin-Resistant Huh-7 Cells as a Model of Nonalcoholic Fatty Liver Disease
Austen Theroux *Dept. of Ecology and Evolutionary Biology*	Derivation and assessment of *de novo* and synthetic viral cheats
Dina Garmroudi *Dept. of Molecular, Cellular, and Developmental Biology*	Regulation of Feeding-State Dependent Behaviors via Microbial Metabolites
Akua Agyemang *Dept. of Molecular Biophysics and Biochemistry*	Persistence Length of Chromatin in the Nuclear Context
Valeria Ceron *Dept. of Neuroscience*	Characterizing Behavior and Brain Activity Phenotypes in Zebrafish Mutants of the Autism Risk Gene, *ADNP*
Joanna Chen *Dept. of Molecular, Cellular, and Developmental Biology*	Functional Effects of Altering HOX Gene Expression in Cancer Cells
Esteban Figueroa *Dept. of Electrical Engineering*	Untethered Shape Change in Real World Deployment
Ernestine Giahyue *Dept. of Neuroscience*	Proteomics in the Medial Prefrontal Cortex of Mice Following Learned Helplessness
Michael Gordon *Dept. of Molecular, Cellular, and Developmental Biology*	Investigation of Alterations of Interneuron Development in Tourette Syndrome Using Telencephalic Organoids
Kayleigh Hackett *Dept of Molecular, Cellular, and Developmental Biology*	Elucidating the Independent Roles of tbx16 and msgn1 in Presomitic Mesoderm Differentiation
Cailin Hoang *Dept. of Molecular Biophysics and Biochemistry*	Stability and Dynamics of Chemically Sensitive VlsE and Crowding Sensitive PGK
Isabelle Staco *Dept. of Molecular, Cellular, and Developmental Biology*	Defining The Role of Persistent DNA Bridges in cGAS-STING Activation by PARPi (Olaparib) Treatment
Kayla Samo *Dept. of Biomedical Engineering*	Characterizing Paracrine Regulatory Mechanisms through Dual Stimulation of Toll-like Receptors
Ximena Leyva Peralta *Dept. of Chemistry*	Applying Machine Learning Green's Function Method for Studying Many-Body Effects in Silicon Nanocrystals
Nishah Jaferi *Dept. of Molecular, Cellular, and Developmental Biology*	Structural and Functional Differences Between LCK and LYN in B-Cell and T-Cell Signaling
Faith Pena *Dept. of Molecular Biophysics and Biochemistry*	Investigation of NonO Interactions with HIV-2 Capsid

Rachel Rivera *Dept. of Molecular Biophysics and Biochemistry*	Deciphering the Regulation of Pro-fibrotic Signaling by Mechanotransduction through Sun2-containing-LINC Complexes
Micky Rose *Dept. of Biomedical Engineering*	Investigating Nanoparticle Stability and Delivery Profile Improvement via Surface Protein Modification
Tori Sodeinde *Dept. of Molecular, Cellular, and Developmental Biology*	Characterizing Telomeric Chromatin Remodeling's Role in Ultrabright Telomere Formation
Wade Colley *Dept. of Physics*	Charge Transport Properties of the Electron Hole Material Copper-Thiocyanate (CuSCN) in Thin-Film Photovoltaic Cells (PVC)
Quazi Rumman Rahman *Dept. of Physics*	Measurement Free Error Correction in Bosonic Modes
Ignacio Ruiz-Sanchez *Dept. of Neuroscience*	Contribution of early life stress in inducing Tourette syndrome relevant pathology
Eric Wang *Dept. of Molecular, Cellular, and Developmental Biology*	Characterizing the Function of *V. cholerae* Biofilm Matrix Components in Protozoan Grazing Resistance

Estimating the effect size of cancer mutations in epistatic contexts with mutation timing information

Jennifer Wang[1, 2], Jeff Mandell[2], Jorge A. Alfaro-Murillo[2], Jeffrey Townsend[2]

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Understanding the genetic basis of cancer is foundational to research and treatment development, and there has been a surge of efforts to identify cancer-driving mutations. However, cancer mutations are frequently discussed in terms of their prevalence in the population, which does not always correlate with their contribution to disease. cancereffectsizeR is an R tool that decomposes a mutation's prevalence into the selective advantage it provides cancerous cells over healthy cells (the cancer effect size) and the gene's baseline mutation rate—which varies across genes, cancers, and stages of disease. This is especially helpful for investigating epistatic selection, where multiple mutations occur, and prior mutations change the context and thus mutation rate and effect size of subsequent mutations. However, due to the low number of patient samples containing various combinations of epistatic mutations, cancereffectsizeR's current model cannot estimate effect size for genes in less common epistatic contexts. By incorporating an estimate for the order in which the mutations occurred, a more nuanced model of epistatic selection was developed, and effect sizes for less common genes may be computed.

Engineering RNA Aptamers by Directed Evolution from a Natural TPP Riboswitch Scaffold

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Current human gene therapy approaches pose safety issues due to a lack of precise, external control of gene expression levels. One solution is the use of riboswitches in gene therapy. Riboswitches are gene regulatory elements typically found in the 5′ untranslated regions of messenger RNAs. With an aptamer domain that selectively binds a ligand and an adjacent expression platform that modulates gene expression, riboswitches provide a mechanism for ligand-induced gene control. Using Systematic Evolutions of Ligands by Exponential Enrichment (SELEX), synthetic aptamers that bind different compounds can be discovered. Here, a thiamin pyrophosphate (TPP) riboswitch aptamer is used as a scaffold for SELEX. After exposing the RNA pool to a four-compound collection (compounds A, B, P, S) for fourteen generations, the pool displays affinity for Compounds P and A by elution profile. The fourth most abundant sequence in the pool (14-4) has an affinity for branaplam (Compound B) as determined by in-line probing, with a dissociation constant (K_D) of 2.27 ± 0.15 μM. Optimizing aptamer affinity and grafting this aptamer onto a viable expression platform could yield a device that may eventually prove useful as gene regulatory devices for therapeutic applications.

Characterizing the Outgassing of Electronegative Impurities in nEXO

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Neutrinoless double beta decay (0vbb) is a hypothetical rare nuclear process that can occur if neutrinos are their own antiparticles, a property that might explain why matter dominates antimatter in the universe. nEXO is an upcoming project searching for this decay in Xenon-136 using a detector filled with 5 tonnes of liquid xenon. When 0vbb occurs, two neutrons decay into two protons, emitting a pair of electrons that carry the entire decay energy. The more efficiently nEXO reconstructs the electron pair's energy, the more accurately the decay energy is known and 0vbb can be separated from backgrounds. However, the outgassing of electronegative impurities via diffusion from detector materials compromises this reconstruction. Our study aims to quantify this diffusion of impurities, compare it across candidate nEXO materials, and develop a model to ensure that nEXO meets its design goals for electronegative impurities.

CFH1 Conservation Sheds Light on Functionally Essential Amino Acids

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The circadian clock is vital to imparting rhythmicity on downstream biological processes, making it both ecologically and agriculturally important. However, while circadian transcriptional regulation has been well studied, far less is understood about the clock's posttranslational mechanisms. Recent work has identified CLOCK-REGULATED F-BOX WITH A LONG HYPOCOTYL 1 (*CFH1*) as a novel circadian output tethering the clock to photomorphogenic growth via protein degradation, but much remains unknown about the protein structure and evolutionary conservation of gene function. By combining evolutionary analysis and structure-function analysis, we determined that CFH1 is widely conserved across land plants—even as far away as *P. patens* which diverged from flowering plants over 400 million years ago—and that this conservation is concentrated in two highly conserved domains: the F-box domain and a previously uncharacterized C-terminal domain. Within this C-terminal domain, we found that particular regions contribute to CFH1's hypocotyl regulation and PIF3 interactions, further illuminating its post-translational role in propagating circadian regulation and providing insight into potential functional orthologs in other species. Studying *CFH1* expands our understanding of how plants integrate various environmental and endogenous signals, and its role downstream of the clock creates new opportunities to regulate growth without disrupting the clock, presenting a novel avenue for future growth manipulation and crop optimization.

Investigating the effect of bacterial diversity on the evolution of *Pseudomonas aeruginosa* virulence in response to phage H6

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Antibiotic-resistant bacterial pathogens are a growing threat to human health. In 2019, the US CDC identified *Pseudomonas aeruginosa* as one of the most serious antibiotic-resistant threats. *P. aeruginosa* is implicated in a variety of human infections, including frequently infecting the lungs of individuals with cystic fibrosis (CF). Phages (viruses that infect bacteria) are an emerging therapy for these antibiotic-resistant infections. However, phage treatment can have effects beyond simply reducing bacterial populations. For instance, it can drive bacterial evolution, including of virulence traits. Moreover, this evolution can be altered by numerous factors, including the presence of other bacterial species. Despite this, how bacterial diversity alters phage-driven evolution of a target pathogen remains unclear. Here, we study the effect of bacterial diversity on the bacterium *P. aeruginosa* in response to phage H6, using *Staphylococcus aureus*, *Enterococcus faecalis*, and *Achromobacter xylosoxidans*. These species are known to co-infect CF patients with *P. aeruginosa* but are not susceptible to H6. We experimentally evolved *P. aeruginosa* in the presence or absence of H6 and the three other bacterial species. We observed evolution in bacterial virulence by measuring biofilm formation, pyocyanin production, growth rates, and motility. Ultimately, this work helps reveal how bacterial diversity can affect pathogen evolutionary responses to phage therapy.

Investigating the Effect of Titan's Hydrologic Cycle on its Surface Environment

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Titan, Saturn's largest moon, is the only world in our solar system with a hydrologic cycle and stable surface liquid other than Earth. Titan's distant orbit causes the surface temperature to be anaverage of 92.9 K allowing for hydrocarbons, such as methane and ethane, to be liquid on the moon's surface. The exchange of hydrocarbons from the subsurface methane table, surface lakes and seas, and the atmosphere create Titan's hydrologic cycle. This hydrologic cycle influences regional patterns of surface temperature, precipitation, and seasonal variation that create distinct climate regions on Titan. Using these three variables and taking inspiration from Earth's Koppen-Geiger Climate Classification we utilized the Titan Atmospheric Model (TAM) to create a climate map for Titan. Modeling Titan's climate regions can inform future missions to Titan aswell as contextualize the influence of a hydrologic cycle on a world. Since the Cassini-Huygens mission observed Saturn and Titan between 2004-2017 and Titan's orbit is over 29 Earth years, Cassini observed less than half of a full Titan year. This means that simulations such as TAM arenecessary to fill in the gaps in observed data. Dividing Titan into climate regions revealed that hydrologic and surface features such as the polar lakes and seas as well as equatorial surface features such as Titan's dunes influence the moon's climate. Creating this classification demonstrates the need for further research into the influence of hydrologic cycles and surface features on climate and emphasizes the importance of understanding climate on other worlds.

Investigating the role of histone deacetylation in critical periods of vertebrate neurodevelopment

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The modification of histones is a critical epigenetic regulation of gene expression that is necessary to correctly specify cells, especially in neurodevelopment. Histone acetylation is an epigenetic modification that works through the balanced addition of acetyl groups by histone acetyltransferases (HATS), and through the removal of these groups by histone deacetylases (HDACs). This balance during early development regulates chromatin accessibility during several physiological and cellular processes. Our lab screened zebrafish larvae for behavioral effects after treatment with HDAC inhibitors, as a readout for affected neurodevelopmental processes. We identified hyperactivity in zebrafish larvae after treating them with trichostatin A (TSA), a pan-histone deacetylase inhibitor. We hypothesized that the altered organismal behavior was due to the disruption to histone acetylation by TSA, which dysregulated normal gene expression and neural cell specification. To test this hypothesis, we are investigating the behavioral, cellular, and molecular phenotypes of zebrafish following TSA treatment. First, we characterized the behavioral parameters affected in the drug-treated zebrafish larvae in a highly quantitative manner using locomotor activity tracking. To understand the cell types that are most affected by TSA treatment, we are imaging different neural cell types, including glutamatergic and GABAergic cells, oligodendrocyte precursor cells, microglia, and astrocytes. Lastly, we are assessing how chromatin accessibility is affected in TSA-treated brains. Our ongoing work will provide insight into the effects of TSA on chromatin structure and will also elucidate the conserved roles of histone acetylation in normal vertebrate neurodevelopment and behavior.

Chimeric Parasites: A Novel Approach for Studying the Role of Cysteine-Rich Protective Antigen (CyRPA) across *Plasmodium* Species

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With an estimated 249 million cases and 608,000 deaths estimated worldwide in 2022, malaria remains a major global health concern. There are two approved vaccines for malaria, but the need for highly efficacious vaccines capable of inducing cross-strain protection remains. Subunit vaccines targeting members of the essential and conserved pentameric PCRCR protein complex have proven particularly promising as next-generation vaccine candidates. PfCyRPA (Cysteine-Rich Protective Antigen) is part of this PCRCR complex. Within *P. falciparum*, PfCyRPA is known to be essential, but the functions of CyRPA orthologs across all human Plasmodium species remain largely unknown. In this study, we find that PfCyRPA is susceptible to cross-strain neutralizing antibodies. In *ex vivo* inhibition assays using field *P. falciparum* isolates from a highly endemic region of Senegal, we found that anti-PfCyRPA monoclonal antibodies displayed up to 60% inhibition individually and up to 80% inhibition when used in combination with each other. The most inhibitory of these combinations was Cy.003+Cy.009 which displayed a mean inhibition range of 56.8% at 25 ug/ml and 81.30% at 200 ug/ml. We did not find evidence of cross-species inhibition when testing the same anti-PfCyRPA monoclonal antibodies against *P. knowlesi.* To further understand the role of CyRPA orthologues, we are currently generating novel CyRPA chimeric parasite lines in both *P. falciparum* and *P. knowlesi,* using all six human Plasmodium CyRPA orthologs. We aim to further characterize CyRPA chimeras for their potential as a cross-species malaria vaccine candidate.

Deciphering the relationship between PRDE-1 and transcriptional regulators in piRNA biogenesis in *C. elegans*

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The Piwi-interacting RNA (piRNA) pathway maintains germline integrity and fertility through the suppression of transposons and nonself nucleic acids. More than 10,000 piRNAs arise from a small number of discrete genomic regions on chromosome IV in *C. elegans*. The factors PRDE-1, SNPC-4, TOFU-5, and TOFU-4 are components of the upstream sequence transcription complex (USTC), which binds strongly across the piRNA gene cluster and is found to promote piRNA expression. Components of the USTC form distinct overlapping foci in the germ line. Recent literature demonstrated that the basal transcriptional regulator, TATA-Box-Binding Protein 1 (TBP-1), physically interacts with PRDE-1, however, the mechanism by which TBP-1 coordinates piRNA expression is unknown. To determine the spatial relationship between TBP-1 and PRDE-1, we performed super-resolution confocal imaging in living worms. We observed that TBP-1 forms multiple distinct foci in *C. elegans* germline nuclei. Surprisingly, we observe spatial-temporal variation in the level of colocalization of TBP-1 and PRDE-1 foci across germline development. We used Z-stack images to generate 3-D models to observe the extent of colocalization in multiple planes. By performing colocalization analysis, we find that TBP-1 and PRDE-1 foci colocalize in regions of the germline where mitotic divisions occur, however, in regions of meiotic divisions, we observe no colocalization. We will continue to investigate the observed spatial-temporal variation and its significance in piRNA biogenesis. This project will provide insight into piRNA biogenesis, germline-specific genomic regulation, and transcriptional mechanisms that have adapted to maintain germline integrity in a wide range of species.

Comparative Analysis of *TP53* Alleles in Pancreatic Ductal Adenocarcinoma

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The transcription factor p53 is a tumor suppressor capable of inducing cell cycle arrest, senescence, and apoptosis. Both truncating loss-of-function mutations and point mutations of the *TP53* gene (mouse gene *Trp53*), which encodes for the p53 protein, are frequently observed across human cancers. While point mutations in p53 result in loss of tumor suppressor function, recent studies suggest that these mutated proteins acquire pro-tumorigenic gain-of-function properties. To explore the differential functions of p53 point (R172H) and deletion mutants in cancer progression, we performed a comparative analysis of *Trp53* alleles *in vivo* using **M**osaic **A**nalysis with **D**ouble **M**arkers (MADM) in mice. MADM uses stochastic mitotic recombination to induce two genotypically distinct daughter cells expressing different *Trp53* variants dependent on the genotype of the mouse and simultaneously label them with unique genetically encoded fluorescent markers. By analyzing the ratio of fluorescently labelled cells, we studied the differences between alleles in driving pancreatic cancer. We found that p53 deletion^{-}cells exhibited greater tumor initiation and cell expansion compared to wild type and point mutant cells. However, point mutant cells were capable of facilitating the transition to advanced PDAC similar to p53 deletion cells. These phenotypic differences imply that p53 point mutants retains tumor suppressive properties in early pancreatic tumorigenesis, but is incapable of constraining progression to advanced disease, arguing that p53 point mutation is a separation of function mutation *in vivo*. Ongoing studies examining the molecular differences between *Trp53* alleles will shed further light onto the underlying mechanisms that explain these phenotypic differences.

Tracking Splicing Mutations in Leukemia

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Leukemia is type of blood cancer that originates in the bone marrow, causing the production of abnormal lymphocytes. In 2023, there were 59,610 new cases and 23,710 deaths due to leukemia in the US alone. Acute myeloid leukemia (AML) accounts for around 30% of all leukemia cases, and like all cancers, AML is largely driven by an accumulation of genetic mutations. The overall objective of this project is to investigate the role of recurrent mutations in AML to further our understanding of disease progression and severity. This project focuses on the role of spliceosome factor (SF) mutations due to their common recurrence, intratumor heterogeneity, and association with poor prognostic outcomes in myelodysplastic syndrome (MDS) and AML patients. To elucidate how these mutant SFs contribute to disease, we will utilize TRIBE-STAMP – a novel technique that allows single-molecule identification of target RNAs of multiple RNA binding proteins (RBPs) within the same cell. By utilizing TRIBE-STAMP, we can identify which RNA transcripts are bound by mutant SFs. This will be done by fusing mutated SFs to RNA deaminase enzymes (ADAR and APOBEC), which when bound, will edit the sequence of RNA transcripts (A to I, ADAR and C to U, APOBEC). Utilizing Bullseye, a pipeline generated by the Meyer Lab, we will determine the location of edits within the transcriptome. In combination with other data generated from my mentor and lab mates, the changes in sequence found in these data will be used to elucidate which RNA transcripts are stably or transiently bound by mutant SFs compared to WT SFs, and thus identify what cellular and biological pathways are affected by SF mutations, and provide insight into how these mutated proteins contribute to disease progression and severity.

Microvessel-on-a-Chip Model to Investigate the Role of TNF-α on Fibrotic Pericyte Signaling

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Fibrosis is the pathological scarring and thickening of tissue caused by the excessive deposition of extracellular matrix (ECM) components in response to injury. Fibrotic diseases can unfold in multiple organs and can lead to organ dysfunction and eventually total organ failure. Engineering an *in vitro* biomimetic microvascular model to simulate vascular dysfunction during fibrosis will allow us to study the mechanisms and propose treatments for the disease. To do so, we successfully developed a microvessel-on-a-chip model using AIM Biotech's commercial idenTx3 tri-channel chip. In the outer channel, we formed a microvessel comprised of human endothelial cells (ECs) and pericytes (PCs). In the middle channel, we injected rat-tail collagen I to form the extracellular matrix (ECM). The third channel serves as a perfusion channel for TNF-α and TGFβ-1, fibrotic and inflammatory signals. By perfusing the device with TNF-α and TGFβ-1, we can produce a fibrotic or inflammatory environment and observe whether inflammation drives the profession of fibrosis within a microvessel-ECM system.

Endothelial Targeting with Improved Nanoparticles for Specific and Localized Use

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In the past 10 years, there has been a push for more innovative approaches to drug therapy. While there have been significant gains, major obstacles for drug delivery remain, including low circulation time, diminished uptake by target cell types, and drug degradation: Challenges which are particularly important for nucleic acid delivery (i.e siRNA, mRNA, or dsDNA). Drug encapsulation in nanoparticles, which have a higher payload (dosage within) than the lone drug, better protects cargo from the physiologic environment and has improved surface tunability for different purposes. Our project focuses on a nanoparticle system to target endothelial cells circulating in the bloodstream. We use poly(lactic acid)-block-poly(ethylene glycol) (PLA-PEG) in combination with fragmented antibodies on nanoparticle surfaces to create a targeted and tunable system for encapsulating multiple drugs and therapeutics. The targeting approach using fragmented antibodies allows for direct targeting of the nanoparticle to specific cell types. Here, we show that our antibody cleavage methodology and nanoparticle formulations are valid through characterization assays for size, charge, and sulfhydryl groups. This approach has the potential for broad impacts on human health as it is tunable, precise in delivery, and versatile, which can decrease off-target effects and complications and promote an increased quality of life for patients.

Insulin-Resistant Huh-7 Cells as a Model of Nonalcoholic Fatty Liver Disease

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Hepatic *de novo* lipogenesis (DNL) is a complex metabolic process in which carbohydrates are converted into fatty acids in the liver. When this pathway becomes dysregulated, it can lead to higher risk of several diseases including nonalcoholic fatty liver disease (NAFLD), the most prevalent liver disease worldwide. NAFLD is often associated with insulin resistance. Because glucose is the primary substrate for DNL and insulin directly impacts glucose uptake, it is important to understand how insulin resistance affects DNL. Previous studies involving hepatic DNL in patients with NAFLD found an increased rate of DNL in these patients compared to healthy patients. However, hepatic DNL has not yet been studied in a cell culture model. DNL is difficult to observe in live cells because of challenges labeling and monitoring metabolic processes. Isotopic labeling is a nonperturbative method that can track glucose metabolism, but traditional IR microscopes lack the spatial resolution to monitor sub-cellular processes. We overcome these obstacles by using optical photothermal infrared microscopy (OPTIR), a super-resolution IR imaging technique, which we recently demonstrated can monitor rates of DNL in live cells. Huh-7 cells were overdosed with insulin to induce insulin resistance, then DNL was measured by the incorporation of ^{13}C-labeled glucose into lipid droplets. We found that DNL occurred at lower rates in insulin-resistant cells, contrary to the increased rates seen in NAFLD patients. These results call for more exploration of contributing factors to DNL regulation in relation to NAFLD.

Derivation and assessment of *de novo* and synthetic viral cheats

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Error-prone viral replication can result in defective genomes that act as cheaters, outcompeting wild-type 'cooperator' viruses that provide missing gene products upon coinfection. One type of cheat, defective interfering particles (DIPs), emerges readily *in vitro* during passaging at high multiplicity of infection (MOI) and has been found to reduce virulence, potently trigger immune responses, and promote persistent infection *in vivo*. However, the principles underlying cheat evolution and function are unclear, with evidence of some viruses developing resistance to and coevolving with their cheats. We experimentally evolved bacteriophage M13 and *Escherichia coli* for 26 passages and obtained *de novo* genomes with deletions in *trans*-acting genes such as capsid and replication-related genes. When mixed with wild-type M13, evolved phage from specific passages induce a reduction in titer, indicating potential cheat interference. We identified recombined genomes with differing deletion profiles, possibly suggesting a form of gene product complementation that mitigates the effect of cheats. We also tested the interfering ability of a synthetic M13 genome with all genes removed except those necessary for replication, theoretically serving as a 'model cheat.' Using growth curves, we found that the wild-type and synthetic genomes independently depress bacterial growth. Mixing the two depresses growth to an intermediate extent between the wild-type's and synthetic phage's effects. This research provides insight into the emergence and impact of DIPs of phage M13, establishing M13 and *E. coli* as a valuable and versatile model system to study fundamental aspects of viral cheating.

Regulation of Feeding-State Dependent Behaviors via Microbial Metabolites

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The "gut-brain-axis" can provide key insights into brain development and neurogenesis, and corresponding behavioral disorders and neurodegenerative disease. Studies have shown microbes colonizing the gut may regulate neurons via the production of neurotransmitters. There is evidence in animals that gut microbiota can impact host feeding decisions, which may benefit resident gut microbes. However, the molecular mechanisms by which gut microbiota impact host feeding behavior are not well understood. We are firstly interested in determining if and how naturally occurring gut commensals impact feeding and feeding-related behaviors using *C. elegans*. Tryptophan-derived metabolites such as serotonin or indole are known to be produced by gut microbiota in both mammals and *C. elegans.* I have preliminarily found that these tryptophan derivatives are important for regulation of feeding behavior in *C. elegans*. First, I will determine if gut-colonizing microbes regulate food ingestion behavior in *C. elegans* via modulation of serotonin receptor signaling pathways. Next, I will determine whether microbially-produced indole impacts host feeding preference via associative learning. The O'Donnell laboratory recently found that microbial indole affects *C. elegans* locomotory behavior circuit via incorporation into glucosides called modular glucosides (MOGLs). I will determine whether food choice behavior is driven by the same molecular pathway as *C. elegans* locomotory behavior. We will explore this behavior with chemotaxis assays paired with calcium imaging of worms grown on indole-producing versus non-indole producing bacteria. Better characterizing the role of gut microbiota in feeding will inform how essential behaviors emerge and are impacted by animals' internal and external environments.

Persistence Length of Chromatin in the Nuclear Context

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Over the past decade, chromatin has emerged as a major contributor to nuclear integrity by providing mechanical support for the nucleus to resist forces. Disruptions to chromatin structure compromises nuclear mechanics, leading to nuclear ruptures, DNA damage, and other nuclear dysfunctions, which are hallmarks of many human diseases. Mechanical properties of the chromatin, such as rigidity, are of particular interest as they underlie formation of chromatin structures, such as loops, and how different chromatin states and topological features impact nuclear mechanics. While the persistence length (i.e. rigidity) of bare, linearized double stranded DNA has been approximated as 150 base pairs (bp) or 50 nanometers (nm), the rigidity of chromatinized DNA is not well characterized. In vitro and in silico methods, such as Bayesian analysis, have yielded chromosome persistence length estimates ranging from 150-5,000 bp. Yet, experimental measurements are still lacking. Our lab has developed an assay in which various loci of chromosome II in the fission yeast *Schizosaccharomyces pombe (S. pombe)* are fluorescently labeled by integration of lacO arrays that bind GFP-LacI and the spindle pole body (SPB), is fluorescently labeled by Sad1-mCherry.Time-lapse fluorescence imaging of these yeast strains allows for visualization of how agitation of centromeres that are attached to the SPB which is continuously pushed by microtubules propagate from the centromeres along the chromatin fiber. Analysis of time lapses has revealed that the perturbations generated at the centromeres result in correlated motion of chromosomal regions up to several hundred kilobases away. Continued imaging and analysis of S. pombe with varying distant foci labeling will provide a quantitative dataset that can be compared to the semi-flexible polymer theory to estimate mechanical properties of chromatin fiber in live cells. Such an approach can be used to measure how chromatin rigidity changes under different stress conditions, such as osmotic shock or cellular aging. The knowledge of chromatin rigidity will allow us to decipher how chromatin impacts overall nuclear dynamics.

Characterizing Behavior and Brain Activity Phenotypes in Zebrafish Mutants of the Autism Risk Gene, *ADNP*

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Autism spectrum disorder (ASD) affects 1 in 36 children in the United States. ASD is a developmental disorder characterized by deficits in communication and social interactions, as well as restrictive and repetitive behaviors. One of the most common genetic causes of ASD is an *ADNP* mutation, accounting for 0.17% of all ASD cases. ADNP Syndrome affects various bodily systems and results from heterozygous loss-of-function in the *ADNP* gene. The mechanism by which *ADNP* affects neural development is not well described. To investigate this, the project aims to identify the behavior and brain activity phenotypes in zebrafish mutants null for the function of *adnp.* We performed behavior assays that generated a behavioral fingerprint for the mutants based on 24 behavioral parameters. We find that *adnpab* mutants show daytime hypoactivity and an increased visual startle response to a lights-on stimulus compared to wild-type fish. We then conducted immunostaining experiments to label pERK, an indicator of active neurons within the last 5-10 minutes before fixation, and tERK for total neurons. Whole-mount confocal microscopy and the Brain Registration and Evaluation for Zebrafish (BREEZE) pipeline were used to quantify changes in activity and volume in the *adnp* mutants. The brain activity analysis revealed that *adnpab*$^{+/-}$ mutants have increased activity in the telencephalon and the thalamus compared to wild-type fish; the brain volume analysis showed a decrease in volume of the optic tectum in *adnpab*$^{+/-}$ mutants versus wild-type fish. In summary, this study will provide insight into the circuit-level functions of *ADNP*, illuminating its contributions to neural activity and behavior.

Functional Effects of Altering HOX Gene Expression in Cancer Cells

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Accumulating evidence supports that the dysregulated expression of HOX transcription factors is involved in cancer biology; however, it is unclear whether there could be a unifying model on how the expression patterns of HOX genes impact human cancers. We observed that solid tumors frequently adopt a HOX expression pattern associated with posterior normal tissues. This observation prompted us to functionally interrogate HOX genes in cancer cell behaviors. One of my goals is to understand how cancer cell function is affected by the loss of posterior HOX patterns. To uncover this relationship, we aim to systematically examine the functional consequences of a complete series of paralogous HOX gene knockouts in multiple cancer cell lines using a loss-of-function genetic screen approach. This method can overcome potential functional redundancy among paralogous HOX genes. We observed that loss of specific HOX paralogs negatively impacts cancer cell viability and this effect is associated with their initial HOX patterns. This data suggests posterior HOX patterns are functionally important in maintaining solid cancer cells. An exception to posterior HOX patterning is seen in leukemia, cancerous blood cells, where its HOX expression pattern tends to be more analogous to expression in mid-body regions. I will further explore the functional effects of HOX dysregulation through overexpression of posterior HOX genes in leukemia cell lines to test the hypothesis that posterior HOX patterns are detrimental to leukemia. Through these experimental studies, I hope to better define the functional consequences of HOX gene dysregulation in solid cancer and leukemia.

Untethered Shape Change in Real World Deployment

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Pneumatic-enabled shape-changing robots have demonstrated efficient locomotion in real world environments. Field-deployable robots require robust, low energy, and adaptable hardware in order to be viable; however, previous shape changing systems are often tethered to large air compressors and valves for actuation. Here we present an untethered solution for pneumatic-based shape-change systems which address the requirements for deployable robots, an Pneumatic Control Unit (PCU). The PCU employs the use of a single miniature pump and four valves to allow for a variety of configurations corresponding to positive and negative pressure actuation and stiffness change. Quantifying the effectiveness of the system involved measuring the power consumption, actuation time, and positive and negative pressure values achieved by our PCU. This has allowed us to measure the cost of morphing and time taken to perform various functions such as inflation, deflation, jamming, and unjamming. We found that the PCU is a viable untethered solution for pneumatically actuated systems, despite morphing sequences taking more time than tethered solutions, the PCU still performs as well in terms of actuation pressure. We are able to eliminate external air compressors for pouch-based pneumatic actuation, which all consume more energy than the PCU. This system opens the door to untethered solutions for field-deployable shape-changing robots and can lead the way to future technologies which can fulfill the requirements for real world deployment without limitations of external pumps and valves with high energetic costs. We verified our system with the actuators of the Amphibious Robotic Turtle platform as a demonstration of utility.

Proteomics in the Medial Prefrontal Cortex of Mice Following Learned Helplessness

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Major depressive disorder (MDD) is a mood disorder that affects around 8.4% of the US population. While most current pharmaceutical treatments for depression work by modulating the monoaminergic or glutamatergic neurotransmitter systems, they are not effective for all patients, suggesting that depression is a multifaceted disorder with multiple etiologies. Therefore, the goal of this project is to study alternative systems that may be involved in MDD, such as the acetylcholine (ACh) neurotransmitter system. Mice that experience an inescapable stressor in the learned helplessness model of depression have elevated levels of ACh in the medial prefrontal cortex (mPFC). To discover the mechanisms behind these cholinergic increases we are studying the proteome of the mPFC in mice. To this end, we dissected the mPFC from mice that went through learned helplessness and ran these samples through a mass spectrometer to determine how inescapable shock changes the ACh-related proteome. Our analysis revealed differences in the concentration of 4 ACh receptors across our groups, with notable sex differences also apparent. Our analysis also identified alterations to the ACh Receptor and Synaptogenesis Signaling Pathways. Overall, this study further implicates mPFC ACh signaling and synaptic alterations in learned helplessness. This research may unveil potential biomarkers for MDD or targets for new pharmacological treatments. Future studies will assess the proteomes of mice resilient or susceptible to the stress of inescapable shock, which will increase our understanding of the individual differences that lead some individuals to develop MDD following stressful life experiences.

Investigation of Alterations of Interneuron Development in Tourette Syndrome Using Telencephalic Organoids

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Tourette Syndrome (TS) is a neuropsychiatric disorder characterized by involuntary motor and vocal tics which is thought to arise from alterations in the cortico-striato-thalamic circuitry controlling movement of the basal ganglia. Interneurons modulate this network at multiple stages and were found to be altered in number and distribution in TS. During embryonic development, inhibitory interneurons are generated within the ventral telencephalon and migrate to the cerebral cortex and basal ganglia. The morphogen sonic hedgehog (SHH) is central to the patterning of the ventral telencephalon. While previous work from our lab implicated differences in signaling downstream of SHH as a potential mechanism leading to the alterations in interneurons observed in TS, the developmental origins of these alterations are largely undefined. To investigate this origin, this project aims to elucidate the molecular mechanisms responsible for striatal interneuron differences observed in brains of patients diagnosed with Tourette's Syndrome using organoid models cultured from patient-derived induced pluripotent stem cells. This analysis aims to compare ventral versus dorsal cellular fates of telencephalic organoids. After 60 days of terminal differentiation, immunostaining revealed the presence of NKX2.1 positive cells in both ventral and dorsal protocols, while somatostatin (SST) and Choline acetyltransferase (ChAT) positive interneurons were consistently more abundant in the ventral forebrain condition and were less abundant or absent in the dorsal forebrain protocol. Combined, our results could potentially support the early neurodevelopmental origin of the alterations in inhibitory interneurons observed in TS and inform additional research into therapeutic targets.

Elucidating the Independent Roles of *tbx16* and *msgn1* in Presomitic Mesoderm Differentiation

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Throughout development, the same gene regulatory networks (GRNs) can produce a wide range of phenotypes using only a small set of genes, achieving a variety of outcomes in different contexts. Although GRN function is key to understanding development, it is challenging to investigate exactly how they work, due to issues of pleiotropy and redundancy amongst genes. Vertebrate body axis elongation involves a series of complex pathways incorporating tissue patterning, cellular differentiation, and tissue morphogenesis, tightly regulated by GRNs. The early embryonic tailbud contains bipotential neuromesodermal progenitor cells, which migrate within the tailbud and differentiate into mesodermal cells. These then move into the presomitic mesoderm and give rise to the somites that build the spine. *Msgn1* and *tbx16* are two well-characterized transcription factors that are critical for the differentiation of mesodermal progenitors. The phenotype produced in *tbx16;msgn1* double and single mutants, the latter of which are less severe, is well documented; however, the mechanisms driving their activities in spinal column development have remained largely unclear due to their semi-redundant activity. This genetic system allows us to study how specific transcription factors differentially regulate downstream GRNs and dynamic morphogenetic processes. We use the heat-shock promoter to drive expression of *tbx16* and *msgn1* to investigate how they control mesodermal differentiation and tissue migration during spinal column development. More broadly, this will give insight into how GRNs are regulated throughout development, as well as a better understanding of the dynamics of spinal column development, with far-reaching implications for human health and medicine.

Investigating the Relationship Between Titan's Methane Lakes and its Surface Temperature to Understand their Role on Variations in Titan's Climate System

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In gaining a perspective on the global climate of Titan, particular focus must be paid to the polarregions where the moon's lakes, Kraken and Ligeia in the north and Ontario in the south, reside.These lakes are composed of methane and are part of a larger hydrological cycle on Titan. Mapping the seasonality in surface temperature at Titan's lakes over 10 Titan years simulated through the Titan Atmospheric Model reveals anomalous surface temperatures around each location. At Kraken there is a significant yet unprecedented drop in temperature to 91.7 K in the spring of the ninth mapped year. Ligeia shows highly variable surface temperatures throughout its spring and summer, occasionally dropping to temperatures as low as 91.2 K, which is also thecoldest it gets during the northern winter. Ontario's spring and summer have the most variability,showing dramatic drops in temperature in the late summer of the first and eighth mapped year. Investigating these uncertainties will reveal important information about Titan's overall climate system and will be crucial to further understanding how hydrological cycles influence a planet ormoon's climate and will help to explain the implications of these behaviors.

Stability and Dynamics of Chemically Sensitive VlsE and Crowding Sensitive PGK

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Cellular environments are infinitely more complex than a test tube. The stability, dynamics, and function of biomolecules are modulated by the multitude of crowding and chemical interactions that they experience in the cell interior. These effects vary in different cell types, necessitating the study of biomolecules in their native environments. Methods of obtaining dynamic, time-resolved data from biomolecules in multicellular living organisms remain limited. My PI, C. Davis, developed a pipeline that combines meganuclease-mediated transformation with fluorescence-detected temperature-jump microscopy to quantify stability and kinetics of FRET-labeled protein in single cells of living zebrafish. This work showed that steric crowding could explain differences in the folding behavior of a crowding sensitive protein in zebrafish eye lens, myocytes, and keratinocytes (1). However, it remains undefined whether steric crowding also regulates the stability and dynamics of proteins more sensitive to non-steric chemical interactions. The aim of this study is to compare the stability and dynamics of a crowding sensitive protein, phosphoglycerate kinase (PGK), and a chemically sensitive protein, variable major protein-like sequence, expressed (VlsE), in living zebrafish tissue. We hypothesize that VlsE will be stabilized in the zebrafish eye lens due to the highly charged surfaces of β-crystallins. Comparison of fPGK melting temperatures obtained using the same methods demonstrated that fPGK is stabilized in cells compared to *in vitro*. Further comparison of the melting temperatures of VlsE showed that VlsE is greatly destabilized in the cellular environment compared to *in vitro.* This work will be used to interpret in vivo experiments in zebrafish.

Defining The Role of Persistent DNA Bridges in cGAS-STING Activation by PARPi (Olaparib) Treatment

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Breast and ovarian cancer are the second and fifth leading cause of cancer death for women in the United States, with individuals who are BRCA1 or BRCA2 mutation germline carriers having an increased risk. Deficiencies in homologous recombination (HR) caused by pathogenic BRCA1 and BRCA2 mutations generate genomic instability contributing to tumorigenesis and breast and ovarian cancers. As these mutations also confer an HR defect, they also generate hypersensitivity to Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi). PARPi, small molecules that bind and inhibit the activity of PARP enzymes, have been demonstrated in the clinic to be a promising treatment to target tumor cells in HR-deficient cancers. However, the mechanism by which PARPi induces cytotoxicity is poorly understood. Preliminary studies from our group suggest that surveillance of mitotic errors by the cGAS-STING innate immune sensing pathway plays a role in the PARPi response. We use BRCA-deficient and BRCA-reconstituted cells to analyze how cGAS-STING activation is achieved at PARPi-induced persistent DNA bridges in BRCA-deficient cells. Immunofluorescence of IRF3, a downstream target of cGAS-STING, shows that bridged nuclei cells contain higher nuclear:cytoplasmic (N:C) IRF3 compared to bridge-free cells. Additionally, RT-qPCR analysis of interferon-stimulated cytokines revealed that cytokine expression is increased with Olaparib treatment and decreased with BRCA reconstitution. Future work includes analyzing the role that the nuclear envelope repair network, which is thought to shield the DNA from innate immune sensing, plays in cGAS-STING signaling in BRCA-deficient, PARPi-treated cells using the N:C IRF3 ratio and interferon-stimulated cytokines expression as outputs. The findings of this project will contribute to designing robust diagnostic tools used in the clinic to help better match PARPi treatment to patients and could help provide a rationale for ongoing attempts in the clinic to combine PARPi with immunotherapies.

Characterizing Paracrine Regulatory Mechanisms through Dual Stimulation of Toll-like Receptors

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The innate immune system is the primary defense mechanism for humans against infection. It produces an inflammatory response and initiates the adaptive immune response. Toll-like receptors (TLRs) are membrane bound, pattern recognition receptors in the innate immune system. These receptors identify pathogen associated molecular patterns; repeated structures commonly associated with pathogenic organisms that are perceived as foreign molecules. When simulated, TLRs transmit signals through either MyD88 or TRIF pathways. These signals produce an inflammatory response by forming proinflammatory cytokines. Viruses and bacteria often activate multiple TLRs simultaneously, and previous research has shown that TLR signaling pathways that are activated simultaneously can result in a synergistic or antagonistic cytokine response. More specifically, it has been observed that the dual stimulation of TLR2 (MyD88) and TLR3 (TRIF) results in a synergistic response of key proinflammatory cytokines. To characterize other combinations of toll-like receptors, we stimulated TLR2 (MyD88) and TLR7 (MyD88) and TLR3 (TRIF) and TLR7 (MyD88). We used enzyme-linked immunosorbent assays (ELISA) to measure the cytokine production of TNF, IL-6, CXCL10, IFNB and determine if dual stimulation elicited synergetic responses. These results inform how infections, which activate multiple signaling pathways, affect inflammatory responses.

Applying Machine Learning Green's Function Method for Studying Many-Body Effects in Silicon Nanocrystals

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Computational methods have become essential in materials science research, accelerating the discovery and fine-tuning processes. Describing systems of multiple interacting particles and their resulting many-body effects is critical to obtaining the density of states (DOS), i.e., photoemission spectra, which provides key insights into the electronic and optical properties of materials. Many-body Green's functions (MBGF) offer a theoretical framework for understanding many-body effects and obtaining the DOS. Despite their accuracy, the high computational scaling of MBGF methods limits their large-scale application in computational discovery. The Zhu group has developed a machine-learning approach for obtaining MBGF results from mean-field MBGF (which assumes no particle interactions), thus bypassing computationally expensive calculation. A graph neural network (GNN) architecture with nodes representing single orbitals and edges representing the overlap of two orbitals was developed. This model has proven successful for organic molecules, and we now present the first proof of its extendibility to materials applications. A new GNN model was trained on 215 silicon nanocrystal structures (containing solely Si and H atoms) ranging from 10 to 36 Si atoms in size. We show agreement between the DOS obtained from MBGF results and the one predicted by the GNN model for (1) a $Si_{10}H_{18}$ structure part of the training data and (2) a $Si_{17}H_{26}$ test structure, demonstrating the validity of the GNN architecture for Si clusters. Future work will improve GNN accuracy through edge pruning and hyperparameter tuning and evaluate the model's extendibility to large clusters of 40+ Si atoms.

Structural and Functional Differences Between LCK and LYN in B-Cell and T-Cell Signaling

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Lymphocytes can be distinguished into T-cells and B-cells which constitute the cell-mediated and humoral immune defense against tumor cells, respectively. Such lymphocytes selectively express Src-family kinases, namely LYN, FYN, BLK, HCK, FGR, and LCK. Src family kinases are known to be highly evolutionarily and structurally conserved tyrosine kinases. They are largely expressed in a cell-specific manner. While LCK is uniquely expressed in T-cells with critical roles in TCR signaling and activation, LYN is primarily expressed in B-cells and BCR signaling. Despite their almost identical structure, LYN and LCK have opposing functions: LCK functions to amplify TCR signaling while LYN functions to attenuate BCR signaling. To our interest, we have found that cross-expression of LCK and LYN can be observed across B-cell malignancies. In an effort to understand the molecular basis of these kinases, our project aims to engineer a genetic knock-in of the inhibitory B-cell kinase LYN in the LCK locus of T-cells and knock-in of the activating kinase T-cell kinase LCK in the LYN locus of B-cells. This work will characterize the functional and structural significance of LYN and LCK in TCR and BCR signaling contexts.

Investigation of NonO Interactions with HIV-2 Capsid

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Human immunodeficiency virus type 2 (HIV-2) is a retrovirus that, if left untreated, proceeds to acquired immunodeficiency syndrome (AIDS) and death. HIV-2 affects millions of people worldwide, yet it has been understudied compared to HIV-1. While HIV-2 is less transmissible and progresses slower than HIV-1, the viruses share important characteristics like their viral life cycle. A key part of HIV's successful infection is the viral capsid (CA) protein's interactions with cofactors and restriction factors that promote or inhibit HIV infection, respectively. NonO is a known restriction factor of HIV-2 that is thought to interact with HIV-2 CA in the nucleus. NonO reduces infectivity of HIV-2, but it does not well restrict HIV-1. Current data indicates this may be due to differential binding between NonO and HIV CA proteins. Our objective is to gain a mechanistic understanding of NonO's interactions with HIV-2 CA lattice by elucidating the structure via cryo-electron microscopy (cryo-EM) and biochemical assays. We have purified to homogeneity a NonO construct (35-312) containing relevant domains that interact with HIV-2 CA. We aim to validate that NonO binds preferentially to HIV-2 CA compared to HIV-1 CA. We also identified biophysical characteristics of the interaction. Initial negative stain and cryo-EM imaging of the complex revealed that the capsid lattice is maintained in presence of NonO. Optimization of freezing conditions will be performed to obtain a high-resolution structure. We intend to generate an atomic model of the interaction, which would reveal details of HIV-2 biology and provide information about HIV-1 restriction escape.

Deciphering the Regulation of Pro-fibrotic Signaling by Mechanotransduction through Sun2-containing-LINC Complexes

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Cellular communication relies extensively on mechanical signaling pathways, with the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex, which spans the nuclear envelope, serving as a direct mechanism for delivering mechanical signals into the nucleus. Deletion of Sun2 in murine models has demonstrated protection against pulmonary fibrosis, including decreased expression of TGF-β target genes that encode components of the extracellular matrix, *in-vitro*. However, our preliminary work shows that the TGF-β pathway remains activated, despite ablation of Sun2. Our research aims to elucidate how Sun2 exerts this influence on the TGF-β pathway. Modeling fibrotic conditions in vitro, using type-2 alveolar epithelial cells and substrates of defined stiffnesses, I will use genomics techniques such as CUT&RUN and ATAC-Seq, to determine how SMAD 2/3 binding and chromatin accessibility at TGF-β target gene promoters are regulated by SUN2. Optimization experiments highlight challenges in DNA yield, prompting us to refine protocols for enhanced efficiency. Anticipated outcomes include the observation of decreased SMAD 2/3 binding at pro-fibrotic gene promoters in SUN2-deficient cells, suggesting that SUN2 primes chromatin for SMAD2/3 binding. These findings promise insights into the mechanisms underlying LINC complex-mediated fibrosis and nuclear mechanotransduction. Further studies will explore the positioning of SUN2-regulated genes in the nucleus by fluorescence in situ hybridization and further in-vivo experiments using mouse models. This comprehensive investigation holds the potential to advance our understanding of fibrosis pathogenesis and unveil novel therapeutic targets in combating fibrotic diseases.

Investigating Nanoparticle Stability and Delivery Profile Improvement via Surface Protein Modification

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In utero gene therapy (IUGT) has the potential to address genetic disorders at the earliest stages of development, mitigating the pathological changes that accumulate after birth. From the variety of potential delivery vector platforms for gene therapies, polymer-based nanoparticles (NPs) are a promising option for *in utero* applications due to their customizability, biocompatibility, and relative ease of administration via the amniotic fluid (AF) space. However, a considerable barrier to NP delivery is the rapid adsorption of endogenous proteins to the particle surface, a process which changes NP biological fate and often decreases delivery efficacy. Previous responses to the challenge of this protein corona (PC) formation include methods to reduce or eliminate protein adsorption. Our approach aims to purposefully design the PC, taking advantage of its role in NP fate to increase desirable delivery outcomes. We first investigated the type and extent of protein adsorption to several polymer-based NPs to assemble stability profiles for key NP characteristics. We then formulated NPs with a single protein PC (SPPC) comprised of vitronectin (VTN)– an abundant glycoprotein with roles in cell adhesion and immune regulation, among others. By examining *in vitro* uptake in different cell lines, we found that SPPC-NPs had higher cellular uptake than their counterparts with either no PC or a natural forming PC. Understanding the effect of the PC on NPs and how we might use this effect to optimize NPs for therapeutic delivery has important implications for the successful translation of NPs for IUGT from the bench to the clinic.

Characterizing Telomeric Chromatin Remodeling's Role in Ultrabright Telomere Formation

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Telomeres are nucleoprotein complexes at the end of chromosomes composed of characteristic DNA repeat sequences and associated proteins. The telomeric shelterin complex, composed of six proteins, provides protection against DNA-damage sensing mechanisms that would recognize telomere ends as broken DNA and promote aberrant DNA repair that leads to chromosomal fusions. Previous research in our lab has shown that TRF2, telomeric-repeat binding factor 2 (TRF2), a shelterin protein whose basic domain ($TRF2^{B}$), cooperates with Rap1 to prevent telomeres from undergoing homology-directed repair (HDR), a type of DNA repair.[1] When TRF2's basic domain is either deleted ($TRF2^{\Delta B}$) or mutated to prevent it from recruiting Rap1 ($TRF2^{L286R}$), telomeres aberrantly engage in HDR, leading to clustering of multiple telomeres into structures termed ultrabright telomeres (UTs). When $TRF2^{B}$ is deleted but Rap1 is present, UTs form at lower frequencies than when Rap1 is absent.[1] We aimed to understand the mechanism of Rap1 and $TRF2^{B}$'s protective roles against HDR. We found that the chromatin modifier ATRX is recruited to telomeres by an unknown mechanism when $TRF2^{B}$ is deleted, but when Rap1 is additionally removed, ATRX is no longer recruited and more UTs form. Thus, we hypothesized that UT formation is facilitated by telomeric chromatin decondensation that allows for HDR-mediated telomere fusions, and that Rap1 controls this process indirectly, since it does not bind directly to ATRX as shown by co-immunoprecipitation. Rap1 is a known chromatin modifier in yeast, but not in mammals. Defining a chromatin-modifying role for Rap1 would advance our understanding of a crucial telomeric protein's roles and of the many ways in which shelterin protects telomeres.

Charge Transport Properties of the Electron Hole Material Copper-Thiocyanate (CuSCN) in Thin-Film Photovoltaic Cells (PVC)

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Photovoltaic solar cells (PVC) are one of the most promising alternatives to fossil fuels for their relatively cheap manufacturing cost and high power conversion efficiency. Despite its massive potential to replace carbon-emitting energy sources, PVC development has slowed due to an efficiency bottleneck centered around the hole-transport layer. A recent breakthrough for this has been the material Copper-Thiocyanate (CuSCN). CuSCN is a hole-transport material with massive potential for increasing PVC stabilization and device performance. Previous research investigated the charge transport mechanism of CuSCN via ultra-vacuumed, cryostat conductivity testing. The result was the Variable Range Hopping (VRH) model of transport. In our experiment, we extend the scope of this research by examining the specific variables of the VRH model with respect to conductivity testing of CuSCN thin-film cells. We found an unusual increase of room temperature conductivity proportional to the aging delay after fabrication, as well as a strong influence of the T_O parameter—and thus density of states and inverse correlation length—on the final conductivity.

Measurement Free Error Correction in Bosonic Modes

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Quantum computing has witnessed a remarkable surge of interest over the last two decades due to its potential to surpass the capabilities of classical computing in tasks including cryptography, simulation, and optimization. However, the realization of practical and scalable quantum computers at present faces a major obstacle: error correction. Qubits are highly susceptible to decoherence from external noise and gate imperfections. While quantum error correction (QEC) protocols, such as surface codes, color codes, and topological codes, have been developed to address these challenges, they traditionally rely on measurement operations that introduce additional concerns such as measurement-induced decoherence. Here we introduce a novel measurement-free error correction approach that utilizes dynamic steering and autonomous feedback mechanisms to naturally evolve quantum systems into error-corrected states, eliminating the need for external measurements and real-time classical control. Our research focuses on implementing this measurement-free protocol in superconducting circuits, leveraging the advantages of bosonic cavity modes encoded with the binomial code. Superconducting circuits are chosen for their balance of coherence, control, and scalability, making them ideal for high fidelity QEC protocols. This approach represents a significant advancement in the pursuit of fault-tolerant quantum computing, offering a promising path toward the realization of scalable and practical quantum computers.

Contribution of early life stress in inducing Tourette syndrome-relevant pathology

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Tourette's syndrome (TS) and other tic-like disorders are a group of neurodevelopmental disorders characterized by motor and vocal tics with a characteristic developmental trajectory. Symptoms usually arise in mid-childhood, peak in early adolescence, and decline in severity in early adulthood. TS symptoms usually arise through interactions of genetic and environmental influences over the course of development, and markedly occurs more prevalently and earlier inmales. Clinical studies have identified early psychological and physical stress, which can be modeled in preclinical research using early life stress (ELS) paradigm, as significant risk factors for the onset of TS and other tic disorders. We apply this ELS paradigm on mice, and compare the impacts of stress on the early development of TS symptoms. We have observed that ELS increases grooming time and increases tic-like head-body twitches in only adolescent male mice, reminiscent of the male preponderance and developmental trajectory in human TS. Stressed mice also show reduction in size of the striatum, involved in higher neurological processing and motor control, and in the number of critical interneurons involved in regulating acetylcholine in the striatum. Similarly, we find significant male-specific neuroinflammation in thedorsal striatum of adolescent mice and increased activity in mPFC neurons that project to the dorsal striatum in stressed mice, suggesting ELS abates control of motor commands observed in human TS. Under this framework, our future studies will examine the sexual dimorphism of ELS-promoted onset of TS symptoms in the developmental trajectory, ushering the development of sex-specific intervention and prevention strategies.

Characterizing the Function of *V. cholerae* Biofilm Matrix Components in Protozoan Grazing Resistance

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In its natural environment, *Vibrio cholerae*, the causative agent in the diarrheal disease cholera, persists often in biofilm form. Biofilm structures arise in response to environmental stressors, strengthening resistance to chemical and physical disturbances. In particular, biofilms deter grazing by protozoa, allowing *V. cholerae* colonies to resist predation and survive during inter-epidemic periods. While the protective nature of fully-formed biofilms is apparent, the role of its constituent elements in generating this mechanism of defense remains largely unknown. Therefore, characterizing the function of biofilm matrix components in the context of predation resistance will elucidate further functionalities of this lifestyle employed by numerous bacterial species. To this end, we break down the *V. cholerae* biofilm into its main structural components, namely the matrix proteins RbmA, RbmC, and Bap1, as well as the exopolysaccharide VPS to investigate the necessity of each matrix component in forming a robust deterrence to predation. Through coincubation experiments of the protist *Tetrahymena pyriformis* with *V. cholerae* mutants with various knockouts of biofilm-matrix components, we measured protist growth rates as a proxy for the efficacy of predation resistance. We found that the presence of matrix protein RbmA limits the efficacy of protozoan grazing. Furthermore, our data suggest that the distribution of matrix components and the quality of the matrix play an important role in determining the defensive capabilities of a biofilm. For rugose strains, the medium-density biofilm provided the greatest degree of protection against protozoan predation, indicating an optimal biofilm growth pattern that maximizes predation defense.

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