HARVARD COLLEGE
PRISE
PROGRAM FOR RESEARCH IN SCIENCE AND ENGINEERING

HARVARD COLLEGE
bliss

HARVARD | BUSINESS | SCHOOL
PRIMO
Program for Research in Markets and Organizations

HARVARD COLLEGE
SHARP
Summer Humanities and Arts Research Program

Harvard College ❁ Harvard Global Health Institute
SURGH
SUMMER UNDERGRADUATE RESEARCH IN GLOBAL HEALTH

Abstracts | 2015

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Letter from the Director

I am pleased to introduce the abstracts of the 2015 Harvard College Summer Undergraduate Research Village, comprised of PRISE (the Program for Research in Science and Engineering), BLISS (Behavioral Laboratory of the Social Sciences), PRIMO (the Program for Research in Markets and Organizations), SHARP (Summer Humanities and Arts Research Program), and our latest addition, SURGH (Summer Undergraduate Research in Global Health). These five programs together form a robust, active, and interdisciplinary residential community of scholars focused on research working with Harvard faculty in formative and substantive projects over ten weeks of the summer.

2015 is a particularly auspicious year, as it also marks the tenth anniversary of PRISE, the foundation program for what has become our Research Village, as well as our return to Leverett House, now that renewal is complete and the facility fully supports the full range and volume of intellectual and social undertakings the Research Village offers throughout the summer.

This summer the fellows have been particularly active—I very much appreciate the synergy of engaged and enthusiastic participants, creative and thought-provoking activities, and well-designed physical spaces that combined have created an unforgettable experience.

Further, as the impressive abstracts in this collection suggests, the 200 fellows across our Research Village programs have committed deeply to interesting and inspiring projects with their Harvard faculty hosts. As you will see, the extraordinary array of experiences tells a persuasive story about the value of a summer devoted to research.

To each and every PRISE, BLISS, PRIMO, SHARP, and SURGH fellow, I wish the best of success as you continue to pursue your academic interests, and hope that the relationships you have nurtured over these weeks as a resident of the Summer Undergraduate Research Village continue to thrive going forward.

Yours truly,

Gregory A. Llacer
Director, *Harvard College Office of Undergraduate Research and Fellowships (URAF)*
Director, *Harvard College Program for Research in Science and Engineering (PRISE)*

Letter from the Editors

Dear PBPSS Fellows,

The Harvard Undergraduate Research Village has been a breeding ground for great ideas. Through the collective efforts of scientific PRISE, thoughtful BLISS, artsy SHARP, determined PRIMO, and worldly SURGH, we have all broadened the scope of our knowledge. This taste of the PBPSS community and the possibilities it offers for the future has whet our desire to learn from our peers and the world around us. We have supported each other in our pursuit of knowledge, overcome the frustrations of conducting research, and, while doing so, forged an unshakeable bond. Memories of amazing outings, great successes in the laboratory, and exciting nights in the common rooms will always hold our community together.

This has been a truly unforgettable summer, and indeed, some may say too brief a summer. Though we may feel a sense of loss as we walk away from Leverett House and leave the great summer weather behind, we will always have amazing memories to cherish and friendships to last a lifetime. This book contains the descriptions of the projects you and your fellow PBPSS peers have been tirelessly exploring this summer. It is our great pleasure to present to you the culmination of this summer's research. Congratulations on an unforgettable summer!

All our best,

Daniel W. Chen '17, Michelle K. Li '17, Monica Lin '17, Jiho Park '18, and Dylan Tan '17
Editors-in-Chief

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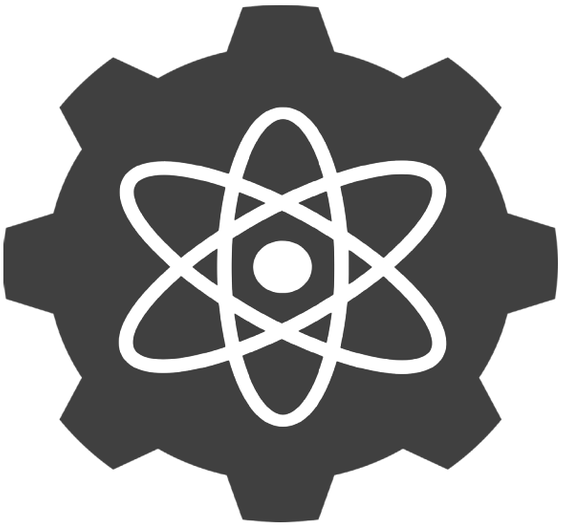

PRISE

Program for Research
In Science and Engineering

Abstracts | *2015*

ASTRONOMY & ASTROPHYSICS

Windows in the Sky: Improving Ground-Based Astronomical Observations by Identifying Spectral Windows in the Earth's Atmosphere

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As light approaches Earth, much of it is refracted by the air molecules in the atmosphere, effectively blurring the light by the time it reaches the ground. This distortion, a function of wavelength, limits the resolution achievable by telescopes on Earth. For observing planets around other stars, this is especially problematic, as extremely precise observations are required to resolve the characteristics of exoplanets. The traditional method to bypass this problem relies on space telescopes. However, there are a limited number of space telescopes, while the number of discovered exoplanets grows at an increasingly fast rate. For this reason, it would be beneficial to be able to take precise observations from the ground. Not only are ground-based telescopes more plentiful, they are also more cost-efficient and can be continually upgraded. Ground-based telescopes can also be more powerful, as the size and sensitivity of a space telescope are limited by its need to survive the trip into orbit. The alternative method examined in this project seeks to improve ground-based observations by defining wavelength bands for which atmospheric distortion is minimal.

Current ground-based observations are carried out by collecting light using wide, historically-defined filters. These filters struggle because they collect light of wavelengths that are strongly affected by the Earth's atmosphere, making it impossible to obtain extremely high-resolution data. This project seeks to define a new set of bins, optimized to filter out wavelengths that experience atmospheric distortion. By doing so, we will be able to obtain observations from the ground with comparable precision to data taken from space. The program produced over the course of this summer will return ideal bin sizes for observations at wavelengths between 540 nm and 800 nm that are wide enough to reduce variance due to random fluctuation, but narrow enough to avoid wavelength ranges for which the Earth's atmosphere is unstable. Future work will expand the wavelength ranges for which we can seek these spectral windows. Ideally, this project will dramatically increase the number of telescopes that are able to perform high-resolution exoplanet observations.

The Physical Properties of the Bones of the Milky Way

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Studying the structure of our Galaxy, the Milky Way, is uniquely challenging, as we cannot gain an outside perspective on it due to our location within it. Because of this, many fundamental questions about the nature of our Galaxy—how many spiral arms does it have, what is the structure between these arms, etc.—remain. In their 2014 paper, "The Bones of the Milky Way," Goodman et. al proposed that it is possible to use very long filamentary infrared dark clouds to trace out our Galaxy's spiral arms and to probe our Galaxy's underlying structure. In this analogy these cold, dense giant molecular clouds are the 'bones' that can be used to study the 'skeleton' of the Milky Way. In my research, I examined ten such clouds, that have been identified as likely candidate 'bones', by Zucker et. al in their forthcoming paper, "The Skeleton of the Milky Way." Using infrared data from the Spitzer and Herschel space telescopes as well as radio data from five separate surveys, I was able to measure the masses, temperatures, and velocity profiles of these clouds. These measurements can be compared to similar measurements from simulations, to contribute to our understanding of the structure and nature of these clouds, and thus, our Galaxy.

An Examination of Starspot-Induced Radial Velocity Shifts and Future Application to Kepler-78

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A starspot is a cool, dark stellar surface feature caused by an enhancement in the local strength of a star's magnetic field, resulting in a suppression of convection. As a star rotates, the presence of starspots creates an imbalance in the flux between the approaching and retreating sides of the stellar disc. This imbalance results in a periodic shift in the apparent radial velocity (RV) of the star (its velocity toward or away from observers). However, similar RV shifts are also caused by planets that orbit the star (exoplanets). Since starspots are quite common, they often act as a significant source of noise when the RV method is used to detect exoplanets.

Often, starspot-induced RV shifts are modeled with little or no physical motivation. However, this approach recovers essentially no information about the physical properties of starspots. We develop a starspot model that uses all available RV data (as well as data on the changing shape of the spectral lines) in order to characterize both an exoplanet and starspots simultaneously. Our model is physically motivated, and therefore reveals much more about the exoplanet's host star, while still recovering essential exoplanet information such as planetary mass. Our method will be applied to Kepler-78, a system for which there is very little starspot information, though starspots affect RV data from the system significantly. A direct extension of this project will be to model starspots at various observation wavelengths and analyze how the starspot to star contrast ratio changes, providing strong constraints on the temperature and size of starspots.

This research will provide valuable results on the effectiveness of using physically motivated models for RV data, which could potentially result in new methods for detecting exoplanets in systems plagued by significant starspot-induced RV noise. This would allow for the discovery of smaller, longer period planets than is currently possible, bringing us one step closer to the discovery of an Earth-like, habitable planet.

BIOENGINEERING

Synthetic Shark Fin

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Each year, upwards of 100 million sharks are finned and thrown back into the ocean— wasting a majority of their meat— for use in Shark Fin Soup, a delicacy in parts of Asia. Continued demand for this dish puts shark populations at risk and decreases the ocean's biodiversity through the loss of apex predators, sharks. Apex predation also results in the accumulation of toxins in shark tissues that pose health risks to consumers. A synthetic alternative to shark fin would be able to lessen the health and environmental impacts of shark finning. We hypothesized that tissue engineering principles, based on recapitulating the structure and biochemistry of the natural fins, could be used to design and build synthetic fins indistinguishable from natural fins and safer for human consumption. To test this hypothesis, we first examined natural shark fins to identify their essential functions and properties. Synthetic fins were then constructed using edible polysaccharides and bioproteins, which were compared with natural fins.

The shark fin as a whole is not the quintessential aspect of creating a tissue engineered synthetic shark fin, rather it is a collagenous ray found within the shark fins. These rays give the texture to shark fin soup that is so highly prized in Chinese cuisine. The unique consistency is due to elastoidin, a type of collagen only found in sharks. Individual fin rays isolated from Dogfish sharks were found to contract on heating, shrink when cooled, and possess excellent shape recovery upon hydration. Scanning electron microscopy revealed a densely packed highly anisotropic (linear) fibrous substructure to the rays. Edible fin rays produced using alginate and gelatin precursors appeared and tasted similar to natural rays but failed to possess similar shape memory. Future work will focus on mimicking the natural ray shape memory using the structural characteristics identified here.

Point-of-care Drop-based Microfluidics Platform using Isothermal Amplification for the Quantitative Detection of *Mycobacterium tuberculosis*

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Tuberculosis (TB) is a serious global health problem with 9 million new cases and approximately 1.5 million deaths worldwide every year. A majority of TB deaths are caused by late or unavailable diagnosis. Given the availability of effective treatment strategies for TB and the extremely frequent airborne transmission of the pathogen *Mycobacterium tuberculosis*, it is vitally important to detect TB at an early stage in patients. Current diagnostic tests, including sputum sample microscopy and the Mantoux skin test, are very slow and characterized by many false-positive results. Thus, a rapid point-of-care diagnostic for TB remains an unresolved challenge.

Nucleic acid amplification tests (NAATs) have shown great promise in quickly detecting genes of interest with high specificity and sensitivity. This study employs the combination of a drop-based microfluidics platform and isothermal DNA amplification to create a breakthrough technology that enables the detection of TB bacteria from the bloodstream or sputum. Advantages of drop-based microfluidics include reduced sample size and reagent consumption, short processing times, and enhanced sensitivity. In our device, TB DNA is rapidly encapsulated in microfluidic drops (water-in-oil emulsions), amplified using loop-mediated isothermal amplification (LAMP), and detected via fluorescent signal. The method allows for all steps, including emulsification with a pipette, amplification at a single temperature, and quantitative detection from a reservoir, to be done on-chip in less than 1 hour. Imaging and quantification of fluorescent drops (indicating the presence of TB DNA) can be achieved by a simple color camera. Such a microfluidic technique would allow for rapid TB diagnosis to be done directly from the blood/sputum in resource-poor locations of the developing world.

-Withheld for Confidentiality-

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-Withheld for Confidentiality-

3D Printing of Vascularized Tissue Constructs

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The three-dimensional (3D) printing of biological materials holds vast promise for the pharmacological and biomedical fields. Since 3D cellular environments more accurately represent human physiological conditions than do 2D environments, they can improve the differentiated state of cells cultured in vitro such that they behave and respond to various stimuli as they would in vivo.

One limitation of 3D bioprinting has been the inability to print vasculature, or channels through which blood flows to transport nutrients and waste throughout the body. Vasculature in conjunction with printed tissues can remain viable for extended periods of time. This summer, I worked with the Lewis Laboratory to print two primary models of embedded tissue vasculature: first, lines arranged in parallel, and second, a convoluted path. A gelatinous extracellular matrix encompassed the structures to provide structural and biological support, and the printed

lines were evacuated to leave behind hollow channels embedded in the matrix. The channels were ultimately seeded with either endothelial or epithelial cells, and after the cells adhered to the inner lining, they were perfused with liquid containing nutrients to model the flow of blood through a cell-lined vessel in the body.

Since 3D cellular environments are more physiologically relevant than 2D environments, drug studies and functionality assays performed in 3D cultures may provide greater insight into drug efficacy, drug toxicity, and cellular behavior. By analyzing the response of cells to the flow of proteins such as albumin and toxins such as cyclosporin A through 3D printed channels, we studied the impact of the third dimension on improving biomimetic accuracy of the cellular culturing environment. We hope to use 3D bioprinting to enhance pharmacological drug testing and screening as well as to ultimately provide a mechanism for the printing of tissues and organs on demand.

Encapsulation of Lambda Bacteriophage for Delivery to the Gut

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Inside the human intestinal system there is an entire microcosmic universe, filled with interacting microbes. Gut microbes can affect our health in many ways, influencing our weight, causing diseases, and even inducing cancer. Along with bacteria, the gut also contains bacteriophages (phages), which are bacteria-specific viruses. Because certain phages integrate themselves into the host's genome, they can be genetically manipulated to shut off toxin producing genes in bacteria. Our project is to encapsulate a well-documented phage, lambda phage, and to deliver it to the gut in a protective oral formulation. Success with lambda phage will show that delivering phage therapies to the gut is possible.

There are several obstacles to getting functional phage into the gut. Because of the high acidity and proteolytic activity of the stomach, we will have to encapsulate the phage in a protective coating. To do this, we will put the phage in a particle of alginate (a derivative of seaweed) and wrap the particle in multiple polymer layers in order to prevent it from being inactivated. The second step is to release the phage from our particle by degrading the outer layers without harming the phage. Preliminary experiments show our polymer layers remain intact during prolonged incubation in acid. We have also created an alginate particle with phage and shown it can be degraded while still releasing active phage. Recently, we have been working on putting both steps together to create an alginate particle with polymer coating that releases functional phage.

Potential Therapeutics for Treating Traumatic Brain Injury through the Identification of Changes in Protein Expression

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Traumatic Brain Injury (TBI) is brain dysfunction caused by an external force, typically a violent blow to the head. TBI can lead to loss of consciousness, memory loss, neuronal death, brain atrophy, and neurodegenerative disease. Moreover, it is the leading cause of disability and death for children and adolescents. Currently, there are no biomarkers approved by the FDA to identify TBI and no drugs available to treat TBI.

We employed bioinformatics tools to identify the main changes in protein expression that occur following TBI. From these main changes, we pinpointed key proteins that can be targeted by drugs to minimize the cascade of micro- and macro-level pathologies characteristic of TBI. As part our research, we analyzed mass spectrometry data of neuronal cultures injured by magnetic twist cytometry (MTC). This vast data, of approximately 2500 detected proteins, was then sorted based on significant changes in expression compared to the uninjured control, on metabolic and cytoskeletal function, and on the existence of drugs associated with these proteins. The drugs identified from these series of filters were further sorted based on the ability to cross the blood-brain barrier (BBB), the guard to the brain consisting of endothelial cells connected by tight junctions. Subsequently, our research focused on the optimization of protocols for dosing *in vitro* neuron cultures with these drugs.

The findings of our studies provided the foundation for future research on the efficacy of these drugs in TBI treatment through the examination of their effects on injured neuron electrophysiology. Given that these identified drugs are already approved by the FDA for other purposes, we expect the results of our innovative research to allow for a faster translation from lab work to TBI therapeutics.

Construction of Vascularized Tissue Constructs via 3D Bioprinting

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Tissue engineering, the process through which functional cells and connective materials can be organized into larger functional tissues and organs, is a rising field with great potential in drug screening, tissue replacement, and understanding the processes of wound healing and general cell organization. Using a novel technique for creating cell-laden tissue constructs via the deposition of cells and biocompatible materials in three dimensions (termed '3D bioprinting'), a number of questions can be investigated simply by modifying the types of cells, patterns of vascularization, and other parameters.

In the first project, open channels were constructed in a gelatinous matrix and seeded with epithelial cells. Via perfusion of growth media through the channels at biomimetic rates, the channels could be kept at a steady state for future experimentation. Experiments were geared towards a) generating constructs that would be as stable and biomimetic as possible and b) examining the response of the seeded cells to certain stressors.

In the future, we plan to investigate how the geometry of the vascular networks affect the structure and behavior of these self-assembling structures. One potential application of this investigation is the patterning of channels with varying diameters and spacing in order to observe changes cell-cell interaction and angiogenesis.

Reuseable TiN Plasmonic Structures for Intracellular Delivery

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Developing a method to efficiently deliver drugs and biomolecules such as DNA into cells is an important area of biomedical research. Intracellular delivery relies on porating cells' membranes to allow exterior molecules to efficiently enter the cell while maintaining high viability. Various techniques, including viral vectors, electroporation, and optoporation, can perform intracellular delivery, but come with significant drawbacks such as high cell death, low throughput, and low efficiency.

We present a new laser-based delivery method that uses a pulsed laser to excite plasmonic Titanium Nitride (TiN) nanostructures for cell poration and offers high efficiency, viability, and throughput. ""Plasmonic"" is a term used to describe the collective oscillations in the Titanium Nitride's free electrons upon laser irradiation. This research explores the use of TiN as a material for these laser-activated nanostructures due to its high robustness and thermal stability. We investigate different fabrication conditions to maximize plasmonic enhancement and stability after prolonged laser exposure. We deliver dye molecules, siRNA, and microspheres to cells to quantify poration efficiency and viability by imaging the target cells at defined time intervals post laser irradiation. Additionally, we use scanning near-field optical microscopy (SNOM) and scanning electron microscopy (SEM) techniques to study nanostructure damage and plasmonic characteristics. Overall, TiN presents a strong opportunity for use in future biomedical devices for intracellular biomolecular delivery and regenerative medicine.

Characterization of Muscular Adaptation Patterns during Powered Soft Exosuit Walking

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Many of us walk for miles each day, but take for granted how carefully orchestrated the process of moving ourselves forward from one leg to the other actually is. Muscles in the legs must fire at precisely the right time to generate a stable, efficient gait. Specifically, for military personnel walking over long distances with heavy backpacks, walking can be a taxing endeavor. In order to decrease the energy expenditure associated with walking, our lab is developing a soft exosuit that generates forces in tandem with the participant's leg muscles during his gait cycle to make walking easier. By finely tuning the design of the suit and the force profile applied during a gait cycle, we can optimize its effectiveness in order to observe the greatest metabolic reduction.

Testing the performance of the exosuit on a treadmill in a controlled lab setting allows us to gather a wide range of physiological measurements such as: metabolic cost, electromyography (EMG), and motion capture data to quantify the way the exosuit is performing and the way the participant is adapting to it. In particular, surface EMG data collected during testing provides information about the way a participant is activating his leg muscles during the course of a stride. The specific goal of my project is to characterize the wearer's muscular adaptation to the external forces applied by the exosuit in order to determine the optimal number and length of suit training sessions to effectively reduce the metabolic cost while walking with this system.

Developing a Materials System for Transfection of HPV-associated Cervical Cancers for Gene Therapy

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Despite the recent development and release of the HPV vaccines, cervical cancer remains one of the most common causes of cancer-related deaths in women worldwide. In 2012, there were an estimated 528,000 cases of cervical cancer. Over an estimated 90% of these cases were linked to a human papillomavirus (HPV) infection. HPV inserts two oncogenes: E6 and E7. E6 marks an essential tumor suppressor gene, p53, for degradation in the cytoplasm. Meanwhile, E7 destabilizes the retinoblastoma (Rb) protein, another tumor suppressor gene. Previous studies have shown that using siRNA—short double-stranded RNAs that interfere with gene expression—targeted at E6 and E7 caused a 50% reduction in tumor size in mice. However, siRNA targets the later step in gene expression, knocking down E6/7 by targeting mRNA to block translation. In this study, we aim to block E6/7 at the most fundamental level by editing the inserted DNA itself using a gene editing tool CRISPR.

To achieve gene editing, we must first develop and optimize a materials system for transfection (i.e. delivery of foreign genetic material into cells), which is the main goal for this summer project. In this project, we have developed and optimized a delivery system using liposomal nanoparticles (lipid vesicles) composed of cationic lipids. We showed that the cationic liposomes efficiently encapsulate plasmids containing reporter genes such as green fluorescent protein (GFP), red fluorescent protein (RFP), or luciferase, and formed nanoparticles with a hydrodynamic size ~100 nm. Using these liposomes, we were able to transfect human cervical cancer cells more efficiently than commercially available transfection reagents. We quantified levels of gene expression for GFP and RFP using flow cytometry and fluorescence microscopy, and used the luciferase assay for luciferase-transfected cells. We were able to optimize the liposome system by varying the quantities of plasmids,

the size of nanoparticles, the concentration of liposomes in solution, and types of packaging materials in the liposomes. To this end, we have determined an optimal design for transfection of human cervical cancer cells.

With this stage of the summer project nearing completion, we will proceed to using CRISPR targeted to E6, delivered using the same liposomes. Preliminary results have shown that we've been able to edit the E6 gene in some human cervical cancer cells, and we will use assays for mutation detection and p53 expression to further optimize the gene editing system.

BIOLOGY | Computational

A New Tool for Interactively Visualizing Integrated Proteomic Data

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Mutations in the genome of an organism can increase, decrease, or have no effect at all on the organism's fitness, or reproductive ability. However, the biological mechanisms by which a mutation affects fitness may not be straight forward. For example, a mutation that decreases a protein's structural stability may be deleterious because it diminishes the amount of active protein or causes toxic new protein interactions, or a combination of these and other mechanisms. It is for these reasons that the systems-level cellular response to genetic perturbations—even small ones such as point mutations—is not well understood. Modeling efforts in population genetics either completely leave out any molecular biological detail or use a schematic relationship between mutation and fitness.

Experimental data from our group is elucidating in detail the biological effects of point mutations on the stability and interactions of particular proteins, as well as mutations' systems-level metabolic effects in E. coli, using in vivo and in vitro techniques. Our goal is to understand if those specific lessons can be generalized across the proteome of an organism using bioinformatic data. To do this, we are developing a flexible, interactive tool for integrating and visualizing diverse biological data about the Escherichia coli (E. coli) proteome. These data include chain length, mutation rate, cellular abundance, taxonomic classification, and function for each protein chain with known structure in E. coli, as well as the structural and sequence similarity and known physical interactions between each possible pair of protein chains. Using a JavaScript visualization library, D3, and other tools, this data was visualized as a graph of protein structures. By allowing the user to set parameters to visualize subsets of proteins and protein relationships within the larger proteome, the result is a tool for exploring the nature of relationships among proteins. Currently, the results are consistent with previous bioinformatic findings, so to delve deeper, we plan to aggregate and integrate further protein characteristics including dosage toxicity and compare our tool against experimental results of the specific proteins studied, as well as expand the tool for use with data from yeast and other species.

Fragment-Based Design of Novel Inhibitors Against Drug-Resistant HIV Protease

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While the introduction of highly active antiretroviral therapy (HAART) has significantly improved clinical outcomes for patients with HIV/AIDS, the emergence of drug-resistant mutations severely hampers the long-term efficacy of HAART. These mutations affect a wide variety of viral proteins, including HIV protease, the enzyme responsible for cleaving the HIV polyprotein into its fundamental components. Mutations in HIV protease's active site, flap regions, and dimerization interface can decrease the potency of currently used inhibitors by up to a thousandfold, creating a pressing need for the discovery of potent, next-generation inhibitors that can overcome drug resistance.

We used OpenGrowth, a software protocol developed by the Shakhnovich Group, to generate novel drug-like compounds in the active site of several mutant varieties of HIV protease. OpenGrowth's fragment-based approach to drug design creates drug candidates that are more likely to have good pharmacokinetic properties (such as solubility and membrane permeability) and successfully pass clinical testing. Moreover, OpenGrowth's approach creates novel compounds that can be reasonably synthesized by conventional methods and techniques. After generating several hundred thousand compounds with OpenGrowth, we will select the top-ranking hits for further analysis, such as molecular dynamics simulations and the MMPBSA protocol to obtain an estimate of how strongly the protein binds to the ligand. We hope that our project will yield several novel drug candidates that are not only potent against wild-type HIV protease, but also retain their potency in drug-resistant variants. Moreover, we hope that our project will identify novel drug scaffolds that will form the basis of a new generation of protease inhibitors used in the clinical treatment of HIV/AIDS.

Quantitative Genome-Wide Analysis of the First Cell Division in *C. Elegans*

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Daniel Needleman
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The first cell division in *Caenorhabditis elegans* embryos is an important model system, but its molecular basis is still not well understood. A key challenge in this analysis is the identification of the genes that are involved in determining quantitative characteristics of the division, such as the size of the embryos, the asymmetry of the division, and the amount of time required for each stage in the cell division. Genomewide gene knockdown data spanning over 10000 genes and videos was produced by Sönnichsen et al. (2005) over 10 years ago, but a systematic analysis of this data has still not been performed. The goal of our research is to develop quantitative analysis of the effect of different genes on various aspects of the first cell division of *C. elegans* knockdowns.

This analysis proceeded in two major steps: developing algorithms to quantify these characteristics of the embryos and performing the necessary statistical tests given these characteristics. In the first part, an elliptical approximation for the embryos was used to determine their size and major axis, and the location of the cleavage site was manually identified to determine the asymmetry of division. The major timepoints of the cell cycle were also manually identified to compute the amount of time required for each stage of cell division. The statistical analysis was completed using t-tests across all knockdowns of a particular gene. The analysis identified most known genes that affect the size and asymmetry of division.The asymmetry of division appears tightly correlated with

the size of the embryo, which could improve our understanding of the mechanisms controlling division asymmetry. Further, the genes affecting cell division timing were associated with chromosome missegregation and DNA replication timing, which corroborates basic cell biology. Thus this analysis appears to be the right framework to understand the molecular basis of cell division in *C. elegans*.

BIOLOGY | HUMAN EVOLUTIONARY

"Born to Run... Slowly?": Characterization of C-Reactive Protein Response to Different Running Intensities

Claire Lo Human Evolutionary Biology
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Can too much exercise be harmful for the heart? Although regular exercise has been associated with lower risk of chronic inflammatory disorders like coronary artery disease and type II diabetes mellitus, a growing body of literature suggests that a concomitantly high intensity, high volume training regime may introduce consequences that outweigh the benefits of moderate exertion. Intense physical exercise induces a transient increase in serum high sensitivity C-reactive protein (hs-CRP), a well-established marker of systemic inflammation, by activating the acute-phase response. It is unknown whether the degree of inflammation, as measured by Δhs-CRP, varies as a function of exercise intensity or as a function of baseline fitness levels. This study examined the relationship between exercise intensity and hs-CRP levels among moderately active, healthy men.

To accomplish this objective, 12 participants completed four (4) 5-mile runs at four different levels of exercise intensity defined by proportion of each individual's VO2 max, the measure of maximal oxygen consumption during activity. Blood samples were collected before, immediately after, 24 hours-post, and 48 hours-post each exercise bout, and they were analyzed for hs-CRP and other serum markers of systemic inflammation. The results of this study may help to characterize an optimal intensity threshold for long-term cardiovascular health.

The Effects of Arm Swing on Angular Momentum during Locomotion

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The evolution of hominins from the last common ancestor (LCA) of chimpanzees and humans has involved many morphological changes in the upper body, many of which are hypothesised to have resulted from selection for bipedal locomotion at the expense of features that were adaptations for arboreal locomotion. An example is the decrease in relative arm length and mass, particularly in the forearm, which is hypothesised to facilitate arm-swing during walking and running at the cost of climbing ability. Arm-swing counteracts leg-driven angular momentum of the body in the vertical axis (known as vertical angular momentum), thus improving the stability and efficiency of locomotion. Our goal is to explore how and why humans tend to flex their elbows only slightly during walking, but to about 90° during running, by investigating the effects of variations in arm-swing on the angular momentum generated. Furthermore, we are simulating variations in the length and mass of the arm by manipulating the inertial properties of the arm.

To test these effects, we took recordings of six participants walking and running on a treadmill using a variety of arm configurations including straight or bent arms, with added hand weights, as well as without any arm swing. Kinetic data were collected on a treadmill with a built-in force plate, and kinematic data were collected with high speed infrared cameras surrounding the treadmill that detect the trajectories of reflective markers attached to joints of the subjects. We then calculated the angular momenta of the whole body and specific body segments, as well as the vertical ground reaction moment, which is generated by leg muscles and further contributes to the regulation of angular momentum.

The results of these investigations will help to determine the effects of arm-swing conditions on the efficiency of locomotion. This may contribute to our understanding of how selection for bipedal locomotion influenced the upper limb morphology.

Why the Long Tendon?": The Role of Muscle Force on Gene Expression and Morphology in the Developing Achilles Tendon

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Human bipedal locomotion, and the capability for endurance running in particular, is in part the result of our unique Achilles tendon, which is the longest of any primate in comparison to muscle length. These morphological differences have a genetic basis, especially via gene expression during development. However, this genetic basis, and specifically the role of muscle force on gene expression and tendon development, is poorly understood. Thus, we seek to reveal the role of muscle force on morphology and gene expression in the developing Achilles tendon. Using botulinum toxin A (Botox), we are able to immobilize mouse calf muscles in order to evaluate the role of muscle loading on postnatal Achilles tendon development and evaluate the theory that muscle force begins to be relevant for tendon development in mice 14 days after birth. We are evaluating the gross morphology of mouse tendons as well as using RNA-seq to evaluate the transcriptome of developing tendons at multiple time points. RNA-seq datasets will reveal potential targets of evolution for further exploration. As the human Achilles tendon has lengthened over the course of our evolution, we have become susceptible to injuries to the area. Datasets created from this project may thus prove to have biomedical relevance as well.

BIOLOGY | Molecular & Cellular

Functional Analysis of Gdf5 Enhancers using CRISPR/Cas-mediated Genome Editing

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Genetic and genomic analysis tools have shown a number of genes in the human genome to be associated with variation in human height and with skeletal disease phenotypes such as osteoarthritis (OA). Interestingly, the gene Gdf5, which encodes a protein (Growth Differentiation Factor 5), is one locus that has repeatedly been associated with these skeletal phenotypes. Gdf5 is expressed in long bone growth plates, joints, tendons and vertebrae and is known to regulate skeletal development. Our laboratory's previous work has focused on locating and analyzing key regulatory regions both upstream and downstream of Gdf5, hoping to understand expression patterns and their evolutionary origin.

We are using a CRISPR-Cas9 system to perform gene knockout mutations for previously identified regulatory regions, called enhancers, of Gdf5 in mouse cell culture. We hope to analyze how this affects Gdf5 expression using assays such as quantitative PCR, and to eventually study it in a mouse model. The use of the CRISPR-Cas9 system is a fairly recent advancement in the life sciences and has shown tremendous promise as an efficient method for genome editing and manipulation. The system consists of an enzyme guided to a specific target DNA sequence by means of small guiding RNA molecules. Once it finds the target sequence, it will cleave the DNA, thus inducing a double strand break which can either lead to effective gene silencing or be further manipulated to change specific bases in the DNA. With regard to the latter, we also plan use the system to perform a single base-pair replacement within Gdf5 at a site found to be important for height variation and OA risk.

We have been able to demonstrate the generation of deletions for two of our candidate enhancers in mouse cell culture, and now plan to inject these constructs into single-cell mouse embryos for the creation of enhancer null mouse lines. This project should help determine the functional contributions of these enhancers to the role of GDF5 in development. Our targeted replacement strategies should also elucidate whether a single base pair change at our target locus is both necessary and sufficient to cause a difference in limb length and/or height, thus providing strong support for its role as causal variant underlying height variation.

Identification of Metabolic Biomarkers for Adiposity Distribution and Associated Cancer Risk

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Obesity underlies ~15-20% of cancer deaths in the U.S. Growing evidence suggests that greater proportions of visceral fat carry an increased risk of cancer. Measures of adiposity such as BMI and waist circumference do not adequately capture body fat distribution, but abdominal imaging is too expensive and difficult for routine screening.

Our project aims to use metabolomics to test the connection between adiposity and cancer. This approach involves quantifying small molecules within a biological sample, such as blood, tissue, or urine. These low-weight metabolites, which comprise the metabolome, are produced, for example, during essential biochemical processes. Each individual has a metabolomic "fingerprint" that reflects their environment, genetics, lifestyle, and health status; thus studying the metabolome could reveal specific aspects of an organism's physiology such as fat distribution and cancer risk.

Blood plasma samples from about 2,000 subjects are being analyzed to isolate a set of metabolic profiles that accurately reflects body fat distribution. The study participants are part of the Multiethnic Cohort (MEC), which includes five ethnicities: African American, Japanese American, Latino(a), Native Hawaiian, and Caucasian. Using nested case-control studies, we plan to test metabolic predictors of fat distribution for association with breast and colorectal cancer risk across the five ethnicities.

To quantify these metabolic predictors, we analyze blood plasma samples from the MEC using High Performance Liquid Chromatography with a coulometric array detector (CoulArray), and CoulArray software is used to identify and quantify the chromatogram peaks that represent individual metabolites. This research will shed light on metabolic biomarkers associated with visceral fat, and potentially enable us to predict risk of breast and colorectal cancer.

A Functional Antioxidant Profile of Breast Cancer Cells

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A hallmark of cancer is the regulation of cellular metabolism, including processes that mediate oxidative stress. The high proliferative rate of cancer cells, which demands increased production of ATP and synthesis of proteins, also results in elevated generation of toxic by-products such as reactive oxygen species (ROS). Cancer cells counteract ROS by increasing the production of antioxidants, which convert ROS into benign species such as water. Recently it was shown that production of glutathione (GSH), the most abundant antioxidant, is necessary for many cancers to not only initiate, but also thrive and progress. The signaling pathways that drive the synthesis of GSH among additional antioxidant programs remain poorly understood.

In my PRISE summer project, we will characterize the dependence of the tumor's antioxidant program on key cellular signaling pathways. We have optimized and carried out a small molecule inhibitor screen in a breast tumor cell line using a compound library that targets a wide range of cellular pathways . Validation of hits from the screen revealed that inhibition of antioxidant pathways synergize with several non-an-

tioxidant pathways to cause cell death. Not only do these results reveal several cellular functions that are dependent on the tumor's antioxidant program, but they also suggest novel therapeutic strategies for treatment of cancer.

Study of Proton Transport in Natural Resistance-Associated Macrophage Proteins

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Natural resistance-associated macrophage proteins (NRAMPs) are a family of transmembrane proteins that transport divalent metals. For example, in humans, one NRAMP homolog is found in the small intestine where it transports Fe^{2+} and Mn^{2+} ions. Iron is used to transport oxygen throughout the body, and manganese is essential to DNA and RNA synthesis. Another human NRAMP homolog is found in the innate immune system where it enhances host resistance by robbing pathogens of metals. Mutations in NRAMPs are associated with increased susceptibility to infection, anemia, and neurological diseases.

Cells couple the transport of divalent metals with protons. Currently, the mechanism and stoichiometry of proton transport via NRAMP is largely unknown. To help elucidate the proton and metal transport mechanisms, I have run cobalt transport assays on a panel of engineered NRAMP variants that have conserved polar residues substituted for alanine. Several mutations on transmembrane region 6 of NRAMP—near the protein's metal binding site—impaired cobalt transport. In contrast, two mutations on transmembrane regions 1 and 2 increased cobalt transport. I also performed a metal toxicity assay that assesses NRAMP's ability to transport Mn^{2+}, a physiological substrate, and saw that certain NRAMP mutants diminish Co^{2+} transport but not Mn^{2+}, and vice versa.

We hypothesize that residues important for metal transport are also important for proton transport. We are currently developing a proton transport assay that measures the change in intracellular pH upon the addition of metal via pHluorin fluorescence. We ultimately hope to identify important residues in the proton transport pathway and see if protonation events induce conformational changes within NRAMP.

TCR Repertoire Profiling by Single-Cell Sequencing

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During lymphocyte development, T cell receptors (TCRs) exhibit somatic V(D)J recombination as well as random insertion/deletion of nucleotides to generate a diverse T cell repertoire, further expanded by combinatorial pairing between the α and β chains. Thus, the study of TCR repertoires promises wide applications in tumor-targeting strategies in cancer. Collaborators at the Broad Institute have devised methods for paired TCRα/β chain single-cell sequencing, and we want to confirm the effectiveness of the Broad's technology by testing the functionality of these identified TCRα/β chains, more specifically, by cloning and expressing them in the TCR-deficient Jurkat Δαβ cell line. We first assembled full TCRα/β constructs against the EBV peptides EBNA3A and BRLF1 in pUC57-Kan, via Golden Gate Assembly, and subsequently cloned them into the lentiviral backbone PEW, before transfecting them into HEK 293T cells (more easily infected than Jurkat cells) along with human CD3 (also in PEW backbone). We then verified the desired TCR expression via flow cytometry, which we observed for the EBNA3A-transfected cells but not the BRLF1-transfected cells, due to a non-ideal antibody. However, we did detect CFP (part of the TCRα/β construct) expression in both samples, which signifies successful transfection, thus providing sufficient motivation to transduce TCR-containing lentivirus into Jurkat Δαβ cells and establish not only TCR expression, but also TCR stimulation when presented with the appropriate antigens.

Unraveling the Genetic Basis of Inflammatory Bowel Disease (IBD)

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The intestinal mucosa functions as an immunological organ, which plays a major role in the development of immunity. The defense response to microbiota in the lumen of the intestine is required to maintain health and to overcome disease. Crohn's disease (CD) and ulcerative colitis (UC) are chronic and relapsing inflammatory diseases of the gastrointestinal tract; they are characterized by injury to the barrier function of the intestine and caused by an exaggerated defense response to the intestinal microbiota. The study of mediators' functions in host defenses, which can regulate both inflammatory and inhibitory immune responses mediated by IBD-associated gene variants.

I am interested in three different neuropeptides that may give insight to the role of neurons in the autoimmune/inflammatory response in the gut – Adrenomedullin (ADM), Proenkephalin-A (PENK), and Neuroligin-2 (NLGN2). Based on RNA sequencing, these genes are highly upregulated in response to bacterial nucleic acids that serve as transcriptional regulators in bacteria, in bone-marrow-derived dendritic cells as part of innate immune responses. We found a selective induction of ADM by cycli-di-Guanine-monophosphate (c-di-GMP), a compound secreted by bacteria that can be detected during invasion of epithelial cells, but not by lipopolysaccharide (LPS), a structure found on the outer membrane of bacteria, suggesting the specific involvement of nucleic acid sensing in the induction of this neuropeptides during innate immune activation. Via qPCR, we then found that baseline expression ADM and NLGN2 is higher in the colon than in the small intestine. This may be due to higher concentrations of bacteria (and thus higher c-di-GMP production) in the colon.

Future experimentation involves the study of these neuropeptides' expression in human IBD and in dextran sulfate sodium (DSS)-induced colitic mice vs. wild type mice. Elucidation of the function of these neuropeptides for dendritic cell responses will provide new insights into the causal mechanisms of enhanced immune responses and lack of their control in IBD patients.

Elucidating the Role of Autophagy-related Proteins in Yeast Gametogenesis

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Autophagy is a key homeostatic process by which cells degrade and recycle dysfunctional proteins and organelles. In yeast and in humans, progression through autophagy is carried out by proteins encoded by autophagy-related (ATG) genes. Mutations in any of the ATG genes block autophagy, causing damaged components to accumulate and drive neurodegenerative diseases, infection, and cancer. Recent unpublished data suggest that one Atg protein, Atg1, may play a second role in addition to its canonical function in autophagy: facilitating completion of meiosis (spore production). When the function of Atg1 is acutely inhibited at the onset of meiosis, an abnormal meiosis phenotype is observed wherein each cell creates eight spores instead of four. My goal is to determine whether this phenotype is related to a novel autophagy-independent function of Atg1 during meiosis, or represents a requirement for autophagic degradation during spore formation. To this end, I am testing whether loss of other Atg proteins causes the same eight-spore phenotype. Because Atg proteins are essential for entry into meiosis, to query the function of a panel of Atg proteins, I have engineered yeast strains that enable the immediate and targeted degradation of Atg proteins when the cell is exposed to a small exogenous signaling molecule. In this way, I have created a novel system for testing whether meiosis in yeast is dependent on Atg protein-specific functions or autophagy more generally.

Investigating the Cardioprotective Effects of Brown Adipose Tissue

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Brown adipose tissue (BAT) is a form of fat tissue that is rich in mitochondria. It has an important thermogenic function in infants. However, recent evidence suggests that there are also BAT deposits in human adults with roles in cardiac metabolism.

BAT releases compounds that may protect against cardiovascular disease. Previous studies in the lab have demonstrated that mice deficient in uncoupling protein 1 (UCP1), an essential protein in BAT, were more susceptible to catecholamine induced cardiac injury compared to wildtype controls. Such injury was decreased by transplantation of wildtype BAT into the UCP1 deficient mice, suggesting that BAT releases substances with a cardioprotective effect.

A model of injury induced by a heart attack, called ischaemia reperfusion injury, is used to study the cardioprotective effects of these proteins. The size of the myocardial infarction is compared against wildtype mice to determine whether the protein under investigation reduces myocardial damage.

The lab is studying the cardioprotective effects of a protein released by BAT. The baseline characteristics of mice deficient in this protein are investigated using tail cuff plethysmography to measure blood pressure, and glucose tolerance tests, which investigate the response to a bolus of glucose. It has been found that the knockout mice develop spontaneous hypertension by six months. This is compelling evidence that the protein has a role in preventing cardiovascular disease. However, hypertension by itself increases the size of myocardial infarction, so younger mice that have not yet developed hypertension are used for ischaemia reperfusion injury experiments. Similarly, glucose intolerance is a confounding factor.

The results indicate that mice at 8 weeks do not differ in their baseline cardiovascular and metabolic characteristics compared to controls, and can therefore be compared to wildtypes in ischaemia reperfusion experiments. If successful, this protein reflects a potential treatment for cardiovascular disease.

Engineering Archaerhodopsin 3 for Efficient All-Optical Electrophysiology

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Studying complex neural activity requires a set of tools that can record and manipulate neuronal transmission in a precise manner. In the previous work, we have already established a plasmid construct with an archaerhodopsin variant, which acts as voltage indicator, and a channelrhodopsin, which acts as a light-gated ion channel. The construct allows simultaneous recording and stimulation of neuron activity. Further improvements in trafficking and combinations with other useful fluorescent proteins are needed to study neuronal activity in vivo. Such modifications were screened in in cultured rat neurons. The first project involved the trafficking of archaerhodopsin 3. Given the evolutionary distance of the archaerhodopsin, archaeal protein, from mammalian proteins and subsequent poor trafficking, an attempt to engineer eukaryotic posttranslational modifications, specifically N-glycoslation, was made. Site-directed mutagenesis was used to engineer specific N-glycosylation sites on the archaerhodopsin, and the mutants were screened for functional performance.

The second project involved the combination of Optopatch with genetically encoded calcium indicators to probe calcium transients in parallel with voltage measurements. Different configurations of the combined archaerhodopsin and calcium sensors, GCaMP and RCaMP, were tested for trafficking and functional activity. A bicistronic construct with GCaMP, a green flurorescent calcium indicator, showed membrane localization and functional activity.

Induction of Fetal Hemoglobin Expression through BCL11A Erythroid-Specific Enhancer Microdeletion

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During developmental hematopoiesis, a switch from fetal to adult

hemoglobin expression occurs in red cells. Individuals with sickle cell anemia or β-thalassemia with higher than normal levels of fetal hemoglobin display milder symptoms of disease, suggesting that derepression of fetal hemoglobin could be a viable therapeutic strategy against hemoglobinopathies. Findings from human genetics, mouse knockouts, and cell lines have identified BCL11A as a repressor of fetal hemoglobin. Therefore, an essential erythroid-specific enhancer in the gene is being pursued as a target for gene therapy.

My project translates the cell culture findings to an in vivo model. Previously, a mouse strain was genetically modified to express the human globins from a yeast artificial chromosome (β-YAC mice). More recently, the lab generated a new mouse strain in which the +62 region BCL11A erythroid-specific enhancer was deleted. I arranged matings between these two mouse strains to produce mice of the expected genotypes to determine the effects of homozygous or heterozygous loss of the +62 region on β-YAC expression. In offspring that do not carry the β-YAC, endogenous mouse globin expression was assayed.

I tested for levels of hemoglobin expression through fetal dissections at embryonic days 12.5, 14.5, 16.5, and 18.5. The fetal livers were extracted and processed to collect mRNA, which was then converted to complementary DNA using reverse transcriptase. Through quantitative PCR analysis, I observed that embryonic mouse globin levels in the homozygous +62 deletion mice were the highest, followed by heterozygous +62 deletion mice. Fetal human globin expression was also higher in β-YAC positive mice. Our data shows that deletion of the +62 region of the enhancer leads to elevated fetal hemoglobin levels. These findings represent a step toward a treatment for hemoglobinopathies.

Charting the Interplay of Sirt6, Phosphorylated RNA Polymerase II, and Negative Elongation Factors in Promoter-Proximal Pausing

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DNA-protein interactions underlie the compactness and dynamism of the eukaryotic genome. The accessibility of chromatin can be controlled through the chemical modification of histones—structural proteins that associate with DNA—while the cross-talk of transcription factors, chromatin regulators and target loci fine-tune gene expression. Of particular interest is the histone deacetylase SIRT6, a chromatin regulator that removes acetyl groups. SIRT6-knockout (KO) mouse models favor rapid glycolysis and take on the metabolic hallmarks of tumor growth and glucose deprivation, but the precise relationship of SIRT6 with other transcriptional machinery is not yet fully understood. Preliminary studies suggest that SIRT6 associates with RNA polymerase II (RNA Pol II) and enables the binding of negative elongation factors (NELF) to stabilize a phenomenon called promoter-proximal pausing—a pre-assembly of RNA Pol II that functions to synchronize metabolic and developmental processes in response to stimuli. Pol II also has regulatory mechanisms of its own: its repetitive C-terminal domain (CTD) undergoes several phosphorylation configurations during transcription.

Elucidating the interplay of SIRT6, NELF, and RNA Pol II in transcriptional pausing demands a systematic approach. In this investigation, we apply wet-lab robotics to the automation and optimization of ChIP-seq—chromatin immunoprecipitation followed by sequencing. We then employ our automated ChIP-seq to map acetylated histones, phosphorylated Pol II, NELF, and other epitopes in wild-type, glucose-deprived, and SIRT6-KO mouse embryonic stem cells (mESCs). Our research aims both to catalyze the technological development of ChIP-seq and to describe the underpinnings of metabolic regulation, transcription, and disease.

Dynamics of NF-κB Nuclear Localization in HeLa Sister Cells in Response to Tumor Necrosis Factor

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NF-κB is a transcription factor present in most animal cells that enters the nucleus when cells are exposed to Tumor Necrosis Factor (TNF), an important regulator of inflammation. The function of a transcription factor is to promote, or repress, the expression of specific genes. Once in the nucleus, NF-κB promotes transcription of genes involved in inflammation and cell survival. Improperly regulated NF-κB has been implicated in cancers and inflammatory diseases. Interestingly despite the importance of proper NF-κB regulation, there exists great variability in nuclear NF-κB levels between cells exposed to the same concentration of TNF. One proposed explanation for this cell-to-cell variability is that NF-κB-dependent transcription relies not on changes in absolute nuclear NF-κB concentration but on fold changes in concentration.

My specific project is to expand on these findings by investigating whether NF-κB dynamics in sister cells are any more similar than those in two unrelated cells. If they are, it would eliminate pure stochastic noise as an explanation for cell-to-cell differences. Furthermore, we are curious if this similarity, if it exists, diminishes with time since cell division, or the "age" of sister cells. If it does, it would eliminate genetic differences as the explanation for cell-to-cell differences, as genetic similarity in sister cells is expected to be long lasting. To this end, I am using HeLa cells expressing a fluorescent-protein-tagged NF-κB RelA subunit (FP-RelA) enabling visual tracking of NF-κB nuclear translocation in single cells pre- and post-TNF exposure. I use live-cell microscopy to create movies of FP-RelA in cells and analyze them using the cell tracking software CellProfiler to quantify nuclear FP-RelA over time in individual cells. Finally, I watch the movies in reverse to determine which cells are sisters. My preliminary results suggest that sister cells do have similar absolute nuclear NF-κB concentrations as well as similar fold changes in NF-κB concentration after TNF exposure.

Functional Analysis of Rare and Common Variation within an Erythroid Enhancer of BCL11A: Toward a Novel Therapy for Hemoglobinopathies

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Hemoglobin, the molecule required to carry oxygen in the blood, comes in multiple forms that are differentially expressed throughout an individual's life. During infancy, the adult form of hemoglobin (HbA) replaces the fetal type (HbF) in a phenomenon known as hemoglobin switching. Both HbF and HbA are tetramers consisting of two α-globins and either two γ-globins (HbF, α2γ2) or two β-globins (HbA, α2β2). Hemoglobinopathies are diseases caused by genetic mutations in any of these globins, resulting in abnormal structure. Many of the most common hemoglobinopathies, including sickle cell disease (SCD) and β-thalassemia, involve mutations in the β-globin gene.

Epidemiological and human genetic studies have revealed that elevation of HbF in adult patients with β-globin disorders can reduce disease severity. Our goal was to investigate the mechanisms responsible for the HbF to HbA switch, and how they can be reversed to provide a novel therapy for patients.

This switch is controlled, at least in part, by the transcription factor BCL11A, which represses HbF. Our lab has identified an erythroid-specific enhancer, a regulatory element required for BCL11A expression in only red blood cells. Due to this specificity, disrupting the enhancer can reduce expression of BCL11A in erythrocytes, increasing HbF expression and reducing disease severity without affecting other tissues.

By sequencing a set of SCD patients with known levels of HbF, we have identified a set of 7 rare single nucleotide polymorphisms (SNPs) within the most active region of the BCL11A enhancer that are associated with high HbF. We aimed to assess the functional effect of each of these SNPs through two different approaches: (1) a reporter-enhancer construct containing each of the SNPs and (2) direct introduction of each SNP into cells using the CRISPR/Cas9 system. SNPs with a functional impact on BCL11A expression (and subsequent HbF repression) would be expected to cause lower expression levels of the reporter gene (green fluorescent protein) and higher levels of HbF in the cells where the SNPs were introduced.

Danger Signaling in Myocardial Infarction

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Myocardial infarction (MI) is the leading cause of death in the US. Survivors often develop adverse ventricular remodeling, which leads to clinical heart failure. MIs are strongly associated with inflammation and activation of the innate immune system; however, the process by which dead cells in the heart are able to recruit and activate inflammatory cells is unknown. During infection, innate immune activation occurs when pathogen associated molecular patterns (PAMPs) are sensed and the transcription factor IRF3 is activated. During MI, when there are no pathogens present, immune activation is thought to occur by sensing of damage associated molecular patterns (DAMPs) released from dying cells; however the molecular nature of these DAMPs is unknown. Since nucleic acids are potent activators of innate immunity during viral and bacterial infections but are also abundantly present in the nucleus and mitochondria of every mammalian cell, we hypothesized that they might be exposed by dying cells and fuel sterile injury in the heart after MI. To test this hypothesis, we examined whether interferon regulatory factor 3 (IRF3), the master transcriptional regulator of pathogen nucleic acid sensing, might also be activated after myocardial infarction (MI).

Remarkably, IRF3 deficient mice were found to have a significant survival advantage over wild type controls. Over the past several months, I learned to harvest infarcted heart tissue and blood from mice after myocardial infarction, extract and quantify RNA and protein, and use molecular techniques such as ELISA, western blotting, and quantitative RT-PCR to obtain evidence that the IRF3 transcription factor is activated after MI, upregulates IRF3-dependent genes, and produces IRF3-dependent proteins. By comparing samples from mice deficient in key adaptors from each of the three known IRF3 activating pathways (TRIF, MAVS, and STING) we have determined the dominant DAMP responsible for MI-induced innate immune activation.

Looking forward we hope to gain a deeper understanding of infarct dynamics using molecular imaging at the single cell level. To enable intravital imaging of the process by which dying cells of the infarct activate innate immune cells in the heart, I helped design, build, and test a modified Langendorff mouse heart perfusion chamber. This approach, which retains the rich complexity of living mammalian heart tissue while enabling unrivaled experimental control, is now poised to reveal never before seen details about the earliest steps connecting cell death to innate immune activation

Investigating the Release of CD44 during Glycosyltrasferase-Programmed Stereosubstitution

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Cell surface glycans are implicated in many fundamental biological processes, including development, cell migration, infection, and coagulation, among others. Glycans refer to polysaccharides that are attached to proteins and lipids, and are variably expressed on the surface of cells. A glycan of primary interest in the Sackstein laboratory is the tetrasaccharide sialyl Lewis X (sLe^x), which can be found at the terminal end of type 2 polylactosamine glycan chains. sLe^x is the essential component of E-selectin ligands that enables their binding to E-selectin, an interaction that is critical for the initial steps of cell homing from the bloodstream to underlying tissues such as bone marrow, skin and to all inflammatory sites. Through the use of specific glycosyltransferases, E-selectin ligands can be engineered on the surface of cells to enable their homing to relevant target tissues. Mesenchymal stem cells (MSCs), for example, display type 2 sialylated lactosaminyl glycans on specific scaffolds, but lack endogenous fucosyltransferases. Thus, MSCs completely lack sLe^x on their cell surface. However, sLe^x can be created on the MSC cell

surface by incubating them with an α-1,3-fucosyltransferase (FT6) and its substrate, GDP-fucose, in optimized buffer conditions. This process, termed glycosyltransferase-programmed stereosubstitution (GPS), creates functional E-selectin ligands on the MSC cell surface, a predominant example being the conversion of CD44 into HCELL, a glycoform of CD44 that acts as a potent E- and L-selectin ligand.

Following the GPS reaction, the cells are centrifuged to remove them from the reaction buffer. Recently, Western Blot analysis has indicated that in addition to its presence on the cell surface, HCELL was also detectable in the supernatant after a GPS reaction. This observation was extended using 'mock' reactions to reveal that CD44 was released into the supernatant independently of its conversion to HCELL, and independently of the presence of the FT6 enzyme or the GDP-fucose substrate. The goal of my project was to determine the mechanism by which the CD44 was released in these conditions. We hypothesized three possible reasons for the CD44 release into the supernatant. Firstly, this release of CD44 may be catalyzed by a specific protease that is selectively shedding CD44 into the supernatant. Secondly, this may be due to a generalized protease that is cleaving cell-surface proteins, but in a nonspecific manner. Lastly, this may be due to physical cell lysis and membrane fragmentation. To address these possibilities, I performed a series of serial centrifugation experiments to determine the origin of the released CD44. After the GPS reaction which was performed at 4° or 37°C, intact MSCs were pelleted using one of two centrifugation methods currently used in the lab: 'standard' (1000g x 3 minutes), or 'rapid' (5000g x 10 seconds). After a second identical centrifugation to ensure removal of all intact cells, two rounds of 'high-speed' centrifugation were performed (20,000g x 1 minute) to isolate any cell membrane fragments present in the initial supernatant. The remaining supernatant (containing any dissolved proteins), the high-speed pellet (containing membrane fragments), and lysate from the intact MSC cell pellet were resolved under reduced SDS conditions, blotted and stained with anti-CD44 antibody. Furthermore, cell recovery was enumerated and viability calculated via Trypan blue exclusion. Results to date suggest that the release of CD44 is correlated directly with centrifuge speed and temperature, and is negatively correlated with viable cell recovery. Taken together, these results indicate that the release of CD44 into the supernatant is likely not an active process but corresponds to cell fragments resulting from cell lysis that depends on the reaction temperature and the centrifugation method.

Co-Crystal Structure of Penicillin Binding Protein with Cell Wall Synthesis Inhibitors May Give Insight into New Strategies to Treat Resistant Bacteria

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Penicillin binding proteins (PBPs) are involved in the synthesis of peptidoglycan, a glycopeptide polymer that comprises bacterial cell walls. This cell wall surrounds the inner cytoplasmic membrane and helps to maintain and stabilize cell shape when there are changes in osmotic pressure. Many antibiotics have been designed to inhibit cell wall biosynthesis because the structural integrity of cell wall is important for bacterial survival. However, bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) continue to gain resistant against antibiotics which are commonly used to treat bacterial infections. Therefore, it is crucial to identify drugs that have new targets to combat increasing resistant bacteria. Lovering et al. (2007) determined the 2.8 angstrom structure of a bifunctional PBP in Staphylococcus aureus called PBP2. The PBP2 construct that was crystallized had both the glycosyltransferase (GT) and transpeptidase (TP) domains which are respectively responsible for polymerizing sugars and cross-linking peptides to form peptidoglycan. Currently, I have crystallized this PBP2 construct using a sitting drop method. Once I have confirmed the structure of my crystals using X-ray crystallography, I hope to co-crystallize the PBP2 construct with multiple inhibitors in order to understand the interactions these inhibitors have with the domains of PBP2. This information may be helpful to identify new strategies to kill highly resistant bacteria.

Using CRISPR/Cas9 to Knockout and Investigate the Role of Has2 in Zebrafish Gastrulation

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Gastrulation is a critical phase in the development of all vertebrates, when the cells of an embryo rearrange to form three different layers. Each resulting layer of cells goes on to produce its own distinct types of tissues. Correct cell migration is required during this process for the animal to develop properly.

Previous research has suggested that the hyaluronan synthase 2 (*has2*) gene is necessary for cells to align and migrate correctly during zebrafish gastrulation. The *has2* gene codes for a protein that catalyzes the formation of hyaluronan, a component of the extracellular matrix that surrounds cells. *Has2* is thought to influence cell migration by promoting the growth of lamellipodia, extrusions on the surface of cells that aid in cell movement.

Knowledge about *has2* is based on a series of experiments that used morpholinos, a gene silencing technique that has since been suggested to be unreliable. In order to confirm and expand upon previous *has2* knowledge we used the CRISPR/Cas9 system to create insertions and deletions directly in the *has2* gene, thereby knocking out Has2 in zebrafish. These *has2* heterozygous mutant fish were identified with PCR and inbred to produce embryos that were homozygous for the *has2* mutant allele.

We are currently studying these embryos for defects in body shape to determine if knockout of *has2* affects the gross anatomy and survival of zebrafish. *Has2* knockout embryos will also be stained for genes marking the three different cell layers to test whether Has2 was necessary for proper cell migration during gastrulation.

Determining Candidate RNA Pol II C-Terminal Domain Protein Binding Partners

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RNA polymerase II (RNAP II) is a multi-subunit enzyme complex responsible for transcribing DNA into mRNA precursors in eukaryotic cells. RNAP II is critically placed to control and coordinate eukaryotic gene expression through the recruitment and binding of various transcriptional factors, chromatin re-modellers and histone modifying proteins. The C-terminal domain (CTD) of the RNAP II subunit, RPB1, has been shown to regulate the progression of transcriptional initiation, elongation, and termination as well other co-transcriptional events. Work in this field has focused on correlations between the stage of transcription and the phosphorylation state of the CTD's 26 (Yeast) heptad repeats. However, less has been done to establish the nature of the binding partners this phosphorylation code acts to recruit. Using a CTD engineered to contain extra lysine residues we are able to efficiently capture even the most transient CTD protein-protein interactions in S.cerevisiae using formaldehyde crosslinking. Both wild type CTD samples and our engineered CTD samples shall be analysed using LC- tandem mass spectrometry. The use of mass spectrometry allows peptides to be sequenced and cross referenced against a vast proteomic library. To be confident that detected proteins are present due to CTD crosslinking, results should be compared to the wild type CTD sample which doesn't contain lysine residues. Any protein matches unique to the engineered CTD samples can be considered as candidate CTD binding proteins. There is promise that proteins discovered in this in vivo experiment will differ from those found in existing literature. The cause of this is that other work has involved pulling-down proteins on recombinant CTD using an affinity column in vitro. Our in vivo approach provides more physiological data and could greatly improve our understanding of the mechanistic basis behind transcriptional regulation.

Cheese Just Not That Into You: An Interaction between Two Species of a Model Cheese Rind Community

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Fermented foods, such as cheese, rely on the reproducible growth of microbial communities. Since similar microbial communities on the human skin and in the human digestive tract are important for human health, yet difficult to study due to their complexity, a lab-based system of bacteria and fungi based on the cheese rind community is a useful model. One interaction within the cheese community is between *Brevibacterium linens* and *Staphylococcus succinus* – both species that are isolated from cheese rind. These two species display an interesting phenotype, as *Brevibacterium* requires the presence of *Staphylococcus* to grow on cheese, but, over time, *Staphylococcus* is killed in the presence of *Brevibacterium*. There are many possibilities for the cause of this growth and death, including nutrients (carbon or nitrogen source), minerals (iron, for example), secreted molecules (toxin or stimulatory molecules), environmental factors (such as pH), or direct cellular contact (through secretion or another mechanism). In the case of *Brevibacterium* and *Staphylococcus*, it is likely that the growth of *Brevibacterium* is due to a combination of pH and altered nutrient levels, while *Staphylococcus* death may be due to a toxin-antitoxin system. Studying how species compete and cooperate under model conditions with both genetics and growth curves is essential to understanding how microbes act in the presence of other organisms.

Developing Diagnostic Tools for Parasitic Disease

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Disclaimer: The specific details about the class of parasites under study are purposely masked as this abstract summarizes the early-stage development of clinical diagnostic tests that may be submitted for US Patent and FDA approval in the future.

Parasites are a diverse eukaryotic class of microbes often associated with human disease (e.g. malaria, sleeping sickness, leishmaniasis, etc.), and infectious parasites are responsible for nearly fourteen million deaths per year. Although there is vast inter-genera diversity among parasites, the disease symptoms (e.g. fever, sweats, and muscular aches) are very similar. Many parasites disrupt physiology by invading human cells, causing local and ultimately systematic pathology. Given the high degree of clinical similarity among parasitic diseases, accurate diagnosis and subsequent targeted treatment is crucial. As such, the aim of this project is to develop and commercialize: (1) a sensitive and specific diagnostic assay to validate clinical diagnosis; and (2) a drug resistance assay, based on underlying parasite genetics, to allow the clinical community to predict whether certain drug regimes will fail and to offer more targeted, personalized therapy. Both assays are being developed using quantitative polymerase chain reaction (qPCR), an established method that quantifies the presence or absence of certain species-specific genes. Some parasites evolve resistance by increasing the genomic copy number of certain genes. As such, this study employs post-qPCR analysis to examine the hypothesized positive correlation between copy number and treatment failure. Direct translational, bench-to-bedside research as represented in this study provides clinicians with improved diagnostic tools to treat patients in a timely, personalized manner.

Development and Investigation of Patterned Cultured Neurons

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Dissociated cultured neurons are a valuable tool for studying neuronal properties in a well-controlled environment. Understanding the network properties of cultured neurons is difficult because synaptic connections can be too complex and long range to study by imaging or electrophysiology. In order to better map out these connections, we have developed a surface coating method for confining cells to arbitrary patterns.

We hypothesized that restricting the number of neighbors a neuron may interact with can change its firing properties. Therefore, we patterned rat hippocampal neurons in squares with side lengths of 100-1000 microns and characterized how island size affects several key neuronal properties.

GCaMP6f measurements also suggest that spontaneous firing rates and patterns may be affected by island size. Measurements of intrinsic excitability by all-optical electrophysiology revealed that island size also seems to affect the intrinsic excitability of single neurons. Further studies are needed into these properties.

We find that island sizes seem to affect both spontaneous firing behavior and intrinsic excitability, which we ascribe to differences in synapse formation in different size islands. Future work will utilize this method to study the synaptic connections of a small system with all-optical electrophysiology. We expect that our method will be generally useful for future studies of network properties of cultured neurons.

Expanding the CRISPR-Cas Genome Editing Toolbox through Characterization of Orthogonal Cas9 Proteins

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Cas9 is an RNA-guided nuclease that finds its target by checking for complementarity between an RNA guide (gRNA) and the target DNA. The protein's targeting activity occurs in three phases. First, it complexes with a guide RNA, comprising of a spacer sequence and a double hairpin. Second, it scans DNA for a short Protospacer Adjacent Motif (PAM) sequence, which is encoded by the protein itself. Third, when a PAM match is found, Cas9 checks the gRNA spacer sequence for complementarity against the adjacent genomic DNA. If there is a match, Cas9 will induce a double stranded break in the DNA at that location. Though changing the spacer sequence on the gRNA reprograms the target of Cas9, there is a natural limitation on its set of genomic targets because of the PAM sequence. For example, the *S. pyogenes* Cas9, which is used by most scientists, has a PAM of 5'-NGG-3', limiting its targeting range to 1 in 8 loci in the human genome.

Recently, we elucidated the gRNA structure and PAM specificity of the *S. aureus* Cas9, confirming that orthogonal Cas9 proteins from other bacterial strains indeed have different PAM sequences. The gRNA sequence was found by bioinformatically analyzing the bacterial genome to determine the locations of CRISPR repeats and the transactivating RNA, which are fused to form the gRNA. The PAM specificity was then determined through a simple negative selection screen. In this study, we use these same methods to characterize the PAM specificities of five Cas9 proteins to further expand the number of genomic sites that are targetable by the CRISPR-Cas genome editing toolbox.

Understanding Gastrointestinal Reflexes of the Vagus Nerve

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The vagus nerve is a major body-brain connection that controls autonomic physiology. Among its many functions, the vagus nerve mediates gastrointestinal reflexes important for normal digestion. Our goal is to determine mechanisms by which the vagus nerve regulates gastric motility in response to nutritional stimuli in the intestine. We measure gastric motility in mice by cannulating the stomach with a pressure transducer. Stimuli such as nutrients are then introduced into the small intestine, through tubes sutured into the duodenum and distal ileum that provide perfusion entry and exit ports. Changes in gastric pressure are recorded before, during, and after intestinal infusion of various test stimuli. Experiments are being done in control mice, as well as mice in which the vagus nerve has been transected below the diaphragm, to determine whether changes in gastric motility are mediated by the vagus nerve. These experiments are ongoing, and progress to date has begun classifying intestinal stimuli that impact gastric pressure. Future studies will use genetically guided neuron ablation to reveal the roles of particular sensory neuron types in mediating this reflex.

Targeting Tumor Cells and Associated Vasculature in Glioblastomas

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Malignant brain tumors, such as glioblastomas (GBM), are a devastating cause of mortality in adults and the leading source of cancer-related death in children and young adults combined. Despite their vast phenotypic heterogeneity, in their proliferative stage, almost all GBMs exhibit constant vascularization via a process known as angiogenesis. Unfortunately, the efficacy and applicability of recently discovered anti-angiogenic agents are limited by their short circulating half-lives, cytotoxicity to healthy cells, and poor permeability across the blood brain barrier. Other tested strategies such as the promotion of tumor-specific apoptosis do not fare much better.

In this study, we have created a novel bi-functional molecule integrating angiogenesis inhibition and apoptosis promotion. The three type-1 repeat (3TSR) domain of thrombospondin-1 (TSP-1) is known to inhibit angiogenesis by targeting tumor-associated endothelial

cells and concurrently suppress the proliferation of tumor cells in a CD36-dependent manner. We hypothesize that the combination of the tumor-specific pro-apoptotic protein TRAIL with the 3TSR domain of TSP-1 will synergistically sensitize and prime non-responsive cells to TRAIL-mediated apoptotic therapy. Furthermore, to ensure a continuous on-site delivery of the novel bi-functional molecule, we employed immortalized human adipose derived mesenchymal stem cells (MSCs). These MSCs were immortalized by combinations of the genes hTERT, SV40T, and mBmi-1. Ultimately, we envision that testing the efficacy of the stem-cell-mediated bi-functional protein to simultaneously target both tumor and associated endothelial cells would offer vast potential for the treatment of a broad spectrum of cancers.

Examining Homophilic Interactions in the Protocadherin Gamma Cluster

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Cadherins are a very prevalent family of cell adhesion and signaling proteins. The clustered protocadherin subfamily plays a role in neural network development and dendrite self- avoidance pathways. There are more than 50 protocadherin isoforms that interact homophilically. The protocadherin isoforms expressed to the neuron membrane are selected for via stochastic promoter choice such that each cell expresses a unique set of protocadherins that are used to distinguish it from neighboring cells leading to proper neural network development. The expressed protocadherins create a biological 'AND' gate, which suggests a complicated signaling process. That is to say one cell will recognize itself if and only if there are homophilic interactions between all of the isoforms that the neuron expresses. Mutations in this protein family have been implicated in neurodegenerative diseases and schizophrenia.

The current study uses x-ray crystallography and other structural methods to learn more about the extracellular domain and hemophilic interactions of clustered protocadherins. While some previous studies have produced structures of the interaction site between individual protocadherins, there is not a good understanding of the overall architecture of these interactions. We wish to uncover the molecular basis of homophilic binding. Our plan is to conjugate cadherins onto DNA origami scaffolds to observe their interactions through electrophoretic motility shift assays or electron microscopy. DNA scaffolds allow us to modify fixed distances between conjugated protocadherins and see whether individual proteins have enough affinity to produce interactions or whether they need to be mounted in clusters to produce strong interactions, which is an overarching question in the field. These controlled conditions will allow us to observe what exactly affects binding specificity between protocadherins.

Selective Pexophagy in *S. cerevisiae*: Examining Atg36

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Cells maintain homeostasis by using sophisticated quality-control pathways to evaluate the fitness of their subcomponents, replace faulty cellular machinery, and synthesize new macromolecules as needed. During the process of selective autophagy, cells sequester entire unwanted organelles into specialized vesicles, condemning them to be broken down and recycled. To avoid both the wasteful degradation of functional organelles and the potential harm of those that are defective, it is crucial that the cell possess a way to quickly assess organelle damage. Our research focuses on the mechanisms by which selective autophagy targets and removes damaged peroxisomes in *S. cerevisiae*. Preliminary findings indicate that peroxisomal surface damage leads to phosphorylation of the autophagy protein Atg36. In order to determine how and why this phosphorylation occurs, we created a series of genetically engineered yeast strains, including a novel system for inducing acute peroxisomal damage. We first used this system to confirm that acute damage causes the phosphorylation of Atg36 *in vivo*. We then showed that a multi-purpose protein activator, Hrr25, is required for the Atg36 phosphorylation event. Separately, we produced several mutations in Pex3, the membrane protein that anchors Atg36 to the peroxisomal surface. When the interaction between Atg36 and Pex3 is forcibly blocked, Atg36 remains unphosphorylated, suggesting the importance of peroxisomal surface interaction for Atg36 phosphorylation. Moving forward, we aspire to use our constructs to further characterize the relationship between Atg36 modification, Hrr25 activity, and Pex3 anchoring. We hope that investigating the specific role of Atg36 in peroxisomal damage detection will provide insight into the underlying molecular logic behind selective autophagy, both for *S. cerevisiae* and within analogous molecular processes across all living systems.

Reconstitution of HIV-1 Envelope Glycoprotein Trimers into Nanodiscs for Vaccine and Structural Studies

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The recent discovery of broadly neutralizing antibodies (bNAbs) against diverse variants of HIV-1 Env, the viral membrane glycoprotein, and the partial protective effects of an Env subunit-based vaccine from a clinical trial in Thailand suggest that an Env immunogen may elicit a protective neutralizing response useful for an HIV vaccine. However, development of Env-based immunogens that faithfully mimic viral Env is impeded in part by the metastability of the native Env trimer, which also hinders structural studies. Currently, the structure of Env in a native conformation remains unsolved, and a complete structure of Env in a membrane context would facilitate both drug therapies and vaccine development. Here we attempt to create and characterize a tool for both

Env vaccine and structural studies by reconstituting HIV-1 Env into nanodiscs, nanoscale lipid bilayer discs enclosed by membrane scaffolding proteins (MSPs). Nanodiscs are stable and homogeneous, and offer a unique native lipid microenvironment for incorporated membrane proteins like Env, thereby protecting vulnerable Env epitopes and preserving Env conformation. We adopted a screening approach to optimize assembly conditions for Env-nandoiscs. Preliminary biochemical and structural characterization of the assembled Env-nanodiscs is in progress. Importantly, the assembled Env-nanodiscs are homogenous, stable, and protect vulnerable Env epitopes even under stringent conditions, and are a promising basis for future work involving vaccine applications and structural studies.

Structural Basis for the Inhibition of Peptidoglycan Glycosyltransferases by Small Molecules

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Peptidoglycan glycosyltransferases (PGTs) are a highly conserved class of proteins present in all bacteria. They polymerize lipid II, the monomer building block of the bacterial cell wall, into long glycan chains, which are then crosslinked to form the mature cell wall. Inhibiting PGT activity would therefore disrupt cell wall synthesis and kill bacteria. There are no approved antibiotics that inhibit PGTs, so the development of PGT inhibitors would represent a new class of antibiotics that could help overcome antibiotic resistance. The natural product moenomycin inhibits PGTs but is a poor drug candidate due to low absorption in humans. Previously however, a moenomycin analog was used to screen small molecules for PGT inhibitory activity, and several "hit" molecules were obtained. To provide detailed structural evidence that these hit molecules bind to PGT, we are attempting to co-crystallize various constructs of penicillin-binding protein 2 (PBP2), a PGT from *Staphylococcus aureus*, with these hit molecules. As PGTs are highly conserved, a co-crystal structure revealing the inhibitory mechanism of a hit molecule would make the molecule a great starting point for developing a new class of broad-spectrum antibiotics.

PI3K/AKT signaling promotes Blimp-1 expression via Akt-mediated inhibition of Foxo1 in T cells

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Multiple Sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system that is mediated primarily by autoreactive T cells. Previous publications have sought to characterize the immunoregulatory defects in these cells. Recently, the cytosolic multiprotein complex HLA-B-associated transcript 3 (Bat-3) has been identified as a key promoter of T cell pathogenicity in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS. Recent studies have demonstrated that Bat-3-deficient T cells exhibit increased activity through the PI3K-AKT signaling pathway, which plays a critical role in the regulation of central cellular functions. Dysregulation of the PI3K-AKT pathway has been implicated in a number of human diseases. Additionally, it has been demonstrated that Bat-3 deficiency in T cells upregulates expression of transcriptional regulator B lymphocyte-induced maturation protein-1 (Blimp-1). Blimp-1 plays a critical role in the maintenance of T cell homeostasis and is crucial to the induction of the key anti-inflammatory cytokines and the suppression of certain pro-inflammatory cytokines. Indeed, Blimp-1 deficiency in T cells leads to uncontrolled inflammation and autoimmunity. Taken together, these findings suggest the possibility of a direct role for Akt signaling in the promotion of Blimp-1 expression and thus an anti-inflammatory state in T cells, though an exact mechanism is undefined.

Foxo1 is a transcriptional regulator that is a central downstream inhibitory target of Akt. Previous studies in B cells demonstrate that Foxo1 drives transcription of the transcription factor Bcl-6, which is a direct repressor of Blimp-1 transcription. In T lymphocytes, however, Bcl-6 expression is relatively low, and Bat-3 deficient T cells actually lead to upregulation of the *Bcl-6* mRNA transcript. We therefore sought another explanation for increased Blimp-1 expression in response to increased Akt signaling in Bat-3-deficient T cells.

Intriguingly, Foxo1 ChIP-sequencing analysis in CD4+ T helper cells revealed direct binding of Foxo1 to the Blimp-1 locus. These results were further validated by ChIP-PCR. Taken together, our findings suggested that Foxo1 might directly repress Blimp-1 expression in T lymphocytes. To confirm our hypothesis, we co-transfected a luciferase reporter dependent on the Blimp-1 promoter with Foxo1 expression plasmid in 293T cells and subsequently measured reporter activity. We observed Foxo1-mediated repression of Blimp-1 promoter activity. Additionally, deletion of the Foxo1 binding site on the Blimp-1 promoter eliminated the ability of Foxo1 to repress Blimp-1 promoter activity. These results confirm direct suppression of Blimp-1 transcription by Foxo1 in T lymphocytes. Taken together, our studies define a mechanism by which PI3K-Akt signaling promotes Blimp-1 expression via Akt-mediated inhibition of Foxo1. Given that dysregulation of the PI3K-Akt pathway has been implicated in autoimmunity, a more detailed molecular understanding of the signaling mechanism is necessary in order to generate effective therapeutic targets.

Involvement of Inflammation in Alzheimer's Disease Pathogenesis

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Alzheimer's disease (AD) is a neurodegenerative disease that affects over 5 million Americans. AD is characterized by the formation of extracellular plaques composed of aggregated amyloid-beta (Aβ) peptides, as well as neurofibrillary tangles in the brain composed of intracellular hyper-phosphorylated Tau protein. Variable sequential cleavage of transmembrane protein APP by β- and γ-secretase results in different-sized Aβ species, most commonly Aβ38, 40, and 42. Mutations involved in familial Alzheimer's disease (fAD) lead to an increase

in Aβ42, the Aβ species most prone to aggregation. This increased ratio of Aβ42 and Aβ40 may lead to the increase in Tau and hyperphosphorylated Tau associated with AD.

Furthermore, recent studies suggest that the inflammatory process may contribute to neuronal degradation and impaired cognitive ability in AD patients, and key players in the inflammatory process such as astrocytes, microglia, and cytokines play a significant role in AD pathogenesis. However, the exact mechanistic contribution of inflammation to AD pathogenesis is not well understood. We hypothesize that toxic levels of secreted Aβ42 observed in the brains of Alzheimer's disease patients lead to an increase in Tau and hyperphosphorylated Tau, and induce an inflammatory response that leads to the development of the pathology of Alzheimer's disease.

The goal of my research project is to understand the relationship between Aβ42 and the inflammatory cascade using neurons and glia derived from human iPSCs. To this end, rat primary neural cultures were treated either with Aβ42-rich condition media from day 100 human fAD neurons or with the same media depleted of Aβ42. Higher levels of astrocyte activation were observed when neurons were exposesd to Aβ42-rich media, suggesting that increased levels of astrocyte activation are associated with the presence of fAD Aβ. Furthermore, Nanostring analysis of fAD neurons showed upregulated RNA expression for proteins involved in the inflammatory cascade such as C1S, LIMK1, MAP3K1, MKNK1, NFE2L2, STAT1, and STAT3 compared to wild type neurons. Similarly, ELISA performed on Aβ42-rich fAD condition media showed increased concentration of inflammatory cytokines such as IL-6 compared to condition media collected from wild type cells. Further experimentation will continue to elucidate the link between inflammation and AD pathogenesis.

BIOLOGY | *NEUROSCIENCE*

Thalamic Reticular Nucleus and Sleep: Auditory sensory gating and sleep spindles

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Recent findings of a genome-wide association study found several candidate genes for schizophrenia, including CACNA1l, a gene responsible for a calcium ion channel expressed largely in the thalamic reticular nucleus (TRn). The TRn is thought to act as a "guardian of the gateway to the cortex," allowing relevant stimuli to travel from sensory areas to the cortex, while filtering out irrelevant stimuli. The calcium ion channels found in the TRn have previously been implicated as regulators for EEG rhythms in non-REM sleep. Studies have also shown that non-REM sleep, specifically sleep spindles (an oscillatory burst of activity seen in the EEG in stage 2 non-REM sleep) correlate with learning improvements during sleep, and, more generally, with I.Q. Interestingly, individuals with schizophrenia tend to show various cognitive impairments, and simultaneously have lower spindle densities than healthy individuals. For example, sensory gating, the tendency of the brain to filter out redundant stimuli, is greatly impaired in individuals with schizophrenia, and this deficiency may explain many of their cognitive and attentional difficulties as a result of sensory overload to cortical areas of the brain.

Although sleep spindles are a purported marker for schizophrenia, the use of polysomnography to collect data during overnight study sessions is burdensome to participants and researchers. Our study seeks to correlate sleep spindles with other cognitive and physiological factors and identify possible surrogate markers for Schizophrenia to be used in future research. Our protocol involves two 90-minute naps, one overnight sleep session, and several tasks including the WASI IQ test, an auditory sensory gating task, a divided attention task, and questionnaires to measure schizotypal personality traits. This study is part of a collaboration with members of MGH, the Broad Institute, and McLean Hospital that seeks to elucidate the neurological and genetic causes of schizophrenia and to identify targets for its treatment and prevention. We are currently looking for a relationship among the above factors in healthy participants, but eventually hope to use our findings to inform further research in schizophrenic populations.

Effect of Developmental Activation of Serotonergic Neurons on Adult Aggression In *Drosophila melanogaster*

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The monoamine serotonin (5HT) is a major neurotransmitter in the central nervous system (CNS). It has been implicated in regulating aggression across species, in addition to its modulation of many other functions such as sleep, memory and courtship. Previous *Drosophila* research has demonstrated that acute inactivation of the entire serotonergic system of neurons reduces aggression, while selective activation increases aggression in adult male flies. Moreover, activating/inactivating a symmetrical pair of 5HT neurons located in the posterior lateral protocerebrum (PLP) yielded similar effects on aggressive behavior in adult males. Despite the importance of these 5HT-PLP neurons in the modulation of aggression, little is known of their morphogenesis. Our goal is to identify a critical developmental window in which these 5HT-PLP neurons are shaped to yield effects on adult aggression.

Using intersectional genetics, we expressed the temperature sensitive dTRPA1 channel in either the entire population of 5HT neurons, or exclusively in the 5HT-PLP neurons. When placed at higher temperatures, the channels open, and the relevant neurons are activated. Here, we show that activation of either the entire 5HT system or the 5HT-PLP neurons for the entirety of development yields adult flies with elevated levels of aggression. Furthermore, we examine sleep and locomotion, other phenotypes influenced by direct manipulations of the 5HT-PLP neurons. We show that full developmental activation has no significant effect on sleep or locomotion. Further research will restrict activation to the final three days of development, when 5HT neurons undergo dramatic reorganization, and will examine the resulting effects on aggression.

This research will help understand the connection between known phases of 5HT neuron morphogenesis, activation of the neurons during those times, and the long-term consequences of the increased neuronal activity during development. Ultimately, this knowledge will help elucidate the organization of aggression-modulating pathways in the *Drosophila* CNS.

Characterizing the Role of the miR-31 Homolog in the C. Elegans Nervous System

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Micro RNAs (miRNAs) are small, non-coding RNAs that negatively regulate gene expression by binding to messenger RNA transcripts, leading to silencing or degradation. These RNAs are highly conserved, with roles in cell development and disease pathology. The human miRNA miR-31 suppresses metastasis in breast and lung cancer, with detection in the blood stream used to diagnose metastatic cancer. However, miR-31's RNA targets, as well its role in cellular function, are not known. Using C. elegans, a model organism used in studying the genetics of development and disease pathology, we sought to understand the role of the miR-31 homologs in the mir-266 miRNA family.

Using GFP expression and single molecule Fluorescent In Situ Hybridization (smFISH), we found that several mir-266 family members are expressed in C. elegans head neurons. To see if mir-266 family members play a role in neuron development or function, we focused on a member (mir-A) expressed in 2 well-characterized neurons and screened for behavioral and developmental phenotypes. We found that the mutant was wild-type for locomotion behaviors such as speed, body bending, and reversal frequency, but demonstrated reduced head

bending. These results suggest that micro RNAs expressed in the nervous system affect behavior, suggesting a role in modulating cellular function. To identify candidate gene targets of mir-A, we utilized Fluorescence Activated Cell Sorting (FACS/RNA-seq) and Translating Ribosomal Affinity Purification (TRAP) to isolate RNA transcripts in neurons. Differences in gene expression levels between the mutant and wild type may suggest direct or indirect regulation by mir-A.

Our results suggest that miRNAs in the C. elegans nervous system play conserved roles in cellular function. Identifying gene targets of miR-31 homologs in this model organism will allow for a greater understanding of how miRNAs modulate gene expression and whether their role is conserved among animals, providing novel therapeutic targets.

Determining the Role of a Residual Motor Memory in Songbird Vocalizations

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Elucidating the mechanism of human vocal learning and control remains a challenge, as it involves a complex interplay between audition and motor functions. The zebra finch, a songbird that learns a complex stereotyped song, offers a tractable model that shares broad neurophysiological similarities with humans. As in human vocal learning, the young zebra finch uses auditory feedback of its own performance to correct deviations from a tutor provided vocal model – a process that results in a remarkably precise copy of the model within a few thousand practice renditions.

While much has been discovered regarding song learning, the process of song maintenance is not fully understood. Songbirds, including adult zebra finches, are known to utilize auditory input to refine and maintain their learned songs, resulting in a consistent and stable song pattern. Yet, it is currently unclear the extent to which such song maintenance relies on the same auditory feedback processes used during initial song learning. Given the fine motor control and repeated practice necessary to produce a good song, might a consolidated motor memory also help the bird retain its learned song, even in the absence of auditory input?

To test this, adult zebra finches were trained using conditional auditory feedback (CAF) to reliably increase the duration of a specific song syllable. After the termination of CAF and spontaneous recovery to their baseline-length songs, these birds were CAF-trained again and surgically deafened. Monitoring the duration of the succeeding bird songs and comparing the rate and magnitude of spontaneous recovery could potentially reveal the presence of a motor memory. A complete reversal to the baseline duration level would indicate a motor memory strong enough to correct the changes brought on by the CAF training, without auditory feedback processes. A more complete understanding of the mechanisms supporting the maintenance of learned skills could have important clinical applications for humans, potentially leading to the development of new therapies for neurological injuries and other diseases that compromise motor function.

A Large Scale CRISPR Screen to Investigate the Genetic Basis of Schizophrenia *In Vivo*

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Schizophrenia is a complex and serious disease of the nervous system affecting roughly 3.5 million Americans. Schizophrenics experience altered perception of reality, delusions, and disturbances to social behavior. While it has been shown that the disease has a strongly genetic component, an understanding of the critical genes involved in development of the disease phenotype *in vivo* remains limited. In this study, we used a large scale CRISPR screen in zebrafish to explore the phenotypic effects of knockout of 134 genes that are most strongly associated with schizophrenia, as identified via GWAS by the Schizophrenia Working Group of the Psychiatric Genomics Consortium. We focused on identifying phenotypic effects using imaging studies and behavioral studies. Imaging studies utilizing MAPK-based activity mapping and immunofluorescence were conducted to investigate changes to stimulus response and synaptic denisty in knockouts. Behavioral studies focused on identifying differences in pre-pulse inhibition behaviors and gross activity levels. We focused on examining genes miR-137,NTM, RAI, RGS6, TMTC, VRK2, ZNF536, and ZSWIM6. We are expected to receive our results shortly, which will move us toward a deeper understanding of the effects of deleterious genetic mutations in genes highly associated with schizophrenia.

Navigational Plasticity after Injury in *Drosophila melanogaster*

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Navigation requires several sensory modalities, among them proprioception, which allows an organism to sense the position of its body parts in three-dimensional space as well as the amount of force being applied by the body to the environment. Mechanosensory neurons that innervate muscles, skin, exoskeleton and other tissues send proprioceptive information to the brain by transducing mechanical energy into an electrical neural signal. For example, the flexing or extension of a joint results in the opening of ion channels that send proprioceptive signals to the central nervous system for further processing. A deeper understanding of proprioception in fruit flies may facilitate better understanding of the proprioceptive sense in humans, as well as disorders that result from faulty proprioception.

We are interested in how the proprioceptive system mediates navigational plasticity after injury in *Drosophila melanogaster*. In particular, we are investigating circling bias plasticity, which is the induced turn bias following amputation of a leg and subsequent recovery to unbiased turning over the following four days. We hypothesize that proprioceptive mutants lack the recovery observed in wild-type flies. Flies are placed in circular arenas and allowed to explore freely while video recording tracks the centroid of the fly during locomotion. We then quantify the turning bias and characterize both the immediate response to

amputation and subsequent recovery. Interestingly, we observe a larger induced circling bias immediately after amputation in wild-type flies compared to the proprioceptive mutants. While the response to amputation results are quite consistent, we are still trying to characterize the subsequent recovery phenotypes for the wild-type and mutant strains.

In addition, we are using the GAL4-UAS system to drive the tissue- and cell-specific expression of tetanus neurotoxin light chain (TNT) in selected neurons, effectively silencing them. We further plan to conduct a circuit screen during which we test many candidate lines that may be involved in proprioception based on the morphology of the proprioceptive neurons we are studying. Thus, we can begin to map out the neuronal circuit involved in processing proprioceptive information in *Drosophila*.

Cannibalistic Larvae: Assessing Feeding Behavior During Development in *Drosophila melanogaster*

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Animals display aggressive behavior to compete for resources necessary for survival and reproduction. Environmental cues and genetic factors contribute to aggressive responses. Previously, my laboratory bred a hyper-aggressive strain of *Drosophila melanogaster* (fruit flies), called "Bullies," by selecting males for fighting ability over 35 generations. Due to its fully sequenced genome, a large and growing number of genetic tools to manipulate function at the single cell level, and well-characterized neurobiology, *Drosophila* is an ideal system to study the neural basis of aggressive phenotypes.

Under nutritional stress, *Drosophila* larvae may exhibit a potential form of aggression, cannibalism towards larger conspecifics (Vijendravarma et al 2013). Starved *Drosophila* larvae use their mouth hooks to grate the skin of wounded wandering larvae (developmental stage before pupal formation). However, as larval mouthparts are not well suited for piercing larval skin, this raises questions as to the evolutionary role, function, and characteristics of cannibalistic behavior in *Drosophila*. Is feeding on conspecifics in *Drosophila* larvae an opportunistic, random encounter, or a directed hunting behavior? If cannibalism is a predatory hunting behavior, do social cues facilitate the localization of prey? Do genes associated with hyper-aggressive behaviors in adults affect cannibalism in larvae?

To answer these questions, I first optimized the protocol to reliably induce the cannibalistic phenotype in the laboratory. I starved larvae of the same developmental stage for two hours before confining them to a petri dish in groups or individually. These larvae were presented with two injured wandering larvae to compare the likelihood of cannibalism in groups and as individuals. Using the above-mentioned strain with a hyper-aggressive phenotype as adults, I also compared the frequency of cannibalism between wild-type and "Bully" larvae. My preliminary results set the stage for further experimentation on the social and environmental cues driving cannibalistic behavior and explorations of its neural basis.

Whole Brain Imaging in *C. elegans* under the Influence of Odours

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The Samuel lab aims to understand how the neural system in animals translates sensory stimuli into behaviour. A simple model organism widely used to examine the neural system is the roundworm *C. elegans*. It contains 302 neurons whose physical connectivity has been extensively mapped in previous studies. Chemicals known as 'odours', such as benzaldehyde and diacetyl, are used to simulate sensory stimuli like a food source. The worm responds to these odours by moving towards or away from the source. From behavioural and genetic studies, each odour is known to be either attractive or repulsive, and to stimulate a specific sensory neuron.

In this project we imaged the whole worm brain to find all neurons active under the influence of nine odours. The worms were placed in a microfluidic chip to immobilise them. In this environment we exposed the worm to the odours and imaged its brain using a spinning disc confocal microscope and fluorescence marked calcium receptors. Using this novel technique, the ultimate goal is to find a network of neurons responsible for chemotaxis.

Capturing Statistical Dependencies in Neural Populations in Mouse Parietal Cortex Using a Generalized Linear Model

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In the past decade, advancements in two-photon fluorescence microscopy have allowed for highly accurate in vivo measurements of neural population activity in mouse cortex. When used in combination with a virtual reality navigation system where mice navigate a virtual maze while running on a stationary ball, fluorescence imaging can capture the activity of hundreds of neurons in parietal cortex as a mouse is performing a decision task. Parietal cortex is thought to be recruited for tasks in which sensory evidence is translated into motor decisions, and measuring its activity in the context of a navigation-based decision task has the potential to uncover the computations that translate sensory input into motor output, as well as to reveal the information that is captured in the population in the context of such computations.

In particular, our work examines neural activity measured during an evidence-accumulation task, in which a mouse keeps track of a series of six visual cues that each correspond to either a left or right turn, and then turns the direction that was most frequently cued. Via the development of a carefully structured generalized linear model (GLM), we seek to produce a detailed description of the statistical dependencies between neurons' activity patterns, and between neurons' activity patterns and the contextual variables of the experiment. This will allow us to characterize for the first time what sensorimotor-related behavioral features are encoded in parietal cortex neurons during navigation decisions. We

will test competing hypotheses about coding mechanisms: One class of models predicts that each neuron encodes single or few behavioral features (e.g. visual cues or locomotor actions) with different groups of neurons encoding different features. An alternative model hypothesizes that each neuron encodes multiple task features (e.g. both visual cues and locomotor actions) resulting in a relatively homogeneous distribution of encoded features across the population of neurons. By comparing the sensitivities of neurons to contextual variables, the GLM will provide insight on the plausibility of these two models.

Investigating the Genetic Basis of Schizophrenia through Knockout Danio Rerio

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Schizophrenia is a chronic neurological disorder particularly prevalent in young adults. Although its symptoms, such as hallucinations, delusions, and catatonia, are widely recognized, its causes are not well understood. In 2014, researchers identified 108 genetic loci associated with the disease (Nature 2014). Our work examines the function of genes within these loci in Danio rerio (zebrafish), a particularly suitable organism for genetic manipulation.

My project specifically focuses on a subset of these genes implicated in neural and immune functions: grin2a, immp2l, lrrn3, kif5c, mbd5, bcl11b, epc2, apopt1, and tsnare1. To examine the phenotypic effects of these genes, we create genetic knockouts, or organisms that lose function of a specific gene. In our lab, we have successfully created zebrafish that are knockout in grin2a, immp2L, epc2, kif5c, mbd5, lrrn3, apopt1, and tsnare1 through CRISPR/Cas technology, a recent method that efficiently allows researchers to manipulate the genome.

We are currently examining the neural activity of these knockout zebrafish through phosphorylated extracellular-regulated kinase (pERK) brain imaging, a technique that documents the full brain activity of the zebrafish at the moment of fixation. Afterwards, we will apply behavioral tests, such as a series of taps and light switches, to knockout zebrafish to examine differences in their response as compared with wild-type fish. We will then compare the neural activity and behavioral traits characteristic of schizophrenia with our findings. We hope to understand both (1) the basic functions of these genes and (2) their relationship with schizophrenia. Only by understanding the genetics and molecular biology behind this disease can we design suitable treatments in the future.

Characterizing the Knockout C9ORF72 ALS Mouse Model

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Amyotrophic lateral sclerosis (ALS), also commonly known as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects the motor system. It results in the death of upper and lower motor neurons. As the disease progresses, patients begin to lose their ability to talk, walk, and eat. At end-stage, patients experience respiratory failure and ultimately die from this symptom of the disease.

Only 10% of ALS cases can be attributed to familial genetics whereas the other 90% are sporadic. 20% of familial cases have been attributed to a mutation in the SOD1 gene. Mutant SOD1 mouse models have been created and these models exhibit ALS pathology. The model is believed to result in ALS due to an accumulation of misfolded proteins. Although this model has been highly studied for the past twenty years, many critics have noted that it may not be a sufficient model for studying the pathology of ALS since the SOD1 mutation only accounts for 2% of all ALS cases.

Recently, a hexanucleotide expansion mutation located in the chromosome nine open reading frame 72 (C9ORF72) has been implicated as the cause of ALS and frontotemporal dementia. Not much is known about the function of this region but this mutation is considered to account for 30% of familial cases and up to 20% of sporadic cases. A knockout mouse model of C9ORF72 results in symptoms characteristic of ALS.

In order to appropriately understand the pathology occurring in these mouse models, I am currently in the process of using immunofluorescence on brain and spinal cord sections of these animals to characterize the cellular and protein interactions occurring in these tissues. I am interested in looking for markers of neuroinflammation and neuronal death. The results found in these tissue studies will allow for better focus moving forward in understanding the effects that the hexanucleotide expansion has in causing ALS.

Mapping the Inferotemporal Cortex in Macaque Monkeys

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When you look at a face, or a tree, or a piece of bacon, you don't think twice about how the raw visual information was packaged into a full-blown perception. The process of visual stimulus integration begins at the back of the retina, travels through a hierarchy of increasingly complex cells in the occipital lobe, and ends in the middle of the temporal lobe. This pathway can be roughly mapped from the posterior of the brain (beginning in the occipital lobe) to the middle of the brain (the temporal lobe), with the degree of complexity increasing as the information moves from posterior to anterior.

The end of the dorsal stream of visual processing is the inferotemporal (IT) cortex, and currently one of the biggest questions in neuroscience is whether or not there is an innate architecture to the organization of cells in this region of the brain. In other words, are we born with patches of the IT cortex already specialized to recognize faces, trees, and bacon? Studies in our lab have provided evidence to support the hypothesis that the IT cortex isn't mapped according to specific stimulus, but according to curvature: moving laterally along this region of the brain, cells respond increasingly to curved objects, which suggests that while there may not be innate 'face patches', or 'bacon patches', there are regions that specialize in recognizing specific objects based on their curvature.

Currently, our lab is performing fMRI scans on face-blind monkeys (young macaque monkeys that have never seen monkey or human faces), to determine whether or not they have an innate 'face patch', despite never having experienced seeing a face. The monkeys are shown faces and non-faces (hands, scenery, etc.) in the MRI machine, and the BOLD (Blood Oxygen Level Dependent) signal, which measures the level of activity in the brain via oxygen consumption, is measured in the IT cortex. fMRI is a subtractive technique, so in order to determine what brain regions are responsible for specific stimulus recognition, the activity of the IT when the monkey is looking at a face is compared to the activity when looking at a non-face. The brain regions that show a difference in activity are then pinpointed as the regions specifically responsive to faces or scenery, respectively. So, if in the upcoming scans we see little difference between activity in the 'face patch' region of the IT during face and non-face presentation, this suggests that the patch isn't innately responsive to faces, and the IT is shaped and mapped by experience.

Chronic Early Life Stress and Attention Skills

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Brain plasticity, or its capacity to reorganize neuronal pathways, is one of the most powerful concepts in neurobiology. Experience molds brain function in a profoundly age-dependent manner through shifts in the balance between excitation and inhibition that regulate the brain's ability to undergo change. By identifying the scope and effect of critical periods for the acquisition of skills associated with diseases we could begin to isolate risk factors and utilize brain plasticity to correct development and recover normal functionality as proven possible in the visual system.

Attention, or the ability to remain focused on an event over long periods of time, is an important component of neurological disorders, including ADHD, schizophrenia and Alzheimer's disease and have been shown to rely heavily on the functions of the prefrontal cortex (PFC). One primary factor associated with impaired PFC development is exposure to chronic early-life stress. Understanding when and how chronic stress affects stress-sensitive brain functions during development, especially sustained attention, has significant clinical importance. Our work aims to unravel this relationship. With this purpose in mind we induced acute stress in wild type mice during varying time-intervals throughout development and evaluated attention performance using a touchscreen visual discrimination task. Ultimately, we hope to identify the specific critical period in development in which introduction of stress maximally affects adult attention performance in mice.

Sensorimotor Learning using Sensory Prediction Errors

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The ability to develop and optimize motor commands is crucial for our interactions with the environment. In order to execute a specific motor task, it is hypothesized that we use the discrepancy between our expectations and the actual feedback from the environment—called a sensory prediction error (SPE)—to update our next motor actions. While SPE has been studied in primates during motor learning, the neural basis of this calculation remains unclear. Previous lesion and inactivation work in the Uchida Laboratory has shown that the motor cortex (M1) is required to learn and execute a complex sensorimotor task. We now aim to understand the role of SPE in updating such motor commands, which originate in M1. The interaction of SPEs in M1 has not been previously studied.

To probe how SPE is encoded at the neural level, we use *Mus musculus* as a model system, and train mice to perform a complex joystick-based sensorimotor task. After mice achieved proficiency at this task with 3-5 weeks of training, we implanted either tetrodes or glass windows into/over M1, and recorded the neurons of expert mice. We then analyzed the firing patterns of M1 neurons for signals that could be influenced by a SPE. Currently, we are recording from the same mice while they receive a perturbation from the environment, thus causing a prediction error signal. We aim to see if and how neurons in M1 modulate their firing after experiencing a SPE. In total, these studies aim to provide a greater understanding of how we use SPEs in executing and learning motor movements.

Characterization of Hyper-aggression in Selected Strains of *Drosophila melanogaster*

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Aggression is a fundamental behavior that many animals display in order to acquire resources, territories, and mates. Fruit flies serve as an excellent model organism to explore this behavior with their structured, quantifiable behaviors, and the availability of powerful genetic tools. By pitting two male fruit flies against each other in a fighting arena in competition for a single food resource, we can readily elicit aggressive behavior. As the flies fight for control over the limited resource, they show stereotypical behavioral patterns such as lunging (mid intensity fighting), and in a few cases, boxing (high intensity fighting). Fighting leads to the formation of a dominance relationship where the winner controls the food resource and chases the loser from the resource every time the two flies meet after the establishment of dominance.

By inbreeding winners for 35 generations, "bully" flies with a hyper-aggressive phenotype can be generated. Bullies start fighting early and go to higher intensity levels like boxing more frequently than the wild type parent strain. Most of our laboratory's previous studies have

focused on the use of a single selected line of bullies. Three additional lines were generated originally, however, that have not yet been fully characterized as to their hyper-aggression phenotype.

My main project has focused on characterizing the three additional lines of bullies with an ultimate goal of exploring genetic differences between the several bully lines. Behavioral assays show that all the bully strains exhibit hyper-aggressive behavior compared to a control strain. This result allows the possibility of comparing gene expression level differences in fly heads between the different bully and control strains. Whole RNA extraction from fly heads of different strains is under way towards that goal. Future work will be directed at identifying critical genes that show expression level differences between hyper-aggressive and control flies.

Social Regulation of Appetite by the Neuropeptide Oxytocin

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Adult *Danio rerio* are robustly social animals with consistent schooling behavior and social interactions that are important in appetite regulation. However, it is not clear whether larval zebrafish also exhibit similarly strong socially driven behaviors. Here we show that the presence of conspecifics augments food intake in seven-day old zebrafish, through a phenomenon known as social buffering. ERK phosphorylation (pERK) immunohistochemistry reveals distinct patterns of neuronal activation in the hypothalamus of fish feeding in groups compared to isolation. A subset of these activated cells co-localized with oxytocin-expressing neurons. Nitroreductase-mediated chemical-genetic ablation of these neurons attenuated the effects of social buffering on feeding. We are currently assessing the effects of genetic deletion of oxytocin on food intake. Overall, these results suggest that oxytocin is involved in the social regulation of appetite, complementing mammalian studies implicating oxytocin as a key factor to understanding the social dimension of appetite.

Visualizing Parvalbumin Circuit Changes in the Rett Syndrome Brain

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Rett syndrome is a rare genetic neurodevelopmental disorder phenotypically similar to autism-spectrum disorders and characterized by developmental regression between 6 to 18 months of age. Caused by a mutation in the MeCP2 gene, Rett syndrome is an X-linked dominant disease and affects girls nearly exclusively. Like other neurodevelopmental disorders, Rett syndrome is unique amongst diseases in that it does not exhibit visible hallmark pathologies; it is currently thought that these disorders lie instead in the connections and circuits formed between neurons, especially during critical periods of development.

Specifically, we are interested in investigating the inhibitory parvalbumin-positive neuron circuits in the visual cortex of MeCP2- knockout mouse models of Rett syndrome, which exhibit hyperconnectivity and hypermaturation when compared to wild-type controls. Previous research has shown that the number of synapses from parvalbumin cells onto pyramidal cells is increased in MeCP2-knockouts; in this project, we explore whether parvalbumin-parvalbumin circuits are similarly altered in mouse models of Rett syndrome.

In order to visualize and analyze parvalbumin circuits in MeCP2-knockouts, we utilize Brainbow technology to label each parvalbumin neuron with a different color. We troubleshoot to optimize Brainbow for our purposes to trace synapses from parvalbumin cells onto other parvalbumin cells. In addition, by modifying the CUBIC protocol used to clear the entire mouse brain through two cocktails of reagents, we seek to adapt the protocol to be optimally compatible with Brainbow immunolabeling. This protocol may enable the visualization of complete neural circuits through confocal or two-photon microscopy, eliminating the need for and the limitations produced by sectioning.

BIOLOGY | Organismic & Evolutionary

Adaptive Evolution - Vibrissae Morphology in Peromyscus Mice

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Adaptation to the environment is a key element of evolution via natural selection. In this way, differential habitats can cause even closely related species or subspecies to develop diverse morphological characteristics. My project involves examining this phenomenon through vibrissae morphology across Peromyscus deer mouse subspecies. The specialized hairs known as vibrissae, or whiskers, are present in almost all mammals except *Homo sapiens*, which suggests they are highly important. It has been hypothesized that vibrissae length is correlated to the habitat of the particular subspecies – more specifically, that arboreal (tree-dwelling) individuals have proportionally longer whiskers than their terrestrial prairie counterparts so as to confer better balance and sensory input for climbing. *Peromyscus*, the most populous mammalian genus in the United States, contains species and subspecies that have radiated into various habitats, and provides a good model system to investigate this hypothesized trend.

To this end, I identified 11 key subspecies among *Peromyscus maniculatus*, *P. polionotus* and *P. leucopus* – some arboreal and some terrestrial/fossorial (burrowing) – and, using specimens from the Museum of Comparative Zoology collections, recorded morphological measurements for individuals of each subspecies. Comparisons of the caudal offset whiskers – the four whiskers that are farthest from the snout and typically the longest – show significant differences in length between most of the subspecies studied. For all but 3 of the subspecies, we see a correlation between length of vibrissae and habitat type, with subspecies occupying forested areas tending to have longer whiskers than those from non-forested environments. We are currently working on further analysis of habitat use and phylogenetic relatedness of the subspecies, and future work could also include identifying the genetic factors affecting this trait. From this initial focused study, I am also planning to more broadly survey whisker morphology between arboreal and terrestrial species or subspecies within other rodent and mammal clades and through this, gain a better understanding of adaptive evolution.

Hybrid Fitness and Reinforcement in Three *Phlox* Species

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One goal of evolutionary biologists is to understand the process of speciation, which involves the accumulation of reproductive isolation. Reproductive barriers can be categorized as prezygotic or postzygotic, where prezygotic barriers prevent the formation of hybrid individuals and postzygotic barriers prevent hybrids from surviving or successfully reproducing. Postzygotic reproductive barriers are equivalent to factors that cause reduced hybrid fitness. One process which increases reproductive isolation is reinforcement. Reinforcement is the natural selection for increased prezygotic barriers due to an existing fitness cost of hybridization from postzygotic barriers. In other words, if it is costly to produce a hybrid zygote, yet the hybrid is not as reproductively successful as a non-hybrid, there is a selective advantage for traits which prevent fertilizations that produce hybrids.

Reinforcement has been observed in Texas wildflowers *Phlox drummondii* and *P. cuspidata*: While the two species generally have similar flower color, reinforcement maintains a difference in flower color where their ranges overlap. I am studying the role of reinforcement in the evolution of three species in the *Phlox* genus, *P. drummondii*, *P. cuspidata*, and *P. roemeriana*. I am interested in quantifying postzygotic reproductive isolation in order to understand the forces driving reinforcement. I evaluate postzygotic reproductive barriers by measuring rates of growth, survival, and fertility in hybrids compared to non-hybrids. Specifically, we are performing controlled crosses between and within species and their hybrids in order to quantify maternal and paternal fertility. To further study paternal fertility, I will stain pollen to determine pollen viability in hybrids. We expect to find that hybrid individuals have lower fertility than non-hybrids, indicating a degree of postzygotic reproductive isolation. The strength of postzygotic reproductive isolation may indicate the strength of selection driving reinforcement. Details in the direction and relative strength of reproductive isolation may help us understand why reinforcement does or does not occur among these species.

Ontogenetic Scaling of Phloem Sieve Tubes in *Quercus rubra*

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The mechanics of water transport through the xylem cells of plants have been well-studied, but the journey of the carbohydrates produced in photosynthesis and transported in the phloem cells to the rest of the plant remains elusive. The phloem consists of specialized conducting tissue made up of cells that are alive at maturity (in contrast, to nonliving xylem cells), though they function without a nucleus or many other organelles. These cells, known as sieve tubes, are responsible for transporting sugars along the length of the plant. The phloem is still poorly understood due to the fact that phloem cells respond quickly to damage. This sensitivity poses many difficulties to researchers attempting to image and study this tissue.

In 1930, the Munch Pressure Flow Hypothesis proposed that carbohydrates move from "source" to "sink", driven by the gradient in turgor pressure that results from the influx of water by osmosis when sugars are loaded into the phloem in sources (e.g., leaves) and the corresponding efflux of waters as sugars are utilized for growth and respiration in sink tissues (e.g., roots). Since 1930, many questions have arisen regarding

the validity of this hypothesis to explain flow in large trees, as there is presumably too much resistance along the pathway of a tree to allow for this type of pressure flow. Recent work in the Holbrook Lab shows that phloem cells widen towards the base of the tree and taper toward the top (Savage, Clerx, and others, unpublished data). This scaling allows for decreased resistance as the path lengthens so that flow along a tall tree is possible.

Previous studies on the scaling of sieve tubes examined mature trees and compared species of different sizes. My project tested the ontogenetic scaling of phloem sieve tubes within a single species, *Quercus rubra* (Red Oak). I sampled phloem at various heights in four different size classes of *Quercus rubra* in the Harvard Forest. For each sample location, phloem was prepared in two ways. In the first, samples were frozen into liquid nitrogen immediately following collection, then, cross-sectioned, radially-sectioned and run through a digest solution that I prepared in the lab specifically for this purpose. After the digestion is complete, the samples will be mounted on specimen mounts, coated in gold to ensure a conductive surface, and imaged in a Scanning Electron Microscope. I will then measure phloem sieve plate diameter, pore number, and pore area. For the remaining samples, I allowed the tissue to produce callose prior to placing them in fixative. Callose is a polysaccharide produced in plants in response to wounding and, in the case of phloem, deposited to block the pores in the sieve plates. The callose deposition allowed me to perform a staining technique that involves aniline blue and calcofluor white dyes to highlight the sieve plates and the cell walls respectively. These samples were imaged using an inverted fluorescent microscope and the sieve cell length and width, as well as the angle of the sieve plate, are in the process of being measured.

These measurements will allow me to calculate the conductivity (k) in sieve cells throughout the phloem, as well as to measure the anatomical differences that lead to variations in conductivity along the length of oak trees that range in size from less than 1 meter tall to over 25 meters in height.

Beesearch

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Bumblebees are among the pollinators essential to food production, and several species have recently been experiencing an alarming decline. The large-scale disappearance of honeybees (deemed Colony Collapse Disorder) is generally attributed to a combination of factors including pesticides and disease, and bumblebees seem to be affected by these factors as well. This summer, I'm working with graduate student Callin Switzer on his experiment to test whether buzz pollination is affected by imidacloprid, an insecticide that has been banned in the European Union but continues to be used in the United States. Imidacloprid is a neonicotinoid (similar in chemical structure to nicotine) used to kill pests that has already been shown to have several negative effects on bees.

The experimental setup includes six hives of bumblebees, three to serve as the treatment group and three to serve as the control group. Foraging bumblebees in the treatment group are fed nectar infused with imidacloprid while the bumblebees in the control group are fed nectar without the pesticide. The bees have access to flowering tomato plants, which produce pollen but not nectar, so the bees drink only the nectar provided. As the treated and untreated bees collect pollen from flowers, we film them with high-speed cameras and analyze the videos. To collect pollen from tomato flowers, bees must engage in a specialized behavior called buzz pollination; in order to shake pollen out of the flowers' anthers, the bees grab onto the anthers and vibrate their bodies using their flight musculature without flapping their wings. Buzz pollination characteristics measured on the videos (buzz frequency and amplitude of flower shaking) can be used to compare how effective bees in the two groups are at removing pollen. Pollen collected by workers is an essential protein source for the queen and the larvae, so any change in pollen-collecting efficiency could have an effect on the overall growth rate of the hive. This experiment will help us determine whether neonicotinoids affect bees' ability to collect pollen via buzz pollination, which will add to our understanding of the ways in which pesticides can affect bees and their behavior.

Testate Amoebae as Hosts for Legionella Bacteria

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Legionella bacteria are a group of gram-negative bacteria that live as intracellular pathogens in various aquatic protozoa. Certain species are known to be able to cause Legionnaire's Disease in humans. Legionnairre's disease is caused by infection of the lung by Legionella bacteria after inhalation of contaminated, aerosolized water. The disease presents itself as a severe form of pneumonia. We looked for the presence of Legionella spp. in testate amoebae of the order Arcella which has not been previously investigated before. PCR and direct sequencing of the 16S rRNA have confirmed the presence of Legionella spp. in testate amoebae. This shows that testate amoebae, which are ubiquitous to aquatic habitats can be another environmental reservoir for Legionella bacteria. Furthermore, as Arcella is a very basal eukaryotic clade that has been relatively unchanged for about 800 million years, these findings support the hypothesis that protozoa gave Legionella bacteria an intracellular environment suitable for Legionella to evolve their current pathogenic capabilities. This could give us a better understanding of the evolution of pathogenicity and the development of intracellular symbiosis.

The Effects of Pregnancy Hormones on Burrowing Behavior in *Peromyscus* Mice

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Pregnancy hormones act in several regions of the brain and thereby can influence female behavior. For example, the endogenous steroid

hormone progesterone suppresses the hypothalamo-pituitary-adrenal axis's response to stress.

Our project aims to uncover the neural and hormonal mechanisms by which pregnancy can alter maternal behaviors in deer mice, with a special focus on burrowing behavior. We are focusing on two sister species: the deermouse (*Peromyscus maniculatus*) and the oldfield mouse (*P. polionotus*). We hypothesize that pregnant mice, perhaps via increased levels of progesterone, would build longer burrows than virgin mice.

Our results suggest that pregnancy differentially affects burrowing behavior in *P. maniculatus* and *P. polionotus* mice. While there was no significant difference in the lengths of burrows produced by *P. maniculatus* female mice, we found that pregnant *P. polionotus* females built significantly longer burrows than virgin females. This differential effect between species may be explained by the fact that pregnant *P. polionotus* mice have significantly higher progesterone levels than pregnant *P. maniculatus* mice. To test this hypothesis, we are currently measuring and then manipulating progesterone levels to test for an effect on burrowing. Specifically, we will inject biologically relevant amounts of progesterone into ovariectomized mice and subsequently measure their burrowing performance to test the specific role of progesterone on burrowing behavior. Together, this work aims to make a link between pregnancy hormones and maternal behavior in mice.

A Timeline of Activity and Nest-Building in *Peromyscus*

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Peromyscus polionotus and *P. maniculatus* are two closely related species of mice that differ in their latency to nest. However, these data were collected at discrete time-points, which disrupted the mice and perhaps altered their nesting behavior. Additionally, although we know that both species will build nests within a 24-hour period, we do not know specifically when nest-building behavior occurs naturally. Thus, we would like build a comprehensive timeline of nesting to understand when and how these mice construct their nests, and what behaviors they exhibit when not nest building. As a first step, we filmed individuals of the two species overnight and scored their nests at half-hour intervals to characterize the general timeline of nest-building. Based on this timeline, we then focused on four hour-long intervals: one shortly after the lights went off in the animal facility ("dusk"), two surrounding the time at which the lights went on ("before dawn" and "after dawn"), and one at the time when the previous data was collected ("standard"). During these hour-long intervals, we created a "time budget" for each animal, from which we noted when they displayed one of eleven non-nesting behaviors or one of six nesting behaviors. This allows us to analyze how the mice are utilizing their time at during these intervals. These time budgets will provide us with an idea of how and when our mice build their nests and allow us to test whether consistent behavioral differences have evolved between these species. These data will provide a broader context to interpret earlier nesting data and allow us to not only place the snapshot data into the timeline of nesting behavior, but also to examine how nesting fits into the larger picture of *Peromyscus* behavior.

Characterizing Differential Gene Expression in Probing Larvae of the Caribbean Coral Species *Porites astreoides*

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Coral reef ecosystems are increasingly threatened by climate change and anthropogenic factors— such as pollution, fertilizer run-off, tourism, and detrimental fishing practices. Approximately twenty percent of the world's coral reef ecosystems have already been either completely destroyed or damaged beyond the point of projected recovery; another twenty-four percent are at risk of similarly collapsing. Conservation efforts have accordingly turned toward understanding the molecular processes of corals to assess the limits of their survival while monitoring global climate change and anthropogenic factors. Though some molecular studies have been conducted on Pacific corals, scientists have only recently begun exploring Caribbean coral genetics. The genetic basis behind coral metabolism in all known species remains poorly understood.

We are characterizing differential gene expression during the larval stages of Porites astreoides, an abundant reef-building coral found in the Atlantic Ocean and Caribbean Sea. We have focused our research on larvae actively probing for substrates to settle on the ocean floor. This is a crucial period for larvae, because it implies that they have detected the necessary environmental cues to prepare for settlement. We have extracted messenger RNA for transcriptomics sequencing of probing larvae. This was done by removing messenger RNA from larval tissue, converting it into complementary DNA, amplifying the DNA, then having the final products sequenced. Once our sequences are processed, we plan to employ bioinformatics to analyze the transcriptomics data. This research will shed light on the coral's various molecular responses to environmental cues and further investigate the genetic basis of coral settlement.

BIOLOGY | Stem Cell & Regenerative

Investigating the Role of Heart Extracellular Matrix in Cardiomyocyte Maturation

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Various groups have demonstrated the robust differentiation capacity of human derived induced pluripotent stem cells, iPS cells; however molecular analysis suggests that cells differentiated from stem cells are not fully mature in most cases. For example, cardiac differentiation yields beating cells with an immature cardiac gene profile in the dish and limited functional ability when transplanted into the mammalian heart including in human clinical trials. Recent evidence suggests that the extracellular matrix can modulate stem cell fate, and cardiomyocyte phenotype. In this project, we hypothesize that the decellularized matrix will improve the maturation of iPS cell-derived cardiomyocytes, a concept that is supported by recent preliminary data. We aim to characterize specific factors in the extracellular matrix that contribute to maturation using biochemical fractionation, proteomic screening, and in vitro studies. Enhanced maturation of cardiomyocytes will provide a clinically relevant model for scientific study with potential to lead to novel therapies for cardiac disease.

Aim 1: To test the hypothesis that the decellularized matrix can improve maturation in differentiated cardiomyocytes.

Aim 2: To test the hypothesis that biochemical deconvolution of decellularized matrix will reveal specific factors that guide cardiomyocyte maturation.

Generation of Dihydroorotate Dehydrogenase Mutant Zebrafish Using CRISPR/Cas9 Genome Editing

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Melanoma is a dangerous form of skin cancer caused by unrepaired DNA mutations in the melanocytes. In recent years, melanoma mortality rates have risen, prompting the search for new and more effective therapies. The Zon Laboratory has identified a chemical called leflunomide that has been shown to reduce melanoma growth. Understanding the mechanism of leflunomide may uncover novel ways of treating melanoma.

Leflunomide is a known inhibitor of Dihydroorotate Dehydrogenase (DHODH), an enzyme involved in de novo pyrimidine biosynthesis. In order to better understand the role of DHODH in vivo we decided to create a zebrafish mutant line for this enzyme using the CRISPR/Cas9 system. We injected embryos with two guide RNAs (gRNAs), one for exon 2 and the other for exon 3, aiming to cause a large deletion of the gene. Once the fish reached adulthood, they were screened for the expected gene mutagenesis. Out of 29 fish, one mutant was found containing a 1.6 kb deletion, which causes a frame shift mutation. The progeny of this mutant will be raised for future studies.

We are also using a novel approach to generate maternal-zygotic mutants for DHODH in collaboration with the Schier Laboratory using CRISPR/Cas9 technology. This method will ensure that no maternal effect genes interfere with any induced mutations during early embryonic development. Since the generation of these mutants might be very inefficient, we are adopting the gRNA blanketing approach used by the Schier lab. The method consists of designing multiple gRNAs to target a specific exon. A total of 12 gRNAs were designed and synthesized: 6 to target each of the exons 2 and 3 of dhodh. Next, these gRNAs plus Cas9 protein will be injected into embryos during the one cell stage. We then will test their mutagenesis efficiency by performing a T7 assay. Finally, we will inject the most effective gRNAs in combination with dead end mRNA into zebrafish embryos in order to create germ cells that contain the dhodh mutation. This new approach should facilitate the generation of mutants to be used for later studies.

Elucidating the Role of ax-Natt and the Wound Epidermis in Axolotl Limb Regeneration

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Axolotl salamanders are capable of regenerating entire limbs upon amputation, but the molecular mechanisms underlying the initiation of this process are still largely unknown. To investigate this mechanism, we examine the role of the specialized wound epidermis that forms immediately following limb amputation, preceding the emergence of a progenitor-rich blastema structure that is essential for regeneration. Single cell RNA-Sequencing data was used to identify ax-Natt as the most highly expressed gene in the wound epidermis, the gene product of which is a Natterin toxin, predicted to have kininogenase and pore-forming activity. Up until now, the role of such activity in regeneration was completely unknown and, given that the axolotl genome has not yet been sequenced, difficult to investigate.

However, by applying a kininogenase inhibitor (aprotinin) to regenerating limbs, we observed severe regenerative defects, highlighting the importance of the kininogenase activity that Natterin is expected to have. Furthermore, misexpression of ax-Natt in intact limbs resulted in a 7% increase in mean cell proliferation ($p=0.0003$), and noticeably higher proliferation in nerve bundles particularly. Immunohistochemical assays were then used to confirm a 23% increase in mean proliferation of nerve bundles specifically ($p=0.013$), demonstrating Natterin's effect on nerve proliferation.

Taken together, our experiments indicate a significant relationship between ax-Natt expression and the induction of nerve cell proliferation. It is possible that the Natterin protein directly causes nerve cells to proliferate, or its kininogenase activity may initiate a pathway with many downstream results including nerve proliferation. Our study highlights

the regenerative importance of ax-Natt expression by the wound epidermis and offers preliminary insights into the Natterin mechanism. Further analysis of Natterin function is necessary to yield a more exact understanding of this important component of regeneration.

Characterization of HLA-C Expression in Human Extravillous Trophoblasts

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Extravillous trophoblasts are essential for the physical anchoring of the placenta to the maternal uterine wall, altering of the vasculature for adequate blood supply, and prevention of maternal immune attack. The molecules involved in allorecognition by maternal immune cells belong to the highly polymorphic major histocompatibility complex (MHC), and are known in humans as human leucocyte antigens (HLA). EVT express HLA-C, HLA-E, and HLA-G (but not HLA-A and HLA-B) and avoid immune attack despite being allogenic. HLA-G+ EVT have been shown to increase maternal regulatory T cells that may suppress maternal allogeneic responses. Term EVT that express allogenic paternal HLA-C are also correlated with an increased maternal lymphocyte response, while matched HLA-C pregnancies are protected from complication. These findings suggest that immune activation by EVT is required to facilitate trophoblast invasion while preventing immune rejection.

To investigate the role of primary EVT in maternal–fetal tolerance, cells are isolated from both villous tissue obtained from first trimester elective terminations and healthy term placentas. HLA-G+ EVT are purified by macroscopic separation from decidual tissue, multiple rounds of digestion, and collection from a density gradient. Cells are then cultured for 1-2 days on fibronectin and analyzed for expression of HLA-G, HLA-C, but also EGFR1 and HLA-E. Certain cytokines, such as tumor necrosis factor-α and interferon-γ, are potent inducers of HLA expression and are used to mimic a more pro-inflammatory environment in culture to induce expression of surface markers and characterize the EVT immune profile.

Towards an *In Vitro* Model of Amyotrophic Lateral Sclerosis Using Directed Differentiation of Human Pluripotent Stem Cells into a Variety of Neuronal Subtypes

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Amyotrophic Lateral Sclerosis (ALS) is a debilitating neurodegenerative disease in which progressive loss of spinal (lower) and cortical (upper) motor neurons causes paralysis and eventual death. ALS is the most common motor neuron disease, with over 140,000 new cases diagnosed every year. The study of the neurodegenerative diseases like ALS can be difficult, however, because of the relative inaccessibility of the affected tissue. Due to these complications, researchers face obstacles in probing the disease at the cellular and molecular level. Furthermore, despite the major genetic component of ALS, traditional in vivo disease models may not capture the full spectrum of the disease, as only 10% of ALS cases are familial, or caused by inherited mutations, whereas the other 90% are sporadic cases, or mutations that result from complex interactions between genetics and the environment.

Developments in stem cell technologies allow for reprogramming of patient cells into induced pluripotent stem cells (iPSCs) while maintaining the genetic background of the cell donor. The ability to differentiate these iPSCs into a variety of lineages and cell types enables the development of an in vitro model of ALS. In this study, we differentiate human iPSCs from patients with different forms of sporadic and familial ALS into deep layer cortical projection neurons and spinal motor neurons, their axonal targets, for the study of ALS disease progression as well as into GABA-ergic cortical interneurons as a control neuron type unaffected by ALS. Results of differentiations were validated using qRT-PCR and immunohistochemistry. Using a combination of reporter lines and surface markers, we have demonstrated the ability to further select for neural progenitors cells (NPCs), mature neurons, and astrocytes from human iPSC-derived cultures generated by these uniform differentiation protocols. ALS is known to be caused by both cell-autonomous and non-cell autonomous factors, such as from glial toxicity. Thus, isolating these subtypes provides an opportunity to create a complete human model of ALS, including glia-neuron interactions. Future studies will focus on characterizing the disease pathologies found in this model.

Dynamic Imaging via the CRISPR/Cas System of a DNA and lncRNA Regulatory Feedback Implicated in Cartilage Formation in Humans

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Long noncoding RNAs (lncRNAs) are a large and distinct category of transcribed RNA molecules that do not encode proteins but fulfill important and versatile roles in our body. LncRNAs have been found to be differentially expressed in various types of cancer and cardiovascular and neurological disorders. The lncRNA of interest in our project is CISTR-ACT, an enhancer encoded regulator on chromosome 12 that interacts with the gene PTHLH on chromosome 12 and with SOX9 on chromosome 17. PTHLH is a hormone whose regulation is essential for the cartilage formation in humans. Any dysregulation leads to skeletal malformations (chondrodysplasia) during embryonic development, including the shortening of fingers and toes.

Our goal is to investigate and image the DNA and lncRNA regulatory interactions between chromosome 12 and 17 implicated in the pathogenesis of chondrodysplasias. We use a microscopical approach in which we localize fluorescent labels to the CISTR-ACT, PTHLH, and SOX9 genomic regions in living mesenchymal stem cells and chrondrocytes (mature cartilage cells). We use a confocal microscope to image and investigate the nature of these interactions between these genomic regions. We further plan to create time-lapse videos of mesenchymal

stem cells to investigate the spatiotemporal interactions between these three regions as they differentiate into mature chrondrocytic cells. We also have created CISTR-ACT knockout mesenchymal stem cells and chrondrocytes to determine a systematic and combinatorial view of how enhancers encoding lncRNAs may crucially regulate gene expression in normal skeletal development. This research will elucidate how lncRNAs play a role in the development and pathophysiology of disease and how they contribute the genomic architecture.

Analyzing and Testing the Effectiveness of New Drug Treatments for Duchenne Muscular Dystrophy using Zebrafish Models

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Duchenne muscular dystrophy (DMD) is a recessive X-linked genetic disease that affects around 1 in every 3600 young males. DMD is a severe form of muscular dystrophy caused by a mutation in the gene coding for the essential muscle building protein dystrophin. The mutation renders dystrophin unable to prevent excess calcium from entering muscle cells, causing mitochondria in the cell to burst that kills the muscle cell. Muscles in affected males will not be able to reform properly after dystrophy and affected individuals will subsequently undergo strong degeneration of muscle in the legs, soon spreading to the arms, spine, and neck regions. Typical life expectancy is around 25 years and as there is currently no known cure, current therapies aim to alleviate symptoms. Current research on DMD focuses on exon-skipping, stem cell replacement therapy, analog up-regulation and gene replacement.

Our work in the Kunkel Lab - where dystrophin was first identified as the protein altered in DMD - focuses on possible drug treatments to alleviate the dystrophy experienced by affected individuals. We currently employ the zebrafish (Danio rerio) model of DMD to study the mutated dystrophin gene and associated protein products. The zebrafish model of DMD, sapje, allows us to observe the effectiveness of treatments in an animal model that exhibits the DMD phenotype and conserves the dystrophin complex. My work focuses on using sapje zebrafish to determine the effectiveness of a new drug treatment under development in conjunction with Karyopharm Therapeutics. The goal is to determine the ability of this drug to alleviate and/or partially correct the DMD phenotype in developing mutant zebrafish. At our current stage, we have observed partial effectiveness in zebrafish drug screens via birefringence scores and are working toward genotyping the screened fish to understand the effect the drug has on the dystrophin gene.

A Comparison of Endogenous Signaling in Human Pluripotent Stem Cells Cultured in Different Maintenance Culture Media

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Human pluripotent stem cells (hPSCs), which include embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs), are valuable tools for studying organ development and regeneration and modeling disease pathophysiology. Although it has been observed that the maintenance conditions in which these cells are cultured affect their propensity to differentiate into different lineages, the mechanisms by which this occurs remain unknown. We hypothesized that signaling pathways activated by factors in these different media preparations influence the ability of hPSCs to respond to exogenous growth factors or small molecules when subjected to differentiation conditions. We analyzed baseline gene and protein expression in H9 hESCs cultured in feeder-free conditions in one of three different serum-free, chemically defined media preparations: mTeSR (Stem Cell Technology), FF2 (ReproCELL), and StemFit (Ajinimoto). Once the cells reached 70% confluence, they were harvested for RNA and protein isolation. Quantitative RT-PCR was performed to evaluate the endogenous expression levels of Nodal, BMP, TGF-beta, and FGF signals previously shown to be involved in the maintenance of pluripotency as well as differentiation of hPSCs. Activation of TGF-beta signaling pathways was examined by assessing the protein expression of phosphorylated Smad2 by Western blot. Defining the effects of different culture media designed to maintain pluripotency on endogenous signaling within hPSCs will provide us with greater insight into how to modulate differentiation conditions to obtain desired cell lineages.

SMYD1 and Acute Heart Regeneration

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On its own the mature human heart cannot significantly regenerate damaged heart tissue. This becomes especially problematic following a myocardial infarction as the hearts of survivors have inadequate function. Preliminary results from two in vitro experiments show that SMYD1, a protein essential for ventricle development, may have some therapeutic potential in increasing the proliferative capacity of cardiomyocytes and therefore offering new strategies for repopulating damaged heart tissue. We have done 3H-Thymidine incorporation assays to show that primary rat cardiomyocytes have an increase in proliferation when overexpressing SMYD1 with lentiviral transfection, compared with control lentivirus constructs. Furthermore, immunofluorescence staining for proliferative cell cycle markers confirms the 3HT assay results. Our preliminary data also suggests that SMYD1 could possibly have a synergistic effect on NRG1 mediated increase in proliferation in

cardiomyocytes. Data from the 3HT assays and immunofluorescence staining showed even higher increases in rat cardiomyocyte proliferation when recombinant NRG1 was added to primary rat cardiomyocyte cultures along with SMYD1 overexpression. Future goals will aim to explore this possible synergistic effect and ultimately develop an acute therapeutic for MIs.

Generating Mouse Models for Lin28b Expression from Early Embryogenesis to Adulthood and its Reactivation Dynamics in Tumorigenesis

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Lin28b is a RNA-binding protein that drives tumorigenesis in many human cancers. As an oncofetal gene, its expression is high in early development but downregulated as growth proceeds. However, in a significant number of human tumors, Lin28b expression is aberrantly reactivated and tends to be associated with advanced disease progression, and poor prognosis and survival. While many gain- and loss-of-function studies show that Lin28b is critical in tumor initiation and maintenance, there are no viable tools to detect its expression in mouse tumor models. The reactivation dynamics of Lin28b in tumorigenesis have yet to be defined, and yet this information is critical to better understand how Lin28b contributes to the initiation and maintenance of tumors and ultimately will help us determine when and where therapeutic targeting of Lin28b is a viable option.

In order to develop the tools necessary to observe Lin28b expression in mice, I will use the CRISPR-Cas9 genome engineering technology to target a fluorescent reporter gene, Venus, to the 3' end of the endogenous Lin28b locus. My goal is to generate Lin28b reporter mice that can be used to characterize Lin28b expression from early embryogenesis into adulthood, and to define the reactivation dynamics of Lin28b in the context of hepatocellular carcinoma.

Ultimately, I hope to cross Lin28b reporter mice with mouse models for liver cancer and analyze the resulting progeny to determine the relationship between Lin28b expression and liver cancer. Besides proving useful in helping us understand the intersection between Lin28b and liver cancer, these reporter mice may additionally give us insight into potential drugs that target liver tumorigenesis and thus have a profound impact on future medical treatments.

Using Cerebral Organoids to Model Autism Spectrum Disorders *In Vitro*

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Autism spectrum disorder (ASD) is a complex and heterogeneous psychiatric disease that often manifests in learning disabilities. The cerebral cortex orchestrates higher-order functions, including learning. Disrupted neuronal activity in the cerebral cortex is implicated in ASD. Genome-wide association studies have identified multiple mutations correlated with ASD, but understanding the role of specific mutations is difficult without a model of neuronal networks in human tissue. An emerging approach to modeling the human cerebral cortex consists of using cerebral organoids. Cerebral organoids are *in vitro* 3D models of the human brain generated from human pluripotent stem cells, which can be induced to self-aggregate and form brain tissue displaying a diversity of cell types. Here, we characterize cerebral organoids molecularly, structurally, and functionally. Using immunohistochemistry toward a variety of cortical markers, we show cerebral organoids recapitulate certain key aspects of the cellular architecture of the developing human brain. To model ASD, cerebral organoids will be generated from embryonic stem cells containing targeted mutations associated with ASD. We will compare wild type and ASD cerebral organoids molecularly and structurally using immunohistochemistry and single cell RNA sequencing. Furthermore, we will transduce organoids with the genetically encoded calcium indicator GCaMP6s. GCaMP6s is a calcium sensor that becomes fluorescent in response to Ca^{2+} influxes, which serve as a proxy for neuronal activity. We will use calcium imaging to compare the spontaneous electrophysiological activity in wild type versus ASD organoids. Differences in electrophysiological activity between mutant and wild type organoids will elucidate the ability of organoids to model the human brain not only structurally but also functionally.

The Effect of GDF11 on a Hypertensive Rat Model

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Cardiac diastolic dysfunction, an abnormality in heart filling during relaxation of cardiac muscle, is often seen in patients with prolonged hypertension. A recent study revealed that circulating GDF11 is reduced in older mice and restoring "youthful" levels of this protein leads to reversal of age-related pathological hypertrophy, cardiac enlargement due to pressure or volume overload (Loffredo et al., 2013). We hypothesized that restoring "youthful" circulating GDF11 levels in an aging deoxycorticosterone acetate (DOCA)-salt hypertensive rat model can reduce diastolic dysfunction. Rats were subjected to uninephrectomy, removal of the right kidney, and implanted with DOCA pellet subcutaneously to mimic human cardiac remodeling including hypertension, hypertrophy, and diastolic dysfunction (Iyer et al., 2010). Aged male DOCA rats (22 months old) will be used as a model of hypertension, as this was shown to develop more quickly in male than female rats (Crofton and Share, 1997). Four weeks after surgery, control and DOCA-salt rats will receive either a daily dose of GDF11 or saline for a period of four weeks. Rats will receive an echocardiographic evaluation before surgery (baseline), four weeks after uninephrectomy and pellet implantation, and at the end of the GDF11 or saline treatment. Eight weeks after surgery, rats will be subjected to a terminal hemodynamic to assess end-systolic and end-diastolic pressure-volumes. Cardiomyocytes' size in hearts harvested from each of the different experimental groups will also be measured to assess cardiac hypertrophy. Finally, we will quantify mRNA levels

of ANP, BNP, SERCA2A and alpha-SKA, genes commonly induced by hypertrophy (Younes et al., 1995), as well as the mRNA expression of procollagen I and III in the left ventricles to evaluate whether GDF11 reduces myocardial fibrosis.

Role of CCBE1 in Normal Differentiation and Proliferation of Human Embryonic Stem Cell Derived Cardiomyocytes

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Cardiac disease is the number one killer in America. Understanding the molecular pathways of cardiac development is essential to develop novel therapeutic approaches for regeneration of the heart. Collagen and Calcium-binding EGF domain-1 (CCBE-1) is a growth factor known to have a role in extracellular matrix remodeling and migration, as well as in lymphatic development. New studies done in cardiac mouse models have suggested CCBE1 is additionally involved in directing differentiation of cardiac precursor lineages. The extent of this role and the function of CCBE1 in human embryonic stem cells (hESC) is still to be determined. This project will focus on defining the expression pattern of CCBE1 in hESC derived cardiomyocytes, and assessing the functionality of CCBE1 in differentiation and proliferation by performing knock out experiments.

Gene expression of CCBE1 on a certain embryonic day will be measured with qPCR to develop a model of expression of CCBE1 in hESC. Function will be assessed by performing knockout studies using the novel CRISPR/CAS9 genome editing system. Indel formation will be achieved in the three protein coding isoforms of CCBE1 by designing complementary guide RNAs to direct the Cas9 protein to introduce double stranded breaks in target DNA, early in the coding sequence. The knockout (KO) hESC line will be maintained in the pluripotent state through passages and then differentiated via the interplay of signaling molecules used to induce the cardiomyocyte fate. Proper differentiation will be assessed using immunohistochemistry (stain for cell specific markers) and RNA seq. Proliferation assays will be done to compare wild-type and KO cell growth in side by side experiments. Normal contractility kinetics, calcium handling and action potential curves of CCBE1 KO cells can also be assessed using quantitative software.

The Role of ApoE in b-Cell *In Vitro* Culture

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The *in vitro* culture of pancreatic β-cells has served as an invaluable tool for studying β-cell biology, and for improving the quality of pancreatic islets for transplantation into patients with type 1 diabetes. Despite these benefits, cultured primary β-cells or whole islets exhibit a decrease in functionality and decreased capacity to reestablish normal blood glucose levels when transplanted into diabetic patients or animal models. Here, we show that the *in vitro* culture of β- cells decrease the expression of key β-cell transcription factors and proteins necessary for the maintenance of both β-cell function and stability. Given reported improvements in β-cell culture using extracellular matrix mixtures, we asked whether the native pancreatic extracellular matrix could increase β-cell gene expression and whether we could identify specific factors within the matrix that could maintain the mature β-cell phenotype when added to the culture environment. We found a certain factor in the decellularized significantly increased the expression of various key β-cell genes including those involved in maintenance of the β-cell transcriptional phenotype, insulin biosynthesis, insulin secretion, and glucose metabolism. Importantly, this effect was seen in both monolayer culture of dissociated islet cells and whole islet culture indicating that this factor can increase β-cell gene expression in both *in vitro* culture models.

Characterizing Human Induced Pluripotent Stem Cell-Derived Hemogenic Endothelium

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Despite numerous advances in research describing the environment of the developing embryo, it has still been a challenge to precisely define and recapitulate the cellular environment that initially gives rise to the hematopoietic stem cell (HSC). HSCs are critically important because they are necessary for establishing the adult hematopoietic system and are responsible for the lifelong production of all types of blood cells; identifying a renewable source of HSCs would undoubtedly prove to be of great therapeutic benefit. Definitive HSCs, as opposed to short-term or lineage-restricted progenitors, are first and autonomously generated in the wall of the dorsal aorta in the aorta-gonad-mesonephros (AGM) region starting from around embryonic day 10.5 in mice. Specifically, long-term HSCs originate from the hemogenic endothelium (HE), a specialized subset of endothelium that yields endothelial cells which bend out and round up and subsequently detach from the vascular wall to form free-floating hematopoietic cells through a process called the endothelial to hematopoietic transition (EHT).

In this study, we differentiate human induced pluripotent stem cells (hiPS cells) into hemogenic endothelial cells using embryoid body formation (a system that recapitulates the spontaneous and random differentiation of hiPS cells into multiple tissue types that represent endoderm, ectoderm, and mesoderm origins) to validate the EHT in vitro. We find that after 7 days of culture, HE cells expressed decreased levels of *Runx1*, *Myb*, *Gata2*, *Tal1*, and *CD34*, indicators of hematopoietic progenitors. Interestingly, analysis of non-adherent round cells that appeared around day 3 of culture showed *increased* levels of the previous hematopoietic markers as well as increased levels of *CD43* and *CD45*, two commonly used blood markers.

It has also been shown that biomechanical forces promote embryonic hematopoiesis and that blood flow itself is a key regulator of the EHT. This study also aims to apply shear stress to hiPS derived HE cells to mimic in vitro blood flow during early development and identify in vitro

shear stress conditions (timing and flow rate) that induce hematopoietic stem cell formation from HE cells. We find that HE cells exposed to wall shear stress exhibit increased levels of *Runx1*, a master regulator of hematopoiesis, compared to static cells. More strikingly, HE cells exposed to *both* wall shear stress and circumferential stress exhibit even higher levels of *Runx1* than cells exposed to wall shear stress alone. Results from this study further elucidate the in-vivo conditions that lead to the formation of HSCs and thus bring us closer to identifying a renewable source of HSCs for therapy.

Elucidating the Role of Ext1 in Hair Follicle Bulge Stem Cells

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Stem cells drive hair growth, which cycles through three phases: production (anagen), destruction (catagen), and rest (telogen). Stem cells have been found in the hair follicle bulge, a region contiguous to the outer root sheath that provides an insertion point for the arrector pili muscle. One of the genes believed to be involved in bulge stem cell proliferation is Exostosin Glycosyltransferase 1 (EXT1), which codes for a protein that catalyzes polymerization of the sugar molecule heparan sulfate. Heparan sulfate, when added to proteins, can amplify or inhibit other signaling pathways involved in cell processes like proliferation.

In order to determine the role of EXT1, we generated conditional knockout mice using the cre-lox system regulated by a bulge stem cell promoter, K15. Mice generated from this system will express the cre recombinase enzyme only in bulge stem cells. The cre recombinase will then locate the target region, EXT1 gene in this case, and excise that region, creating a mouse without a functional copy of EXT1. In order to temporally control cre recombinase activity, I used an inducible cre recombinase fused to a mutant form of progesterone receptor, which will only exert recombinase activity in the presence of progesterone analog RU486.

When cre recombinase was induced in the back skin of mice at 21-day postnatal, EXT1-knockout mice appear to enter anagen stage much faster than wild type controls. Additionally, after the first hair cycle, wildtype mice skin usually will not uniformly be in the same hair stage, but the EXT1-knockout mice were still entering anagen uniformly. Surprisingly, EXT1-knockout cells tagged with yellow fluorescent protein (YFP) did not contribute much to the hair follicles. Though these findings are still preliminary, one potential explanation is that EXT1 might inhibit a non-cell autonomous signal that drives proliferation in the skin.

Investigating the FSTL3-Dependent Regulation of GDF11/8: Potential Therapeutic Targets for Age-Related Cardiac Hypertrophy

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Growth differentiation factor 11 (GDF11) and 8 (GDF8) are members of the TGF-β superfamily that share 90% protein sequence homology. GDF11/8 activate SMAD signal transduction, which regulates cell differentiation, proliferation, migration, and apoptosis. Circulating levels of GDF11/8 decrease with age, and restoration of youthful GDF11/8 levels has been shown to reverse several debilitating age-related conditions, including decreased neurogenesis, sarcopenia, and cardiac hypertrophy. Preliminary data indicates that GDF11 may be inhibited by follistatin-like 3 (FSTL3), a known inhibitor of GDF8. FSTL3 has been found to enhance cell death in models of cardiac injury and shows elevated expression in patients with heart failure. We hypothesize that the cardio-degenerative effects observed in high FSTL3 conditions result from the inhibitory relationship between FSTL3 and GDF11/8. Our goal is to determine the role of FSTL3 as a regulator of GDF11/8 signaling, its downstream pathways, and cardiac hypertrophy.

We initially confirmed the presence of an inhibitory relationship between GDF11/8 and FSTL3 using a bioactivity assay in a K562 cell culture system. We then examined the dose response for recombinant GDF11/8 and FSTL3 on SMAD signaling in neonatal rat cardiomyocytes. Through ongoing in vivo experiments, we are investigating the effects of GDF11/8 on multiple tissues in wild type mice injected with varying doses of GDF11/8. We are also mirroring these GDF11/8 injections in FSTL3-null mice to determine whether endogenous FSTL3 inhibits the response to exogenous GDF11/8. Further experiments will examine the effect of GDF11/8 on FSTL3-null mice with induced cardiac hypertrophy via transverse aortic constriction (TAC). In demonstrating the role of FSTL3 as a regulator of GDF11/8, we hope to elucidate the workings of a complex biological system and provide potential translational targets for the treatment of age-related cardiac hypertrophy.

The Effect of Soluble IL-13 Receptor a1 on Hepatic Glucose Production

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Hyperglycemia, or increased blood sugar, is a hallmark of diabetes. With a worldwide increase in both Type I and Type II diabetes, it is essential to understand how blood sugar is controlled.

Recent studies have revealed a surprising role of cytokines, a group of proteins involved in immune responses and cell signaling, in metabolism, supporting an association between inflammation and metabolic

diseases. Genetic deletion of the cytokine interleukin 13 (IL-13) has been shown to cause disregulation of key glucose production genes in the liver. This has prompted a search for possible IL-13 interaction partners, such as soluble receptors, that can regulate this pathway.

We have found in human blood a soluble IL-13 receptor α1 (sIL-13Rα1). After injecting mice with adeno-associated viruses (AAV) that produce sIL-13Rα1, IL-13, or both proteins, we analyzed changes in expression of glucose producing genes in the liver by QPCR. Additionally we optimized a primary hepatocyte isolation protocol and obtained primary hepatocytes to treat with sIL-13Rα1 and/or IL-13 for protein assays and further QPCR analysis. Our results suggest that sIL-13Ra1 acts as an IL-13 agonist, which reduces the expression of hepatic gluconeogenic genes.

In the future we plan to study the molecular mechanism of sIL-13Rα1 that causes these changes, such as whether or not sIL-13Rα1 acts through competitive inhibition or enhancing interactions with IL-13. We also plan to analyze levels of sIL-13Rα1 in humans, which will give greater insight into the potential of this pathway for metabolic diseases.

Interrogating the Role of Circadian Rhythm in Leukemogenesis and Hematopoiesis

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With the development of the capacity to analyze ever more massive quantities of bioinformatics data, biomedical research today increasingly uses computational methods to drive experimental progress. For example, CellNet is a computation platform that analyzes published global expression profiling data to generate gene regulatory networks (GRNs), which can be used to compare in vitro derived cells to their native counterparts. CellNet analysis of blood GRNs suggests a relationship between hematopoiesis and circadian rhythm (CR). Leukemia, as a disorder of blood development, may also be affected by CR genes. Alterations of the MLL (Mixed Lineage Leukemia) gene, located at 11q23, are some of the most common mutations found in childhood AML. However, not only is MLL strongly associated with AML, but the MLL family of genes is also known to play a key role in regulating circadian rhythm. Previous studies have shown that MLL3 is a clock-controlled factor that also affects other circadian rhythm genes, and MLL1 has a demonstrated role in regulating the CLOCK-BMAL1 complex. Thus there exist well-established connections between mixed lineage leukemia genes and circadian rhythm, further suggesting a link between CR genes and leukemia, and thereby between CR and hematopoiesis. This connection will be examined by manipulating circadian rhythm genes in both in vitro and in vivo blood models of hematopoiesis and leukemia.

CHEMISTRY

-Withheld for Confidentiality-

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--Withheld for Confidentiality--

Development of a Biocompatible Catalyst to Interfere with Bacterial Quorum Sensing

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Quorum sensing is a signaling mechanism used by many bacteria to modulate gene expression based on population density. Small molecule autoinducers are secreted by bacteria and maintain concentrations proportional to cell density. The buildup of these autoinducers results in changes in gene expression in the bacteria. Our goal is to interfere with quorum sensing through the use of biocompatible chemistry: nonenzymatic reactions capable of modifying metabolites as they are made by living organisms. We envision employing a small-molecule catalyst that can break down acyl-homoserine lactones (AHLs), a class of bacterial autoinducers that have been shown to regulate several pathways including pathogenicity in P. aeruginosa, by hydrolyzing the lactone ring into a carboxylic acid.

We have identified several bimetallic zinc complexes as potential catalysts based on their resemblance to the active site of acyl-homoserine lactonase, an enzyme that performs our desired reaction, as well as their reported activity catalyzing other hydrolysis reactions like phosphate diester bond cleavage under physiologically relevant conditions. We have successfully accessed several AHLs and ligands of potential catalysts. In addition, we are developing an assay to screen for hydrolytic activity of our catalysts using quorum sensing-dependent bioluminescence found in a strain of marine bacteria V. fischeri. Ultimately, we seek to use a successful biocompatible catalyst to influence microbial communities through the disruption of cell-to-cell communication as a means to further study such systems and prevent unwanted biological pathways like virulence.

Characterization of Glycyl Radical Enzymes in the Human Gut Microbiome

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There are more bacteria in the human gut than there are host cells in the entire body. These bacteria belong to over 500 different species and affect human health in both positive and negative ways. While it is commonly acknowledged that pathogens like *C. difficile* can cause serious health issues, other organisms like *R. inulinivorans* have a beneficial role in host metabolism. For example, the short-chain fatty acid propionate regulates gut hormones and is part of a potential therapy for obesity and type-2 diabetes.

Propionate is derived from the metabolism of L-fucose. One of the most chemically challenging steps in this pathway is the transformation of the intermediate (*S*)-1,2-propanediol to propionaldehyde. This reaction is predominately catalyzed by propanediol dehydratase (PD), a glycyl radical enzyme (GRE). GREs are abundant in the gut microbiota and catalyze unique biochemical reactions not possible by the human host alone. Our goal is to gain a better understanding of this class of enzymes, especially the mechanism of PD, and to use that knowledge to help develop treatments for disease.

In addition to PD, we have also been working on the characterization of another GRE known as PFL3. It was found in the *E. coli* genome and is highly similar to that of other GREs but its function is unknown. We want to characterize this enzyme, determine its function, and see how it affects the host-bacteria relationship in the gastrointestinal tract.

Synthesis of Non-Natural Protein-Like Polymers

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Chronic illnesses affect millions worldwide and are often untreatable with existing technologies. Researchers have recently begun applying protein-based biologics to the treatment of these diseases. However, the short half-lives, immunogenicity, and high costs of protein drugs have limited their use for many diseases. These shortcomings have created a demand for complementary technologies that offer the advantages of protein therapeutics but may lack these drawbacks.

In this project I will be developing and applying a novel process for synthesizing protein-like polymers with the ability to bind to other molecules. In a process similar to translation, non-natural monomers hybridize to a DNA template and then are covalently linked to neighboring monomers as well as the strand of DNA. This process of DNA-templated polymer synthesis (DTS) results in a diverse library of sequence-specific polymers encoded by the DNA template. The resulting library can be selected in vitro for the ability to bind to a disease-associated target. Hits, selectively retained by their target binding, are then elucidated by DNA sequencing and tested for binding to a target molecule, in this case the protein thrombin. Promising candidates are then validated using a variety of assays to confirm their function.

Given that multiple products might be produced from a single DNA template, confirmation of the structure of the binding molecule is an essential part of the validation process. One method of structure confirmation is synthesis of the polymer through a different synthetic pathway. Validation is achieved if the product produced through independent means binds to thrombin with an affinity similar to that of the DTS product. If one such product is found, this approach will be expanded to

address other targets. We are currently in the process of validating one such candidate that emerged from the selection of a DNA-templated polymer library for binding to thrombin.

The successful development and application of this approach could eventually lead to new generations of sequence-defined synthetic polymers with therapeutic properties.

Characterization and Reactivity of a Mixed-Valent Dicobalt Monosodium Complex

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Inspired by the unique reaction chemistry available to solid state catalysts and enzymes with multinuclear active sites, ongoing work in the Betley group aims to explore the electronic structure and reactivity of polynuclear metal clusters. A series of first-row transition metal trinuclear clusters ($^{tbs}LM^{II}_3$, M = Cr, Mn, Fe, Co, Ni, Zn) have been synthesized, supported by the pre-organizing ligand platform [1,3,5-C_6H_9-(NC_6H_4-o-NSi^tBuMe_2)$_3$]$^{6-}$ (^{tbs}L). Each arm of the ligand platform binds a divalent metal atom, with the organizing cyclohexyl backbone holding all three arms in close proximity. Treatment of these clusters with two-electron group transfer reagents results in oxidation of the clusters, generating bound atomic adducts featuring mixed-valent metal (II/III) centers. Additionally, electrochemical studies on molecules synthesized in the group suggest that high valent late transition metal compounds (Ni^{IV}, Co^{IV}) are viable on this platform. Complexes bearing high-valent late transition metals are attractive synthetic targets due to the implication of their use as reactive intermediates in small molecule activation, such as the proposed $Co^{III}Co^{IV}$ bridging oxo as an active site for water oxidation, which may be useful in capturing solar energy.

Targeting a simpler system that will aid in the understanding of the electronic communication in these clusters and provide a viable synthon for the synthesis and isolation of Co^{IV}, we have synthesized both the binuclear Co^{II}/Co^{II} complex, [$^{tbs}LCo_2Na(thf)$]Na, and, by oxidation of this cluster, a Co^{II}/Co^{III} complex, $^{tbs}LCo_2Na(thf)$. By replacing a redox active Co center with an alkali metal, we simultaneously reduce the complexity of electronic coupling and encourage formation of higher valent Co. We aim to explore the reactivity of these complexes with two electron group-transfer reagents in an effort to synthesize a cluster featuring a nominally Co(IV) center, and to use various spectroscopic methods to interrogate the nature of electronic exchange in the mixed-valent binuclear cluster $^{tbs}LCo_2Na(thf)$.

Applying Quantum Chemistry to Estimate the Thermodynamics of Metabolic Reactions: The "Nearest Neighbor" Theory

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Thermodynamics, a physics concept that relates heat and temperature to the energy and work of a system, uses standard Gibbs reactions energies, $\Delta Gr'^{\circ}$, to determine the chemical potential of a reaction to proceed forward or backward. While experimental $\Delta Gr'^{\circ}$ values exist, the current database accounts for a mere fraction of all known metabolic reactions. The deficiency in known $\Delta Gr'^{\circ}$ values poses a major problem for the future of comprehensively understanding metabolic processes. Using quantum chemical approaches to accurately estimate $\Delta Gr'^{\circ}$ values, we can close this gap in knowledge. As a means of increasing the accuracy of $\Delta Gr'^{\circ}$ quantum chemical estimations, we apply a "Nearest Neighbor" theory based on the high specificity of enzymes and the relative "neighbors" in their class.

We hypothesize that we can implicitly estimate the $\Delta Gr'^{\circ}$ of enzymes missing experimental data by estimating the $\Delta Gr'^{\circ}$ of their "nearest neighbors" that have experimental data. To estimate the Gibbs energy of each nearest neighbor reaction, we use the ORCA quantum chemical program with a combination of parameters that optimizes the geometry, protonation state, and density of the molecules involved. By focusing on isomerase and transferase enzymes, we are able to accurately estimate $\Delta Gr'^{\circ}$ of nearest neighbors, and subsequently the $\Delta Gr'^{\circ}$ of the target enzymes missing experimental data, with low error comparable to experimental error.

While the $\Delta Gr'^{\circ}$ of reactions with fewer and smaller molecules proved easier to accurately estimate using quantum chemical methods, we faced the challenge of modeling large molecules such as ATP/ADP and NAD(P)/NAD(P)H. As a way to address these quantum chemically challenging molecules, we combined known experimental data for the larger molecules with the quantum chemical estimations for smaller molecules involved in these reactions to accurately estimate the overall $\Delta Gr'^{\circ}$ of the reaction. For future study, we plan to find a precise way to model the larger cofactors using quantum chemical estimations in order to create a more comprehensive model for estimating $\Delta Gr'^{\circ}$ than costly and timely experimental methods.

Oxygen Reduction Reactivity of Manganese (III) Hangman Porphyrin

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A growing need to reduce the world's exponentially-growing CO_2 emission relies on the development of carbon-neutral, sustainable, and reliable energy sources. Cost effective technologies to challenge the current energy infrastructure requires the design of earth-abundant catalysts for the generation (water-splitting) and use (fuel cells) of renewable energy.

Metallated porphyrins are stable compounds for the oxygen reduction reaction (ORR), a 4-proton 4-electron reduction reaction crucial to fuel cells and one that also sheds light on the mechanism of its reverse reaction, water splitting. In particular, metallated hangman porphyrins bearing a hanging carboxylic group above the porphyrin platform have shown increased ORR activity, likely due to the proximity of the acidic carboxylic group to the metal ion increasing the rate of proton-coupled electron transfer (PCET) via a phenomenon known as the Hangman Effect. This coupling of electrons to protons lowers the activation energy of ORR. We are interested in studying 5,10,15,20-tetrakisphenyl porphyrinatomanganese(III)chloride for ORR because it can be synthesized in multi-gram quantities and its ORR activity has not yet been

explored. Initial studies of this catalyst's ORR activity by cyclic voltammetry have shown promising results.

To explore the PCET reaction mechanism of ORR, we synthesized manganese(III)hangman porphyrin with xanthene backbone at one meso position, and then characterized its ORR activity by electrochemical measurements. Synthesis of this compound required high dilution Lindsey porphyrin-formation reaction, delivery of the hanging group by microwave-assisted deprotection of the methoxy group, and manganese insertion. The target compounds have been characterized by ^{1}H NMR spectroscopy, absorption spectroscopy, and high resolution mass spectrometry.

Preliminary electrochemical experiments show that we can successfully reduce oxygen to water using 5,10,15,20-tetrakisphenyl porphyrinatomanganese(III) chloride and the corresponding Hangman porphyrin in presence of an external proton donor. The Faradaic yields in water are respectively 99% and 98%. These results indicate that PCET-driven ORR is efficient and represents a promising approach to the design of high performing energy conversion catalysts.

Investigation of Enantioselective Methods for Catalysis of the [2,3]-Wittig and oxy-Cope Rearrangements

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A challenge presented in the development of synthetic organic methods for the production of pharmaceuticals lies in the control of absolute stereochemistry. In the absence of a chiral reagent or catalyst, a reaction produces equal amounts of both enantiomers (mirror-image isomers) of the desired product. However, these enantiomers have the potential to interact with biological systems in distinct ways. Thus, it is important to develop methods for selective synthesis of only the desired enantiomer of such compounds. Toward this aim, others in the group have previously developed a catalyst system to facilitate enantioselective anionic rearrangements, wherein the hydrogen-bond-donor catalyst stabilizes the redistribution of negative charge on the rearranging species while simultaneously withdrawing the cation away from the substrate. Herein, we—myself, my mentor Rose Kennedy, and Professor Eric Jacobsen—describe exploration of this catalyst system in new, synthetically valuable transformations including variants of the [2,3]-Wittig rearrangement and the oxy-Cope rearrangement.

Optopatch Screening for Subtype Specific Modulators of the $Na_V1.7$ Channel, an Emerging Target in Pain Therapy

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Voltage-gated sodium (Na_V) channels are key components for mediating the depolarization phase of an action potential in excitable cells (e.g. neurons, cardiomyocytes) and represent therapeutic targets for treating various types of human diseases. Nine different subtypes of Na_Vs have been reported, and among them $Na_V1.7$ is the subtype mainly expressed in peripheral sensory neurons such as dorsal root ganglion (DRG) cells, whereas $Na_V1.5$ is the subtype mainly expressed in cardiomyocytes. Subtype selective compounds targeting $Na_V1.7$ without blocking $Na_V1.5$ would serve as excellent painkillers by suppressing sensory perception without risking cardiac arrhythmia. To find such compounds, we established a screening platform for a 1000-compound library of possible sodium channel modulators.

Because native DRG cells express multiple types of channels and because they do not proliferate in culture, we engineered a synthetic excitable system by transfecting HEK cells, which naturally have no ion channels, with the potassium channel $K_{ir}2.1$ and either $Na_V1.5$ or $Na_V1.7$. We also use all-optical electrophysiology, or the "Optopatch" construct, to monitor the average relative membrane potential of a large number of cells. The construct combines a light-gated ion channel (CheRiff) and a genetically encoded voltage indicator (QuasAr2), which are spectrally orthogonal. Emitted fluorescence from QuasAr2 reflects the average membrane potential of the observed cells. We can observe the inhibitory effect of classic Na_V inhibitors, such as lidocaine and TTX, and find that the lidocaine effect is clearly state and use dependent. We plan to perform a screening of a 1000-compound library to find $Na_V1.7$ subtype specific compounds. More investigation into such compounds is necessary to determine effective concentrations and delivery methods.

Catalytically Controlled Glycosylation Chemistry

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Sugars are essential building blocks of a wide range of biologically active molecules. The positioning of carbon substituents on sugar rings plays a crucial role in determining the shape and potential function of such molecules in highly specific biological systems. The development of spatially selective glycosylation reactions—additions to sugars—could thus have broad synthetic application. Furthermore, this chemistry is compelling because sugars often have multiple chiral centers, meaning the behavior of these molecules can be quite varied. Developing catalysts that control glycosylation reactions for different types of sugars, as well as an understanding of how these catalysts work, could potentially elucidate the stereo- and electronic effects of the different elements of various types of sugars.

The Jacobsen laboratory has previously explored the use of chiral catalysts that function via anion binding. These molecules bind substrate counter-anions with hydrogen bonds, thus creating spatially controlled environments around charged components in reaction transition states. These catalysts vary in the nature of their chiral portions, causing different catalysts to be influential in different types of reactions. These and related catalysts are being tested for their utility in glycosylation chemistry with a variety of sugar substrates, both in an attempt to find effective catalysts for each type of sugar and to probe the effects of the differences between the sugars. Additionally, simplified but sugar-related substrates, that could produce potentially interesting products themselves, are being tested with reaction conditions to examine the

behavior of reaction components. Finally, different sugar reaction partners are being screened to establish the limitations of the stereo-selective reaction being developed.

Effective catalysts for several sugar substrates have been determined. These results suggest that the family of catalysts being examined have the potential for stereo-selective glycosylation. However, it has been found that effective catalysts do not generalize broadly for multiple sugar substrates—different types of sugars require different catalysts, meaning that more research is needed to develop stereo-selective reactions for a variety of starting materials.

UV Activated Cytidine to Uridine Conversion

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An extensive subfield of Origins of Life research is focused on prebiotic chemistry, the study of chemical pathways that could have plausibly formed the building blocks of life from basic molecular structures. RNA (composed of four nucleobases: A, C, G, and U) is considered by many scientists to be the original carrier of genetic information in an idea known as the RNA world hypothesis. Because prebiotic chemistry focuses on the transition from chemistry to biology, it is of great interest to learn more about the properties of RNA. Powner et al. (2007) discovered that, when irradiated with 254 nm UV light, cyclic cytidine 2', 3'-monophosphate (C) converts to cyclic uridine 2', 3'-monophosphate (U). They hypothesize that the UV light activates a protective mechanism whereby the 5'-hydroxyl of the ribose sugar creates a "locked" structure that prevents the molecule from being degraded while irradiated with UV light. This reaction is noteworthy because it allows for a seamless conversion from C to U with few byproducts.

To follow up on the Powner et al. study, we are investigating the thermodynamics and kinetics of the C to U conversion. In order to analyze the kinetics of the reaction, we make use of UV-Vis spectroscopy, a method that allows us to track changes in the concentrations of different molecular species in solution over time. Nuclear magnetic resonance (NMR) is used in order to identify the change in structure of cyclic C as it is irradiated. Though experiments are still being performed, preliminary results suggest that the C to U conversion requires an irradiation step to form a key intermediate, followed by a heating step to form the final product. We are ultimately working toward completing a kinetic model of the reaction and obtaining thermodynamic data.

Implications of Volatile Organic Compound Co-Contamination and Isomer Tracing for Perfluoroalkyl Acid Groundwater Transport

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Perfluoroalkyl acids (PFAAs) are organic surfactants used in paint, non-stick coatings, and fire retardants, notably aqueous film-forming foam (AFFF). AFFF use contributes significantly to high groundwater PFAA concentrations at point sources. Their environmental persistence, bioaccumulation, and chronic health effects as likely carcinogens and immunotoxins have made PFAAs emerging contaminants of concern. The transport properties of PFAAs in groundwater, however, are still mostly unknown.

Examining PFAA interactions with other subsurface constituents is particularly important in understanding PFAA transport. Using Joint Base Cape Cod (JBCC), a site with known PFAA and volatile organic compound (VOC) contamination from AFFF fire training exercises, as a representative field site, this study investigates the impacts of VOCs on PFAA transport. Specifically, we consider the effects of methyl tert-butyl ether (MTBE), a gasoline additive, and the industrial solvents tetrachloroethylene (PCE) and trichloroethylene (TCE) and their degradation product cis-1,2-dichloroethylene (DCE). PCE, TCE, and DCE are ubiquitous and toxic groundwater contaminants that often co-occur with PFAA contamination at JBCC. Groundwater collected from a background location near JBCC was used in constructing batch sorption reactors. Following equilibration, liquid and solid phases were extracted and analyzed for PFAAs by using triple quadrupole liquid chromatography- mass spectrometry (LC/MS/MS). Resulting sediment-water distribution coefficients (K_d) and isotherms were used to determine the influence of VOCs on PFAA sorption.

In addition to co-contaminant investigations, examining whether nearby downgradient wastewater-infiltration beds may also be a historical PFAA source will further enhance understanding of PFAA transport. To assess this, structural isomers of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) were separated by using LC/MS/MS and identified in groundwater impacted by wastewater effluent and by AFFF. Observed isomer distribution patterns, when compared to previously published isomer profiles, suggest the possibility of plume mixing and provide a viable method for PFAA source tracing.

COMPUTER SCIENCE

Improving Efficiency and Performance of Flash Datastores via Exploitation of Data Death-Time Distributions

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Flash memory is rapidly becoming the standard for computer data storage, as it is cheaper, more efficient, and much faster than traditional disk drives. However, flash memory has very slow random writes — in order to write a single random byte, an entire block of flash must be erased. In the context of file systems and databases, this problem is usually solved by performing all writes into a sequential log. However, once the disk or database file fills up, the existing data must be compacted to make space for new data. This can lead to significant write amplification, or more than one database write happening per intended write from the client. In this work, we present Persephone, a fast, persistent key-value store designed for flash memory which takes advantage of workloads with a skewed write distribution. Persephone attempts to alleviate the problem of write amplification by performing inference of the death-time distributions of items in the database, using metadata kept in memory about the distribution of client writes. This allows us to write keys together into blocks which will likely expire at the same time (keys expire when that key is written again — all old values of that key are now garbage), and thus make the task of compaction easier. Though other work has used some of these same ideas at the file system or flash translation layer level, this is the first application of such ideas to a key-value store. Using this method, we obtain significantly lower write amplification and higher write throughput on several realistic workloads over a traditional, death-time oblivious database architecture. These results could mean much faster big data applications.

tlmalloc: A Fast, Scalable Memory Allocator with Usage Hints

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All nontrivial computer programs require some way to efficiently allocate memory from the operating system, and in C this is often accomplished using general purpose memory allocators via the malloc() and free() interface. The field of memory allocation has been well researched, but the programmer often has more information about the usage pattern of the allocated memory than most existing allocators take into account. This information could allow an allocator to improve its speed and efficiency. Since faster and more scalable allocation can lead to significant speedups across an entire application, in many cases it is worth a programmer's effort to pass this information to the allocator in the form of optimization hints. I am designing and implementing a fast, scalable memory allocator that is able to make use of such hints. The design of the new allocator, called tlmalloc, takes inspiration from such allocators as Facebook's jemalloc and Shanghai Jiao Tong University's SSmalloc. In tlmalloc memory allocations are located in constant-sized chunks, which allow for fast allocation and freeing. These chunks are owned by thread-local chunk stores, minimizing the time spent coordinating access to data in a multithreaded environment. Very large allocations are recorded in a radix there, as they are in Google's tcmalloc, allowing for highly efficient reuse of large data regions. Preliminary performance benchmarks are promising, and tlmalloc performs well against jemalloc, the glibc malloc implementation, and tcmalloc in many test cases

Predicting Age from Text

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Structured clinical data and formal patient electronic health records are customarily utilized in a variety of medical data analysis tasks. We explore online health forums as a novel source of unstructured information for learning stages and patterns of cooccurrence in Autism Spectrum Disorder. In this work we applied multinomial logistic regression and other machine learning algorithms to optimize precision for the task of automated age prediction from text. These online forums typically involve discussions by parents relating to behaviors, symptoms, and lifestyles of their children and contain a wealth of unprocessed information.

Given a forum post at random, what is the most likely age of the aforementioned child or person? In order to be precise about our prediction, we must identify important age-specific word features. We develop a natural language processor for extracting ages from a given forum post using regular expression matches. We also map vernacular user language to medical concept identifications to bridge the discrepancy between terms used by laypersons and vocabulary employed by health professionals. Given the prevalence of noisy unstructured data, we describe several methods for representing textual input as a fixed-length feature vector suitable for analysis. These proposed methods range from the commonly used bag-of-n-grams weighting (tf-idf) to the more advanced continuously distributed representations of sentences (word2vec) and documents (doc2vec). The framework in this age prediction task can be extended to converting textual input into distinguishable predictors for regression or classification for a variety of different medical disorders or diseases.

Quantifying Undergraduate Coursework Diversity

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One goal of many institutions of higher learning is to provide their students with a liberal education. Diversity of coursework is often considered to be an important part of a liberal education; students who take a wide range of courses are often said to have received a more liberal education than those who took courses in, for example, only a single discipline. It is important for many universities be able to measure the diversity of any given student's coursework. For example, many universities require all students to achieve a certain amount of coursework diversity before they are allowed to graduate. Universities sometimes implement this policy using distributional requirements; successful completion of these requirements is a very coarse measurement of a student's coursework diversity. Universities also often use coursework diversity as a criterion for awarding certain academic honors and fellowships. However, it is difficult to define precisely what diversity of coursework means, and it is even more difficult to quantify more finely the extent to which a particular student's coursework exhibits this diversity.

To address this difficulty, we have developed three methods for measuring the coursework diversity of Harvard students using data from graduating classes of 2009-2014. The first method looks for clusters of courses that tend to co-occur on students' transcripts. It then measures coursework diversity by looking at how spread out an individual's transcript is over these clusters. The second method calculates coursework diversity by looking at how spread out the courses on an individual's transcript are over the three academic divisions (Humanities, Sciences, and Social Sciences). The last method calculates a distance between every pair of courses by looking at how often that pair co-occurs on transcripts. It then calculates the coursework diversity of a specific transcript by measuring what percent of all courses lie within a specified distance of the courses that appear on that transcript. We hope to evaluate the efficacy of these methods more thoroughly by consulting with educational experts in the fall.

Making Computers get Faster with Practice: Automatically Scalable Computation

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Automatically Scalable Computation (ASC) is a technique for improving the performance of computer programs by taking advantage of whatever computational resources (e.g. CPUs and memory) are available. Our current implementation takes sequential (i.e. single-threaded) programs as input and distributes their work over multiple processors by pre-executing parts of the computation that are likely to be useful in the future. In this manner, ASC permits writing conceptually-simpler sequential code while benefiting from the speedup of parallelized code.

ASC treats program execution as a walk in a high-dimensional vector space corresponding to the contents of the computer's memory (including registers). The complete execution of a program produces a trajectory through this high-dimensional space. In theory, we'd like to partition the trajectory into N equal-sized pieces, each of which can be run on a different processor. In practice, we have to make strategic decisions about where to partition the trajectory. The goal of my research is to automate and improve the quality of those decisions, which were previously made by hand.

The quality of these partitioning decisions corresponds to the ease of predicting what trajectory segments will turn out to be useful, which results in shorter runtimes once ASC has had sufficient practice with the target program. However, attaining sufficient practice for each possible partitioning is prohibitively expensive, so shrinking the search space is essential. Using information stored in the target program executable and data from short experiments, ASC predicts how well it will do at speeding up the target program using a given partitioning. This lets ASC focus its resources on the most promising candidates, reducing wasted work.

ASC is now able to learn its own parameters without human intervention. The settings it discovers outperform the manual settings: the reduction in runtime is larger by as much as a factor of 3. This removes a barrier to using ASC, which lends support to ASC's viability as a tool for common use.

EARTH & PLANETARY SCIENCES

The Suppression of Arctic Air Formation by Cloud Radiative Effects in a Two-Dimensional Cloud Resolving Model

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To better understand the warm equable climate of the early Eocene epoch--a period of low equator-to-pole temperature gradients during which continental interiors poleward of 45 degrees latitude were sufficiently warm to support palm trees--and to elucidate the mechanisms behind Arctic-amplified warming in recent decades, a two-dimensional idealized cloud-resolving model is used to investigate Arctic air formation during polar night under a variety of initial temperature profiles and atmospheric CO_2 concentrations. Arctic air forms when relatively warm marine air is transported over a snow-covered land surface and cools rapidly due to snow's high emissivity, which allows it to effectively radiate longwave (infrared) radiation back to space. Qualitatively consistent with previous work using a single-column model, the amount of surface cooling decreases substantially as the initial temperature profile is warmed, and characteristics of Arctic air such as surface inversions (increases in temperature with height at low levels) take much longer to develop under warmer initial conditions. These results are attributed to the development of optically thick low-level liquid clouds in the warmer initial states that reflect some of the outgoing longwave radiation back to the surface. This moderates surface cooling and creates a positive feedback mechanism for Arctic warming. The use of a two-dimensional model as opposed to a single column model allows for the observation that warmer initial conditions are accompanied by significant turbulence, which acts to diffuse cooling vertically throughout the atmosphere instead of keeping it concentrated near the surface. Since each doubling of atmospheric CO_2 concentration (without changes to the initial temperature profiles) decreases average surface cooling only slightly, temperature feedbacks like the cloud feedback described above, rather than direct CO_2 forcing, are the primary factors behind Arctic warming during polar night.

Forecasting California Wildfire Prevalence Using Early Season Drought Indicators

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As drought severity increases with climate change in the western United States, particularly in California, an increased attention is given to the forecasting of annual trends in wildfire prevalence. The statistical prediction of burned area totals in California would both aid in planning wildfire suppression efforts and complement existing post-fire observational methods for determining burned areas. Such data is then useful for the purpose of calculating emissions inventories that record total atmospheric intake of potentially harmful (to human health and to climate) pollutants.

The study is motivated by similar statistical work done for other regions of the world with highly active fire seasons. We examine correlations between multiple drought indicators, including precipitation levels and normalized drought or precipitation indices, and annual fire prevalence data from satellite observation. The goal is to find strong correlations, and even explicit functional relationships up to a reasonable uncertainty, between early season (January-May) drought indicators and late season (June-October) fire prevalence outcomes. Such findings would provide a quantitative forecasting model for use in 2015 and future years.

Current work has demonstrated a strong potential for standardized precipitation index (SPI) as a forecasting tool for annual statewide fire totals. Furthermore, we find a striking exponential dependence of annual fire prevalence on precipitation during February through April in the Sierra Nevada and Great Valley regions. Such an outcome enables a prediction of fire prevalence for a region that typically includes nearly half of statewide fires, and our model accounts for roughly four fifths of the variance in fire totals in the local region.

ENGINEERING

Quinone Redox Chemistry Applied to Semi-Solid Flow Batteries

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Solar, wind, and other renewable energy sources provide inherently intermittent power, and thus cheap and effective energy storage is critical to their continued adoption into electricity grids. Conventional energy storage technologies, such as lithium-ion batteries, lack a high enough energy:power ratio to effectively deliver high amounts of energy for extended periods of time, thus limiting their efficacy. Redox flow batteries (RFBs) are potentially a cheap and effective way to store electrical energy generated from solar and wind farms. RFBs decouple energy storage capacity from power density, allowing for arbitrarily large energy storage tanks and correspondingly large energy:power ratios. Quinone flow batteries, developed by the Aziz group, are also remarkably cheap. Where Vanadium flow batteries cost between $200-$300 per kWh for the redox active materials, quinone RFB chemistry could cost as little as $27/kWh.

Semi-solid flow batteries (SSFBs) are closely related to flow batteries. SSFBs suspend the redox active species in a suspension that includes percolating conductive networks, which replace the electrode in RFBs. I apply this battery technology to quinone RFB chemistry. SSFBs using quinone as the redox active compound should have higher energy densities relative to existing quinone RFBs. This higher energy density will expand the range of applications for quinone battery chemistry. I first determine that a semisolid suspension of carbon black will not suffer from egregious resistive losses by measuring its electronic conductivity. I measure the conductivity of various suspension compositions, ranging from 0.5-3vol% Ketjen Black. I also determine the optimum dispersant that does not compromise conductivity while simultaneously minimizing viscosity and the associated pumping losses in the battery. I accomplish this by characterizing the rheology of the suspension.

Large Scale Self-Folding

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Most current methods of robotic fabrication require intensive human involvement. Robots are usually pre-assembled before deployment, making them difficult and expensive to transport. An alternative method of deployment, self-folding assembly on site, offers significant advantages over the traditional methods. Robots can be transported in a single planar sheet and self-folded into their active configuration on site without any human assistance. The current state of self-folding research has been focused on the development of micro-robots, with many of its methods not scalable to large scale applications. Fortunately, one method that may be applicable in large robotics was developed recently. Using a planar pneumatic system, researchers at the Wyss institute have been able to create a miniature self-actuating gripper that starts as a flat surface and is able to assemble and grip autonomously. This method works by inflating pouches along hinges of the robot that pulls two sides closer together to achieve folding. For my project, my goal is to implement this system in the assembly of much larger structures. Although the concept behind the folding is the same, I face many different challenges from the scaling process. A few challenges include the upper bounds of the torque generated from this method and the need to create a locking mechanism that prevents the natural deflation of the pouches. Finally, I have developed a large-scale self-folding prototype that demonstrates the robustness of this new fabrication method.

Finding New Legs

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Recent advances in the manufacturing of millimeter-scale structures have enabled the development of insect-scale robots capable of dynamic movement including running, jumping, and locomotion over diverse terrain. Inspired by the highly efficient and adaptable motion of the cockroach, The Harvard Ambulatory MicroRobot (HAMR), a 1.27g legged robot capable of reaching speeds of 0.44 m/s (10.1 body lengths/s), is one of the smallest and fastest legged robots.

The design focus for HAMR over its six generations has been on the transmission kinematics, body morphology, manufacturing and actuation. The HAMR leg design, however, has not been extensively studied. Variation in leg design especially those that alter body posture such as hip height and sprawl, are hypothesized to have substantial effects on locomotion characteristics such as speed and force output.

Using the printed circuit MEMS fabrication processes, stiff, lightweight carbon fiber legs of various heights and lateral lengths were manufactured. These legs serve as the mechanical output for HAMR's piezoelectric drive actuators. Upon analysis of non-inclined walking gaits, an experimental study will be conducted to elucidate the effect of leg design on the body dynamics and forward speed of HAMR. Moreover, this project will potentially demonstrate the ability of leg design to optimize locomotion, allowing HAMR to move faster and more efficiently without increasing fabrication cost and time.

MATHEMATICS

Stable Homotopy Theory

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Topology is an area of geometry that studies objects locally, considering an object to be unchanged when it undergoes a transformation that fixes the local properties, such as stretching or bending. The central maneuver of such a transformation is called a homotopy, which detects when two transformations on an object are the same after some amount of stretching or bending. When we take continuous functions from spheres to an object of interest, and we impose the equivalence relation on them given by homotopy, the resulting set has a natural group structure, and these groups are called the homotopy groups of the object. It turns out that these groups can tell us just about everything we would want to know about the local properties of the object. Hence, homotopy groups are a fundamental area of study in homotopy theory.

My research this summer has been in a subset of homotopy theory called stable homotopy theory. Stable homotopy theory studies the stabilization of homotopical properties under an iterative process called suspension. Intuitively, suspending an object forms a cylinder whose top and bottom are the shape of the object, then collapses the top and bottom each to a point. The first theorem one learns in stable homotopy theory is the Freudenthal Suspension Theorem, which says that, after suspending an object enough times, the homotopy groups stabilize. This theorem tells us that stable homotopy theory is a natural environment in which to study homotopy theory. The goal for my reading this summer is to get through enough material to be able to derive a tool called the Adams Spectral Sequence, which computes many homotopy groups of spheres.

Applications of Forcing

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In mathematics, the ""powerset"" of an object can be thought of an object that contains all possible ways of breaking apart the initial object. For instance, the powerset of the integers contains all possible subsets of the integers: the even integers, the odd integers, the square integers, the integers produced by a random number generator, and so on. A classic problem in mathematics concerns determining how large the powerset of an object can be. Cantor's famous diagonalization argument shows that the set of integers is strictly smaller than its powerset, which may be identified with the real numbers. However, it turns out that the question of how much larger the powerset is is actually undetermined: the size of the power set does not have a completely determined value.

The reason for this is that in ZFC, the standard axiomatization of set theory (that is, a broad set of ""rules"" that determine what sets exist and how one can form new sets out of them) there may be subsets that one can never explicitly ""write down."" This result was established through the method of forcing, an extremely powerful technique which allows one to build so-called ""models"" of ZFC with a set with a certain specified property, which may or may not exist in the original universe. This technique has been critical for establishing the independence of many important questions in set theory and closely related areas, such as model theory and functional analysis. Unfortunately, there are difficulties in making this argument rigorous. The goal of my reading for the summer is to understand various approaches to forcing, such as Boolean-valued and partial-ordering approaches, and formalizations of forcing, such as in WKL0 (Weak Konig's Lemma), which allow one to make sense of these and other ""universe-expanding"" techniques.

The Alpha-Invariant for Irregular Sasakian Manifolds

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The Kahler-Einstein (K-E) problem is a famous problem in differential geometry over the complex numbers. It asks whether a given compact space with the structure of a complex manifold admits a solution to the Einstein equations, a set of partial differential equations that describe how space curves in the vacuum. While a solution always exists in the cases of negative or zero cosmological constant, obstructions to finding solutions do exist in the case of positive cosmological constant. A result of Tian tells us that if a certain numerical invariant, the alpha invariant, is large enough, then a solution to the Einstein equation exists. This has been used to produce many examples of K-E spaces with positive cosmological constant.

This work considers a generalization of the K-E problem, namely, replacing Kahler geometry with Sasakian geometry, to form the Sasaki-Einstein (S-E) problem. Sasakian geometry is a close cousin of Kahler geometry, and has recently come under close study, due to its relation to the AdS/ CFT correspondence in superstring theory. A Sasakian space locally looks like the product of a Kahler space and the real line, but globally it may not correspond to any Kahler space. When this occurs, the Sasakian space is called irregular. We extend the definition of the alpha invariant to a general Sasakian space, and prove that if it is large enough, a solution to the S-E problem exists. We then look for examples of irregular Sasakian manifolds for which this result applies, to produce new examples of Einstein spaces.

PHYSICS & APPLIED PHYSICS

Cloaking Device Using Transformation Optics

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Cloaking works by manipulating the material properties of a device to control the path a light makes in such a way that the object of interest becomes invisible. To be able to do that, we have to tailor the refractive index at each point of the material to guide the light around the object so reflection and absorption of light will be greatly reduced to enhance invisibility. Meta-materials (artificially- structured composites) are used in our research since they have material properties that are not found in natural materials.

In my research I currently use silicon and silver. In the first half of my research, I have been doing analytical calculations by using Effective medium theory for meta-materials made of spherical particles of silver in a host medium of air. Then, I extended my research to make the particles core-shell (a small spherical particle inside another bigger sphere) where the core is made of silica and the shell made of silver. We want to control a range of frequencies, particularly optical frequencies, to achieve invisibility. Currently optical frequency cloaks are absorptive and the goal is to come up with less absorptive designs. Hence, Core-shell structures give us a lot of freedom to control the permittivity, permeability, absorption and other light-matter interaction properties. In the second half of my research, I use core-shell structure for ellipsoids rather than spheres to extend my choice of parameters by including aspect ratio in the geometry that I am using. I use numerical simulation software FDTD to study the permittivity from the S-parameters (reflection and transmission coefficients). Determining this will enable me to model the structure easily and come up with less absorptive model.

A Model for Ds-DNA Pairing Based on Two Colliding, Rigid Rods

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An astounding feature of living systems is their ability to spontaneously and reliably self-assemble into their functional configuration. For instance, polypeptides fold into 3D proteins, and protein subunits come together to form complex molecular machines. In this work, we consider the homology dependent pairing of chromosomes, as it occurs in meiosis. This process faces two challenges that are universal to all self-assembly processes. First, the maternal chromosome 1 must discriminate its true partner-- paternal chromosome 1--from other chromosomes, such as chromosome 2 (even if 2 and 1 are similar in some regions by chance). Second, once two chromosome 1 molecules meet, they must form a stable and durable complex. These two requirements ARE generally incompatible. Namely, if chromosomes 1 and 1 form a stable complex, yet 1 is, by chance, similar to 2 in some regions, then 1 and 2 should also form a partially stable complex. But experiments have shown that DNA pairing achieves both stability and specificity, even without the help of proteins. How this happens is not understood. Using a mathematical model, we show that the conflict between speed and specificity can be resolved if DNA sequences test each other for similarity in a series of stages akin to dates. In the "first date", two DNA molecules collide at an angle. This angle prevents the molecules from interacting too tightly at first, so mismatching sequences easily come apart (even if they have regions of accidental similarity beyond the collision region). But if the pairing is correct, then the regions flanking the collision match, so these regions attract and "zip up" the rest of the molecule. Thus, only true matches stably pair. The simplicity of this argument makes it attractive as a model for self-assembly in DNA pairing as well as other systems, be they biological or artificial.

Electroplating on Diamond for Reliable Microwave Delivery to Nanomechanical Devices

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Point defects in diamonds have emerged as a remarkable material property for nanoscale photonics and quantum optics. Nitrogen-vacancy (NV) color center is one of the many point defects in diamonds. The NV center is comprised of a pair of a lattice vacancy and a neighboring nitrogen atom which substitutes a carbon atom. NV centers are room-temperature sources of single photons whose spin state can be optically read-out. Additionally, their spins can be manipulated at room temperature by applying microwave radiation whose frequency matches the energy difference between its lower energy spin states. The ease of manipulating spin states of NV centers in diamonds at room temperature makes them an excellent candidate for a range of applications, such as fabrication of nanophotonic devices with NV centers for room temperature quantum cryptography, quantum information processing, and biocompatible devices for photonics-based chemical sensing schemes. Development in this field could potentially allow for things like higher resolution MRI and faster and more powerful (quantum) computers.

My work focuses on the application of microwave on the CVD diamond sample to manipulate the spin state of the NV centers, to hopefully allow a realized robust system to deliver a large magnetic field at a specific site with a desired frequency. The ultimate goal of this research is to design and fabricate a planar transmission line, preferably either a spiral inductor, meandering structures or a combination of both on a 4mm x 4mm diamond substrate, using electroplating to improve the inductance and current—this leads to enhanced magnetic field delivery. Target frequency of the microwave is at 2.87 GHz, which matches the zero field splitting between spin $|0\rangle$ and $|\pm1\rangle$ of the ground state. This involves the use of Finite Element Method (FEM). For this I used COMSOL Multiphysics to design the optimal structure for efficiently delivering microwaves on the diamond chip. Established design is implemented with the combination of photolithography for patterning a seed layer and electroplating for a thicker wire.

Normal Modes of an Exponential Block-Spring System

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A system consisting of an infinite line of blocks of the same mass connected by springs with spring constant $k_0 \times s^j$ between blocks j and j + 1 is considered. For the familiar case of s = 1, the normal modes are harmonic and spread throughout all of space. For $s \neq 1$, the modes are localized and can be found by deriving a recurrence relation and solving it using a generating function constructed out of the block amplitudes. The modes are constructed to be orthonormal, from which we obtain a family of transformations indexed by s that go between position space and mode space. For s = 1 this is simply a Fourier transformation but for $s \neq 1$ the mode space interpolates between position space and Fourier space. This suggests looking for applications of these mode transformations wherever Fourier decomposition is applied, such as in image/audio compression or signal processing.

Analyzing Dirac Cone Dispersion in Zero Index Materials with Multiple Scattering and Effective Medium Theories

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Materials with an index of refraction near zero cause light to propagate through them with an infinite phase velocity, promising applications in cloaking, optical communications, and quantum computing. They have recently been demonstrated in various metamaterials, which are materials that derive their properties from their physical structure rather than their chemical composition. Zero-index behavior in these metamaterials has been demonstrated to occur when its band structure, which describes the relationship between the spatial wavelength of light and its frequency, demonstrates a Dirac cone at the gamma point of the Brillouin zone. A Dirac cone is characterized by crossing linear bands, which each plot the frequency of light as a function of the wavenumber inside a material, thus forming touching cones, and the gamma point by definition corresponds to the point where the wavenumber is zero (i.e. the wavelength is infinite).

The occurrence of zero index behavior for certain crystal structures (e.g. air holes in a square lattice in silicon) or at high frequencies of light, however, is not well grounded in existing physical theory. To accomplish this, we model the response of the metamaterial to light using a multiple scattering theory of a periodic array of Mie scatterers in 2-D. We then seek conditions for zero index behavior by extracting effective medium properties. By establishing understanding of Dirac cone induced zero-index phenomena at a fundamental level from the perspective of physical theory (via the effective medium approach) and band structures (via multiple scattering), we can relate band structures to material properties and predict the band structures themselves from the observed field profiles of the eigenmodes of the material. Our work furthermore may suggest new engineering approaches to preserving zero-index behavior at higher frequencies of light, with potential applications in nonlinear optics. Overall, our work establishes the relationship between material properties and zero index behavior in 2-D metamaterials.

Three Dimensional Videography of Metallic Dendrites Growing with Time

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Materials scientists have long been fascinated by the growth of crystalline dendrites in undercooled liquids. Dendrites are fractal-like branching structures that form as a liquid transitions to a solid in regions of local undercooling. The most famous example of these structures are the branches of a stereotypical snowflake, but understanding these ornate ice crystals is far from the only application of dendritic theory. The ubiquity of dendrites in the microstructure of metallic alloys requires a complete understanding of dendritic theory in order to accurately predict the mechanical properties of metal components in which they reside.

Our work seeks to shed new light on dendritic growth in metallic alloys by revisiting a classic mid-twentieth century experiment with a myriad of contemporary microscopy techniques. By growing dendrites in an optically clear binary organic system that exhibits metallic solidification behavior, we can peer inside the formation of these crystalline branches using advanced microscopy techniques. Our project utilizes Confocal, Confocal Fluorescence, Phase Contrast, and Raman Confocal microscopy to construct three dimensional, time-dependent models of dendrites growing in carefully controlled steady-state conditions. This provides real world data to complement our current mathematical understanding of dendritic growth.

In areas of engineering where eking a few more degrees out of a jet turbine's melt temperature can save thousands of gallons of fuel or where the difference in strength between the passenger compartment and crumple zones of a car can make the difference between life and death in an accident, it is especially important to understand the connection between a metal's manufacturing conditions and its microstructure. Our project, by modeling the solidification transition between molten and liquid metals, hopes to answer important questions which lead the way to this understanding.

Advancing the State of the Art for Cryogenic Amplifiers for Antiproton Magnetic Moment Experiment

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Extremely high precision measurements of properties of fundamental particles have been obtained by confining these to a small region of space using a system of electric and magnetic fields called a Penning trap. The particle oscillates inside the trap with a few different modes, and measuring the frequency of oscillation accurately is what allows us to obtain such large levels of accuracy. We were working specifically with protons and antiprotons, using CERN's ability to manufacture antiprotons to conduct an accurate comparison between the properties of matter and antimatter.

The measurement is done by amplifying a tiny current induced in the electrodes until it is large enough to measure directly. The component that does this consists of an electrical (LC) resonator attached to a transistor board that amplifies the resonant signal. The capacitance of this comes mainly from the electrodes themselves, while we build the inductors ourselves. We aim for the Q, or quality factor of oscillations, to be as high as possible as this allows us to take measurements more quickly. To this end, our project was to build an amplifier with a superconducting inductor, a change from previous designs which used copper, as this should have lower resistance and hence higher Q. We built several versions of the inductor, mostly with a toroidal geometry, before settling on one that used thick strips of Niobium-Titanium supercondutor to better confine the flux and give increased robustness. The current experiment uses a resonator with an Q of around 1,500 (unloaded); preliminary measurements suggest the new component we developed could have a much larger Q. The work of confirming this result in ongoing.

A He3 Magnometer for Use at 4.2K

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The electron magnetic moment, roughly a proportionality constant between an electron's spin and the strength of its magnetic field, is the most precisely measured fundamental property of an elementary particle. Comparing the measurement to the theoretical prediction is the most precise test of the Standard Model of particle physics, the current best understanding of interactions of fundamental particles.

Herein are described improvements to a prototype helium-3 magnetometer for use at low temperatures and strong magnetic fields, an innovation that is essential because standard room-temperature water NMR techniques are impossible in cold-bore magnet of the new apparatus to measure the electron's magnetic moment. The magnetometer uses pulsed NMR of He-3 gas located in a sample volume located within the entire region of interest. The linewidth and shape of the free induction decay, the signal from the probe, is used to as a guide to shim the magnetic field homogeneity. Using our probe, we expect to demonstrate superior homogeneities to those reported in a 2008 measurement of the electron magnetic moment. This work is done with the intention of providing a more uniform background field for the next generation of electron and positron magnetic moment measurements.

Analysis of the Quantum and Semiclassical Horseshoe Maps

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In classical mechanics, the time evolution of a system is given by the change of its position and momentum coordinates in phase space. In chaotic systems, nearby initial conditions separate exponentially with time. The horseshoe map is a non-area-preserving map on a unit square in phase space which is found to be approximately embedded in many chaotic systems with hyperbolic dynamics, which implies expansion along one direction and contraction along another. We studied the properties of the quantized version of the horseshoe map, and also defined a semiclassical horseshoe map, along the lines of the semiclassical Van Vleck propagators for Hamiltonian systems, which express the probability of going from an initial state to a final one in terms of classical expressions.

We found good agreement between the semiclassical and quantum propagators for the initial steps, to approximately the same extent as the agreement between the quantum and semiclassical propagators for the baker's map (an area-preserving chaotic map nearly analogous to the horseshoe). We analytically found an expression for the density of states of the semiclassical propagator in terms of a sum over the classical periodic orbits, in analogy to Gutzwiller's trace formula, a well-known similar result for Hamiltonian systems. Attempts to numerically verify that the density of states predicted by this expression is approximately equal to the density of states from the exact quantum propagator have not yet been successful, and this might be due to computational errors.

We also compared loss of area with successive steps in the classical and quantum versions of the map. As expected from quantum mechanical interference effects, the area retained quantum mechanically at each step was larger. We found that, independent of the stretching parameter of the horseshoe map, after a large number of steps (on the order of 100), the fractional quantum mechanical area retained was the square root of the fractional classical retained area, and are in the process of trying to analytically understand what causes this.

Microwave Spectroscopy at Low Temperatures

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In quantum mechanics, the rotational energy states of a molecule are quantized, and the energy differences between nearby states fall in the microwave region of the electromagnetic spectrum. Therefore, microwaves can be used to excite molecules, and the resulting emission can be recorded as a microwave spectrum. Microwave spectra are hard to

interpret when done with room temperature samples, due to thermal noise. However, at five degrees Kelvin, microwave spectra are much clearer. This advantage can be exploited to perform mixture analysis, since every molecule has unique spectral signatures that rarely overlap. We have successfully identified a mixture of acetone, benzonitrile and carvone. These spectral signatures are determined by the mass distribution of the molecule, so microwave spectroscopy can be used to detect small changes in a molecule, such as the substitution of an atom with one of its isotopes. We have successfully observed substituted acetone.

To obtain interpretable spectrum, we need to cool our sample to five degrees Kelvin. We use the novel method of Buffer Gas Cooling, which involves cooling the molecules through collisions with an inert gas, such as helium. We can control the cooling by adjusting the density of the inert gas in our spectroscopy cell, because the greater the density, the greater the number of collisions. We have observed the cooling of several different spatial conformations of 1,2-propanediol by using microwave spectroscopy at different buffer gas densities. We hope to also determine the cooling pathways for these conformations.

Measuring the Temperature of Superheated Water Using Laser Diffraction Patterns in a Solid-State Nanopore

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Superheating occurs when a liquid is heated up to a temperature above its boiling point but does not boil. The ideal environment for superheating is a container with a perfectly smooth surface because imperfections such as indentations on the surface of a container can facilitate heterogeneous bubble formation and lead to boiling. Until now, superheated water had not been achieved under atmospheric pressure; therefore, it was not possible to determine the physical properties of water in this particular state.

In July 2014, the Harvard Nanopore Group has achieved superheating near the critical temperature of water and homogeneous nucleation in an electrolyte solution within a nanopore in a thin silicon nitride membrane. This is an ideal environment for superheating because silicon nitride is smooth, wettable by water and at a lower temperature than the water surrounding it. This result has paved the way to use solid-state nanopores in order to investigate the physical properties of superheated water. One of the most interesting physical properties to be investigated is the refractive index, the ratio of the speed of light in vacuum to that in a medium, because the refractive index changes over time with the temperature of the superheated water.

My research involves fabricating nanoscale slits in a silicon nitride membrane and using a laser to create diffraction patterns due to the wave property of light. Then, the intensity of the diffracted laser beam will be measured via a silicon photodetector. The dimensions of these diffraction patterns will lead to measuring the refractive index and therefore the temperature of the superheated water. An application of the experiment would be to use the nanopore with superheated water as an adjustable lens whose refractive index changes as one changes the temperature.

STATISTICS

Gridded Population Sampling: A Method for Implementing Cluster Samples with Gridded Population Data

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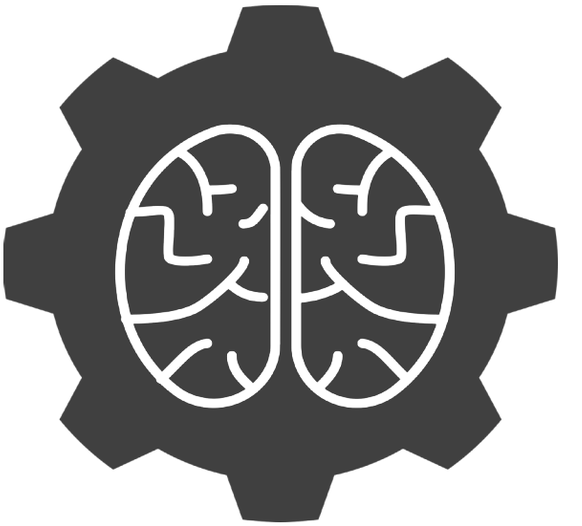
The availability of up to date information is crucial for monitoring and evaluating programs, planning new policies, prioritizing actions, and overall decision-making in health, education, and urban planning. However, the standard household survey sample design is costly and time-intensive to implement with a typical DHS (Demographic and Health Survey) costing approximately US$500,000 and a year and a half. An important challenge is the deficient or non-existent up to date census data. A household survey based on incorrect census totals will not reflect the underlying population distribution, which violates the fundamental sampling principle that everyone in the population has an equal or known probability of being sampled.

An alternative to census data is to utilize gridded population data, which estimate total population for regular-sized grid cells using a spatial model of population data, and several inputs, such as population data from varied sources, satellite imagery, transportation network, and settlement locations. Gridded population data facilitates the sampling of spatially representative information and serves as an alternative when up to date census data are not available. Additionally, it may reduce survey design time and costs (by eliminating the dependency on national statistical agencies to provide a list of enumeration areas to be sampled) and facilitate the sampling of spatially representative primary sampling units. Ultimately, we aim to utilize gridded population data's ability to leverage uniformly sized grid cells to select samples that are representative across space for improved spatial analysis of population data.



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Limits to Arbitrage: Evidence from Event Studies on Siamese Twin Stocks

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Siamese twin stocks are separate stocks that pool dividends and voting rights. The benchmark model of behaviors in financial markets is the efficient market hypothesis: market prices reflect all available information. The fact that twin prices can significantly diverge from their theoretical parity despite having the same underlying fundamentals is one of the clearest pieces of evidence that the market is inefficient. We want to know how they are inefficient, especially what prevents informed traders to profit by arbitraging away existing inefficiencies.

We examined the changes in Siamese twin prices after earning surprises, as they are critical pieces of information and are systematically used to check market efficiency. Quick information incorporation is due to informed arbitrageurs, and since arbitrageurs know that one stock is overvalued relative to the other, the reaction should be asymmetric. However, we found that this is not the case. The twin prices move in tandem after earning surprises and do not move after market-wide shocks such as currency shocks. This comovement result holds both when we compare two fixed stocks in a pair or the less expensive versus the more expensive. Moreover, the return difference between one twin pair correlates positively with that of another twin pair, even after controlling for autocorrelation, time zone differences and country-specific factors.

We are in the process of building a mathematical model to explain this phenomenon by incorporating one or more of the following features: (i) arbitrageurs do not commit their full capital to correcting inefficiencies because noise traders might push the price even more out of line, forcing them to unwind their positions at substantial loss (ii) smart money predict the reaction of noise traders and front-run them, destabilizing prices from fundamental values (iii) arbitrageurs hold long-short positions in several twin pairs, so when prices of a twin diverge significantly for some reason, they get margin calls and have to reduce their positions in other pairs, causing the price gaps of other pairs to widen at the same time.

Economic and Political Impacts of the Vietnam War

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How does war affect a country's economy, politics, and health? What types of wartime strategies are most effective at pacifying insurgents? Our research investigates these questions in the context of the Vietnam War.

During the war, the United States assigned security classifications to locations in South Vietnam and based its military interventions and economic assistance on these classifications. A location that was controlled by the Viet Cong would receive a "V" classification and, likely, be heavily bombed, while a location with no Viet Cong activity would receive an "A" classification and would be the target of little military action. Our research into military documentation and datasets suggests that many places which received one classification could very well have received another if the classification algorithm had been different. By comparing locations that had similar security situations but were assigned different overall scores and were treated differently by the U.S., we can isolate the impact of the U.S.'s wartime actions.

These actions may have affected both short-run security outcomes and long-run economic, political, and health outcomes. Thus, we aim to analyze whether bombing tended to increase or decrease Viet Cong activity. The question of whether "carrots" (economic aid) or "sticks" (bombing) are more effective has important implications for current U.S. counterinsurgency policy. We are also interested in how herbicides sprayed by the U.S. military affected health and how the Vietnam War affected income per capita, industrialization, and financial markets over the long term.

Our role in this project so far focused on (1) preparing historical military datasets, (2) creating maps and visualizations of the data, and (3) estimating the U.S.'s algorithm for classifying hamlets. We have not yet run regressions, but we have prepared a rich dataset that will allow us to estimate effects in the near future.

Intra-ethnic Conflict and Genomics

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Despite attention given to inequality by academics and the public at large, observers sometimes portray class divides between races or ethnicities without addressing intra-group differences. Our first project explores whether African-Americans and Hispanics, respectively, demonstrate internal political divisions, particularly -- but not exclusively -- on class lines.

To gain more qualitative insight into these political divisions, we have done preliminary research on case studies of New York City, Los Angeles, Chicago and Atlanta, which highlight internal Black or Hispanic conflicts over issues like policing or housing policy. We are now writing a survey to be completed by several thousand respondents in twelve metropolitan areas, who we will ask about these and other local issues. The resulting data will give us a quantitative perspective into intra-group divides, which will in turn further inform our case studies and interviews with experts on local politics in the specific cities.

My second project consists of research on the politics of emerging genetic technologies. This project investigates the politics of genomics along multiple axes. First, my review of the literature focuses on divergently optimistic or pessimistic views of emerging technology and how various disciplines conceptualize those attitudes. I then examine writing on nature and nurture as conceived by psychologists, sociologists, religious thinkers, and others. We intend to analyze how scholars and the public think about the 'opposite' of nature, and how understandings of nature, chance, free will, luck, and fate relate to optimism or pessimism about genetic science and its policy implications.

Predictive Coding Model of Mental State Inference

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Matt from lab is a BLISS intern. You observe Matt at work - he is sitting at his desk, typing. You then see Matt yawn, get up and leave the room and return with a cup of coffee. Instead of drinking the coffee, he dumps it in the flower pot. Not only is this action surprising, but it causes us to make specific revisions to our theory about Matt – what he wants, believes, and might do next. This scenario illustrates the core premise of social prospection and predictive coding model.

Social prospection is the ability to reason about possible future actions, [Matt is walking back with coffee --> Matt will drink the coffee], based on inferences about a person's mind: an unobservable, causal structure, tracking goals [he wants to boost his energy], preferences [likes coffee] and personality traits [gets sleepy when he works]. Predictive coding argues that the brain generates continuous predictions of upcoming events [Matt is getting coffee —> to drink coffee] and then adjusts these predictions [when sees him pour coffee in plant] by computing an error signal that tracks deviations between predicted and observed events. This project uses predictive coding to characterize the neural basis of social prospection.

We have a good understanding of which brain regions support social prospection. However, not much is known about how social prospection is carried out. The project I am working on aims to answer this by question by exploring whether specific neural populations are responsible for social prospection, what network/pathways are used, how this information is coded, and how it affects other regions of the brain. Data for the project has been collected using neuroimaging techniques (fMRI) that track whether predictor and error neuron populations within the brain respond to expected and unexpected social scenarios, while participants are making predictions about other's actions and preferences.

The Effect of Linguistic Structure on Children's Interpretation of Verb Meaning

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How do we learn a language? As children, we indeed learn grammar in school, but long before that, we are still able to perform the fundamental, and arguably more difficult task of matching words to their real-world referents. Despite the statistical likelihood that they will incorrectly make these pairings, children learn the meaning of words with extreme speed and impressive accuracy (Carey, 1978). Previous research has suggested a series of constraints that guide children's word learning by reducing the number of plausible referents in a conceptual space, but these mechanisms do not speak to the added difficulty of pairing words to abstract, dynamic referents (i.e. pairing verbs with their real-world events or actions). Given that parsing out the meaning of a verb requires higher-level abstraction than simply pointing to a noun in the world and pairing it with the proper term, we are interested in what sorts of cues children use to guide this learning process, and at what age these mechanisms come online. We hypothesize that children make use of one rather salient distinction as they attend to the essential features of events (and the verbs that describe them): *how* something is done versus the *result* of what has been done. To explore this, our experiment uses a rational actor imitation paradigm in which children see a novel event (turning on a toy with my head) paired with one of two novel phrases that either encodes manner (*how*) or outcome (*result*). They are then asked to imitate the event themselves. We predicted that children who heard the manner phrase ("I *daxed to* my toy") would be more likely to infer that *how* I turned on the toy was an essential component to the event, and therefore imitate it more frequently than children who heard the event described in the outcome phrase ("I *daxed* my toy"), and who would likely take the simplest means to imitate the *result* (the toy turning on). This pattern of results was confirmed in 2-year-olds, and I am currently extending this paradigm to younger children (17;00 – 19;00 months) to see if their interpretation of novel events is similarly affected by the manner versus outcome syntactic distinction.

When Two of America's Most Eminent Psychologists Erred in Prediction

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In August of 1961, Stanley Milgram began what would be known as one of the most famous collections of experiments of all time—the Obedience Experiments. Inspired by the Nazi stronghold in Germany in the 1930s and early 40s, Milgram was interested in looking at why an entire population of people could seemingly accept the systematic execution of the Jews and other minorities. Exactly 10 years later, Philip Zimbardo would begin his own experiment, this one on the study of prison life. With the Stanford Prison Experiment, Zimbardo looked to challenge the idea that the abuse that occurred in prisons was the result of inherent pathological traits among prison guards (and in fact, that these traits were present in all humans). Both scientists were in for a surprise when they analyzed the results.

There are many points of comparison between these scientists who were fascinated by the human condition and their controversial experiments. There is, however, one point of comparison that is less frequently mentioned in literature describing Milgram and Zimbardo, whether studied individually or together: the idea that both scientists were remarkably wrong in their hypotheses for each of their experiments.

My goal was to prove that it was not necessarily a scientific miscalculation as much as it was a failure to remove the optimistic filter on human nature. Thus, I argued that the two experimenters implicitly believed people were moral regardless of circumstance and would act as such despite the outward attempt to demonstrate the more sinister side of human nature. The participants failed to do so, making the findings of the experiment surprising to all, the scientists and the public alike. For my approach, I have used a combination of books and articles on the experiments as well as archival materials.

Appreciation Jolt: the Benefits of Social Approval

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Appreciation jolt is the psychophysical phenomenon resulting from positive reinforcement from one's social group. Previous research has demonstrated that appreciation jolt is associated with positive emotions and positive physiological responses, including reduced stress and a strengthened immune system. In addition, when applied in group settings, appreciation jolt is correlated with more creative problem-solving and better team function and performance. This study continues the investigation into group performance by analyzing the effect of appreciation jolt on information sharing in a virtual task.

In order to create appreciation jolt, we requested that participants ask members of their social groups to submit stories about the participants' best selves. We then collected and delivered the stories to the participants either before they participated in a group task (the treatment group) or after they participated in the task (the control group). The treatment group was asked to reflect on their best selves, thus ensuring that they would experience appreciation jolt. Then the participants entered a virtual chat room, where they formed a consensus regarding a mock real estate purchase. Each group member had access to some information that the others did not; after the task was complete, we analyzed how readily that information was shared. We also analyzed the balance within the group and the speed and tone of their performance, and asked participants to respond to a series of questions about their subjective experience. Ideally, appreciation jolt would be shown to be related to improved group communication. However, the opposite may be true; appreciation jolt may instead be correlated with impaired communication due to decreased willingness to accept other points of view. Our investigation should provide further information about the costs and benefits of appreciation jolt within group settings, which could lead to more effective protocols for collaborative tasks in the workplace.

Determining Cognitive Learning Style

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Cognitive style determines an individual's method of information-processing, particularly in perceptual tasks. One aspect of cognitive style, "field-dependence/field-independence," describes how individuals analyze perceptual patterns. In a field-dependent learning strategy, people form a holistic organization of the total perceptual field, while in a field-independent learning strategy people more often distinguish and focus on specific parts of the field from the deconstructed whole. Past research has tested the extent to which participants are reliant upon field dependence-field independence through perceptual tasks known as the Portable Rod and Frame Task (PRFT) and the Framed Line Test (FLT).

This study seeks to understand how the FLT And PRFT relate. While both tasks are effective in determining an individual's dominant cognitive style, they differ in accessibility and ease of use. While the PRFT requires a great deal of equipment, the FLT requires only a pencil and paper to test the same concepts. However, it is unknown exactly how well the PRFT and FLT correlate, and, if they do correlate, if the FLT can be used as a mobile proxy for the PRFT. Furthermore, this proposed study seeks to understand, to the extent that the PRFT and FLT do or do not correlate, if the FLT can identify FDI-mobiles (people those whose cognitive style fluctuates between field independence and field dependence due to task demand).

Participants will partake in both the FLT and PRFT tasks in a within-subjects study design. As a research assistant, I have designed the stimuli and will be running participants upon study approval by the IRB.

Identifying your cognitive style as FI or FD may provide insight in how you function in physical, cognitive, and psychosocial areas. Our proposed study hopes to discover a more efficient process in identifying cognitive style, and build on existing research concerning FDI-mobiles.

Measurement and Modification of Suicide-Related Cognition (MSRC)

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Despite recent advances in our understanding of suicidal behavior, there are limitations in our ability to detect and modify the cognitions and mental states that lead Soldiers and Veterans to think about and attempt suicide. To address these limitations, this research will develop and test several new methods of measuring and modifying past, present, and future-oriented cognitive processes related to suicidal thoughts and behavior among Veterans. In addition to developing objective assessments and targeted interventions for suicide risk factors, this research has the potential to improve our understanding of how and why these risk factors are related to suicidal behaviors, which could lead to further improvements in prediction and prevention. Thus, this research has the potential to improve the understanding, prediction, and prevention of suicidal behavior among Veterans at high risk for these outcomes.

What If Draco Had Killed Dumbledore?: Causality's Role in Moral Judgments

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John and Mary are assassins whose sniper rifles are aimed at Ron. Despite his better vantage point, John shoots and misses; Mary then shoots and kills Ron. While we have clear moral intuitions about John and Mary's actions, we do not yet clearly understand the the ways in which our brains process complex causal relationships between moral agents and their victims. Here we identify the brain regions which process complex causal events in order to see how these 'causality' regions relate to the brain regions which make moral judgments. Based on recent findings, we predict that the brain regions that handle abstract causal rela-

tionships will be located in prefrontal areas and that there may be co-activation in regions responsible for other forms of abstract processing.

This summer, my research group had participants read various vignettes while undergoing fMRI (functional magnetic resonance imaging). In these vignettes, causality was either simple (e.g. John successfully shoots Ron) or complex (e.g. John fails to shoot Ron, and Mary unexpectedly completes the act). By varying the complexity of the causal relationships in the vignettes, we will be able to identify the brain regions that process abstract causal relationships. Critically, after reading these vignettes, we asked participants to judge how much punishment the perpetrator of the harm deserved for his or her action. Thus, we will also able to identify regions that make moral judgments of punishment. Finally, we will use connectivity analyses (which index the degree to which brain areas communicate with each other) to characterize the role that causal processing plays in moral judgment.

Petitions in Early American History, 1789-1819

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Early American petitions provided critical channels of communication and expression for citizens and residents of the new republic. Petitions represented the voices of people across the country, from the wealthiest landowners to disenfranchised groups such as women, Native Americans, and African-Americans. To date, little quantitative research has been done on these early petitions. To begin such research, we first amassed a database of demographic, geographic, and thematic information from the thousands of petitions presented to the first fifteen U.S. Congresses. I reviewed these petitions to extract the relevant information from the original text of the Annals of Congress. With this data, we uncovered patterns of civic engagement and institutional development that have never been previously studied. I performed statistical analysis on this database to track these petitions after they were submitted to Congress and looked for patterns related to demographic and geographic factors. For example, petitions submitted by women were referred to congressional committees at the same rate as those submitted by men. Using a GIS (Geographic Information Systems) program, we will develop a functional and interactive map of these petitions by state, county, and town for both public users and future researchers. Further work will focus on the study of the development of specialized congressional committees and how the early American Congress transformed as an institution with respect to petitions. This work will also address the evolution of the First Amendment right to petition from the ratification of the Constitution until the present day.

Investigating a Link Between Future Thinking and Reciprocity

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In this study, we hope to examine the cognitive processes that underlie children's sharing behavior, specifically seeking to evaluate those specific cognitive abilities that contribute to a child's ability to share reciprocally. Reciprocal sharing – the ability to give away a reward in the present in exchange for a reward in the future – has long been and remains crucial for human survival. We have identified three cognitive traits that we hypothesize may play an important role in reciprocal sharing: theory of mind (the ability to attribute diverse beliefs and opinions to oneself and others), prospection/mental time travel (the ability to think about and plan for the future), and delay of gratification (the ability to choose a large reward in the future over a small reward in the present). By evaluating children's capacity for displaying these cognitive abilities and juxtaposing those results with children's performance on a reciprocal sharing activity, we hope to elucidate any connections between these mechanisms that may develop with age.

Our study evaluates the cognitive abilities of typically developing three-, four-, and five-year-old children recruited from Boston and the surrounding area. In the first 30-minute phase of the study, children undergo a battery of cognitive tasks, which allow us to evaluate traits such as mental time travel (putting oneself in a future situation), prospective memory (remembering something to be done in the future), future planning, and delay of gratification. Children return to the lab seven to ten days later and engage in a 30-minute reciprocal sharing task. Our preliminary results have indicated that as children grow older, their cognitive abilities develop and mature in each of the examined traits. However, we have yet to analyze the Visit 1 and Visit 2 data concurrently, and so cannot draw any conclusions at this time.

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Hiring Challenges in Developing Countries

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Over 600,000 engineers graduate from Indian colleges every year, yet, by many accounts, only about 10% of them are employable. In this context, how do businesses make decisions about shortlisting and hiring candidates to fill open engineering positions, and can the market act to fill this gap?

Over the summer, I developed an exercise for a course taught by Professor Tarun Khanna called "Contemporary South Asia: Entrepreneurial Solutions to Intractable Social & Economic Problems". In the exercise, students are placed in the position of human resource managers, provided with job candidate data and then tasked with developing the optimal hiring strategy to fill empty positions while minimizing hiring costs. In doing so, the students encounter the challenges facing higher education systems and businesses in developing countries.

I developed this exercise based on versions used in past courses. The project involved first cleaning and detailing the data on thousands of Indian engineering graduates and then creating an exercise for students from various disciplines that would challenge them to use the dataset. The final version involves 1) an easy-to-use interface on Excel that allows students to try out different strategies and checks to ensure that the constraints are satisfied; 2) a program for instructors that checks, compiles and provides feedback on the assignments submitted by students; and 3) instructional material for both students and teachers based on existing literature on the employability of graduates from institutes of technical education in India. Students using this interface in classes to come will grapple with some of the central challenges in ensuring the continued economic and human capital growth of developing countries.

Financial Decision Making, An Investigation

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In our ever-changing consumerist society, individuals are continuously faced with decisions of whether to save or to spend their money. Resources for advice in financial decision-making are plentiful, but we at the GiNorton Lab are interested in how consumers make these decisions under specific conditions. It has been found that individuals who feel they are in positions of power are more likely to save money and do so in greater quantities— likely due to greater confidence in their financial management abilities and foresight into their future financial situations (Garbinsky et al.). Our investigation aimed to delve deeper into this phenomena by examining how different types of income (base salary, bonuses, windfalls, etc.) affect one's saving and spending habits, and under what conditions the savings trends associated with power hold true. After experiment design has been completed, these experiments will be run in the CLER lab with the support of Harvard Business School and results will be appended to this abstract.

Improving the Value of Health Care Delivery

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As the funding structure of the American health care system changes, providers increasingly need to understand and control their costs. A common practice in health care accounting is to use a cost-to-charge ratio, which is an estimate of cost that has little basis in the daily activities that drive costs. A more accurate form of cost measurement is time-driven activity-based costing (TDABC).

TDABC requires that providers understand how long each resource—whether personnel, space, supplies, or technology—is required during a cycle of care for any given medical process. Our research centers on the use of TDABC to improve the value of health care. In one project, we analyzed which of two surgeries offers better value for treating diabetes patients, comparing health outcomes and TDABC data. In another project, I observed a hospital's pharmacy operations and designed a process map to better understand the breakdown of work and time. These observations will facilitate standardized data collection for TDABC research in hospital pharmacies nationwide. Our ultimate goal is to understand how to deliver quality health care in the most time-efficient manner possible, keeping costs low and quality high.

Corporate Governance at Wholly Owned Subsidiaries

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Corporate law treats the corporation as a monolithic entity. The empirical reality, however, is that virtually no significant business today is organized as a single corporate entity. Instead, most businesses are organized into a vast array of subsidiaries and holding companies. Names like "General Electric" or "Facebook" are merely shorthand for thousands of corporate subsidiaries organized in a vast array under a single parent. The need to fulfill basic corporate law requirements for each subsidiary raises two complex corporate governance questions: (1) To what extent do the policies and procedures at subsidiary company boards need to resemble those at the parent company level?, and (2) To what extent do subsidiary directors need to exercise independent business judgment from the parent company directors? The answers to these questions have important implications when assessing if subsidiary directors fulfilled the duties of care and loyalty owed to their shareholders and creditors. Professor Subramanian and I are preparing, to our knowledge, the first systematic investigation of how these businesses are organized.

Our article has both descriptive and prescriptive objectives. First, we present the first systematic data on large American holding company structures. Based on this evidence, we attempt to discern the rationale for the variation that we see in the data to construct a taxonomy of holding company structures. Second, we provide recommendations for subsidiary boards of directors and Delaware courts (more than 50% of NYSE-traded companies incorporate in Delaware) on the appropriate

answers to the corporate governance questions posed above. In general, we believe that ultimate business objectives and overall social welfare are best served by substantially stripped-down processes at subsidiary boards, with minimal effort to protect subsidiary creditors. Doctrinally, this means that Delaware courts should explicitly narrow the fiduciary duty to creditors at the subsidiary level, just as they have done in cases regarding parent companies.

Decision Making and Behavioral Economics

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Michael I. Norton, Franschesca Gino, Leslie K. John, Alison Woods Brooks, Ryan W. Buell
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Lying at the intersection of psychology and economics is the study of decision-making and consumer behavior. The research conducted in the GiNorton uses to use fundamental psychological concepts to investigate human judgment and motivation. Throughout the summer I worked on a variety of projects related to these fields. One project investigated the increased prevalence of "humble bragging," the phenomenon in which an individual complains and brags simultaneously. Through surveying and qualitative coding, we investigated how this form of self-expression is received by others and how it compares to less subtle forms of bragging. In another project, we analyzed campaign finance and how transparency in campaign contributions can aid or hurt political candidates electability. Through creating surveys with different hypothetical political websites, we tested how transparency affects perceptions of political candidates. We also examined which factors make constituents most likely to give to a candidate's campaign, which may include include the number of other candidates, quantity of donations, and methods of sharing this information. These projects can provide insights for companies not only into on the minds of stakeholders (both consumers and employees), but also into ourselves and our everyday decision-making processes.

Exploring Innovation in HealthCare

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Ariel Stern
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Professor Ariel Stern's research focuses on the empirical analysis of health care markets, health care policy, and innovation incentives faced by medical technology firms. In working with her this summer, I've had the opportunity to explore many facets of this field. In one project, we are examining the role of FDA in the design of clinical trials for new drugs and devices in the United States, and how that role is characterized in academic literature. The Food and Drug Administration (FDA) is required to provide the least burdensome route to approval for new technology, and thus typically provides clear criteria for approval at each stage to manufacturers. FDA thus has significant influence on the targets and direction of clinical trials. To explore this, I assembled a novel dataset of clinical trial publications in three major medical journals over a five-year period, and parsed that data for new, primary-indication drugs and devices. We have begun analyzing this data to examine the degree to which clinical trial design is attributed to FDA in academic publications by authors. Additionally, we've begun writing an HBS case for use in Professor Stern's class on Technology and Operations Management. The case examines the Brigham Innovation Hub, a department at Brigham and Women's Hospital dedicated to transforming the ideas of Brigham employees into products to improve health care delivery. Through research and employee interviews, we've focused on the case on how the Innovation Hub should prioritize revenue streams and define appropriate scope.

How Star Women Succeed

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In today's age of technology and innovation, new business concepts and trends are constantly emerging. Just as firms are evolving to keep up with the world around them, the organizational structures supporting them must grow and change in parallel. My work this summer has focused on how organizations are re-tooling their conception of the workforce and expanding administrative structures to accommodate the expanding needs of their organization. In one project we explored the gamut of new and original C-Suite positions that companies have been adding to their leadership team. By looking at the number of people in a variety of c-suite positions over the past 15-years we were able to determine how the traditional c-suite positions have fared and how quickly new positions have gained prominence within the corporate structure. Another project is looked at diversity and inclusion practices. By talking with professionals from a wide range of industries and positions, we were able to learn why companies find diversity so valuable to their performance, how they view diversity and inclusion, and the steps that they take to measure these characteristics within their organization.

Strategy and Innovation in Nascent Markets

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The vast majority of research in business strategy has focused on examining established firms in mature industries, i.e. those with known threats of entry, an observant and informed government, and clear consumers for an already-defined product. This is not always the case. Nascent markets are small and newly developing, and consequently, the usual strategies in mature markets are not necessarily applicable and may even be disadvantageous.

In order to better understand strategy in nascent markets, I have been closely analysing the direct-to-consumer personalized genomics industry. Here there are five key firms from which detailed case histories can be built. By iterating between theory and evidence in this industry, we are exploring the effect of non-market strategies, including the role of government regulation and its interaction with the new market, on competition between firms and the establishment of a new industry as a whole. One question we are exploring in detail is whether encouraging regulation is an effective means to remove competition in an industry.

This analysis is a long-term project and will provide important insights into the role of business-regulator interactions in nascent markets.

Ethical Dilemmas and Narrow-margin Failures

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The way individuals and groups make decisions and act provides a rich opportunity for researchers to study human behavior in markets and organizations. This summer, I collaborated with the GiNorton lab, a group of professors, researchers, and doctoral students from diverse backgrounds including organizational behavior, management, and marketing. The lab focuses on aspects of human behavior in markets and organizations such as ethical decision making, ritual performance, and effective leadership. I worked with doctoral students and faculty on two projects that relate to ethical dilemmas and narrow-margin failures. In the ethics project, we sought to study how one's moral identity and creativity are affected in a "could" as opposed to a "should" mindset in thinking about moral and amoral situations. While people are often aware of popular ethical dilemmas such as the Trolley problem, the hypothetical utilitarian or deontological answers they provide come from a "should" mindset, limiting their answers and removing the opportunity to engage creatively with moral questions. In real life, however, we face challenges of conflicting values where the right and wrong do not seem distinct. Knowing how one could handle these situations proves to be a relevant and important skill for individuals in organizational settings. Another project I worked on explored the psychology of narrow-margin and wide-margin failures. An example of a narrow-margin failure would be missing a flight by a few minutes, while a wide-margin failure would be missing a flight by a day. Since one's reaction to failures in life is very important for self-identity and character development, studying the difference between the motivating effects of failing by narrow-margin and wide-margin failures would allow us to understand how and why we react to failures by affirming our sense of self and engaging in progress-oriented activities.

The Impact of Surrounding Visual Cues on Purchasing Behavior

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Marketing (consumer behavior) research investigates the science of how and why people choose to purchase some products over others. As our understanding of human behavior has improved with advances in neurobiology and psychology, marketing and more traditional forms of science have converged to form new, interdisciplinary fields. One feature that has been shown to affect the purchase interest of a consumer is the presence of other products and information, which can increase or decrease an individual's willingness to purchase depending on the type of item. Our research examines these types of influence when the "distracting" or non-target items are unavailable. In this line of research, we have also shown that the value of these outside items does not appear to be the factor that is affecting purchasing rate. Here, through online behavioral studies and laboratory experiments, we further investigated this phenomenon by varying the neighboring items that are shown around a target product. We also piloted a study of how visual attention varies with analyses of participant gaze using eye-tracking software. Understanding the impact of such environmental cues is relevant to the marketing world as firms delve further into the neurological underpinnings of decision making to better predict consumer behavior and assess marketing techniques. Studies such as this, for instance, have direct implications in both the physical and virtual world, in store settings such as product displays, and in online marketplaces such as Amazon.

Music and Media: Surviving, Transforming and Thriving in the Digital Age

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The music industry has long been at the forefront of digital disruption and innovation. With the technological transitions from LPs to CDs to digital downloads to streams, the industry has faced widespread challenges to its business models, especially because means of production, promotion and distribution have become more democratized. Artists and labels have both lost traditional market power and gained new capacity. While artists are less dependent on labels for marketing and creative development, streaming services and other digital platforms innovating around the music experience, which emerged in response to both artist and audience preferences, have forced labels to experiment with alternative revenue models.

In this project, we use both qualitative and quantitative methods to analyze on a deeper level the positive and negative impacts of technology on the music industry, and to shed light on how emerging artists can make a living and how companies can gain traction and capture value in this constantly shifting environment. In addition to interviewing artists, record label executives, activists and entrepreneurs to identify new capabilities and opportunities for innovation in the industry, we investigate the economic and legal issues of streaming platforms such as Spotify and Apple Music, as well as incorporate cases and data-driven research in our examination of emerging artists' social strategies on platforms such as Facebook, Youtube, Soundcloud and Bandpage. Using these micro and macro perspectives on digital music, we not only integrate maps of the industry's players and cash flows, but also make recommendations for improving and streamlining the industry, in order to ensure that artists of all career stages and genres can continue making music everyone can enjoy. Ultimately, we hope to extend our insights into digital music to other industries such as gaming, fashion, film, and TV that are grappling with the threats and opportunities of the digital transformation of the economy.

Decision Making and Behavioral Economics

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Traditional economic theory declares that every dollar has equal value and that every item has equal selling and buying prices. Human behavior, however, often defies rationality, and behavioral economics is a field studying when and why such inconsistencies occur. This summer, I was part of the GiNorton lab, a collaborative group of researchers who study human behavior and discover surprising ways in which we act. In one of our projects, we investigated unintended negative consequences of recommendations: specifically, we asked whether recommending a product associated with a certain age, gender, or race to a target demographic might actually backfire. We posit that such recommendations may make people feel constrained and typecast, even leading them to choose a product they would end up liking less. We pursued field work to find out how people respond to having their vote count in a majority, in a minority, or not at all -- in this last case, they were "expressing preference." People were more likely to vote when they were in a majority and less likely to vote when they were in a minority. However, even when people knew their vote would not impact the outcome, they were more likely to vote than people in the minority. Businesses considering allowing customers to voice their opinions with a vote should keep in mind this unintended consequence: allowing people to have only a small say in a vote may backfire, and they may be better off asking customers their preferences in other ways. These, along with several other projects I was involved in, share an underlying theme: to answer the question, "When do humans act this way?" while never forgetting to address, "So what?".

Contracting as a Source of Value in Private Equity

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The goal of this project was to deepen understanding of the sources of value in private equity. The sources of value creation in private equity are somewhat elusive. The central hypothesis is that debt structuring; debt management (including leveraged recapitalization and restructuring), and even direct investment in debt are integral aspects of the private equity value proposition. Specifically, this project examined innovative techniques private equity firms use in drafting contracts.

Professor Victoria Ivashina's previous work shows that private equity firms—and specifically the biggest private equity firms—have large bargaining power vis-à-vis their originating lender. This new study dove into the specifics of loan contracts. For this purpose, Professor Ivashina and Professor Boris Valle acquired substantial loan-contract data from a legal firm that specializes in analyzing debt contracts. I focused my work on shaping these summaries and parsing out important data. Next, I merged different data sets in order to create a database of contractual clauses from the summaries. This database could be filtered to look for certain contractual terms, which I then coded in order to be able to perform analysis. Our goal was to look at whether private equity firms creatively negotiate financing terms, putting emphasis on ex-post renegotiation flexibility. Examining these terms help us to better understand the ability of innovative firms to create value though creative contract structuring.

Diversity in the Venture Capital Industry

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Paul Gompers
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The venture capital industry is one of the fastest growing industries in the world, particularly in Silicon Valley, a blooming entrepreneurial hub. A hot topic within this industry right now is the lack of diversity. Many companies within the industry have dedicated a lot of financial resources and time to this issue. My research this summer focused on proving whether diversity directly affects performance of companies within the industry. The research team and I focused on diversity across the dimensions of gender, education, geography, and family makeup. Our methodology involves using various databases and alumni and archival records from various universities to obtain diversity information about venture capitalists and founders within the industry. We used numerous regressions and other statistical processes with the information that we collected to assess the role of diversity on performance. At this point, we are unable to report any findings as data collection is ongoing. However, in the end, we hope to unearth the true nature of the relationship between diversity and performance and enhance the current discussions in industries across America.

Technology, Strategy, and Innovation in Platform-Based Markets

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Feng Zhu
Harvard Business School

Platform-based markets are more prevalent than ever in today's increasingly interconnected society. From search engines' bringing together of users and advertisers to video game consoles' uniting of players and publishers, platform-based markets now comprise a massive and rapidly growing share of today's economy. Taking into consideration the overwhelming success of current platform owners like Apple, Google, Facebook, LinkedIn, and Yahoo, many companies whose business models once centered around a product or service are now transitioning to a more platform-centric model. My research with Professor Feng Zhu is concerned with several topics in this field. In one project, we are exploring whether innovation actually pays off under the threat of imitation in the sponsored search engine market. This study primarily focuses on Google, Bing, and Yahoo! Search and attempts to document whether it is beneficial for a platform to innovate given the fact that other players in the space will almost surely imitate any successful innovation.

Another one of our projects focuses on the lack of concentration in the Brazilian healthcare group purchasing organization (GPO) industry. Often, platforms become more valuable to their users as their cus-

tomer bases grow. Facebook users have more people to interact with, gamers have access to a wider range of video games, and content-sharing networks such as YouTube have more users to drive the creation of new content. In this particular space, a GPO creates value when it negotiates bulk discounts for its constituents, a task made easier by larger memberships. However, in contrast to the highly concentrated industry in the United States (6 firms possess a 90% market share), the Brazilian market is far more fragmented. Our research aims to identify contributing factors to this difference in market structures.

From the innovation and imitation of sponsored search engines to the international variations between group purchasing organizations (GPOs) in the healthcare space, our work tries to document the best practices for firms to adopt a platform-centric business model.

Meaning and Identity in Work

Stephen Turban Statistics
Currier House *Class of 2017*

Teresa Amabile
Harvard Business School

How much do you identify with your work? In what ways - if any - does your job define who you are?

In this summer's research, I helped Professor Teresa Amabile look at the effect of identity on an individuals retirement transition. Specifically, I helped with qualitative analysis of conversations with newly retired and newly employed workers.

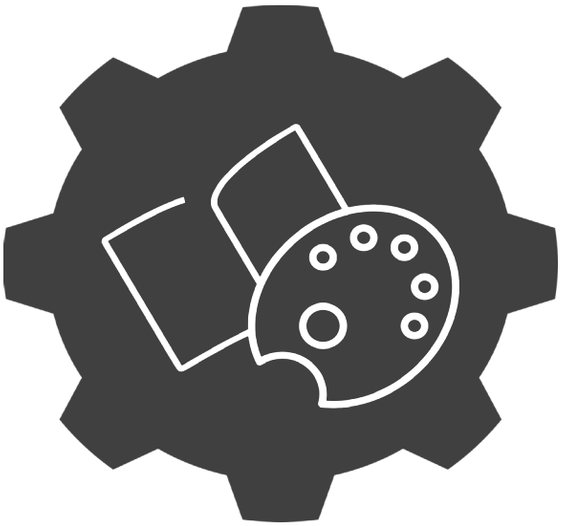
I also helped Mike Lee, Hayley Blunden, and Andrew Brodsky with their projects. With Mike, we looked at the effect of ambiguity on the formation of hierarchy. With Hayley and Andrew, we began research on impression making in online communication.

Examining the Innovative Output of MIT Graduates

Nathaniel Ver Steeg Applied Mathematics
Eliot House *Class of 2017*

Pian Shu
Harvard Business School

We aim to contribute to the growing literature on the economics of innovation by investigating how economic conditions at the time of college graduation impact the long-term innovative output of the bachelor's graduates at MIT. We use patents and scientific publications to measure innovative output, and my role has consisted primarily of helping match the MIT alumni to the patent and publication databases. This is made difficult by missing, misspelled, or misordered individual and/or firm names. Our most recent work involves using search engines and designing a probabilistic matching algorithm to solve this problem.



SHARP

Summer Humanities and Arts Research Program

Abstracts | 2015

From Radio to Rochow: Research, Curation, and Exhibition Development at the Collection of Historical Scientific Instruments (CHSI)

Alona Bach History of Science
Cabot House *Class of 2016*

Melissa Rodman History and Literature/History of Science
Dunster House *Class of 2018*

Jean-Francois Gauvin
Department of the History of Science

"We're live in 5...4...3...(2)...(1)...," a producer says to actors about to broadcast the daily installment of a radio drama. Such a scenario took place around the United States—and indeed around the world—as people took to the airwaves for music, news, and storytelling in the late nineteenth and early twentieth centuries.

We worked this summer at the Collection of Historical Scientific Instruments (CHSI) to design and develop an exhibition about the history, technology, and culture surrounding the radio. Opening March 2016, the exhibition will feature three types of interaction with the radio: "listening" (how families and individuals incorporated radio programs in their day-to-day lives); "tinkering" (how amateurs and professionals studied and replicated the technology behind the radio); and "broadcasting" (how announcers and studio owners created, produced, and distributed live shows). To produce an exhibition that both informs and engages visitors, we conducted research, created detailed design drawings, and selected objects for display from CHSI's off-site storage facility.

For another CHSI project, we catalogued and made searchable databases for over nine hundred previously unexamined lantern slides, which were donated to CHSI by Harvard's Chemistry Department. Our research in the Harvard University Archives (HUA) confirmed that many of the slides belonged to Professor Eugene George Rochow, a Harvard Chemistry professor from 1948 through 1970. Together, the slides and HUA materials provide a new perspective on Rochow's research, career, and character. Our final report for CHSI advises curators to accession (catalogue and add objects to the collection) and conserve the slides for further research.

Touring the Harvard Art Museums

Bonnie Bennett Undecided
Lowell House *Class of 2018*

Jessica Martinez, David Odo
Harvard Art Museums

After a seven year renovation project, the Harvard Art Museums reopened last fall. The Harvard Art Museums are comprised of three separate museums—the Fogg Museum, Busch-Reisinger Museum, and Arthur M. Sackler Museum—each with a different history, collection, guiding philosophy, and identity. The Harvard Art Museums' recent renovation and expansion builds on the legacies of these three museums and unites their remarkable collections under one roof for the first time.

Throughout my summer at the museum, I worked with curators, conservators, and the Division of Academic and Public Programs on various projects, including extensive research into the Museums' collections in order to create one-of-a-kind public tours. I focused my tours on the theme of audience, analyzing how the intended audience of a piece affects its creation. The tours, which are led six times a week, explore interesting, unexpected thematic links between artworks and artists in the Harvard collections.

I also helped develop an upcoming project at the Harvard Art Museums connected with the fall exhibition Corita Kent and the Language of Pop. The Museums are working with StoryCorps, the NPR oral history project, to record local stories that connect to the work of Corita Kent, a pop artist nun and educator who lived in Boston from 1968 until her death in 1986. On September 4, 5 and 6, StoryCorp's signature MobileBooth will be parked at the Harvard Science Center plaza to record interviews with community volunteers who either have stories about Corita or who have stories that connect to themes in the exhibition. Each interview is structured as 40 minutes of uninterrupted time for meaningful conversation between two people who know each other well. The interviews will intersect with the concern of food and social justice and the South Boston community close to Corita's "Rainbow Swash" gas tank, one of Corita's most prominent pop objects.

Poetry in America and the Digital Humanities

Colin Criss Sociology
Kirkland House *Class of 2017*

Elisa New
Department of English

In Elisa New's *Poetry in America*, a multiplatform, multimedia poetry project, I have found intellectual challenges across many disciplines. Besides daily critical analysis and discussion of poetry, I have had extensive exposure to coding in HTML, filming and editing video, and producing educational content using a variety of media. The project is trying to push poetry into the corners of our society with the belief that the humanities play a pivotal role in our multimedia-soaked world. This summer I shot and edited American Poetry-related video across the northeast that will be incorporated into a poetry-themed PBS television show currently in production. I thought out poetic integrity when editing in Final Cut Pro, and I developed a personal style in representing poetic image in professional photography and video.

When not shooting or editing video, I was designing and coding an online course named ""Poetry of the City,"" slated to be offered for credit by the Harvard Graduate School of Education. It will be their first for-credit online course when it launches, making my course design particularly challenging and important. Using the Canvas platform, I created a custom interface for the course, thinking creatively on a macro level as to how the audience (future teachers) should be introduced to poetic and pedagogical content. A well-built custom design in Canvas was previously non-existent at Harvard, and required my entire portfolio of liberal arts skills to create.

This summer, poetry was the root of my growth in the digital humanities and the liberal arts. I researched pedagogy; I researched professional skills. But I also discovered the role of poetry and creativity in human working life.

Circling Things: An Exploration of Art, Design, and Media with Prof. Jeffrey Schnapp and the metaLAB Team

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Quincy House *Class of 2018*

Jeffrey Schnapp
Department of Comparative Literature, Department of Romance Languages and Literatures

How do we look at objects, or "things"? Ostensibly part of the everyday, untouched by conversation and scholarship, objects and collections of them raise a number of issues, which may be as complex as how to curate collections for diverse audience, to as simple as, "What is this?" This summer, with Jeffrey Schnapp, FAS Professor of Romance Languages & Literatures and Comparative Literature and GSD Professor of Architecture, I explored new curatorial possibilities that have come from digital humanities, new media, and recent developments in critical theory and philosophy.

My research began with locating and examining archival materials in the United States and Japan for Professor Schnapp's large-scale book on the modernist Italian artist, designer, and educator Bruno Munari. My search focused on work that blurred distinctions between art and design, which made him a controversial, if not neglected figure in the art historical canon. I also assisted Professor Schnapp with the production of a publication on radical pedagogy in art schools during the 1960's.

With the metaLAB team, I helped organize a workshop for art historians, curators, other museum professionals, and artists to learn about and implement new ways of thinking about objects in their institutions. I specifically helped with documenting the workshop, through text and photographs, and contributed to the ongoing production of an experimental digital publication that uses the workshop's findings to prompt critical and design thinking about collecting.

Rethinking Translation: Paul Celan and Shakespeare's Sonnets

Alice Ju Philosophy
Kirkland House *Class of 2018*

Andy Troska Slavic Languages and Literatures
Leverett House *Class of 2017*

Sandra Naddaff, Stephanie Sandler
Department of Comparative Literature (Naddaff), Department of Slavic Languages and Literatures (Sandler), Mahindra Humanities Center

As a German-language Jewish poet writing during and after the Holocaust, Paul Celan embodied a tension between language and its philological weight. Through his poetry and poetics, Celan seeks to make language new, alien, and true: severed from or perhaps even cleansed of its cultural history and free from claims of ownership. His translations of 21 of Shakespeare's sonnets thus provide a starting point from which not only to understand Celan's theory of translation, but also to explore a radical new theory not rooted in a so-called fidelity to the original text, but rather in the creation of new works that speak through the tension between similarity and discord with the original text. To further this project, we are studying the process and philosophy of retranslation, a relatively untouched phenomenon of back-translating into the source language.

To build our understanding surrounding Celan's Shakespeare translations, we are looking at both primary and biographical sources, as well as scholarship surrounding his poetry and translations. We are also examining how Celan's motivations and work intersect with contemporary Continental thinkers, engaging with existential phenomenology, hermeneutics, and critical theory.

In collaboration with Christina Svendsen, lecturer in Comparative Literature, we are building a syllabus for the 2015-16 Rethinking Translation seminar, led by professors Sandra Naddaff and Stephanie Sandler. Drawing on the unorthodox approaches to retranslating this part of Celan's oeuvre spearheaded by Versatorium, a collective of student researchers and translators at the University of Vienna led by poet and translator Peter Waterhouse, we will strive to broaden the discussion surrounding translation of poetry and the creative potential of retranslation.

Cultural Agents Initiative: The Contribution of Student Interns to Arts-Integrated Service

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Doris Sommer
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The Cultural Agents Initiative at Harvard is founded on the belief that the methods of humanistic and artistic study offer innovative solutions to pressing societal issues. Participation in the arts comes in many forms, including theater classes that allow troubled communities to rehearse solutions to conflict, public murals that rejuvenate marginalized neighborhoods, and after school orchestras that build self-confidence and discipline in at-risk youth. The experience of surprise that art engenders can break down barriers among a diverse audience, allowing for a unified civic identity to emerge. This summer, I have been working with the Cultural Agents Initiative to produce a list of internship opportunities for college students that combine the arts, service, and academic work. These opportunities include positions with the Initiative on campus, with the Pre-Texts literacy program in schools around the world, and with partnering organizations. My work included establishing connections with organizations that share the Cultural Agents Initiative's goals, drafting website content, and producing outreach materials to encourage students on campus to get involved. I considered the comparative benefits of the arts as a method for social change, including the potential to produce a sense of civic agency, the ability to promote understanding within diverse populations, and the ability to make invisible issues emotionally and immediately relevant. I also considered the unique contributions that students can make as interns - namely, their inclination towards cross-disciplinary thinking and an optimistic outlook on change. Although Harvard is home to many talented artists and passionate activists, these pursuits are not often combined. Through my work this summer, I hope to encourage students across disciplines to consider how, as interns, they can apply the methods and thinking of the arts to the problems they care about to produce more effective change.

The Hand of the Artist and the Harvard Art Museums

Jessica Reese History of Art and Architecture
Kirkland House *Class of 2016*

Jessica Martinez, David Odo
Harvard Art Museums

The reopening of the Harvard Art Museums in November 2014, following a six year renovation, has ushered in a new era for the arts at Harvard. The building on 32 Quincy Street, formerly home solely to the Fogg collection of European and American art, now houses the University's three unique collections: the aforementioned Fogg; the Busch-Reisinger, a collection of Germanic art; and the Sackler, a collection of Mediterranean and Asian art. Brought together in a single physical space, the collections' object are, for the first time, able to communicate with one another across cultural, geographic and temporal boundaries. Navigating these cross-cultural and -temporal dialogues was a central focus of my research this summer. Speaking with curators and reading through the Museums' curatorial files, I was able to identify unifying philosophical tensions across the collections' broad spectrum of objects. The results of this research were concentrated into a public tour. Focusing on three objects and spanning from 3500 BC to 1954, the narrative arc of my tour explores instances of artistic gesture in order to contemplate the importance assigned to the perceived physical connection between artist and artwork, both historically and in modern times. To what degree does the hand of the artist inform our perception of an object as a work of art? Can art ever be truly anonymous? Or is its meaning and importance located, always, in its perceived connection to a creator?

Poetry in America: Modernism and Magazines

Maia Silber History and Literature
Eliot House *Class of 2017*

Elisa New
Department of English

Poetry in America is a survey of nearly 400 years of language and history. Led by Harvard English Professor Elisa New, the multiplatform initiative combines online lectures and discussions with archival expeditions and visits to historic sites.. My work this summer focused primarily on developing an outline for an upcoming HarvardX module on modernism, and collecting supplemental archive material for that course.

Much of this material came from a collection early 20th-century magazines, including both small literary magazines and larger commercial magazines. The breadth of this collection exceeded the conventionally defined parameters of "modernist" publications. In his 1930 essay "Small Magazines," Ezra Pound argued that modern literature could only flourish in independent publications with limited funds and circulation. Yet magazines from the wartime propaganda publication *The Red Cross* to the mass-market *Century Magazine* also shed light on modernist concerns. Modernist writers drew inspiration from nearly every political, scientific, and cultural event of their time. As students of modernism, we should cast our scholarly nets as widely.

This approach suggested an outline organized around the theme "The Worlds of Modernism." This structure seeks to recreate the "worlds" of Edna St. Vincent Millay's Greenwich Village, Marianne Moore's Chicago, and T.S. Eliot's London. The archival materials selected to illustrate these worlds vary widely in content and form; the course will draw on newspaper accounts, letters and manuscripts, art, and scientific data.

As a secondary project, I provided editorial assistance on *How to Read Poetry*, helping to select and structure close-readings of a variety of poems.

"Freedom from Want": Domestic Egalitarianism and International Human Rights

Fran Swanson History and Literature
Winthrop House *Class of 2017*

Samuel Moyn
Harvard Law School

While the mid-twentieth century was a time of great turmoil, it also bore witness to two fascinating developments: the rise of the welfare state in North Atlantic nations and the emergence of "human rights" as a concept. While existing scholarship confirms that North Atlantic countries experienced the highest levels of equality at this time and the Universal Declaration of Human Rights (1948) is considered the starting point for the pursuit of human rights as an ideal, the question of why these developments occurred contemporaneously has yet to be answered. Did the human rights advocates draw on the welfare state's ideological underpinnings? Was there a transatlantic dialogue, among scholars or the public?

To answer these questions, I closely read primary texts to animate secondary sources, pursuing salient phrases and historical figures. One such phrase was "fair shares for all"; its usage to justify wartime rationing in Britain evolved into the Labor Party's 1945 rallying cry, quickly becoming associated with domestic egalitarian policies. The phrase took on international significance when, in the late 1940s, it was used to describe the goals of the United Nations. The phrase "freedom from want" also proved significant. Its use in Roosevelt's 1941 State of the Union bridges the anti-destitution policies of the New Deal and the international landscape envisioned by human rights advocates in the postwar era. These examples point to a transatlantic exchange of ideas in which domestic egalitarianism shaped the pursuit of human rights on the international stage.

Femmes Littératures: Une Histoire Culturelle

Ian Van Wye History and Literature
Mather House *Class of 2017*

Christie McDonald
Department of Romance Languages and Literatures; Department of Comparative Literature

Eighteenth century France is synonymous with social transformation and the birth of new modes of thinking, but the groundbreaking contributions of women to the written culture of the francophone Enlightenment have yet to be thoroughly studied. Femmes littératures: une histoire culturelle will encompass sections of the literary landscape that remain largely unknown to many scholars, with special consideration given to traditionally peripheral genres such as letters, private journals, translations, and perhaps even scientific texts. Through a topical ex-

amination of these and other modes of writing including novels, plays, and treatises, this project will illuminate the involvement of eighteenth century women in fields as diverse as education, the natural sciences, religion, and the family. We aim to understand how women writers conceived of themselves and their roles in the context of a culture that grew increasingly masculinized as the 18th century progressed, and why so many women whose work was widely read both within and beyond the borders of France are excluded from the present-day Enlightenment canon.

Supporting Home Languages

Caroline Zhang History and Literature
Winthrop House *Class of 2016*

Maria Luisa Parra
Department of Romance Languages and Literatures

While multilingualism is still subject to numerous misconceptions, language attitudes have begun to shift in recent years and popular literature has begun to embrace the skill as an intellectual and cultural advantage. The past two decades have seen the rise of bilingual parenting books, guiding the process of teaching a child two or more languages. However, these books fail to distinguish between foreign language learners and heritage speakers—those who grew up in a language and culture different from the dominant language—even as a growing number of scholars have addressed the topic. Furthermore, they largely treat bilingualism as a market commodity and do not consider its social and cultural implications, or its impact on identity formation. This summer, I have worked with Dr. Maria Luisa Parra to conduct preliminary research for a book about heritage language learning. Directed at parents from an immigrant background, this book will bridge the gap between academic scholarship and popular nonfiction. It will investigate language development in children growing up in a multilingual environment as well as the significant role language plays in identity formation. I have researched secondary sources about the complex role of language in an increasingly diverse society and conducted interviews with heritage speakers about their experiences growing up in multilingual families. Drawing on this research, we have outlined a the table of contents of a book which argues that heritage language learning is vital to social and cultural understandings, and thus to the identities we enact.

SURGH

Summer Undergraduate Research in Global Health

Abstracts | 2015

Child Mental Health in Rwanda

Giora Ashkenazi Social Studies
Currier House *Class of 2017*

Theresa Betancourt
T. H. Chan School of Public Health

Social protection is now widely recognized as an investment in addressing not only current poverty but in providing a foundation for graduation from poverty. Early childhood development (ECD) services delivered through social protection systems can complement income support interventions aimed at improving livelihoods, as well as those promoting ECD to help break intergenerational cycles of poverty.

Dr. Betancourt's team developed The Family Strengthening Intervention for Early Childhood Development (FSI-ECD) program, which offers home-based coaching to caregivers of young children to promote early stimulation and responsive parenting. The FSI-ECD curriculum is comprised of 15 modules offering education about early childhood development, responsive parenting, reducing family conflict and promoting good caregiver-child relationships, nutrition, and hygiene. The model has been developed and tested in Rwanda and is ready for consideration by leading policymakers in Rwanda.

Through the National Commission for Children, the FSI-ECD model will train community-based volunteers to work with all caregivers (including fathers) to promote and model enriched responsive parenting to children under age 6. The team will test the effectiveness of the FSI-ECD alone and in combination with income support through Rwanda's national social protection program for caregivers in Rwanda ranked as among the poorest served by the social protection system.

Long-Range HIV-1 Subtype C Genotyping and its Impact on Phylogenetic Analyses

Andrew Chang Undecided
Mather House *Class of 2018*

Max Essex
T. H. Chan School of Public Health

The goal of the study is to expand upon the existing protocol of long-range genotyping and observe its impact on cluster analyses performed on HIV-1 samples. The long-range HIV genotyping protocol of Novitsky et al. provided sequencing directions for two amplicons, which cover about 80% of critical regions across the HIV-1 genome, including the *pol* and *env* genes. While this methodology is cost-efficient, the resulted products are isolated amplicons with the gap over a critical region of viral genome. This study aims to achieve better integrity of generated viral sequences by amplifying a new region, which would cover the gap between amplicon-1 and amplicon-2 and improve the long-range HIV genotyping protocol. We use samples from the ongoing clinical trial in Botswana and applied the modified protocol to obtain amplicon-3 sequences.

Upon amplification and sequencing clinical specimens, we infer phylogeny and conduct cluster analyses with and without amplicon-3 sequences. From our comparative analysis, we comprehend the extent amplicon-3 provided informative sites for cluster identification. We perform phylogenetic cluster analyses in order to understand the magnitude and patterns of HIV transmission networks across different communities. Many factors can impact the credibility of the cluster analysis, including the complexity, size, and number of informative sites in the sequence alignment of the targeted clinical samples. This research seeks to improve current HIV cluster analysis and develop a more comprehensive public health strategy to prevent expansion of HIV transmission networks.

Optimization of Genome-Wide Association Studies with Uncertain Case-Control Definitions: Application to Lassa Fever in Nigeria and Sierra Leone

Sarah Chapin Biomedical Engineering
Leverett House *Class of 2016*

Pardis Sabeti
Broad Institute of MIT and Harvard, Department of Immunology and Infectious Diseases, Department of Organismic and Evolutionary Biology, T. H. Chan School of Public Health

Lassa Fever (LF), caused by the Lassa virus (LSV), is a virulent hemorrhagic fever endemic in West Africa. We are conducting a genome-wide association study (GWAS) of LF, analyzing the genomes of LF cases and controls from Nigeria and Sierra Leone. We aim to identify genetic variants associated with LF cases, with the underlying assumption that these variants likely confer LF susceptibility.

Diagnostic uncertainty is a critical challenge in GWAS's of LF and of infectious diseases in developing countries generally, as misdiagnosed cases are common in resource-limited settings and can dramatically decrease study power. In our studies, PCR and ELISA assays are performed at field hospitals to detect LSV and identify suspected cases. However, these assays have low specificity (high false positive rates). Suspected case samples are further tested for LSV RNA via sequencing and/or RT-qPCR in Boston. To avoid misdiagnosed cases, only patients with positive sequencing results are incorporated into the case-cohort, resulting in the removal of 85% of initially suspected cases and dramatically reducing the study sample size and power. Furthermore, while sequencing assays have high specificity, they have low sensitivity (high false negative rates). Thus, there is a degree of uncertainty regarding the true case-control status of study individuals. Ideally, an analytical method could increase study power to detect genetic association by including all sample data while correctly representing uncertainty about their case-control status.

Here we develop a machine-learning method that explicitly models the uncertainty in the case-control statuses introduced by multiple diagnostic tests with different specificities and sensitivities. This approach simultaneously learns the uncertainty associated with each diagnostic category while identifying the best-associated genetic variants. Specifically, we use an expectation-maximization framework, iterating between identifying the best-associated variants using weighted logistic regression, and learning the sample-weights that best reflect the uncertainty associated with each diagnostic test. We are currently optimizing the methodology for simulated data and will then analyze data collected from Nigeria and Sierra Leone.

The Role of Clp Proteins as Bacterial Targets of Granzyme

Andres Binker Cosen Molecular and Cellular Biology
Eliot House *Class of 2017*

Judy Lieberman
Boston Children's Hospital

Cytotoxic T lymphocytes (CTLs) play a fundamental role in the human immune system, killing pathogen-infected cells and cancer cells. Once a CTL has identified a cell which needs to be eliminated, it forms a synaptic cleft with the target and releases granules containing pore-forming proteins, perforin and granulysin, and a set of serine proteases, called granzymes, principally granzymes A and B. Granzymes induce apoptosis, or programmed cell death, of the host or transformed cell. However, their effect on non-viral pathogens is less characterized. Recently, the Lieberman lab has shown that granzymes are delivered by granulysin into microbial pathogens, which they rapidly kill.

Based on 2-D proteomics assays of granzyme targets, the chaperone-protease family of caseinolytic proteins (Clp) is a likely target of granzymes in bacteria. Clp proteins are essential to bacterial growth and survival because of their role in protein quality control. Under stress, many proteins misfold during or after translation and must be removed to avoid aggregation and malfunction. Clp proteins form barrel-like complexes that unfold misfolded proteins and then cleave them into peptides. Their importance in bacterial survival makes Clp proteases a potential target for antimicrobial drugs.

CTLs are central to immune defense against the pathogenic bacterium Listeria monocytogenes. I am investigating whether granzyme B (GrzB) degrades the Listeria Clp proteases. To do so, I generated and purified recombinant versions of most of the Clp proteins in L. monocytogenes. Treating these Clp proteins with varying concentrations of GrzB resulted in dose-dependent degradation of clpB, X, P1 and P2. ClpB and clpX are chaperones responsible for protein unfolding, while clpP1 and clpP2 are proteases responsible for cleavage. ClpE, another chaperone, was not affected by GrzB. Other work from the lab suggests that the Clp system in E. coli is also disrupted by GzmB. These results suggest that CTLs may kill bacteria (at least in part) by disregulating their protein quality control mechanisms. Further studies will elucidate whether Clp protein degradation occurs during killer cell-mediated death of bacteria, whether it disrupts Clp function, and the importance of disabling the Clp system to bacterial immune defense.

University of Global Health Equity

Ishaan Desai Molecular and Cellular Biology
Kirkland House *Class of 2015*

Peter Drobac
Harvard Medical School

The University of Global Health Equity (UGHE) is a health sciences university in Rwanda that will train the next generation of leaders in health care delivery. Rwanda has achieved unparalleled improvements in population health and poverty reduction through a relentless focus on delivering effective and equitable care through comprehensive, integrated health systems. With support from philanthropic partners and the Rwandan Ministries of Health and Education, UGHE will open in September 2015 with its flagship degree program – the Master of Science in Global Health Delivery. I spent this summer developing the curriculum of this inaugural degree program. Specifically, I worked with partners in Rwanda and Boston to review global health curricula, noted their strengths and weaknesses, and identified common themes. I then contributed to a semester-long instruction sequence to map these themes in an arrangement that maximizes student understanding. Books, articles, and multimedia resources were reviewed on topics such as the history of global health; health systems; burden of disease; determinants of health disparities; epidemiology; health and human rights; and health care financing. Finally, I learned that just as important as the substantive content is the delivery of this content in a way that fits with age- and context-appropriate learning styles. To this end, I researched theories of adult learning and existing pedagogical methods in Rwanda.

Investigating a Rebound in Malaria Transmission Using Molecular Barcoding

Caleb Irvine Molecular and Cellular Biology
Dunster House *Class of 2016*

Dyann Wirth
T. H. Chan School of Public Health

Recent efforts to eradicate malaria have focused on regional control and elimination. Interventions are made to reduce the disease's spread, but total elimination strategies are only pursued once local transmission has reached sufficiently low levels. Consequently, public health efforts rely on constant surveillance of transmission dynamics. One way to deduce such dynamics is by looking at the number of different parasite strains within a region. Where transmission is high, people tend to host multiple strains of parasites at once. When those parasites reproduce, they recombine to form offspring with unique genomic identities. However, where transmission is low, people rarely host more than one strain at a time, and parasites of the same strain join together to form offspring that are genomically identical to their parents. Thus, the number of genomically identical parasites in a region may reflect the area's transmission levels.

Our lab has developed a "molecular barcode" with which to track parasite strains in a region. Each strain is identified by its unique barcode, which consists of the genotypes at 24 different bi-allelic, neutral, and highly polymorphic Single Nucleotide Polymorphisms (SNPs). This method leverages the low probability of two strains sharing alleles at all 24 loci by chance, and provides a fast and cheap means of differentiating strains without having to fully sequence every sample.

Our lab has been studying transmission in Thiès, Senegal since an extensive malaria control initiative was implemented in 2006. Barcode and epidemiological data over the years indicated that transmission was declining, but beginning in 2011 the Thiès barcode data reversed, suggesting an unexpected rebound in transmission that continued through 2013. We plan on barcoding the region's 2014 samples to see if the data indicates a continued rebound in transmission, which would have serious implications for the area's malaria control efforts.

Chronic HIV Infection, the Gut Microbial Community, and Cardiovascular Health in a Ugandan Cohort

Kendall Jackson Human Developmental and
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Class of 2017

Douglas Kwon, M.D. Ph.D
The Ragon Institute of Massachusetts General Hospital, MIT and Harvard

The human body has ten times the amount of bacterial cells as mammalian cells, and these bacteria – collectively known as the microbiota – play a significant role in many aspects of health and disease (NIH Human Microbiome Project, 2012). Emerging research has linked changes in the gut microbial community structure to outcomes of systemic inflammation brought on by the onset of HIV infection and more recently, to an increase in inflammatory diseases, such as cardiovascular disease (CVD) (Lozupone et al., 2014, Ford et al., 2010). It is our goal to study the role that the gut microbiome (and within that, specific microbial populations) plays in systemic inflammation and an increased risk of CVD.

To study this connection, we are utilizing a cohort of 171 individuals in Mbarara, Uganda enrolled in a cardiovascular study from which we have stool and serum samples and metadata, including age, diet, gender, blood pressure, and other known markers of CVD such as Carotid Intima Medial Thickness (CIMT).

We will characterize the gut microbiota compositions through DNA extractions from stool; polymerase chain reactions (PCR) to amplify the bacterial 16S rRNA gene - a conserved marker gene that allows us to identify which bacterial taxa are present in a given stool sample – and finally, high-throughput sequencing of the amplicons.

We plan to connect the results of the microbiome structures with the available metadata to gain better insight into the mechanism by which HIV infection may alter microbial communities, up-regulate systemic inflammation, and increase one's risk of inflammatory diseases like cardiovascular disease. Interventions based on this model could decrease the burden of cardiovascular disease and other inflammatory diseases in chronic HIV infected patients.

Looking at Identity and Emotions in Conflict Negotiation and Resolution

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Daniel L. Shapiro
Harvard Law School

Conflict is universal and present in every aspect of our lives from the micro-scale--how will an on going tense situation with my roommate affect how comfortable I feel in my room--to the macro-scale--how will the current negotiations in Congress affect my student loan rates? While conflicts may seem insurmountable and fraught with emotional tension even the most seemingly nonnegotiable situations ARE negotiable if negotiators are able to better understand the underlying aspects present in the situation.

The International Negotiation Project (INP) at the Harvard Law School conducts research about how emotions and personal identity play into conflicts and how they can be used to bring about successful negotiations on both a personal and a global scale. The INP is not only working to research and present solutions but also is working to develop free curriculum for both teachers and global leaders to implement in their negotiations and teaching seminars.

Recently Professor Daniel L. Shapiro, the founder and director of INP, wrote a book examining specifically what parts of identity are present in conflict situations and how to navigate and resolve the issues that identity brings about. This summer I am working with Bessie Zhang to create a universal curriculum for this book that can be taught to undergraduates, business and government leaders, and leaders of non-profits. Together we have developed a chapter-by-chapter set of workbook questions and classroom exercises, pulling resources from various academic studies, personal experiences, and real-life examples.

Mental Health in Resettled Refugee Youth

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Numerous studies have found that compared to youth in the general United States population, resettled refugee youth in the US face a disproportionate amount of mental health syndromes. For instance, the prevalence of post-traumatic stress disorder (PTSD) and depression was seen to be 54% and 30% in refugee youth, respectively and 5% and 11% in general youth, respectively. The stresses of fleeing from one's country of origin combined with displacement in a refugee camp and third country resettlement increase the risk of being exposed to stressors that lead to adverse mental health outcomes (i.e., depression, PTSD, anxiety).

For this project, we employed Community Based Participatory Research (CBPR), an approach that seeks to equally involve researchers and community members in the research process, to study mental health discrepancies among Bhutanese and Somali Bantu youth resettled in the Greater Boston area. By partnering with community members, we were able to better understand the cultural context of mental health and associated stigmas, with the ultimate goal of designing intervention programs community members could implement. Upon identifying the specific conditions within each community through translation and extensive analyses of key informant interviews, we searched for pre-existing, applicable psychological assessments and supporting academic literature on the matters. Discussing each question with community members to gauge a sense of cultural relevance, we modified the assessments to best fit the needs of each community, removing questions that were not relevant and rephrasing to minimize confusion.

Currently, we are administering the first round of assessments in a six month study examining the effectiveness of a home-based family strengthening intervention aimed at strengthening parent-child relationships, promoting mental health, and improving mental health outcomes among refugee youth and their families in New England.

"Start with the Youth": Evaluation of a Community-Based Pilot Program to Educate Boston Youth on HIV/AIDS

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Despite the wealth of medical resources and knowledge in Boston, the city's youth continue to become infected with HIV at rates considerably higher than the rest of the state of Massachusetts. To address the issue of HIV/AIDS among Boston youth, researchers and community representatives affiliated with the Harvard University Center for AIDS Research developed and implemented the Community Youth Engagement via Media and Social Network Messaging Project. The program's three central objectives were to educate Boston youth on HIV/AIDS, increase community involvement among youth, and use media and messaging to effect change in issues surrounding HIV. The program, which began in February 2015 and ended in May 2015, involved lectures from guest speakers, site visits, and group activities in order to address topics related to HIV/AIDS. At the end of the program, the youth created a brief media message that was played on a local television station. To evaluate this program, qualitative interviews with the students (n=6) and their adult mentors (n=5) were conducted. These interviews were then coded for themes related to program feedback, program impact, community, and ideas for social change. Results suggested that some, but not all, participants viewed HIV as an issue that affects their communities. Most participants gave positive feedback regarding the program, citing satisfaction with guest speakers and a wealth of information presented on HIV. Negative feedback centered on program logistics, particularly traveling between various sites. Nonetheless, participants reported an increase in HIV-related knowledge, including history of HIV and HIV transmission and prevention. Participants further noted that the program impacted their goals for higher education, feelings of community connection, and desire for community involvement. Finally, many participants conveyed that a similar project could be applied to affect other issues within their communities. Adult participants emphasized the potential of youth in change, particularly in relation to the role of social media and messaging. Taken together, these results support the potential of the program to increase HIV knowledge and community involvement and further highlight the unique role of media as a means of intervention to address issues related to HIV among urban youth.

Plasmodium knowlesi as Surrogate for *P. vivax* to Study Duffy Antigen Receptor for Chemokines (DARC) Polymorphism

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Resistance to *Plasmodium vivax*, a malaria-causing pathogen, is linked to the absence of the duffy antigen receptor for chemokines (DARC) on the surface of red blood cells (RBCs). However, recent studies have shown that the *Plasmodium* parasite is apparently evolving alternative methods to invade DARC-negative RBCs. Since *P. vivax* cannot be kept in continuous in-vitro culture for reasons unknown, establishing a model system for *P. vivax* is of great importance. In this project, *Plasmodium knowlesi* is used as a surrogate for *P. vivax* to provide insight into the evolving invasion pathways of *P. vivax* as well as the role of DARC polymorphism in the invasion process. To directly study ligand-receptor interactions, a *P. knowlesi* invasion ligand essential for human RBC infection will be replaced with the *P. vivax* homologue. In addition to studying the invasion process, the use of this chimeric parasite line will serve as a model system to test intervention strategies such as antibody inhibition assays. To achieve the intended gene replacement, *P. knowlesi* parasites will be transfected with two plasmids. Plasmids are independent, circular DNA molecules that can carry specific genes or other genetic elements. They are useful for a number of applications, including gene knockdown and overexpression experiments. After cloning of the desired elements, the recombinant plasmids are inserted into bacteria via heat shock in a process known as transformation. The bacteria are allowed to grow on an antibiotic-containing plate to select for successfully transformed single bacteria. Transfection of plasmids into *Plasmodium* parasites is achieved through an electrical pulse and subsequent drug selection. The parasites are allowed to multiply until a stable population is established that can be used for further studies.

Studying Protein-Protein Interactions Between Type III Secreted Effectors and Cytoplasmic Components of the Apparatus

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Many Gram-negative bacteria use Type III Secretion Systems (T3SSs) to deliver effector proteins into eukaryotic cells. *Shigella*, the causative agent of bacillary dysentery, secretes over 30 effector proteins that target numerous host cellular processes and foster bacterial survival and proliferation. Although the traditional understanding was that T3 chaperones are required for effector secretion, recent data indicate that the majority of *Shigella* effectors do not bind to a known chaperone, suggesting a chaperone-independent (CI) secretion pathway. While effectors bound to chaperones can be recognized by an ATPase, which unwinds the effector to allow it to pass through the apparatus, it is not clear how CI effectors are delivered and entered into the secretion apparatus. It is possible that these effectors directly interact with cytoplasmic components of the Type III secretion apparatus (T3SA). This project uses both the Protein Interaction Platform (PIP) and Yeast Two-Hybrid (Y2H) assays to screen for potential binary interactions between secreted effectors and components of the T3SA. The PIP assay involves fusing protein A to μNS (a scaffolding protein) and protein B to a fluorescent tag such that the presence of foci indicates interaction between the two proteins. The Y2H assay involves separating a functional transcription factor into two domains and fusing each to a protein of interest so that protein-protein interaction would reconstitute the transcription factor and drive the expression of a reporter gene. These experiments will help elucidate the mechanism of secreted effectors and pave the way for developing novel therapeutic strategies targeted to this machine.

The Role of Identity in Conflict Resolution

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What is conflict? Anything from a five-minute argument between friends to a long history of tension and violence between countries can have significant consequences, especially on the health and well-being of people affected. Continuous arguments between two parents can have negative long-term impacts on a child's emotional health; while a negotiation turned sour between two countries' political leaders can result in unnecessary violence. While immense efforts are put into caring for those who have suffered mental or physical harm, and for good reason, so long as the conditions that caused this harm remain, there will always be people who continue to suffer unnecessarily.

The International Negotiation Project (INP), based at the Harvard Law School under the Program on Negotiation, examines and spreads knowledge on how emotions and identity play into conflict and negotiation on a personal and global scale. Recently, Daniel L. Shapiro, Founder and Director of INP, wrote a book based on decades of accumulated findings in this field of research. This summer, I am working with Brooke McLain to create a curriculum based on Professor Shapiro's book, to be taught to Harvard undergraduates, businessmen and women, and political leaders. The curriculum contains a chapter-by-chapter set of classroom exercises, workbook questions and personal research projects, to concretize the knowledge in the book. Creating this curriculum has consisted of analyzing the contents of the book as well as creatively thinking of material that can bring the contents to life. Brooke and I have drawn on our experiences in curriculum development (ex. high school education and outdoor camp) and researched into areas of curriculum development that we are less familiar with (ex. theatre).

TB or Not TB: Studying the Role of FtsQ in Cell Division in *Mycobacterium smegmatis*

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Tuberculosis, caused by the inhalation of aerosols containing the pathogen Mycobacterium tuberculosis (Mtb), is one of the world's deadliest infectious diseases that is currently still present in all regions of the globe. A key characteristic of the bacteria's success as a pathogen is its ability to develop drug persistence and adapt to changing stressful environments within the host. Because cell division is essential for a successful infection, it is important to understand the molecular mechanisms of cell division during adaptation to infection stress. The factors that mediate cell division are largely conserved from the model organism E. coli to Mtb; however, it is apparent that the regulation of these factors is different in Mtb. In particular, Mtb has several protein kinases that are important for cell growth and division as well as infection; in addition, many cell growth and division factors are phosphorylated in Mtb.

FtsQ is an essential cell division protein that in E. coli helps link together major events of cell division and associates with other key cell division factors. FtsQ has been shown to be phosphorylated in Mtb, but has not otherwise been studied in mycobacteria. We hypothesize that in mycobacteria, phosphorylation of FtsQ may plays an important role in regulating cell division in response to environmental stresses, specifically in cell septation (the actual act of division). Our work this summer has been to elucidate the role that phosphorylation plays in FtsQ activity using Mycobacterium smegmatis, a model organism for Mtb. We ran pulldowns to isolate FtsQ and sent the samples for modification analysis and identification of putative interactors via mass spectrometry. We have also been working on generating a GFP-tagged strain of FtsQ to observe its localization through time lapse microscopy and generating a conditional knockout of FtsQ such that the resulting phenotype from FtsQ depletion can be determined. We hope that strengthening the understanding of key players in cell division will allow for more clarity in targeting bacterial populations during infection and ultimately lead to better treatments for patients.

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