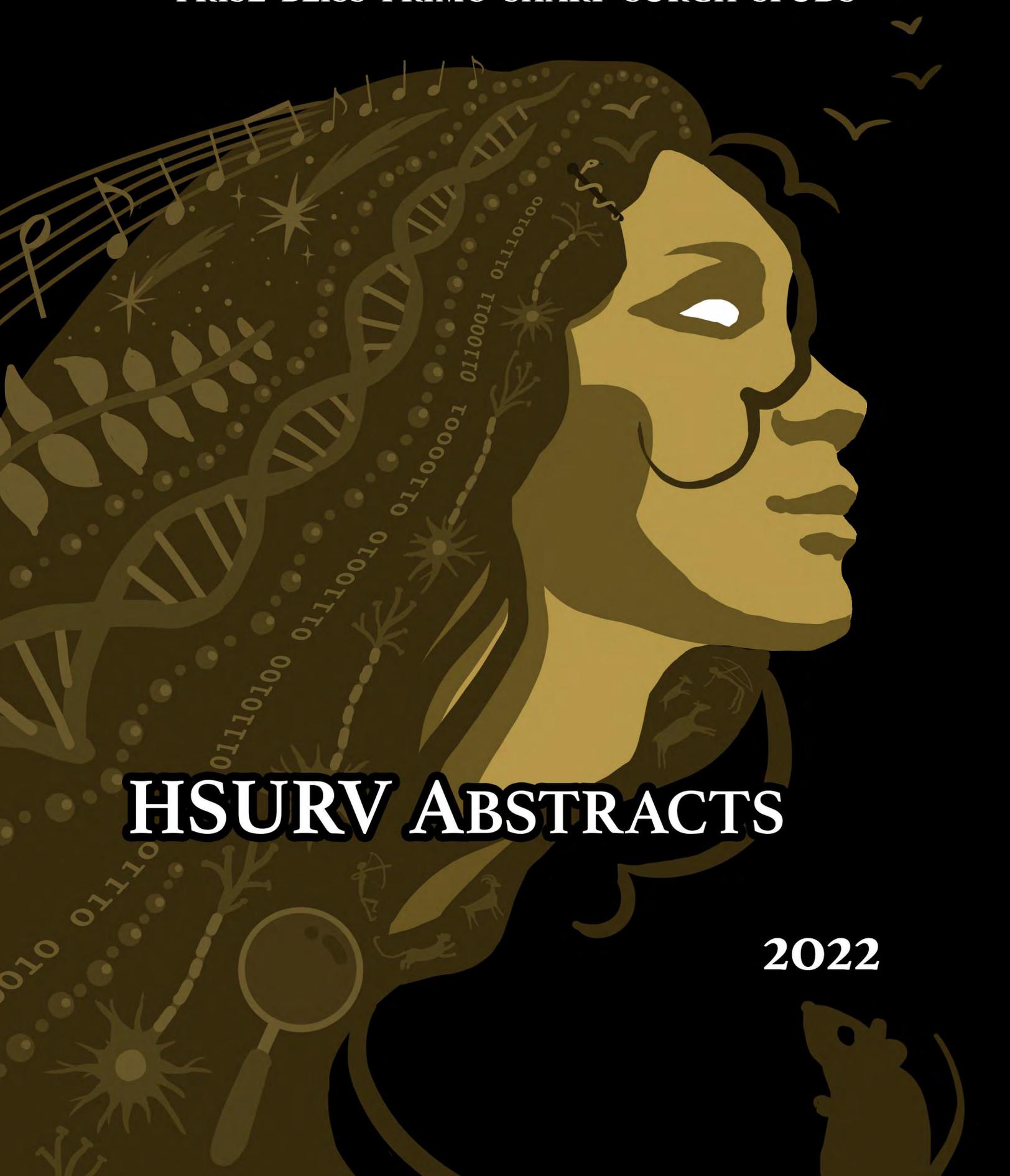


PRISE BLISS PRIMO SHARP SURGH SPUDS



# HSURV ABSTRACTS

2022

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**HSURV ABSTRACT BOOK 2022**

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# Harvard Summer Undergraduate Research Village

2022 Abstract Book

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Summer Humanities and Arts Research Program (SHARP)

Summer Undergraduate Research in Global Health (SURGH)

Summer Program for Undergraduates in Data Science (SPUDS)

Office of Undergraduate Research and Fellowships  
Cambridge, Massachusetts  
Harvard University



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# Letter from the Director

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I am delighted to introduce the 17th edition of the Abstract Book, culminating the scholarly experiences of the fellows in the 2022 Harvard College Summer Undergraduate Research Village, comprised of PRISE (Science and Engineering), BLISS (Social Sciences), PRIMO (Markets and Organizations, co-hosted by Harvard Business School), SHARP (Humanities and Arts), and SURGH (Global Health, co-hosted by the Harvard Global Health Institute), and our most recent addition to Research Village programs, SPUDS, the Summer Program for Undergraduates in Data Science.

This summer has been particularly noteworthy following two years of improvisation during the uncertainty wrought by the COVID-19 pandemic. Surely we have learned that, while our horizons have been broadened by virtual tools we hadn't really thought of pedagogically, there is nothing that compares to the richness of in-person experiences and the ability to enjoy and deeply engage in an environment that fortifies personal growth and the opportunity to learn from the great relationships that develop, a fundamental and critical mission of the Research Village.

I very much appreciate and am grateful for the tireless efforts of our amazing proctors and program assistants who have stewarded a bursting schedule of opportunities for everyone to meet and engage throughout the summer. Further, our collection of abstracts here would not have been possible without the dedication and fortitude sustained by the group of Research Village editors whose voluntary charge has been to collect, organize, and publish the works of all the fellows. I would especially like to thank program assistant Troy Powell for taking the initiative and seeing this important project through.

To the Summer Undergraduate Research Village fellows of 2022, I admire the degree of bonhomie, inclusivity, and energy you have put into our ten weeks together this summer. I am confident the connections you've made here will endure through your undergraduate years and beyond. I wish you the best of success as your academic trajectory evolves and continues, and hope that you may be able to share (and host!) like experiences in your own residential and academic communities going forward.

Sincerely,

Gregory A. Llacer  
Director, Harvard College Office of Undergraduate Research and Fellowships

# Letter from the Editors

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Dear Readers,

This summer, we returned to a fully in-person research community for the first time in three years — and it has been a spectacular experience for us all. Research fellows spent ten weeks learning with — and from — each other, bonding over more than just discussions about projects. We have all found so much joy in being part of the Research Village, and we will walk away with memories of a summer full of intellectual exploration, bonding through activities and excursions, and personal growth. It is incredible to witness how this community has blossomed over the past ten weeks.

Fellows have conducted research on subjects ranging from gene therapy to graphic novels, from mental health interventions to quantum computing. It has been fascinating to learn about the breadth and depth of the research projects that everyone is so passionate about, and we have all enjoyed exploring and sharing our interests with each other. We recognize the unfathomable magnitude of effort that has gone into each project this summer — from each research fellow as well as the advisors and mentors who welcomed us — and we are proud to be sharing this compilation of abstracts with you.

We are extremely grateful to all the people who have made this experience possible. Thank you to the student program assistants and proctors for all the time and energy you have spent cultivating a social community by promoting and supporting student-led activities. Thank you to the building staff for making sure that Winthrop House was always a welcoming place to return to, and the dining staff for all your care in welcoming us to the dining hall — time spent meeting and talking with our peers over meals has been incredibly meaningful to all of us. We are especially grateful to the program directors for creating this opportunity for us fellows and making us feel so supported during our time here. Thank you to Troy Powell '23 for facilitating Abstract Book team meetings and assisting us in our operations. Thank you to Chris Kabacinski for wading through emails with such enthusiasm to ensure all our logistical needs were provided for. A tremendous thank you to Greg Llacer for going out of his way to transform the Research Village into a vibrant, cohesive community. And, finally, thank you to all the research fellows who have made this summer such an unforgettable experience.

Sincerely,  
The 2022 HSURV Abstract Book Team

# Thoughts of the Artist

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## “Origins and Futures”

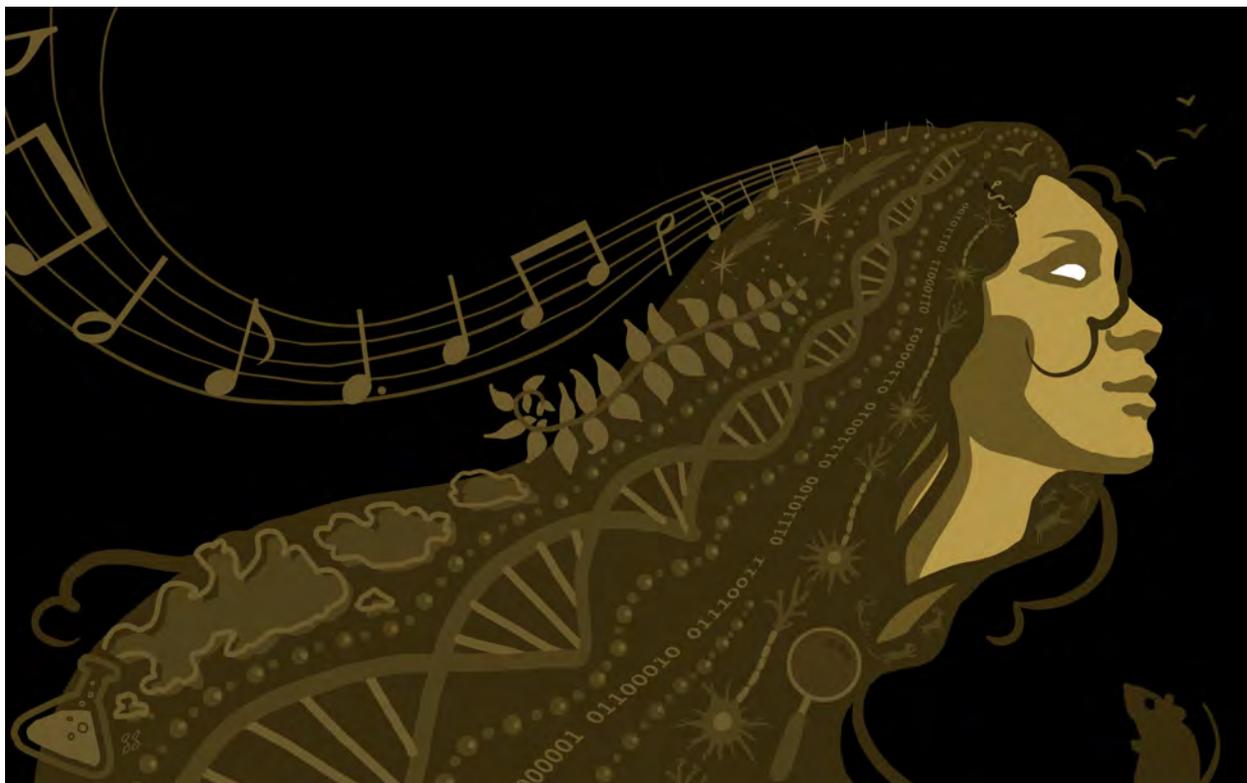
The cover art highlights a feminine figure, symbolic of so many challenges at the fore of our world and our minds today. She stands for historically underrepresented groups within research and academia, she embodies Mother Earth, and she confronts the political, social, and economic obstacles of being a woman in today’s society. She is our origin story and our mother who has fostered our past growth. This mother, like us researchers, is the recordkeeper of histories, celebrant of past discoveries, and a creator pregnant with ideas to be born in the future.

Just as science, history, nature, and art flow from her bronze locks, her gaze flows off into the distance. She looks to the future, chin up and resolute, striving toward the equitable advancement of knowledge.

\*\*\*

The interior graphics are symbolic profiles that were selected to align with the original cover illustration. They represent who we are and what we do as researchers, and, in an abstract way, they reflect the essence of that which preoccupies our time, energy, and minds.

Summer J. Smentek  
PRISE Fellow, Cover Illustrator and Interior Graphics Designer



# Program Overview

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The 2022 Harvard Summer Undergraduate Research Village is a 10-week residential community that comprises Research Fellows from the following programs:

**PRISE:** The Program for Research in Science and Engineering (PRISE) is a 10-week summer program that aims to build community and stimulate creativity among Harvard and Cambridge undergraduate researchers in the life, physical/natural, engineering and applied sciences. To participate in PRISE, you must find a research position on your own, and apply to PRISE separately. (NOTE: it is not necessary to have secured a research position by the PRISE application deadline). Selected fellows work on projects with Harvard-affiliated researchers and get to live with other PRISE fellows in one of the Harvard College houses and participate in extremely rich evening programming (that includes both social and academic activities). In addition to receiving free lodging and being members of a diverse, vibrant intellectual and social community, fellows also receive a nominal stipend, and partial board.

**BLISS:** Build Learning through Inquiry in the Social Sciences (BLISS) is a 10-week summer residential program for Harvard undergraduates, designed to provide a formative and substantive social science research experience and to promote community, creativity, and scholarship. A diverse cohort of BLISS Fellows works on research projects led by Harvard faculty, and live in one of the Harvard College houses with the other fellows in the Harvard Summer Undergraduate Research Village. In addition to conducting full time research, BLISS Fellows participate in a rich variety of programming, including both social and academic activities. To participate, undergrads in good standing must apply and be selected to work on one of the pre-designated BLISS research projects.

**PRIMO:** The Program for Research in Markets and Organizations (PRIMO) is a 10-week summer program that aims to build community and stimulate creativity among undergraduate researchers in business and related fields. To participate in PRIMO, you must apply and be selected to work in one of the research areas which span diverse topics (finance, organizational behavior, marketing, etc.), disciplines (Psychology, Economics, Sociology), as well as methods (quantitative or qualitative). Successful fellows will be placed with pre-designed faculty projects at Harvard Business School. As part of the residential community of researchers, students will participate in enrichment activities such as faculty lectures, professional development workshops, presentation opportunities, and social events. PRIMO fellows are offered Harvard campus housing, a partial board plan, and modest research support.

**SHARP:** The Summer Humanities and Arts Research Program (SHARP) is a 10-week immersive summer program that aims to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in the humanities and arts. SHARP fellows work on research projects with Harvard-affiliated faculty, researchers, and senior library and museum staff. Fellows live together in one of the Harvard College houses and participate in rich evening programming that includes both social and academic activities. To participate in SHARP, you must apply and be selected to work on one of the available SHARP research projects.

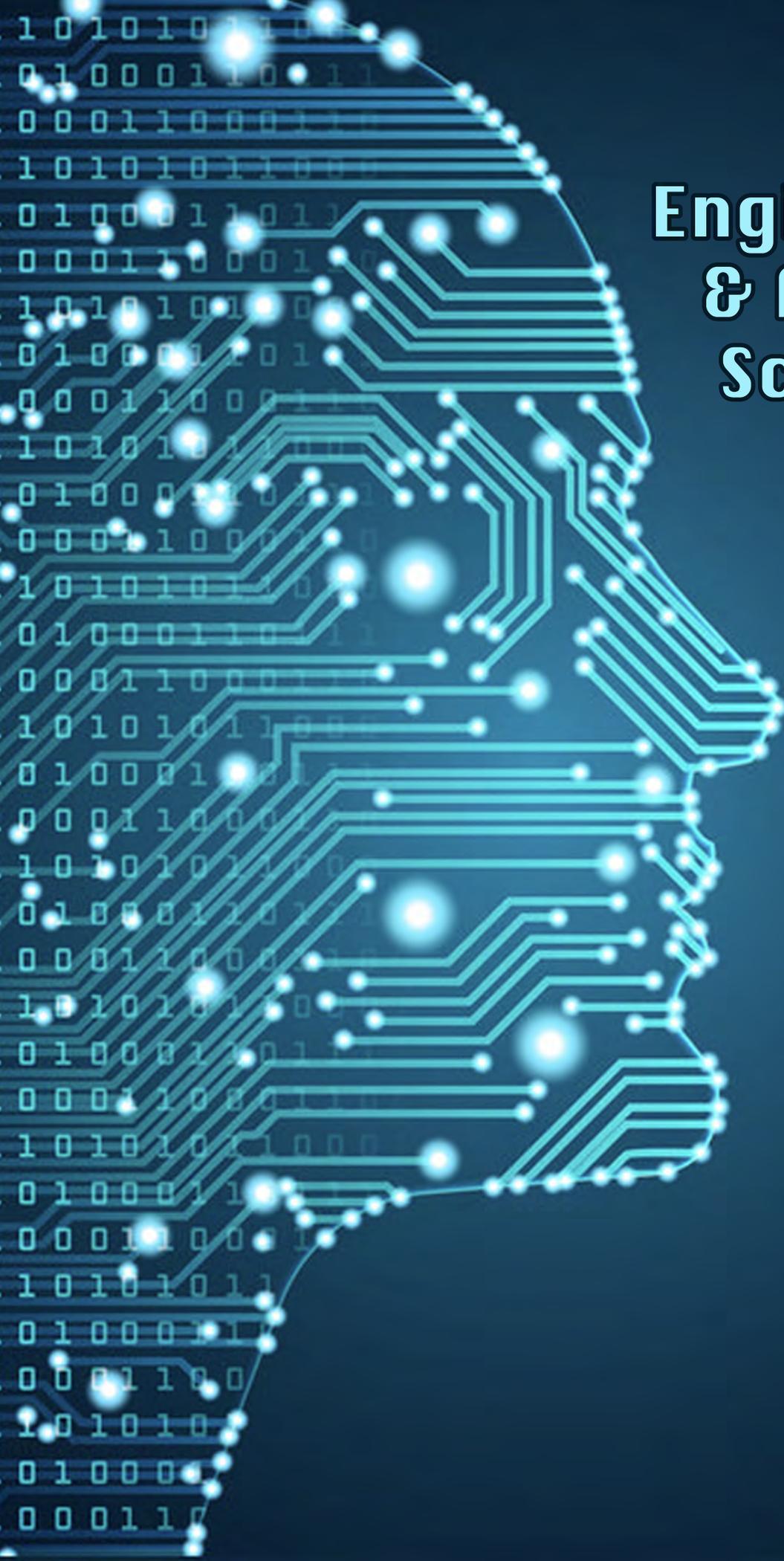
**SURGH:** The Summer Undergraduate Research in Global Health (SURGH) program is a 10-week summer program that aims to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in global health. SURGH fellows work on research projects with Harvard-affiliated faculty and researchers. Fellows live together in one of the Harvard College houses and participate in rich evening programming which includes both social and academic activities. To participate in SURGH, you must apply and be selected to work on one of the pre-designated SURGH research projects (usually announced in mid-January).

# Program Overview (continued)

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**SPUDS:** The new Summer Program for Undergraduates in Data Science (SPUDS) is a 10-week summer program, co-sponsored by Harvard College and the Harvard Data Science Initiative (HDSI), that aims to provide a formative and substantive data science research experience and to promote community, creativity, and scholarship amongst Harvard College students. SPUDS will support Fellows with interests in computer science, mathematics, and statistics, including those who are interested in data science applications across the arts, humanities, sciences and more. We also encourage SPUDS projects that focus on or emphasize ethical practices in data science research. To participate in SPUDS, prospective fellows should seek a research collaboration with a Harvard faculty host, and apply to SPUDS directly through the Office of Undergraduate Research and Fellowships. It is not necessary to have secured a research position by the SPUDS application deadline. Fellows will work with Harvard-affiliated researchers and live in one of the Harvard College houses with other fellows in the Harvard Summer Undergraduate Research Village. As part of SPUDS, fellows will participate in rich evening programming, including both social and academic activities, and become members of a vibrant intellectual and social summer community.



# Engineering & Applied Sciences

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## Applied Math

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### Towards an Algorithmic Understanding of Ant Trail Tracking Behavior

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**Jonah Brenner**

SPUDS Fellow

Applied Mathematics, 2025

Harvard College, Cabot House

Harvard Faculty of Arts and Sciences

Advisor: Venkatesh Murthy

Supervisor: Souvik Mandal

---

Pheromone signaling is the primary form of communication for ants, a social insect. It is utilized to coordinate complex tasks such as cooperative nest defense and foraging. To optimize the colony's foraging efficiency, ants lay pheromone trails that direct others back to the location of newly discovered food sources. It is vital that they follow these invisible, olfaction-based trails quickly and accurately to maintain the colony's food supply. However, the strategies that ants use to achieve this remain unclear. In this study, we utilize novel computer vision based pose tracking techniques to uncover the behavioral and algorithmic strategies behind ant trail tracking. We test the validity of two principal hypotheses in this field: chemotaxis, the use of a pheromone concentration gradient between the two antennae sensors to direct the ant, and sector search, the probabilistic use of  $n$  past trail contact points to predict the future trail heading. We also explore the modulation of olfactory trail sampling frequency, a measurement of how often an ant "looks" for the trail's location. Combining this knowledge, we hope to create a model that predicts an ant's future trajectory and olfactory sample rate based on its past experiences. In the future, such an algorithm could direct biologically-inspired robots that mimic ants' fast and efficient olfactory tracking behavior.

### A Dynamic Learning Approach to Forecast the Importation of Monkeypox in the U.S. using Novel Data Sources and Machine Learning

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**Iris Lang**

SPUDS Fellow

Computer Science & Statistics, 2025

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Network Science Institute at

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Advisor: Mauricio Santillana

---

Monkeypox is an infectious viral disease similar to smallpox caused by the monkeypox virus. The first human case of monkeypox was recorded in 1970, and prior to the 2022 outbreak, human to human transmission of the virus was relatively rare. The 2022 outbreak, declared a global health emergency in July, began in the United Kingdom around May and is rapidly spreading in a number of countries and regions around the world. Here, we present a novel, real-time machine learning forecasting technique that allows us to make predictions about where Monkeypox cases may be observed next given the locations it has been observed at already. Particularly, we focus on the United States, using monkeypox-related Google search queries and airline traffic data. Our analysis suggests that the combination of both data sources serve as powerful predictive tools that can be leveraged to make predictions weeks ahead of time about where and when the outbreak will manifest in a specific region. This method generalizes to a variety of spatial scales and may prove useful in guiding public health interventions in other locations, or for future outbreaks.

### An Interpretable Single-Cell Transcriptomic Aging Clock for Hematopoietic Stem Cells

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**George Cai**

SPUDS Fellow

Physics & Chemical and Physical Biology, 2024

Harvard College, Mather House

Wyss Institute & Harvard Medical School

Advisor: George Church

Supervisor: Alexandru Plesa

---

Aging is a complex process that leads to many major chronic diseases with significant costs to society. Beyond the unquantifiable human suffering, a recent analysis shows that slowing aging to increase the U.S. life expectancy by one year is worth 38 trillion U.S. dollars. Furthermore, aging is interconnected with many biological processes of both scientific and medical interest, so understanding the underpinnings of aging has significant transferable value to other areas of biology. In this project, we aim to develop an aging clock by training machine learning models to predict the biological age of cells from single-cell RNA sequencing (scRNA-seq) measurements. Although pan-tissue clocks are feasible, previous studies show that cell type-specific clocks are more accurate and interpretable. Thus, we are targeting hematopoietic stem cells (HSCs) for rejuvenation due to their systemic effect on the cardiovascular and immune systems, medical importance, and biological sample availability. Currently, I am aligning and integrating multiple scRNA-seq HSC datasets and plan to train several machine learning models to predict the age of the sample donor. Due to technical noise from different sequencing platforms and limited numbers of donors, I am experimenting with quality control and normalization methods to remove batch effects while preserving true biological variation. After training the aging clock, we will validate its response to age-modulating conditions such as diabetes and progeria. Then, we plan to screen candidate genes for rejuvenative effects by modulating their expression levels. Lastly, putative rejuvenation genes identified by the clock assay will be functionally validated in subsequent experiments.

### Development of an Interactive Webapp to Visualize Air Pollution Disparities

---

**Ethan McFarlin**

PRISE Fellow

Computer Science, 2024

Harvard College, Leverett House

Harvard T. H. Chan School of Public Health

Advisor: Francesca Dominici

Supervisor: Falco Bargagli Stoffi

---

Exposure to harmful air pollution components varies precipitously across different socioeconomic groups and is a burden often born disproportionately by minority communities. Existing research in this space focuses on unpacking the causal health effects of exposure to pollution, but lacks emphasis on communicating such disparities in a medium that is public-facing and widely digestible to those outside the field. To rectify this issue, an interactive, web-based air pollution mapper was developed by the researchers in this project. In the data-wrangling phase, several distinct types of data were combined, including demographic data from the Decennial Census (DC) and predictions of air pollution components from a national model by Dr. Heresh Amini. To visualize the relationship between subset variables in each of these categories, the ArcGIS Javascript API was used, in conjunction with QGIS and R for pre-processing. With controls in place to modify the selected measures and preferred style of visualization, the interface is optimized for user interaction. Once released, the application will draw increased attention towards the population subgroups who are exposed to the greatest levels of air pollution. This research has broad applications in informing policy outcomes and making air quality data more accessible to the wider public.

## Humoral Correlates of Protection against Respiratory Syncytial Virus in Infants

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**Maanasa Mendu**

SURGH Fellow

Neuroscience, 2024

Harvard College, Kirkland House

Ragon Institute

Advisor: Galit Alter

Supervisors: Wonyeong Jung and Nadege Nziza

---

Respiratory syncytial virus (RSV) is a leading cause of death in the first year of life in resource-limited countries. RSV infection severity varies from mild cold-like symptoms to severe lower respiratory tract infection. While many demographic, behavioral, and genomic factors have been associated with RSV infection severity, predicting clinical disease progression proves challenging during the acute phase. The quality of the humoral response to RSV infection has not been extensively characterized across time. We used a systems serology approach to characterize RSV-specific antibody responses. Plasma samples were collected from 36 controls and 154 infants with RSV at three different time points post diagnosis. We first examined differences in humoral features by clinical status and strain type using univariate statistical tests. To identify features that best discriminate infants infected with RSV A and B, we used LASSO regression and Partial Least Squares Discriminant Analysis. Lastly, we predicted mild, moderate, and severe RSV infection using subsets of clinical, demographic, and humoral data. Preliminary findings suggest that infants with RSV rapidly develop specialized, cross-reactive immune responses compared to controls. By day 30, infants with RSV exhibit more strain-specific immune responses. Infants with RSV A had significantly higher rates of antibody feature expansion between day 1 and 30. A K-nearest neighbors algorithm fitted on clinical and RSV-specific antibody features had the highest class balanced testing accuracy of 88.69% out of the 90 models evaluated. Identifying the humoral correlates of RSV infection could help inform rational-vaccine design and provide an inexpensive biomarker for clinical decision-making.

## Analysis of the N2 NSCLC Survival Trend in the Past Decade

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**Alaha Nasari**

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History and Science, 2024

Harvard College, Cabot House

Massachusetts General Hospital

Advisor: Chi-Fu Jeffrey Yang

Supervisor: Arvind Kumar

---

Recent data has revealed improved survival for patients with N2 non-small-cell lung cancer (NSCLC). This study sought to assess the extent of improvement in survival for patients with N2 NSCLC over the last decade. Patients diagnosed with clinical T1-4, N2, M0 NSCLC from 2006-2015 who underwent surgery with chemotherapy or concurrent chemoradiation in the National Cancer Database were included. Overall survival was compared between patients, stratified by three year of diagnosis groups (2006-08, 2009-11, 2012-15), using Kaplan-Meier analysis and Cox proportional hazards modeling, adjusting for twelve common covariates. Of the 39,197 patients diagnosed with N2 NSCLC, 10,022 (25.6%), 11,787 (30.1%), and 17,388 (44.4%) were diagnosed between 2006-08, 2009-11, and 2012-15, respectively. Kaplan-Meier analysis demonstrated that 5-year overall survival was highest for patients diagnosed between 2012-15 ( $p < 0.001$ ). In Cox proportional hazards analysis of the entire cohort, overall survival improved for patients diagnosed between 2009-11 compared with patients diagnosed between 2006-08 (Hazard Ratio [HR] 0.91; 95% CI: 0.87-0.94;  $p < 0.001$ ) and for patients diagnosed between 2012-15 compared with patients diagnosed between 2009-11 (Hazard Ratio [HR], 0.91; 95% CI: 0.88-0.94;  $p < 0.001$ ). These results were consistent in analyses of only patients who received surgery with chemotherapy, and only patients who received concurrent chemoradiation. In this national analysis, overall survival of patients with N2 NSCLC improved throughout the study period. These findings suggest that N2 NSCLC should not be associated with its historically poor prognosis, and factors should be further evaluated.

# Cross-Trait Meta-Analysis Reveals Shared Genetic Architecture between PCOS and Chronic Inflammation Markers

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**Lillian Petersen**

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Applied Mathematics, 2024

Harvard College, Pforzheimer House

Harvard T. H. Chan School of Public Health

Advisor: Liming Liang

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Polycystic ovarian syndrome (PCOS) is a common hormonal disorder with a prevalence of approximately 10% worldwide and is the leading cause of female infertility. PCOS is known to be closely related to inflammatory markers, but the genetic and causal basis of this relationship is not yet understood. We report results of the largest-to-date meta-analysis of PCOS using data from UK Biobank, Partners Biobank, and prior studies of FinnGen, Estonian Biobank and additional cohorts (cases = 10,005, controls = 498,227). We further conduct meta-analyses for inflammation markers combining recent proteome and biobank cohorts (N ranges from 38860 to 505,690) to obtain the largest GWAS for a broad panel of 138 inflammation markers. We find statistically significant ( $FDR < 0.05$ ) genetic correlation between PCOS and CRP ( $R_g = 0.35$ ,  $P = 1.0 \times 10^{-5}$ ), Leptin ( $R_g = 0.4$ ,  $P = 0.33 \times 10^{-5}$ ), white blood cell count ( $R_g = 0.21$ ,  $P = 8.0 \times 10^{-4}$ ), lymphocyte count ( $R_g = 0.19$ ,  $P = 1.1 \times 10^{-3}$ ), and SLAMF1 ( $R_g = 0.52$ ,  $P = 1.3 \times 10^{-3}$ ). We further find statistically significant genetic correlation between PCOS, SHBG ( $R_g = 0.40$ ,  $P = 1.1 \times 10^{-14}$ ) and BMI ( $R_g = 0.34$ ,  $P = 3 \times 10^{-13}$ ). Our findings highlight the genetic architecture underlying PCOS which is closely related to obesity and chronic inflammation. The results further our understanding of PCOS pathogenesis and enable our downstream analyses for causal inference between inflammation status and PCOS based on Mendelian randomization.

# Causal Effects of Air Pollution on Hospitalization with Alzheimer’s and Related Dementias

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**Michelle Qin**

PRISE Fellow

Statistics, 2023

Harvard College, Leverett House

Harvard T. H. Chan School of Public Health

Advisor: Francesca Dominici

Supervisor: Daniel Mork

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Exposure to increased levels of air pollution has been linked to cardiovascular disease, respiratory disease, and premature mortality, but its effects on neurological diseases are less established. To better understand air pollution’s causal effect on Alzheimer’s and related dementias (ADRD), this project estimated the effects of fine particulate matter (PM<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>), and ozone (O<sub>3</sub>) on the rate of Medicare Fee-for-Service enrollees being hospitalized with an ADRD-related diagnosis for the first time. We obtained annual, ZIP-code-level PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> exposures from a validated prediction model. To limit potential confounding, we controlled for 4 variables at the individual level (sex, race, age, and Medicaid eligibility) and multiple socioeconomic and demographic variables at the ZIP code level. Since this was an observational study with a continuous treatment, three methods were used to establish causality: matching observations based on their generalized propensity score (i.e., their probability of being exposed to each possible level of pollutant, estimated using state-of-the-art machine learning methods), weighting observations based on generalized propensity score, and including generalized propensity score as a covariate in the regression. Based on a random subset of 100,000 observations (0.57% of the full data), preliminary results suggested that an interquartile-range (IQR) increase in PM<sub>2.5</sub> (3.85  $\mu\text{g}/\text{m}^3$ ) corresponds to a hazard ratio of 1.146. These results add evidence that PM<sub>2.5</sub> exposure promotes the development of neurological conditions such as ADRD. We hope that our study will help U.S. decision makers retain or revise air pollution standards.

# Data-Drive Identification of Clinically Meaningful Subtypes of BPD

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**Cindy Wang**

SURGH Fellow

Statistics, 2024

Harvard College, Leverett House

Harvard T. H. Chan School of Public Health

Advisor: Andrew Beam

Supervisor: David Bellamy

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Bronchopulmonary dysplasia (BPD) is a disease involving chronic lung dysfunction arising from impaired lung development in extremely preterm infants, and it is one of the most common complications of preterm birth. One critical step towards developing more effective treatment strategies for BPD is to identify and characterize clinically meaningful subtypes of severe BPD to improve our understanding of the pathophysiology of BPD. Recent attempts to identify subtypes of BPD have relied on clustering limited datasets of patients diagnosed with BPD using a small number of clinical variables, possibly missing key information regarding a patient's changes over time. In this study, we are applying longitudinal clustering to an extensive dataset consisting of daily support, medications, procedures, and weight data for over 80,000 pre-term infants, including nearly 1000 infants with severe BPD. Specifically, we employed a transformer model trained on over 60,000 preterm infants to efficiently encode each patient's trajectory to developing BPD over time in the form of continuous vectors. We investigated various combinations of dimensionality reduction and unsupervised clustering algorithms to identify robust clusters and conducted evaluations using silhouette scores, cophenetic correlation coefficients and permutation tests. Preliminary clusterings suggest that there exist two key subtypes within severe, grade 3 BPD with key differences in birth weight, gestational age, and level of fluctuation in oxygen support. We are currently investigating differences in treatment strategies and outcomes on each subtype to enable earlier diagnosis of severe BPD into subtypes to inform treatment approaches and improve patient outcomes.

## Extending Goldeneye to Support Mixed-Precision and Faster Design Space Exploration

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**Tarek Aloui**

PRISE Fellow

Computer Science, 2024

Harvard College, Adams House

Harvard School of Engineering and Applied Sciences

Advisor: David Brooks

Supervisor: Abdulrahman Mahmoud

---

Mixed-precision computing can provide great benefits in terms of speeding up the training and inference of deep neural networks (DNNs) without sacrificing accuracy. This is done by implementing different numbers systems at different parts of the neural network. Despite these benefits, the study of mixed-precision for resilient DNNs is still lacking. One of the main challenges is that most CPUs and GPUs rely on the standardized IEEE 754 floating point format, so testing mixed-precision configurations directly on hardware is impractical because it would require building a completely different DNN accelerator for each experiment. To address this issue, we open-sourced a tool called Goldeneye which operates on the software level and allows for the simulation of different number systems with fault injection capabilities. While Goldeneye presents a practical solution for simulating data formats, it is still incapable of mixing and matching them on a layer-by-layer granularity, i.e mixed-precision. Moreover, Goldeneye's design space exploration (DSE) feature, which allows for finding optimal data formats for a given model, can only explore networks with a shared data format across all layers. This significantly limits the possible configurations that could be explored. This work aims to provide an improvement on the GoldenEye framework to support reliability analysis on mixed-precision models. It also aims to extend the DSE feature to allow for faster search through genetic algorithms. These two key-improvements could potentially allow us to find mixed-precision configurations that provide greater resiliency and efficiency at a lower accuracy tradeoff.

## AtomXR: The First Head-Mounted Display (HMD) Game Engine Driven with Natural Language

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**Alice Cai**

SPUDS Fellow

Special Concentrations, 2025

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Harvard Faculty of Arts and Sciences

Advisor: Jeffrey Schnapp

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Extended reality (XR) game development suffers from three major inefficiencies and entry barriers: 1) the inaccessibility and steep learning curve of game engines and IDEs to non-technicals, 2) the mismatch between development environment on 2D screens and ultimate 3D user experience inside head-mounted displays (HMDs), and 3) the long deployment cycles for testing and iteration onto target HMDs. These immaturities of extended reality (XR) development practices repel talent, slow down progress within the field, and exclude a large portion of the population, in particular those from non computer science backgrounds, reducing the diversity and richness of applications created in XR. The ability to easily develop XR applications inside the headset would not only improve the creation process, but also democratize XR for laymen. We introduce AtomXR, the first natural language-driven, at-runtime game engine. Designed with low floors and high ceilings for a wide range of users, AtomXR allows anyone to create any application using intuitive, non-technical interactions, all at runtime. Users can design 3D environments, spawn objects, and add functionality through natural language input, complemented by physical interactions to redesign, reposition, and resize components. Akin to industry-standard game engines, AtomXR provides out-of-the-box functionality for buttons, user interfaces, collectible items, path finding, and more. Beyond this, users can add game logic of arbitrary complexity- boolean operators, loops, conditionals- anything that can be described in natural language can be implemented with AtomXR. With AtomXR, anything you can imagine, you can create.

# Deep Learning for Automated Annotation of Endotracheal Tube Presence and Position on Chest Radiographs

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**Nikhil Datar**

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Computer Science, 2025

Harvard College, Adams House

Harvard Medical School

Advisor: Pranav Rajpurkar

Supervisor: Henrik Marklund

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Endotracheal tubes (ETT) are used in intensive care unit settings to assist patients with breathing. Assessment of ETT placement is a time-intensive, yet necessary task for radiologists to ensure patient safety. Computer vision machine learning models serve as a promising alternative to manual annotation of ETT placement. However, there remains a lack of annotated data from a diverse set of hospitals. Currently, the RANZCR-CLiP dataset, a subset of the NIH public chest x-ray dataset, is the only publicly available dataset with an ETT placement label. Several other publicly available datasets such as MIMIC-CXR and CheXpert contain chest radiographs, but are not annotated for ETT placement, and manual annotation is expensive. The purpose of this study was to train a deep learning (DL) model on RANZCR-CLiP to 1) detect ETT presence, and 2) classify whether ETTs are accurately placed or not. This model was then applied to MIMIC-CXR and CheXpert for automated annotation. In particular, we fine-tuned a pre-trained GLoRIA resnet50 backbone model on RANZCR-CLiP, achieving an area under the receiver operator characteristic curve (AUROC) of 0.9959 for detecting the lack of an ETT, 0.9763 for determining an ETT was correctly placed, 0.9149 for determining an ETT was borderline abnormally placed, and 0.9190 for determining an ETT was abnormally placed. Preliminary results on MIMIC-CXR are difficult to gauge because of the lack of a groundtruth. Regardless, the model performs relatively well at detecting ETT presence, yet struggles at detecting abnormally positioned ETT cases. Overall, the study shows that DL models can aid annotation of public datasets.

# Learning an Effective Controller to Accelerate the Maturation of Cardiac Organoids Using Electrical Impulses as the Input

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Our goal is to learn an effective controller, using electrical impulses as the input, for the acceleration of the maturation of a cardiac organoid, a self-organized three-dimensional tissue culture that has a similar function to a heart. To do so, we plan to use Reinforcement Learning (RL), a popular approach for learning how to act in unknown environments, to learn such a controller. Since there are many RL algorithms available, our first task is to select an appropriate RL algorithm (from a list of candidate choices) for our problem. A challenge in identifying such an RL algorithm is that it is expensive to run experiments on the actual cardiac organoids, making it infeasible to evaluate and compare different RL algorithms by performing multiple experiments in the lab for each RL algorithm. Given this challenge, our approach to selecting an appropriate algorithm is the following. We first design many simulated cardiac organoids with different settings, each with artificial dynamics for how the cells' dynamics evolve. Our design of the artificial dynamics is informed by simple biological priors that we expect the dynamics should satisfy, as well as existing experimental data from the actual organoids. We then evaluate the various candidate RL algorithms in these simulated RL environments and identify the best performing algorithm(s) across the different environments. This allows us to select a good RL algorithm for use in actual lab experiments, reducing experimental costs.

## Shaping the Neural Linear Model

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Neural Linear Models (NLMs) are a class of Bayesian machine learning methods which apply Bayesian inference on a deep neural network’s hidden features. Traditionally, Gaussian Processes (GPs) are a popular model used for regression tasks in which predictive uncertainty is desired. However, fixed kernel GPs do not necessarily provide desirable predictions under all circumstances. NLMs are a parametrized, data adaptive, and scalable alternative to GPs. My project seeks to characterize the circumstances and tasks under which either NLMs or GPs perform better through empirical experiments on both synthetic and real-world regression datasets. Moreover, I develop a novel training method for the NLM which allows the behavior of the model to mimic either a traditionally-trained NLM, or a GP with a pre-specified kernel, to a degree which can be controlled via a hyperparameter. Empirical results demonstrate that this novel method can capture the benefits of both the NLM and a fixed kernel GP.

## Evaluating Static Representations Reduced from Pretrained and Stacked Contextualized Embeddings for Pharmacovigilance in Sleep Medicine

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The proportion of adults being prescribed off-label medications for insomnia has increased in recent years, necessitating epidemiologic studies. Cohort identification of off-label drug users for insomnia from structured electronic health records is challenging as insomnia and patient-reported ADEs are undercoded; unstructured texts capture this information better. Scalable information extraction from unstructured text entails NLP tasks and thus word representation, where approaches have shifted from using static to contextualized embeddings. Recent studies show that static embeddings distilled from contextualized models intrinsically outperform baseline static embeddings, provide interpretability, and enhance latent knowledge discovery. Experimenting with decontextualization algorithms, we distilled static embeddings from a pretrained contextualized model and a model created by stacking the pretrained model with a static model trained on patient-generated texts. We conducted biomedical intrinsic evaluations and a proposed intrinsic evaluation that assesses distances between static word embeddings to determine the relation to insomnia medications. Preliminary results indicate that decontextualized stacked embeddings outperform decontextualized pretrained embeddings and thus capture better semantic understanding; both outperform baseline static embeddings. Next steps include comparing the performances of the aforementioned contextual, decontextualized, and baseline static models in the downstream tasks of NER and RE on clinician- and patient-generated texts. We plan to perform NER and RE on unstructured EHR data from MGB’s Research Patient Data Registry.

## Explicating Our History: Natural Language Processing on Newspaper Databases

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Automatic document analysis and content extraction using deep learning-based approaches can systematically reveal rich information lost in historic documents. This method enables sentiment analysis on newspaper databases from different time periods, greatly informing retroactive understanding of historic events like presidential administrations, oil crises, crime, and military conflicts, as well as downstream tasks like visualizing sentiment formation along geographic and longitudinal time-based axes. Using an Optical Character Recognition (OCR) model, a deep learning pipeline to extract digitized text from over 50 million page image scans and 10,000 historical U.S. newspapers (1880-1978) has been developed by the lab. However, challenges include the lack of systematic tools to cluster stories at different levels of granularity and the entity-level sentiment analysis for editorials. OCR output texts were used to train Sentence Bidirectional Encoder Representations from Transformers models (SBERT), supervised models that embed the text as 768-dimensional vector representations. Story clustering is then accomplished using contrastive learning to push similar stories closer in high-dimensional space, with clustering of these vector embeddings using a rules-based cosine similarity metric. Additionally, a multitude of diagnostic tests were conducted to understand the entity-level task's feasibility, benchmark the robustness of pre-trained models, and visualize the story cluster outputs. Interactive multi-dimensional cluster graphs and nearest neighbor article outputs show promising potential of a proof-of-concept product for historic newspaper story clustering and entity-level newspaper sentiment analysis.

## Integrating Super-Pixels into Active Learning for Semantic Segmentation

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This research explores the use of super-pixels in active learning for semantic segmentation. Semantic segmentation is computer vision task for which high-quality annotations are expensive to obtain, especially for its applications in fields such as medical imaging where precise annotation are time-consuming and requires highly skilled physicians. This condition renders active learning particularly beneficial as active learning methods can increase the annotation efficiency of machine learning models. Based on the machine learning model, active learning algorithms adaptively select the most informative samples for humans to annotate, and machine learning models augmented with active learning can achieve performance comparable to full annotation at a fraction of the annotation cost. Previously works have mostly treated semantic segmentation as pixel-level classification task; this approach fails to take advantage of semantic similarity between neighboring pixels. We propose to integrate super-pixels, a well-developed computer vision method of grouping spatially and semantically related pixels, into the framework to better adapt active learning methods originally intended for classification for semantic segmentation tasks.

# Scientific Image Segmentation Using Deep Neural Networks

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The manual analysis of scientific imaging data is a time-intensive task impeding scientific research. Computer automated annotation and segmentation can accelerate research, however most software is highly specified towards the image modality and annotation task and requires vast quantities of hard-to-obtain annotated data. To overcome this issue, we propose a generalized, user-friendly tool for scientific image segmentation using convolutional neural networks and transfer learning. In this study, we explored if a Mask R-CNN model pre-trained on MS COCO, a dataset containing 328,000 images of everyday objects, can be transferred to several scientific image segmentation tasks. We first trained a model on 32 manually annotated, highly stereotyped x-ray images to identify, segment, and measure the tibia and pelvis. The model generated a prediction 100% of the time, and these predicted tibias and pelvises had mean 79.11% and 71.21% pixel overlaps with the ground truth images. Their predicted lengths had concordance correlation coefficients of 0.79 and 0.47 with the ground truth, respectively. We next trained a model to solve a harder task: segmenting the dorsal region from fluorescent *in situ* images of spinal sections with significant shape and color intensity variation. The model, trained on 133 images made by computationally augmenting 19 manually annotated images, generated a prediction 83% of the time. These predicted dorsal regions had a mean 76.24% pixel overlap with the ground truth. The models' successes demonstrate the promise of transfer learning in automating the analysis of scientific images to accelerate scientific research.

# NormOut: A Sparse, Competitive Dropout Regime Identifies Winning Lottery Tickets

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Artificial neural networks (ANNs) are subject to constraints on both plasticity (required for the integration of new knowledge) and stability (required to prevent catastrophic forgetting of old knowledge). The optimal solution to these constraints requires generalization, since a network with generally applicable knowledge can minimize its plasticity without adversely affecting its performance on novel tasks. Recent work has shown the existence of “winning lottery tickets,” or sparse, trainable subnetworks at initialization which generalize as well or better than the original network. In this work, we modify Dropout, a classic regularization technique for improving generalization, by directly modelling it on the phenomenon of probabilistic synaptic transmission in the brain, also known as synaptic failure. We design a novel activation function called NormOut which computes the ratio of a neuron’s activation to the maximum activation in some set of neurons, and then uses that ratio as the neuron’s keep probability during Dropout. We propose variants of NormOut inspired by lateral inhibition and neuronal firing thresholds in the brain, and further improve them by incorporating neural network distillation. NormOut imposes a strong structuring influence on the stochasticity and sparsity of Dropout by making larger activations more likely to be kept, and vice versa. We hypothesize this allows NormOut to identify “winning lottery tickets” early in training, leading to better generalization. We are currently testing NormOut using VGG16 on CIFAR10, in both the standard and class-incremental settings. Initial results suggest high sparsity (over 95%) without loss of validation accuracy.

# Continual Learning with CRUMB: Compositional Replay Using Memory Blocks

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Humans learn visual perceptual skills entirely from a stream of highly temporally correlated inputs as they move about the world. Artificial neural networks that learn well from shuffled datasets often perform poorly under such conditions, catastrophically forgetting previous knowledge when they encounter new tasks or stimuli. One way the human brain mitigates forgetting is by “replaying” episodic memories, drawing on generalizable object features to reconstruct them efficiently. Inspired by how brains learn, we propose a new continual learning algorithm, Compositional Replay Using Memory Blocks (CRUMB). Re-usable vectors (“blocks”) acquire representations of important image features during the learning process. These blocks are used to recompose feature maps from a deep neural network layer. CRUMB stores the indices of memory blocks activated during processing of new stimuli, enabling memory replay with a minimal memory footprint. We train CRUMB for image classification by exposing it to a series of video clips, learning multiple distinct classification tasks in an ordered sequence. We are also investigating CRUMB’s ability to learn to play Atari 2600 games in sequence with a limited memory footprint. Our image classification results show that CRUMB’s compositional replay mitigates forgetting more effectively than raw pixel replay when the number of stored image examples is held constant, despite occupying dramatically less computer memory. Given a fixed memory budget, CRUMB also outperforms state-of-the-art continual learning algorithms across multiple datasets. These results suggest that compositional feature-level replay is a promising method for algorithms to approach human-like learning in continually evolving environments.

# In Network Compression Aggregation (INCA) on Programmable Switches for Distributed Machine Learning Applications

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Recent trends in data centers and large companies have focused on training machine learning models with parameters numbering on the order of hundreds of millions or even billions, a task that has become impossible on a single machine. However, distributing the computational task over many machines introduces a large inter-machine communication overhead which bottlenecks the speed at which these models can be trained, so it has become increasingly important to improve these networks. One popular setup of distributed training relies on a parameter server (PS) that keeps a central copy of the model, but this requires that the PS communicate the parameters to the workers every time the model is updated. We instead propose replacing the PS with a programmable switch to eliminate this communication by keeping local copies of the model on each worker and performing in network aggregation of gradients with a custom stochastic compression algorithm. Simulations and experiments on Harvard’s high-performance cluster have shown that this new network can theoretically decrease the communication overhead without significant loss of accuracy. These findings suggest that the future implementation of the network should be able to improve on the current parameter server setup.

### Composite Hinges Control Designer Properties of Architected Materials

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Metamaterials are physical structures with counter-intuitive properties that emerge from their internal architecture. With thoughtful design, they can be used to manipulate optical, acoustic, and thermal fields. We focus on a paradigmatic mechanical metamaterial based on a mechanism of counter-rotating hinged squares. It has received significant attention due to its effective negative Poisson's ratio and ability to propagate solitary pulses. Realization of this metamaterial at large scales requires the ability to fabricate robust hinges capable of large rotations at low energy cost. Current strategies rely on living hinges, whose compliance is determined by the hinge geometry. By fabricating composite hinges from silicone and textiles, we've expanded the hinge design space to reach lower bending energy with greater durability than living hinges. We assess the impact of multi-material use on energy cost of deformation, structure durability, and transmission loss. By comparing composite and living hinges in single hinge ( $n=1$ ), small array ( $n=4$ ), and large array ( $n=190$ ) scenarios, we illustrate both the scalability of composite hinge properties and the feasibility of their fabrication. This work provides a guide for fabricating composite hinges and for exploring the potential of composite fabrication to strengthen and optimize metamaterials for practical use.

### Developing Ultrasensitive DNA Methylation Sensing for Early Cancer Detection

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Early cancer detection greatly improves patient outcomes. Such detection could be achieved by the detection of tumor-derived cell-free DNA (tdcDNA), small DNA fragments released by dying cancer cells found in blood, urine, and other sample types. Multiple multi-cancer diagnostics using sequencing-based tdcDNA detection methods are in development, but these tests have low sensitivity for early-stage cancers: sequencing-based methods cannot reliably detect tdcDNA when it is present in a low amount relative to non-tumor cell-free DNA (cfDNA) background. In this project, we aim to develop a technology capable of detecting extremely low abundance tdcDNA. Some tdcDNAs can be distinguished from non-tumor cfDNAs via the presence of cytosine methylation on specific DNA sequences. The Shih Lab recently developed Crisscross, a technology that can reliably detect a DNA biomarker sequence in the presence of a large background of non-biomarker DNA. We are therefore developing Methyl-Sensitive Crisscross Amplification (MeSCA), a modified Crisscross technology to detect methylated tdcDNAs with high specificity in the presence of a large background of non-tumor cfDNA. To do so, we apply the Tet enzyme to convert methylated cytosine (5mC) in to hydroxymethylcytosine (5hmC), and then use the enzyme  $\beta$ -glucosyltransferase to tag 5hmC with an azide functional group. This compound can then react with a dibenzocyclooctyne- ssDNA handle compound, attaching an ssDNA handle to the target DNA molecule. Then, Crisscross is applied to simultaneously detect the DNA sequence and presence of two methylated cytosines. Once validated, we plan to apply this technology to early cancer detection.

## Designing Compliant, Comfortable Soles for an Ankle Exoskeleton

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Rigid exoskeletons can augment human locomotion and reduce the metabolic cost of movement. The Harvard Biodesign Lab's hinged ankle exoskeleton, for example, was designed to improve post-stroke patients' walking speeds. As with many rigid exoskeleton projects, attaching the device to users both securely and comfortably poses a challenge where tradeoffs must often be made between rigid components which transmit force efficiently and soft components which are more comfortable to wear. When this exoskeleton operates, forces are applied to the body at the bottom of the foot from a metal plate through a plastic sole then through a foam insole to the user's foot. If the plastic sole component is too rigid, the device cannot bend along with the user's natural foot flexing, resulting in misalignment of the exoskeleton. If the sole is too flexible, it does not distribute pressure effectively, resulting in discomfort from high peak pressure. In this research, a variety of sole designs were created and evaluated on the basis of flexibility, pressure distribution, and comfort. Many designs including flexure patterns and layering produced adequately flexible soles. Comfort testing of participants indicated that these flexible soles may retain the ability to comfortably distribute pressure. Future analysis of peak pressures will identify the flexible insole which distributes pressure most effectively, moving us toward a final product that will be able to provide comfortable assistance for hours at a time.

## Tuning Porosity of Engineered Nanofiber Cardiac Valves

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Heart valve disease is a leading cause of mortality and morbidity worldwide and leads to the replacement of roughly 300,000 valves annually. Current replacement options include mechanical and bioprosthetic valves. Unfortunately, both of these approaches are limited in their longevity and require repeat surgeries in many cases. To bypass the potential of repeat surgeries, work has emerged in developing regenerative valve implants that will grow alongside the patients. Previous regenerative implants have struggled to achieve adequate cellular infiltration and remodeling due to the lack of controlled porosity. Using novel focused rotary jet spinning (FRJS), we spun nanofiber heart valves that included sacrificial fibers, meant to be washed away and leave behind a more porous scaffold. To effectively create the porosity necessary for valvular interstitial cell (VIC) infiltration, we co-spun poly(caprolactone) (PCL), an insoluble biocompatible polymer, and poly(vinylpyrrolidone) (PVP), a highly water-soluble biocompatible polymer, onto valve-shaped mandrels. Using a water washing method, we demonstrated removal of the PVP fibers, resulting in increased porosity. To examine the porosity changes, we cultured VICs on the fibrous scaffolds and measured their infiltration depth, seeing increased infiltration on the scaffolds that included the sacrificial PVP fibers. The valve's ability to maintain unidirectional flows in a cardiac environment were evaluated in a pulse duplicator system, showing the PCL/PVP valves provided adequate functionality. This sacrificial fiber approach to tuning porosity in three dimensional scaffolds can help speed regenerative valve's integration with their hosts and improve implantation outcomes by encouraging rapid cellular infiltration and remodeling.

## Improving the Mechanical Design and Functionality of the Hinged Ankle Project

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Wearable robotic devices have demonstrated their use for rehabilitation and assistance for those with limited mobility. The Harvard Biodesign Lab's Hinged Ankle Device is a wearable robotic device prototype intended to assist the foot in plantarflexion and dorsiflexion using driven cables. The prototype is currently suffering from mechanical failures, bulkiness, and an inconvenient assembly process. Most of the structural failures occur at the pulley which converts force from the cables to torque about a rotational axis through a pulley disk. The bulkiness issue of the device is partially due to an on-axis encoder that must sit in-line with the rotational axis, and thus adds unwanted thickness. The difficulty of assembly is attributed to both the on-axis encoder, as well as the pulley's housing. In this summer's research, all of these issues were addressed through design changes, and were validated through stress and functionality tests. A stress test bench was created to test the new pulley disk design against the current one, and preliminary results of the new design show an approximately 70% increase in mechanical strength. The pulley housing was separated into a two-part design to address the difficulty of assembly. To address the form factor issues, an off-axis rotary encoder is being implemented, which will significantly reduce how much the device extends from the ankle and simplify assembly. All these improvements should help bring the device closer to its intended functionality and closer to helping those in rehabilitation following a stroke or related injury.

## Epicutaneous Immunotherapy Using Ionic Liquids as a Transport Mechanism and Adjuvant

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Food allergy affects over 220 million people worldwide, and allergen avoidance has been the mainstay of prevention of illness. However, desensitization, through allergen-specific immunotherapy, is also a viable alternative to reduce illness from food allergies. Current methods of allergen immunotherapy use oral (OIT), sublingual (SLIT), subcutaneous (SCIT), and epicutaneous (EPIT) routes of administration. EPIT is most desirable because it is less invasive and has a lower risk of systemic reactions. In EPIT, the allergen is transdermally delivered to the skin's epidermal and dermal layers to utilize the skin's unique immune system for the induction of allergen desensitization. Here ionic liquids (ILs), which have successfully been used for transdermal drug delivery, were investigated as permeability enhancers and adjuvants for EPIT applications. Different formulations of ILs and model allergens were tested for solubility of allergen in solution, stability of allergen while in formulation, and transport of the allergen through the skin. Ex-vivo porcine skin models were employed to investigate the successful transport of the chosen formulation of IL (choline sorbate) and allergen. Preliminary observations indicate that ILs can efficiently deliver the model allergen to the epidermis and dermal layers of the skin. In the next steps, the formulation will be investigated for its allergen-specific immune response and maintenance of cell viability in culture. This work suggests that ionic liquids can potentially be used as permeation enhancers and adjuvants in EPIT to enhance the desensitization immune response, and ultimately help lower the global burden of food allergy.

# Promoting iPSC-Derived Vascular Cell Maturation in a Tissue-Engineered Blood Vessel Model

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Cell sourcing for the engineering of physiologically-representative, small diameter arterial blood vessels remains challenging due to the lack of availability of primary smooth muscle cells and endothelial cells. While human pluripotent stem cells (iPSCs) are a promising alternative, current methods incorporating these cells into engineered tissues have failed due to challenges in promoting and maintaining a mature phenotype. To determine the biophysical cues that contribute to cell fate decision, our overall objective is to compare gene expression levels of key maturation markers for iPSC-derived smooth muscle cell and endothelial cell in 2D versus 3D environments. Biophysical cues that arise from the collagen biomaterial-based microenvironment and physiological shear and pressure will additionally be applied to vascular cells seeded in tissue-engineered blood vessels. The extent of maturation will be quantified through assays like qPCR and flow cytometry. We anticipate that iPSC-derived vascular cells cultured in a 3D environment will show higher gene expression of maturation markers compared to those cultured in a 2D flask. Additional mechanical conditioning through exposure to physiological pressure and flow rate will further drive maturation of iPSC-derived vascular cells towards a fully differentiated phenotype. This study will look at the factors that drive cell maturation and the role of biophysical cues in promoting differentiation within a 3D tissue-engineered blood vessel environment. This work will take tissue-engineered blood vessels a step closer to serving as an accurate *in vitro* disease model and an effective graft for transplantation.

# A Sensor for DNA Supercoiling

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DNA in the cell takes on a double helical structure that is then formed into larger loops, compacting into a supercoil. These supercoils are the result of mechanical torsional forces caused by over or underwound DNA. Supercoiling plays a strong role in chromatin compaction and gene expression; and the work of topoisomerases, which wind and unwind the DNA, are able to change topology of the DNA to facilitate transcription or replication. Despite the importance of supercoiling in DNA topology and DNA's cellular function as a whole, there is not currently a single molecule sensor that can optically measure the degree of DNA supercoiling. This research proposes a design, synthesis protocol, and incorporation protocol for a sensor that reports twist in DNA strands via fluorescence lifetime imaging (FLIM). The protocol proposed here suggests a synthesis derived from the commercially available Flip-TR molecule, resulting in a sensor that can be attached to alkyne-painted DNA strands via a bioorthogonal Click Chemistry reaction. Initial data indicate that the sensor synthesized following the developed protocol can be delivered to living *E. Coli* cells, but further testing will be required to confirm the attachment of the sensor to the chromosome and to calibrate the FLIM response of the sensor to DNA twist. Successful completion of this project may allow for the observation of DNA supercoiling through the cell cycle and a greater understanding of the roles supercoiling may have in segregation of chromosome copies between daughter cells during the cell division.

## Designing a Measurably Compliant End-Effector for the Pheeno Swarm Robot

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Compliance, the property that allows a robot to passively deform when acted upon, is a critical yet under-appreciated feature in robotic manipulation as it allows for increased capabilities including the handling of fragile objects and safer operation around humans. This feature is especially crucial in robotic swarm tasks such as repositioning a rigid object due to the tendency of these maneuvers to become over-constrained. The ability to exert forces and torques on an environment or other agents in a controlled way, while still retaining the capability to be acted upon and deform when necessary, is a core feature of soft robotics but is slow to be adopted outside of this field for small-scale, swarm robots. This study introduces a design for an inexpensive two degree of freedom arm to interface with a Pheeno robot. The arm is designed to provide measurable compliance in two dimensions and provide the sensing capabilities to report displacements in real time. In preliminary experiments, this design is able to permit and sense linear displacement in a horizontal plane between 1 mm and 5 mm, and is sensitive within 1mm. This design allows for physical testing of swarm algorithms requiring manipulation, which can vary wildly from their simulation predictions. In this way, this design closes the gap between simulations that idealize both agent-environment and agent-agent interactions and physical, realistic experiments with hardware.

## Continuum Robotic Device for Assisting the Movement of the Shoulder Joint

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Neurological injuries or conditions such as stroke or Parkinson's Disease can negatively impact the quality of life of an individual. Exoskeletons can aid in restoring quality of life for these individuals by assisting the movements of the wearer. However, an issue within the field of wearable robotics is that devices can be too heavy and bulky to rationalize long term daily use. Additionally, joint misalignment can occur, where the center of rotation of the biological joint becomes offset from the exoskeleton joint, causing discomfort for the user and possibly leading to injury over time. A potential solution to these issues are continuum robots. Continuum robots are robots that have infinite degrees of freedom. Generally they are made up of segments that are attached to each other through a central connector and are controlled by cables that are routed through each segment. This design allows for low profile devices that have more range of motion than more traditional assistive exoskeletons while still maintaining the ability to exert force in a controlled manner. By analyzing past wearable robotics and applying engineering principles of design, this study has developed a wearable continuum robot for the shoulder, the joint with the largest range of motion. Thus far, a design that allows for the full range of motion of the shoulder has been developed and the control system for the device is being optimized. If successful, this device will improve the quality of life of the wearer by enabling them to perform everyday tasks.

# Understanding the Relationship between Membrane Conductivity and Electrolyte Composition in Aqueous Organic Redox Flow Batteries

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Sustainable, grid-scale energy storage must be developed for full reliance on renewable, intermittently generated energy. Aqueous organic and metalorganic redox flow batteries (AORFBs) made from earth-abundant, accessible elements hold promise. A cation exchange membrane separates the electrolytes, allowing charge transport whilst preventing active species crossover. This research evaluates how the electrochemically active ferrocyanide concentration, pH, and supporting electrolyte cations (sodium or potassium) affect membrane performance. The active specie concentration is proportional to battery capacity; hence maximisation must account for membrane detriment. This research aims to improve understanding of membrane performance across operational conditions, which will inform the design and choice of membranes in AORFBs. Nafion, a fluorinated cation exchange membrane incumbent to earlier flow battery research, and a lesser-known, non-fluorinated hydrocarbon-based cation exchange membrane from Fumatech (E-620K) were tested. The resistance and water uptake of each membrane were measured. The results show that Nafion is highly sensitive to the supporting electrolyte cation, being over 50% more conductive when sodium is used over potassium. The water uptake data follows the same trend over the concentration range (0.01-4M), supporting the theory that water uptake increases the amount and size of transport channels through the membrane, thus raising the conductivity. In contrast, E-620K conductivity is independent of cation up to pH14. Both membranes experienced a greater than 50% drop in conductivity over pH7-14 when 0.05M ferrocyanide is introduced into the electrolyte. Hence, conductivity and volumetric capacity become a trade-off, highlighting the importance of considering membrane resistance when designing an AORFB for maximum efficiency.

# Developing an Accessible Hardware Interface for Community FES Device

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Individuals post-stroke suffer from hemi-paresis, which limits volitional muscle control and results in dorsiflexion deficits during walking. Functional Electrical Stimulation (FES) can be used to assist walking by supplying current through electrode pads attached over the lower leg muscles to induce muscle contractions. FES requires precise placement of skin electrodes, often by trained clinicians, to achieve desired foot motion, and can be difficult for users to replicate without expert supervision. An array-based electrode approach was developed as a solution, but the system cannot be donned while seated and has long cables, making it suboptimal. We designed a user-friendly textile hardware interface for this array that enables easy, accurate, and repeatable donning for use in everyday life. Design goals for an ideal system were to enable quick donning time and be reliably applied with one hand. The new interface was developed through an iterative design process, resulting in a sticker-based interface fabricated using CAD, sewing, and 3D printing. We tested with a post-stroke participant and evaluated the system's donning time with two different wrap styles and accuracy of donning location, which were compared to the existing research system. The foam wrap was donned 22.5% faster with lateral displacement of 9.6mm compared to control. Preliminary results show desired motion can be stimulated with up to 13mm of lateral misplacement. With its faster donning time, the new interface is an acceptable solution. Incorporating participant feedback, the ideal design is a calf wrap that combines this sticker interface with one-handed friendly features.

# Using Artificial Intelligence to Identify Surgical Anatomy and Phases during Robotic-Assisted Thoracoscopic Surgery

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Lung cancer is the leading cause of cancer deaths worldwide. The increasing advancement of robotic-assisted thoracic surgery (RATS) has expanded treatment options for patients. However, intraoperative catastrophes still occur, including major hemorrhage from the pulmonary artery. Fortunately, the ability to record these operations has allowed for a new era of data generation that can utilize artificial intelligence improve outcomes. Therefore, we aimed to develop a dataset of annotated thoracic surgeries to generate a conditional generative adversarial network (cGAN)-based computer vision to identify surgical anatomy and a ResNet+LSTM architecture system to automatically recognize the phases of an operation. Spatial annotations for the anatomical identification and segmentation were done using an open source, web-based image and video annotation tool. Temporal annotations for the automated phase segmentation of the various steps of the operations were done using an annotation platform created by our collaborators. For surgical anatomy recognition, we generated a preliminary dataset of 750 training images. We trained a network to segment the artery and observed better Intersection Over Union (IOU) scores for binary class segmentation compared to multi-class segmentations. For automatic phase recognition, we have created a concept map for right lower lobectomies and temporally labeled a few full procedures. Our findings show that the neural network predicts same-patient structures with a fairly high accuracy. Limitations include the generalizability of our model and the generation of labeled dataset. Nonetheless, our project demonstrates the role that AI models have in the future of thoracic surgery education and improving patient outcomes.

# Life Sciences



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## Molecular and Cellular Biology

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### Rett Syndrome and the Reactivation of the Inactive X Chromosome

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Rett Syndrome is a neurodevelopmental disorder caused by mutations in the MECP2 gene on the X chromosome. It is fatal in males, due to its identity as an X-linked disorder and is found on the active X chromosome (or Xa) in females. Rett Syndrome has no cure but can be treated in females by reactivating the inactivated X chromosome (or Xi), which allows the wild-type copy of MECP2 to mask and overcome the effects of the mutant MECP2. A “cocktail” is developed, using various RNAs — such as the long noncoding RNA (lncRNA), X inactive specific transcript, or Xist — that block or enhance different epigenetic mechanisms in order to facilitate the reactivation of wild-type MECP2 on the Xi. Then the “cocktail” is injected, via intracerebroventricular injection (ICV injection), into the mice models that bear the genotype of the MECP2 mutation on the Xi. The treated mice are then observed and put through various cognitive neuroscience tests. Preliminary observations have shown that treated mice appear to have normalized mobility levels, as demonstrated through CatWalk tests. Additionally, treated mice appear to demonstrate normalized anxiety and nourishment levels as demonstrated through stranger tests, elevated walkway tests, and observation. Different cocktails are being tested to see which is most efficient in crossing the blood brain barrier, especially as the main ingredient cannot cross the blood brain barrier readily. Furthermore, collecting data on a larger sample size of mice modeling Rett syndrome and receiving treatment for it will aid in determining the significance of results.

### Examining the Influence of Paternal Metabolism on Offspring Health via the Male Germ Cell Epigenome

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Obesity and its associated diseases afflict millions worldwide. As expected, obesity in the parental generation is associated with obesity in offspring. It is well established that adverse epigenetic changes to the parental germ line are a mediator of this phenomenon. Epigenetics refers to modifications in gene expression without altering the genetic sequence itself. Epigenetic mediators—the environment, one’s diet, exercise, medications, etc.—may cause beneficial/detrimental metabolic genes to express or repress. In this study, we seek to dissect the epigenetic mechanisms underlying paternal transmission of metabolism. We hypothesize that this phenotypic change is being imparted to the sperm. This will be tested via single-cell chromatin and transcriptome assays of the testes and transcriptome assays of the sperm. Sperm and testes were taken from four-month-old mice in four different diet cohorts: LFD mice, HFD mice, HFD mice on canagliflozin, and mice weight-matched to the canagliflozin mice. Testes cell nuclei and sperm were extracted and sent for a joint gene expression and chromatin accessibility assay. The future results may highlight differentially regulated epigenetic targets in the sperm DNA between groups. Examining these targets would allow us to analyze the molecular mechanisms by which paternal phenotype influences offspring phenotype.

## Estimating Pathogenicity through the Functional Assessment of Quantitative Trait Outcomes

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Rare genetic coding variants can significantly increase low-density lipoprotein (LDL) cholesterol levels, increasing the risk of coronary artery disease (CAD), one of the leading causes of mortality in America. However, due to their low frequency, it can be difficult to statistically assess whether individual rare variants have a significant effect on LDL levels as there are so few observations of each variant. High-throughput CRISPR gene-editing technologies, such as deep mutational scanning and base editing, are helpful for assessing the functional impact of individual LDL receptor (LDLR) coding variants. This functional assay data is integrated with clinical data from over 200,000 individuals in the UK Biobank to identify variants which have sufficient evidence of pathogenicity to be shared with patients. Preliminary results indicate that there is a predictable relationship between experimentally-derived estimates of functional impact for LDLR variants and LDL levels in carriers. We are developing a statistical framework for using such data to improve variant pathogenicity assessments when following existing ACMG/AMP clinical classification guidelines. We have identified high correlations between functional scores and changes in LDL levels and a preliminary predictive model, which appear to be robust to several parameters we have evaluated. Using functional data and quantitative analysis to determine changes in LDL levels and update variant annotations will allow clinicians to communicate the most accurate and complete information to patients regarding their health.

## Assessing the Role of the Regulator of Protein Deacetylation, HIM-22, during Meiosis

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Lascarez Lagunas

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One cause of infertility is meiotic errors, like DNA double-strand breaks that never undergo repair. To investigate the genetic basis of infertility, the lab works with *C. elegans* whose short lifespan and transparent reproductive system make it an ideal model organism. HIM-22 shares conservation with the human ASHL1 histone methyltransferase and when knocked down, causes late Prophase I impairments. Preliminary data shows that *him-22* influences meiotic recombination, chromosome synapsis, and both the formation and repair of DNA double-strand breaks. To further characterize *him-22*'s function, the lab generated a *him-22* Flag-tagged line with CRISPR-Cas9 to localize and chemically manipulate the protein. To ensure the reliability of this line as a control, we tracked the fertility rate of both tagged and untagged worms by counting the offspring of each genotype through their adulthood. We also immunostained both genotypes' gonads to ensure that their chromatin structure matched. Our preliminary data suggests that the tagged line indeed behaves as a wildtype, so we can continue to use this strain. We can now use this tagged line to immunoprecipitate HIM-22 and apply mass spectrometry to identify its interaction with other proteins. Future studies could explore whether *him-22* deletions cause more severe damage at higher temperatures, which preliminary data suggests may be the case. Ultimately, characterization of *him-22* will shed light on meiotic causes of human infertility to better inform future treatment.

# Solving the Structures of Mini-Protocadherin-15 Proteins to Rationally Inform Gene Therapy Design

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Usher syndrome type 1F (USH1F) is a condition caused by mutations in the protocadherin-15 gene (*PCDH15*) and is characterized by congenital deafness and balance deficits, along with the onset of retinal degeneration during adolescence. Previous in-prep research from the Indzhukulian lab, in collaboration with others, has established the efficacy of utilizing adeno-associated viruses packaged with miniature versions of *Pcdh15*, in which some extracellular cadherin repeats of this dimeric, chainlike protein are deleted, as a promising gene therapy. One such mini-PCDH15 proved capable of significantly rescuing hearing in mice, while two others showed greatly reduced capability. Building upon this research, current work is directed at solving the structures of the now synthetically connected regions of the three different mini-PCDH15s through x-ray crystallography. Thus far, DNA has been isolated for these artificial regions through primer design and DNA ligation, following PCR, and *E. coli* cells are now being utilized to express these protein fragments. After concentrating the protein, crystallization trays are then prepared to crystallize these fragments for x-ray crystallography. As of now, crystals have been obtained for one of two synthetically connected regions in mini-PCDH15 V7, which only shows partial rescue of hearing when used as a gene therapy in mice, and the conditions that led to crystal formation are being refined through subsequent crystallization trays. Resolving the structures of these protein fragments will provide relevant information about the mechanics of PCDH15 and will be informative in designing subsequent, optimized versions of the USH1F gene therapy.

# Synthetic Gene Circuits for Cancer Immunotherapy

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Synthetic biology has enabled advanced targeting of cancer cells through synthetic gene circuits that can sense and respond to oncogenic signals. We developed a programmable gene circuit platform to target cancer cells with a tumor-localized therapeutic that recruits and activates immune cells. Using Boolean-logic computation, this circuit can detect multiple intracellular cancer-specific signals to determine whether the cell is cancerous. When the activities of these factors are detected by a Boolean AND gate, the circuit is programmed to express the SCIP combinatorial immunotherapy, which consists of the Surface T-cell Engager (a membrane-bound anti-CD3 scFv domain that can activate T cells, leading to T-cell mediated killing of the expressing cell), the chemokine CCL21, the cytokine IL-12, and the anti-PD1 antibody. This platform can be adapted to target multiple tumor types and to express any genetically encodable immunomodulator. Furthermore, this platform has the potential to be applied beyond cancer to target genetic diseases by designing the circuit to detect disease-specific transcription factors.

## Targeting the Genomic Instability of Cohesin-Mutant Myelodysplastic Syndromes and Acute Myeloid Leukemia

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The cohesin complex is a multimeric protein complex that plays an important role in genomic organization, sister chromatid cohesion, DNA repair, and transcriptional regulation. Components of the cohesin complex are frequently mutated in myelodysplastic syndromes (MDS) and secondary acute myeloid leukemia (sAML), and are associated with poor overall survival, making the investigation of treatments for cohesin-mutant tumors vital. Cohesin-mutant AML cells exhibit impaired DNA damage repair and subsequently accumulate double-stranded DNA (dsDNA) breaks, causing these cells to become dependent on non-homologous end joining (NHEJ) repair and creating a synthetic lethality to drugs that inhibit DNA damage repair. One such drug is talazoparib, a poly(ADP-ribose) polymerase (PARP) inhibitor. In this report, we utilized immunofluorescence staining, microscopy, and a CellProfiler image analysis pipeline to quantify the cellular effects of talazoparib in primary patient samples isolated from cohesin-mutant patients. We stained samples pre- and post-talazoparib treatment for RAD51, a marker of homologous-recombination (HR), and gH2AX, a marker of dsDNA breaks. We hypothesized that patients responding to treatment will have dysfunctional HR function and will generate a smaller number of RAD51 puncta. Preliminary data has shown that there is an increase in gH2AX signal after talazoparib treatment, indicating that talazoparib is effectively inducing dsDNA damage. We expect to see a correlation between low RAD51 and high gH2AX levels, which would suggest that cells with defective HR are more sensitive to talazoparib. These analyses will enable us to ascertain the efficacy of talazoparib therapy in patients with cohesin-mutant AML and evaluate biomarkers for sensitivity to talazoparib treatment.

## Understanding Host Phagosomal Membrane Repair Factors during Tuberculosis Infection

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*Mycobacterium tuberculosis* (Mtb), the intracellular bacterium that causes tuberculosis (TB), remains one of the largest leading causes of infectious disease death globally. Macrophages are the first cells infected by Mtb in the course of infection. One key aspect of Mtb's success as a pathogen is its ability to weaken macrophage responses. Specifically, Mtb is able to disrupt the membrane of the phagosome, which are vesicles formed around particles through phagocytosis, and this disruption subsequently shapes the infection outcome by changing both cell biology processes and innate immune responses. Recent work in the field has investigated the role of Mtb virulence factors such as ESX-1 and PDIM in damaging the phagosomal membrane of macrophages, but the host factors that play a role in repairing Mtb-mediated phagosomal membrane damage remain largely unknown. In previous work using a CRISPR whole genome screening approach, the Barczak laboratory identified candidate host factors that contribute to repair of the Mtb-containing phagosomal membrane. My project seeks to build upon that data by investigating the roles of two genes, GALNT9 and CD68, identified in that screen. I hypothesize that GALNT8 and CD68 contribute to repair of the Mtb-containing phagosomal membrane, and this link will be investigated through qPCR and PrimeFlow methods utilizing flow cytometry as well as immunofluorescent imaging. These results will allow for a deeper understanding into the host-pathogen associations of Mtb and the human host and could potentially lead to further development of more efficient host-directed therapeutics against TB infection.

## The CINCH Project

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The human parasite *Plasmodium falciparum*, which causes malaria, spreads through the body via a process called schizogony. Schizogony is when a single parasite replicates asexually to produce multiple daughter cells. To undergo schizogony, *Plasmodium* parasites must carry out multiple rounds of nuclear replication without cytokinesis and then segment the contents of the resulting multinucleated cell into individual daughters. The basal complex of *P. falciparum* drives this segmentation process. PfcINCH is a crucial protein in the basal complex; however, its function remains unknown. In this work, we test whether PkCINCH, a smaller but closely related version of the CINCH gene derived from *P. knowlesi*, is a functional complement to PfcINCH. If PkCINCH can indeed complement, the homology of the PkCINCH protein would make it easier to identify and test mutations that interfere with the activity and localization of CINCH. This would allow us to elucidate the function of PfcINCH within the basal complex. Our results show that parasites that replace endogenous PfcINCH with PkCINCH expressed from the PfMORN promoter do not grow in culture but do localize to the basal complex. This suggests that PkCINCH is not a true complement of PfcINCH. However, the MORN promoter is weaker than the CINCH promoter. Expressing PkCINCH from a promoter that has higher expression levels could affect these results, since the lack of complementation could be due to low expression. Thus, we are in the process of testing different promoter combinations to further investigate these results.

## Ramp-Up Dynamic BH3 Profiling May Predict Effective Drug Therapies in Tumors in a Cell-Conservative Manner

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An emerging strategy for treating cancer is to identify the ideal drug for a single patient, or the ideal patient population for a single drug—commonly referred to as “precision medicine.” While precision cancer medicine is typically based on genomic sequencing of patient tumors, an emerging class of precision cancer medicine (called functional precision medicine), attempts to identify the ideal match between a patient and a drug by exposing patient-derived cancer cells to drugs and measuring a phenotypic response. One of the methods for performing functional precision medicine is dynamic BH3 profiling (DBP). DBP determines if a brief drug treatment moves a cell toward the apoptotic threshold. Unfortunately, the current protocol requires on the order of  $10^6$  cells which is not trivial to obtain with current clinical workflows, particularly from late-stage cancer patients. Here, we provide a proof of concept for a new assay called ramp-up dynamic BH3 profiling (RU-DBP) that requires fewer cells. I hypothesized that the protocol requires a minimum number of cells to yield reproducible results, and it can retrospectively predict in-vivo drug response. Preliminary data on a few cell lines suggests that we can go down as low as 50 cells/well when we plate in a 384 well-plate and still obtain reproducible results. Furthermore, data on mouse mammary tumor samples (MMTV) for which we know which drugs worked and which drugs did not suggest RU-DBP can predict *in vivo* drug response. Taken together, this early data suggest RU-DBP may identify therapies for late-stage cancer patients.

## The Role of Long Noncoding RNA CEBPA-AS1 in Acute Myeloid Leukemia

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Acute Myeloid Leukemia (AML), the most common form of leukemia, accounts for ~32% of all adult cases. With a 5-year survivorship of only 27%, improvements in treatment are crucial. Recent technological developments have allowed investigation of roles that long non-coding RNAs (lncRNAs) play in various illnesses. One such lncRNA, CEBPA-AS1, appears to be enriched in AML patients. While CEBPA-AS1 is known to play functional roles in promoting gastric cancer, oral squamous cell carcinoma (OSCC), and liver cancer, little is known about its potential function in AML. Based on previous findings, I hypothesize that CEBPA-AS1 promotes cell growth and blocks differentiation in AML. Analysis of previous expression profile data confirmed CEBPA-AS1's upregulation in AML. To investigate whether this enrichment is indicative of a functional role, I've knocked down (KD) CEBPA-AS1, using antisense oligonucleotides, and plan to overexpress (OE) CEBPA-AS1, via cDNA transfection, in human leukemia cells. While CEBPA-AS1 KD decreased CEBPA mRNA expression in OSCC, it had no such influence in AML cells, though I plan to assess KD influence on CEBPA protein levels. Moving forward, KD is expected to increase proliferation, and decrease apoptosis and differentiation, while the opposite is expected for OE. Additionally, to determine a potential mechanism of CEBPA-AS1 in AML, I will assess whether CEBPA-AS1 depletion influences the genetic expression profiles of AML cells, as well as identify any RNA-protein interactions. Determining a functional role and mechanism of CEBPA-AS1 in AML could establish CEBPA-AS1 as a therapeutic target and may lead to improvements in AML treatment outcomes.

## Investigating the Effects of Probiotic Treatment on the Gut Microbiome in Preterm Infants Using Genome-Scale Metabolic Models

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Infants born prematurely have an abnormal set of birth conditions that lead to a sparse, low-diversity population of microbes initially colonizing their guts. Several studies have shown the ability of probiotic treatments to shift the preterm microbiome to resemble that of a healthy, term infant, however, the functional mechanisms that underlie probiotic's therapeutic effects remain unknown. To understand the role of probiotics in the maturation of the preterm gut microbiome, we aimed to use metagenomic data from a longitudinal study of preterm infant gut development to reconstruct genome-scale models (GEMs) of metabolism for each microbiome sample in the study (infants sampled from birth to three months). To simulate the probiotic treatment, we also reconstructed GEMs for all species that made up the multi-strain probiotic used in the study. We then integrated GEMs of species present in each sample into a community model representative of the fecal microbiota in that sample and ran simulations to predict community metabolic behavior in the presence and absence of the probiotic treatment strains. Comparing the metabolite production between community models with and without the presence of the probiotic treatment over the sampling time allowed us to identify differentially produced metabolites of interest and to trace back microbial species that are responsible for the production of these metabolites. Overall, our study is expected to provide unprecedented insight into species and metabolite-level mechanisms of how probiotic treatment accelerates the maturation of the preterm infant gut microbiome.

## Elucidating the Role of Ypl225w in the Folding of Elongation Factor 1A Protein

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Harvard Faculty of Arts and Sciences

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The elongation factor 1A protein (EF1A), which delivers tRNAs to the ribosome, is one of the most abundant proteins in the cell. Recent work in the Denic Lab demonstrated that overexpressing Zpr1, an EF1A chaperone, can reduce the strong heat shock response caused by the deletion of an uncharacterized gene, Ypl225w, in *Saccharomyces cerevisiae*. In order to determine its role, Ypl225w was deleted from a *S. cerevisiae* strain with fluorescently tagged translation elongation factor EF-1 alpha (Tef1). The Ypl225w cells resulted in Tef1 cytosolic aggregation, a phenotype that could not be rescued by overexpressing Zpr1 on a 2-micron plasmid. This supports the hypothesis that Ypl225w is a chaperone involved in the folding of EF1A, operating on a domain distinct from that of Zpr1. Because AlphaFold modeling predicted the physical interaction of Ypl225w with the EF1A G-domain, a plasmid encoding a fluorescently tagged Tef1 G-domain protein was transformed into strains with and without Ypl225w. Tef1 G-domain protein aggregation occurred only in Ypl225w cells, indicating G-domain specificity. To allow for the identification of key residues, point mutations of Ypl225w were designed to inhibit its predicted interaction with EF1A. Additionally, since Ypl225w has been demonstrated to physically interact with the heat shock protein 90 (HSP90) chaperoning system, this plausible connection was investigated, with evidence suggesting that Ypl225w operates via a mechanism independent of the Hsp90 system. Together, these experiments provide evidence supporting the working hypothesis that Ypl225w acts as a chaperone to enable the proper folding of EF1A by stabilizing its G-domain.

## Overcoming Proliferative Vitreoretinopathy Treatment Limitations through the Drug Repurposing of Netarsudil

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Proliferative vitreoretinopathy (PVR) is an ocular disease that commonly develops post-retinal detachment repair surgery or eyeball trauma through the formation of a contractile fibrous membrane during the healing process. Formation of this membrane is characterized by accumulation of the extracellular matrix (ECM), whose mechanics and composition are regulated by epithelial-mesenchymal transition (EMT). During organ fibrosis, EMT often responds to continuous inflammation and leads to organ destruction. This study explores the drug repositioning of netarsudil, an FDA-approved rho-kinase inhibiting drug that reduces glaucoma through EMT inhibition, to treat PVR. We used single-cell RNA-sequencing techniques to analyze retinal samples from PVR patients and identify differentially expressed genes correlated with ECM development, encouraging further experimentation with netarsudil. We tested 7 different concentrations of netarsudil treatment on primary human culture PVR15 cells. After observing toxicity-induced deaths and phenotypical changes among the concentrations, we chose 1.0 micromolar as the optimal netarsudil concentration for experimentation. Western Blot analysis of PVR15 cells after 2 hours of treatment with 1 $\mu$ M netarsudil showed a decreased expression of EMT marker proteins like Cyclin D1 and alpha-smooth muscle actin, signifying a correlation with slowed epithelial-mesenchymal transition. Further analysis will be performed to confirm and explore these results. These results suggest that netarsudil may be an effective drug for preventing and treating PVR development.

## Homology-Directed Repair (HDR) Gene Therapy Advancements

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### Lauren Hill

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia that has fatal consequences that is linked to mutations in the ryanodine receptor (RYR2). In response to both physical and emotional stress, the arrhythmias occur when Ca<sup>2+</sup>-calmodulin-dependent protein kinase II (CaMKII) phosphorylates serine 2814 on RYR2. Research has shown that using an adeno-associated viral vector (AAV) to express a CaMKII inhibitory peptide (AIP) downstream of a cardiomyocyte selective promoter is effective for disrupting the CPVT phenotype in mice models. We aim to develop a more clinically relevant AAV approach by integrating the therapeutic into cardiac loci using homology-directed repair (HDR). We will determine whether strandedness of the AAV influences the rate of successful repair by HDR through delivering identical repair templates using single stranded AAV and double stranded scAAV vectors. Repair templates contain homology arms at the Myh6 locus and an mScarlet transgene to label successfully repaired cardiomyocytes. These experiments depend upon a Cre-inducible Cas9 expressing mouse model. To make HDR repair more clinically relevant, we will test a protein, Cas12f, that fits within the limit of AAV (~5kb), allowing for the creation of a complete therapeutic vector. Using the optimized HDR approach, we will permanently encode AIP in the genome of a CPVT mouse model and test its therapeutic efficiency. Determining whether single or double stranded AAV is more efficient for homology directed repair integration and combining this result with the use of the Cas12 enzyme will create a more clinically relevant CPVT therapy approach.

## Investigating the Epigenetic Activity of DNMT3A

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### Derek Hwang

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DNA methylation is an integral process in the human body that controls gene regulation. Methyl groups are attached to DNA by a protein named DNA methyltransferase 3 alpha, also known as DNMT3A. This epigenetic modifier operates by methylating cytosines in CpG islands—highly cytosine- and guanine-enriched areas of the genome—and is regulated by its three distinct domains: the PWWP domain, the ADD domain, and the MTase domain. Deactivating malfunctions of DNMT3A can lead to developmental issues such as cancer and are specifically commonly observed in cases of acute myeloid leukemia and other hematological diseases. Previously, our lab has used a base editor screen to study the structure and functionality of the domains of the protein. The results of the screen identified several activating mutations, including D781Y, D604-K607del, and C541Y. Here, by cloning, expressing, and purifying these mutations, we identify the mechanisms by which these mutations cause gain-of-function. We then measure the enzyme activity and thermal stability of these mutants to investigate the functionality of these mutations. Additionally, we also cloned truncated versions of these mutants—with the PWWP domain removed—to investigate how domain-domain interactions affect the activity of the protein. Furthermore, we measure enzyme activity of these truncated mutations before and after reintroducing the PWWP domain to study the PWWP's inter-domain role and its effect on the whole protein. This study will give us a clearer picture of the mechanism by which DNMT3A operates.

## Determining the Ability of EKylated ELPs to Prevent Protein Corona Formation

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Elastin-like polypeptides (ELPs) are engineered derivatives of the human protein tropoelastin whose thermally responsive self-assembly and biocompatibility have made them appealing candidates for nanoparticle (NP)-based delivery systems. The promising *in vitro* delivery efficacy of these ELP NPs has largely not been reproducible *in vivo*, likely in part due to protein adsorption onto the NP surface in physiological fluids. Zwitterionic peptides contain a series of paired cationic and anionic residues, inducing the formation of a well-hydrated, compact surface that prevents protein adsorption via steric hindrance. To test whether the addition of zwitterionic peptides could improve ELP NP resistance to protein fouling, I recombinantly expressed three ELP-based RNA delivery constructs containing varying glutamate-lysine repeats (EKylation) in a novel zwitterionic block. For further characterization, I will employ dynamic light scattering (DLS) to determine the size and polydispersity index of the NPs as well as their surface charge by measuring zeta potential. Comparisons of the novel EKylated ELP NPs to current constructs after incubation in serum-containing buffer will help elucidate how effectively each construct is preventing corona formation. Finally, I will measure the siRNA encapsulation efficiency of the EKylated ELP NPs using RiboGreen fluorescence and gel shift assays. I anticipate that the EKylation of these ELP NPs should improve their stability in serum for better biodistribution of the therapeutic nucleic acid cargo *in vivo*.

## Investigating the Presence of LINE-1 Insertions in the Human Heart Genome via HAT-Seq

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Transposable elements (TEs) comprise nearly half of the human genome, and their mobilization is a significant source of genomic variation and human diseases. The long interspersed nuclear element-1 (LINE-1 or L1) is the only actively reproducing retrotransposon in the human genome. L1 retrotransposition has also been associated with increased inflammation. However, the presence, frequency, and effects of these insertions in the heart has not been investigated. The goal of my research is to investigate the difference in LINE-1 insertion frequency and location in single human cardiomyocytes based on age and cardiovascular disease. The lab has previously established the method for evaluation of Human Active Transposons (HATs) in single cell cardiomyocytes and the method includes isolating these cells from fresh frozen heart tissue using fluorescence activated nuclei sorting (FANS), amplifying the LINE-1 sequence using targeted polymerase chain reactions (PCRs), sequencing the samples, and performing a genomic analysis. I have performed single cell whole genome amplification from isolated single cardiomyocytes of young, aged and diseased heart muscle. I plan to utilize the HAT-seq method to evaluate the presence or absence of repetitive L1 regions in the cardiomyocyte genome. Previous data from the lab suggests that there is an increase in LINE-1 insertion frequency with age, a trend which we hypothesize will continue with samples from patients with cardiovascular disease. This research will help the field better understand the importance of L1 retrotransposons in heart disease.

# Designing and Optimizing a Dual-Targeting CAR T-Cell Therapy for Multiple Myeloma

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Multiple Myeloma (MM) is an aggressive hematologic malignancy of plasma cells; uncontrolled growth of these cancerous cells and the clonal antibodies they produce can cause low blood counts, kidney damage, increased risk of infection, and bone (painful lytic lesions, fractures) and calcium problems. Increasing understanding of the biology of the disease has led to better treatment options in the form of immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies. However, over the last decade, immunotherapy, particularly the advancements made in the field of CAR-T cell therapy, has revolutionized the management of multiple myeloma. Chimeric Antigen Receptor (CAR) T-cell therapy is a novel treatment approach for cancers that uses the body's immune system to target and kill cancer cells. The FDA approved BCMA targeted CAR T-cell therapies demonstrate remarkable response rates in MM patients. But despite the success of the mono-targeted approaches, relapse driven by antigen low/negative cells is still predicted in these patients. We hypothesize that developing a CAR-T cell therapy targeting two different antigens for MM, expressed on both differentiated and less differentiated B cells respectively, would help overcome this problem. Additionally, we would develop high throughput functional screening assays to identify the most optimal dual-targeted CAR-T therapy for future clinical translation.

# Perception of Nutrient Cues in the TOR Signalling Pathway in *Saccharomyces cerevisiae*

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**Izavel Lee**

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Natural Sciences, 2023

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The Target of Rapamycin (TOR) signaling pathway is a highly-conserved eukaryotic pathway critical to growth regulation. In *Saccharomyces cerevisiae*, TOR Complex 1 (TORC1) regulates growth rates in response to various nutrient cues. However, it is unclear whether different modes of nutrient sensing are involved in signaling to TORC1. In this study, we investigate whether the leucine sensor, leucine aminoacyl-synthetase (LeuRS), and the glutamine sensor, Pib2, modulate their signaling output to TORC1 in response to changes in amino acid concentration (concentration sensing) or flux (flux sensing). To differentiate between these sensing modes, knockout yeast strains for each gene were constructed, and the activity of each gene will be varied either by titrating the level of expression or introducing deactivating mutations into the LeuRS editing domain. The effect on TORC1 activation and growth rates in yeast was then measured. Theoretical modeling work suggests that for a flux sensor, TORC1 activation should be independent of sensor concentration, while for a concentration sensor, TORC1 activation should be dependent on sensor concentration. The use of different sensing modes may thus allow cells to integrate different kinds of information about their environment. As nutrient-responsive pathways are generally conserved, insights from *S. cerevisiae* may have wider applications to higher eukaryotes.

## Mechanisms of Clonal Evolution in High-Grade Serous Ovarian Cancer

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Cancer cells are inherently genetically and epigenetically heterogeneous and unstable, which facilitates selection of resistant subclones during therapy, leading to evolution of population-level resistance. In high-grade serous ovarian cancer (HG-SOC), about half are homologous recombination deficient (HRD) and maintenance or restoration of HR proficiency (HRP) is an important mechanism of therapy resistance. HR uses the sister chromatid as a template for comparatively error-free repair of DNA double-stranded breaks (DSB). HR status correlates with prognosis. HRD tumors are more sensitive than HRP tumors to DSBs induced by carboplatin chemotherapy. To better understand how mechanisms of clonal evolution interact with HR status, we treated HGSOc cell lines PEA1 and JHOS2, which harbor mutations in HR pathway genes BARD1 and BRCA1, respectively, with standard-of-care combination carboplatin-paclitaxel and used genetic barcoding to track genetic, epigenetic, and transcriptomic changes across clones during treatment. To quantify HR proficiency, PEA1 and JHOS2 are nucleofected with a guide RNA targeting the ACTB locus, a CRISPR/Cas9 expression vector and an HR donor plasmid with regions homologous to ACTB flanking a short exogenous DNA sequence from GFP. Repair of Cas9-induced DSBs via donor plasmid-mediated HR results in insertion of a GFP sequence measurable by quantitative PCR (qPCR). PEA1 and JHOS2 HR status will be compared to 293t cells (no HR pathway mutations) and to parental PEA1 and JHOS2 after short hairpin RNA (shRNA) knockdown of BRCA1/2. Subsequent experiments will quantify HR status of subclones pre- and post-treatment to examine mechanisms of clonal evolution in response to standard-of-care chemotherapy.

## Identifying the Genetic Basis for the Meiotic Phenotype of Y55 *S. cerevisiae* in the Absence of the Clb4 Cyclin

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Faults in meiosis can result in miscarriages and various human genetic disorders, such as Down Syndrome. However, gaps exist in our understanding of the mechanisms that guard against errors in chromosome segregation. Typically, when diploid *S. cerevisiae* undergo meiosis, they form asci with four haploid spores, but the effect of the *clb4* $\Delta$  mutation differs between two strains, Y55 and W303: *clb4* $\Delta$  Y55 cells form asci with two diploid spores (dyads) while *clb4* $\Delta$  W303 cells form asci with four haploid spores (tetrads). Prior experiments have indicated seven regions in the genome which may contain genes responsible for the phenotypic differences between Y55 and W303. To test this, I have marked these regions with selectable markers and crossed *clb4* $\Delta$  Y55 haploids with the marker with *clb4* $\Delta$  W303 haploids to form hybrids. I will then isolate haploids and back-cross them with *clb4* $\Delta$  Y55 cells, sporulate them, and quantify their frequency of dyad asci. The results from my experiments will help identify the loci responsible for the meiotic phenotype of *clb4* $\Delta$  Y55 cells and greatly narrow down the number of genes that may have a causal impact on the phenotype. Through identifying genes that allow *S. cerevisiae* cells to delay meiosis after detecting the presence of chromosomes that are incorrectly aligned by the chromosome segregation machinery, along with examining the presence and absence of these genes across fungal evolution, we can better understand the evolution of the mechanisms that use recombination to direct chromosome segregation in meiosis.

## Assessment of Possible Concerted Chromosome Loss in Yeast Cells

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Maintaining the appropriate amount of DNA is often considered essential to life. Paradoxically, cancer cells and fungal pathogens that are resistant to treatment display aneuploidy (abnormal chromosome content), and they also often show meiotic gene expression. Our work compares the pattern of chromosome loss in mitotically dividing yeast cells with and without overexpression of meiotic genes. We hypothesized that there is a molecular mechanism leading to concerted chromosome loss in the cells that inappropriately express meiotic genes. If chromosomes are lost independently, the loss rate should decrease exponentially as more chromosomes are lost; in a concerted mechanism, the rates should decrease much more slowly with the number of lost chromosomes. To distinguish between these two possibilities, we overexpressed meiotic genes from a galactose-induced promoter and assayed the rate of chromosome loss using heterozygous markers in a system developed previously in the lab. In addition, we used flow cytometry to quantify cellular DNA content after inducing meiotic gene expression. So far, results suggest that while certain meiotic genes significantly increase overall chromosome loss rates (especially NDT80), chromosome loss appears to act in a concerted way even in the absence of meiotic gene overexpression. This is a phenomenon that hasn't been analyzed in detail before, and further experiments will investigate the mechanism behind it. Understanding this process is relevant to both our current knowledge of cell division processes and human disease, and may provide us with target genes to treat resistant cancers and fungal infections.

## Construction of a *Salmonella*-Lux Strain for Use in Zebrafish Models

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Our lab is studying the role of the kynurenine pathway in host-pathogen interactions via intravascular *Salmonella* infection of zebrafish larvae. Zebrafish infected with *Salmonella* Typhimurium can be rescued through administration of 3-hydroxykynurenine (3-HK), a metabolite in the kynurenine pathway of tryptophan degradation which our lab has found to be important to the host immune response. The aim of this project was to engineer a *Salmonella* Typhimurium strain containing the luciferase (Lux) operon, which would allow bacterial load measurement by correlation to light production. This was achieved through Gibson assemblies designed to insert the Lux operon into a TOPO vector plasmid, flanked by sequences known as intervening sequences (IVS). IVSs are found within the region of the bacterial genome encoding for ribosomes (specifically, regions of ribosomal RNA that produce hairpins and get cleaved off after transcription), and since such regions are strongly upregulated, this would allow for incorporation of the Lux operon into the bacterial genome via homologous recombination and ensure high expression of luciferase. We are currently in the process of troubleshooting Gibson assembly of the construct and sequencing recently assembled plasmids.

## Zooarchaeology of the Indus Valley: New Approaches to ZooMS Protocols for Degraded Faunal Material

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Zooarchaeology by Mass Spectrometry (ZooMS) is a proteomic method that allows for the taxonomic identification of collagenous tissue remains (e.g. bone, skin, scales, etc...) using collagen type I. There are a few different variations of collagen extraction for ZooMS, some of which are better suited to use on heavily degraded archaeological samples. However, there has been little research regarding variations in the purification step of ZooMS, which uses a ZipTip (pipette tip with C18 resin meant for concentrating and/or purification of proteins before mass spectrometry analysis). In this research project, archaeological samples which are at different levels of degradation along with variations of the purification protocol will be analyzed. It is known that taxonomic identification of poorly preserved bones is often difficult to due low collagen content and quality. For this reason, we selected animal bones from Harappa, Mehrgarh, and Nausharo- Indus Civilization sites from 7000-1500 BCE. These bones range in quality from medium to poorly preserved and no biochemical taxonomic identification has been performed on them. For comparison we selected bones from the well-preserved site of Tepe Yahya (Iran) and modern reference bones from the Zooarchaeology Lab in the Anthropology Department. Preliminary ZooMS data has shown that many of the selected bone samples contain some collagen available for analysis. After conducting the method tests on the bones with collagen content, we will be able to compare the resulting spectra for each sample and determine which methods gave better or comparable spectra. Additionally, we will also be able to provide more accurate taxonomic identifications of the never-analyzed bone samples from these sites.

## Elucidating the Biogenesis of Beta-Barrel Proteins in the Outer Membrane of Gram-Negative Bacteria

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The issue of antibiotic resistance is an important public health issue that can lead to high medical costs and increased mortality rates. Many pathogens, including the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*) pathogens, the leading cause of nosocomial infections throughout the world, are multidrug resistant. One approach to tackle this issue is to develop new drugs that target bacterial structures. In addition to the cytoplasmic membrane, the cell envelope of the Gram-negative bacteria contains a thin layer of peptidoglycan and an outer membrane. The outer membrane is impermeable to several clinical antibiotics, which complicates the treatment of infections. Therefore, the machines that make the outer membrane of Gram-negative bacteria are important targets for drug development. Several protein complexes are involved in the biogenesis of the outer membrane in Gram-negative bacteria. The goal of our research is to understand the mechanism through which the BAM complex folds  $\beta$ -barrels and inserts them into the outer membrane. An essential substrate of the BAM complex is LptD, an outer membrane protein that transports lipopolysaccharide to the outer leaflet of the outer membrane. To study the folding of LptD, we are mapping the interactions between LptD and the BAM complex by using *in vivo* cysteine-cysteine cross linking, with a primary focus on the interactions between the extracellular loops of LptD and the interior region of Bam A. By understanding how these two proteins interact during folding, we hope to elucidate mechanistic details of bacterial  $\beta$ -barrel biogenesis and contribute to the development of mechanism-based inhibitors that target this process.

## Cell Cycle Synchronization in *Mycobacterium smegmatis*

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Harvard T. H. Chan School of Public Health

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Tuberculosis (TB) remains one of the world's leading causes of death from a single infectious agent. Over  $\frac{1}{4}$  of the world's population is thought to be latently infected with *Mycobacterium tuberculosis* (*Mtb*) and with an estimated 10 million new cases in 2020 (WHO TB report, 2021). Currently, TB treatment and prevention methods are limited by the emergence of antibiotic resistance and a vaccine ineffective in adults. Additionally, with a 24-hour doubling time, it can be difficult to work with *Mtb* in the laboratory, so my project uses *Mycobacterium smegmatis* (*M. smegmatis*), a non-pathogenic model organism of *Mtb*. Very little is known about the structure of mycobacteria chromatin; however, the folding of chromatin has important implications for accessibility of transcription machinery and subsequently gene expression. In this project, we attempted to study chromatin structure by first generating a strain of cell cycle synchronizable *M. smegmatis*. In bacteria, replication initiates at *OriC* with the help of DnaA. Comparing *M. smegmatis* DnaA mutants with wildtype variants through multiple assays can help us understand whether the cell cycle is aligned. In turn, the synchronizable strain would be used to generate a high-resolution heatmap using chromatin-conformation capture (Hi-C) whereby regions that are closer to one another can be hypothesized to interact more. This project will assist in understanding processes heavily connected to spatial organization such as chromosome segregation. In the future, this can hopefully be applied to creating novel approaches for treating, studying, and preventing tuberculosis.

## Understanding the Role of the Tumor Microenvironment in Classical Hodgkin Lymphoma

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Molecular and Cellular Biology, 2023

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Broad Institute of MIT and Harvard

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Classical Hodgkin Lymphoma (cHL) is defined by a tumor microenvironment enriched with immune cell populations. The contribution of these immune cells to cHL is not fully understood. Spatial transcriptomics (ST) allows for the quantification and mapping of gene expression within a tissue sample. ST can be used to identify the localization of cell populations within a tissue and to infer cell-to-cell interactions. We carried out a computational analysis of spatial transcriptomic data of lymph node tissue resected from cHL patients to determine whether the immune infiltrate of cHL is enriched for certain immune cell types, as well as to detect whether higher RNA-capture ST technologies such as Visium would identify gene expression programs not captured by lower RNA-capture ST technologies such as SlideSeq. Analysis using guided cell type identification and differential gene expression testing with pilot data generated from two patients revealed that macrophages and CD4+ T cells are enriched in the lymph node proximal to Hodgkin and Reed-Sternberg (HRS) cells. In addition, we found that higher cellular resolution, as opposed to higher RNA capture, increases the strength of detection of unique gene expression programs. Our finding that certain immune cell types are enriched proximal to HRS cells suggests that cHL remodels the lymph node during tumor growth. Ongoing work will help clarify whether this remodeling serves to promote tumor survival through enhanced pro-survival signaling from macrophages and CD4+ T cells or to strengthen the tumor's evasion from immune-dependent killing by cytotoxic T cells.

## Characterizing the Role of eIF3 in Promoting Chemoresistance in Cancer Cells

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Chemoresistance occurs in cancer cells when they do not react to chemotherapy drugs and remain persistent, which leads to the recurrence of cancer. Research has shown that RNA chemical modification plays a role in promoting chemoresistance in cancer cells. Eukaryotic translation initiation factor 3a (eIF3a) is a protein that has been found to be a proto-oncogene involved with cancer occurrence and growth. It is involved in initiating non-traditional translation – under cellular stress, such as cancer, eIF3a binds mRNAs with 5' UTR m6A modification to mediate their translation. METTL3 is a subunit of the m6A methyl transferase complex responsible for adding m6A RNA modifications and is upregulated in chemoresistant cells. Our project tests the mechanism of eIF3a in promoting chemoresistance and determines whether eIF3a regulates METTL3 in chemoresistant cells. MCF7 breast cancer cells were grown and treated with the chemotherapy, doxorubicin. The cells were crosslinked and immunoprecipitation was performed by incubating protein extracts from these cells with antibodies against eIF3a followed by precipitation over protein G agarose beads. The immunoprecipitates underwent RNA analysis by qPCR to test for the presence of associated RNAs. The qPCR showed that METTL3 came down with eIF3a, showing that eIF3a is associated with METTL3 and that it may regulate METTL3 in chemoresistant cells. Further research is required to investigate whether other subunits of the eIF3 family, such as eIF3e and eIF3g, also regulate METTL3. Understanding the role of eIF3 in regulating METTL3 will reveal insights and new therapeutic strategies for chemoresistance.

## Analysis of CD8+ T Cells in the Blood of Accepted vs Rejected Transplants

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Current treatments for organ transplants involve a universal suppression of the immune system that leaves recipients vulnerable to infections. A better understanding of the mechanisms and signs associated with acceptance and rejection of an organ transplant could avoid this issue. Using a transplant mouse model with a DBA strain donor and B6 strain recipient, I analysed the CD8 T cells in the blood of mice receiving accepted kidney transplants and rejected heart transplants to determine the levels of different T Cell markers present at different time points post-transplant. The markers included Eomes and PD-1, which are exhaustion markers, and FoxP3, CD122, and FGL2, which are associated with the regulatory phenotype. So far, the analysis has revealed that there are much lower levels of activated, cytotoxic CD8 cells in the blood of kidney transplanted mice than in heart transplanted mice. The circulating CD8 T cells showed an increase in PD-1 and CD122 expression over time in kidney transplant recipients, while the opposite is true in heart transplant recipients. Further experimentation is necessary but these results suggest that it's possible that cytotoxic CD8 cells are migrating into the kidney and being turned off. Identifying the mechanism by which the kidney does this could help facilitate the development of therapeutics that will increase organ transplant survival in future patients. Monitoring the levels of different markers expressed in the blood could also be a potential method of screening for rejection, instead of performing a more invasive biopsy on the organ.

## Understanding DNA Binding and Gene Regulatory Differences between Transcription Factor Isoforms in Breast Cancer

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Transcription factors (TFs) are molecules that regulate the expression of genes in a cell, either by activation or repression. Alternative splicing of these TFs generates isoforms, which can have different binding properties and functions in cells. Splicing is particularly dysregulated in cancer, resulting in many cancer-specific TF isoforms that play distinct roles. HES4 is a TF that shows significant isoform expression differences in breast cancer tumors compared to normal controls. In order to characterize its role in breast cancer, we sought to perform isoform-specific knockdown of HES4 isoforms in breast cancer cell lines. I used reverse transcription-quantitative PCR (RT-qPCR) to quantify the expression levels of HES4 isoforms in MCF7 breast cancer cells and HEK293T human embryonic kidney cells. We will employ the RNA-targeting CRISPR system Cas13d to do isoform-specific knockdowns, but single guide RNAs (sgRNAs) first need to be prepared. To this end, I cloned sgRNAs designed for HES4 knockdowns. Our immediate next steps are to use these sgRNAs to perform knockdowns in MCF7 and HEK293T cells and assay the effect of knockdown on cell growth and gene regulation. In parallel, we are developing computational approaches to understand the *in vitro* DNA-binding preferences of TF isoforms. This involves updating and improving old analysis pipelines, such as the universal protein binding microarray (*upbm*) pipeline and the seed-and-wobble pipeline. Uncovering the mechanisms by which TF isoforms, such as the HES4 isoforms, control specific pathways can help us identify the drivers of many human diseases, including various types of cancers.

## Examining the Relationship of Stress-Related Affect Reactivity and Salivary Cytokine Il-6 in Relation to Depression

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The recent unfolding of the COVID-19 pandemic presented significant challenges regarding the population's physical and mental health. Given emerging anxiety, stress, and depression in the global population, the health care system is and will be in urgent need of support in the prevention and monitoring efforts aimed at mediating mental health impacts the pandemic has created. Using participants enrolled in cognitive-based group therapy, mindfulness-based group therapy, or monitoring alone at our center, this sub-study explores both biological and psychological methods of stress-related depression prevention. We aim to investigate the relationship of stress-related affect reactivity and inflammation in relation to depression. Collecting daily diaries from participants allowed us a method of measuring affect reactivity—the change in levels of affect on days when stressors occurred, compared to one's typical affect on non-stressor days. Collecting salivary cytokine Interleukin-6 allowed us a noninvasive method of measuring biological indicators of inflammation/stress in study participants. In our exploratory analysis, we expect to see a positive correlation between Il-6 levels and both depression and affect reactivity. Lastly, COVID-19 stressors and daily stressful events are counted both individually and together: an exploratory aim is to look at the comparative impacts of COVID-19 stressors versus normal daily stressors. Furthering our understanding of both biological and psychological factors in relation to depression will be integral to the ongoing improvement of the public health sector.

## Using Adeno-Associated Viruses to Insert Protocadherin-15 as a Possible Treatment for Usher Syndrome

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Protocadherin-15(PCDH15), a protein found at the tip of hair cells predominantly in the eye and ear, has been identified as necessary for normal balance, hearing, and vision. Those without PCDH15 have been found to be born congenitally deaf with issues in balance and later in life lose their vision, leading to a condition known as Usher Syndrome. Usher Syndrome affects nearly 25,000 people in the United States and currently has no treatment. However, it was found that when PCDH15 was split in half and injected by two separate viruses into mice with Usher Syndrome, the two halves of PCDH15 were able to recombine within the inner ear of the mouse and form a functional protein using homologous chromosomes. This technique of splitting the PCDH15 was necessary since the protein could not be inserted whole due to its large size, however, since the virus contained regions to promote recombination the two halves of the protein were able to join together in the ear. After using immunocytochemistry and scanning electron microscopy, results indicated that this method of inserting PCDH15 using Adeno-associated viruses was successful in both the expression of PCDH15 in the cell and the prevention of hair cell degeneration over time, indicating that the delivery can be useful in both regeneration and prevention of further deficit of PCDH15.

## Characterizing the Therapeutic Efficiency of Anti-CD47 Nanobody against Glioblastoma

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Medicine, 2024

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The role of the tumor microenvironment in cancer development is being increasingly recognized. CD47 is an immunoglobulin overexpressed in several types of cancer cells, which forms a complex with signal regulatory protein- $\alpha$  (SIRP $\alpha$ ), a receptor expressed on myeloid cells like macrophages. The CD47-SIRP $\alpha$  interaction prevents macrophage phagocytosis of tumor cells. Clinical trials blocking this myeloid checkpoint with monoclonal antibodies have shown efficacy in liquid tumors while solid tumors remain elusive to monotherapies. In addition, the high expression of CD47 on red blood cells and platelets can result in thrombocytopenia and anemia. Therefore, we developed a mouse anti-CD47 nanobody, which is more stable and less immunogenic than an antibody. To avoid systemic toxicities, we utilized mesenchymal stem cells (MSCs), which can naturally home to tumors, as carriers to produce and locally deliver the nanobody. Our project aims to characterize its efficacy in blocking the CD47-SIRP $\alpha$  interaction and the increased phagocytosis as a result. We initially cloned and transformed the nanobody producing plasmid into bacteria and MSCs. *In vitro* characterization of the nanobody's binding and blocking efficiency was performed using ELISA, and its ability to induce phagocytosis through flow cytometry. Following this, *in vivo* studies will be conducted on mice resected glioblastoma models. Since previous studies have shown that targeting CD47 itself without engaging the Fc receptors on macrophages is ineffective, we plan to combine this treatment with opsonizing antibodies specific to tumor-associated antigens. If therapeutic benefit is observed, this can be used to facilitate the development of more effective combination therapies.

## Membrane Proteins Affecting Tension Propagation

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Membrane tension is widely thought to be an important pathway that cells use to regulate their processes. Currently, there are large discrepancies in literature reports between how fast a cell membrane can mechanically relax after a perturbation. This project aims to determine why there are such large differences in observed timescales, as we hypothesize differing amounts of mobile and immobile proteins play a large role in determining these timescales. Using a photoactivatable fluorescent cross-linker, we will specifically target proteins on the membrane. The photoactivity of the compound allows us to measure the amount of immobile proteins in a sub-cellular region, as the mobile proteins will diffuse away. We will then induce a perturbation to the cell membrane, measure how it decays across the cell, and investigate how this depends on the immobile proteins. To approach this goal, we will work to calibrate a genetically encoded fluorescent membrane tension sensor. This sensor will be expressed in the cells of interest, and as the tension of the cell membrane changes, the fluorescence level of the sensor will also change. This will allow us to image changes in membrane tension in real time.

## Characterizing Cell Death of Embryos from Vitellogenin-Deficient *Anopheles gambiae* Mosquitoes

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*Anopheles gambiae* mosquitoes, as vectors of malaria-causing *Plasmodium falciparum*, have been targets of insecticides. However, rising insecticide resistance necessitates alternative strategies. Previous research found that depletion of vitellogenin (Vg), a yolk precursor protein, in *An. gambiae* females caused complete infertility. Vg is the amino acid source for the developing embryo, and vitellogenin-deficient eggs failed to melanize, decomposing instead of hatching. In this study, female *An. gambiae* were injected with dsRNA to knock down vitellogenin, and the embryos from these mosquitoes were compared to those of control mosquitoes. Western Blot analysis confirmed successful Vg-knockdown and showed that in control embryos, Vg is partially degraded within the first 5 hours of laying. DAPI staining of embryos, a nuclear stain, showed that development was halted before the syncytial blastoderm stage, which occurs at 4.5 hours post-oviposition. Blebbing of the nuclei, characteristic of apoptotic cells, was present in Vg-knockdown embryos. Samples were submitted for metabolomic and lipidomic analysis to further investigate the processes aberrant in Vg-deficient embryo development. We hypothesize that embryo development halts at an early stage prior to 4.5 hours post-laying because Vg-depleted eggs lack sufficient amino acid resources for development. Gaining a comprehensive understanding of the mechanisms contributing to infertility could aid vector control strategy development. Inducing infertility would effectively reduce the vectorial capacity of *A. gambiae* to spread malaria by lowering their vector density.

## CRISPR-Cas9 Mediated Mutation of the *rosy* Gene in *Oncopeltus fasciatus*

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**Ashley Watts**

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Integrative Biology, 2023

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Harvard Faculty of Arts and Sciences

Advisor: Cassandra Extavour

Supervisor: Jonchee Kao

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The large milkweed bug, *Oncopeltus fasciatus*, is an emerging model organism for the study of insect development. The development of genetic manipulation tools such as CRISPR-Cas9 will make it an even better model. So far, CRISPR-Cas9 has been used to mutate the *Of-white* gene, which resulted in mosaic pigment loss across the whole body. However, this mutation was homozygous lethal and a stable line could not be established. The goal of my project is to use CRISPR-Cas9 to knock out the pigment gene *rosy* to generate a pigmentless line of *O. fasciatus* useful for future study. The *O. fasciatus* genome has two homologs of this gene, *rosy* and *rosy2*. I designed gRNAs to target each gene, which I cloned and synthesized via *in vitro* transcription. I then injected *O. fasciatus* embryos with Cas9 and gRNA for either one or both of the *rosy* genes. Preliminary results have not demonstrated loss of pigment in any group. However, it can not yet be assumed that *rosy* and *rosy2* are not responsible for pigmentation, as only 14 experimental embryos have hatched, representing less than 10% of those injected. In the future, I will perform RNAi experiments targeting *rosy* and *rosy2* in both embryos and adult females to confirm the role that these genes play in pigmentation. Additionally, I will test different gRNAs, as well as higher concentrations of Cas9 and gRNA.

## Characterizing Early-Onset Colorectal Cancer

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Dana-Farber Cancer Institute

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Supervisor: Jonathan Rennhack

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Colorectal cancer (CRC) is the third most deadly cancer in the United States. While overall CRC incidence and death rates have decreased, the incidence of early-onset (EO) CRC (CRC diagnosed in people under 50 years) has increased in the past few decades, with many people experiencing aggressive disease in their 20's. More research must be done to understand metastatic disease, especially in the EO population. To understand metastasis in an age-agnostic setting, previous Hahn lab data identified three genes differentially expressed in non-metastatic and metastatic patient tumors: SATB1, TCF7, and SIRPA. Further studies have shown the importance of a chemokine CCL2 in the liver microenvironment in regulating these genes to drive metastatic colonization. Cell-line data shows CCL2 is an upstream regulator of TCF7, which regulates SIRPA and subsequent metastasis. Completion of CCL2 treatment and quantitative reverse transcriptase PCR to measure TCF7 expression levels in patient-derived organoids will test the sufficiency of CCL2/CCR2 signaling to upregulate metastatic factors (TCF7) in a highly translational model. To understand the conservation of this signaling node in EO patients, we will use age-specific patient-derived organoids (two lines derived from patients <50 years and two from patients >50 years) to confirm the TCF7 signaling node or suggest different mechanisms of action that cause EO CRC to be more aggressive. The completion of such studies may inform future therapeutics or screening methods to improve patient prognosis through drugs that can target certain gene products in patients with aggressive CRC in an age-specific manner.

# Characterization of the Pyruvate Carboxylase-Directed $\beta$ -cell Protective Program

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The  $\beta$ -cells of the pancreatic islets play a critical role in maintaining glucose homeostasis through the secretion of insulin. Glucose-derived metabolic signals are not only required for insulin secretion but can also influence  $\beta$ -cell survival, proliferation and differentiation, ultimately determining the functional  $\beta$ -cell mass. When protective, glucose metabolism enhances  $\beta$ -cell proliferation and survival, but chronic exposure to supraphysiologic glucose concentrations as in the diabetic milieu and attendant oxidative stress is detrimental to the  $\beta$ -cell (glucotoxicity). Previous work from the Danial lab has found that protective glucose metabolism works through Pyruvate Carboxylase (PC) to protect  $\beta$ -cells from oxidative, nitrosative and inflammation stress. The protective aspects of this PC-driven pathway involve urea cycle activation and de novo glutathione (GSH) synthesis. We are further investigating the molecular metabolic events influenced by the PC-driven program that are required for protection from oxidative stressors and glucotoxicity. Our work in the Danial lab has helped identify the importance of de novo GSH synthesis in maintaining the viability of mouse pancreatic islets under inflammation stress and reducing the accumulation of reactive oxygen species (ROS) under these conditions. Continued investigation into this arm of the protective program will focus on determining the metabolic route by which glucose carbons contribute to de novo GSH synthesis. Preliminary data demonstrates that the other branch of the PC-directed pathway, which involves urea cycle activation, is also relevant for  $\beta$ -cell stress resistance through polyamine synthesis, since these polyamines regulate cell fate, survival, and proliferation.

### Abnormal Brain Development in Human Fetuses with niMSBBDs

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The relevance of the input from the periphery for fetal brain development is widely accepted. However, while decreased environmental stimuli leads to altered patterning of the cerebral cortex, it remains unknown whether and how proprioceptive stimuli, which arise within the body, affect fetal brain development. Impaired or altered proprioception is associated with several congenital conditions that fall into the category of non-syndromic isolated musculoskeletal structural body birth defects (niMSBBDs) that are associated with an increased risk of neurodevelopmental disabilities. Despite being among the leading causes of vulnerability to pediatric mortality, whether fetuses with these conditions have abnormal brain development remains a critical knowledge gap. We aimed to identify whether fetuses with niMSBBDs have altered brain development before birth. In-vivo fetal brain T2-weighted MRIs of 69 fetuses, consisting of 30 controls and 39 cases between 17-37 gestational weeks, were retrospectively collected, automatically reconstructed, and segmented using state-of-the-art MRI tools. Volumes of transient fetal compartments (ganglionic eminence, cortical plate, proliferative, subplate, and intermediate zones), lateral ventricles, and other brain regions (limbic, basal ganglia with the thalamus, cerebellum) were calculated. Relative hemispheric volumes were calculated, log-transformed, and used as a dependent variable in the linear mixed model. Compared to the controls and after correction for multiple comparisons, fetuses with niMSBBDs had significantly smaller intermediate zones ( $-51.2 \pm 7.5\%$  SE) and cerebellums ( $-47.4 \pm 8.0\%$  SE), structures known to play a major role in the transfer of proprioceptive input from the body.

### Deletion of the Glucocorticoid Receptor in GABAergic Neurons Modulates the Reproductive Axis in Female Mice

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Glucocorticoid (GC) secretion induced by stress negatively impacts reproductive processes by inhibition of gonadotrophin-releasing hormone (GnRH) and luteinizing hormone (LH) release. KNDy neurons, expressing kisspeptin, neurokinin B and dynorphin A, generate GnRH and LH pulses and play an important role in mediating the effects of stress on reproduction; however, the exact mechanisms are unknown. KNDy neurons are subject to regulation by neural networks, in which GABAergic neurons appear to play a determinant role. GABAergic neurons express glucocorticoid receptors (GR), leading us to hypothesize that stress, through action of GC on GR in GABAergic neurons, affects KNDy neuron activity to impact reproductive function. We generated mice with conditional deletion of GR in GABAergic neurons by crossing VgatCre with GRlox/lox mice to generate VgatCre:GRlox/lox (GABAGRKO). The pubertal phenotype and estrous cyclicity of GABAGRKO mice and their littermate controls were characterized. Pubertal timing was determined by vaginal opening (VO) and first estrus, and estrous cyclicity defined by vaginal cells. The absence of GR in GABAergic neurons results in earlier puberty onset but greater suppression of estrous cycles during restraint. These findings suggest a possible role of glucocorticoids acting on GR in GABAergic neurons upstream of KNDy neurons to modulate the reproductive axis.

## CCR2 in Retinal Vascularization

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Retinal vascular growth is an important step in our development. This process occurs at about thirty three weeks of gestation and ends at forty weeks, or just prior to birth. Issues during this process can lead to a variety of diseases, such as retinopathy of prematurity (ROP). As a result of underdeveloped vascular growth, the retina proceeds to overshoot and begin growing an abundance of blood vessels. This can result in retinal scarring and ultimately blindness. In this study, tests were conducted which looked into the chemokine system, specifically the CCR2 receptor and its ligands. In order to see the temporal and spatial effects of vascular growth in different environments, CCR2 knockout and wild type mice eyes were used at different days past birth. Their retinas were immunostained to show blood vessel growth pathways as well as to see where different cell types were located, such as astrocytes and microglia. These retinas were then observed and imaged under a fluorescent microscope and compared. The results showed that CCR2 may have an effect on retinal vascular development, as there was more stable growth shown in the fluorescent images with CCR2 wild type mice. With further analysis and more sample collection, a definitive link between CCR2 and vascular growth could be shown.

## The Influence of Hippocampal Suppression on Memory Consolidation

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Research shows that memories are stored in the brain via a process called reactivation, in which the patterns of neural activity that occurred during the initial encoding event are repeated. The hippocampus helps initiate reactivation; thus, if the hippocampus is suppressed, reactivation events should be less likely to occur, preventing memories from stabilizing. Hippocampal activity is affected in a graded manner by a working memory task called the N-Back Task: as task difficulty increases, cognitive load increases and hippocampal activity decreases. This study investigates whether using the N-Back Task to suppress hippocampal activity results in a graded reduction of memory according to task difficulty. Participants were shown pictures of objects displayed in different locations on a screen, then completed one of two versions of the N-Back Task. They were tested on their memory of the object-location pairs immediately after completing the N-Back Task and 24 hours later. A continuous rather than discrete measure of memory was used, allowing for identification of smaller differences in memory performances. We expect that participants who complete the harder N-Back Task will have worse memory of the object-location pairs. This would suggest that hippocampal suppression disrupts post-encoding reactivation in a graded manner according to the level of cognitive load, which would expand current understandings of memory consolidation and how it goes wrong. If our results are significant, we will repeat this study using fMRI to measure reactivation, tying the behavioral results of this study to neurological phenomena.

# Investigating the Temporal Relationship between Neural Activity and the Learned Motor Behaviors

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Acquisition and execution of learned motor behaviors is widely hypothesized to be sustained by the dorsolateral striatum (DLS), which is the input region of basal ganglia in the rodent. Prior work has shown that DLS activity is required for the execution of learned behaviors. One emerging hypothesis based on this data is that DLS drives the motor output. If this is true, we hypothesize that neural activity should predict the upcoming behavior after learning. However, the temporal relationship between striatal activity and the execution of learned novel behavior has not been examined. Thus, to test this hypothesis, we first recorded striatal activity while the animal learned a new motor sequence. We then built a statistical model that quantifies how behavioral kinematics influence neural activity. Thus far, the model was able to explain spiking variance for 79% of cells, consistent with prior studies. By shifting the spike train relative to behavioral kinematics and re-fitting the statistical model, we were able to identify whether neural activity for a given cell is most related to upcoming movements, or movements in the recent past. Overall, we found that most cells predict upcoming movements, consistent with our hypothesis. Further, we observed that within a motor sequence, cells that are predictive of behavior tend to spike towards the beginning of the behavior, while cells that reflect previous movement tend to spike at the end. These preliminary results offer a glimpse into potential learning mechanisms by which striatum allows to associate the behavior with the outcome.

# Investigating Long Non-Coding RNAs as Novel Therapeutic Targets for Alzheimer's Disease

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Despite the prevalence and burden of Alzheimer's disease (AD), there is a lack of effective treatments for this neurodegenerative disorder. Drug development conventionally focuses on disease-associated proteins, but RNA has shown great promise as new therapeutic targets. About 70% of the human genome encodes for non-coding RNAs (ncRNAs) that are not translated into proteins. ncRNAs play critical roles in modulating protein expression by gene regulation at the epigenetic, transcriptional, and posttranscriptional levels. ncRNA dysregulation, whether through underexpression, overexpression, or mutations, has been associated with neurological disorders. The largest and most diverse class of ncRNAs is long ncRNAs (lncRNAs), which are longer than 200 nucleotides. However, few studies have examined lncRNA dysregulation in AD. This project is among the first to investigate novel human and brain specific lncRNA dysregulation in AD. We identified lncRNA candidates dysregulated in the frontal cortex of AD patients from the Religious Orders Study (ROS) and Memory and Aging Project (MAP) longitudinal studies and validated the aberrant lncRNA levels in human AD cell models. The top candidates will be overexpressed via plasmid transfection or lentiviral constructs to determine their functions. Future research includes knockdown of lncRNA candidates with RNA interference, elucidation of the pathological mechanisms of these lncRNAs, and validation in iPSC human neurons and additional AD patient samples. Ultimately, this research will help expand the pool of biomarkers and therapeutic targets in AD, paving the way for new ncRNA technologies to treat brain disorders.

## Investigating the Role of the Corticospinal Tract on the Dexterity of Deer Mice

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In the last 10,000 years, prairie-dwelling mice colonized forested areas and developed skilled motor behaviors due to small neural circuitry changes. Specifically, forest-dwelling deer mice are better at climbing than prairie-dwelling deer mice. Previous experiments on primates revealed a correlation between dexterity and CST size, suggesting forest mice may have evolved these skilled behaviors by developing larger and more complex corticospinal tracts (CST), neuronal tracts that connect the motor cortex to the spinal cord. To test this hypothesis, the CST projections of two independently evolved pairs of forest and prairie-dwelling deer mice were compared. Additionally, the pairs were subjected to a pellet-reaching assay where they were tasked with reaching for a pellet through a thin slit as a marker of their dexterity. Forest mice were found to have a higher success rate on the pellet-reaching task and larger CST projections. These results suggest a positive correlation between CST size and dexterity and can potentially shed light on the evolution of neural circuits, specifically how they evolve in parallel.

## Investigating the Dynamics of Cell Proliferation and Cell Death of Dorsal Root Ganglia Cells during Nerve Regeneration

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Peripheral nerve injuries (PNI) occur in approximately 360,000 individuals annually in the United States. These injuries arise from traumatic events of automobile accidents, sports, and deliveries of babies. PNI ranges from overstretching the nerve to complete tearing. To complement studies examining the repair of PNIs in mammalian models, such as mice, we are exploring the capacity of axolotls, highly-regenerative salamanders, to successfully repair PNIs. We hypothesize that axolotls may also exhibit enhanced PNI repair in comparison to mammals, such as mice and humans, as they do with respect to other tissues, including full limbs. The limb is innervated with a bundle of brachial plexus nerves that provide sensation and motor function to the arm; thus, injury to brachial plexus nerves can result in lifelong impairments in humans. We have identified candidate genes that mediate successful PNS regeneration in axolotls with global gene expression analysis from regenerating nerve samples. We hypothesize that canonical cell-death pathways may be activated during—and may support—nerve regeneration. To explore this hypothesis, we are applying immunohistochemistry to regenerating PNS samples from axolotls.

# Developing a Genetic Approach to Characterize Ribosome-Associated Subcellular Translational Controls Involved in Neuronal Subtype-Specific Circuit Development

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Supervisor: Tien Tran

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Projection neurons (PN) extend long-range axonal connections to subtype-specific and distant targets, forming critical circuitry of the mammalian cerebral cortex. During development, growth cones (GCs) sense local cues and direct axonal pathfinding and synapse formation semi-autonomously. These processes are likely controlled at least partly by local subcellular translational regulation, and evidence suggests that translational control may be mediated by specialized protein compositions of GC ribosomes. Thus, we investigated whether ribosomes have distinct protein compositions in compartments of PN, employing ribosome immunoprecipitation in mice with HA-tagged ribosomal protein L22, and focusing on callosal PN. To extend this approach in GCs, I am investigating whether HA-tagged ribosomes are present in axons and GCs with immunocytochemistry (ICC) in primary CPN culture. Since ICC with only anti-HA resulted in poor signal-to-noise ratio in axons, we are developing a proximity-ligation assay (PLA), by which anti-HA is combined with antibodies against a ribosomal component to produce fluorescence when they are within 40 nm. We first tested the specificity of anti-HA, anti-RPL22, and anti-rRNA. The anti-HA western blot appropriately detected one band of expected size in RPL22-HA-expressing samples, and anti-rRNA ICC intensity is decreased upon treatment of RNA nucleases, consistent with their specificity. We next optimized for ICC anti-Tau (axon) and anti-MAP2 (somato-dendritic) antibodies as neuronal markers. Using these validated antibodies, we will perform PLA to investigate the potential presence of HA-tagged ribosomes in axons and GCs to elucidate subcellular translational controls over PN circuit development.

# Effect of Ketamine on Treatment-Resistant Bipolar Disorder using EEG

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Fear of Harm (FOH), a phenotype of Bipolar Disorder (BD) is a collection of behaviors including aggression, extreme anxiety, and parasomnias, which often receives little benefit from standard pharmacotherapy. Recently, clinical trials have shown ketamine's rapid antidepressant effect, particularly for the depression phase in treatment-resistant BD. Patients who have undergone the trials reported a substantial reduction in symptoms of FOH including mania, fear of harm, and aggression after ketamine intake. However, little evidence demonstrates the correspondence between behavioral effect and brain response to ketamine. Frequency domain analysis was conducted to assess the neuronal activity across all frequency bands using continuous electroencephalography of pre, during and post intranasal ketamine administration. Linear mixed model was fitted on spectral density of 33 electrodes of 8 patients. Ketamine was associated with a significant reduction in higher frequency band (low beta, high beta, and low gamma) spectral power in frontal or lateral temporal electrodes which likely corresponds to a reduction in regions involved in threat detection and response.

## Studying the Role of BRN2 in Stem Cell-Derived Post-Mitotic Neurons

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The development and maintenance of the human brain are tightly controlled by a series of gene regulations. One important regulatory component is BRN2, a neural transcription factor implicated in neurodevelopmental disorders. While BRN2 has been widely studied in the context of neurodevelopment, its role in the adult brain is not well understood. Data from our lab shows that BRN2 is clearly expressed in the adult brain in cortical post-mitotic neurons in both mice and humans and is a potential driver of a gene co-expression module that is upregulated in Alzheimer's disease, warranting investigation of its role in the adult brain. To characterize the role of BRN2 in post-mitotic neurons, human induced pluripotent stem cell (iPSC)-derived neurons were generated following disruption of *Brn2* via CRISPR-Cas9 mutagenesis. BRN2 mutant neurons were tested for aging-relevant phenotypes, such as accumulation of disease-associated amyloid-beta (A $\beta$ ) peptides and phosphorylation of tau. The results of this research could improve our understanding of the role of BRN2 in the adult brain and may provide insights into its contribution to age-related diseases of the brain.

## Olfactory Evidence Accumulation in Laboratory Mice

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In order to make decisions about new dangers, food availability, or mating, animals gather and integrate sensory information until a decision can be made to favor certain choices over others. This process, which is known as sensory evidence accumulation, has been extensively studied in laboratory animals using different behavioral paradigms based on the accumulation of visual or auditory evidence, to understand the process of decision-making. However, little is known about the behavioral and neurophysiological features of olfactory evidence accumulation. Studying evidence accumulation in specific regards to the olfactory system is important for improving our understanding of natural behaviors, in which animals are presented with a stimulus that varies in the identity and frequency of its components. In this study, my goal is to understand if mice are able to use olfactory evidence accumulation to distinguish between conditions in which the statistics of a given odor stimulus are variable while it is being presented on top of a background odor. First, I trained head-fixed mice to lick only after the end of a time window during which a monomolecular odor (5% ethyl valerate) was presented. Once the animals become proficient in this task (more than 80% of success in a session), I am planning to train them in a two-alternative forced choice paradigm in which they have to distinguish between trials that differ in the total number of odor pulses (utilizing an odor different from ethyl valerate) delivered on top of the ethyl valerate background odor pulse.

# The Role of Parent-Child Play Interactions in the Association Between Parental Mental Health and Early Childhood Social Cognition

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Parents experiencing depression – and similar issues of poor mental health – exhibit significantly higher levels of disengaged and negative parenting behaviors than non-depressed parents. Parenting techniques and the parent-child relationship influence the developing brain's structure and function; however, many of the underlying mechanisms remain unknown. The current study aims to elucidate the mechanisms determining deficits in children's social information processing due to compromised parent-child relationships. In this study, we used functional near-infrared spectroscopy (fNIRS) to assess neural responses to social and nonsocial stimuli in 2- and 5-year-old children living in a low-resource neighborhood in Dhaka, Bangladesh. Additionally, free-play and structured play sessions involving the parent and child were observed and coded for factors such as parental sensitivity and attentiveness. We evaluated the associations between neural social information processing, parent-child interactions, and markers of parental mental health and life stress assessed using the Childhood Psychosocial Adversity Scale (CPAS). Parent-child interactions might thus mediate the association between parental mental health and childhood social cognition deficits. The potential mediation effect of parent-child interactions suggests an opportunity for early intervention and parental education to mitigate the risks of childhood exposure to parental depression.

# Examining the Impact of Early Life Stress on Complex Social Behaviors in Translational Mouse Models

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Early life is a period of high sensitivity and plasticity where the brain undergoes dramatic changes that prime the organism for future stages of life. The scale of brain configuration that takes place during early life is unique to this period of development. With the importance of this stage in mind, much research has been dedicated to early life and the impacts that environmental inputs can have on later behavior. The most well-studied of these inputs—particularly as it pertains to humans—is stress. Currently, the field relies on observational studies done in human populations and translational studies using model animals. Translational studies in mice have demonstrated that animals can experience resilience or vulnerability later in life as a response to different early life stressors. However, this research has predominantly relied on methods inducing stress that require high levels of researcher interference. Additionally, the assays used to measure the impacts of early life stress in these studies are largely simplistic and limited in their ethological applications. This research seeks to investigate the question of ELS using mouse animal models and the recently developed Limited Bedding and Nesting (LBN) paradigm, which minimizes researcher interference. Moreover, this study assays complex mouse social behaviors such as mating, aggression, and parenting that have previously been absent from ELS studies. Using more ethologically valid paradigms and stress assays can provide a more comprehensive understanding of the impacts of ELS on behavior. Eventually, this may be used as a gateway to understanding the molecular impacts of ELS and translational applications for humans.

# Social Isolation in Mice Results in Sensory Hyperactivity, Anxiety-Like Behaviors, and Reduced Connections between Low-Threshold Mechanoreceptors and Inhibitory Spinal Cord Interneurons

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Although not yet well-characterized or understood, research has established a link between social isolation and negative effects on health. Our research seeks to understand chronic social isolation and tactile deprivation as conditions that lead to detrimental health problems. The activation of low-threshold mechanoreceptors (LTMRs) precede the perception of touch in mammals, the information of which is processed first in the spinal cord. Our research focuses on how chronic social isolation alters the anatomical and functional connections between subtypes of LTMRs and spinal cord interneurons, and how that affects animals' responses to gentle touch. In our experiments, we separated mice into either single-housed or group-housed conditions to create a model for social isolation and sensory deprivation. We found that single-housed mice displayed tactile overactivity and altered social and anxiety-like behaviors in behavioral assays. Histological analyses showed that LTMR connections with inhibitory spinal cord interneurons are reduced in single-housed mice. Our findings suggest a potential mechanism explaining how altered tactile experience during development leads to alterations in tactile perceptions and complex behaviors.

# CaMKII Promotes Retinal Ganglion Cell Survival but Suppresses Axon Regeneration under Pro-Regenerative Treatment

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Injury to the optic nerve often results in an irreversible loss of vision due to the inability of retinal ganglion cell (RGC) axons to regenerate. Critically, the degeneration of RGCs following axonal injury limits the regenerative capacity of the optic nerve even under pro-regenerative treatments. Prior research has demonstrated that overexpression of a constitutively active mutant of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) strongly improves the survival of RGCs following several types of insult in mice. Here, we further explore the role of CaMKII in axonal regeneration following optic nerve injury. We performed optic nerve crush following AAV2-mediated gene transfer of the CaMKII mutant into mouse retinas, in combination with intravitreal injection of previously characterized pro-regenerative treatments. We confirm the result that CaMKII improves RGC survival after crush and report that CaMKII alone does not induce regeneration after crush. We also find that CaMKII improves RGC survival following optic nerve injury when combined with 1) zymosan, 2) oncomodulin, SDF1, and CPT-cAMP, or 3) AAV2-CNTF. However, CaMKII overexpression greatly diminishes the regenerative effect of all three treatments after optic nerve injury. These results extend the current understanding of the neuroprotective effects of CaMKII while revealing a novel suppressive effect on regeneration. Further research will address the effect of CaMKII on other pro-regenerative treatments as well as the mechanisms by which CaMKII-mediated regeneration suppression takes place, providing the basis for further studies on methods to simultaneously support high levels of RGC survival and axon regeneration.

# Revealing Pathological Cortical Microcircuitry Using Laminar Electrode Recordings of Seizures

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Epilepsy is one of the most common neurological disorders, yet a thorough understanding of how seizures begin and how the brain's neuronal circuitry causes seizures to spread is lacking. This knowledge gap is largely due to a technological inability to record neuronal activity at certain scales of spatial resolution. While intracranial EEGs have become a key tool for identifying seizure onset zones in patients requiring surgical interventions, difficulty with isolating microcircuits (networks that facilitate layer-to-layer interaction) in the brain has persisted. We were able to record neuronal activity of the human cortex in unprecedented breadth and resolution using novel experimental laminar electrodes. With recording contacts distributed along the length of the electrode, all six layers of the human neocortex were simultaneously monitored during seizure activity with micron-scale resolution. This breakthrough approach enables a cohesive quantitative analysis of the local field potentials, current flows, and multi-unit activities in the cortex and particularly, through neuronal microcircuits. Our electrode recordings indicated that within the seizure onset zone, the electrical currents were flowing solely within the granular and infra-granular layers of the cortex. Outside of the seizure onset zone, ictal spikes detected showed current flow relegated to the supra-granular layers. Furthermore, our data revealed that electrical activity patterns evolved; current sinks and sources developed into the deeper layers of the cortex. Given these unprecedented results, we propose a model that describes the cortical dynamics of seizures following these recordings. With a new model of cortical microcircuitry, clinical interventions for epilepsy can be improved.

# HaloTag Hybrid Proteins for Multicolor Labeling of Synapses

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The comprehensive study of brain functions is limited by the scientific tools available to provide information about the location, strength, and time span of neural contacts. Techniques effective *in vivo* have to be created to enable the research of complex phenomena such as memory formation. The current study aims to build such a synaptic labeling method by introducing a protein tag, HaloTag (HT), in the DNA sequence of a presynaptic protein, such that they are expressed together. Two hybrid proteins, VGlut1-HT and Synapto-HT, have been created using molecular cloning methods, and inserted into a plasmid that can be used for lentiviral transduction of neurons. To test the constructs' ability to label synapses while not interfering with the brain's function, the proteins will be tested in cultured neurons. Further experiments *in vivo* are required to conclusively mark this new method as a safe and effective synaptic labeling technique.

# The Regulation of Sleep by Mating in *Drosophila melanogaster*

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Harvard Medical School  
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Despite sleep's vital, highly conserved, and extremely regular nature, sleep itself is incredibly flexible. While it is understood that many internal and external factors can regulate sleep, virtually no progress has been made in determining how these factors change the output of sleep circuitry to better align with the needs and circumstances of the animal. Studying this at a molecular, cellular, and circuit level first requires a paradigm where discrete changes in internal state yield strong and predictable changes in sleep. Towards this end, we report the novel finding that mating promotes sleep in female *Drosophila melanogaster*. We find that this effect is specific to females, near instantaneous, and lasts around 10 days – mirroring the time scale of other behavioral changes associated with fertile matings, such as egg laying. Impressively, mating can rescue sleep in several wake promoting mutants, but does not force the fly to sleep through undesirable situations, when they are starved for example. This suggests that mating isn't so sleep promoting to force sleep regardless of the state of the animal, but rather sleep circuitry integrates and weighs competing inputs to arrive at a desirable output. Finally, we show evidence that mating promotes sleep by modulating specific dopaminergic neurons. This system provides the opportunity to study how nervous systems account for natural daily fluctuations in physiology and motivation and how they calibrate behavioral outputs accordingly.

# Hypothalamic MC4R Neurons Regulate Gradual Hunger-Satiety Dynamics via cAMP

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Agouti-related peptide (AGRP) and pro-opiomelanocortin (POMC) expressing neurons in the arcuate nucleus (Arc) exert powerful, opposing effects on food intake, energy expenditure, and body weight. Both AgRP and POMC neurons produce hunger and satiety related effects, respectively, in part via signaling to satiety-promoting melanocortin-4 (MC4R) receptor-expressing neurons in the paraventricular nucleus of the hypothalamus (PVH). Furthermore, I previously found that coordinated, opposing changes in AgRP and POMC neuron activity and peptide release regulates spiking in MC4R neurons via competing decreases and increases in intracellular secondary messenger cAMP, respectively. However, how these opposing effects on cAMP within MC4R neurons work to modulate hunger and behavior is not well understood. To study the importance of cAMP, I blocked cAMP signaling with viral expression of phosphodiesterase (PDE) in PVH MC4R neurons in adult mice which increased food intake and quickly resulted in severe obesity. Contrarily, induction of cAMP production using optogenetic adenylyl cyclase biPAC resulted in faster satiety during feeding. I then trained mice to lick at a tone for food reward and tested the effect of biPAC stimulation. Although biPAC stimulation did not affect feeding acutely on a trial-by-trial basis, it was sufficient to accelerate satiety across multiple trials over time. Thus, these recent results indicate cAMP signaling in PVH MC4R neurons is critical for regulating energy balance and promotes satiety on a gradual timescale. These experiments help further our understanding of the neural circuitry governing energy balance and its dysregulation in obesity and associated metabolic disorders.

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# Organismic and Evolutionary Biology

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## Contrafreeloading in a Novel Species, *Cacatua alba*

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Human and animal motivation alike are complex, as demonstrated by phenomena such as contrafreeloading, which directly contradicts the widely supported Optimal Foraging Theory. Contrafreeloading is the choice to do unnecessary work to earn a reward in the presence of an equally valuable free alternative. Smith et al. (2021) recently suggested play as a primary motivation to contrafreeload in satiated, untrained African Grey parrots (*Psittacus erithacus*) in two tasks, one of which is unshelling nuts. To test for the presence and degree of contrafreeloading in a novel species and to enable a cross-species comparison, we presented the same unshelling task used by Smith et al. (2021) to four Umbrella Cockatoos (*Cacatua alba*). Preliminary data indicates that, like Greys, Cockatoos do contrafeedload– and the presence and degree of the contrafreeloading is highly variable between individuals. This suggests that results from any one individual aren't enough to definitively categorize the foraging preferences of that species. While there are trends within a species, contrafreeloading tasks are not species-specific behaviors. They are complex, individual preferences, with many potential factors contributing to an individual's choice to contrafreeload, such as time, task type, hunger level, task novelty, subject-specific side biases, and many others. Unraveling the trends in these preferences could help fill the gaps between contrafreeloading theories and provide insight into the science behind motivation and work ethic.

## From Base Pair to Bipedal Gait: Identifying Regulatory Networks Modulating Human Pelvic Ilium Development

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**Naomi Freilich**

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While numerous biological traits distinguish human beings from non-human primates, human pelvic morphology is especially distinct. The essential biological functions of bipedalism, thermoregulation, and childbirth in humans have presented strong selection pressures on the development and anatomy of the pelvis. The consequences of these evolutionary pressures on pelvic shape have undoubtedly resulted in the proliferation of bone-related diseases and disorders, as 32.5 million adults in the United States are affected by osteoarthritis and over 300,000 people in the United States fracture their hips each year. The intersection of human accelerated regions (HARs), i.e., sequences reflecting ancient natural selection, with DNA regulatory sequences identified from distinct pelvic regions has revealed that the ilium (or superior pelvis) is especially enriched for these intersections, thus highlighting the unique nature of the human ilium and the accumulation of human-specific mutations in regions of likely functional regulatory importance. Ultimately, my research now is focused on functionally characterizing ilium-specific regulatory regions that overlap with HARs in order to shed light onto the genetic mechanisms underlying human-specific ilium development. This investigation also sheds light onto the genetic mechanisms underlying osteoarthritis and bone fracture, and our inherent risks for these diseases. Namely, at the crux of understanding the genetics underlying human-specific ilium growth and development as it relates to bipedalism is the search for genetic pathways at play with the biomedical ramifications of walking on two legs.

## Kinship in the Ceramic Caribbean

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Advisor: David Reich

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Indigenous Caribbean ancestry is defined by two waves of migration: the Archaic, which emerged around six-thousand years ago, and the Ceramic, which began to replace it twenty-five hundred years ago. The Ceramic Era has been characterized by small population sizes and regional spread facilitated by matrilineal organization (Keegan 2019). We provide genetic analyses of Ceramic Era kinship at La Caleta, Dominican Republic and nearby sites, which all belong to an ancestral subclade (Fernandes Sirak et al 2021). We utilized analysis of pairwise identical-by-descent (IBD) tracts of DNA between individuals and relative coefficients for individuals for whom IBD analysis was not possible, to determine relationships. We also used Y and mitochondrial haplotypes, long runs of homozygosity (ROH), and male-X IBD. Considering individuals connected through likely-third degree relationships as members of the same family, we detect a large family (n=137) primarily based at La Caleta and including three male individuals from Andres. Within it, the largest pedigree we constructed includes fourteen members, extends over seven generations, and shows both male and female descent paths. We find two other cross-site families. Our results affirm a view of a La Caleta in this era which is isolated but shares ancestry with Andres, Atajadizo, and El Soco. The presence of both matri- and patrilineal descent suggest that perhaps neither strict matri- nor patrilocality were practiced. We also demonstrate great temporal ancestral persistence in this site, evidenced both by the large pedigree constructed and the range of dates for extended family members.

## Species Distribution Modelling as an Exploratory Tool in Range-Edge Populations

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Harvard Faculty of Arts and Sciences

Advisor: Robin Hopkins

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Changing environmental variables present a challenge to plants and other sessile organisms that cannot seek more suitable habitats. Range-edge dynamics may help us understand a species future response to stress and extremes. *Phlox drummondii* is a Texas endemic annual wildflower with a distribution featuring a distinct core and edge population. Species distribution modelling (SDM) uses datasets of known environmental variables and records of species presence-absence to train algorithms to identify a relationship between environmental variables and the distribution of a species. The diversity of algorithms used in SDM offers a unique tool for exploration of which environmental factors determine a species range by comparing the performance of multiple models trained on various subsets of the available data. Preliminary results from various models indicate amount of rainfall during germination and growth months as well as soil clay fraction as influential variables in determining the abundance of *P. drummondii*. Additional results suggest that the distinct core and edge populations are broadly sensitive to the same environmental variables, and are predicted to respond similarly to future climate forecasts.

## From Mines to Museums: The Categorization of Amber Fossils as a Reflection of Historical, Scientific, and Cultural Values

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Supervisors: Beatrice Steinert and Richard Knecht

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I am studying a collection of roughly 2,000 fossil ant specimens preserved in Dominican amber from the late Oligocene/early Miocene period (~25 million years ago). Over the course of a decade, the late Harvard biologist E.O. Wilson curated this collection through a network of purchases with ant biologists and amber dealers around the world. This summer, I performed both scientific (cataloguing, light microscopy, microCT scanning) and historical research (archival visits) with the specimens to a.) describe novel occurrences of *Crematogaster* and *Pseudoponera* species within the Dominican fossil record and b.) understand the evolutionary, economic, scientific, and cultural history of this collection and how it came from the Dominican Republic to the Museum of Comparative Zoology. Through my methodology of personally cataloging Wilson's entire amber collection, I was able to experience firsthand the transformation of an object in the natural world (a piece of amber from a mine) to an object of science (a categorized specimen in a laboratory environment). I argue that the naturalist's obsession with classifying objects in natural world to confer scientific legitimacy strips the objects of their own agency; hence, the different interactions with this amber collection across time and space have impacted its value—culturally, historically, and scientifically. Ultimately, by intertwining the disciplines of history and evolutionary biology, this project reveals how interdisciplinary studies can be used to deepen both fields and approach the study of museum collections in new ways.

## Pre-Lupus Immune Dysfunction and Vitamin D Study

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**Emily Sanchez**

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Systemic lupus erythematosus (SLE) is a life-threatening multi-organ autoimmune disorder characterized by relapsing disease flares and heterogeneous manifestations. On average, lupus takes four years to be diagnosed after initial symptoms appear. This delay leads to worse disease outcomes, increased organ damage, and greater health care utilization. Past studies have demonstrated that patients with active SLE have lower circulating vitamin-D and omega-3 levels and supplementation reduces symptoms of autoimmune disease. However, it is unknown whether vitamin-D and omega-3 fatty acid circulating blood levels are involved in SLE pathogenesis. This research study recruits patients who are thought to be at high-risk for developing SLE, but do not meet the classification criteria for diagnosis and control subjects who have positive antinuclear antibodies, but no suspicion of clinical SLEs. All subjects complete questionnaires about their vitamins and supplements intake, and have blood drawn to identify serological and cellular abnormalities as well as vitamin-D and omega-3 levels. A longitudinal analysis of patient bloodwork and surveys will allow for a comparison between subjects that display lupus disease progression against those that do not. The study aims to identify immune dysfunctions in pre-lupus patients and evaluate their association with lower circulating vitamin-D and omega-3 fatty acid. Potentially, this research will determine the association between low levels of vitamin D and cellular impairment, supporting supplementation in early stages of SLE disease. These findings will also be important in identifying novel disease risk biomarkers in hopes of reducing the average SLE diagnosis time and perhaps preventing its development altogether.

## Moving beyond the Respirometer: Correlating Body Movements to Metabolic Rate in Fish

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Supervisor: Connor White

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Quantifying energy expenditure in animals is important for ecologically understanding the costs of behaviors. However, measuring energy expenditure in the field is difficult with many methodological limitations. The cost of a specific behavior includes the increase in the instantaneous metabolic rate as well as the excess post-exercise oxygen consumption (EPOC) - costs that are incurred after the height of exercise occurs. Measuring the animal's overall dynamic body acceleration (ODBA) has been proposed as a proxy for determining instantaneous metabolic rate and allowing field measurements when animals can perform natural behaviors. In an aim to correlate the ODBA to metabolism, a brook trout was tagged with a tri-axial accelerometer and swum in a flow respirometer at speeds ranging from 0.5 to 4 body lengths per second. After each speed, the fish was rested to measure EPOC. Preliminary results show a significant positive correlation between instantaneous metabolic rate and ODBA. Further progress aims to add EPOC measurements to this regression with the goal of discovering the error in calculations that omit this variable. Successful completion of the project will enable an accurate metabolic rate to be estimated based without the use of a respirometer. This will ultimately allow tags to more precisely estimate the metabolic rate of fish in the field, with a multitude of applications to the conservation and ecology of this important native recreational species in the age of climate change.

## Evolutionary History of Complex Burrowing in Deer Mice (Genus *Peromyscus*)

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Much is yet to be known about the evolutionary history of complex behavioral traits, especially in comparison to that of morphological traits. Deer mice (genus *Peromyscus*) exhibit variation in burrowing behavior, which can easily be studied due to its quantifiable and heritable nature. Studying burrowing behavior within the context of closely related sister species, *P. polionotus* and *P. maniculatus*, that are specialized to different environments and have strong differences in burrowing behavior, offers an opportunity to investigate how behavior phenotypes emerge. A parallel approach using both a sandbox assay to examine burrow morphology and a simulated burrow tube assay to record digging movement behaviors has allowed for unique insights into which behavior traits are shared across *Peromyscus* and which are specific to certain clades. Previous research has suggested that complex burrow traits emerged through novel mutations in *P. polionotus*. We hypothesize that the appearance of different phenotypes across taxa can be attributed to either repeated evolution of complex burrow traits or selection on standing variation. Preliminary data supports the idea that there was originally existing standing variation in burrow shape and size, which was further expanded upon through novel mutations in the *P. polionotus* lineage. With this knowledge, there may be additional implications for how similar behaviors emerge in other systems, especially other fossorial species. These findings will ultimately contribute toward our understanding of how phenotypes accumulate and are expanded upon over time, as well as an overall better understanding of animal behavior evolution.

# Investigating the Effects of Serotonin on the Preferences of *Drosophila melanogaster*

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Previous research has shown the temperature preferences of *Drosophila melanogaster* change over time, a concept we have named “drift.” However, the effect that serotonin has on drift is still unclear. We first compared flies reared with traditional food against flies who had consumed  $\alpha$ -methyl-tryptophan (aMW), a serotonin depressor, over 3 weeks. Through this time period, we assessed their “handedness,” a term that describes a fruit fly’s bias to routinely turn either right or left when placed in a Y-Maze. The handedness of these flies was analyzed by using an insect tracking platform, the Massively Automated Real-time GUI for Object-tracking (MARGO), and we examined whether or not it changed over their lifetimes. Although this is an ongoing experiment, there is varying evidence from previous research on whether serotonin suppresses, increases, or has no effect on the variability of other fly behavior. If the first situation is the case, we would likely see the flies who fed on aMW display less drift as they age than the flies reared on the traditional food. However, it is very possible that the serotonin-depressed flies show an increase in variability as they age.

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## Stem Cell and Regenerative Biology

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### Arrestin Domain Containing Protein 4 is a Regulator of Glucagon Signaling

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**Jake Benoit**

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Harvard Faculty of Arts and Sciences

Advisor: Richard Lee

Supervisor: Sezin Dagdeviren

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Blood sugar regulation in mammals is substantially controlled by two counteracting hormones: insulin and glucagon. My host laboratory as well as others have shown that alpha arrestin-domain containing protein 4 (ARRDC4), a highly conserved mammalian protein, helps regulate glucose metabolism, although the mechanism by which it does so has previously remained unknown. Using an *in vivo* ARRDC4-knockout model, we have shown that ARRDC4 is downregulated by insulin and facilitates glucagon signaling. We hypothesize that ARRDC4 facilitates glucagon signaling via ubiquitin-mediated protein degradation of the glucagon receptor (GCGR), thus allowing GCGR turnover. We are currently testing this hypothesis via a co-immunoprecipitation (Co-IP) experiment, and we have shown that ARRDC4 binds to GCGR proteins. If ARRDC4 facilitates ubiquitin-mediated protein degradation of GCGR proteins, then we expect GCGR proteins from cells transfected with ARRDC4 to be tagged with higher levels of ubiquitin than GCGR proteins from cells not transfected with ARRDC4. This research is on track to implicate ARRDC4 as a critical regulator of glucose metabolism at the intersection of the insulin and glucagon signaling pathways. Furthermore, we expect this research to be important for both understanding the pathology of type 2 diabetes as well as developing new therapeutic targets for this disease.

### Upregulation of Early Gonadal Genes via Stem Cell Activators and Inhibitors

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**Edward Dong**

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Molecular and Cellular Biology, 2025

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Wyss Institute

Advisor: George Church

Supervisor: Merrick Pierson Smela

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Gonad development is regulated by a series of pathways that differentiate initial, sexually bipotential precursors to the gonads into mature ovaries in females and testes in males. Disruption within these pathways result in disorders in sexual development (DSDs), a broad range of conditions where an individual's sex is unclear or does not match their chromosomal sex. Though a necessary field of study affecting hundreds of thousands of individuals globally, the study of DSDs is hampered by the lack of a suitable *in vitro* model. In this project, we aim to test an array of stem cell activators and inhibitors to investigate their effect on early gonadal cell development. We will then treat human induced pluripotent stem cells (hiPSCs) with these substances to induce early gonadal cell-like cells. Success in modeling early gonadal cells *in vitro* will be evaluated by measuring key marker genes including *NR5A1* and *AMHR2*. We measured expression of these genes using a dual analysis of qPCR and flow cytometry. Results thus far have shown that early FGF9 treatment combined with later SHH treatment produced cells carrying enhanced expression of early gonadal markers. Further investigation will focus on optimizing SHH treatment to efficiently induce early gonadal cell development.

## Expanding Educational Resources for Cochlear Implant Surgery

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**Alex Dyer**

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Electrical Engineering, 2024

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Massachusetts Eye and Ear

Advisor: Aaron Remenschneider

Supervisor: Dhrumi Gandhi

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Many patients with severe to profound hearing loss do not experience significant benefits from traditional hearing aid devices. When sound amplification alone is inadequate for speech understanding, patients may consider a different approach to auditory rehabilitation: direct auditory nerve stimulation. Cochlear implants are neural prosthetics that permit sound and speech understanding in patients with severe to profound hearing loss. Unlike hearing aids, however, cochlear implants require a delicate surgery through the skull base to access the cochlea and implant the device. A thorough understanding of the placement of a neural prosthetic is central to safe medical practice and the basis for future innovation. Additionally, knowledge of surgical steps is essential for hearing health providers and acoustic engineers to develop next-generation devices. Existing educational materials are currently limited. The primary aim of this project is to create educational content to inform these stakeholders. Through the development of surgical walkthroughs and accompanying reports, this project has worked to develop a robust catalog of information for future collaborators to reference. Description of critical elements, such as electrode access to the cochlea and electrode design, offer insights for future development. Surgeons must familiarize themselves with potential challenges during implantation, including anomalous anatomy, cochlear ossification, and tumors of the cochlea, such as a schwannoma. Designing devices around these complications will ensure access to an extensive list of approaches for cochlear implants. Increased access to cochlear implant surgery media will enhance the ability of developers to innovate aggressively in the next generation of implantable devices.

## Design and Generation of GDF11 and GDF8 Prodomain Chimeras

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**Justis Gordon**

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Harvard College, Winthrop House

Harvard Faculty of Arts and Sciences

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Supervisor: Tomohiro Kato

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The growth differentiation factor 11 (GDF11) protein and the closely related protein GDF8 (Myostatin) are members of the transforming growth factor  $\beta$  (TGF $\beta$ ) superfamily, and they may regulate cardiomyocyte size. Clinical trials showed that GDF11/8 levels in blood circulation can predict the mortality in patients with cardiovascular disease. Though they are considered to serve similar roles since they share 90% identity in their mature domains, they have shown to have distinct functions *in vivo*. Given that recent reports have shown that their mature domains work similarly both *in vitro* and *in vivo*, and their prodomains are more different, only about 49% identical, it is reasonable to assume that the prodomains regulate the mature domain activity. Therefore, we are focusing on prodomains to understand the different behavior of these proteins. The main questions we are trying to answer with this project are the following: how do prodomains regulate mature domain activity, and are GDF8 and GDF11 prodomains functionally specific *in vivo*? Here we are using CRISPR as a genome-editing tool and donor vectors as a gene delivery method for swapping exons of GDF8 and GDF11 prodomains in mice respectively. We have generated a mouse line whose GDF8 prodomain is swapped with GDF11 prodomain. Once transgenic mice are generated, we plan to run different sets of experiments to answer our questions. Our mice will provide us deeper understanding of the regulation mechanism of GDF11/8, helping us utilize these ligands as biomarkers and new therapeutic targets.

# Reconstituting the Brain Tumor Microenvironment with Microglia-Containing Human Cortical Organoids

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Chemistry and Physics & Social Studies, 2025

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Boston Children's Hospital

Advisor: Xin Tang

Supervisor: Emma Majercak

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Brain cancer is the most prevalent form of solid cancer in the United States with high fatality rates among children. Current brain tumor research relies heavily on mouse models or cultured human tumor cells that do not fully capture the complexity of tumor microenvironment, especially the contributions from microglia. Human stem cell-derived brain organoids have recently emerged as promising models of brain development. However, cortical organoids generated with standard protocols do not contain any microglial cells. We seek to grow a novel type of cortical organoids with a neuroimmune component as the basis for *in vitro* modeling of brain tumors. Towards this goal, we embedded microglia tagged with green fluorescent protein into brain organoids, grew them under various medium conditions, and imaged the organoids weekly for two months to track their growth and microglial distribution. After two months, the organoids were sectioned and immunostained for various markers to assess how different culture conditions may affect organoid growth and cellular composition in order to optimize microglia-containing organoid culture procedures. We then fused microglia-containing brain organoids with brain tumor organoids derived from resected clinical cancer samples, and performed preliminary studies to investigate how microglia interact with cancer cells within a brain tissue context. Ultimately, this project aims to create robust, reproducible, and scalable human brain tumor organoid models as a testing platform for developing novel immune cell therapy strategies for detecting and eliminating brain cancer cells.

# Investigating the Promise of RNA Transplantation for Cellular Age Reversal

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Wyss Institute for Biologically Inspired Engineering

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Aging is a complex degenerative process that creates great suffering for people, increases the probability of diseases ranging from Alzheimer's to cancer, and places a huge economic burden on global health-care systems. It has been demonstrated in multiple species and across human cell types that the transcriptomic state of a cell is sufficient to predict its age. However, it remains to be seen if inducing a youthful transcriptomic state in an old cell would be sufficient to reverse aging. Despite this uncertainty, much of the aging field centers around reversing transcriptomic age using small molecules, genetic modifications, or behavioral changes (i.e. caloric restriction), assuming a youthful transcriptome is causal for a youthful cell. Our group's transcriptome replacement project seeks to test this assumption. In this method, we extract and isolate total mRNA from young cells and transplant it into old cells. This project has clear interpretations of our results—obtained from specialized aging clocks developed by our group. If cells become younger, then transcriptomic rejuvenation is sufficient for age reversal; if cells fail to become younger, then transcriptomic rejuvenation is not sufficient for age reversal. Using GFP RNA to 1) assess the time of degradation of RNA transfected into cells and 2) determine the ideal concentration to transfect for optimal absorption, we are able to efficiently pursue young-to-old cell total RNA transplantation and accurately assess for age reversal.

# Potential Reversal of Dabrafenib Resistance of the BRAF(V600E) Mutation via Inhibition of the Unfolded Protein Response

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Human Developmental and Regenerative Biology, 2023

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Boston Children's Hospital

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Supervisor: Magge Chassé

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Melanoma is the most lethal form of skin cancer and its incidence and mortality rates are rising. 50 to 60% of human melanomas have mutations in the serine/threonine kinase BRAF which leads to abhorrent activation of the MAPK pathway. While MAPK inhibitors like dabrafenib show promise in improving patient prognosis — treatment resulted in 5 years of progression free survival for 19% of patients — in certain cases the tumor cells survive and gain resistance by reprogramming transcriptional circuitry to adapt to the therapeutic stress. ATAC-seq identified a drug resistance population enriched with stress-related factors, such as XBP1. Spliced XBP1 (sXBP1) is the primary effector of the unfolded protein response (UPR). We transfected A375 human melanoma cells with a plasmid to drive the production of sXBP1 to model UPR activation. We confirmed overexpression with a western blot. We will determine if this increased production of sXBP1 has an effect on dabrafenib sensitivity. In parallel, our lab has developed a resistant zebrafish model for high throughput of human melanoma targeting the most common driving mutation, BRAF(V600E). In the fish, the MiniCoopR MITF mini gene is injected into p53<sup>-/-</sup>;mitfa<sup>-/-</sup>;mitfa<sup>BRAFV600E</sup> mutated fish which rescues melanocyte function and allows for the growth of pigmented melanoma. In this *in vivo* system, we will treat the melanoma with the dabrafenib and predict an up regulation in sXBP1. Overall, this project will explore if the UPR is a source of dabrafenib drug tolerance and if it can be reversed through inhibition of stress factors.

# Protection of Hypoimmunogenic Stem Cell Lines from Natural Killer Cell Attack

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**Conrad Hock**

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Molecular and Cellular Biology, 2024

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Beth Israel Deaconess Medical Center

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Supervisor: Elliot Chaikof

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Adoptive cell therapy, or the transplantation of human cells into patients, represents a promising avenue for the treatment of various diseases. Key to the affordability and scalability of such treatments, however, will be overcoming the immune barrier to avoid rejection of transplanted cells. Toward this goal, “hypo-immunogenic” stem cell lines have been generated, in which the human leukocyte antigens HLA-A, -B, and -C that allow recognition of non-self by T cells have been knocked out. This alone, however, is not sufficient to avoid immune rejection, as the lack of HLA renders cells susceptible to attack by other arms of the immune system, specifically natural killer (NK) cells. Thus, a combinatorial approach in which HLA are knocked out—but additional factors inhibiting these other arms of the immune system are expressed—could prove most promising. HLA-E is a protein that inhibits many natural killer cells, but it requires a leader peptide provided by other HLA to traffic to the cell surface. In order to restore its cell surface localization in HLA-deficient cells, I aim to transiently express a viral protein, UL40, which is known to provide the leader peptide that allows HLA-E surface trafficking. I anticipate that HLA-E surface expression should be restored in HLA-deficient cells transfected with viral UL40. Further, if these factors shield cells from NK cells, then decreased cell death should be observed in NK “killing” assays relative to “hypo-immunogenic” cells not transfected with UL40.

## Identification of Novel Atoh1 Regulators for Hearing Regeneration

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Massachusetts Eye and Ear

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Supervisor: Dunia Abdul-Aziz

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Currently, over 430 million people worldwide suffer from some sort of disabling hearing loss and by 2050, this number is expected to approach 1 billion. The majority of hearing loss cases in mammals are characterized by dysfunctional inner ear sensory hair cells. The currently observed permanence of mammalian hearing loss stems from the hair cells' ostensible inability to regenerate. However, it has been previously discovered that newborn mice retain hair cell regeneration up to 5 days after birth. This project aims to pinpoint and characterize novel co-regulators of this regeneration mechanism with a specific focus on regulation of master hair cell transcription factor, ATOH1. After analyzing transcriptomes, chromatin accessibility profiles, and histone modifications of hair cells and supporting cells in neonatal mice, we have identified prime candidates—namely, *Fzd4*, *Hes6*, and *Lhx3*—for Atoh1 co-regulation in addition to other known regulators. By directly targeting these interactions, we seek to define the mechanism underlying hair cell development and regeneration. After generating a short list of genes of interest, mouse embryonic fibroblasts (MEFs) were used to study the epigenetic interactions underlying the generation of induced hair cell-like cells (iHCs). Using ATAC-seq and subsequent computational analysis, we were then able to characterize the transcriptomic behavior of our primary gene of interest in relation to ATOH1 expression in the iHCs. From this, it became clear that *Fzd4*, *Hes6*, and *Lhx3* play a key role in ATOH1 regulation and as such, are viable candidate for inclusion in regenerative therapies.

## The Functionality of the Bud-Like Blastema in Axolotl Limb Regeneration

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Harvard Faculty of Arts and Sciences

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Axolotls possess the ability to regenerate their limbs upon amputation through the formation of special structures called blastemas at the amputation site. This structure is thought to undergo proliferation and differentiation to mimic embryonic limb morphogenesis and regenerate lost appendages. During larval stage, this function has been supplanted by bud-like blastemas, which are formed upon amputation of limb buds. It is currently unclear how the bud-like blastema computes injury information and coordinates the appropriate cells to undergo limb generation. Moreover, it is uncertain why limb buds fail to regenerate the limb upon transplant. Given this gap in the literature, we hypothesized that bud-like blastemas function as progenitor cells and designed two independent experiments to test their functionality. First, RNA was extracted from limb buds, bud-like blastemas, and adult blastemas to perform RNA-sequencing. Next, bud-like blastemas were harvested from green fluorescent protein (GFP)-expressing larvae and transplanted onto amputation sites of same-stage larvae and adults that do not express GFP. The origin of the generated limbs was tracked with fluorescent imaging, and subsequently immunohistochemistry staining will be utilized to investigate tissue types expressing GFP. Our results demonstrate that bud-like blastemas contribute to limb development upon transplant, with newly generated limbs expressing GFP in both adults and larvae. This indicates that bud-like blastemas have the potency to generate the same structure despite their disparate starting state from adult blastemas. With further experimental data, our results will provide unique insights to improve regenerative medicine, as each patient presents unique characteristics in limb loss.

## Fishing For Cures: Developing a Novel *In Vivo* Model for Pediatric Acute Myeloid Leukemia

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**Khushi Kohli**

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Harvard Faculty of Arts and Sciences

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Supervisor: Dorothee Bornhorst

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Pediatric acute myeloid leukemia (AML) remains a leading cause of childhood death, yet its underlying molecular mechanisms are not well-understood. An *in vivo* AML model can serve as a key tool in elucidating these pathways; however, current leukemia models use oncogenes that are not specific for pediatric AML. Thus, this project aims to develop the first zebrafish model that phenocopies human pediatric AML. We hypothesized that pediatric AML initiates when a hematopoietic stem cell (HSC) acquires mutations and produces a dominant clone of highly proliferative, leukemic white blood cells. To generate pediatric AML in zebrafish, plasmids containing the mutant *FLT3-ITD* and *NPM1c* alleles were injected under the HSC-specific draculin promoter, while *asxl1*, *cepba*, *ptpn11a*, *tp53*, *wt1a*, *wt1b*, and *tet3* gRNAs were injected to knock-out tumor-suppressor genes using CRISPR-Cas9 technology. To determine if injected zebrafish displayed pediatric AML at 12 months, peripheral blood and kidney marrow cells were analyzed using FACS analysis and Giemsa staining. Kidney marrow FACS analysis suggested that injected zebrafish had elevated myeloid and reduced lymphoid cell counts. Further, Giemsa staining visualized leukemic blast cells in kidney marrow of several injected zebrafish, suggesting the development of an AML subtype. In addition, the clonal nature of normal and malignant stem cells will be elucidated using the Zebrabow system, in which each HSC and its descendants are barcoded with uniquely colored fluorescent proteins. Ultimately, a robust zebrafish pediatric AML model will be invaluable in identifying gene expression profiles of dominant leukemic clones and novel target genes for pediatric AML therapeutics.

## Correlating FOS Expression with Hematopoietic Stem Cell Proliferation

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Harvard Faculty of Arts and Sciences

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Hematopoietic stem cells (HSCs) have the unique ability to self-renew and differentiate into all cells of the blood and immune systems. Through transplantation, HSCs are used to treat patients with life-threatening hematological, oncological, hereditary, and immunological diseases. However, a major constraint to transplantation is that the number of HSCs are limited, which is why studying the proliferation, differentiation, and self-renewal of HSCs is extremely important. FOS, an immediate early gene, expression has been shown to mark a subset of another adult stem cell, muscle satellite cells, that have enhanced regenerative activity. Therefore, we hypothesized that FOS expression may also correlate with enhanced proliferation in HSCs. To explore this link, we are applying proliferation and cell cycle assays on Fos expressing and non-expressing HSCs in expansion culture and on FosEGFP transgenic mice.

## Development of a Deep Convolutional Network for the Analysis of the Development of Skin Organoids

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**Chinazo Okeke**

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Boston Children's Hospital  
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Supervisor: Phuong Le

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This skin is an essential organ equipped with various accessory structures that are vital for thermoregulation, protection from pathogens, mediating sensory interaction from the environment and retention of bodily fluids. The research focuses on the production of organoid culture system that utilises transforming growth factor  $\beta$  (TGF  $\beta$ ) and fibroblast growth factor (FGF) pathways to induce the formation of cranial epithelial cells and neural crest cells within a spherical aggregate which after an incubation period of 4-5 months develops into a cyst-like skin organoid with hair-follicles. However, the likelihood of success of the culture is usually unknown for a few months, which makes the process time-consuming and inefficient. Using a deep convolutional neural network model built within Python, it was possible to train a model based on microscopy images collected from day 15 of the organoid development which can predict the likelihood of a successful organoid development with up to 97% training accuracy and 96% testing accuracy. Such promising figures mean that the process of developing these skin organoids can be optimised at a much faster rate, helping to advance this field of research further. Further data collection from new organoids being grown can help to further facilitate the training of this model to improve accuracy over time. Given the success of the initial basic program, the next steps are to train different varieties of these models that detect other forms of data such as organoid circularity and proportions of different tissues to facilitate further discoveries.

## Uncovering Novel Players in Macrophage-Mediated Lung Repair

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**McKenna Reale**

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Supervisor: Alan Baez Vazquez

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The lung endures continuous exposure to pathogens, toxins, and noxious environmental stimuli and thus survival depends on robust responses to damage. While repair mechanisms driven by epithelial stem and progenitor cell populations are relatively well-understood, the role of immune cells in repair remains an area of active research. Macrophages, tissue-resident innate immune cells, play important functions in host defense, development, tissue repair, and homeostasis. We hypothesize that macrophages engage a conserved “tissue-building” program during both lung development and repair. By identifying this shared transcriptional program, we may uncover novel regulators of lung regeneration. Here we compared two publicly available single cell RNA-sequencing datasets and identified a list of genes that are upregulated in conditions of both lung development and repair. In future experiments, we will investigate whether gene(s)-of-interest are induced in mouse models of lung damage and then determine whether they are necessary for optimal tissue repair. This work aims to identify genes that have yet to be associated with repair and may represent potential novel therapeutic targets to enhance repair in the respiratory tract.

## Senescence Suppression to Promote Maturation of Stem Cell-Derived Cardiomyocytes

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Velayutham

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Heart disease is the leading cause of death in the United States. However, adult cardiomyocytes are post-mitotic and unable to regenerate the heart via proliferation after myocardial infarction. Current efforts to differentiate induced pluripotent stem cells into cardiomyocytes for clinical translation are limited by the relative immaturity of the differentiated cells. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) exhibit fetal characteristics and cause arrhythmias when injected into large animals after myocardial infarction. In mammals, cardiomyocytes transition from a proliferative state *in utero* into a state of reversible cell cycle arrest known as quiescence after birth. However, *in vitro*, iPSC-CMs are thought to be senescent, a state of irreversible cell cycle arrest. The present study aims to push iPSC-CMs toward a more mature, quiescent state similar to adult cardiomyocytes by manipulating pathways that regulate cell cycle changes from proliferation to quiescence or senescence. We hypothesized that treating iPSC-CMs with senolytic agents such as quercetin, a flavonoid that causes selective apoptosis in senescent cells, will eliminate immature iPSC-CMs, thereby improving maturation of remaining cells by suppression of senescence associated secretory phenotype. We found that treatment with quercetin increases markers for cardiomyocyte maturation at the RNA/protein level and improves mitochondrial and contractile function. In particular, quercetin treatment increases expression of *KIR2.1*, an ion channel that regulates resting membrane potential and prevents arrhythmias when expressed at higher levels. These results suggest that senolytic agents improve iPSC-CM maturation and is a promising strategy for improving the quality of iPSC-CMs for potential clinical translation.

## Drug Screening in a Zebrafish Model of the KLHL41 Gene

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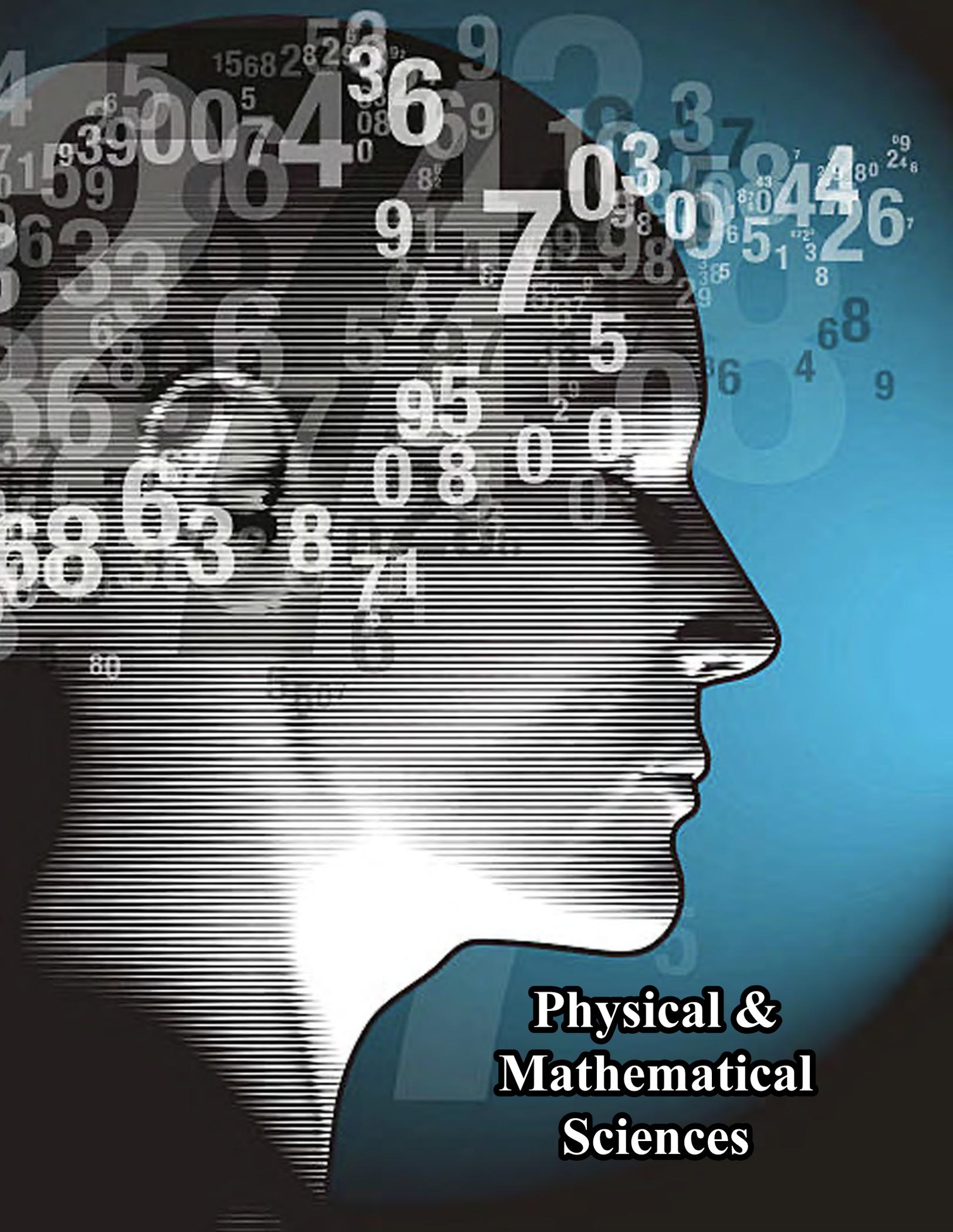
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Nemaline Myopathy (NM), the most common form of congenital myopathy, is characterized by hypotonia and muscle weakness that results in impaired mobility in affected patients. NM is caused by mutations in any of 11 genes: nebulin, alpha( $\alpha$ )-actin, beta( $\beta$ )-tropomyosins, troponin T type 1 and cofilin 2, leimodin3 and myosin 18B and Kelch proteins (KBTBD13, KLHL40, KLHL41). Although the disease is genetically heterogeneous, mutations in all of these genes affect formation and/or function of thin filaments suggesting common pathological processes in different subtypes of nemaline myopathy. Currently, there are no therapies available for nemaline myopathy and related diseases. Therefore, the proposed work will be focused on identifying FDA approved small molecule disease regulators of nemaline myopathy *in vivo* in zebrafish model of *klhl41* deficiency. My preliminary work has optimized time points and assay conditions to evaluate the effect of small molecules on improvement of muscle function. I will be applying small throughput automated activity analysis to quantify swimming behavior of mutant fish and will evaluate the effect of different compounds (2000 FDA approved drugs) on improvement on the swimming function in the *klhl41* knockout fish. Different nemaline myopathy subtypes share common disease pathology, therefore compounds identified from this work will also be evaluated in other zebrafish and mouse models of nemaline myopathy. This work will ultimately allow us to identify therapeutic strategies for intervention in affected patients.





**Physical &  
Mathematical  
Sciences**

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## Chemistry

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### Enantioselective Photochemical Diels-Alder Reaction Catalyzed by Chiral Hydrogen-Bond Donors

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Enantiomers are molecules that are mirror images of one another and possess identical chemical and physical properties. However, enantiomers can interact differently with biological systems. Therefore, it is critical to find approaches to access enantiomerically pure molecules for use as drugs or agrochemicals. The discovery of reaction pathways that allow preparation of one enantiomer selectively is of immense importance to organic chemists. One such way that we can do this is through catalysis. Our group focuses on development and study of chiral organic catalysts that engage in hydrogen-bonding interactions with substrates or reagents to ensure high levels of enantioselectivity. Hydrogen-bond-donor catalysts have been demonstrated to interact cooperatively with a variety of achiral catalysts such as Brønsted and Lewis acids, and transition-metal complexes through association with anions of these species. In my project, I aim to extend this co-catalysis concept to other classes of achiral compounds. Specifically, I focus on combining chiral hydrogen-bond donors with organic salts that can be activated by light to promote reactions proceeding through reactive cation radical intermediates. We envision that the hydrogen-bond-donor co-catalyst may interact with the counterion of this ionic intermediate to control its reactivity and induce enantioselectivity. We explore this hypothesis in the context of Diels-Alder reactions with substrates that do not react under standard thermal conditions and do not contain functional groups that could enable other known classes of chiral catalysts to be employed effectively.

### Stereoselective Functionalizations of Enantioenriched Cyclobutanones

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Cyclobutanone is a small cyclic molecule and an important subunit in organic synthesis due to its versatility. However, given the limited examples for stereoselective construction of the cyclobutanone scaffold, many potential routes to molecules of interest remain under explored. Research in the Jacobsen group has targeted preparation of enantioenriched cyclobutanones bearing a quaternary stereocenter at the alpha carbon through the development of an asymmetric semipinacol rearrangement reaction. This work builds upon this advancement and aims to analyze five stereoselective derivatization reactions of these enantioenriched cyclobutanones: the Baeyer-Villiger oxidation, ketone reduction, vinyl Grignard addition, Beckmann rearrangement, and reductive amination. The racemic model substrate was exposed to the various reaction conditions to identify and confirm formation of the intended products. Once optimal reaction conditions were identified, the reactions were further explored with the enantioenriched cyclobutanone substrate. Initial results suggest that enantio- and diastereospecific transformations on sterically hindered cyclobutanone substrates are feasible, and ongoing research is focused on further improving access to these valuable compounds.

## Ion Selective Electrodes to Determine the Concentration of Lead in Water and Its Mechanism as a Neurotoxin

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Water quality issues arose for Flint, Michigan residents in 2014. By 2016, lead levels exceeded 15 parts per billion. Increased lead levels are dangerous as the ion is considered a neurotoxin. The mechanism for neurotoxicity is unknown; however, there are theories on lead as an acetylcholinesterase inhibitor. Currently, there are two methods to determine these ions in water: laboratory testing and paper strips. Paper strips leave waste and do not provide a clear difference between concentration categories, while laboratory tests require travel, expensive equipment, and specialized labor. Ion-selective electrodes measure the concentration of ions in a portable and inexpensive manner, without the need for large volumes of water. Ion-selective electrodes are efficient and widely accepted in light monovalent ions such as sodium and potassium; however, in heavier polyvalent ions, there are gaps in quantifying the efficiency among different ISE types. This research analyzed lead using ion-selective electrodes in the concentration range of Flint, Michigan, and validated the theory that there is inhibition of acetylcholine hydrolysis in the presence of lead. In a comparison with Inductively coupled plasma mass spectrometry, the ion-selective electrode does not have the same lower detection limit. The limit of detection is within the upper parts per billion range indicating it is useful with larger concentrations of lead. With more optimization, ISEs can be used alongside other detection methods for lead such as ICP-MS.

## A Survey of Nitrile Chemistry in Massive Star-Forming Regions

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The regions around massive young stellar objects (MYSOs) are characterized by an exotic chemistry resulting from physical changes that take place as massive stars form and evolve. Carbon-based molecules with a C–N triple bond, known as nitriles, are of particular interest due to their role in prebiotic, carbon-based, and life-forming chemistry and their relative brightness detectable at millimeter wavelengths. Using observations from the Submillimeter Array, we observed four MYSOs and used radio interferometric techniques to image the data into a format ready for analysis. Within these sources, I produced images of four spectral lines of the HC<sub>3</sub>N nitrile molecule – selected because of its brightness, abundance, and large spatial extent. With the ultimate goal of deriving the temperatures and densities of these molecular clouds, we made maps of the HC<sub>3</sub>N gas distribution through plots showing the intensity distribution for each detected line. Using rotational diagrams generated from this analysis, I determined the rotational temperature and column density of this molecule to produce a comprehensive picture of its physical characteristics. I created an isotopologue map displaying the distribution of HC<sub>3</sub>N compared to its less abundant isotopes, providing insights into the cloud’s molecular structure and chemical processes. We performed this analysis on multiple MYSOs, with our aim to determine their physical and chemical properties. High-mass stars play an important role in cosmic formation and galactic evolution, and exploring protostellar nitrile chemistry yields insights into massive star formation and other large-scale physical processes, such as planet formation and the origin of life.

## Investigating the Mechanism of Suppression of Crystallin Aggregation by Myo-Inositol

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Supervisors: Eugene Serebryany and Srivastav

Ranganathan

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Cataracts are the leading cause of blindness worldwide, but there are no approved treatment options beyond surgery, which is inaccessible in many parts of the world. Cataracts develop when crystallin proteins in the aging eye lens misfold and form light-scattering aggregates, and  $\gamma$ D-crystallin is the main protein implicated in this process. Recent biophysical experiments have shown that myo-inositol, a small molecule, disrupts the aggregation of  $\gamma$ D-crystallin *in vitro*, but its mechanism of action is not well understood. Theoretical Chemistry techniques can complement these experiments by providing more detailed, atomistic insights into its mechanism of aggregation suppression. In this project, statistical mechanics (Monte Carlo Protein Unfolding) simulations are used to elucidate the folding pathways for  $\gamma$ D-crystallin and several constructs with experimentally relevant, aggregation-prone mutations. Molecular Dynamics simulations are also used to probe the transient chemical interactions between myo-inositol and  $\gamma$ D-crystallin structures at different stages along its folding pathway. It is hoped that these results will reveal the key chemical interactions responsible for aggregation suppression by myo-inositol, which can be further refined and developed into a therapeutic agent to treat or even prevent cataracts disease. In fact, these chemical insights into how a small molecule disrupts protein aggregation may be transferrable to drug design strategies for other protein misfolding diseases, such as Alzheimer's or Parkinson's diseases.

## Synthesis of PROTACs to Investigate C-terminal Cyclic Anhydrides as Potential E3 Ligase Degrons

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E3 ubiquitin ligase complexes mediate protein degradation via the ubiquitin-proteasome system in the biological system and select specific protein substrates by the recognition of degrons, specific amino acid sequences that promote degradation of substrates in which they are embedded. C-terminal cyclic anhydrides, overlooked post-translational modifications (PTMs) prevalently found in meta-analysis of public proteomics datasets, could serve as degrons for E3 ligase complexes. The investigation of the functional engagement of C-terminal cyclic anhydrides by their cognate E3 ligases can be achieved using heterobifunctional small-molecule degraders commonly known as PROTACs (proteolysis-targeting chimeras), and progress has been made towards the synthesis of two PROTAC molecules to investigate this potential functionality. These molecules are designed to aim at the cellular degradation of known substrates by tethering the C-terminal cyclic anhydride moiety to an established ligand that binds to the target substrate with high affinity and specificity. Specifically, the degraders are receptive to two different model substrates, BRD4 and HaloTag7 fusion proteins, and will potentially form a ternary complex between the substrates and E3 ligase complexes to induce the degradation by proximity. In future experimentation, these PROTACs will be utilized in assays *in vitro* and *in vivo* to assess the degradation of BRD4 and HaloTag7, which is indicative of the degron functionality of C-terminal cyclic anhydrides. Identification of cyclic anhydrides as degrons for specific E3 ligases in the proteome may pave the way for further E3 ligase biology studies and novel modalities in the field of targeted protein degradation.

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# Mathematics

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## Mostow Rigidity and Geometrization

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Mostow rigidity is the remarkable theorem stating the uniqueness of hyperbolic structures on manifolds of dimension at least three. This is in contrast to the case of two dimensional manifolds which have a 3g-3 dimensional moduli of hyperbolic structures given by the uniformization theorem. Any map between two hyperbolic manifolds can be perturbed to be an isometry. This means that any geometric invariant is also a topological invariant and gives a rich toolkit to study these manifolds. The two main proofs of Mostow rigidity first hinge on extending the initial map between two hyperbolic manifolds to the boundary of hyperbolic space, the universal cover of both manifolds. Such a map exists since hyperbolic manifolds are Eilenberg-MacLane spaces from the uniformization theorem. Once on the boundary, Mostow's original proof utilizes the ergodicity of the geodesic flow to show that this map is conformal, and therefore extends to a unique isometry on hyperbolic space. This map descends to an isometry between the manifolds homotopic to the original map. Gromov gave a beautiful proof by defining a norm which captures the complexity of the fundamental class of a manifold. After extending the map to the boundary, the geometry of simplices of maximal volume shows that the map can be perturbed to an isometry. Thurston's geometrization conjecture says that hyperbolic geometry is one of only eight model geometries for three dimensional manifolds, almost all of which are hyperbolic. Therefore, the result of Mostow states that almost all the topology is determined by geometry.

## Investigating Algebraic Fundamental Groups of Curves

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Algebraic geometry investigates objects called *algebraic varieties*, which are, roughly speaking, solution sets to collections of polynomial equations, and *algebraic morphisms* between them, which are, roughly speaking, functions given by polynomials. Algebraic curves, which are varieties of dimension one, are some of the simplest examples of varieties, and yet lend themselves to a vast and rich theory. A plane curve, i.e. the zero set of a single polynomial equation  $f(x, y) \in k[x, y]$  in two variables over some algebraically closed field  $k$  (like the field of complex numbers), is an algebraic curve, but not all curves are plane curves. For instance, the twisted cubic curve is the curve in three-space given parametrically by  $t \mapsto (t, t^2, t^3)$ . It is an example of a rational normal curve, which are curves of minimal degree in projective space. Curves form a rich theory because they can be investigated from many different perspectives, for instance from that of the complex analysis of Riemann surfaces, or of the commutative algebra of Dedekind domains and field extensions, or of the algebraic geometry of one-dimensional varieties in projective space. In this project, we employ these different techniques to study various classes of curves and what the connection between these different approaches have to say about their geometry. In particular, we explore the relationship between the Galois theory of the function fields of curves and the geometry and topology captured by their fundamental groups, both topological and algebraic.

# Characterizing Output of an Updated Compression Driver to Assess Nonlinear Growth of Middle-Ear Responses

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High-intensity sounds can damage middle ear structures (resulting in tympanic perforations) and cause severe conductive hearing loss. However, our knowledge of how the middle ear conducts loud sounds to the inner ear is insufficient, limiting our ability to protect our ears from damage by loud sounds. With low to moderate level sounds, the middle ear linearly transmits sound energy from the environment to the inner ear. With louder sounds, the middle ear is expected to behave nonlinearly, but frequency and level dependence of middle ear nonlinearity has not been well-described. The lab will utilize cadaveric human temporal bones and laser measurement techniques to systematically quantify vibrations of middle ear structures in response to multiple levels of sounds across a broad frequency range. As a first step, this summer research project will investigate an updated compression driver (loud speaker) that will generate sound stimuli from 200 to 20000 Hz and a wide level range between 60 and 180 dB SPL to induce middle ear nonlinear responses. In prior work, the loudspeaker used in our study had a significant roll-off at frequencies above 4000 Hz. The current compression driver is expected to operate with greater efficiency, especially at high frequencies. We will adjust stimulus parameters in the control software to characterize the output of the compression driver in terms of a function of the stimulus level and frequency. It is important to ensure the linear growth of sound stimuli generated by the speaker with increasing stimulus levels, used to study nonlinear responses of the middle ear.

## Combined Impacts of Parameter Uncertainties on the Redshift Evolution of Double Compact Object Merger Rates

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Supervisor: Floor Broekgaarden

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Population synthesis predictions are valuable for understanding the rapidly increasing population of double compact object (DCO) merger observations. Population synthesis models, however, contain uncertainties and unknowns that are vital to allowing meaningful comparison with observations. Past studies have probed the impact of such uncertainties individually, but few investigate the combined impact of varying multiple parameters at once—as these simulations are highly computationally expensive. Thus far, we have varied the common envelope efficiency ( $\alpha_{\text{CE}}$ ), the accretion rate limit ( $\beta$ ), and the metallicity-specific star formation history ( $S(Z, z)$ ) in tandem. We calculate the rate and characteristic distributions of detectable binary black hole (BHBH), binary neutron star (NSNS), and black hole-neutron star binaries (BHNS). We use a double broken power law regression to quantify the shape of the merger rate. Whereas it is generally expected that the rate of DCO mergers follows the star formation rate, preliminary results indicate that the shape is highly dependent on assumed  $\alpha_{\text{CE}}$  and  $\beta$  parameters. Successful completion of the project might further describe the combined impact of  $\alpha_{\text{CE}}$  and  $\beta$  (and other parameters) on the merger rate of DCOs by quantifying how they shift the characteristic slopes and peak of the double broken power law fit. Our work will help understand how to best explore parameters given limited computational time in order to constrain the stages of stellar and binary evolution. This will provide an important step forward in learning about the formation, lives and deaths of massive stars from gravitational waves.

## Motional Degrees of Freedom for an Impurity Coupled to a Two-Dimensional Atomic Array

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Supervisor: Stefan Ostermann

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The collective modes of two-dimensional ordered atomic arrays can modify the radiative environment of embedded atomic impurities. In particular, dipole-dipole interactions generate effective potentials that modify the motion of impurities introduced to the lattice. We analyze the interaction between spin population dynamics and the kinetic degrees of freedom for an impurity in the single excitation manifold. The optical decay dynamics of static impurities match the dynamics of impurities fixed in place by models that do not contain motional degrees of freedom, revealing stable equilibria in lattice plaquettes. For impurities with non-zero initial momenta, we find that trajectories have a strong dependence on the polarizations of the lattice atoms. Motion within potentials becomes non-periodic when impurity decay rates are sufficiently high, due to dynamical couplings that are continuously modified by exchanges of spin population.

# TOI-5401b: A Newly Discovered Brown Dwarf around an A-type Sub-Giant from NASA’s TESS Mission

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Supervisors: Allyson Bieryla and Samuel Quinn

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We present the discovery and characterization of TOI-5401b, a transiting Brown dwarf (BD) orbiting an A-type star from the TESS mission. The system is twofold interesting: the companion falls within the sparsely populated “Brown dwarf desert,” and its host star is an evolved, unusually hot sub-giant. We perform a joint analysis of lightcurves from NASA’s TESS mission and our high-resolution spectroscopy from the Tillinghast Reflector Echelle Spectrograph (TRES). We find that TOI-5401b has a radius of  $R = 1.159 \pm 0.048$  Jupiter radii, a mass of  $M = 46.2 \pm 2.4$  Jupiter masses, and orbits its host star every  $6.829103 \pm 0.000011$  days. The host star has a mass of  $2.68 \pm 0.2$  Solar masses, a radius of  $4.36 \pm 0.16$  Solar radii, and an effective temperature of  $T = 9260 \pm 270$  K. We derive the age of the system using MIST and YY stellar isochrone models, arriving at a solution of  $448 \pm 61$  Myr. Hence, we add another valuable data point to the small sample of only 6 well-characterized transiting Brown dwarfs with reliable age estimates. We use this opportunity to test the latest substellar evolutionary models. By assessing the circularization timescales, we find that no firm conclusion can be drawn about whether the system is dynamically young. Finally, we consider the implications of this discovery on planetary formation theories, namely the upper mass limit for objects that form by core accretion from the massive protoplanetary disks of sub-giant stars.

# Design of a Fabry-Perot Cavity under Ultra-High Vacuum

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Supervisor: Mark Babin

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A longstanding problem in quantum mechanics is the many-body problem: predicting the behavior of a microscopic system composed of many interacting particles. Ultra-long-range Rydberg molecules, molecular species formed by the bonding of a Rydberg atom (an atom with an electron in a very high energy state) with another atom or molecule, exhibit a novel platform to study many-body quantum mechanical systems. The Ni Lab has devised a way to prepare Rydberg atoms and molecules through a two-photon excitation scheme and detect them by ionizing the Rydberg species. These experiments require very precise lasers with high stability, and thus it is necessary to stabilize their output to a stable external reference. Fabry–Perot cavities are one of such references; by fine-tuning the parameters of the transfer cavity one can make sure that the optical system is locked, and the laser light will always be of the desired frequency. The goal of this project is to build a Fabry–Perot cavity in a vacuum chamber such that much better control is attained on the laser system, greatly improving the spectroscopic experiment’s resolution. For this, many different computer-aided designs have been iterated over to perfect the design of a vacuum chamber to hold a Fabry-Perot cavity. The design of the chamber and cavity is nearing its completion, with the next steps being to acquire ultra-high-vacuum parts and to start machining and modifying the components. Once this is done, the cavity will replace the current optical transfer cavity used in our ionizing laser for the Rydberg molecules.

# Performing Modulation Transfer Spectroscopy in Atomic Sodium

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Quantum computers are an emerging technology that have the potential to revolutionize the world of information technology and scientific research. One of the most promising realizations of a quantum bit ('qubit'), the quantum analogue of the classical computational bit, is based on so-called Rydberg states of atoms. Rydberg states are very high energy states of an atom that can readily interact with nearby atoms. This technique uses the ground and Rydberg state of an atom to encode a single qubit, with the ground state corresponding to the logical '0' state and a chosen Rydberg state corresponding to the logical '1' state. The Ni Lab has developed a setup that is able to trap individual atoms in arbitrary-geometry arrays of optical tweezers and excite transitions between their energy levels by shining laser light that carries the energy required for a desired transition. In this contribution, I will present a project whose goal is to locate the  $3S_{1/2}$  to the  $3P_{1/2}$  state in sodium, which is used as an intermediate state for the ground-to-Rydberg transition. The experimental procedure, known as modulation transfer spectroscopy (MTS), involves shining two counter-propagated laser beams into a cell containing sodium vapor and monitoring the light intensity of one of the beams after it has passed through the cell. The optical setup required for MTS has been successfully assembled, and the work in progress revolves around building the laser that will be used, implementing the electronic setup necessary to observe and process the optical signal, and performing analysis of the data recorded.

# Scanning Four-Probe Microscopy

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Scanning probe microscopy (SPM) scans a sharp tip across a flat sample and measures the electrical current one pixel at a time, to take atomic resolution images of quantum materials. The tip of the SPM is brought very close to the sample in order to image surfaces at their atomic level. The procedure of bringing the tip very close to the sample, so-called coarse positioning mechanism, is utilized via piezoelectric chips stacked face-to-face and bonded via epoxy. The shearing movement of the electric actuators directly converts electrical energy into linear motion. From those simple piezoelectric effects, the whole system is capable of imaging a surface with picometer precision and creating atomically resolved images of local properties such as surface height and electron energy levels. This project introduces a new design for scanning probe microscopy. The design of the 1 Kelvin, 9 Tesla, scanning 4-probe microscope (S4PM) system will combine the SPM technique as well as transport measurements, which is essential for figuring out the electrical properties of the quantum materials. The new compact design responsible for these improvements is an offset stage in cylindrical coordinates, as opposed to the traditional cartesian offset stage for coarse positioning, which is very bulky and unstable. The preliminary tests and results indicate successful rotation, z, and r movement of the walkers for coarse positioning of this four probe system.

## Nesting States and Their Consequences for Pseudo Gaps and Strange Metals

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Lattice vibrations confine electrons, and at low energy, they find small pockets or "nesting" states. Nesting states have been ignored in physics because the conventional understanding is that electrons don't interact with crystal vibrations, or if they do, then in some inelastic exchange of energy and momentum (aka perturbation theory). However, in 1957, Hanberry Brown & Twiss used two telescope mirrors at variable distances apart to show light arriving from the star Sirius in a wave, thus establishing the wave interpretation. Back to crystals and electrons, current crystal vibration models have received exclusively particle treatment. We realized through our study of these models that the wave-particle duality was never fitted for vibrations of crystals. We should note here that the particle picture is factually correct (as waves & particles are a duality). Our discontent is not only pure accuracy but also the desire for a more candidly evocative-of-nature portrayal of electron-lattice interactions. The wave picture is far richer; the vibrations of the crystals cause an effective field that the electrons feel, akin to waves at sea tossing, turning, and thrusting a small canoe. This more synoptic quantum mechanical view of physical systems proves powerful; the phenomenon of nesting, which was my niche of study for the summer, is one of the side quests manifesting from a wave picture. Nesting states could lead to an understanding of strange metals; more precisely, riddles of Lifshitz tails and density of states. We are continuing to collect data and run simulations.

## A Tunable Terahertz Light Source for the Optical Control of Quantum Materials

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Supervisor: Haricharan Padmanabhan

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The properties of solids are primarily decided by their crystal structure. Rationally controlling the structure would allow one to manipulate the properties of the solid. Light pulses of specific frequencies can resonantly drive vibrational modes (phonons) in crystals to large amplitudes. The structural deformities thus induced in crystals result in interesting properties. However, laser pulses in the 4-18 THz frequency range, where most crystal phonons are, cannot be usually produced. As such, the project involved building an optical parametric amplifier (OPA) that can generate tunable pulses between 4-18 THz. The project consisted of two main stages, amplification using twin-OPAs and mixing two linearly chirped pulses in the organic nonlinear crystal DSTMS. We are currently completing the first stage, that is, building an OPA. An OPA uses optical rectification of femtosecond pulses to produce THz pulses. Optical rectification is a nonlinear optical effect. Optical pulses are generated by exposing materials to external electromagnetic fields. In contrast to linear optics, where the radiated pulse will have the same frequency as the external field, nonlinear optics can radiate pulses with frequencies different from the external field. This is used to produce pulses in the 4-18 THz range. During the project, I assisted in building the OPA by characterizing pulses using the SHG-FROG technique and compiled a guide on building an OPA. The project's success opens possibilities, such as coherently driving and controlling insulator-metal transitions and magnetization dynamics.

# Effective Theory Interpretation of Fluctuations of Klebanov-Strassler Geometry

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The cosmological constant, or vacuum energy density, in general relativity (GR) is believed to be the source for the observed accelerated expansion of the universe. Known as the cosmological constant problem, the discrepancy between its value calculated in quantum field theory (QFT) and its observed value is as high as 120 orders of magnitude. As a problem related to both GR and QFT, a quantum gravity theory is needed to solve it, the most promising of which is string theory. However, constructions of string theory vacua typically are Anti-de Sitter (AdS), corresponding to a negative cosmological constant, as opposed to a positive one, corresponding to a de Sitter (dS) vacuum, required by observations. In the model proposed by Kachru, Kallosh, Linde, Trivedi (KKLT), an anti-D3 brane is added to a highly warped region of the AdS Klebanov-Strassler (KS) background to produce a dS vacuum. The warping is crucial to ensure that the resulting positive cosmological constant is small due to gravitational redshift. However, the addition of the anti-D3 brane will deform the background geometry. To understand the deformation, we need to calculate the possible fluctuations of the KS geometry, namely the Kaluza-Klein (KK) modes of the geometry. We will then compare these KK modes with the variations of the warp factor and the internal metric as functions of the conifold deformation parameter calculated in a recent work. If successful, this research will provide a better understanding of the stability of the KKLT model.

# Low-Resistance Contacts for MoSe<sub>2</sub>

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Supervisor: Andrés Mier Valdivia

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Transition metal dichalcogenides (TMDs) are a class of 2D nanomaterials made of strong, covalently bonded atom-thick sheets. TMDs are of great interest, as they exhibit favorable properties such as enhanced light-matter interactions and strong electron-electron interactions, making them promising platforms for novel physics and a variety of electronics applications. However, these phenomena cannot be observed without good electrical contacts. Synthesizing such contacts will open up this material for further study, opening the doors for the investigation of phenomena such as Wigner crystallization and Bose-Einstein condensation. The main challenge is synthesizing Ohmic contacts that will allow us to perform reliable transport measurements. When synthesizing metal-semiconductor contacts, there are two possible junctions that can be formed - Ohmic junctions and Schottky junctions. If the workfunction of the metal and the semiconductor material differ, charge transfer occurs until their Fermi levels reach equilibrium, causing the junction to behave as a rectifying diode. These junctions have strongly nonlinear voltage-current relations, making the interpretation of electrical measurements difficult. Thus far, a good recipe for Ohmic contacts to MoSe<sub>2</sub> has not been found. Recent experiments demonstrated that palladium and bismuth are good candidates to produce Ohmic contacts to TMD MoSe<sub>2</sub>. We fabricate MoSe<sub>2</sub> devices using various thicknesses of Pd and Bi to determine the optimal recipe. Controlling thickness of contacts allows us to better match the workfunctions of the two materials, creating an Ohmic junction, which has a linear current-voltage relationship. We will perform transfer length measurements to determine contact resistance on each of our devices.

# Constructing a 4-Probe Scanning Tunneling Microscope

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Scanning tunneling microscopes (STM) are an essential tool used to study the electronic states of the materials and image samples with atomic resolution. A STM works by scanning an atomically sharp probe over the surface of a conducting sample while applying voltage to the sample. By measuring the current that tunnels from the sample to the probe, we can determine the distance between them and the density of states, a measure of the energy levels of electrons in the sample. By using multiple probes, we can study properties at different scales. This project consists of designing and building a 4-probe Scanning Tunneling Microscope that can use two probes to measure transport of electrons and the other two to understand activity on the atomic scale. We can study the conductivity of the material, but the other probes are helpful to understand why the electrons are transported in this way. In order to ensure the quality of the measurements, the STM assembly including the tip and the sample are best kept under an ultra-high vacuum environment. The assembly is kept in vacuum chambers made of stainless steel 316, which are pumped down using scroll pumps, turbo pumps, and ion pumps. At the current stage we are almost done with setting up the hardware, although not able to scan any materials yet, but the progress this summer suggests we should start getting results by the end of the year.

# Deep Learning Detection and Classification of Binary Merger Gravitational Wave Signals

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The Laser Interferometer Gravitational-Wave Observatory (LIGO) and Virgo Interferometer Collaborations have now detected all three classes of compact binary mergers: binary black hole (BBH), binary neutron star (BNS), and neutron star-black hole (NSBH). For mergers involving neutron stars, multi-messenger astronomy, the simultaneous observation of gravitational and electromagnetic radiation produced by an event, has broad potential to enhance our understanding of these events and probe fundamental physics. However, electromagnetic follow-ups to gravitational wave events require rapid, real-time detection of gravitational wave signals, and conventional matched-filtering approaches are computationally prohibitive for the anticipated event rates of next-generation gravitational wave detectors. To this end, deep learning approaches are a natural solution because once trained, they allow for fast and computationally cheap inference from the gravitational wave data stream. In this work, we present the first deep learning results for distinguishing all three classes of compact binary merger and noise. Specifically, we train a convolutional neural network on  $\sim 500,000$  data samples of real LIGO noise with injected BBH, BNS, and NSBH waveform signals and we show our network has high sensitivity and accuracy. We successfully recover all but one BBH merger from Gravitational Wave Transient Catalogs 1 and 2, as well as the only two confirmed BNS mergers to-date (GW170817 and GW190425) and the only two confirmed NSBH events to-date (GW200105 and GW200115). These results are an important step towards low-latency real-time gravitational wave detection and enabling multi-messenger astronomy.

# Can the Photometry of Two $z \sim 13$ Galaxy Candidates be Explained by a Pop III Starburst?

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The discovery of two  $z \sim 13$  galaxy candidates, potentially the farthest objects found in the universe, has the potential of being revolutionary in our understanding of the very early Universe, i.e. the period when the first stars and black holes formed. The two  $z \sim 13$  sources are extremely UV bright, possibly implying either extreme star formation rates or accretion-powered activity by a super-massive black hole of  $10^8$  solar masses. Here, we study the possibility that the photometry of these sources can be explained by the spectral energy distribution produced by stars born from a top-heavy initial mass function, typical of Pop III stars. We use the code Yggdrasil to explore different initial mass functions and different properties of the starburst and identify the region of the parameter space that reproduces the observational properties of the two  $z \sim 13$  sources. We find that Pop III initial mass functions offer the best fit for the photometric data at our disposal, suggesting a total stellar mass of the hosts of  $10^{11}$  solar masses. We further explored the possibility that the additional emission from an active black hole would reduce the stellar mass required, rendering it more sustainable at  $z \sim 13$ .

# Do Spiral Arms Form Molecular Clouds?

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It is hypothesised that spiral arms serve as a formation mechanism for molecular clouds, or diffuse nebulae, in which stars form. These molecular clouds are seen to be gathered around these spiral arms in our own galaxy, the Milky Way, as well as other galaxies (such as M33). The hypothesised star formation mechanism is as follows: the interstellar medium (ISM) collects upstream of the spiral arm, high density regions of the ISM form clouds upstream of the spiral arm, and then stars are formed downstream. In the framework of this project, I simulate the movement of molecular clouds over a 100 Myr time period using data from snapshots of a simulation of a Milky Way like galaxy. The snapshots have a period of 1 Myr and the simulation is used to track the spiral arms and reproduce any changes in the molecular and atomic gas densities. This obtains an insight into how the molecular and atomic gas evolves through the arms. My simulations can be used to compare with observational data and form conclusions about molecular cloud formation through the spiral arms. My preliminary results from the simulation show that the gas density lies on the spiral arms of the stellar disc and that the density increases through an arm in M33.

# Strontium Ruthenate Backside Coatings for Molecular-Beam Epitaxy

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Thin film deposition using molecular-beam epitaxy (MBE), as done in the Mundy lab enables the design and synthesis of new materials such as superconductors for energy, computing, and sensing applications. The process requires a template, or “substrate,” that needs to be heated uniformly to temperatures as high as 1000°C. To do so, the substrate needs a backside coating with high thermal conductivity. However, current methods of backside coating may lack thermal uniformity or stability in the strong oxidizing conditions used in MBE. In this study, we pursue a method of achieving a backside coating with high thermal uniformity by sputtering strontium ruthenate ( $\text{SrRuO}_3$ ).  $\text{SrRuO}_3$  is a metallic, thermally conductive and oxygen-resistant oxide material. Substrates must be coated evenly, with a thickness sufficient to hold high temperatures, and smoothly cover the rough back side. Moreover, the process needs to be optimized so that the front-sides of the substrates remain uncoated. The two main goals of the project were (a) to determine deposition rates and ideal layer thickness for  $\text{SrRuO}_3$  backside coatings by tuning sputtering parameters, and (b) to test different methods of loading substrates such that their front-sides remain pristine. Preliminary results show that sufficient coating may be achievable at  $\leq 150$  Watts of power when sputtered for  $>3$  hours. Both specialized semiconductor tape and a custom  $10 \times 10 \text{ mm}^2$  substrate holder are able to protect the substrate front-side. This evidence indicates that sputtering  $\text{SrRuO}_3$  has promising implications for clean, effective backside coatings.

# Analysis of a Neptune Losing its Atmosphere

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To date, over 5,000 exoplanets have been discovered and their characterizations provide insight into how planetary systems were formed and the evolution they undertake. Neptune-sized planets harboring a short period are rarely found deeming this region around a host star to be called the “Neptune Desert.” The area causes strong stellar irradiation where planets are affected by photoevaporative mass loss rates, causing them to lose their atmosphere, and eventually leaving them with a rocky core. TOI-1420 was identified by NASA’s Transiting Exoplanet Satellite Survey (TESS) as a stellar object with a planetary candidate that lies at the lower edge of this Neptune Desert. An extended light curve was produced from a collection of TESS transit data and a series of ground-based observations; the ground-based photometry confirmed that the transits were originating from the target star and provided better spatial resolution. Follow-up spectroscopy from the Tillinghast Reflector Echelle Spectrograph and the High Accuracy Radial velocity Planet Searcher for the Northern Hemisphere provided radial velocity measurements which led to the calculation of the planet’s mass as well as stellar parameters used to determine the host star mass and radius. Combining these datasets with EXOFASTv2, a fitting tool used to model planetary systems, a fully converged joint orbital solution was produced. The mass and radius derived from TOI-1420’s model will help to calculate the scale height of the planet’s atmosphere to understand mass loss rates derived from transit observations in the He 1083 nm line obtained by collaborators with the Palomar 200-inch telescope.

## Using Enhanced Watershed Dashboards to Inform New Precision Targets for FIA Small Area Estimates

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The Forestry Inventory and Analysis Program (FIA) has historically used two estimators, the Horvitz-Thompson estimator (HT) and the post stratified estimator (PS), to estimate forest parameters such as basal area in both small and large regions of the U.S. But the ongoing advancement of statistical and computing capabilities show that there are better model-assisted and model-based estimators that offer more precise estimates, especially in small areas. In this paper, we review and evaluate eight estimators suggested by FIA for estimating forestry attributes in watersheds as well as make recommendations for sensible alterations to current FIA precision estimates. The general framework used to evaluate models was gleaned from Tzavidis et al. 2018 which specifies three major steps of small area estimation namely: specification, analysis and adaptation, and evaluation. Our study shows that there are three estimators that perform well in small area estimates namely the Hierarchical Bayesian unit level estimator, the unit level Empirical Best Linear Unbiased Predictor estimator, and the generalized regression estimator. The choice of best models depended on the following five attributes: simplicity (parsimony), low variance, unbiasedness, few NAs produced (low data loss), and computational complexity. Although FIA seeks to find one best estimation technique that could be used in small area estimates, our research shows that there could be more than one best estimator depending on the response variable and auxiliary variables used.

## Empirical Bayes Approach for Constructing Higher-Order Coverage Confidence Intervals

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In classical multivariate analysis, there is an outcome variable of interest such as a patient having cardiovascular disease and several covariates such as age, weight, and smoking status, which are potentially associated with the outcome. In the era of big data, with tens of thousands of variables of interest like gene expression data for predicting cancer outcomes, different methods are needed. In high dimensions, a challenge is identifying which are relevant to the outcome variable, after which inference is performed like hypothesis testing. One appealing approach toeing the line between the two primary frameworks of statistical inference — frequentist and Bayesian — is Empirical Bayes, which shares properties of Bayesian methods such as allowing for the use of data multiple times in constructing a model and then performing analysis, but has weaker prior assumptions. We introduce a new method for uncertainty quantification, a major goal of high-dimensional inference involving ranges rather than point estimates, using EB by a convolution of posterior distributions around an estimated parameter from the data. The method allows any choice of prior or data generating distribution, and we show that it has correct  $1 - \alpha$  coverage asymptotically up to order  $O(1/m)$ , where  $m$  is the number of data points, an improvement compared to naïve EB, which has correct coverage up to  $O(m^{1/2})$ . Using simulation study, we also empirically show that using our method results in intervals with desired coverage and is robust to choice of model, in addition to outperforming naïve EB for moderate  $m$  values.

# Zero Inflation in Small Area Estimation Models: Improving Forest Inventory Estimates

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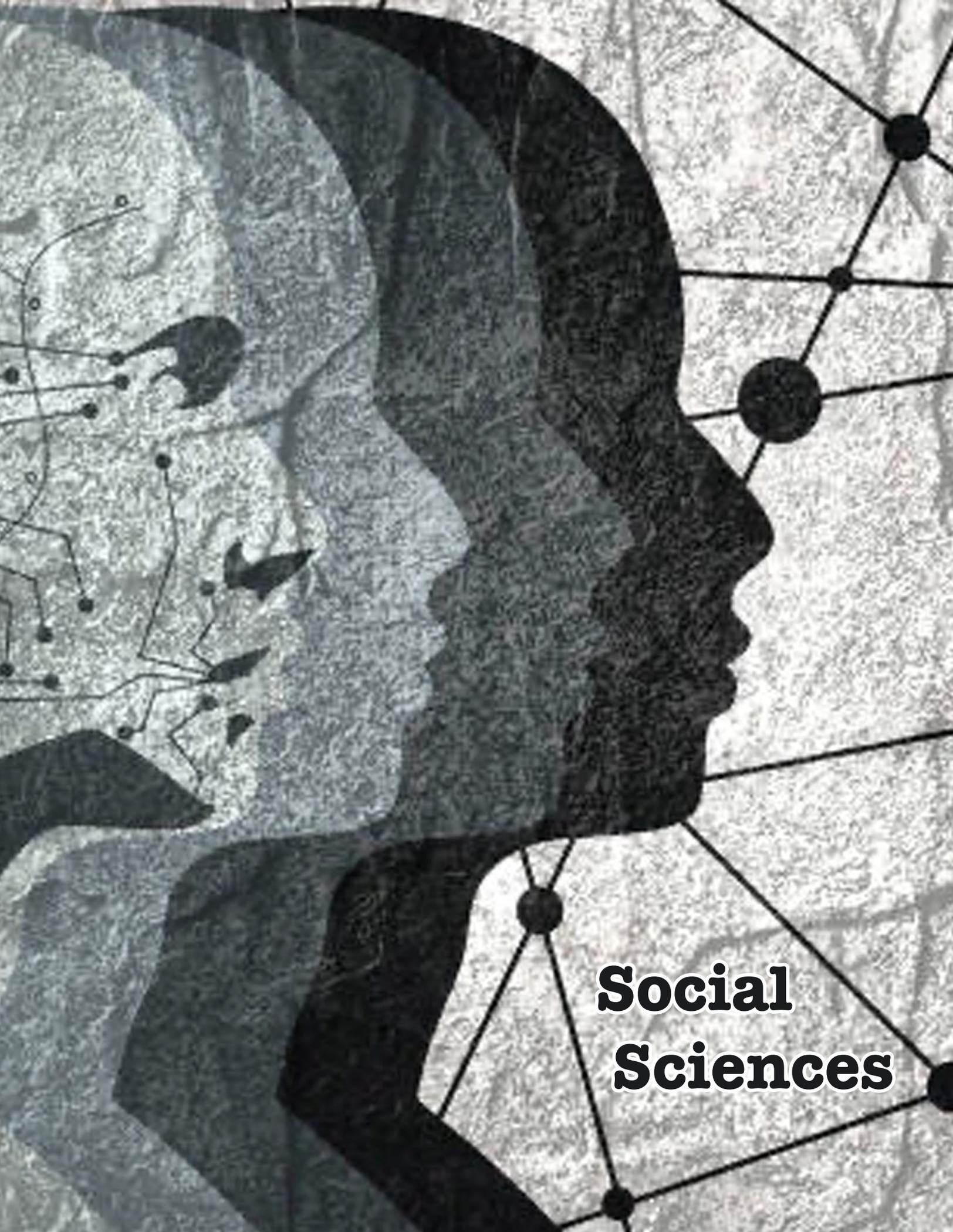
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Estimation of forest resources typically combines *in situ* ground plot observations with remote sensing layers to improve accuracy. The U.S. Forest Inventory and Analysis Program (FIA) is tasked with developing statistical techniques to improve estimation of forest metrics, such as tree volume and basal area, across small regions where typically only a few *in situ* measurements are made. Using estimators, such as post-stratification, area level empirical best linear unbiased prediction (EBLUP), and unit level EBLUP, that borrow strength across multiple regions in tandem with remote sensing, the FIA is able to significantly reduce the mean squared error (MSE) of their estimates. However, in regions where a significant portion of the plot measurements are zero, applying current estimators results in model mis-specification and poor confidence interval coverage. Using FIA data from an ecologically homogeneous region in the Northern U.S. Rocky Mountains as an example, we examine how using zero-inflation small area estimators (ZI-SAE) could improve upon current estimators. By tracking MSE, confidence interval coverage, bias, and variance in a simulation study, we find that when the level of zero-inflation is low, roughly 20% of the observations are zero, there is little benefit to using ZI-SAE estimators. We hope to show that at higher levels of zero-inflation, the ZI-SAE model begins to increasingly outperform other estimators, in particular the unit-EBLUP. We close with a framework for advising the FIA as to when to consider using ZI-SAE.





# **Social Sciences**

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## Economics

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### **The Effect of Clinical Trial Deaths on Innovation**

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In 1999, a young man named Jesse Gelsinger died in a clinical trial investigating a gene therapy. In the aftermath of this event, investment into gene therapies severely diminished. Some critics have argued this withdrawal of investment was an overreaction, and more generally, that society should be more risk tolerant when it comes to identifying new therapies. We, therefore, seek to answer the question: do we overreact to clinical trial deaths? Our analyses combine data from publications, patents, clinical trials, venture capital investments, and 10-K filings. We undertake a specific investigation of the case of gene therapy as well as a more general investigation of deaths across all clinical trials in order to quantify the public and private markets' responses to these deaths. These findings may serve to guide policies surrounding risk tolerance in clinical trials, with the hopes of optimizing incentives for the development of life-saving technologies.

### **The Wandering Scholars: Understanding the Heterogeneity of University Commercialization**

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Academic research has been one of the driving factors behind innovation and growth. However, one of the major shortcomings of academic research is that it never fully achieves its social benefits. Commercialization of academic research happens in many forms such as patents, start-up, scientific advisory boards etc. However, this commercialization varies greatly from university to university. In order to understand the reason behind this heterogeneity, we observe changes in commercialization when academics move between universities. We define commercialization as when academics are cited in patents, have startups, serve on scientific boards of firms, or are board members of companies. We employ an event study set up to measure how these commercial spillovers can be attributed to university specific factors. In our initial analysis of the data we find that at least 20-30% of variation is due to place specific factors. Further exploration of this variation will further help us understand the factors that drive the differences in innovation commercialization across universities. This would help us better inform policy such that society utilizes the maximum benefits that academic research has to offer.

## The Idea-Talent Gap

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Great ideas require talented teams to scale. This study documents that ideas focusing on the needs of women, people of color, and the elderly face a talent gap because of the underrepresentation of these groups in the U.S. startup workforce. Using recent observational data on the near-universe of incubated, seed-funded, and venture-backed U.S. startups, we find that ideas that cater to women, the elderly, non-U.S. customers, people of color, and other historically underserved groups are less likely to hire the talent needed to turn the idea into a thriving firm. To better isolate this idea-talent gap mechanism, we then launched a hiring field experiment to discover the true job preferences of those who are in or hope to join the tech startup workforce. By varying aspects of startup information in the hiring context, this platform can elicit detailed consumer preferences that will validate our idea-talent gap model. This study documents that there are profound differences in the types of startup ideas that attract talent and those that do not. Preliminary findings imply that potential startup workers are less likely to decide to apply to a job at startups that have ideas that are more focused on women and other minorities unless the job seeker is from a matching demographic group. As a result, ideas focused on these historically marginalized groups end up demographically matched to a much smaller pool of workers. Hence, this study implies that a lack of diversity in the talent pool for startups may systematically bias the direction of innovation.

## Improved Smart Reserve Systems for Vaccine Allocation: Fairer Outcomes, More Efficient Algorithms

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During the COVID-19 pandemic, the limitations of existing priority systems for allocating scarce medical resources became apparent. This prompted theoretical work by market designers, with the resulting mechanisms implemented in the field by policymakers in the health industry. These mechanisms can be used to satisfy conflicting ethical considerations by simultaneously reserving medical resources for multiple populations, such as health care professionals, the elderly, and the general public. We propose an economic model for the design of reserve systems, in which each reserve category can have its own independent beneficiary-eligibility criteria and its own priority ordering of agents. Using tools from market design and matching theory, we give multiple algorithms that extend the *fairness* properties from the previous framework to our more general model and are more computationally efficient than previously proposed ones. Our results show the possibility of simultaneously satisfying universal domain and maximality in beneficiary assignment, allowing independent priority orderings in categories and maximizing the number of patients receiving vaccines from a category they are beneficiaries of. This framework can also be applied in other situations such as affirmative action processes.

## A Tale of 3 Product Groups: The Disproportionate Consumption of Menthol Cigarettes, Skin Bleaching Products, and Feminine Hygiene Products in the U.S. by Black Consumers

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Menthol cigarettes, skin bleaching products, and vaginal hygiene products: all three product groups are harmful to their users, and all three are purchased in disproportionate amounts in the U.S. by Black consumers. To identify the root cause and mechanisms behind this discrepancy, this paper examines the history behind these products and how and where they were advertised. Understanding the long-lived effects of historical mechanisms like targeted advertising will help evaluate efforts today to mitigate the harmful effects of certain product groups on consumers, such as the 2022 FDA proposal to ban the sale of menthol cigarettes.

## Evaluating the Effects of ESG Disclosure on the Financial Market through Textual Mining of Quarterly Earnings Calls

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We investigate the information gap between firms and investors on their Environment Social Governance (ESG) policies, actions and beliefs. Quarterly Earning Calls are the main form of communications between firms and investors. They can be broken down into three components: prepared remarks, questions and answers. Using natural language processing tools such as BERT: Google's pre-trained deep bidirectional transformers and Hugging Face transformers, each component of the conference call's ESG sentiment can be quantified. The first model breaks down the text into E, S, G or None, while the second to further breaks it down into 25 subcategories of ESG. After transforming the text into, we can now look at the effects of the conference calls on three indicators: Stock Performance, Financial Information and ESG Ratings.

## Optimal Traffic Routing in Rio De Janeiro

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Road traffic in Rio De Janeiro results in billions of hours spent in vehicles each year, and may affect access to work and labor supply in a city riven by inequalities. In this empirical work, we use rich real-time camera data on car sightings to study how commuters in Rio De Janeiro respond to traffic shocks like floods, accidents, and cultural events. Using billions of sightings of cars throughout the city, we construct a road network graph that represents how traffic flows through the city — using statistical techniques on large graphs to accommodate for missing data — and the unique different paths that commuters take between their origin and destination. We superimpose data about traffic shocks on this, and study commuter responses to such shocks in terms of their route choice. We test for arbitrage in terms of shortest paths, and estimate a model where commuter responses are non-linear due to inattention, idiosyncratic preferences or switching costs. In the estimated model, we analyze the impact of the propagation of shocks in the network due to non-linear individual responses.

## An Investigation of Omnichannel Retail Pricing

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The expansion of online retail and machine learning technology has prompted the investigation of pricing algorithms and their implications to market competition. However, as more firms switch to omnichannel retail, the effects of complementary strategies such as geographic pricing and price matching within the online realm are still unknown. In this report, I use a combination of high frequency data and discussions with practitioners to assess pricing practices across geographies, price matching policies, and potential implications to competition. Thus far, preliminary results suggest that there exist differences in pricing strategies between online and in-store channels, including a higher degree of geographic price dispersion across brick and mortar stores. Furthermore, industry research suggests that, effectively, variations in pricing policies are tied to retailers' operational capacity, product features, and characteristics of their respective markets. Implications for competitive pricing include allowing retailers with a greater operational capacity and a lower degree of price transparency to increase their profits through the employment of geographic pricing strategies.

## Intercollegiate Varsity Athletes: Career Performance

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Varsity athletes make up over 10% of students at elite colleges in the U.S. Colleges heavily invest in athletics and student athletes spend a significant amount of time training and competing. However, it remains unclear how athletics contribute to the participants' human capital development. Existing research shows that on average, student athletes have lower GPAs upon both college entry and graduation relative to their non-athlete peers, while anecdotal evidence suggests that many athletes achieve comparable, if not better, career outcomes. To this day, few studies have rigorously examined the athletes' career preferences and outcomes after graduation. We fill the gap by investigating the differences between Ivy League athletes and their non-athlete peers in early career preferences, advanced degree attainment, and general career success measured by the speed of their career progression. Using over 273,530 resumes of Ivy League graduates from a prominent professional networking website as well as hand-collected, public data on intercollegiate varsity athletes, we show that athletes are more likely to enter an industry of high status and high pay (such as finance, consulting, and technology) upon college graduation, more likely to obtain an MBA degree, and less likely to obtain non-MBA advanced degrees. Moreover, athletes show significantly faster growth starting from the second year after graduation and eventually achieve positions of higher seniority than their non-athlete peers.

## Artificial Intelligence and Alternative Data in Commercial Banking for Credit Risk Management

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Advisor: Suraj Srinivasan

Supervisor: Jung Koo Kang

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Credit risk is the risk lenders face when a borrower does not pay back the principal and interest loan amounts. Artificial intelligence and big data continue to disrupt the banking and financial industries and can help financial institutions better manage credit risk. Many studies have looked into how banks and financial technology use artificial intelligence and big data in their business processes. However, the insights of such studies aggregate their findings and fail to drill down to investigate how banks specifically use machine learning techniques and alternative data for their middle office credit risk management operations. Machine learning refers to the subset of artificial intelligence that gives computers the ability to learn from datasets without being explicitly programmed to do so. Alternative data describes potentially decision-relevant but underutilized data sources, which are only available in unstructured form and cannot be used in established forecasting or risk models without prior processing. This study uses a quantitative methodology by surveying banks on how they implement artificial intelligence and alternative data in their credit risk management. We are especially interested in how banks use machine learning and alternative data to comply with Financial Accounting Standards Board (FASB) accounting standards for allowances for and provision of credit losses under accounting standards update (ASU) 2016-13. This study will provide insights to the current state of adoption of artificial intelligence and alternative data in commercial banks for credit risk management and provide recommendations to increase the state of adoption.

## Employee Ownership

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The predominant workplace model in the United States, the wage-labor system, leaves room for incentive divides between a firm's employee workforce and upper management (i.e., employees generally seek to maximize their hours to accrue payment, meanwhile lacking the incentive to devote their best effort to the firm). We study the recent phenomenon of private equity firm KKR purchasing companies and concurrently implementing an employee ownership model (whereby employees are entitled to stocks of the company, stock options, or some variation of ownership) and its effects on employee compensation, employee satisfaction, firm performance, and the viability of investment as a private equity firm. We contextualize and contrast this variation of the employee ownership model with more orthodox variations, specifically employee stock ownership plans (ESOPs). Historical ESOP performance provides us with the basis that employee-owned firms outperform those that are not employee-owned, yet the usage of ESOPs has declined in recent years – primarily due to their tax benefits being continually slashed since the late 1980s. Preliminary findings (in the form of KKR case studies, e.g., the buyout, restructuring, and sale of CHI Overhead Doors) suggest that there is great potential for private equity firms to implement employee ownership schemes when purchasing a company, insofar as employee compensation, employee satisfaction, and firm performance increases. Although these results are promising, more empirical research is needed to definitively parse successful implementation strategies and the generalizability of these results.

## What Alternative Data Are Credit Techs Using?

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With the emergence of innovative financial technology and fintech companies has come many new financial areas and services. One such area is credit tech. Credit tech is an alternative to credit bureaus and traditional credit scores around the world and possibly a future replacement as they are expanding the accessibility to affordable loans. These companies assess creditworthiness based on traditional and non-traditional data, also known as alternative data. The need for credit techs stems from the fact that many people around the world do not have access to credit scores through a credit bureau, which makes it extremely difficult or impossible to get affordable loans. Through interviewing and reading various academic articles, companies' websites, and companies' documents, this paper has discovered several forms of alternative data with illustrations of how companies are using them. Some examples of alternative data that credit techs are using to assess creditworthiness are people's personal online history, social media, apps, spending behavior based on past transactions, and text messages. Because of the sensitive information credit techs are using for their creditworthiness assessments, it is very important for entrepreneurs and consumers to understand how and what information these companies are using.

## Career Seniority and Historical Social Mobility of U.S. College Graduates

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Supervisors: Will Levinson and George Hu

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The study applies and enhances a previously proposed non-pecuniary measure of career achievement, Seniority, defined as the median time in years it takes a person to first achieve a position in a given industry. Prior to this measure, human capital across fields was assessed almost exclusively on wages which neglected non-monetary influences in career choice that would often downplay the accomplishments of entrepreneurs and other non-traditional professions. Using data containing over 200 million resumes, the study tracks the geographic information, education levels, and career paths of college graduates in the United States from the 1950s. This is achieved by matching the individuals identified in the resumes to a database storing the Social Security Numbers, addresses, and birth dates of over 236 million people. Once matched, the seniority variable is calculated for each identifiable person to compare trends in the labour market outcomes and moving patterns of entrepreneurs and non-entrepreneurs. Thus far, the study is in the process of optimising the matching algorithm used to track people in the databases, and new factors such as firm size and differences in cross-industry characteristics are being incorporated into the seniority measure.

## How Much Do You Owe in Property Taxes? Depends When You Ask

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**Spencer Tyson**

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Advisor: Lauren Cohen

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Property tax assessors appraise the value of homes by utilizing algorithms and a localized set of criteria, but frequently, they simply determine the valuations at their discretion. These inconsistencies result in a remarkable observed phenomenon: on average, property tax assessors have lowered the valuations of their own homes relative to their neighbors and, therefore, pay less than their fair share in property taxes. We have analyzed an expansive repository of thousands of tax assessors nationwide, which includes data on average assessed property values, average tax payments, the value of the home relative to neighbors, the length of home ownership, and the length of political office. There appears to be a strong (-.5091) correlation between the time in office and the value difference compared to neighbors among the ten states studied, thus far. This correlation suggests that as assessors become more established politically, they are often more likely to fraudulently assess their properties. By manipulating these values, tax assessors and their political allies are not paying an equitable share of property taxes, and by analyzing both the macro trends and providing in-depth case studies, we will build a compelling argument for prosecutors. Future study will incorporate data on neighbors to observe whether this devaluation of homes occurs most frequently in high density areas or low density areas.

## Secular Stagnation and the Space Frontier

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Economic growth has recently slowed in several high-income countries, sparking fears of secular stagnation. Modern theories of secular stagnation suggest that these prolonged periods of sluggish economic growth occur despite low interest rates because of weak aggregate demand and a high propensity to save. Among the proposed causes are the lack of a frontier economy and a shift of investment away from capital-intensive activities. However, during the past two decades, significant private investment and innovation has driven unprecedented change in the space sector. Three features of current activity in space suggest the sector may offer a promising way to escape from stagnation traps: it is remarkably capital-intensive, requires significant innovation that resembles frontiers throughout history, and is beginning to leverage private investment that is highly responsive to public investment. Integrating existing work on frontier theory and the effects of the culture of individualism associated with it, this research proposes a link between space and innovation, framing space as a frontier that could incentivize increased innovation, R&D, and entrepreneurial activity. Then, an endogenous growth model describing secular stagnation is used to formally estimate the scale of required investment in space, with preliminary calculations suggesting that a government subsidy of roughly 5.5% could be sufficient to push the U.S. economy out of a stagnation trap.

## To Follow or Not to Follow: Self-Regulation and Imitation

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Advisor: Dennis Yao

Supervisor: Young Hou

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This project examines product business adjustment strategies following changing industry dynamics. We approach two specific industry shifts: when major competitors reposition products, and when the government threatens firms with regulation. The first study addresses the dynamics of self-regulation to avoid formal regulation. The second study examines how smaller businesses responded to product positioning moves by industry leaders to also avoid regulation. The RTE cereal industry is ideal for these studies because it consists of an oligopoly in which each firm produces differentiated products, and it faced government pressure to improve the nutritional value of its products. The latter pressure arguably led to self-regulation in major leaders' products and ensuing product positioning changes. In the first study, we build a simple theoretical model to capture firm dynamics and incentives. Then, using data from the children's segment of the RTE industry, we test counterfactuals on various regulation parameters to see which firms participate. The analysis examines how different pre-self-regulation market positions affect the ultimate choice of self-regulation. In the second study, we take advantage of the natural experiment created through self-regulation and match imitations and "parent" products. This identification allows us to use regression analysis with fixed effects to evaluate how imitators deviate from "parent" products in nutrition and performance data. Preliminary results suggest that branded and generic products follow similar trends, but additional analysis is required to explain subtleties in product changes. This research may have implications for broader firm strategy, especially in oligopolistic markets where product differentiation and imitation exist.

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## Government

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### Wall Street and Washington: How Banks Influence Financial Regulation

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Mathematics & Computer Science, 2025

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Harvard Faculty of Arts and Sciences

Advisor: Daniel Carpenter

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Regulations passed by administrative agencies play a central role in the American government, as these regulations are enforced as strictly as laws and extensive resources are deployed in the regulation-making process. In the present work, we examine interactions in the context of banking. We aim to find the resources bank holding companies utilize to interact with government financial institutions. Using bank holding company information on legal expenses from consolidated financial statements; agency enforcement actions released by the Federal Reserve, the Federal Financial Institutions Examination Council, the Federal Deposit Insurance Corporation, and the Office of the Comptroller of Currency; and litigation information from the Federal Judicial Center, we investigate correlations between various banking activities and bank legal expenses. We can analyze the most significant predictors of bank legal expenses to determine how legal resources are invested. Findings about the resources deployed toward influencing government agencies can be used to uncover interactions that affect both policymaking and sources of inequality in American democracy.

### Measuring Gerrymandering in Congressional Redistricting

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Harvard Faculty of Arts and Sciences

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Supervisors: Christopher Kenny, Cory McCartan,  
Philip O'Sullivan, and Tyler Simko

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The Forestry Inventory and Analysis Program (FIA) has historically used two estimators, the Horvitz-Thompson estimator (HT) and the post stratified estimator (PS), to estimate forest parameters such as basal area in both small and large regions of the U.S. But the ongoing advancement of statistical and computing capabilities show that there are better model-assisted and model-based estimators that offer more precise estimates, especially in small areas. In this paper, we review and evaluate eight estimators suggested by FIA for estimating forestry attributes in watersheds as well as make recommendations for sensible alterations to current FIA precision estimates. The general framework used to evaluate models was gleaned from Tzavidis et al. 2018 which specifies three major steps of small area estimation namely: specification, analysis and adaptation, and evaluation. Our study shows that there are three estimators that perform well in small area estimates namely the Hierarchical Bayesian unit level estimator, the unit level Empirical Best Linear Unbiased Predictor estimator, and the generalized regression estimator. The choice of best models depended on the following five attributes: simplicity (parsimony), low variance, unbiasedness, few NAs produced (low data loss), and computational complexity. Although FIA seeks to find one best estimation technique that could be used in small area estimates, our research shows that there could be more than one best estimator depending on the response variable and auxiliary variables used.

## When We Go All: The Evolution of Far Right Ideology on Parler

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This study assesses ideological framing discourses on social media among members of the contemporary American far right from November 1st, 2020 to the Capitol insurrection on January 6th, 2021. It investigates the ways in which meanings of terminology relating to collective action evolve in response to online dialogue. I employ a mixed-methods approach that combines structural topic modeling and in-depth qualitative analysis of topics to analyze approximately 3 million posts and comments from the right-wing website Parler. After determining the topics discussed by users, I extract posts relating to violence, overthrowing the government, and religion and analyze them qualitatively. Informed by Mikhail Bahktin's notion of dialogue, I combine posts using these terms into a singular text and perform a "reading." I treat each post as a unique voice that informs the collective ideological function of each term, and track the evolution of terminology in posts over time. This study not only sheds light on the nature of online discourse relating to far right collective action, but also the rhetorical techniques used by various users to justify violence. I find that a plurality of Parler users believed by the time of January 6th that the government had already been overthrown on November 6th. I also find that, in comparison to this previous "coup," the events of the insurrection seemed insignificant if not entirely justified to Parler users.

## United States Party Organizations in a Polarizing Era: State Party Chairs, 1980-2022

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Supervisors: Kirsten Walters and Ben TerMaat

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Despite being critical nodes of authority and resource deployment for national and local politics, state parties are often understudied in the field of political science. Thus, this project aims to break new empirical and theoretical ground by using newly assembled data from newspaper archives and other primary sources on Republican and Democratic party chair transitions across states from 1980 to the present to answer the question on how state party organizations have changed as national politics become increasingly polarized? We examine trends in contestation of chair elections, reasons for resignations and leadership changes, timing of turnovers in relation to national and state-level political events, and career lines of state party chairs. Our preliminary findings suggest important parallels and divergences between Democratic and Republican party organizations and operations. In key states, we find that contestation of chair elections partially depends on state traditions, like the influence of the governor or gubernatorial candidate on the nominee for chair, and the success of the state party in the most recent elections. In regard to early resignations and career lines, the Arizona Democratic party stood out as an example of the chair position being a stepping stone for political career due to the high rate of early resignations of chairs to run for public office. Furthermore, we plan to examine a range of institutional and contextual factors contributing to factional changes within each party orbit, such as those occurring in the Trump-era, to get a better understanding of state parties from 1980 to the present.

# From Health Education to HIV: Utilizing Policy to Inform Communities

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Fenway Health

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Supervisor: Alyvia Norris

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In Massachusetts, schools that teach sex education are not bound by any regulations concerning LGBTQ+ inclusion, medical accuracy, and overall comprehensiveness. For over a decade, legislative action under the Healthy Youth Act (S.2541) has aimed to address these needs. By implementing legislative pressure, such as organizing a rally backed by a coalition of sex education supporting organizations, we hope to bring this bill to the floor for a vote by the end of the legislative session. To further educate communities, we worked under Getting to Zero Massachusetts, an organization that aims for zero new HIV diagnoses, zero stigma, and zero AIDS-related deaths in the state of Massachusetts. Guiding communities both inside and outside of Massachusetts in making informed choices, we hosted a series of free webinars through “The People’s Sex Ed.” During these, anyone, especially folks coming from underrepresented communities, can learn about how topics like LGBTQ+ identities, disabilities, intersectionality, pleasure, and media literacy impact their health. Furthermore, focusing specifically on HIV/AIDS advocacy, we created guidebooks and educational materials to train individuals to take action in their communities through the “Activist Academy.” Each event is both driven and improved by participant and organizer feedback. After gathering and analyzing these evaluations, we found that many individuals expressed that they lacked adequate and inclusive sex education in school, do not feel equipped with tools to take on HIV/AIDS activism, and do feel the need to expand health education curriculum on all fronts. These results indicate the impact advocacy and urgent legislative action on health education can have on communities making informed choices.

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## History

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### An Americanist Studies His Civil War

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**Emmy Cho**

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Harvard Faculty of Arts and Sciences & Houghton  
Library

Advisor: Drew Faust

Supervisors: Kristine Greive and Zoe Hill

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Influenced by the interdisciplinary ethos of the American Studies program, “An Americanist Studies His Civil War” integrates archival research, historical-literary analysis, and narrative prose to better understand the fraught but fruitful relation between facts, fictions, and truths of a national past. This meta-dynamic is observed through the life of one scholar from his graduate studies at Harvard University during the 1930s to the completion of his literary investigation of the American Civil War in 1973. Nearly seventy-five years after the Battle of Appomattox, Aaron received the University’s first degree in American Studies. Throughout a distinguished career, he sought to understand the country’s elusive past and tumultuous present by historicizing its literature and discerning the literary value of its history. His integrative approach was applied to one of our nation’s most contested events with *The Unwritten War: American Writers and the Civil War*, which translated a public history through the interiors of literary figures made legible by their published words. This paper derives its life blood from a selection of over 125 boxes of Professor Aaron’s personal archives. Stored inside Houghton Library, Harvard’s home for rare books and manuscripts, these documents teach us how to excavate immaterial truths about the Civil War from its physical remains. The author argues that Aaron’s treatment of the writer as historical figure and literature as historical document calls for a definitional broadening of the “archive.” She concludes with why facility in multiple humanistic languages is essential to gain fluency in the truth of the past.

### Urban Futures in History

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Advisor: Bruno Carvalho

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As urban populations skyrocketed in the early twentieth century, envisioning the future of cities became a transatlantic obsession. The structure of these future cities (their architecture and layout as well as their politics) can shed light on the competing ideas of what and who belonged in the urbanized world. To support Professor Bruno Carvalho’s forthcoming book, I looked at a wide variety of early science fiction narratives, magazine advertisements, and histories of city planning, analyzing their representations of urban futures. My research shows how these sources, influenced by New York City, overwhelmingly imagined an abundance of sleek, metallic skyscrapers laid out along a highly-organized grid. Many early dystopian narratives pessimistically portrayed this vertical dimension as a means of class segregation. As well, illustrations of the 1920s and 1930s in particular imagined monorails, trains, and airplanes dominating future cities, rather than cars. As part of Professor Carvalho’s history of urbanization, this research helps show the integral role that popular imaginings of future cities played in urban development.

# Analyzing Spanish-American War Art through the Lens of the White Savior Industrial Complex

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Harvard Faculty of Arts and Sciences & Houghton Library

Advisor: Kristine Greive

Supervisor: Zoe Hill

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This project is a series of video essays discussing the White Savior Industrial Complex (WSIC) as present in works of art from the Spanish-American War. Most research on the WSIC in art focuses on contemporary works. Yet, in the United States, the WSIC is present in art as old as the nation itself. Art depicting the Spanish-American War often reflects the narrative that the United States joined the war and annexed the former Spanish colonies for moral and ethical reasons rather than financial and political ones. Through this project, I add to the limited discussions of portrayals of colonized people of color in said art. All of the works of art, which include chocolate trading cards, patriotic newspaper poems, and photographs, are part of Houghton Library archives. My findings include that colonized people are often portrayed as powerless in the war and the depiction of the WSIC in art is not exclusive to the United States. Ultimately, understanding the presence of the WSIC in art surrounding the Spanish-American War serves two purposes: one, it highlights the gaps in our understanding of this time period and two, it contextualizes contemporary conversations on the WSIC in the present-day.

# Amend: Rewriting the Constitution

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As the supreme law of the United States, originally penned in 1787, the Constitution has undergone copious attempts at amendment. To understand our Constitution in today's context, we endeavored to explore all attempts to amend it. Along with secondary sources, I used the "Black Women Suffragists" section of the "Women and Social Movements in the United States, 1600-2000" collection in Alexander Street, a digitized database. My aim has been to catalog and analyze arguments made by Black women specifically pertaining to amendments and/or the Constitution, focusing on the abolition and suffrage movements. I also explored the Archive of Americana "Hispanic American Newspapers" database, focusing on the Hispanic community's contribution to the constitutional conversation in the first half of the twentieth century, including the enactment of new state constitutions and comparisons between the U.S. and Mexican Constitutions. Within this research arose meaningful and complex contributions to constitutional discourse, many of which are largely left out of our country's constitutional memory. One noteworthy element is the prevalence of written constitutionalism within both these communities, with regard to societies, associations, and state constitutions. Though the U.S. Constitution proved nearly impossible to amend, Black women and Hispanic communities utilized written constitutionalism with their own processes of amendment in their struggle for political rights, the constitutions doubly functioning to codify their purpose and demonstrate their political ability. Though proposals for amendments are relatively scarce within these communities, they utilized constitutionalism in other forms to define their political situation in the United States.

## Crowley-Thoth Tarot: Mysticism for the Masses

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Harvard Faculty of Arts and Sciences & Houghton  
Library

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Tarot is a mainstay of New Age paraphernalia, typically used in the occult practice of divination. Though the 78-card playing deck has been around since at least the 15th century, it has only been associated with divination since the late 19th century. This video essay will examine one popular tarot deck, the “Crowley-Thoth Deck,” by discussing its creators, occultists Aleister Crowley and Lady Freida Harris, its influences, and its intended usage as a part of occultist practice. The video makes use of footage of rare documents in Houghton library to visually demonstrate the development of tarot; books and letters from the Houghton archives illuminate personal and overlooked details of the deck’s creators. Just as tarot is seen as an accessible, visual way to access “hidden knowledge,” this video essay is meant to make the theory behind tarot more accessible and bring its often-forgotten history into public view.

## Margaret Sanger Graphic Novel

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This graphic novelette enriches and complicates the legacy of Margaret Sanger, the founder of Planned Parenthood, by exploring her life as a wife and mother in addition to her work as an activist. The graphic novel consists of an illustrated short story that contends with Sanger’s anti-abortion views and support of the eugenics movement while also including her volunteer work as a nurse on the Lower East Side and her early birth control activism. Anchoring itself in the very personal and traumatic loss of her youngest child and only daughter, Peggy Sanger, the novelette further addresses her dedicated search for an answer to the question of birth control. The Margaret Sanger Papers in Houghton Library served as the primary source of research, with Sanger’s personal letters on the loss of her daughter and her decision to leave the United States in 1914 as the central plot points. Sanger’s memoir, *My Fight for Birth Control*, and secondary sources from academic journals and newspaper articles served as supplemental research material. The graphic novel offers a new means to understand the complex historical legacy of Sanger that challenges any one-sided perspectives of her birth control activism while reflecting on the problematic views she held. Further, most research conducted today that challenges Sanger’s legacy does so without fully exploring her anti-abortion views; the graphic novel is unique in contending with Sanger’s personal life, activist work, association with the eugenics movement, and anti-abortion views in one creative project.

## Digitally Mapping the Creation and Movement of Ancient Wealth

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Ancient Roman maritime trade routes, whether in the Republican, Imperial, or Late Antique era, stretched throughout and beyond the Mediterranean carrying people, raw materials, and complex objects. Few texts providing economic data survive from this era, so knowledge about Roman maritime trade comes primarily from shipwrecks. This project compiles and maps a database of Ancient Roman shipwrecks found throughout the Mediterranean and as far as the United Kingdom and central Africa, ranging approximately from 700 BC to 800 AD. The 2,340 database entries come from archaeological field reports and syntheses of archaeological excavations done within the past fifty years, found through a systematic review of the scholarly literature, and represent a significant expansion from the 1,259 entries in Parker's 1992 Roman shipwreck dataset, as well as Harvard's previous 1,936 entry dataset. The database contains locations, ship types, detailed descriptions of ship contents, date ranges, and more data for a massive amount of shipwrecks, and is restructured to expedite and simplify data analysis. We used kepler.gl software to map these shipwrecks over time, allowing for analysis of individual metals and Roman amphoras, and found trends in the locations of shipwrecks containing lead ingots, bronze objects, or amphoras. Combined with data procured and mapped about Roman mining of precious metals, this database provides a greater understanding of Roman economics visible and understandable by historians and laypeople alike.

## The Justinianic Plague: Telling the Story of the World's First Pandemic

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When the outbreak of bubonic plague known as the Justinianic Pandemic struck the Mediterranean world in 541 CE, the societies of the late- and post-Roman world encountered *Yersinia pestis*, the deadliest pathogen in human history. Over the next 250 years, repeated outbreaks of the plague killed millions of people, devastated local economies, and changed survivors' relationships with religion and mortality. This project uses the ArcGIS StoryMaps tool to present the Justinianic Plague in an accessible, interactive format in order to help non-specialists understand the significance of the first plague pandemic. The Justinianic Plague is often credited for the transition from late antiquity to the Middle Ages. Parallels to the Covid-19 pandemic abound, from the personal experience of terror to the restructuring of global commerce. However, public understanding of the Justinianic Plague is limited by the obscurity of available data. Ancient texts are difficult to translate, let alone interpret, because they are deeply embedded in a classical tradition and reflect a religious, as well as scientific, causal framework. But texts are not the only evidence: archaeological techniques such as ancient DNA analysis have allowed major breakthroughs, such as finding plague victims in regions where no written sources mentioned an outbreak. This is an exciting growth area for the field that the StoryMap makes accessible to teachers and students alike. The Justinianic Plague StoryMap is a teaching tool that explains the pandemic from a variety of approaches, including pathological, archaeological geospatial, and emotional perspectives, in order to reach a wide audience.

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## Psychology

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### Contextual Constraint Effects on Spoken-Word Recognition

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An important part of understanding spoken language is identifying the words a listener hears. This project uses visual-world eye-tracking to analyze whether listeners use sentence context in addition to the sounds of a word to help with its recognition. Participants are shown a critical image, a task image, and two distractors. While their eye movements are recorded, they hear sentences with either a high semantic constraint on the target noun (the HC condition; e.g. *the sleepy child lay on his bed...*) or a low constraint, meaning the context allows for more possible inputs (the LC condition; e.g. *the happy child showed his friend his bed...*). They must select the image matching a word in the sentence (the task image). The critical image is manipulated so it either appears with a target starting with the same phonemes (the cohort condition) or a target for which it is not a cohort competitor (the control condition). We expect more fixations to critical images (e.g. *belt*) as listeners hear the target in the cohort condition (e.g. with target *bed*) than the control condition (e.g. with target *car*). We are investigating whether this effect differs in HC and LC sentences. Our adult pilot study (n=24) shows that listeners fixate on critical images more in the cohort condition, with a large effect in the LC condition and no effect in the HC condition. This suggests that listeners use the HC sentence context to aid word recognition by ruling out cohort competitors as possible input matches. We will compare adult results to 4 to 7 year-old children, since children's reduced cognitive maturity and language experience may make context harder to consider.

### Feeling Seen: Leader Eye Gaze Promotes Psychological Safety, Participation, and Voice

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Psychology & Business Administration , 2023

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Harvard Business School

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Supervisors: David Levari, Jennifer Abel, and Nicole Abi-Esber

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Psychological safety is essential to an effective and efficient team. Prior research suggests that leaders can influence employees' feelings of psychological safety, willingness to participate, and voice decisions. Although we know leaders can influence employee emotions and actions, little is known about "the specific behaviors leaders employ to lead employees to assess an interaction as safe to speak" (Morrison, 2011). In a lab study of face-to-face group interactions, participants are asked to role-play as different managers at a small bookstore trying to decide on a supply methodology. A confederate study design was used to influence a person's willingness to participate in a group's decision-making process by mitigating eye gaze (Eye gaze is the act of making eye contact with another person). In this experiment, the leader (the confederate) either ignores or makes eye contact with a group member. We hypothesize that the group member who does not receive the leader's eye gaze will be less likely to participate in the decision-making process. We also hypothesize that this result will be moderated by individual characteristics of group members, such that the effects of eye gaze will be stronger for racial minorities and more introverted individuals.

## Attention to Variability (ATV) with Persons with Epilepsy (PWE)

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Epilepsy is a neurological condition that is categorized by abnormal neuronal activity in the brain. Currently, there is no cure for epilepsy, but there is a way to manage seizures with anti-epileptic drugs (AEDs). Approximately, one in three people with epilepsy (PWE) have break through seizures, which means that they cannot control their seizures. The question, though, is whether or not attention to variability is something that can improve health outcomes and reduce symptoms with PWE such as stress, fatigue, and more. The study would consist of approximately twenty participants from the 18-40 age group. These PWE would all currently be taking AEDs that do not currently control their seizures. Participants will be asked to keep a diary to record their daily activities for a two week period. They'd have to diary their observations, and any patterns they may notice regarding how their body feels and their health habits such as food intake or sleep every day. This will allow them to get to notice symptoms, such as before and after an epileptic episode. By being more mindful and recognizing these patterns, PWE can develop healthier habits and potentially decrease the risk of having a seizure. Before and after the study they will take the Quality of Life in Epilepsy Survey. We expect that being more mindful and attentive to daily needs will allow PWE to reflect on their daily routine and actively improve health habits. This will lead to a reduction in symptoms that can trigger seizures.

## EMPOWER: Building the World's Mental Health Workforce: Formative Research with Non-Specialist and Specialist Providers

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Supervisors: Natali Carmio and Margaux Amara

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Mental disorders such as depression and anxiety comprise the leading cause of disability amongst the global population, emphasizing the urgent need for healthcare professionals trained in evidence-based psychological interventions. The chief barrier preventing individuals afflicted with mental illness from receiving proper treatment is a shortage of providers versed in the aforementioned training, though there exists cogent evidence of non-specialist providers successfully delivering these treatments in primary and community care settings. The EMPOWER project operates with the goal of leveraging digital training technologies to facilitate the development of necessary clinical skills in non-specialist professionals such that they become well-acquainted with the knowledge of evidence-based therapies and can eventually perform psychological interventions in individuals who suffer from mild mental disorders. With the help of non-specialist and specialist providers, we have co-created culturally and contextually relevant training content that has been compiled into online courses that healthcare professionals can complete with the ultimate aim of delivering comprehensive mental healthcare to clients. This work is particularly salient in rural and low-resource areas where access to psychotherapy is extremely limited, but need remains high. Courses have been developed in "Foundational Skills" and "Behavioral Activation" using the Cornerstone learning management system, and the project is currently in its formative research stage where we have conducted focus groups with community health professionals, registered nurses, clinical social workers, and clinical psychologists who have taken the courses to garner feedback regarding the structure of the digital platform and the content of the training courses.

# Examining Ways to Increase Quality Improvement Engagement in Healthcare Workers

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Engaging all healthcare workers in quality improvement (QI) efforts is vital to boosting the United States healthcare system. Hospitals have used monetary incentives such as payment systems as well as other “perks” systems to extrinsically motivate workers. However, there is a lack of research demonstrating how intrinsic motivators can be used to engage healthcare workers in quality improvement efforts. In our research, we will be drawing on job characteristics and psychological safety theories to examine how to motivate healthcare workers to engage in quality improvement. Job characteristics theory states that core job characteristics such as skill variety, task identity, task significance, autonomy, and feedback predict intrinsic motivation and work engagement. Psychological safety theory predicts that when there is a shared understanding among members that the team is safe to take interpersonal risks, they are more likely to engage in quality improvement. Our hypotheses are as follows; core job characteristics are positively correlated with QI engagement; psychological safety is positively correlated with QI engagement; psychological safety positively moderates the relationship between job characteristics and QI engagement. We will be conducting a survey of a large academic health system using previously validated measures to test our hypotheses.

# Perceiving Biological and Artificial Objects across Shape Transformations

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Objects are not static but change shape over time. We propose that object recognition involves the perception of this change and is based in category-specific knowledge. To explore this hypothesis, we focus on two kinds of objects: biological kinds and artificial kinds. These object kinds are inductively rich: organisms grow, move, and generate their own shape changes; artifacts are fixed in size, inanimate, and passively manufactured, deformed and repaired. We propose that our perceptual representations of objects specify these kind-specific transformations. This lets us predict the future forms of objects and generalize inferences to novel objects. Expectations about biological transformations likely embody early-developing, evolved “core knowledge,” while expectations about artificial transformations are likely late-developing and culturally varied. To test this, we define 6 shape transformations and apply them to 2D stimuli of three categories: animals, plants and artifacts. We perform two experiments on infants, children, and adults: an object recognition task, where subjects judge whether a kind-specific stimulus is the same object before and after a transformation, and a categorization task, where subjects categorize objects portrayed by the original stimulus based on transformation. We predict that older children and adults accept only kind-appropriate transformations as identity-preserving, whilst infants predominantly accept biologically appropriate transformations. We then build a generative model using probabilistic context-free grammars to empirical data. This research builds on the emerging probabilistic generative approach to cognition, specifically to explain how rich categories and concepts are represented in perception.

## The Tainted Donor Dilemma

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Tainted donations, donations that come from a source associated with scandal, pose a large threat to nonprofits, raising the question whether it is ethical to accept the money and put it to good use or refuse to accept it. Although the donations may be used in a way that aligns with consumer beliefs, consumers view nonprofits that accept tainted donations as less moral and unworthy of their trust. Consumers are in turn less likely to donate, and this effect applies to both low and high donation amounts, and monetary and goods donations. There are numerous ways to mitigate negative consumer reactions ranging from emphasizing all the good the nonprofit will be able to achieve with the donation to returning the donation or redirecting the donation to another nonprofit. This research explores the consequences a nonprofit may face when they receive tainted donations and solutions to the challenges they may encounter.

## MATCH

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MATCH is a psychotherapy designed for adolescents with multiple mental health concerns, featuring 33 modules within four protocols: anxiety, trauma, depression, and conduct. Research on the effectiveness of MATCH has been mixed, and experts have suggested that identifying methods to optimize the complex decision-making in MATCH might enhance benefits. MATCH clinicians are encouraged to use data provided by clients at the beginning of treatment to inform decision-making, but there is variability in the extent to which clinicians do so. Using data from a randomized trial of MATCH (n=200), we developed and applied a decision tool to identify the “best-fit” MATCH protocol for each client, according to adolescent reports of their symptoms before treatment. We then determined the degree to which these “best-fit” protocols aligned with the protocol that the clinician actually selected, resulting in two categories: whether the clinician-selected protocol aligned with client reports or did not. We tested this categorical variable as a predictor of adolescent-reported symptoms across treatment. Adolescents reported significantly fewer symptoms across treatment when the clinician-selected MATCH protocol aligned with their reports, relative to when it did not align with their reports ( $b=2.26$ ,  $p = 0.012$ ). These data offer preliminary evidence that the extent to which clinicians use client reports of their symptoms to inform decisions during psychotherapy might impact important clinical outcomes.

# Speedy Activists: Firm Response Time to Sociopolitical Events Influences Consumer Behavior

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In the current sociopolitical climate, companies face growing pressure from consumers and shareholders to take a stand publicly on sociopolitical issues, such as “Black Lives Matter” (BLM) and other current events in the media. But how can brands best publicly respond to sociopolitical issues? Using large-scale field data from Instagram and online experiments, we examine various cues that brands can take on with their public statement that affect consumer sentiment, brand preferences, and positive associative memory. Preliminary results seem to suggest that firms that react swiftly to sociopolitical events accrue outsized benefits, and late-movers can face significant reputational penalties for which sacrificing profits cannot compensate.

# Impact of Managers’ Beliefs about Low-Wage Jobs on Labor Conditions

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Working conditions in low-wage jobs have historically been substandard, even as various groups have advocated for improved labor conditions. This line of work investigated whether managers’ beliefs about low-wage jobs inform the labor conditions they think workers in those jobs deserve, an area of research that has garnered little attention. We ran a between-subjects experiment ( $N = 400$ ), with a sample of managers on Prolific Academic. Managers were randomly assigned to read a description of a low-wage or professional job and read a list of job factors (e.g., job security, benefits, flexibility of hours, etc.). Managers were then asked to rate the difficulty of improving the three job factors that they listed as most important using a Likert item measure of difficulty. If they rated a factor as being difficult to improve, they were asked to list one to five barriers. We conducted open coding of the various barriers managers listed for pay, benefits, and job security. Results suggested that overall, some commonly perceived barriers to improved pay included inflation, the quantity of workers, and overall education level. Managers were also more likely to list a greater number of barriers to improving pay in low-wage jobs. These results suggest that improvements to low-wage jobs may be more attainable than anticipated. Future work will explore other psychological barriers to improvements of low-wage jobs, such as the belief that low-wage jobs are low-skill and can be done by anyone.

## Pronouns and Prejudice

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Observers' perceptions of others and the stereotypes individuals hold about groups have been studied extensively in social psychology; most existing research has been conducted using social categories such as sex, race, or religion. To date, very little experimental research on perceptions of individuals who use gender-neutral pronouns has been done. The present study investigates the stereotypes, attitudes, and judgements involved in the perception of nonbinary people. Specifically, we investigate how perceptions of a student biography are modulated by nonbinary gender identity markers (pronouns) and race markers (affinity group). Harvard undergraduates will be recruited to complete a survey and randomly assigned to one of twelve student biography conditions, pairing three gender pronoun options and four racial affinity group options. Participants will be prompted to imagine that the student is their upper-level peer mentor for the upcoming academic year and asked to evaluate them on a variety of traits related to competence and warmth in line with previous stereotype content research. If our hypotheses are supported, then we will see an effect of pronouns and race on judgements of competence and warmth. We expect that targets with nonbinary gender identities and/or non-White racial backgrounds will be judged as less competent and/or warm than binary and/or White targets. The implications of this research are important given that nonbinary people face discrimination at the structural level, and gaining a better understanding of how this treatment extends interpersonally is a solid foundation to begin addressing these issues.

## Influence of Informative Language on Toddlers' Understanding of Others' Perspectives

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Previous work has shown that toddlers are sensitive to whether others can see an object, but that toddlers are egocentric when evaluating others' perspectives of said objects. The present study aims to examine if the use of informative versus uninformative language impacts toddlers' understanding of others' perspectives on non-human faces. In this study, toddlers were presented over Zoom with a video of an actor consistently reaching for one of two drawings, which depicted the same picture in different orientations. The animal depicted either appeared to be a duck or a bunny depending on the orientation. During the familiarization phase, the actor's perspective was consistent with that of the toddler's. In one condition, informative language was used when voicing which drawing the actor intended to reach for (i.e., "I want the bunny"). In the other condition, uninformative language was used (i.e., "I want one now"). From the actor's selective reaching, an observer could infer that the actor had a desire to act on pictures in a particular orientation. After this familiarization phase, the actor in the video switched seating positions so their perspective was now opposite that of the toddler: what looked like a rabbit to the actor instead looked like a duck to the toddler, and vice versa. Toddlers' looking times were then measured to determine if infants expected the actor to reach for the animal consistent with their own perspective, or that of the actor's. Results indicated that toddlers were more often ego-centric when uninformative language was used, but more often considered differing perspectives when informative language was used.

## Examining Intellectual Safetyism: Developing a Safetyism Scale and Characterizing Its Associations in a Sample of College Students

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Intellectual safetyism describes a rising movement across American colleges to shield students from ideas considered potentially harmful, curtailing free speech and stifling academic discourse. Though widely discussed because of its association with controversial topics, safetyism has not been clearly defined or understood. By developing and validating a scale to measure safetyism, then administering the scale alongside other measures, this study will clarify the construct, identify whether safetyism may lead to positive or negative outcomes, and provide a foundation for future research. Following the validation of the safetyism scale, the relationships between safetyism and Moral Foundations, deontological reasoning, personality, resilience, locus of control, meaning in life, empathy, demographics, prior trauma, and centralization of marginalized identity will be evaluated. Results will indicate what moral, emotional, and cognitive factors safetyism may arise from, as well as whether safetyism may be harming or helping American college students.

## Analyzing Predictors of Warmth and Competence Signaling

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Humans have a fundamental need to categorize other people through their interactions and stereotype them based on their perceived level of warmth and competence. This study utilized a bottom-up approach to understand humans' utilization and effectiveness when incorporating warmth and competence signals in natural language. Participants were recruited through Prolific Academic. In order to assess warmth and competence signaling, there were three conditions; competence, warmth, and control. Participants were asked to write a message and introduce themselves to other Prolific participants. If they were placed in the competence or warmth condition, they were asked to present themselves as a competent or warm person. If they were placed in the control condition, they were told to write a short introduction about themselves. The study sample had 900 participants, with 300 participants in each condition. Supervised machine-learning models were used to determine how people signal warmth and competence in natural language. Future findings will use a repository of over five hundred natural language processing (NLP) features and lasso models to reveal which of our NLP features were most predictive of warmth and competence signaling.

# Predicting Suicide Risk Using Health Records, Surveys, and Genomic Data

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Suicide is a global issue: the worldwide annual mortality rate is 10.7 per 100,000, and the prevalence rates for suicidal ideation and behavior are 9.2% (s.e.=0.1) and 2.7% (s.e.=0.1) respectively. Suicide risk factors include being female, previous suicide attempt, and psychiatric disorder comorbidity and family history. Suicide's complex etiology significantly interferes with the accuracy of clinician diagnoses, prompting the need for an objective assessment of suicide risk. Our team previously developed a machine learning model to predict suicide attempt 1 month and 6 months after an emergency department visit for psychiatric issues. The best-performing model uses electronic health records, clinician assessments, and patient surveys to achieve 64.8% sensitivity rate and 30.7% positive predictive value for 1-month prediction for high-risk patients. To improve predictive performance, we incorporated polygenic risk scores (PRS) into the existing model using ensemble machine learning R package SuperLearner. We used largest available GWAS summary statistics for major depressive disorder, bipolar disorder, schizophrenia, suicide attempt and generated respective PRS using Bayesian polygenic prediction method PRS-CS for 1497 patients (age = [41.1, 12.17]; female at birth = 604 [40.3%]) who were admitted to Mass General Hospital Department of Psychiatry Acute Psychiatry Service between 02/04/2015 and 03/13/2017. Preliminary results suggest that the addition of PRS would increase the accuracy of suicide risk prediction among high-risk patients. Our research contributes to the growing effort of identifying high-risk patients and providing them with appropriate care.

# Children's Understanding of Tallying as a Means of Representing Natural Numbers

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Understanding how humans develop the ability to represent exact, large numbers (i.e., numbers  $>4$ ) is central to unveiling the ontogenetic origins of natural number representations. Children and adults who do not know how to count struggle when asked to reproduce sets containing large numbers of objects, leading to a widespread belief that large exact number representations depend on learning how to count. However, before mastering counting, children can describe large set sizes more accurately with their fingers than with number words. And before the invention of counting, cultures represented large exact numbers using tally systems involving arbitrary symbols (e.g., notches) placed in one-to-one correspondence with objects. The present study investigated whether finger tallies could support exact large number representations independent of counting mastery. We tested 36-to-54-months-olds on a task where finger tallies were provided in one-to-one correspondence with objects entering and exiting a box. If children intuitively understand how tallies can represent exact large numbers, then we should expect to see improvement on this task compared to results from the same task without finger tallies, regardless of children's counting knowledge. Indeed, all children, regardless of counting knowledge, improved to perform at ceiling when provided with finger tallies. Our results suggest that learning how to count is not an exclusive means towards representing the exact numerosity of large sets, and that understanding one-to-one correspondence may have paved the way for the construction of counting as a means of representing natural numbers.

## Online College Student Mental Health and (Un)Wellness

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What do college students' posts on social media reveal about their experience of mental health and (un)wellness, specifically during the transition to their first fully online semester/school year due to the COVID-19 pandemic? To answer this research question, I analyzed 128 posts related to mental Health and (un)wellness from the "Zoom Memes for Self-Quaranteens" Facebook group in the timeline from August 1 to September 30, 2020 using a sociological content analysis in order to answer this question. I found a myriad of reasons detailing students' experiences of mental health and (un)wellness during the pandemic, with an overwhelming majority expressing this in a negative tone. Students expressed their mental health suffering regarding anxiety, depression, and insomnia, in addition to feelings of exhaustion, overwhelmedness, and overall "pain." Students broadly discussed insecurity as coming from pressures around academics, social life, and "the future" (career, adulting, etc.). Regarding academics, insecurity was around one's achievement, productivity, ability to focus, and coping mechanisms (i.e., TV shows, entertainment, etc.), as compared to their peers. Regarding social life, insecurity was around social skills, relationships, and emotional stability (i.e., loneliness, isolation, etc.), as compared to their peers. Regarding "adulthood," insecurity was around the challenges associated with a highly competitive job market, in addition to other feelings of anxiety and uncertainty. Though this analysis was of college student posts in late 2020, most other posts share similar sentiments. These findings motivate me to consider how we can move out of the online "suffer" culture and into a more proactive "healthy" or "healing" culture, as there are still societal and institutional challenges that cause "suffering."

## Alliance between a Gay and a Lesbian: Contract Marriage (*xinghun*) and Internalized Heteronormativity

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Regardless of their sexualities, the Chinese face familial and social expectations to marry the opposite sex and have children once they reach the appropriate age. Queers deal with this pressure by doing *xinghun* (contract marriage)— a performative, reciprocal marriage between gay men and lesbians. While the external factors leading gay men and lesbians into contract marriage have been extensively documented, contract marriage and its practice remain relatively unexamined from the perspective of individual beliefs. To fill this gap, this project aims to explore the relationship between Chinese queers' internalized heteronormativity and their decision of contract marriage and childbearing. Adopting an innovative mixed-methods approach, this research employed both qualitative data from in-depth interviews with 10 Chinese queers and quantitative data from an online contract marriage mate-matching website. One initial finding was that queers who choose contract marriage as a strategy usually present a higher level of internalization of heteronormative norms and values — including gender conformity, homonegativity, and pursuit of an ideal heterosexual nuclear family — and the same pattern was even more evident among contract marriage participants who want to have a child. In terms of this point, the heteronormative culture not only affects queer people externally in the form of familial and social pressure but also influences their responses internally and unconsciously. Recognizing Chinese queers' struggles, this study reveals the deeply-rooted heteronormative culture in China and destigmatizes queer people who participate in the performative union.

## Who Matters: How to Redefine Worth in Our Divided World

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The American dream— that economic prosperity is possible through simple hard work— is a falsehood for many Americans today across the class spectrum. In fact, most people are unable to access a higher socioeconomic status than their parents, and since the neoliberal turn in the 1980s, national obsessions with ideals like materialism and individual will have given rise to increased emotional distress, affecting stigmatized groups such as people of color, the LGBTQA+, people with disabilities, and those of lower economic class the most. It is for these reasons that a future of inclusion and equity must be created not just through institutional and political change, but also through shifting narratives that define worth, thus broadening who feels valued in American society. Through interviewing college students in the Midwest and Northeast, change agents who push messages of inclusion, and gathering data from various national surveys, *Who Matters* investigates how new narratives and social scripts are taking shape to reduce— eliminate— the mistreatment and devaluation of the aforementioned stigmatized groups. It was found that the predominant concept of the American dream is being displaced by universalist values of diversity, equity, and activism through art, entertainment, social media, and community organizing. Amid uncertain, divided times in the United States today, this analysis delineates sources of hope in demonstrating the powerful and salient implications of cultural change and collective action towards a broader, national narrative of acceptance.

## Formation of an American Identity: Civic Education in Massachusetts Public Schools

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In 2018, Massachusetts implemented a state-wide, eighth grade civic education requirement, including a student-led civics project, prompting questions involving how the curriculum should be implemented. Civics challenges the decline of faith in the democratic process evident in increased polarization, politicization of non-partisan institutions, and involvement in local government. The Democratic Knowledge Project developed and implemented an original curriculum across select Massachusetts public schools. Using teacher and focus group interviews, we identified patterns tracking impact on student's civic skills and dispositions including civic reciprocity, civic self-confidence, and civic self care. The curriculum underwent a redesign process based on identified patterns in 2019, 2020, and 2021. Each redesign focused on specific units covering themes like citizen-government interactions, various levers of change, or the powers of the presidency. The 2022 redesign focuses on assessment and accessibility specifically over the improvement of the identity, bill of rights, and elections units. The culmination of the curriculum is a student-led civics project encouraging students to identify issues and create solutions including interactions with government agencies. Cultivating a civics curriculum maximizes the potential for future and current citizen participation by encouraging a strong sense of investment in the democratic process at the community level.

## Assessing Gender Bias in National Surveys: A Case Study of the UNICEF MICS Survey

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Gender bias in global health surveys can result in public policies and interventions that overlook the needs of women, girls, and gender minorities. UNICEF's Multiple Indicator Cluster Survey (MICS) is one of the largest international household survey programs focused on women and children. This study aimed to develop and apply methods for measuring gender bias in the MICS survey to inform recommendations on gender sensitive survey development, data collection, and analysis. A narrative literature review was performed to define key terms, understand how gender is currently measured in global surveys, and identify good practices for gender sensitive data collection. MICS6 questionnaires, fieldwork preparation tools, and reports were then evaluated for gender bias and data missingness. Our analysis found shortcomings in MICS via the (1) lack of data on gender identity, (2) missing information on men and gender minorities, (3) the reinforcement of gender norms in question construction, (4) a focus on reproductive health over women's health, and (5) ineffective measurement of unpaid and domestic labor. These findings underscore the need to explicitly consider gender in global surveys to more effectively understand the roots of gender-based inequities and inform responsive interventions.

## Advancing Equity and Family Engagement in K-12 In-School Civic Learning

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Schools play a critical role in catalyzing interest in civic engagement, yet civic learning has increasingly become an afterthought in youth education. Disinvestment and decline in civic education pose dangerous consequences for our democracy, especially in the face of today's political dysfunction and polarized media. The Democratic Knowledge Project (DKP) co-designs curricula alongside K-16 schools and educators in Massachusetts to equip students with crucial civic knowledge and the skills necessary to contribute to a healthy democracy. By conducting a qualitative assessment of 8th grade student work and teacher interviews, our team analyzed the effectiveness of the DKP's current civics curriculum and project-based learning model with respect to accessibility, academic readiness, ideological diversity, and cultural relevance. Such insights informed our revisions for future curricular iterations, which will better assist our partner teachers in fostering deeper civic learning and cultivating civic agency within their classrooms. The outcomes of our sustained efforts will aid Massachusetts students in developing idiosyncratic civic identities, encouraging civil discourse in diametrically opposing political environments, and obtaining a holistic understanding of the United States' civic past, present, and future.

## A Study of the Expansion of Medical Schools across Africa

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Harvard T. H. Chan School of Public Health & Ariadne Labs

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Data on the number of medical education institutions across Africa is extremely outdated. Medical schools in the continent have not been mapped since the Sub-Saharan African Medical Schools Study (SAMSS) in 2012, which reported a total of 168 medical schools in the region. To update the existing knowledge on the state of medical education in Africa, a comprehensive database of African medical schools was built and data was collected about each institution, including location, founding year, and degree programs offered. The database was built by compiling various existing but outdated databases and updating them with online Google Maps and individual website searches. Local medical school members were also asked for their input and verification. The findings of this research show that there has been a considerable increase in the number of medical schools in the continent, as they have nearly doubled in the last decade, to a total of 346 in the Sub-Saharan region, and surmounting to 430 in the entire continent. Such significant growth in the programs training physicians could have multiple causes, such as escalating demand for healthcare services, or increasing investment in building the health workforce across the continent. Further research and analysis is still needed to understand why there has been such a tremendous increase in schools, identify patterns in growth, and assess what the impacts of this expansion could be.

## Diversity and Discrimination at the Frontlines

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Emerging research has shown that discrimination occurs in customer service contexts, with individuals from minority backgrounds (with regard to race, gender, and income) receiving fewer and less attentive responses from frontline employees. This research explores interventions to improve the quality of service provided to minority groups. The experimental design involved participants ( $n=279$ ) on Amazon Mechanical Turk adopting the role of a customer service employee at a luxury watch company. Participants were assigned to one of two instructions conditions and told that their performance would be assessed either by how satisfactory their service was (control condition) or how fair their service was (intervention condition). Participants were then asked to respond to six customer emails, all requesting ineligible returns. Four emails were from prototypical (high-income) customers and two emails were from non-prototypical (low-income) customers. As the main dependent variable, participants could make exceptions to the return policy at their discretion. Results were consistent with discrimination documented in prior literature — across both conditions, participants were more likely to make exceptions for high-income customers. A pre-trained natural language processing model was then used to analyze the content of emails that participants wrote to customers. Findings demonstrated that on average, responses to low-income customers were less positive and polite in tone. To better understand how bias at the frontlines manifests, we are now coding email responses by their “creativity,” building on prior literature that identifies creativity as an aspect of quality service. In future work, we explore differences in how employees prioritize replying to emails by customer income, machine learning strategies to classify quality service, and additional interventions to close gaps in the treatment minority customers receive.

# Collective Courage

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Courageous leadership is a concept that has been talked about for a long time, but less is understood about the psychological and sociological foundations that enabled it to do so. Therefore, this project examined when and how leaders made courageous decisions and how they have been translated into a bigger movement as "collective courage," analyzing historical cases: Medicines Sans Frontieres, Skilled Veterans Corps for Fukushima, and Tokkottai (Japanese teams that went on suicidal missions during the WWII).

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## Study of Women, Gender, and Sexuality

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### **The Race and Gender of Armed Self-Defense**

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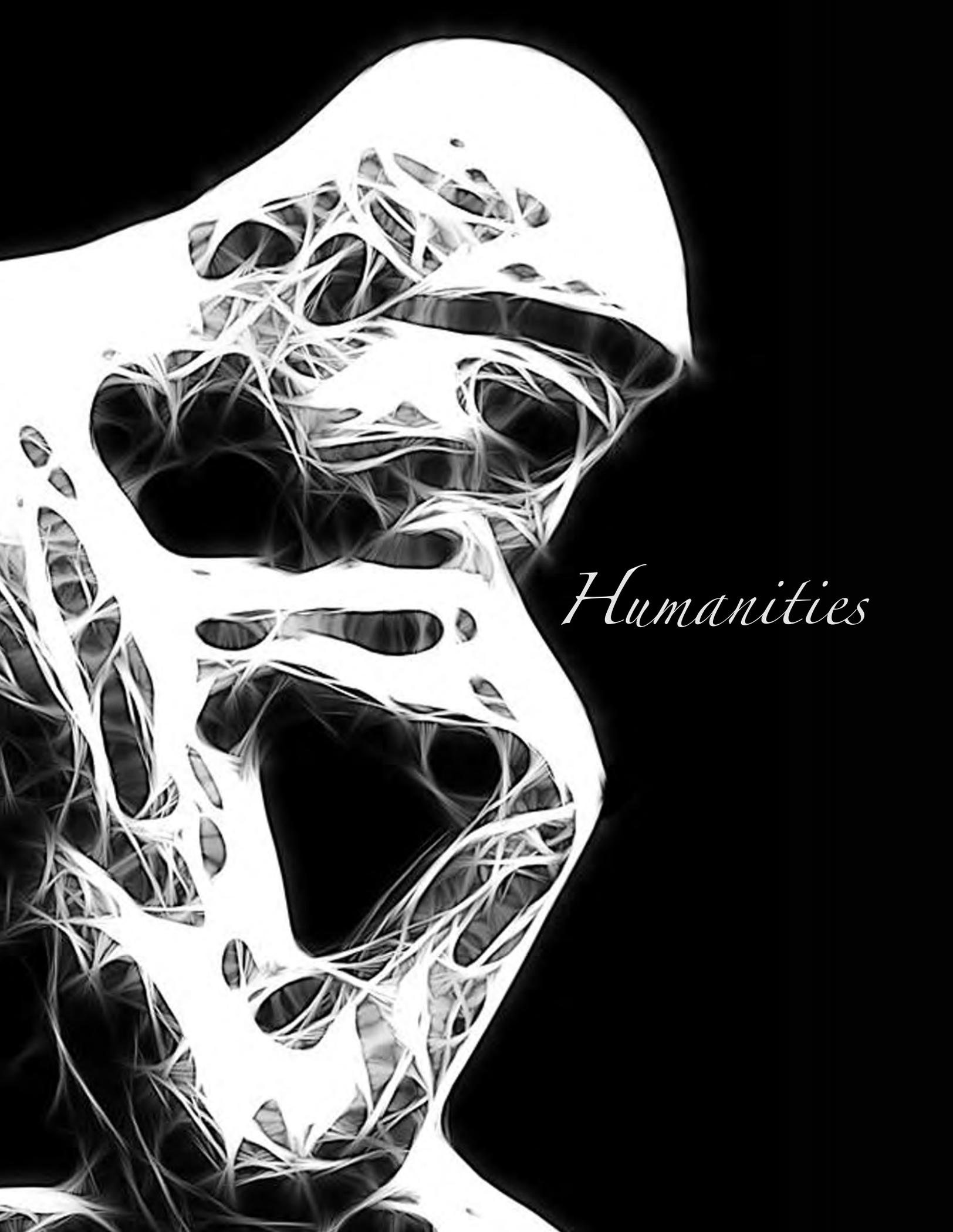
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Since Florida's enactment of a "stand your ground" law in 2005, 30 states have implemented similar statutes. Still eight others have similar policies embedded within their case law and jury instructions. These laws change existing self-defense laws by removing the duty to retreat when a person reasonably perceives a threat wherever they may legally be. While supporters of these laws claim the statutes improve public safety, the laws have been found to correlate with increased homicide rates and to amplify racial inequities in the context of violent conflicts. Our work seeks to further elucidate that contradiction through the simultaneous lenses of race and gender. Using court documents and news reports, we compiled a database of self-defense cases involving intimate partner violence. We also examined state statutes regarding justifiable homicide, teasing out interstate differences with a focus on protections for IPV survivors. Our work thus far seems to concur with legal scholarship on the positioning of women (particularly women of color) in justifiable homicide cases — both the text and application of self-defense laws disregard the plight of women, who most often kill in situations of repeated physical and sexual violence. Despite these concerning implications, public awareness around stand your ground laws remains startlingly low. We expect that this effort will not only provide insight into the exclusion of vulnerable populations from the safety stand your ground laws claim to provide, but will also serve as the foundation of a public information campaign about the nature and effects of stand your ground laws.





*Humanities*

### Determining the Sindhian Substrate of the Indus Civilization

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Following the Mohen-jo Daro excavations (Sindh, Pakistan) in the early 1920's, the linguistic state of the civilization became a question that has spurred many theories regarding substrates in the region. In particular, Sindhi, and its proto-Sindhian counterpart, have garnered attention due to their largely unchanged linguistic structure. This means, in theory, that one should be able to trace the Sindhi language back to its prehistoric roots through language analysis, finding the language that may have been spoken by the Harappans in the Indus civilization. However, the vocabulary of Sindhi has been influenced extensively through colonization and globalization. Now, the language's vocabulary contains words from the Germanic, Semitic, Dravidian, and its native Indo-Aryan family. Our research project attempts to analyze a Sindhi lexical archive by removing the layers of lexical influence, and discover the "true" pre-Sindhian words that may have been in use during the period of Indus. Given our Sindhi data, we would need to use literary sources such as Turner's Comparative Dictionary of the Indo-Aryan Languages, Burrow's A Dravidian Etymological Dictionary, and Platts' A Dictionary of Urdu, Classical Hindi, and English to scan and remove recurring words from our digitized Sindhi word database. After removing recurring words, we would research more about the words that remain, as these are the unchanged Sindhi words. Through our preliminary tests, we have found that a majority of the Sindhi database is of Indo-Aryan origin, but determining the exact number of words that are purely Sindhian require more lexical databases.

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## Art History

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### Harvard ArtLab “Works in Progress” Podcast

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**Emily Berlinghof**

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Harvard Faculty of Arts and Sciences

Advisor: Bree Edwards

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Art is a journey, but we rarely get to witness the creative evolutionary process that precedes every great work. Wouldn't you love to have asked Leonardo da Vinci what he thought when he painted the Mona Lisa? Have you ever wondered what inspired an artist to create an abstract piece of art? Focusing on the work of artists working at Harvard's ArtLab, the podcast "Works in Progress" engages in thought-provoking conversations about contemporary art and creative research. Hosted by ArtLab's director Bree Edwards, the podcast features conversations with established and emerging guest artists, art professors, and students at Harvard. Through the research of artists' backgrounds, artworks, and creative process this podcast creates an archive of the ArtLab's activity and is recorded in the Mead Production Lab. By approaching art as an explorative process of research, we better understand these artists' enigmatic historical significance. This podcast provides scholars and critics with a sonic tool to better interpret where divergent historical and contemporary art comes from, how it is created, and its impact.

### Harvard Art Museums Community Partners: Teaching Civics

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**Hannah Gadway**

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Harvard College, Eliot House

Harvard Faculty of Arts and Sciences & Harvard Art Museums

Advisor: Jeanne Burke and Camran Mani

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Aspiring U.S. citizens must pass the U.S. Citizenship Test (also known as the Naturalization Interview and Test) in order to gain citizenship. The test includes a Civics section, which assesses participants' knowledge of American history, geography, government, and federal holidays. The Harvard Art Museums has partnered with the St. Mark Community Education Program, a non-religious Dorchester-based program that prepares aspiring American citizens of all ages for the U.S. Citizenship Test, to teach the Civics content of the test using works from the museums' American art collection. Information for the objects used for the program was gathered through the use of curatorial files, books from Harvard's Fine Arts library, and the guidance of St. Mark's. The program will be free to aspiring citizens in the fall of 2022, and will use museum tours to teach both the content of the test through viewing American art as well as develop museum-going skills and a sense of inclusion and belonging in museum spaces. This project also included the presentation of tours to the general public which shared how the Harvard Art Museums will use three specific works in the St. Mark's partnership.

# Seeing in Art and Medical Imaging at Harvard Art Museums

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**Genesis Nam**

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Harvard Faculty of Arts and Sciences & Harvard Art  
Museums

Advisor: Jennifer Thum

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Working in the medical field, physicians sometimes overlook the fact that, at its core, medicine is an extremely human science. In an attempt to strengthen these clinical skills, the Harvard Art Museums have developed programs in partnership with Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, and others. Specifically, the program Seeing in Art and Medical Imaging (SAMI) teaches first-year residents in the Diagnostic Radiology and Joint Program in Nuclear Medicine at Brigham and Women's Hospital empathy, mindfulness, and tolerance for ambiguity using selected works of art from the Harvard Art Museums' collection. Through close-looking and engaging discussions on the collaborative relationship between art and science, physicians are able to take these humanistic techniques and apply them to their practice. A condensed form of this curriculum is also used in Project Success and Case-Based Introduction to Medical Imaging (CBIMI), two summer programs designed for high school students interested in studying medicine provided through Harvard Medical School. During the fellowship, we developed three of these summer sessions highlighting objects from the collection to practice observation, interpretation, and narration and help students explore how these translate into the hospital work environment. In addition, we designed a public tour of the museums to showcase the work and research that has been done in these programs and to emphasize the importance of interdisciplinarity in art museums.

**The Orations of Urian Oakes:  
17th Century Latin Pedagogy  
and a Harvard President's  
Latin Prose Composition**

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**Vivi Lu**

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Classics, 2024

Harvard College, Adams House

Harvard Faculty of Arts and Sciences

Advisor: Irene Peirano Garrison

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Harvard students in the 17th century studied classical languages and rhetoric through Latin textbooks, culminating in an annual Commencement exercise featuring Latin orations. Urian Oakes, who graduated from Harvard College in 1649 and served as its fourth president from 1675 to 1680, wrote a series of four Commencement speeches in Latin that demonstrate the rigor of classical education and the politics of New England schooling. By using stock phrases drawn from Latin phrasebooks as well as references from classical works, Oakes discusses contemporary issues in the manner of a Roman orator. Transcribing and translating Oakes' oration of 1677 preserved in John Leverett's papers at the Harvard University Archives, this project analyzes references to Cicero and other classical authors in Oakes' work. Beyond showing that students composed Latin declamations using Latin textbooks, my research shows that Oakes' orations draw on sources to provide context for his audience and elevate the speech's style. Oakes' work in particular draws heavily from Cicero's rhetorical devices and humor by alluding to *In Catilinam* and comparing the College to the Roman republic. These references exhibit not only the standard of classical education at 17th-century Harvard but also the mastery of Latin in Oakes' speeches, a precursor of the Latin Commencement orations that survive as a beloved University tradition even today.

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## English

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### A Winter's Tale: Karen Blixen in America

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**Ben Roberts**

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Comparative Literature & History, 2023

Harvard College, Kirkland House

Harvard Faculty of Arts and Sciences

Advisor: Thomas Wisniewski

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The documentary at the heart of this research project is titled, “A Winter’s Tale: Karen Blixen in America.” The film, to be produced by Zentropa, is a collaboration between a team of researchers at Harvard and a team in Copenhagen, Denmark. It draws on archival materials that document Blixen’s visit to the United States and will feature interviews with Blixen scholars and Harvard faculty, with the aim of celebrating the work of an extraordinary woman writer who bridged literary culture across the Atlantic in the mid-twentieth-century. To that end, the film follows the Danish writer’s earliest transatlantic publications in the United States. It opens with her brief escape from Nazi-occupied Denmark as she sends off the manuscript for *Winter’s Tales*, her second collection of short fiction, to her New York publishers. The film then moves back to 1934, when her first book, *Seven Gothic Tales*, was published under her nom de plume of Isak Dinesen. Moving forward in time, the film then features Blixen’s own crossing of the Atlantic for her 1959 American tour, sponsored by the Ford Foundation in honor of the world’s greatest living writers. Three years before her death, suffering from lifelong syphilitic after-shocks and arsenic poisoning, the Baroness Blixen traveled through the Eastern Seaboard, visiting New York City, and coming to Harvard, where she spoke at Radcliffe and gave an extraordinary reading of her work. The film closes with her return to Denmark and her death in the fall of 1962.

### Making the Memory Musical

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**Jonah Sorscher**

SHARP Fellow

Theater, Dance, & Media, 2025

Harvard College, Mather House

Harvard Faculty of Arts and Sciences & Houghton Library

Advisor: Kristine Greive

Supervisor: Zoe Hill

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In 1944, Tennessee Williams’ *The Glass Menagerie* premiered, and with it came a new type of play to the world of drama – the “memory play.” By exploring primary sources from Houghton Library’s Tennessee Williams Collection such as journals, letters, and annotated script drafts, this project aimed to apply Williams’ narrative techniques in a very new context – a “memory musical.” Memory plays are typically told through the recollection of a single narrator who might distort the reality of the events that occurred, clouded by emotion. They often rely heavily on musical accompaniment and lighting to create a dream-like atmosphere. The musical builds upon these fundamental elements in many ways. Beyond musical accompaniment, the characters actually sing their dialogue, further distancing the story from reality. Additionally, it’s told from the perspective of two narrators, rather than one. In this way, it aims to explore how two people can remember the same events differently, examining what they choose to focus on and what they’ve left behind as their narratives unfurl side by side. By asking how much trust we can place in our memories, it begs a more insidious question: when does a memory distortion become a lie? Through the creation of this musical, I hope to show how the style of writing Williams pioneered so many years ago can be used as a framework to tell stories relevant to our current moment.

# Fandom Fiction: Dramatizing 1950s Science Fiction Fan Correspondences

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**Mireya Sánchez-Maes**

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English & Theater, Dance, & Media, 2024

Harvard College, Currier House

Harvard Faculty of Arts and Sciences & Houghton  
Library

Advisor: Kristine Greive and Zoe Hill

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Fandoms occupy an increasingly large space in today's cultural consciousness. For example, comic conventions attract millions every year. Science fiction has become an invaluable staple of the entertainment industry and social media platforms such as TikTok have transformed fans' ability to create and share content. However, many of the practices associated with contemporary fan culture had their start in post-war science fiction fan groups whose members, almost exclusively white men, would contribute to science fiction's paradoxical reputation as a safe haven for "acceptable" outsiders. My project seeks to explore this legacy by narrativizing Houghton Library's Dick Clarkson papers, a collection of photos, letters, compositions, and science fiction convention memorabilia collected by Dick Clarkson from 1951-1953. These correspondences inspire the events of an original comedic stage play exploring how science fiction fan culture operates in moments of cultural change. Beyond providing a humorous and entertaining narrative, this play offers a historically accurate account of science fiction clubs in the 1950s. The vast majority of dialogue is taken directly from the Dick Clarkson papers and every character is based on a real-life correspondent. This play is constructed such that any viewer might come away with an accurate conception of the contents of the Dick Clarkson collection. In dramatizing the realities of fan culture during this formative time, we become better equipped to recognize the short comings and contradictions that persist within fandoms today.

## An Archival Intervention in the Philosophy of Psychedelics

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Philosophy, 2023

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Harvard Faculty of Arts and Sciences & Houghton  
Library

Advisor: Kristine Greive

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As researchers today explore the potential of psychedelics to treat anxiety, depression, and other conditions, philosophers have expressed concern that the drugs only improve psychosocial functioning by precipitating mystical-type beliefs in patients (i.e., “there is eternal life,” “there is a cosmic consciousness.”) Philosophers who subscribe to scientific naturalism consider the provocation of such beliefs to be an “epistemic harm”—that is, a harm insofar as it interferes with an individual’s imperative to maximize belief in truths and minimize beliefs in falsehoods. This essay deploys archival materials surrounding American 1960s psychedelic culture from Houghton Library’s Ludlow-Santo Domingo collection to show that the epistemic profile of psychedelics—that is, their ability to facilitate or hinder access to knowledge—is likely to be of popular interest and not merely an abstruse philosophical concern. The archival materials demonstrate how, in the 60s, public arguments for the ethical imperative of either promoting or suppressing psychedelics related explicitly to the drugs’ perceived epistemic profile. This essay goes on to engage with the work of Chris Letheby—a thinker at the forefront of the philosophy of psychedelics—who argues that psychedelics offer patients counterbalancing “epistemic benefits” that render their therapeutic use morally permissible. Archival materials complicate Letheby’s calculus around the epistemic profile of these drugs, however, showing how people in the 60s cultural milieu were subject to types of epistemic harm that his analysis neglects. These further types of epistemic harm have implications for clinicians today engaged in psychedelic therapy, and relevance to the decision-making of those who seek to grow the burgeoning field in an ethical way.





# **Environmental Sciences**

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## Earth and Planetary Sciences

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### Magnetic Mapping of Iron Oxides in the Human Brain Using the Quantum Diamond Microscope

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**Gabriel Maxemin**

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Earth and Planetary Sciences & Chemistry and Physics, 2024

Harvard College, Eliot House

Harvard Faculty of Arts and Sciences

Advisor: Roger Fu

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Iron oxides have been detected in the human brain; however, their origin is unclear. This project seeks to create a magnetic map of human brain samples to better understand the location, provenance, and possible involvement in pathology of these particles. The first part of the project looks at magnetic contamination from sources that may also be present in the brain samples. The location of the particles may reveal whether the particles are vestigial or have an external source such as pollution. Brain samples embedded in epoxy were prepared for analysis through two main techniques: sanding and microtome. Instruments and solutions such as solvents and epoxies used were washed and filtered to minimize external magnetic contamination. Solutions were tested before and after filtering to examine how much they magnetically contaminate a sample. We employ the Quantum Diamond Microscope (QDM) in order to look at magnetism in a brain sample at  $\sim 1 \mu\text{m}$  resolution. Preliminary results indicate that using tap water and epoxy result in significant contamination as compared to isopropanol and acetone. Images of samples from the QDM indicate some candidates for magnetic sources, but more analysis, based partly on newly prepared samples following a stricter contamination protocol may confirm that these sources are not contaminants. I plan to generate more extensive magnetic maps of the brain, comparing different techniques used to generate them. Additionally, results from procedures that minimize magnetic contamination of the samples will be important for determining whether magnetic sources are actually due to the iron oxide particles.

### Compound-Specific Stable Isotope Fractionation in Photosynthetic Microorganisms

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Advisor: Ann Pearson

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Compound-specific nitrogen isotope analyses can provide a robust proxy for nutrient cycles and community compositions in both ancient and modern marine environments. Specifically, the  $\delta^{15}\text{N}$  value of chlorophyll porphyrins, along with its offset with the  $\delta^{15}\text{N}$  value of total biomass as described by the quantity  $\epsilon_{por}$ , is a major point of interest, as key marine photosynthetic microorganisms all produce chlorophyll, the porphyrin nitrogen is not changed by diagenesis, and past laboratory studies have shown that  $\epsilon_{por}$  varies taxonomically. However, broader use of chlorophyll nitrogen isotopes requires that the value of  $\epsilon_{por}$  be more vigorously constrained for a comprehensive range of marine microorganisms, and that the biochemical basis for the observed taxonomic differences be identified. This study adds to the literature of amino acid and chlorophyll  $\delta^{15}\text{N}$  data for *Rhodospseudomonas palustris* CGA009, a versatile species of purple nonsulfur bacteria that uniquely uses glycine in its chlorophyll biosynthesis pathway, so that its  $\epsilon_{por}$  trend can be identified and explained. The *R. Palustris* samples were grown phototrophically and  $\delta^{15}\text{N}$  measurements for chlorophyll, free amino acids, and bulk biomass were made using gas chromatography combustion isotope ratio mass spectrometry. The  $\delta^{15}\text{N}$  measurements will be used in combination with prior data collected from other microorganisms in a computational model of nitrogen fluxes in an unicellular organism. This analysis will result in a greater understanding of the mechanistic processes of porphyrin biosynthesis in major marine microorganisms, and has implications for paleoceanographic studies of sedimentary samples.

### **Modeling the Effects of Environmental Predictors on Time-Use Patterns across the Contiguous United States in a Changing Climate**

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Environmental Science and Public Policy, 2023

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Supervisor: Jonathan Proctor

---

The increased frequency and magnitude of hazardous environmental conditions caused by anthropogenic climate change will trigger adaptive responses in some populations. Hotter summer conditions may push those with access to cool indoor environments to retreat indoors. Patterns of sleep and physical activity will likely be altered. Heat-exposed workers may have to postpone or forgo labor. The attendant health and economic consequences are potentially large, yet little is known about the relative importance of temperature, precipitation, solar radiation, and other environmental predictors in determining how Americans choose to spend their time. To address these questions, 2003 - 2019 American Time-Use Survey data are paired with historical temperature and precipitation data from Oregon State University's PRISM group and solar radiation measurements from NASA's CERES project, with the goal of coupling results with CMIP climate models to illustrate possible spatio-temporal changes in time use patterns in the contiguous United States over the coming 80 years. Weighted fixed-effects panel regression techniques are utilized. Out-of-sample cross validation informs model selection. Initial findings indicate that increases in daily maximum temperature above 25°C may be associated with a 1 min./°C reduction in physical activity and temperatures above 22°C with a 5 min./°C reduction in time spent working, studying, or volunteering. Non-linearities and causality will be further informed through analysis of environmental and socioeconomic covariates.

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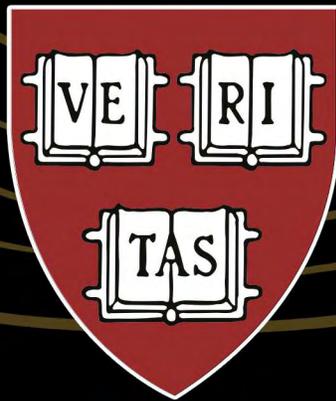
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