



PRISE
BLISS
PRIMO
SHARP

ABSTRACTS

2014

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I am pleased to write this letter of introduction for the 2014 Harvard College Summer Undergraduate Research Village Abstract Book. The Village now encompasses the full range of academic disciplines through our four signature programs, the Program for Research in Science and Engineering (PRISE, year 9), the Behavioral Laboratory in the Social Sciences (BLISS, year 4), the Program for Research in Markets and Organizations (PRIMO, co-hosted by Harvard Business School, year 4), and the Summer Humanities and Arts Research Program (SHARP, year 2). While each of these programs is designed to foster their own identities, we know from our experience this summer that the residential experience and its relationship to research is compelling and rewarding.

However, the magic of H-SURV is manifested in the relationships created among the “PBPS” fellows themselves: inclusive, creative, active, and enthusiastic, these summer residents of Mather House, in the span of ten weeks, have initiated and organized a remarkable calendar of activities that fosters intellectual growth and social engagement across the whole community.

The projects described in this book of abstracts demonstrate the range and variety of intellectual exploration through research among the 150 residents of our community working closely with Harvard faculty. As you can see, the impressive array of experiences tells a persuasive story about the value of a summer devoted to research. To each of you PRISE, BLISS, PRIMO, and SHARP fellows, I wish the best of success as you continue to pursue your academic interests, and hope that the relationships you have built over these weeks as a member of the Summer Undergraduate Research Village continue to thrive going forward.

Yours truly,



Gregory A. Llacer

Director, Harvard College Office of Undergraduate Research and Fellowships (URAF)
Director, Harvard College Program for Research in Science and Engineering (PRISE)

Dear PBPS Community,

In this book, you'll find abstracts covering topics ranging from chemical synthesis, to the experience of rejoining society after imprisonment, to innovative ways to improve health care systems, to the lives of musicians in diaspora, and much more. This summer, each of us had a unique opportunity to delve deeply into a project and immerse ourselves in Harvard's incredible research community on a level not possible during the academic year. As a result of spending an entire summer on a single topic, our interests and research skills evolved so rapidly that by the time this book is printed many projects will have gone through profound changes or found new results. The research we engaged in will hardly end with the summer though; the valuable lessons we learned will remain with us as we continue on in our academic pursuits. We hope that you share our awe and excitement at both the breadth and depth of the projects the 2014 PBPS Fellows have taken on and that this book will both commemorate our work and spark many conversations like those that we have cherished all summer long.

The PBPS Abstract Book Team

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BLISS

Improving Educational Outcomes by Increasing Parental Involvement

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One of the most promising areas of education research involves increasing parental involvement in student's education. Research shows that there is a positive correlation between providing parents more information about their student's education and student outcomes. My work this summer with Professor Todd Rogers and his team focuses on two projects that aim to discover the best information to provide to parents to increase student attendance and performance.

It is a well-known psychological phenomenon that people tend to conform to the behavior of others. While descriptive social norms have been shown to affect behavior in other settings, it has yet to be tested in education research. The main project I am working on involves leveraging social norms to increase parent engagement and investigating its effects on student attendance and performance. The sample for this project is the students that have the highest rate of absences compared to peers in the same school and grade in a large urban school district. The design contains three conditions – one control and two treatment arms. Parents of students in the control condition receive no new information from the student's school. Parents of students in the first treatment condition receive a mailing at regular intervals during the school year informing them of their student's attendance. Parents of students in the second treatment condition receive a mailing at regular intervals during the school year with their student's attendance and the attendance of the typical student in that student's school and grade. The research questions include (a) Does student absenteeism decrease when parents receive information about their student's school attendance? and (b) Does providing the social norm information about how a student's attendance compares to their peers have an effect on student attendance?

The second project I am working on focuses on understanding what information parents would want to receive to increase their involvement in their student's education. I am managing and running this project with a colleague. The project is executed via crowdsourcing and involves two stages. First, we are posting a general question on Reddit forums asking parents what information they would want to receive to increase their engagement in their student's education. Then we are using Amazon's Mechani-

cal Turk to survey parents and collect more detailed information to determine which pieces of information correlate most strongly with higher levels of parental involvement. These projects are intended to have a broad impact, and the aim is to produce effective and easily scalable ways to increase student attendance and performance.

Reorganizing the World: Executive Function and Conceptual Change

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In addition to explicit knowledge, children possess conceptual frameworks that organize and define their conception of the world. These frameworks change and develop in childhood and throughout the adult lifespan, moving the child from simply understanding the world as he perceives it to understanding highly complex and abstract concepts such as theories of matter, evolution, and thermodynamics. I assisted in research investigating the cognitive mechanisms that support the construction and expression of advanced concepts. We paid particular attention to executive function, a suite of functions including working memory, the inhibition of inappropriate actions, and shifting between sets or contexts. Previous research has suggested that executive functions are involved in conceptual change on some level, but many questions remain unanswered.

This study focused on one domain of conceptual change, namely biology. Children were tested on their understanding of vitalist biology, the theory that living things acquire vital energy from food, air, and water and that to be alive is to possess and maintain this vital energy. 83 children ages four to seven were tested on their understanding of biology before and after a teaching intervention aimed at improving their knowledge of one specific aspect of vitalist biology, the function of human body parts. Preliminary results showed that children were able to integrate the limited information they received into a new conceptual framework, and work this summer has focused on further examining this trend. My work this summer has also included designing a new phase of this experiment aimed at improving children's understanding of physics.

Theoretical and Applied Issues in the Analysis of Text via Topic Models / The Role of Visual Heuristics in the Perception of Group Affiliation

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Dustin Tingley and Ryan D. Enos
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Statistical topic models are a class of unsupervised learning algorithms used to uncover low-dimensional latent structure in complex bodies of textual data. These tools allow researchers to identify and explore the thematic content of textual corpora, opening up novel possibilities for data browsing, classification, and search. Together with Prof. Tingley's research team, I explored both theoretical and applied issues in the implementation of topic models.

Latent feature models often have highly multi-modal likelihoods, meaning that different parameter initializations tend to cause severe fluctuations in output. We developed tools to assess the stability of fitted topic models and evaluated their application to the problem of model selection. Our team also worked on the algorithmic implementation of the Structural Topic Model (STM), a model of this kind. I implemented tools to evaluate and quantify the semantic interpretability of a fitted STM model, as well as to detect the presence of aberrations of different kinds. I also worked on optimizing our software, developing a port of the Orthant-Wise Limited-Memory Quasi-Newton Optimizer (OWL-QN) for L1-regularized objectives, for use in the STM.

On top of this, I worked with Prof. Enos to design and execute experiments assessing the role of visual cues in human subjects' judgment of outsiders' group affiliation. Our work has particularly focused on the perception of ethnicity. We asked human subjects to classify faces as belonging to one of two different ethnic groups, allowing for some degree of uncertainty. We hypothesize that the subject's perception of ethnic affiliation will be more polarized if the faces are clustered and segregated according to their morphological characteristics and skin tone a priori by the researcher.

Studying Social Activism: Petitions for Women's Rights

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Petitioning might be considered the "least-well known"

of the First Amendment rights, but it has a unique role in the development of political rights in the United States. Petitions were typically written by organizations dedicated to the pursuit of a cause and members often gathered signatures by walking from door to door. Lacking the ability to vote and other political rights, women, African Americans, and Native Americans used petitioning as a means of addressing their grievances to Congress. Of particular interest to researchers in political science is the capacity of petitioning for social change and as being spurs for localized political activity and civic-mindedness. Thus, Professor Carpenter's research has largely focused on petitioning by women and minority groups as a mechanism for indicating the gradual incorporation of these groups into the political sphere.

My research this summer has focused on petitions for woman's suffrage after the Civil War. The primary goal of the project is a comprehensive map of suffrage petitions that were sent to Congress from 1874 to the passage of the suffrage amendment in 1920. After formulating a database of suffrage petitions taken from the online Congressional Record, including relevant county information, I am mapping the petitions in ArcMap (a GIS software) according to census maps from the decade the petitions were written in. At the conclusion of the project we will hopefully be able to deduce patterns in local activity related to campaigns for woman's suffrage and infer what this might mean for how women remobilized politically after the Civil War. I am supplementing this research through archival work at the Massachusetts Archives, looking at woman's suffrage petitions sent to the state legislature, both as a separate project of documentation and to be able to study the nature of some suffrage petitions in depth.

The Causal Effects of Goal Orientation on Performance

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The existing literature on goal orientation and performance has shown that learning-oriented employees tend to outperform their performance-oriented co-workers in the work place. These employees are more likely to try harder, have more motivation to learn, and take on more challenging opportunities compared to other performance-oriented individuals. However, thus far, this result has not been designed into an intervention technique that can be implemented in the work place. This study develops a learning-oriented intervention technique and investigates its causal effects on performance within a lab setting.

In order to test this intervention, the physiological response of participants was measured using blood pressure cuffs at various stages throughout the experiment. A baseline blood pressure measurement was taken after showing a neutral video at the start of the study. We manipulated participants' goal orientations by having them respond to a prompt that asked them to write about a specific experience, which primed them with one of three conditions: a learning orientation, a performance orientation, or a control. Using an adapted Trier Social Stress Test (TSST) protocol, we then subjected participants to a mock job interview and thereafter took a physiological measure that served to measure their performance. Such an investigation may be able to illuminate the effectiveness of this learning-oriented intervention technique, which may potentially be utilized in the future to produce better employee workplace performance.

Nonverbal Communication and Word Order

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Natural human languages employ various devices to communicate information about actions, people, and objects. Many of the world's languages use a systematic word order to convey the relations between different entities, using the three basic constituents of subject, verb, and object. Depending on where these constituents are in a sentence we can convey more details about who did what to whom. For example the standard word order in English is Subject-Verb-Object (SVO) which means we can say, "The boy eats a cookie", while deviations from this canonical word order, like "Eats the boy a cookie," are rendered ungrammatical. Other languages like Japanese predominantly use a Subject-Object-Verb (SOV) ordering. Interestingly enough, these two word orders make up a large majority of the world's language—so this begs the question, is there a "natural" word order?

Nonverbal communication may be the key in figuring out if there is a natural word order that humans prefer. Previous research looking at how people express events using manual gestures has suggested that there may be preferred word orders that people use to communicate different kinds of information. Our study aims to examine what motivates the emergence of these word orders in the gestural modality, and how that compares with verbal word order. We also manipulate the type of event to see whether or not this results in a shift in gestural word order. In understanding how people convey events we can then gain valuable insight into how certain cognitive constraints and

biases influence the structures of human languages.

No One Saw That, Right?: The Effect of Others' Evidence on Self-Reports of Transgressions

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Two major factors influence our likelihood to admit to our own transgressions: (1) the perception of the transgression as minor and (2) increased evidence of the transgression. The present research explores the effect of knowing others have evidence of transgressions on subsequent self-reports of transgression. Participants were asked to listen attentively to another person's emotional story; afterward, some were told that another experimenter had monitored their attention in real time as they listened, though in reality no such measurement was taken. Participants told that someone else gathered evidence of their lapses of attention (i.e. "zoning out") are predicted to report that they zoned out less compared to participants who were not told they were being monitored. These findings will contribute to a growing body of evidence suggesting that knowing others have evidence of our transgressions may make them appear less minor. Ironically, then, certain types of increased evidence may make us less likely to acknowledge the error of our ways.

The Effects of Social Deprivation on Cognition

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Placing people under social deprivation causes them to have fewer self-referential thoughts, thoughts that involve thinking of oneself. Preliminary research that utilized fMRI data and linguistic analysis has indicated that people who are under social deprivation show a decreased level of activity in brain regions involved in self-referential thought. Our goal is to explore unanswered questions and attain a better understanding of the cognitive changes that occur during social deprivation.

The study consists of two parts: a research/analysis component and an experimental component. The research/analysis component involves compiling literary works written by authors who have undergone a period of

social deprivation. Using the Linguistic Inquiry and Word Count (LIWC), we will analyze the texts and determine whether any correlations exist between whether a work was written under social deprivation and the prevalence of self-referential words in the text.

The experimental component is a continuation of the research that first indicated the negative correlation between social deprivation and self-referential thoughts. We first randomly assign participants to either the social deprivation group or the non-social deprivation group. All participants must then complete a Stroop Task and Lexical Decision Task to measure how receptive they are to self-referential phrases, like “my body” or “my life.” For the next six hours, those in the social deprivation group are then kept alone in a room while those in the non-social deprivation group are free to leave. Every hour, each participant must report their thoughts so they can be later be analyzed by LIWC. After the six-hour period, all participants must then complete the same tasks they did earlier in addition to a Mind Wandering Task to measure their level of personal cognition again. Through this experiment, we hope to validate our hypothesis that social deprivation has a causal effect on decreasing self-referential thoughts.

An Analysis of Responses to Ethno-Racial Stigmatization

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Professor Michèle Lamont
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How does racism manifest itself around the world, and how do victims of racism respond? These are the questions at the foundation of the “Responses to Stigmatization” project, a collaborative effort by researchers in the United States, Brazil, and Israel. Our goal has been to catalogue, in a more detailed way than has previously been done, the types of incidents that racial and ethnic groups experience that in some way stigmatize them and, more important, the diverse ways in which members of these groups choose to respond. To this end, we collected data by interviewing subjects from target groups about their past experiences of being stigmatized. The data are broken down in various ways—such as by type of incident; nature of the response; age, class, and gender of the interviewees; and so forth—in order to better understand the role that these experiences play in the lives of those affected. We have then compared the data from the three subject countries in an effort to draw more universal conclusions about the nature and effects of ethno-racial stigmatization.

I have primarily been responsible for organizing one type of response, “confronting” (which may involve, for

example, speaking out or reacting physically), into sub-categories in order to determine if any trends emerge in the manner in which respondents choose to confront stigmatization. I have also edited the work of the lead authors, allowing me to see some of the patterns in the data and the conclusions the lead researchers draw from these patterns. The result of this project has been a better understanding of social challenges faced by certain ethno-racial groups and the way they handle such challenges.

Boston Reentry Study

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Over the last four decades, the United States has seen an increase in incarceration rates like never before. Nearly 1.5 million people are in prisons across the country. The majority of these individuals are male minorities with low levels of education. For them, incarceration has become an expected life event. Due to historically high levels of incarceration, each year 700,000 of these individuals are released from prisons mostly to poor neighborhoods where they are expected to become productive members of society. For these individuals who are released to the margins of society, the task of reentry proves incredibly difficult.

The Boston Reentry Study combines a quantitative and qualitative approach to track the lives of 122 recently released men and women in the Boston area over the year following their release from Massachusetts state prisons. The study aims to understand people’s incarceration and transition out of prison within the context of their life histories.

My work this summer has focused on listening to interview audio files and reviewing interviewer notes to compile a life history timeline for each respondent. These timelines identify different social contexts, relationships, contact with the criminal justice system and other major life events. In these interviews we identify recurring themes as well as include direct transcriptions from respondents. This allows us to look at the associations between childhood life conditions and a respondent’s ability to reintegrate after their release as an adult. This research is conducted in the hopes of contributing to criminal justice reform and policy as well as providing a new approach to the problem of prisoner reentry. Furthermore, it provides a platform for the voices of those who exist outside the view of mainstream society to be heard.

American Identity among “America’s Enemies”

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Professor Bonikowski’s previous research has shown that the literature on nationalism characterizes four distinct types of nationalistic feeling. These, which he terms “national attachment,” “national identity,” “national pride,” and “national hubris” describe national identification as, respectively, an individual’s salient identity, an association with determined national symbols and traits, a sense of positive feeling towards the nation, and a belief that one’s nation is better than other nations. This varied literature illustrates the complex interplay of meanings that make up an individual’s experience nationalist identification. These meanings become even more complex when they associate with or conflict with the various other meaning systems any individual might experience, such as those wrought in a racial identity, a transnational identity, a class identity etc. Tracing the interactions of such complex meaning systems can help us to understand the nuance and profound heterogeneity of the experience of being part of a national community.

The project on which I’m working aims at better understanding of the complex network of meanings that comprise the experience of nationalism for individuals who have been cast as “enemies of the nation.” The project is still in its earliest stages, so my task has been a comprehensive review of literature written in sociology, anthropology, political science and some history on the experiences of Arab-Americans, other Middle Eastern Americans, and Muslim Americans. I’ve spent the past month reading and organizing 150 articles, books, and book chapters, ultimately composing a document reporting on the notable trends found in the literature. After consideration of the apparent interactions between American nationalisms and other identifications reported in the literature, the project will continue on to develop a research question and produce interview questions that will probe experiences of nationalisms among Arab, Middle Eastern, and Muslim Americans in the Boston area.

Measuring Rape Culture

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Rape and sexual assault—and the response people have

to instances of either—have developed into one of the most pressing issues on college campuses and in local communities. Despite frequent references to an increasingly prominent “rape culture,” few truly understand the nature and implications of the way rape is discussed, particularly in media. In Professors Cohen and Baum’s project, we are, for the first time, attempting to define rape culture and establish its role in society.

To do this, we are examining countless articles from a wide selection of newspapers to identify what scholars have determined are signs of rape culture. These indicators include victim-blaming language (excessively discussing a victim’s alcohol consumption), empathy for perpetrators (commenting on the perpetrator’s damaged future), or questioning the victim’s credibility. They also include language that makes light of rape. After coding thousands of documents, we will run potentially millions of articles through a coding machine to determine existence, nature, and prominence of these indicators of rape culture in media. Aside from reading and coding over a thousand documents, I have worked on case studies to highlight particular instances of rape culture. These include the Kobe Bryant rape trial and the Duke Lacrosse Team rape case.

Ultimately, this project will try to determine not only what rape culture is and how prominently it exists, but also in what situations it is most prominent. We will compare our data on rape culture with regional data on socioeconomic status, voting trends, crime data, and media consumption trends to determine where rape culture exists and to fundamentally attempt to deepen our understanding of people’s portrayals and responses to rape and sexual assault.

PRIMO

Decision Making and Behavioral Economics

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Economics
Class of 2017

Michael I. Norton, Alison Wood Brooks, Ryan W. Buell, Francesca Gino, and Leslie K. John
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The field of economics relies heavily on the concept of homo economicus, or “economic human,” which characterizes humans as rational, self-interested beings that attempt to maximize their utility. Although this belief has become standard across economic theory, behavioral economics highlights the unpredictability and irrationality of human behavior. The GiNorton Lab’s research deviates from classic economic thought by integrating psychological factors into economic decision-making. By analyzing fundamental psychological concepts—such as heuristics

tics, morality, framing, emotional filters, risk aversion, and reciprocity—the lab’s profound research challenges the way we think about human judgment. My research this summer has spanned a wide range of topics related to this field. In one project, we explored the consumers’ reactions to recommendations from companies like Netflix and Spotify and advertising matching strategies employed by Facebook and Google. Some speculations are that consumers will feel stereotyped by such recommendations or, in some cases, feel threatened that corporations are infringing upon their right to privacy. Another project deals with humans’ tendency to be risk-averse and how this characteristic molds our decision-making. In this project, we explore the role of “The Uncertainty Effect”, a condition in which an individual values a risky option less than the worst possible outcome, and how this theory leads us to opt for “worse-but-apparent” situations rather than “better-but-unclear” situations. The ground-breaking work produced in the GiNorton Lab can persuade corporations to reevaluate consumers not only as perfectly rational economic agents but also as the complex and imperfect individuals that we are.

Analyzing the Transition into Entrepreneurship and Career Progressions of HBS Alumni

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Policy-makers, business school faculty and administrators have shown an increasing interest in the promotion of entrepreneurship. Although the literature has mainly investigated the transition into entrepreneurship, very interesting questions arise when considering how and to what extent entrepreneurial experience affects an individual’s career path. In this respect, we aim at quantifying the causal impact of past entrepreneurial experience on labor market outcomes for potential, high-impact entrepreneurs. The key ingredient to measure such causal impact is to use the exogenous assignment into sections of first-year Harvard Business School students. The analysis then proceeds in two steps. We first take into account the students’ characteristics that may affect their tendency to become post-MBA entrepreneurs. This step aims to separate an individual’s own tendency to become entrepreneur from external factors affecting their choice. Then, we perform a second analysis to estimate the impact of entrepreneurial experience on career paths, controlling for an individual’s own entrepreneurial skills. As a PRIMO fellow, my project specifically regarded the first stage of the analysis. In particular, it consisted of two parts: 1) organizing and clean-

ing the data and 2) performing robustness checks of the data, using Lerner and Malmendier (2013) as the main reference. This study has broad implications in terms of policy-making, as it may ultimately shed light on how the labor market values an individual’s choice of becoming an entrepreneur.

Negotiation

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Whether it takes place in the conference room, via Skype, or on a barstool, negotiation is an art with a myriad of mediums. Negotiation is much more than closing a deal: it is a continuous process of seeking Pareto efficiency and creating value while maintaining effective relationships. In every sense of being a good leader, it is important to for one to continually visualize his or her surroundings as a negotiating table. Harvard Business School teaches negotiation through simulations grounded in case studies. These simulations provide not only an opportunity to put a case into practice but also a method to empirically examine the negotiation process. My research aimed to comprehensively understand the negotiating process. To do so, I helped design surveys to track multiple roles within each negotiation through business deals, acquisitions, and mergers. Specifically we looked at final sale price, net values of negotiated contracts, levels of happiness and change in trust, and the impact of conditional contracts. Furthermore, the research applied a code to analyze the relative performance of each student. We also used a broad range of historical data to develop regressions with high confidence indicators that point to negotiation principles such as the midpoint rule and the first mover effect. Additionally, while the survey and code are able to make sense of the past, they are also designed to assist professors with future simulations from which they can track the progression of common negotiation techniques and emerging methods of success.

The Impact of Timing and Reversibility on Decision-Making Processes

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As understanding of the processes that guide human behavior has increased, we have come to realize that minor alterations in environment can lead to significant dif-

ferences in behavior and thought. Exploring one such change, we looked at the impact that information timing has on decision-making processes. Stemming from neuroscience research on the importance of timing in information processing, our research looks at how changing the timing of decision closure information, or information about the reversibility of a decision, can lead to differing outcomes. We explored how providing consumers with information about a purchase decision's reversibility either before or after the decision has been made alters their decision satisfaction and their subsequent assessment of the product and alternatives. This research has potential impacts in a variety of realms. From a marketing perspective, better understanding of product evaluation processes can help companies create more effective means of transmitting product information. More specifically, we hope that our research will provide insight into what purchase reversibility policies should be implemented and when these policies should be revealed to the consumers to maximize decision confidence and product satisfaction. Furthermore, from a behavioral point of view, new insights into information processing can help us better understand how and why individuals make their decisions. Our findings about processing may also be useful to any group working to relay information to the public. Overall, we hope that our research will lead to greater understanding of the impact of timing and reversibility on decision-making.

A Comparative Study of Microfinance Institutions in Latin America and Asia

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Financial services are key to households for a variety of reasons. They allow people to respond to unexpected shocks and take full advantage of business opportunities by leveraging their assets. Many analysts claim that making financial resources available to all parts of the population is key for sustained economic growth.

Microfinance is a broad term describing all financial services to low-income individuals or to those who do not have access to typical banking services. The belief that individuals will have the ability to lift themselves out of poverty is the very foundation of microfinance activities. Microfinance clients are often self-employed, household-based entrepreneurs whose diverse "microenterprises" include street vending, artisan manufacture, and service provision.

Apart from the traditional function of providing micro-credit, Microfinance Institutions (MFIs) today provide a

wide variety of financial services such as consumer loans, savings accounts, time deposits, micro-insurance, and international money transfers. These services help provide a financial ecosystem that facilitates the creation of an inclusive growth model. Even the most rigorous econometric studies have proven that microfinance can smooth consumption levels and significantly reduce the need among poor people to sell assets to meet basic needs. Therefore, a robust infrastructure needs to be created for safe and efficient delivery of microfinance services to the poor.

More than half of the world's adult population does not use formal or semiformal financial services, and many of these people live in Latin America and Asia. My research looks at the differences in development and challenges faced by MFIs in these two regions through a business lens of profitability, commercialization, and ability to scale.

The Effects of Gender Attitudes in the Home and Workplace

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Economics
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Kathleen McGinn
Harvard Business School

Social expectations of how men and women ought to behave, also known as gender norms, influence the allocation of work in the household and the opportunities realized by men and women in the workplace. A problem facing many couples today is deciding how to balance their professional and personal life. Due to the prevalence of policies that assume traditional gender roles – such as a lack of paid paternity leave – men and women who want to exercise a non-traditional division of labor often find it challenging to do so. I worked alongside Professor Kathleen McGinn and her doctoral students to identify existing gender attitudes and their effects in the home and in the workplace. In one study, we are in the process of surveying female and male employees from eight different companies in Mexico. The survey asks questions about demographics, parental attitudes towards the division of labor, personal attitudes towards gender, and satisfaction with company policies. After these surveys are completed and the data is analyzed, we plan to prepare a report for each company that includes a recommendation of which policies they should adopt to improve their retention and promotion of women. In another survey, we interviewed female and male MBA students to observe how they plan to balance their career and family in the future. Using qualitative coding, we identified themes across the interviews of MBA students. Though the data is likely to yield multiple papers, the first paper will analyze the influence of familial and non-familial role models on the students' plans for the future. Other projects include the effects of

negotiation trading on young girls in Zambia and the analysis of refugee officer training material. My hope is that through changes in company policies and gender attitudes, men and women will have more options to choose from when deciding how to balance their professional and personal life.

Social Psychology in Organizations

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Psychology
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Harvard Business School

To gain a deeper understanding of the intersection between social psychology and the business world, the research of the Cuddy lab focuses on the ways in which people behave and interact in organizational contexts. Particularly, the lab explores how nonverbal behavior and emotional expression can influence how people act, how they interact with others, and how others perceive them. Prior literature suggests that small changes in body language and nonverbal behavior can affect how people behave in profound ways, and based on this knowledge, we are delving deeper to understand the mechanisms and consequences of these effects. The questions we ask are about what these changes are, how they affect people both intrapersonally and interpersonally, and how these effects can be observed in organizational settings. We are exploring the link between nonverbal behavior and performance; how warmth, competence, and power are communicated and interpreted from nonverbal behavior; and how emotional expressions influence behavior and judgments. We also explore how perceptions of employees are influenced by demographic characteristics, such as gender and race. We use experimental methods including eye-tracking equipment, physiological measures, hormonal assays, and voice analysis to explore the effects of nonverbal behavior in the lab, online, and in the field.

Gun Regulation Formation and Effects of Implementation

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Economics
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Harvard Business School

In the year following the mass shooting at Sandy Hook Elementary School in Newtown, Connecticut, about 1,500 state gun bills have been introduced; of those, 109 have become law. Seemingly against intuition, nearly two thirds of the bills signed into law, or 70 of 109, contribute to the loosening of gun restrictions. Our project consists of

two steps. The first step is to analyze the process of gun legislation formation. Our goal is to determine what factors contribute to the introduction and/or passage of bills and how events like mass shootings and their related news media coverage influence this process. The second step is to analyze the effects, if any, of the laws when enacted. For example, we aim to determine whether conceal carry weapon (CCW) laws have the desired effect of reducing gun related violence, or instead do more harm. Our preliminary beliefs, and existing literature, suggest that mass shootings can be triggers for legislation proposal and passage. However, implementation of CCW laws does not seem to have the desired effect of reducing gun related violence. It is suggested that this observation can be explained by evidence which shows women and young children as the more frequent victims of gun related violent crimes, particularly in cases of homicide, and upon implementation of CCW, these individuals are most unlikely to carry weapons for protection. Further analysis and investigation is needed, but we hope to provide more understanding about the impact of gun related violence to both those in decision-making policy positions and the general public.

Performance Improvement in Health Care Organizations

Adam Joseph
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Organizational Behavior
Class of 2015

Anita Tucker
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In health care delivery organizations, a great deal of focus has been placed on improving patient experience, lowering costs, and improving clinical outcomes. Though performance improvement has been well studied in other industries like manufacturing, health care warrants its own coverage of this topic due to the unique combination of certain conditions, including the importance of patient experience, the variation inherent to the delivery of medical care, the high stakes of experimenting with human life, and the influence of various stakeholders such as government, insurance companies, the patient, etc. In our manuscript, we propose a Model for Transformational Performance Improvement (TPI) in health care organizations, which includes six components: (1) develop and communicate a system-level goal; (2) develop and use system-level measures to evaluate performance; (3) create an organizational engine for learning and change; (4) account for interdependencies within the system that impact the ability to achieve the goal; (5) implement a portfolio of improvement projects that are aligned to achieve the strategic goal; and (6) implement, spread, and sustain the changes. The manuscript reviews the operations management (OM) lit-

erature on performance improvement in health care organizations with a special focus on OM tools and principles that help with successful implementation of the six components in our model for TPI. Our work provides a framework that may be useful for OM scholars teaching OM tools and health care leaders looking for practical knowledge about OM techniques that help improve performance.

Career Gaps and Re-entry to the Workforce

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Economics
Class of 2017

Boris Groysberg
Harvard Business School

The concept of returning to the workforce after a career break has always existed, but until the past decade, re-entry had never truly occupied a separate category in the job search process. Recently, however, there has been a proliferation of companies establishing re-entry programs, which are essentially internships geared towards those who have taken voluntary, extended career breaks. Because more than a quarter of people leave the workforce at some point in their careers and often face difficulty trying to return after an extended gap, re-entry programs affect a large pool of the labor force. My research has involved collecting information about career gaps, documenting the history and evolution of the re-entry phenomenon, finding and classifying existing re-entry programs, and attempting to discern the purpose of these programs for both the company and the interns. Because many firms have launched re-entry programs in the past decade, at a rate that has never been seen before, this research could shed light on the necessity and benefits of the programs, as well as its scalability. Additional projects that I have also worked on include classifying companies into their industries using The Global Industry Classification Standard, finding potential case study protagonists, and studying the relationship between executives and stress.

Transparency and Organizational Productivity

Jonathan Roberts
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Economics
Class of 2017

Professor Ethan Bernstein
Harvard Business School

The role of transparency in modern financial institutions has brought into question the traditional relationships between consumers, workers, and executives. Professor Ethan Bernstein notes that around the world “organizations have striven for transparency in the workplace, lit-

erally tearing down walls in an effort to let managers and employees observe each other.” My work this summer attempted to examine the changes that companies and governments have made in their pursuits of openness. My research consisted of two independent projects:

The first project involved a collaborative study between Harvard Business School and a natural gas company. Field notes were taken at various worksites in Alabama in order to observe the effects of a small transparency initiative within the company. It was expected that the initiative would affect employees’ performance, certain work-related decisions, and their attitudes toward company managers. However, as the project was still in its pilot stages (and had yet to implemented company-wide), it was unclear whether or not the initiative was beneficial. A generalized report was submitted to participating supervisors to provide a guide for further discussion.

The second project involved writing a case for a class to be taught during the 2014-2015 school year at Harvard Business School. The case will be centered on the hiring decisions made at the early stages of a government agency. The case will attempt to highlight the parallels between the public and private sectors and allow students to shape a model institution through choosing its leader. Students will have to consider both how leadership affects early organizational decisions and the role of the founder in shaping an agency. The case will be based on Elizabeth Warren and her time at the Consumer Financial Protection Bureau.

Researching Creativity, Learning and Management Strategies

Nourhan Shaaban
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Psychology
Class of 2015

Teresa Amabile
HBS

This summer, I worked with my faculty adviser, Professor Teresa Amabile, and her three doctoral students on five different projects. For the first project, I analyzed survey data collected from a large international private school system in Asia. The goal of the project was to inform the school system about teachers and parents’ satisfaction levels, as well as the methods teachers and parents used for communication. I assisted in producing a report that made recommendations to improve various aspects of the school, specifically in regards to communication between teachers and parents. For my second project, I conducted an extensive literature review on Retirement, Creativity and Well-being. My third project involved reading, summarizing, and synthesizing various historical and theoretical papers related to self-management. Examples of the questions that I have been exploring are: Can an organi-

zation be truly democratic? What role does power and authority play in organizations? And how can we increase worker's freedom and at the same time maintain control? My fourth project explored the various psychophysiological measures that have been used in social psychological research such as cardiovascular measures, eye movement, and skin conductance. The goal of this project was to make recommendations for which method should be used in a study exploring negative arousal in negotiation contexts. My final project focused on the impact of reflection on learning at work. My role involved looking at people's reflections regarding what they learned at work and creating a detailed coding scheme that can be used to rigorously and reliably analyze the data.

Transparency in Online Customer Service

Steven Lee
Adams House

Economics
Class of 2016

Professors Max Bazerman, Alison Wood Brooks, Ryan W. Buell, Francesca Gino, Leslie K. John, and Michael I. Norton
Harvard Business School

Since the development of economics as a field of study, researchers have often operated under the assumption that individuals make rational decisions. More specifically, these rational decisions entail making the financially optimal choice based on all of the available information. However, further research has shown that individuals do not behave rationally, as their behavior is oftentimes heavily influenced by cognitive and emotional biases. Researchers at the GiNorton Lab, explore these effects in a variety of areas and looks at the impact of these effects on consumer and organizational behavior. One project that I worked on this summer through the GiNorton Lab examines the effect of operational transparency on customer satisfaction and employee efficiency. Previous research has demonstrated that customer satisfaction rises when companies are transparent about their operations. However, other studies have shown that making employee actions more transparent to managers may actually lead to negative outcomes. The project tests these concepts in the online customer service chat setting through Amazon's Mechanical Turk service, which hosts thousands of human intelligence tasks that individuals can complete for payment. Individuals on the service will be asked to participate in a live online chat with one participant playing the part of a customer with a defective item and another participant playing the part of an employee assisting the customer. After running this preliminary study, we plan to reach out to firms with customer service chat systems to implement the experiment in the field.

Globalization in the Wireless Telecommunications and Semiconductor Industries

Julie Chang
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Economics
Class of 2016

Juan Alcacer
Harvard Business School

Globalization has long generated debates in the realm of politics, management, and public policy. In his best-selling book, *The World Is Flat*, Thomas Friedman emphasizes the need for adaptation from governments and corporations in the face of globalization, which continues to level the playing field between countries (2005). However, the long-term effects of globalization, particularly within technology, remain relatively unexplored.

I assist research with two projects—one in the global wireless telecommunications industry and another in the semiconductor industry.

The first project explores the strategies of multinational telecommunications companies in over 200 countries across a 30-year time period. By examining a broad range of factors related to market evolution, firm competition, and institutional environment, the project analyzes how firms choose the location and timing of their international expansions. The project aims to determine the most successful companies, the reasons for their success, and an optimal strategy for international expansion.

The second project investigates the effect of offshoring on innovation in the semiconductor industry from 1950 to 2010. Specifically, it examines how the innovation levels in both the home and host countries change when firms choose to offshore manufacturing operations. The project uses data sets composed of patents and scientific research publications to measure innovation. A cluster location analysis combines these data sets with locations of semiconductor manufacturing plants to determine the effects of offshoring on innovation levels.

Ultimately, these projects will help inform managers and policy-makers alike on how to improve their companies and countries in an increasingly globalized world.

Reimagining Strategy

Kristen Shim
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Economics and English
Class of 2017

Cynthia Montgomery
Harvard Business School

This summer, Professor Montgomery and I worked to create a new seminar course on strategy for second-year MBA students. Today, the literature depicts strategy as a left-brain analytical exercise, a problem that can be solved

and settled, often by experts such as outside consultants. In this seminar, we present strategy as an essential, creative, and dynamic process, acknowledging the need for robust analytics, but complementing it with qualities that have the potential to make strategy even more compelling and more meaningful to an organization.

While planning the course, we asked, “How do companies create a difference that matters, a reason for existing that sets them apart from their competitors? Can qualities such as creativity, emotion, and meaning play a role in corporate strategy?” And most importantly, “how do leaders harness these qualities to shape both the strategy and essence of their organizations?”

I worked to find fresh and provocative sources that would spark in-class discussion. A series of photos from National Geographic’s *Work: The World in Photographs* depicts individuals who find meaning in their work. Giovanni Gavetti’s case history *Polaroid: Entering Digital Imaging* illustrates the vital role strategy plays in an organization, and the consequences that can follow when it ossifies. The book *Leading by Design: The IKEA Story* reveals how IKEA’s unique purpose shapes its entire organization and sets it apart from competitors. Additional sources such as videos and oral histories illustrate how qualities such as emotion and design can engender innovative approaches to traditional industries.

SpaceX: Understanding Alternative Models of Startup Funding

Darwin Hsu
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Economics
Class of 2016

Professor Rory M. McDonald
Harvard Business School

Startups face challenges and barriers that limit their opportunities to survive and succeed. Early partnerships provide entrepreneurs with much needed capital and management expertise that help overcome some of these disadvantages. In the past, new businesses had few choices when seeking these partnerships, and most turned to venture capital. In recent years, however, there has been an explosion in alternative funding partners and business models, allowing a new generation of startups new avenues to flourish. To better understand the alternative methods to startup funding, I investigated an increasingly lucrative and relatively nascent emerging market: commercial spaceflight. Specifically, my research focused on one of the most prominent players in the commercial spaceflight startup market: Space Exploration Technologies Corporation. Also known as SpaceX, the company has succeeded in an industry that had previously been too costly for commercial companies to profit without significant government subsidies. SpaceX has managed to become a ma-

jor disruptor in the industry by offering space missions at prices reduced up to 90%, initiating a wave of innovation and competition the industry has not seen in decades. My research attempts to understand how SpaceX has become so successful by first assessing the fundamentals of the spaceflight industry and then analyzing SpaceX’s business model, innovations, and sources of competitive advantage. Using a relevant and exciting company as a lens to understand innovative disruption, I hope to extract the keys behind SpaceX’s success in a way that can translate into success in other industries also facing stagnant innovation trends and high entrance costs. Applying methodical techniques to disrupt any industry can expedite the innovation process, and, as has been seen with SpaceX, can potentially revolutionize the possibilities of human life.

Using Time-Driven Activity-Based Costing to Improve Hospital Cost Reduction Efforts

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History and Science
Class of 2016

Robert S. Kaplan
Harvard Business School

To some extent, the escalation of costs in health care is a symptom of the fact that providers lack a good understanding of the real costs of patient care delivery. Currently, hospital costing methods are based on reimbursement mechanisms and only measure the costs of individual departments or services. Pilot projects at hospitals in the U.S. and Europe demonstrate the value of measuring health care costs at the level of all resources used by an individual patient with a given medical condition over a complete cycle of care. Specifically, this approach involves Time-Driven Activity-Based Costing (TDABC), in which hospitals develop process maps for each activity in a delivery chain and estimate the capacity cost rate (fixed expense per unit time) of resources in order to capture the total costs associated with a patient care cycle and determine the best ways to reduce overall costs without compromising care. In one program we are running with the Institute for Health Improvement on total joint replacement at 32 different hospitals, we have analyzed individual hospital TDABC data and compared processes across hospitals to identify potential cost reduction interventions. At the Interventional Radiology Department at Massachusetts General Hospital, we are developing detailed process maps that will help determine how the treatment of dialysis patients could be modified to reduce costs and improve efficiency. My other research has included reviewing the methods used by the U.S. government to measure costs in the health care sector and summarizing information about U.S. hospital and health system layoffs. This research is part of our larger effort to understand how var-

ious actors in the health care system currently think about and respond to the growing costs of medical care.

Various Projects in Venture Capital and Private Equity

Robert Doles
Mather House

Economics
Class of 2016

Professor Paul Gompers
Harvard Business School

This summer I worked under Professor Paul Gompers on his research in venture capital and private equity. The primary paper I worked on investigates the different strategies employed by private equity investors. A survey sent to the top private equity firms confirmed that investing practices vary across firms. The part of the paper I was most involved with looks specifically at how the educational backgrounds and employment histories of founders and top executives of these firms influence investment strategies. Though we are still analyzing the data, preliminary factor analysis reveals a connection between the backgrounds of these executives and the strategies used by their firms.

I also collected data for another project that examines the hiring decisions made by venture capital firms. We have found that, controlling for quality of school, having attended the same university as current firm employees increases the probability of being hired. We find that these people typically get to do more deals when they start working at the firm, but that there is no significant difference in future success between them and those that did not attend the same school as employees at the firm.

Professor Gompers also assisted me in taking on a project of my own related to his previous paper on venture capital investment cycles. I have not yet decided which path this project will take, but I hope to discover new insights into the causes and effects of booms within specific industries that venture capitalists invest in.

PRISE

Geometric Morphometry of Adaptive Cranial Diversity in Phyllostomid Bats

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Eliot House

Integrative Biology
Class of 2016

Arkhat Abzhanov
Harvard FAS (OEB Department)

The striking diversity in the geometry of complex body structures like the bird beak and the vertebrate skull enables the adaptive radiation of ecologically important functions like feeding and navigation. Yet developmental constraints often limit potential shape variation to a restricted set of linear transformations. In songbird beaks, for example, the shear and scaling transformations account for essentially all observed variation in 2D curvature. Similarly, our geometric morphometric analysis of phyllostomid bat skulls reveals three principal component (PC) linear transformations that together account for over 65% of observed variation in 3D whole-skull geometry and finds that the facial, cranial, and auditory skeletal regions emerge as distinct evolutionary modules that vary with relative independence according to unique transformation sets. Specimens were found to cluster by taxon in morphospaces defined by whole-skull PCs, which confirms a central prediction of a novel evolutionary dynamical model that generates feasible mutations in skull geometry by spontaneously applying PC transformations over time.

Moreover, estimated phylogenetic trajectories in whole-skull morphospace radiate along three distinct arms that associate with feeding habit, and preliminary data from embryonic and fetal bat skulls suggest that ontogenic trajectories largely track these phylogenetic trajectories, with embryonic morphologies similar to the insectivorous ancestral type. This supports the hypothesis that more evolutionarily recent differences in phenotype tend to emerge at later stages of development as an outcome of genetic changes in key developmental pathways. We propose that the first whole-skull principal component, a measure of craniofacial length that varies with cranial vault, is primarily determined by the genetically controlled mechanism of endochondral ossification, in which a precursor cartilage model is gradually replaced by bone. Overall, this mathematical approach is a powerful, effective means of describing and rationalizing morphological diversity in organisms with well-defined geometries.

Single Cell sub-classification Pipeline

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Neurobiology
Class of 2016

Dr. Aviv Regev
Broad Institute

A major impediment in characterizing neural circuits, and understanding their abrogation in disease, is our dearth of knowledge of neuronal cell subtypes. Incomplete classification of cellular subtypes has created a barrier to better understanding their functional and structural roles. The neurons of the retina are an ideal model for cell subtype exploration. Three of the retinal neural cell subtypes (photoreceptor, horizontal and bipolar) have known histological subtypes, while amacrine and ganglion cells subtypes have not yet been defined at a similar level of resolution. With the advent of methods for single-cell transcriptome profiling, data driven sub-classification of cell types has become possible. Single-cell expression data, however, is very different from traditional RNASeq expression data, due to both biological (transcriptional bursting) and technical (dropout during amplification) noise, resulting in zero-inflated measurements.

Here, we developed a pipeline for exploring cell classification using single-cell RNASeq expression and applied it to single cell profiles collected for a subset of retinal neurons. Specifically, we aimed to explore potential additional cellular subtypes among a population of KCNG4 retinal ganglion cells, a broad classification of retinal ganglions known to express the marker gene KCNG4. Initially, principal component analysis (PCA) was used to identify genes that are variably expressed among cells. Patterns of differentially expressed genes were then used to divide cells into sub-clusters, using a combination of PCA analysis and hierarchical clustering of genes corresponding to extreme axes of the top principal components. Using ANOVA, we identified genes that were significantly differentially expressed between cell clusters. We further examined clusters of co-regulated, differentially expressed genes in the context of their patterns of correlation with cell subtypes, and their underlying biological functions. Our methods and work open the possibility of systematic analysis of neuronal subtypes first in the retina and subsequently in other brain regions.

Mathematical Modeling of Cancer Dynamics in a Hierarchical System

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Applied Math
Class of 2016

Dr. Franziska Michor
Dana Farber Cancer Institute

Cancer arises from genetic and epigenetic changes,

which confer fitness advantages that can lead to uncontrolled proliferation. Healthy tissue consists of a hierarchically organized system of cells. The cancer stem cell (CSC) hypothesis posits that a tumor can also be viewed as such a hierarchical system: only a subpopulation in a tumor has the potential for self-renewal. So far, phenotypically distinct subpopulations of CSCs has been demonstrated to exist in a number of human cancers including forms of leukemia, breast cancer, and lung cancer. Based on the CSC hypothesis, we first develop a deterministic model consisting of a system of ordinary differential equations. This system models the dynamics of a single subclone. We assume that in every time step a CSC can do one of three things: self renew, differentiate, or die. All differentiated cancer cells can further divide for a fixed number of times, or die at every time step with a rate depending on the total subclone population size. Using this model, we can predict the cancer stem cell fraction based on total tumor size, calculate the time at which a tumor transitions into a slow dynamic equilibrium phase, and simulate tumor cell population dynamics in response to different treatment schedules. Next we want to account for the emergence of tumor heterogeneity, as well as cancer cell plasticity. We ask how and when phenotypically distinct subclones within a single tumor can arise, and seek to describe tumors in which differentiated cancer cells can regain stem-like properties. To this end, we develop a stochastic, individual-based model. By means of stochastic simulations we aim at a more realistic representation of the complexity and variable heterogeneity found in actual human tumors. Through these simulations, we hope to quantify how probabilistic mutations influence treatment strategies and prospects.

Analysis of Essentiality Profiles (RNAi) to Identify Novel Cancer-Relevant Genes

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Computer Science
Class of 2016

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Broad Institute

Beyond simply isolating genes that are heavily altered or overexpressed in cancer genomes, analyzing genes' functional essentiality in cancer cell lines is crucial for identifying novel cancer-relevant targets. Given our limited understanding of the diverse mutation and transcriptional states that produce cancer hallmarks, we must identify functionally relevant genes without necessarily knowing the cellular contexts in which they are essential. Here, we develop metrics to suggest potential cancer-relevant genes by analyzing the Achilles data set, generated from a genome-scale shRNA screen assessing cell viability. We used a manually curated benchmark list of 72 known

functionally relevant cancer genes to evaluate metrics that identify genes differentially essential across Achilles cell lines. Given benchmark performance, we isolate genes with strong outlier dependencies by fitting skew-t distributions to the genes' essentiality profiles and boosting outlier values in these distributions. We found that 50% of benchmark genes ranked in the top 10% of genes ranked by this skew-boost metric, demonstrating that essentiality profiles can serve as a useful signal for oncogenic potential. To focus on genes with behavior close to known cancer targets, we isolated top skew-boost genes whose essentiality had high mutual information with its own genomic alterations (driver genes) or with cancer benchmark genomic alterations. Furthermore, to understand the contexts in which these genes' essentialities vary without incurring biases towards known cancer states, we are clustering gene essentiality profiles via non-negative matrix factorization and hierarchical clustering, finding cellular states common to top-performing skew-boost gene hits. We are moving to biologically validate some interesting dependencies highlighted by this analysis via gene knockdown experiments. We hope that such validation will add to benchmark evidence to demonstrate that RNAi data can provide crucial functional signals, directing future research on cancer-relevant pathways and ultimately identifying novel key cancer targets more systematically.

Software for Principled Quality Control of Metagenomic and Metatranscriptomic Sequencing Data

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Statistics
Class of 2016

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The human microbiome has been implicated in diseases such as colon cancer and Crohn's disease, and plays an important role in human health. To study this massive microbial community, researchers are turning to high-throughput metagenomic sequencing approaches. But, these large data sets contain large amounts of noise. Biological samples, such as human tongue swabs, or gastrointestinal tract samples, can have a prohibitively high ratio of host to bacterial sequencing reads. In metatranscriptomic sequencing, a large fraction of the microbial sequencing reads are ribosomal RNA (rRNA). Most research applications, however, only want the bacterial genomic or messenger RNA (mRNA) reads—these help infer bacterial species/strain identity and bacterial gene expression. In our project, we tested several methods to remove the contaminant rRNA and host reads. One method uses the alignment of a read to an rRNA or host genome

reference database to determine whether to remove a read. These alignment-based tools include Bowtie2, Burrows-Wheeler Aligner (BWA), and Usearch. But, these tools are slow and computationally expensive. To solve this problem we tested a k-mer based algorithm, BMTagger. It uses the presence or absence of k base pair-length nucleotide sequences in the reads and the reference databases to classify a read as contaminant. Using BMTagger at the core, we developed KneadR, a metagenomics quality control software. Our software incorporates read quality checks and BMTagger to quickly and accurately identify and remove host and rRNA contamination. We plan to validate KneadR's specificity, sensitivity, and runtime on synthetic and real data from metagenomic and metatranscriptomic sequencing. We will use this validation to tune KneadR's parameters and compare its performance to the alignment-based tools. KneadR will allow researchers to perform efficient and principled quality control backed by rigorous and reproducible testing and experimentation. KneadR resides on Bitbucket at <https://bitbucket.org/biobakery/kneaddata>.

Examining Demographic Factors in the Emergence of Drug Resistance in *Plasmodium falciparum*

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Statistics
Class of 2017

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Plasmodium falciparum is an important eukaryotic pathogen that causes malaria, an ancient human disease that has significantly impacted the course of human evolution. In turn, humans have played a crucial role in the evolution of *P. falciparum* as well. For example, over the course of thousands of years, human migration events and the selective pressures imposed by the human immune response have influenced how *P. falciparum* evolved. Today, the role of humans in the evolution of *P. falciparum* has grown to encompass intervention measures—notably, the employment of drugs. The rates with which *P. falciparum* develops drug resistance are alarming. Throughout the past few decades, populations of drug-resistant *P. falciparum* parasites have developed and spread. Most recently, resistance to artemisinin, our current last line drug, has started appearing in areas of Southeast Asia. Interestingly, previous instances of drug-resistant parasites have also originated from this area. Consequently, we hope to further investigate the population structures of *P. falciparum* to determine reasons for this region's propensity for developing resistance. Previously, the Sanger Institute sequenced the complete genome sequences of over 800

parasite samples from various regions of Africa and Asia. These samples suggested the presence of significant population structure amongst global parasite strains as well as the presence of additional substructure within Southeast Asia. To examine whether or not demographic factors play a role in the emergence of drug resistance, we first sort the parasites into different populations via STRUCTURE, PCA analysis, and phylogenetic trees. Doing so allows us to examine population-specific parameters, which require the differentiation of distinct populations. In the future, we hope to use these tools and our knowledge of the population substructures to study the interplay between demographic history and population size in developing drug resistance.

Active Galactic Nuclei

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Math, CS, or Astrophysics
Class of 2017

Belinda Wilkes
Center for Astrophysics

Active galactic nuclei (AGN) are among the brightest objects in the Universe; they can often outshine their entire host galaxy. Their activity, extending from radio to gamma rays, is centered in a small nuclear region called the “central engine”, which consists of a supermassive black hole with a hot accretion disk of gas emitting strong optical to X-ray emission called the “big blue bump”. Some of this emission is absorbed by circumnuclear dust, producing infrared emission that forms the “infrared bump”. There are many different classes of AGN, with differing spectral and continuum properties, which according to the “unification models” are the same central engine viewed from different angles/through different amounts of obscuration. Some AGN, called “radio-loud AGN”, are relatively bright in the radio band; their radio emission is powered by jets resulting from powerful magnetic fields. Our group is studying a low-redshift ($0.5 < z < 1$) 3CRR sample of radio-loud AGN. The sample includes sources with a full range of inclination angles, and the radio core fraction gives us an estimate of the AGN orientation. We analyzed Chandra X-ray data of these sources to obtain hardness ratios and generate spectra, which we then modeled to determine the underlying power law and intrinsic obscuration. Additionally, for each AGN we generated a radio to X-ray spectral energy distribution (SED) from previously published and archival data. These SEDs will allow us to determine luminosities (bolometric, optical/UV, and X-ray), test the SEDs dependence on orientation, find obscuration in the optical/UV to compare with obscuration from the X-ray analysis, and thus test the unification models. I also compiled a database consisting of webpages for each of the low and high redshift 3CRR objects, presenting their cor-

responding images (in the radio, infrared, optical, ultraviolet, and X-ray bands), X-ray spectral fits, and published references.

In-line laser sintering of silver nanoparticle ink for direct ink writing of microelectrodes

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Engineering Sciences
Class of 2016

Jennifer Lewis
Harvard University

Direct ink writing, a printing technique where a viscoelastic ink is extruded out of a movable nozzle, is an emerging technology that allows fabrication of electronic architectures that would be both challenging and costly to achieve through conventional patterning techniques. Such electrode architectures are necessary for manufacturing solar cells, flexible displays, radio frequency identification tags, antennas etc.

Since solid metal cannot be extruded out of a nozzle, a silver nanoparticle ink has been developed that is compatible with direct ink writing. To achieve conductive electrodes, the patterned silver ink must be annealed at high temperatures (> 200 °C) to drive off all the organic materials. Unfortunately, these temperatures are incompatible with many plastic and paper substrates. Furthermore, since the ink is viscoelastic, it is not possible to print three-dimensional, unsupported electrode architectures without structural failure.

To tackle these issues, we designed an in-line laser sintering system, where a high-power laser, attached alongside the nozzle, immediately sinters the extruded silver filament. To print in all directions, the orientation of the laser relative to the printed path must be modulated so that the laser spot traces the path accordingly. Although this can be accomplished by moving the laser, for practical reasons, we fixed the laser position and moved the substrate using a rotary stage. The conductivity of the laser-sintered silver is comparable to that achieved by high-temperature baking. However, since the ink is annealed through localized heating, laser sintering affords a larger substrate tolerance. Moreover, because sintering solidifies the silver, our technique allows us to print free-standing structures such as coils. The in-line laser sintering technique we have developed adds another level of versatility to direct ink writing of electrodes, enabling fabrication of intricate electronic devices.

Scheduling Algorithm for the Large Scale Synoptic Survey Telescope

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The Large Scale Synoptic Telescope (LSST) is a wide-field telescope currently under construction and scheduled to be deployed in Chile by 2022 and operate for a ten-year survey. As a ground-based telescope with the largest field of view ever and the ability to take images approximately once every thirty seconds, the LSST will be able to capture the entirety of the observable sky every few nights at a number of different band passes. With these remarkable features, LSST is primed to provide the scientific community with invaluable data in numerous areas of astronomy, including the observation of near-Earth asteroids, the detection of transient optical events such as supernovae, and the study of dark matter and energy through weak gravitational lensing.

In order to maximize the utility that LSST will provide toward achieving these scientific objectives, it proves necessary to develop a flexible scheduling algorithm for the telescope which both optimizes its observational efficiency and allows for adjustment based on the needs of the astronomical community. Current techniques for such algorithms, however, fall spectacularly short of the standards necessary for this project; the primary implementations have numerous shortcomings, including a failure to sufficiently account for degradation of visibility conditions due to basic phenomena such as sky brightness and cloud cover.

This work seeks to remedy this condition by constructing a new function that accurately captures the urgency of observing a particular field in the sky as a function of time elapsed since last observed, viewing conditions, and a measure of scientific interest in the field. The problem of minimizing the total value of this urgency function, summed across the entire observable sky, is then reduced to a classic variant of the dynamic traveling salesman problem. We introduce a new approximation technique that appears particularly well suited for this data and analyze its effectiveness in resolving this problem, obtaining some promising results.

Physics/Math

Class of 2017

Coupling NV Centers with Diamond Nanomechanical Resonators

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Physics

Class of 2015

Control of quantum systems, such as the nitrogen-vacancy (NV) center in diamond, is a topic in contemporary physics research that has many wide-reaching applications in metrology, quantum communication, and quantum computing technologies. The spin state of the NV center can be manipulated and measured at room temperature, and the NV center's high reliability and stability make it an ideal candidate as a quantum system.

Computational simulations are used to model the behavior of NV centers in various diamond nanostructures with sub-micron dimensions, and are used to calculate the spin-strain coupling of the NV center with the resonator and the consequent frequency shifts due to thermal motion or induced mechanical deformation. Dimensions of the structures are optimized to maximize the coupling. Additionally, an experimental scheme is designed and built to apply complex microwave pulse sequences to NV centers that can extend the coherence time of NV centers, thus improving its sensitivity and stability. These experiments are also integrated with tracking software that tracks the NV centers through confocal microscopy.

Finding Objects with 1/1000 the Mass of the Moon around White Dwarfs

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Physics

Class of 2017

Since white dwarfs are exceptionally dim due to their small size, the contrast between the thermal emission of an orbiting object and the white dwarf's spectrum is dramatically improved over main sequence hosts. Furthermore, objects much smaller than the mass of the moon will have no atmospheres, and close to the Roche zone these objects will be tidally locked. We show that this leads to temperature contrasts between the exposed day and night side of order unity $\Delta T/T \sim O(1)$. By targeting periodic variations in flux from ~ 10 hr orbits, we calculate that the Hubble Space Telescope (HST) could detect objects with a mass as small as $1/100$ the mass of the moon M_L within a few orbits. The James Webb Space Telescope will be able to detect objects as small as $10^{-4}M_L$ for these hot white dwarfs, and will see objects down to $10^{-3}M_L$ for cooler

white dwarfs. Constraining the abundance of planetesimals and minor planets around white dwarfs as a function of varying white dwarf temperatures (and therefore age) would be a novel probe of the physics of planetary formation.

Exploring Life's First Steps: Using Quantum Yield Curves to Determine Reaction Feasibility Under Primordial Conditions

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Biogenesis arose from a sequence of remarkable chemical events that are just beginning to be systematically unearthed. Current efforts to examine prebiotic chemistry often overlook the dramatic constraints imposed by environmental conditions on the primordial Earth; consequently, it is of great interest to confirm the plausibility of such chemistry within the parameters of ultraviolet flux, atmospheric absorbance, abundance of water, and surface temperature. Our investigation probes several key prebiotic reactions from an astrophysical perspective to determine their chemical feasibility in various planetary environments.

Our efforts are focused on the ultraviolet mechanisms employed by several prebiotic chemical reactions known to selectively yield desired biologic precursors. These include the synthesis of simple sugars necessary to build RNA catalyzed by a cyanocuprate complex in dilute hydrogen cyanide solution, as well as the selective destruction of co-products by ultraviolet irradiation to yield the RNA pyrimidines necessary for life. Using analysis tools like quantum yield curves, we are able to evaluate the plausibility of these mechanistic claims.

Quantum yield curves provide information about reaction progression as a function of wavelength. By constructing a quantum yield curve for a reaction, we gain valuable insight into the mechanism of the ultraviolet event and its wavelength sensitivity. When combined with models of atmospheric absorbance and ultraviolet flux from the host star, these quantum curves help determine the plausibility of these prebiotic chemical events occurring within the parameters of a given planetary system. Not only will these predictions be valuable in determining which chemical reactions support the chemistry of life's origins on our own planet, but also they will play a pivotal role in the search for life on other worlds by constraining which exoplanet systems can viably host such chemistry.

Reduced graphene oxide thin films

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Graphene (a sheet of sp^2 -bonded carbon atoms in a hexagonal lattice) is a two-dimensional material with favorable properties such as high conductivity, low permeability, high breaking strength and high Young's modulus, giving it a wide range of applications, from water filtration to transparent conducting films. Graphene oxide (GO) is a single graphene sheet decorated with oxygen-containing functional groups. This project focuses on the production of reduced graphene oxide (rGO) films using an oxidation-exfoliation-reduction process which produces micron-scale rGO platelets from graphite. These platelets, suspended in ethanol, can be injected at an air-water interface and wet-deposited on a flat hydrophilic substrate. By controlling the extent of photoreduction of the platelets, the concentration of platelets at the interface, and the ionic strength of the water subphase (giving different amounts of shielding of charged functional groups on the particles), the structure of the resulting monolayer can be controlled. We aim to study the intraparticle (rolling up/scrolling of individual particles) and interparticle interactions (cluster formation) and model the forces involved using DLVO (Derjaguin-Landau-Verwey-Overbeek) theory, which describes the combined effects of van der Waals attraction and electrostatic repulsion between charged particles. The objective is to quantify the range of both short-range repulsive and long-range attractive forces by investigating the effect of bulk density and ionic strength on cluster size, particle stacking (single or multiple layer films) and characteristic nearest-neighbour distance. Ultimately, this would allow production of self-assembled films of rGO which can be reduced further and cross-linked covalently to produce large-area films with controlled properties.

The Effect of the Coupling Energy between Qu-bits Comprising a Composite Qu-bit on the Probability of Success of an Adiabatic Quantum Computation

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Adiabatic quantum computation (AQC) is an approach to quantum computation that is alternative to the usual quantum gates model. Given an optimization problem of

interest, typically formulated in terms of “qu-bits” (objects which can take on values of 0, 1, or a quantum superposition of 0 and 1), AQC finds the optimal assignment by using the quantum adiabatic theorem. In the last few years, the interest in AQC has greatly grown thanks to the physical realization of dedicated quantum computers. However, due to physical limitations on the connectivity between qu-bits in a computer, it is often necessary to create a “logical” qu-bit, composed of two or more actual “physical” qu-bits that can leverage the connections of its constituent physical qu-bits to attain higher connectivity. In this project, we studied, from both the theoretical and numerical point of view, the effects of this overhead procedure on the performance of AQC. We did this by modeling an adiabatic quantum computer as a system of n logical qu-bits, where each logical qu-bit is comprised of two (in principle strongly) coupled physical qu-bits. Because of the exponentially large computational cost of simulating quantum systems in an exact way, we have limited our analysis up to $n = 9$ logical qu-bits (that is to say to a physical Hilbert space of dimension 2^{18}). In particular, we have found that there exists a specific coupling strength such that the probability of success for a given evolution time is maximized. This result is consistent with recent empirical observation using existing adiabatic quantum computers, namely D-wave machines.

Characterization of Nonlinearities within Diamond Nanoelectromechanical Resonators

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The interest in and practical demand for miniaturized electronics have blossomed over the past decade, and with them the field of nanoelectromechanical systems (NEMS). Recently, novel advances in the fabrication and control of NEMS systems have made it possible to make and accurately characterize the behavior of devices on the sub-micron scale. Capitalizing on these new techniques, this project seeks to experimentally study the origins and behavior of nonlinearities in these system, both to better understand potential applications for these devices and to provide greater insight into the field of nonlinear dynamics. Specifically, through the use of dielectric force-based actuation and laser-based transduction, our group has carefully characterized the mechanical resonant response of diamond resonators (doubly-clamped beams and cantilevers), which measure on the order of only microns long and hundreds of nanometers wide. Data collected thus far demonstrates nonlinear response when devices

are driven above critical amplitude, manifesting in conventional Duffing nonlinearity as well as nonlinear dissipation. Through the use of ABAQUS FEA (Finite Element Analysis) software, we aim to explain the origins of observed nonlinearities by introducing a physical model governed by an elasticity equation. With this model, we seek to experimentally verify the coherence of the behavior of these systems to a modified Duffing Equation, the nonlinear ordinary differential equation that purportedly governs the response of these devices, by matching experimental data with those of the proposed physical model implemented by ABAQUS. Potential next steps include systematically analyzing nonlinear damping in these systems as well as examining the behavior of coupled systems. In the future, NEMS devices will form the heart of consumer electronics as well as state-of-the-art scientific sensors, and the work of this project will serve as a necessary and fundamental foundation for such exciting later applications.

Light-Matter interaction between tapered fibers and optical cavities

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My host laboratory, the Evelyn Hu research group, has been involved in the improvement of on chip photonic structures. In line with the research of the Hu group, I will be working on a project involving the coupling of microdisk optical cavities, with a tapered optical fiber. There are two main components to this project: the optical cavity and the tapered fiber. An optical cavity is an arrangement of reflective material, which confines light inside a cavity. A tapered fiber is a very thin fiber (0.7-1.5 μm range in our experiment) developed through adiabatic stretching of an optical fiber over a torch flame. The small diameter fiber allows infrared light to evanescently leak out and couple with the optical device (placed in its immediate vicinity); by monitoring transmission, the tapered fiber can serve as an optical probe for measurements of interest. A figure of merit in our project is the microdisk quality (Q)-factor, which gives us the photon lifetime of an optical mode in the cavity. In layman’s terms, the Q tells us how many times the ray reflects within the cavity before escaping. The importance of the Q derives from the fact that our goal is to couple cavity photons to artificial atoms known as quantum dots (QDs), which are embedded in the microdisk cavity. In order to increase the fidelity of optically initializing, manipulating, or reading out a qubit state within a QD, one needs a large probability (given by a high

Q factor) of the cavity photon interacting with the artificial atom. My research is particularly interested in ZnO and GaN microdisk optical cavities, and the optimization of their coupling and Q-factors with changes in size, shape, height and surroundings. Currently, such optical cavities are widely used in lasers, and are expected to be used in the future for quantum communication and information processing.

Cationic Cascade Cyclizations through Activation of $C\equiv C$ with InI_2^+

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The conversion of straight-chain organic molecules to polycyclic structures is a process found throughout all of nature. These polycyclic structures dominate a large portion of biologically active and important molecules holding such functions as defense and growth. Moreover, many polycycles have medicinal value, with some showing anti-viral, anti-inflammatory or anti-cancer capabilities. The complexity of these polycycles has inspired and challenged organic chemists to synthesize these natural products in a lab setting as efficiently and precisely as possible.

In the Corey lab, current research centers on creating catalysts for the cyclization of acyclic molecules. Recently, it has been found that the metal indium, supplied in the form of InI_3 , coordinates extremely well with triple bonds and can initiate a cationic cyclization cascade in molecules containing triple bonds (alkynes). Further, when this reactive indium species is dehalogenated to cationic InI_2^+ , the bivalent becomes an even better catalyst for the cyclization of alkynes. This high affinity for triple bonds may be due to the presence of two vacant, orthogonal and low-energy p -orbitals in the indium species that can coordinate with the π -electrons of triple bonds. Most recently, we have begun to focus on the possibility for enantioselectivity, favoring one specific configuration of bonds, in these cationic cyclizations by experimenting with ligands the indium can favorably complex with.

Overall, the production of an enantioselective cyclization catalyst could have vast consequences for the future of biomimetic organic synthesis. The assembly of an efficient and effective catalyst for cyclization would have great utility across all branches of synthetic chemistry. Eventually, this catalyst could provide an easy route for the creation of biologically active natural products with therapeutic potential.

Creating Small, Low-Cost, and Highly Precise and Accurate Density Standards

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Various techniques, such as AMPS and MagLev, measure the densities of solid objects and separate objects based on density, and have been used for many applications, including analyzing food samples and making medical diagnoses. These techniques often rely on solid density standards as calibrations, reference points, and/or controls, but in many cases – particularly on smaller scales – the precision of these techniques surpasses the precision and accuracy of currently available density standards. My project establishes a simple, low-cost method of creating small yet highly precise and accurate solid density standards.

We use aqueous multiphase systems (AMPSs), in which aqueous solutions of polymers, surfactants, and/or salts spontaneously separate into stable phases with distinct densities. Two-phase AMPS are tuned to have small differences in density between the two phases, and are mixed with polymer beads to concentrate only beads denser than the top phase but less dense than the bottom phase at the interface between the phases. Beads are extracted from the interface and used as density standards. With this method, we can match the precision of the best commercially available density standards (± 0.0002 g cm^{-3}), while producing ours for a fraction of the cost ($< 10\text{¢}/\text{bead}$ compared to $\$100/\text{bead}$) and with much smaller beads (≥ 50 μm diameters compared to 5–6 mm diameters).

We apply these density standards as controls for an AMPS-based sickle cell disease diagnostic that separates sickled and non-sickled red blood cells by density. These controls must be small enough ($\leq 300\mu\text{m}$) to fit in the capillary tubes the tests are run in and precise enough to detect subtle changes to the phase densities of the diagnostic AMPS. Our density standards – unlike anything previously available – satisfy these requirements, and are effective controls for the sickle cell diagnostic. We are currently finalizing these controls for clinical field trials early next year.

Efficient Synthesis of Tetraarylbenzoquinones and their Applications

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Quinones are a diverse class of intensely colored, redox-capable molecules with applications as colorants, chemical tags, electron shuttles, and battery electrolytes. A novel route to tetraarylbenzoquinones is reported in which derivatives of dibenzylketone and chalcone are annulated and subsequently oxidized. The mild conditions presented allow for a high degree of functionalization prior to or following annulation and an appreciable group tolerance. Several representatively diversified tetraarylbenzoquinones are presented including brominated, fluorinated, methylated, and sulfonated variants. The visual and redox properties of these derivatives are explored through spectroscopic and electrochemical methods. Their application as chemical tags and organic electrolytes is also discussed.

Reconstructing Temperature and Hydrological Conditions at Mono Lake during the Holocene and Last Deglaciation through Clumped Isotope Thermometry

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Periods of rapid warming in Earth history can provide valuable information about the mechanisms and the effects associated with rising global temperatures in the present day. One such warming event is the last major deglaciation, which extended roughly from 19,000 to 11,000 years ago. This project assesses the effects of the last deglaciation in the Western U.S. by measuring temperature and precipitation changes at Mono Lake, California, a saline, closed-basin lake. We use a recently developed paleoclimate proxy: clumped isotope thermometry. This consists of measuring the number of oxygen-18 isotopes ($\delta^{18}\text{O}$) and carbon-13 isotopes ($\delta^{13}\text{C}$) within a carbonate molecule. These isotopes are more likely to occur together at higher temperatures, so a relationship exists between the number of carbonates that contain both $\delta^{18}\text{O}$ and $\delta^{13}\text{C}$ and absolute temperature. Furthermore, the independently determined $\delta^{18}\text{O}$ values provide information about precipitation and ice volume changes. We apply this technique of clumped isotope thermometry to

ostracods, a class of crustacean, from Mono Lake. Our data demonstrates a shift in temperature and precipitation patterns around 12,300 years ago, which falls within the Younger Dryas time period, a cooling event that interrupted the deglaciation. This may imply that climate patterns in the Western U.S. closely follow global changes in the jet stream, ocean circulation, ice sheet shrinking, or other factors rather than exhibiting regional variation and decreased sensitivity to global climate events.

Synthesis of a phosphatidylcholine hydrogelator

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Hydrogels – water-swollen polymeric networks – often comprise amphiphilic monomers featuring a hydrophilic “head” linked to a hydrophobic “tail”. The greasy tails of these hydrogelators bind together in a hydrophobic “pocket,” while the polar heads engage in hydrogen bonding with surrounding water molecules, leading to gelation. Factors including concentration, pH, and temperature of the solution all influence the properties of the resulting gel, and may even hinder its formation entirely.

One common class of hydrogelator is the lipid, although these frequently exhibit behavior other than gelation; for instance, phospholipids self-assemble into nanostructures (e.g. liposomes, micelles, and lipid bilayers), also as a result of the molecules’ amphiphilicity. Both the individual lipid’s structure and solution conditions are determining factors in the type of structure formed during self-assembly. It should therefore be possible to balance these conditions such that a species of phospholipid can self-assemble in one solution and interact with a different species of lipid to form a gel in another. Finding that balance may open a new application of existing targeted liposomal delivery methods; tuning gelation conditions to the intracellular environment would prohibit extracellular gelation, and the required presence of both species would prohibit gelation in non-target cells.

The Ritter Group is synthesizing two species of two-tailed phospholipids based on a glycerophosphocholine (GPC) moiety, coupled to fatty acids capped with norbornene and tetrazine groups, respectively. These functional groups were chosen for their ability to interact in a “Click” coupling reaction, named for its speed and tolerance of a wide range of conditions. When exposed to each other, the phospholipids should therefore polymerize, forming an amphiphilic network similar to known hydrogels. Both solution conditions and length of the greasy

tails will be varied to optimize gelation. Subsequently, each species will be assayed individually to determine a gradient for self-assembly conditions.

Improving the Fidelity of Template Directed Non-enzymatic RNA replication

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The RNA world hypothesis postulates that the first molecule of life was a catalytic RNA molecule capable of replicating itself. The molecule would be a ribozyme, an RNA molecule that, like protein based enzymes, is capable of catalyzing chemical reactions. This ribozyme would then act as both enzyme and genetic material. The development of an RNA complex enough to display replicase activity would seem to require a method of replicating long RNA sequences that does not require a replicase. It has been shown that replication of RNA (or other analogous genetic polymers) can be conducted without enzymes, and chemical modifications to the leaving groups of the monomers have greatly improved the rate and efficiency of non-enzymatic template directed RNA synthesis. One such leaving group modification is the addition of 2-Methyl Imidazole to the 5' phosphate of the RNA. Such replication can go fairly efficiently and accurately in when the template includes only G and C, but when A and U are added, replication becomes much slower and less efficient. In RNA, wobble base pairing can occur between G and U, providing a similarly stable pairing option that competes with the desired Watson-Crick pairings GC and AU. This results in point mutations during replication. In preliminary results, the addition of 3-mer oligonucleotides that match the template and bind just downstream of the adding nucleotide also improve rates of primer extension. The focus of my work will be to deep sequence these primer extension reactions and demonstrate that this method improves both the accuracy and efficiency of replication.

Developing an iron complex for enantioselective C-H functionalization

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Hydrocarbons make up the bulk of crude oil, and serve as the primary “feedstocks” of the chemical industry. However, due to the strength of carbon-hydrogen (C—H)

bonds, hydrocarbons are relatively inert. The ability to chemically activate and functionalize C—H bonds catalytically and on an industrial scale could allow the direct conversion of hydrocarbons into more reactive molecules, which have greater functionality and therefore greater value. Previous work has led to the synthesis of an iron-based organometallic complex that can catalyze such reactions. However, this catalyst cannot influence the stereochemical outcome of the reaction. Being able to exert selectivity over the chirality of the product formed could have important implications for applications of the catalyst, particularly for biologically relevant uses (e.g., in drug synthesis), where stereochemistry is extremely important. This project aims to design and synthesize an iron-based organometallic catalyst that will be able to control the stereochemistry of the C—H functionalization reaction. Specifically, we will synthesize a chiral ligand, in an attempt to partially occlude the catalyst’s reactive site and thus influence the orientation of the substrate upon binding to the catalyst. We hope to show that the chiral cleft created by the ligand will influence the stereochemistry of the products formed. By introducing chiral moieties at different locations on the catalyst, we aim to probe how the catalyst may influence the C—H functionalization reaction, and tune the enantioselectivity of the catalyst toward its substrates. Ultimately, we hope that this catalyst will see applications in the chemical industry, presenting a novel method to introduce both chirality and reactivity into the simplest chemical “feedstocks.”

Modeling a system for an enantioselective [2,3]-Wittig rearrangement

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A common challenge in organic chemistry is getting multiple products out of a reaction when only one of those products is actually desired. In particular, reactions often give rise to a special pairing of molecules known as “enantiomers”—these are molecules that are mirror images of each other, but when placed on top of one another, do not completely overlap. Importantly, because of the different spatial arrangement of their atoms, enantiomers can have different reactive properties when interacting with other “handed” molecules. In making drugs and other useful products, it is often ideal to produce only a single enantiomer, so that your product has a single set of reactive properties. To offer a solution to the challenge of getting both enantiomers out of a reaction, the Jacobsen lab designs “enantioselective catalysts”—molecules that

help a reaction form one enantiomer in excess by lowering the energetic pathway leading to one enantiomer relative to the energetic pathway leading to the other enantiomer. This summer, I am modeling a reaction known as the [2,3]-Wittig rearrangement, a synthetically useful reaction for which my mentor has developed an enantioselective catalyst. The ultimate goal of this modeling is to get a qualitative picture of how catalyst and substrate interact at the highest energy point of the reaction pathway, a point known as the “transition state”. Often, an enantioselective catalyst makes favorable interactions with substrate in the transition state leading to one enantiomer, but not in the transition state leading to the other enantiomer; it is through these interactions that enantioselective catalyst lowers the barrier to one enantiomer, and favors the formation of that enantiomer. I hope to identify the interactions that could be present in the developed system for an enantioselective [2,3]-Wittig rearrangement, which could improve catalyst design in the current system.

Asymmetric Vicinal Diamine Synthesis via Chiral Auxiliary-Mediated Mannich Reaction

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Vicinal diamines are useful for the synthesis of β -lactam antibiotics, like penicillin, and as well as other natural products. Vicinal diamino acids, also known as α,β -diamino acids, have a basic three-carbon backbone with the two amine functionalities placed on adjacent carbons. In a non-stereoselective synthesis, these amine functional groups can exist in four configurations, called diastereomers. Because each diastereomer can have different biological and chemical properties, a highly stereoselective route is desired in order to produce only the target configuration.

Previously published work by the Myers group provided access to β -amino- α -hydroxy acids via condensation of (*R,R*)-pseudoephedrine-glycinamide enolate and aldehydes or ketones in an aldol reaction that proceeds with high stereoselectivity. The use of chiral auxiliaries like (*R,R*)-pseudoephedrine permit certain reactions to take place in a stereoselective manner. By differentiating the two faces of the desired substrate, chiral auxiliaries ensure that reagents and substrates react in an asymmetric manner. The high stereoselectivity and effective nature of the pseudoephedrine chiral auxiliary makes it a powerful synthetic tool.

The objective of this work is to provide α,β -

diamino acids via a similar condensation of (*R,R*)-pseudoephedrine-glycinamide and imines in what is known as a Mannich reaction. The importance and success of this work rests in our ability to set two stereocenters in a single step with high selectivity. Using this method we have accessed a variety of vicinal diamine products, which have been carried toward the synthesis of β -lactam antibiotics.

β -lactams are one of the most widely used classes of antibiotics. Unfortunately, like many other antibiotics, β -lactams have been largely disarmed by resistant bacterial strains. We hope this short and stereoselective synthesis to β -lactams will enable the synthesis of new and more potent antibiotics.

Identification of Novel Catalysts for Antitumoral Scaffold in Lomaiviticin Biosynthesis

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Since their discovery in 1966, angucyclines have been of scientific interest due to their many interesting properties, including the natural product's cytotoxicity to human cancer cells. As secondary metabolites—compounds that are not directly utilized for growth—of marine gram-positive bacteria, members of the angucycline family share the same initial steps in their biosynthetic pathways which subsequently branch into different analogs, such as kinamycin and lomaiviticin. It has been hypothesized that upon undergoing an aromatic ring-contraction reaction, the “branching step” for kinamycin, an intermediate called dehydrabelomycin is catalyzed into kinobscurinone, in which the diazotetrahydrobenzo[*b*]fluorene scaffold and pharmacophore is found. Interestingly, this unique scaffold is also characterized in lomaiviticin, suggesting a similarity between the reaction mechanisms for lomaiviticin and kinamycin assembly. Despite the numerous studies centered on their biosyntheses, key enzymes involved in the pathway of most angucycline members remain unknown. However, the recent sequencing of the kinamycin gene cluster from *Streptomyces murayamaensis* and *S. ambofaciens* and the lomaiviticin gene cluster from *Salinispora pacifica* has opened up the possibility of using comparative genomics as a powerful guidance tool by coupling bioinformatics with genome analysis. Using comparative genomic analysis, we identified three sets of homologous candidate enzymes for their ring-contraction reactions: AlpJ-AlpG, KinG-KinO2, and Lom28-Lom24. With further gene knock-out studies and *in vitro* assays, we

aim to characterize the novel post-polyketide synthetic tailoring reactions in kinamycin and lomaiviticin biosynthesis. Ultimately, these endeavors will build the foundations for the optimal generation of potent antitumor molecules and other angucycline analogs.

Electronic Effects in Anion Abstraction Catalysis

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As technology and medicine progress, access to complex organic molecules is increasingly important for developing new pharmaceutical agents, chemical probes, and innovative materials. The efficient and selective formation of carbon-carbon bonds is critical for building the diverse structures involved in these applications. In recent years, hydrogen bond-donor catalysis has emerged as a strategy for effecting C–C bond formation with high spatial selectivity (stereoselectivity). This method of catalysis imitates an active chemical structure found in nature, using electron-deficient hydrogen atoms to stabilize a build-up of negative charge during a reaction. A particularly interesting mode of reactivity involves the ionization of a neutral molecule to form a hydrogen-bonded anion and reactive cationic electrophile. Urea and thiourea motifs can catalyze this “anion abstraction” and control the stereoselectivity of nucleophilic addition to the resulting cation. While these catalysts can achieve high stereoselectivity, long reaction times and high catalyst loadings are often required to compensate for poor efficiency. Therefore, we sought to gain a better understanding of the system in order to improve catalyst efficiency. Ongoing work in the Jacobsen group has shown that for simple bisaryl ureas, the reaction rate of a model anion abstraction reaction correlates quantitatively with the electronic nature of the aryl substituents. The work described here outlines a systematic study of thiourea electronics. We observe that the activity of thiourea catalysts is complicated by the Lewis basicity of sulfur. Interactions between the thiourea sulfur and the reactive cation have a marked negative effect on reaction efficiency, suggesting that electron rich thioureas should be avoided in anion abstraction systems. This can inform future catalyst development and use.

Predicting Chemical Reactivity in the Molecular Generation Phase of the Harvard Clean Energy Project

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Renewable energy is gaining traction and popularity as the problem of sustainability looms large. Solar energy, in particular, continues to show promise in this area. But while organic photovoltaics (OPVs) promise more affordability, reliability, and durability over their more popular inorganic counterparts, they have yet to achieve the efficiency benchmarks of inorganic photovoltaics. With the hope of improving OPV efficiency to more competitive levels, the Harvard Clean Energy Project (the CEP) seeks novel organic compounds in high-throughput screening, utilizing IBM’s World Community Grid to efficiently distribute the computation time required to screen and rank new OPVs.

Our candidate molecules are built using a 26 fragment molecular library inspired by promising OPV candidates of past research. Currently, the sites on which reactions can take place are determined by an experimental chemist—but only for the initial 26 fragments. Therefore, subsequent combinatorial molecular generation can potentially explore parts of chemical space which are synthetically unavailable: clearly an undesirable result. We investigate and seek to improve the reliability of this approach for developing synthetically accessible libraries by investigating different predictive models for reactivity.

In order to provide a means to measure the ‘reactivity’ of different sites on the initial fragments, Reaxys— an online chemical database— was data mined for all reported molecules containing any of our fragments as a substructure. Following this, we calculated the probabilities of substitution given substitution of different heteroatoms at various locations around each fragment. We then sought to characterize each fragment with various descriptors. We will compare the predictions of these calculated properties with the data retrieved from Reaxys and the initial ‘guesses’ used in the generation phase of CEP. In so doing, we can note any discrepancies we find and then apply this new knowledge in the molecular generation phase of the CEP, thereby better ensuring that libraries generated with combinatorial methods contain molecules which are synthetically feasible.

Mononuclear complexes for redox flow batteries

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There is substantial need for enhanced energy storage in the form of more efficient battery cells. While the recent investment in renewable energy sources has greatly advanced energy harvest techniques, existing technology does not permit the storage of this energy, and energy that is not used upon generation is lost. A large-scale energy storage solution would aid in the delivery and distribution of electricity to match the irregular fluctuations in energy demand, and allow for the full utilization of energy harvesting technology. Redox flow batteries can be readily scaled by increasing the size of the electrolyte reservoir, making them ideal for large-scale energy storage. Current redox flow batteries employ molecules that undergo single electron transfer redox events. Engineering species that can undergo multiple redox chemistry at the anode and cathode could greatly enhance the energy density of the electrochemical cell. Current efforts are focused on exploring coordination complexes of first row transition metals that will serve as the catholyte and anolyte species. Voltammetric characterization of the compounds made has given promising results. Further optimization of these species will be based on rational design that considers the electronic structure of the ligands and transition metal core. After identifying molecules that possess the desired redox capabilities, assembling a working battery requires optimization of concentration, membrane, and solvent. While an optimal anolyte has yet to be discovered, demonstration of the feasibility of this concept is major advancement in this field and a step towards achieving renewable energy storage.

Fingerprinting Periodic Crystals for Machine Learning of Band Gaps

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Efficient and accurate crystal band gap calculations will enable high-throughput molecular screening for photovoltaics and other applications; however, traditional density functional calculations poorly calculate crystal band gaps. Machine learning methods have been useful for finding energetic properties of discrete molecules, but periodic crystals' theoretically infinite lengths make them difficult

to represent in machine-learnable fingerprints. We explore two fingerprinting methods as applied to learning the experimental band gaps of semiconductor crystals from density functional calculations of their crystal structures and band gaps. The Bravais-Coulomb representation extends the popular Coulomb matrix discrete-molecule representation to crystals by combining the Coulomb matrix of the Niggli-reduced crystal cell with the crystal's reduced lattice vectors. The partial radial distribution function (PRDF) representation considers the number of type B atoms at successive distance ranges from the average type A atom for all atom type pairings A and B; we compare the success of different atom type groupings, such as by periodic group number. We run both Gaussian process and neural network machine learning methods on these fingerprints and in the former case explore different distance metrics between fingerprint pairs. We aim to find a crystal fingerprint that enables accurate band gap predictions from density functional data and aids the search for novel photovoltaic materials.

Fluorine-18 Heterocycles

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Chemical compounds with the radioactive fluorine-18 label have important biological applications, such as positron emission tomography (PET) imaging, a powerful tool for various sorts of medical imaging. However, there is currently no general method to synthesize electron-rich fluorine-18 heterocycles such as furans, thiophenes, and pyrroles. Finding a method would greatly benefit science and medicine, because 20% of the world's commercial pharmaceuticals contain fluorine, and most of these pharmaceuticals are heterocycles. Finding a way to synthesize the fluorine-18 analog of these pharmaceuticals will enable us to biologically track the drug as it makes its way through the human body by medical imaging.

I am collaborating with a graduate student to develop a method to synthesize heterocycles fluorinated with fluorine-18 that is mediated by a new nickel complex. I synthesize many precursors, as well as the fluorine-19 analogs of our desired radioactive fluorinated heterocycles. Synthesis of the fluorine-19 analog is necessary to confirm the structure of the desired fluorine-18 heterocycles. These heterocycles are characterized by their retention time in chromatographic methods. To prove that a fluorine-18 compound has been synthesized, the fluorine-19 analog must show to have the same retention time as the fluorine 18 compound. Comparing the characteris-

tics of the fluorine-18 compounds against their fluorine-19 analogs is necessary because fluorine-18 compounds are often synthesized at the nanomole scale, which is not enough for extensive characterization that is usually necessary.

My next step for the project will further explore the reactivity of the same novel nickel complex used in the current fluorination reaction.

Synthesis and Characterization of Macroporous Cryogels for Delivering Cancer Immunotherapy Agents

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There is a high demand to cure cancer, and potential lies in the combination of materials science and immunology. Cancer immunotherapy techniques stimulate the immune system to attack cancer cells. Many previous attempts at bolus delivery of immunomodulatory agents have limited clinical efficacy due to their toxicity and easy clearance by the body. To circumvent these problems and moreover provide minimally invasive therapy, the Mooney lab has recently developed biocompatible, macroporous, syringe-and-needle injectable cryogel scaffolds that have the ability to slowly release immunomodulatory agents. Cryogels are made by covalently cross-linking methacrylated alginate polymer in water and then freezing it. The crystals formed by freezing the gels translate to a macroporous structure upon thawing, creating niches where host cells can gather. These cryogels have been shown to release most of the contained agents over a few days.

The current materials system, however, is not mechanically robust, so we have been developing gels reinforced with ionic crosslinking. By soaking these cryogels in CaCl₂, calcium cations bind to negatively charged parts of the alginate polymer and ionically crosslink. Upon injection, these bonds can break and then reform, dissipating energy that would otherwise break the covalent crosslinks while also facilitating gel shape reformation.

Currently, efforts are focused on further delaying the release kinetics of immunomodulatory agents from the cryogels. Cancer immunomodulatory agents include: a dendritic cell (a type of immune cell) recruitment factor, the cytokine called granulocyte-macrophage colony-stimulating factor (GM-CSF); a danger signal that stimulates dendritic cells, cytosine-guanosine oligonucleotide (CpG-ODN); and tumor lysate as an antigen source that the dendritic cells can relay to the immune system as harmful. Controlling the release of these agents by manipulat-

ing biomaterials will allow us to optimize activation of the immune system to fight cancer.

Prediction of the Development of Autism Spectrum Disorder using Integrated Learning and Reasoning

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Medical professionals will often wish to predict the development of a syndrome so that more focussed and effective treatment plans can be designed for their patients. Of particular interest is development of Autism, which is fraught with comorbidities and other complexities. This project aims to answer the following question: given the diseases an autistic child has, and background knowledge on the relationship between these diseases, how can a doctor predict the onset of epilepsy, psychiatric disorders and other pathological conditions during the patient's teenage years? The approach we use here is that of robust logics – a theory that combines logical reasoning and statistical learning in one coherent framework. In doing so, robust logics can combine the desirable, and otherwise mutually exclusive, characteristics of logical deduction and robustness to noise. At no point do we make an attempt to model the distribution of data, and our logical approach thus circumvents the large computational cost required with more explicit machine learning algorithms. We begin by supplying data of patients and their symptoms to our inferential system, along with a knowledge base that encodes the hierarchy of all diseases. The knowledge base allows us to reason the presence of more general types of diseases - information that is not present in the raw data. We combine these two sources using our robust logics approach, and our system outputs the best logical statements to predict for a particular target disease. These statements – essentially the "hidden" rules of autism for a given target disorder – are learnt empirically, and are guaranteed to be approximately correct. Further, these induced rules are powerful and noise-tolerant.

Effects of Matrix Mechanics on Constitutive Exocytosis

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Mesenchymal stem cells (MSCs) in bone marrow are

exposed to a variety of microenvironments with distinct mechanical properties ranging from soft, spongy marrow to stiff, compact bone. By adhering to and pulling on the extracellular matrix, MSCs can sense the stiffness of their microenvironment. As part of this ‘stiffness sensing’ process, the cells generate contractile forces that activate intracellular signaling pathways, leading to a range of biological responses in MSCs including differentiation and migration. In addition to interacting with the matrix by direct contact, MSCs also communicate with neighboring cells over short and long distances. To communicate, MSCs likely depend on protein release into the extracellular space, which is regulated by exocytosis. Interestingly, exocytosis also depends on the contractile forces within the cell. However, it remains unclear how these forces generated by cell-matrix interactions influence distant cell-cell communication.

This study tests the hypothesis that matrix stiffness impacts constitutive exocytosis of proteins from MSCs. Constitutively expressed proteins are continually translated, so their release is likely only affected by regulation of post-translational events like exocytosis. To study this, mouse MSCs are engineered to constitutively express Gaussia Luciferase (GLuc), a secreted form of luciferase (a bioluminescent enzyme). These cells are encapsulated in alginate hydrogels of varying stiffness to simulate distinct mechanical microenvironments. Then, the media surrounding each hydrogel is collected periodically over time to quantify the protein released from the encapsulated cells. Efforts thus far have focused on optimizing protein quantification with the GLuc assay and ensuring that the alginate cell encapsulation method produces consistent gel stiffness values while maintaining cell viability. Once general protein release of GLuc is understood, specific native proteins of interest will be quantified including those involved in regulating blood production. A deep understanding of matrix effects on release of these proteins could lead to improved outcomes for patients with hematopoietic disorders.

Creation of a multipurpose uniaxial driven carriage

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Micro-Electro-Mechanical Systems (MEMS) have numerous applications due to their size. The Harvard Biodesign Lab has worked on developing “pop-up” MEMS robots for medical purposes. Particularly, this group has focused on the attachment of these systems to surgical

tools for in vivo applications, especially for the exertion and measurement of forces within the patient. The current method for detecting such forces is through an external sensor, attached to a surgical tool but kept outside the body. This method is unreliable and generally inaccurate, as multiple external factors, such as the surgeon’s touch and even breath, can affect the reading of the tool. The proposed solution is to develop a new class of surgical end-effectors, with embedded sensors and actuators, that can be inserted into the body during surgery to perform surgical interventions. These devices must be shown to provide accurate feedback on forces and maintain rigid structure to avoid medical failure. To test these devices and characterize on-board sensors and actuators, this group has begun design of an evaluation and control system that can produce precise linear motion with closed-loop feedback of both displacement and force output. This will allow for very precise positioning and accurate measurement of force and linear motion. Comparing the force delivered to that measured by the MEMS robot will allow for the characterization of the accuracy of the sensor. Similarly, the use of a laser displacement sensor will allow for precise detection of deformation of the robot under various forces, as well as characterize the transfer function of on-board actuators. The proposed machine will have a customizable carriage such that sensors and tools can be interchanged such that the machine can be used in a large variety of applications. In addition to characterization, the system will have the infrastructure necessary to perform real-time position and force control tasks, thus becoming a platform to perform benchtop tests and experiments.

Innovative delivery methods of growth factors for therapeutic angiogenesis

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Ischemic diseases have been the world’s leading cause of death over the past decade. Many therapies to return perfusion to affected areas have been met with limited success, especially in the elderly. We hope to promote local tissue vascularization by developing a material that sequentially delivers vascular endothelial growth factor (VEGF) to stimulate the growth of blood vessels followed by insulin-like growth factor 1 (IGF-1) to stimulate immune cell mediated maturation of vessels. We hypothesize that IGF-1 can alter the polarization of macrophages to a phenotype that promotes their ability to remodel blood vessels. Bolus delivery of growth factors has minimal benefits due to their short half-life in vivo and the lack of

spatiotemporal control of these factors at the injury site. Alginate hydrogels have been shown to provide sustained release of VEGF, but they do not provide the necessary delayed, sequential release of IGF-1. This project will focus on methods of providing sequential, delayed release of IGF-1 from alginate hydrogels. One such method includes the encapsulation of IGF-1 in poly(lactic-co-glycolic acid) (PLGA) microspheres. Factors such as polymer composition and incorporation of carrier molecules are critical for achieving the desired release profile of IGF-1 from these microspheres. Another method that will be explored is the conjugation of IGF-1 to gold nanoparticles. The release of IGF-1 from nanoparticles is affected by chemical bonding mechanism and nanoparticle size. Successful creation of such materials will be one of the first steps towards targeting the nexus of angiogenesis, immunology, and aging.

Characterization of Biotin-Streptavidin Alginate Aggregation to Study Cell-Cell Communication in the Hematopoietic Stem Cell Niche

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Hematopoietic stem cells (HSCs) have the ability to generate various myeloid and lymphoid cells. Recently, there has been much interest to use HSCs to study blood-related diseases and increase blood availability. However, a clear understanding of the complex cell-cell interactions in the HSC niche must be obtained to promote HSC maintenance, renewal, and differentiation. In this project, I report a new method of studying mesenchymal stem cell-endothelial cell interaction using self-assembly of alginate, a favorable biomaterial, beads. Each cell is encapsulated in biotin or streptavidin alginate beads, which form aggregates through a strong biotin-streptavidin bond. We found the optimal aggregate formation condition to be a 6 to 1 ratio of biotin to streptavidin, and we needed HFE oil to facilitate aggregate formation. Characterizations of aggregates' sizes were determined in order to study the effect of ratio of each cell type, absolute number of cells in each aggregate, and distance between aggregates. Further, click chemistry using norbornene and tetrazine was used to enhance aggregation. Results were confirmed using a variety of alginates conjugated to different amounts of biotin and fluorophores. This project puts forward a novel method of studying cell-cell interaction using a non-invasive, self-assembly method.

Control System for a Soft, Wearable, Hip-actuating Exosuit

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The overarching goal of the project is to develop a soft, wearable robotic device to augment the user's physical capacity and help reduce overall metabolic effort by applying assistive forces. The exosuit itself assists hip extension by transmitting forces from a brushless DC motor attached to a backpack frame to the user's thigh via a soft brace. Heavy duty fishing lines are used to connect the motor and thigh brace. If the motor reels in the spectral line, it generates a pulling force which results in an assistive moment around the hip joint. Designing such a wearable robotic device involves implementing a control system which senses the user's intent and times the application of force to be in synchrony with the wearer.

The control system at hand divides this task between two modes: tracking and assisting. The system consists of a motor controller, current meter, position encoder, and load cells. In tracking mode, the control system uses motor torque/current feedback to exert a constant small force, monitored by the load cells, on the user's thigh. While this force is too small to be felt by the user, it allows the device to track the user's hip motion with minimal delay. When the user takes a large step, an indicator of the intent to walk, the device detects this condition by monitoring the motor encoder counts and enters assisting mode. In this mode, a predetermined torque profile is applied by the motor to the user's thigh in phase with the user's motion. The device then returns to tracking mode and the cycle repeats with each step. The motor controller serves as a microprocessor which controls the motor's response based on inputs from the current sensor, encoder, and load cells.

Online Spike Sorting in Large Data Sets

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Extracellular recordings from electrodes implanted in a subject's brain are often used to gather neurological data. Spike sorting is the problem of first detecting neural spikes in these recordings and then, since spikes from many different neurons are found in each recording, sorting the spikes by which neuron they came from. Spike sorting is an important problem in neuroscience with a long history, and many approaches exist that tackle this problem. In our

particular setup, we aim to use spike sorting on a continuous live data stream from arrays of four closely bunched electrodes in the brains of rats. These electrodes monitor neural activity as a rat learns a simple task, such as pulling a lever to get food. Two particular difficulties that come with this approach are that over our long observation period electrodes may shift, causing spike profiles from a given neuron to change over time, and that the sheer size of the data makes many existing approaches computationally intractable.

We aim to resolve both of these issues, and to develop a spike sorting algorithm based on a generative model that more completely uses information about spatial layout of the electrode array. This model can allow us to better understand how a spike's observed profile evolves as factors, such as distance to electrode and background noise level, change. We hope that incorporating this information will both improve the performance of the spike sorting algorithm and allow us to resolve interesting related questions such as whether a spike profile changing over time comes simply from the drift of an electrode or from a change in neuron physiology. Ultimately, we hope that our approach can allow us to learn about how neural structure changes as learning takes place.

Refillable Vascular Grafts

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Cardiovascular disease is the leading cause of death, both in America and worldwide. Vascular grafts have been a key player in helping combat this disease, but like any foreign body, they elicit an immune response leading to thrombosis, or blood clotting. One approach that has been taken to mitigate this risk is to coat the grafts with thrombomodulin (TM). TM is a vasculoprotective protein found on the surface of endothelial cells, which line blood vessels, and its purpose is to inhibit thrombosis. However, with current technologies, the initial TM degrades over time, only delaying thrombosis. This project develops a technique for reloading fresh TM onto the vascular grafts utilizing a process called DNA toehold exchange. This procedure involves using DNA in order to home in on the targeted region. To achieve this, identical strands of DNA are attached to the surface of the graft. The reloading agent, in this case TM, is then covalently linked to the complementary DNA strand. The modified TM can then be inserted into the blood stream intravenously, binding the complementary DNA strands and allowing the TM to be expressed only at the location of the graft, rather than

throughout the entire body. Because of the unique nature of the sequences, a newly introduced strand can displace a previously bound one, allowing for an indefinite replenishment of TM to the vascular graft. This method provides a theoretically infinite lifetime of preventing thrombosis of vascular grafts without the need for additional invasive surgeries. In the future, this technology could be further applied to any number of drug or protein-refilling systems.

Engineering Mesenchymal Stem Cells as Targeting Agents for Cancer Cell Therapeutics

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Metastatic prostate cancer has a 27.9% five-year survival rate, and is considered to be a fatal disease. Current standards of treatment for metastatic prostate cancer involve prostatectomy and chemotherapy. While improving outcomes, these treatments provide only short-term solutions to what is a complicated disease. They are palliative, and lack the ability to target sites of metastasis, which are usually found in the adrenal gland, bone, liver and lungs. We propose here an alternative targeting method. This is the use of mesenchymal stromal cells (MSCs). MSCs are promising targeting agents for prostate cancer therapeutics because they show preferential homing to sites of cancer, and can be administered allogeneically without significant side effects. Our group aims to encapsulate a prostate-specific drug in microparticles made from a poly(lactic-co-glycolic acid) polymer, and subsequently internalize these drug-microparticles into MSCs. We will then administer these drug-microparticle loaded MSCs to xenograft mouse models of metastatic prostate cancer to assess their engraftment and their ability to improve therapeutic outcomes. This delivery method attempts to address the issues related to non-targeted drug delivery in the treatment of metastatic prostate disease, and perhaps in the treatment of other diseases.

Soft Sensing Suit for Rehabilitation in Developmentally Delayed Infants

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Developmental disabilities result in impaired motor de-

velopment, poor balance and posture, abnormal movement patterns, and limited gait. The most common motor disability, cerebral palsy, affects 3 in 1000 children in the United States, only 50% of which are able to walk independently. While early intervention treatment during infancy is critical for rebuilding damaged neural networks and improving motor control and gait development, diagnosis is very difficult before the age of two. Furthermore, even for infants with known risks for this disorder such as perinatal brain injury and preterm birth, treatment is often inaccessible due to high costs and limited clinical resources. There are currently no active orthotic devices designed for infants so supplementing this limited clinical therapy with home-based treatment is virtually impossible. This project presents a soft, wearable home-based device that monitors infant leg cues, encourages increased independent motion, and actively assists kicking. An external stimulus in the form of a mobile acts as a reward to encourage spontaneous infant kicking, an important stage of motor development that helps rebuild damaged neural connections, and teach reciprocal movement and motor planning - critical skills for later gait development. By pairing this sensing system with a previously designed pneumatic actuator suit, variable levels of physical assistance can be provided during kicking if the infant is unable to perform the movement independently. This project presents the first active assistive orthotic device designed specifically for infants. Using wearable soft robotic technology to make early intervention treatment more accessible for infants with developmental delays will decrease the need for costly treatments and surgeries in the future, and increase physical ability and quality of life.

Development of Automated Sizing System to Optimize Patient Accessibility to Assistive Soft Pneumatic Glove

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Patient survivors of strokes, cerebral palsy, and spinal cord injuries often face weakness or paralysis on one side of the body, creating a high unmet demand for physical therapists to assist in repetitive task practice (RTP) rehabilitation. A soft robotic glove uses water pressure to displace finger-shaped actuators, or motors, and the design allows for a flexible, safe, and portable alternative to lengthy and expensive clinical rehab, providing patients with an at-home system to assist in activities of daily living (ADL) such as grasping and pinching. The fiber-reinforced actuators of the glove contain segments that either bend or

extend; the product is custom-designed to contour to joint positions and muscle lengthening in each finger. We are re-evaluating the working formulas used to size actuators to create a sleeker design and a shorter fabrication process. By developing a computerized sizing system, we can rapidly determine either a custom size for actuators or a variable (small-medium-large) size, and statistical analysis of a hand study determined the necessary ranges in a variable sizing system. Taking into account factors such as ease of fabrication, market incentives that increase the likelihood that patients will pay for custom designs, and optimization of a glove size that performs successfully without causing pressure points or undue discomfort, we hope to translate our custom sizing and glove technology into the lives of patients for whom it would benefit.

Precise Human Genome “Surgery”: CRISPR-on-a-Chip as a Universal Platform to engineer cures for genetic diseases

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Though the understanding of our human genome and the genetic basis of devastating diseases has greatly increased over the past decade due to the bloom in DNA sequencing technologies, our ability to directly modify genes is severely limited. Current gene editing technologies leave scientists helpless to correct even well-characterized genetic diseases—as current gene therapies crudely insert genetic material at random locations. Recent advancements in genetic engineering’s CRISPR (clustered regularly interspaced short palindromic repeats) system, however, with an RNA programmable DNA nuclease called Cas9, allow us to flexibly engineer guide RNA sequence to program the nuclease to excise or replace genes in exact locations, down to base-pair level precision.

As therapeutic development from this technology is still hampered by slow drug screening systems and poor clinical models, we developed a microchip platform that streamlines engineering and testing of clinically translatable cures.

To test our system’s efficacy, CRISPR-on-a-Chip was applied to correcting the cystic fibrosis (CF) mutation, since it is distinctly caused by an F508 deletion mutation, and a successful correction will reverse the pathophysiology of CF. Combining patient-derived CF cells and tissue engineered microfluidic chips with a three-dimensional airway architecture, a CF diseased human lung with pulmonary physiology (“lung-on-a-chip”) can be recapitulated.

A CRISPR/CFTR construct that specifically delivers and inserts, through homologous recombination, the corrected F508 amino acid sequence was designed. Then, after assaying a variety of transfection methods, our optimal delivery system was able to correct more than 25% of the F508 mutations (a clinically significant efficiency that reverts Cl-/Na+ immobility in the respiratory epithelium, thick mucus accumulation and clogged mucociliary clearance). This result demonstrates great promise for not only for CF therapy, but also more importantly the ability of CRISPR-on-a-chip as an extremely versatile system to develop cures for distinctly genetic cardiovascular and neurological diseases, cancers or even orphan diseases.

Characterization and Optimization of Segmented Bead Catheter of Variable Stiffness for Cardiac Surgery

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Physicians use catheters for various cardiovascular diagnostic and therapeutic procedures that frequently utilize the tip of the catheter to apply forces to tissue. However, the fixed flexibility of current catheters limits their full potential use in minimally invasive surgical procedures that are performed through tiny incisions rather than a large opening. Moreover, for a cardiac procedure that requires both large and small forces, switching between multiple catheters of varying stiffness levels becomes time consuming and highly inefficient. Thus, a catheter with the ability to switch from a flexible mode for vascular navigation and stiff mode for force application could be useful for both new and existing cardiac catheter procedures.

A segmented bead design capable of changing stiffness was chosen as a potential catheter design. When the wires connecting the string of beads are tensioned, the frictional force between adjacent beads increases, causing the catheter to stiffen. Conversely, relaxing the wires increases the catheter's flexibility. This project focuses on determining an optimal bead design for the variable stiffness catheter by developing an analytical model to optimize the friction between the beads. The model is developed based on empirical data obtained from iterative bead designs. An experimental fixture was developed that utilized a force sensor to determine the applied force on the catheter tip and an optical tracker to record catheter tip displacement to compare the spring/stiffness constants of different bead designs. From the data collected, an analytical model of the forces between two conjoining beads was proposed to explain the differences.

Primes of the form $x^2 + ny^2$

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Algebraic number theory concerns itself with the generalization of familiar concepts (e.g. prime factorization) of the integers \mathbb{Z} to any given ring of algebraic integers O_K of an algebraic number field K , leading to beautiful results ranging from the finiteness of the class group to Dirichlet's unit theorem. The study is believed to have been largely influenced by the theory of binary quadratic forms, a specific case of the more general number field.

First thoroughly discussed in Gauss' *Disquisitiones Arithmeticae*, binary quadratic forms are motivated by Fermat's classic result in 1640 that an odd prime p can be expressed in the form $x^2 + y^2$ for x, y positive integers if and only if $p \equiv 1 \pmod{4}$. This project seeks to solve the representation problem of finding the primes representable by any arbitrary quadratic form of the form $x^2 + ny^2$ for positive integer n . The approach first used utilizes the theory of forms, followed by an alternate approach implementing Minkowski's geometry of numbers (1910). The study furthers itself by exploring Gauss' natural composition law on the set of classes of binary quadratic forms of any given discriminant D and finding methods to explicitly compute the class groups of quadratic fields this composition law induces.

Reverse Mathematics

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Mathematical logic is the study of formal systems, which formalize mathematical reasoning. The proofs of ordinary mathematics are formalized as derivations in formal systems proceeding from fundamental assumptions (axioms) and the allowed rules of inference. Mathematical logic makes it possible to articulate and interrogate those fundamental assumptions. Which axioms are the "right" foundation for mathematics?

Zermelo-Fraenkel set theory with Choice (ZFC) is sufficiently strong to prove all the theorems of everyday mathematics. But ZFC is logical overkill. Very rarely does one use the full strength of the system. Most theorems of number theory, analysis, and algebra use only a subsystem of ZFC, called second-order arithmetic, Z_2 . Even Z_2 is overkill, though: still weaker subsystems of Z_2 suffice to prove very many theorems.

What's the "best possible" result, i.e., the weakest axiom system sufficient to prove a given theorem? (For instance, does a given theorem require the real numbers, or is it "elementary"?) This is the central question of reverse mathematics. The surprising method of reverse mathematics is to start with your theorem of interest and to "reverse" it, proving the axioms from the theorem, thus determining the theorem's precise logical strength in one deft maneuver.

By reverse mathematics, most theorems have been shown to be logically equivalent to one of five major subsystems of second-order arithmetic.

The goal of my project is to become acquainted with the techniques of reverse mathematics with a view to understanding better the logical strength of certain theorems of complex analysis (provisionally, the Riemann mapping theorem).

Local Fields: Topological Methods in Algebraic Number Theory

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A lemma of C. F. Gauss shows any rational solution to a monic integral polynomial must be integral. This generalizes integers \mathbb{Z} for number fields K via the ring of integers $\mathcal{O}_K \subset K$, i.e. those $\alpha \in K$ satisfying a monic integral polynomial.

Unlike \mathbb{Z} , \mathcal{O}_K does not necessarily respect unique prime factorization of elements, a phenomenon responsible for a possible mistake in Fermat's "proof" of his last theorem (though a mistake worthy of a first-rate mathematician at the time!). As R. Dedekind discovered in the 19th century, \mathcal{O}_K yields unique factorization of fractional ideals $I = \prod_{\mathfrak{p} \in \text{Spec}(\mathcal{O}_K)} \mathfrak{p}^{v_{\mathfrak{p}}(I)}$, motivating an algebraic theory as in P. Samuel's text. We study the data of prime ideals via the embedding $\mathbb{Z} \hookrightarrow \mathcal{O}_K$ in their prime decompositions in \mathcal{O}_K . For unramified primes, there exists a well-defined (up to Galois conjugation) Artin map via the canonical Frobenius automorphism.

For ramified primes, however, a nontrivial inertia group disrupts constructing a canonical Artin map. To remedy this, we appeal to local fields – locally compact topological fields with respect to a (not necessarily Archimedean) valuation. For instance, in the case of non-Archimedean valuations on \mathbb{Q} , Ostrowski's theorem allows focusing on exactly the completions via p -adic valuations, $v_p : \mathbb{Q} \rightarrow \mathbb{Z}$, denoted \mathbb{Q}_p , called the p -adic numbers. The locally compact topology via similar valuations reconciles our algebraic and topological theories, allowing us to interpret the

valuation ring \mathcal{O} of a local field as the closed, compact unit ball, and the group of multiplicatively invertible elements, \mathcal{O}^* , as the unit sphere. Via topological notions and developing algebraic gadgets (e.g. DVRs), local fields contribute a substantial theory to studying ill-behaved primes individually, while providing context for class field theory and the theory of elliptic curves.

HIV-1 Subtype C Genotyping in Treatment-as-Prevention Studies

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Effective HIV prevention interventions that inhibit HIV-1 transmissions are essential to controlling the HIV/AIDS epidemic. HIV testing is a critical part of Treatment as Prevention (TasP), a strategy that aims to initiate antiretroviral therapy (ARV) in HIV-infected individuals. The current TasP in Botswana is focusing on individuals with a high viral RNA load, as they could pose the greatest risk of spreading new infections. Phylogenetic mapping of viral lineages circulating in communities is important for understanding the structure and dynamics of HIV transmission networks, and monitoring prevention interventions. This approach helps to distinguish HIV transmissions within the community from transmissions from outside sources. Such an analysis is crucial for understanding whether interventions such as TasP aimed at HIV-positive community members are sufficient for controlling HIV spread in the community, or if alternative methods, such as Pre-Exposure Prophylaxis, might also be appropriate in this community.

The Essex lab employed routine population-based sequencing of the HIV-1C env gp120 V1C5 region from samples collected across communities within Botswana. Since the V1C5 region evolves rapidly and is highly variable, it presents challenges for phylogenetic cluster analysis of chronic HIV infections. To improve resolution of HIV cluster analysis, the current efforts of the lab are focused on also sequencing the more conserved pol gene encoding viral reverse transcriptase, protease and integrase. The combination of viral sequences spanning these two HIV-1C regions coupled with high-density sampling increases the number of informative sites, and results in more meaningful and informative phylogenetic cluster analysis. After optimizing HIV genotyping in a single-community model, it can be applied to a large-scale TasP trial to map transmission networks around Botswana and inform HIV prevention interventions.

Co-expression of transcription factors **Foxp2** and **Satb1** defines a putative retinal ganglion cell type

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The mammalian retina contains approximately 30 subtypes of retinal ganglion cells (RGCs) that detect discrete visual features, including color, contrast, or motion in a single direction. Each RGC subtype can be anatomically identified in two ways: first, their soma form a lattice-like array across the retina (termed a mosaic) required to monitor the entire visual field; second, their dendrites take on specific shapes which influence their mode of visual processing. Many RGC subtypes have been characterized morphologically and functionally using genetic approaches in adults, however, the majority of RGC subtypes still lack precise molecular definitions, and little is known about the formation of RGC mosaics during development. Recently, our lab has used intersectional immunolabeling to identify RGCs. This has identified expression of the transcription factor *Foxp2* in a small population of RGCs. Within the *Foxp2*-positive population, I have determined that coexpression of *Foxp2* and a second transcription factor, *Satb1*, marks a putative RGC subtype with mosaic organization. The *Foxp2*+/*Satb1*+ (F2S1) RGCs comprise 12.4% of the *Foxp2* population, and 2.2% of total RGCs, making them a relatively sparse subtype. Moreover, F2S1 cells are negative for markers of previously characterized RGCs, suggesting they may comprise a novel subtype. Here I characterize the dendritic morphology of F2S1 cells and analyze their mosaic development across multiple pre- and post-natal time points. Taken together, these studies will establish molecular definitions for a potentially new RGC subtype, and provide some of the first insights into the development of a single RGC mosaic.

Design and synthesis of a robust information encoding system in *Escherichia coli* biofilms

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Natural cellular mechanisms are often co-opted by synthetic biologists for use in biological sensors. However, typical sensory outputs, such as colored or fluorescent proteins, are only detectable while cells are still alive. For sensing applications outside the lab environment, cells may die before their signal is recorded. In order to cir-

cumvent this problem, we propose a method to encode information that survives cell death.

E. coli, along with many other gram-negative bacteria, produce beta-amyloid proteins called curli which form the basis of their biofilms. These amyloid structures are highly resistant to degradation and can survive extreme pH and temperature changes. Such robust features of curli proteins make them a great medium for the stable encoding of information. Additionally, curli fibers are assembled extracellularly throughout the lifetime of the cells, so information stored in curli can be read even after cells have died.

We designed a sensing system in *E. coli* to store information about the cells' environment by linking curli proteins to half of a strong affinity tag pairing. The two peptides that compose an affinity tag pair bind only to each other, allowing information to be stored until both peptides are present. Using a variety of affinity tags, we placed each one under the control of a different inducible promoter. The ratio of different affinity-tagged curli produced by the cells is determined by the relative concentrations of the inducers present in the environment. Next, we created fusion chromoproteins with the orthogonal affinity tags. By applying a standard mixture of affinity-tagged chromoproteins, we identify the ratio of bound chromoproteins via an RYB color system. This ratio corresponds to the information encoded by the *E. coli*. This work has potential applications in the fields of cryptography, information storage, as well as the formation of a new reporting toolbox for synthetic biology.

A Vaccine Strategy Permitting B Cells to Drive a CD8 T Cell Response

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Ulrich von Andrian
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One of the primary functions of the adaptive immune system is to generate specific host organism responses to foreign antigens. The type of immune response is determined by a particular host antigen presentation pathway, leading to production of neutralizing antibodies or activation of cytotoxic T lymphocytes (CTLs) that induce apoptosis of infected cells. While most vaccines drive antibodies and provide long-term protection against infection, a CTL-activating vaccine may provide some early protection against intracellular pathogens such as HIV that modify their own surface proteins and evade host microbicidal mechanisms. However, it has been difficult to create these vaccines because: 1) the antigen must be localized in the cytoplasm of the antigen presenting cell (APC) and 2) the APC must be able to co-localize with CD8+ T cells in pe-

ripheral lymphoid organs. We are piloting an approach using a microfluidics cell squeeze device (SQZ) that allows cytoplasmic delivery of macromolecules into naïve B cells to induce antigen presentation to CD8+ T cells on major histocompatibility complex class I (MHCI) molecule. Preliminary cell cultures with lipopolysaccharide (LPS) suggested significant upregulation of costimulatory markers on B cells. We also demonstrated that OVA delivered to B cells using SQZ could be presented on MHCI. In vivo, naïve B cells express CXCR5, a chemokine receptor necessary for B cell homing to follicles in the periphery of the spleen and lymph nodes where they are excluded from interactions with T cells. We plan to use SQZ to administer siRNA knockdown of CXCR5 *in vitro*, which we will verify functionally using chemotaxis assays. Due to the crucial role of CXCR5 in homing, we expect adoptively transferred, OVA-loaded CXCR5 knockdown B cells to become temporarily arrested in the T cell zone, where they can activate naïve CD8+ T cells following entry from high endothelial venules (HEVs). We will check for CD8+ T cell activation and clonal expansion in vivo using intracellular cytokine staining and fluorescence activated cell sorting (FACS). Finally, we hope to visualize the localization of immunological synapses between T cell receptors (TCRs) on CD8+ T cells and peptide-loaded MHCI on B cells using confocal microscopy and 2-photon intravital microscopy (2P-IVM).

Design and synthesis of a robust information encoding system in *Escherichia coli* biofilms

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Natural cellular mechanisms are often co-opted by synthetic biologists for use in biological sensors. However, typical sensory outputs, such as colored or fluorescent proteins, are only detectable while cells are still alive. For sensing applications outside the lab environment, cells may die before their signal is recorded. In order to circumvent this problem, we propose a method to encode information that survives cell death.

E. coli, along with many other gram-negative bacteria, produce beta-amyloid proteins called curli which form the basis of their biofilms. These amyloid structures are highly resistant to degradation and can survive extreme pH and temperature changes. Such robust features of curli proteins make them a great medium for the stable encoding of information. Additionally, curli fibers are assembled extracellularly throughout the lifetime of the cells, so information stored in curli can be read even after cells have

died.

We designed a sensing system in *E. coli* to store information about the cells' environment by linking curli proteins to half of a strong affinity tag pairing. The two peptides that compose an affinity tag pair bind only to each other, allowing information to be stored until both peptides are present. Using a variety of affinity tags, we placed each one under the control of a different inducible promoter. The ratio of different affinity-tagged curli produced by the cells is determined by the relative concentrations of the inducers present in the environment. Next, we created fusion chromoproteins with the orthogonal affinity tags. By applying a standard mixture of affinity-tagged chromoproteins, we identify the ratio of bound chromoproteins via an RYB color system. This ratio corresponds to the information encoded by the *E. coli*. This work has potential applications in the fields of cryptography, information storage, as well as the formation of a new reporting toolbox for synthetic biology.

Modulating Behavior through Engineered Gut Microbes

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We are only just beginning to understand the complex roles the microbiome plays in relation to human health and disease. In this project, we seek to answer a simple question: can this relationship be harnessed for good?

In 2011, Professors Sonnenberg at Stanford and Fischbach at UCSF suggested that endowing the microbiota with new functionalities via genetic engineering could be a powerful way to treat various diseases. In particular, they suggest: "It may even be possible to engineer our microbiota to produce diffusible small molecules that enter our bloodstream, cross the blood-brain barrier, and exert neurological activities. One day, our microbiota may be engineered to produce stimulants, antidepressants, and satiety-inducing drugs, and if designed thoughtfully, microbial production could be modulated by dietary inputs dictated by the host or by microbial sensing of host biochemistry."

We seek to make this idea a reality via the tools of the emerging field of synthetic biology. The objective of this project is to engineer an intestinal microbe to stably associate in the small intestine and inducibly secrete caffeine, a central nervous system stimulant. This proof-of-concept project will demonstrate the practical value of an engineered brain-gut-microbe communication route and will also lay the foundation for future studies integrating syn-

thetic circuits into intestinal microbiota. As of July 2014, we report the successful cloning of an inducible caffeine biosynthetic operon in *E. coli* and the detection of caffeine production via HPLC. Our next steps will include flux balance analysis to increase yield and mice experiments for in vivo testing. We hope that this project will provide inspiration for microbial-based, long-lasting therapeutics for various neurological and intestinal disorders.

Engineering a Model Vesicle that Allows For Non-Enzymatic Primer Extension without Dilution Impairment

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As an essential feature of life, the cell membrane provides a simple boundary that allows for self-replication of molecules that confer a selective advantage without dilution impairment. Many studies focus on the evolution of these prebiotic antecedents of modern cells into the complex and autonomous units ubiquitous today. Given the framework of Darwinian evolution, these structures must have allowed for the emergence of molecular mechanisms that conveyed a heritable selective advantage. Yet, current protocell models that utilize chemical, nonenzymatic template-directed synthesis of RNA experience low reaction rates and are highly error prone, making repeated cycles of replication nearly impossible.

Model protocells most frequently utilize short chains of RNA and DNA as templates upon which single RNA or DNA nucleotides oligomerize. Prebiotic nucleotide replication parallels that of modern DNA replication, save the role of catalytic enzymes. As such, our methods must substantially increase effective concentration by sequestering reactants in order to ensure potential for replication. The earliest cells may have consisted of a self-replicating genetic polymer encapsulated by a self-replicating membrane vesicle. Composed of single-chain amphiphiles such as fatty acids, fatty alcohols, and fatty-acid glycerol esters, these vesicles demonstrate thermostability and permeability necessary for both template-copying chemistry and nucleotide uptake. Typical procedures in the field utilize oleic acid to form unilamellar vesicles that, primarily due to hydrogen bonding, limit diffusion across the membrane.

Recent studies indicate that vesicles composed of myristoleic acid and glycerol 1-monomyristoleate (i.e. the glycerol ester of myristoleic acid) demonstrate increased permeability while maintaining membrane integrity. Here, I engineer a model vesicle using these lipids

to optimize its permeability, increasing the effective concentration of monomers, trimmers, and oligonucleotides in order to promote replication and primer extension.

Dynamics of Herpes Simplex Virus protein US11 in Glioblastoma Stem Cells

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Oncolytic herpes simplex viruses (oHSVs) are genetically engineered viruses that selectively target cancer cells and are currently involved in several clinical trials to treat melanoma and glioblastoma. Glioblastoma (GBM) is an aggressive primary brain tumor that is resistant to conventional surgery, temozolomide (chemotherapeutic) and radiation treatment. To limit harmful effects, oHSV vectors have deletions and mutations to mitigate the pathogenicity of HSV in humans. These mutations bestow safety to the vector at the cost of reducing viral replication and spread. In particular, deletion of the γ 34.5 gene prevents HSV-caused encephalitis while also targeting HSV to replicating GBM tumor cells. However, a subset of GBM tumors is made up of glioblastoma stem cells (GSCs), which are resistant to γ 34.5-deleted HSV. GSCs are thought to be responsible for treatment failure and driving tumor invasion of distant brain tissue. Our lab demonstrated γ 34.5-deficient HSV replication is rescued in GSCs when the HSV protein US11 is expressed in the immediate-early stage of HSV protein translation. My project focuses on determining which domains of the US11 protein are responsible for rescuing γ 34.5-deficient HSV replication in GSCs. To achieve this goal, I constructed lentiviral vectors expressing different domains of US11 (along with the full-length protein), transfected GSCs with these vectors, and infected these cells with a γ 34.5-deficient oHSV (G207) to see whether US11 expression rescues viral replication and to determine which domain of US11 is sufficient for replication. This research provides deeper insight into the molecular interactions between HSV and GSCs, specifically the mechanism by which GSCs block viral replication. This project will inform the work of researchers as they attempt to study more effective forms of oncolytic viruses for glioblastoma treatment and has implications for developing therapies to target unique cell types within the same tumor.

Characterising the chemotherapeutic sensitivity of NOTCH1-mutant versus NOTCH1-wild type T-cell acute lymphoblastic leukaemia cell lines'

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T-cell acute lymphoblastic leukaemia (T-ALL) is a cancer of undifferentiated T-cell precursors (lymphoblasts), with a prevalence of around 6,000 annual cases in the US. Most current treatment regimens involve a complex battery of chemotherapeutic agents, as surgery and radiotherapy have limited efficacy against such disseminated malignancies. However, the choice, and indeed efficacy of chemotherapeutic combination therapies varies according to the age of the patient, and the genotype of the malignancy. The Benes lab. screens different T-ALL cell lines, with different mutation profiles, for sensitivity to both novel drugs in pre-clinical trials, and to combination therapies involving both established and pre-clinical drugs. If combination therapies can be identified, which potentiate the sum of the efficacies of their constituent drugs taken in isolation, this allows lower doses of each drug to be used, reducing noxious side effects. Over 60% of T-ALL cell lines have mutations in the NOTCH signalling pathway - a signalling cascade essential to normal T-cell differentiation. Using Flow Cytometry to assay Annexin V, a recognized biomarker for apoptosis, we measured the amount of apoptotic cell death in both NOTCH1-wild type, then NOTCH1-mutant cell lines, in response to a given therapy. We then used Western blotting to identify the levels of protein biomarkers in each cell line, after 24 hours of incubation with the drugs. By examining the expression levels of both cell cycle proteins such as aurora kinases A and B, and biomarkers for cellular stress, such as cleaved caspase 3, we have elucidated the molecular basis of various chemotherapeutic sensitivities, by determining which essential cellular processes are being disrupted. This knowledge will facilitate the development of further, more effective combination therapies, which could be personalised to the genotype of a patient's cancer.

The relationship between desiccation resistance and oxidation in bdelloid rotifers

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Bdelloid rotifers are microscopic aquatic invertebrates that exhibit many characteristics uncommon among animal species. They reproduce exclusively through parthenogenesis, and they have unusually high resistance against desiccation and ionizing radiation. Both desiccation and ionizing radiation generate an excess of reactive oxidant species (ROS) inside the cell; ROSs can damage proteins and DNA, impairing normal cell function. One of the principal ways in which ROSs act is by oxidizing cellular proteins. Bdelloids' resistance against desiccation and IR should be reflected in lower levels of protein and DNA damage, which can come from either repair or prevention of damage. This project measures protein carbonylation as a proxy for protein damage. By measuring the carbonylation levels in rotifers in different stages of the desiccation process, subject to different times of desiccation, and of different ages, it seeks to assess whether there exists a relationship between ability to recover from desiccation and carbonylation levels. The relationship between age and resistance to desiccation is of special interest. One of the most popular theories of aging posits that aging, defined as an increase in mortality rates with age, is a reflection of the accumulation of cellular damage caused by ROSs. Studying bdelloids' resistance to oxidation, and specifically, determining whether or not this resistance is age-dependent or not, may help in understanding whether ROSs are involved in the aging process.

The Role of Cell Compaction in Tumor Angiogenesis and Breast Cancer Progression

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Recently, it has been shown that physical compaction and accompanied collagen remodeling induce brain tumor angiogenesis and progression by changing the expression of a major angiogenic factor, Vascular Endothelial Growth Factor (VEGF) (Mammoto et al 2013). It is known that tumor cell compaction is involved in the resistance to chemotherapy in ovarian and breast cancer, and to radiotherapy in colon cancer. Thus, in this project, we hypothesize that modification of physical cell compaction, which

causes a change in the tumor microenvironment, may be able to improve the response and prevent resistance to radiotherapy in breast cancer. This summer, we have investigated whether mechanical compression of breast cancer cells alters their response to irradiation. First, we examined the effects of irradiation on 4T1 breast cancer cells in-vitro. Irradiation of 4T1 cells causes DNA fragmentation detected by p53BP1 staining 4 hours post-irradiation, while it is partially recovered 24 hours later. It was shown that expression of the angiogenic factor, Platelet Derived Growth Factor-b (PDGF-b), increases in the breast cancer cells 24 hours after irradiation, suggesting that PDGF-b may mediate recovery from radiation-induced DNA damage. We are currently exploring whether mechanical compression and subsequent changes in ECM structure will contribute to these effects by plating breast cancer cells at different densities and by compressing tumor tissues. We are planning to use a mouse breast cancer model to analyze whether mechanical force alters the effects of irradiation on tumor angiogenesis and breast cancer progression in-vivo. These approaches, which focus on chemical signaling and mechanical forces, are expected to normalize the breast cancer cells and improve the response of these cells to radiotherapy.

Reconstitution of HIV-1 Envelope Glycoprotein into Nanodiscs

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Recent efforts to develop an HIV-1 vaccine have focused on novel immunogens that present to the immune system various components of the virus in different backgrounds. In particular, immunogen development has centered around the HIV-1 envelope glycoprotein (Env), a trimeric transmembrane glycoprotein in the membrane of HIV-1 that allows the virus to identify and fuse with its target T-cells. Env is essential for HIV-1 infectivity, and is the only target HIV-1 presents to the immune system; however, vaccine candidates attempting to elicit broadly neutralizing antibodies (bNAbs) that bind Env epitopes and moderate viral infectivity have failed. Here, we attempt to reconstitute Env into nanodiscs—lipid bilayer discs enclosed by apolipoprotein A domains (MSPs)— as a novel immunogen that will stabilize the trimer in a near-native membrane environment, and present epitopes in a context that could improve the stimulation of bNAbs. We first purified Env from CHO cells under several detergent conditions to optimize purification of antigenically native and trimeric Env. After identifying several detergent conditions through size-exclusion chromatography (SEC) and

co-immunoprecipitation assays against several bNAbs, we screened lipid extracts similar in lipid composition to the HIV lipidome to determine which detergent and lipid condition allowed liposome formation, a step in nanodisc assembly, upon detergent removal via SEC and Biobeads (hydrophobic chromatography). We then attempted to reconstitute Env into liposomes, and screened various MSPs under the best proteoliposome condition to attempt Env reconstitution into the nanodisc construct. Biophysical characterization of the Env proteoliposomes and nanodiscs via chromatography, co-IPs, mass spectrometry, multi-angle light scattering, and cryo-electron microscopy are currently ongoing.

Characterizing immune deficiency in *prkdc* mutant zebrafish

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Prkdc is a protein kinase implicated in nonhomologous end joining, a pathway of DNA repair which is necessary for variable, diverse, and joining [V(D)J] segment recombination during immune system development. Specifically, V(D)J recombination is essential for T and B cell differentiation. Prkdc knockout mice are immune deficient and are capable of accepting xenogeneic and allogeneic cellular transplants. These immune deficient mouse strains have proven to be powerful tools for the study of cancer, stem cell, and regenerative biology, as they do not reject foreign tissue.

Using genome engineering technology, the Langenau Lab has created a zebrafish line harboring an 8-nucleotide deletion at the *prkdc* locus, causing a frame-shift-stop mutation prior to the catalytic domain of the kinase. This mutation renders the protein functionally null. Our group has determined that this zebrafish line is immune deficient by using an array of genetic, cellular, and functional assays. Quantification of Hematoxylin and Eosin staining of histological sections reveals thymic involution and a significant reduction in thymic size. T and B cell receptor rearrangement analysis suggests that V(D)J recombination is inhibited in *prkdc* mutant fish, providing evidence of a functional knockout. Additionally, transplantation assays show robust tumor engraftment in mutant fish but not in heterozygotes or wildtype fish. Fecundity and overall health are currently being assessed.

We expect later assays to reveal a reduction or absence of T and B cell markers along with a concomitant loss of differentiated lymphocytes. Our group believes that this line, along with various other genetic models we are char-

acterizing, will be useful additions to the array of model organisms currently used in the field.

Investigation of the role of AQP4 Autoantibodies in Neuromyelitis Optica

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Neuromyelitis optica (NMO) is an inflammatory autoimmune disease of the central nervous system characterized by lesions in the optic nerves and spinal cord. Autoantibodies (molecules targeting one or more of the body's own proteins) against the water channel protein aquaporin-4 (AQP4) are used as a diagnostic marker for the disease, but it remains unclear whether these autoantibodies contribute to disease development. Thus, the establishment of an animal model to study the development of NMO is important. To this end, my work this summer focuses on helping establish such an animal model by generating a genetically engineered mouse that expresses an NMO patient derived antibody from the endogenous heavy chain locus. Prior work in the lab generated the genetically engineered mouse embryonic stem cells (ES cells), and through PCR, sequencing, and Southern blot analysis, we confirmed that the ES cells contained the correct AQP4 coding region.

We next sought to establish a diagnostic test to measure the presence of AQP4 autoantibody in the transgenic mice before and after immunization with AQP4 protein. Hospitals have used the binding between AQP4 autoantibody and AQP4 protein expressed on the surface of transfectant cells to determine the presence of the antibody in patients' blood. Using a similar method, we can measure the presence of antibody in the serum from transgenic mice.

Finally, we want to determine the B cell populations that exist in normal wild type mice in order to compare them to that of transgenic mice immunized with the AQP4 protein. Using flow cytometry, we sorted cells isolated from the spleen and lymph nodes of wild type mice and looked for the percentages of B-1a, B-1b, B2 cells and regulatory B cells that exist under "normal" conditions. In this way, we hope to elucidate how the B cell population changes in response to the presence of AQP4 antibody and shed more light upon the induction of this debilitating disease.

Neural Correlates of Imitation in Children with Autism and Their Unaffected Siblings

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Autism spectrum disorder (ASD) is characterized by deficits in one's ability to socially interact with others and communicate. Though most research on ASD has focused on children directly affected by autism, the unaffected siblings (UnS) of those with ASD have received less attention. By learning more about this population, we can potentially advance our understanding and eventual treatment of ASD.

A 2010 fMRI study by Kaiser et al. revealed that when UnS viewed point-light animations of biological motion, they had regions of shared dysfunction with ASD children, in addition to regions of unique activity. Using these findings, this project aims to further analyze brain activation in ASD and UnS groups in the context of imitation, a behavior important for social learning and understanding.

In our experiment, typically developing (TD), ASD, and UnS children (ages 3.5 - 6) engage in an imitation task where they first observe a video demonstration of an actress activating a toy's outcome, and then play with the toy themselves. For this task, the children are fitted with an fNIRS cap, which measures changes in oxy- and deoxyhemoglobin in the bilateral frontal and temporal cortical regions. Their eyetracking patterns are simultaneously recorded/analyzed as percentage fixations to the face/body/object during video observation, and their behaviors during free play are manually coded to determine how closely they imitate the demonstration. The data streams from ASD, UnS, and TD children are compared to determine differences in behavior, attention, and neural processing. We hope to use this data to explain discrepancies in imitation between the groups.

By analyzing the brain activity unique to UnS, we may better understand the mechanisms that allow UnS to compensate for ASD risk and avoid fully manifesting the signs of ASD. These mechanisms may provide useful targets for ASD interventions which capitalize upon the unique ways that those at risk for ASD learn.

Investigating Dopaminergic Neural Circuits in the Olfactory Bulb

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The mammalian olfactory bulb not only has crucial functions for identification and processing in the sense of smell, but also is one of two regions of the brain that undergoes adult neurogenesis. A subset of the neurons in the olfactory bulb are neurons whose primary neurotransmitter is dopamine. These dopaminergic neurons are believed to be involved in processing between different odor channels due to their multiple projections.

In the present study, I am examining how demand to an odor processing circuit changes the connectivity of the circuit over time, particularly connectivity with dopaminergic neurons. This is accomplished through exposing mice to odors known to act as agonists for a particular neural circuit of interest. Labeling in optogenetic mouse strains facilitates easy identification of these circuits. The exposure to the odor is controlled through a behavioral task where the mouse is required to sample the odor and identify it correctly in order to receive a water reward. This will be compared to a control group of mice who will be passively exposed to the odor through environmental enrichment rather than actively identifying the odor.

In the next phase of the project, I will perform in vivo imaging and electrophysiological recordings to demonstrate how the connectivity of the processing circuit changes to support greater demand. The conclusions from these results may be applicable to many other systems of the brain. In addition, understanding the connectivity of adult dopaminergic neurons could lead to future study of how newborn neurons in the olfactory bulb are integrated as functional members of these circuits.

The effects of environmental enrichment on microglial interaction toward soluble amyloid- β oligomers

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Alzheimer's disease (AD), marked by the aggregation of amyloid- β ($A\beta$) protein as amyloid plaques in the aging brain, is the most prevalent form of neurodegenerative disease in the United States. Recently, there is a growing interest in researching the innate immune response to the disease by studying microglial response to the

neurotoxicity of $A\beta$. Furthermore, the disease is largely sporadic, suggesting that environmental factors may play an important role in the development of the disease. To study environmental factors, we utilize the environmental enrichment paradigm. Environmental enrichment is a housing condition designed to provide physical, cognitive, and sensory stimulation to mice. In this experiment, we aim to better understand how the interaction between microglia and $A\beta$ is affected by environmental enrichment. To understand how environmental enrichment modifies disease progression, we apply soluble $A\beta$ oligomers from human (AD) postmortem cortex in vivo through hippocampal injections in wild-type mice in standard housing conditions and in wild-type mice trained in enriched environments. We isolate and characterize $A\beta$ dimers and monomers from human cortex using size exclusion chromatography. With this unique human source of soluble $A\beta$ oligomers, the main neurotoxic species in the disease, we are able to more closely mimic the natural disease state. After injection, we will compare the microglial responses in the two classes of mice by observing changes to microglial morphology and microglia-specific protein changes in the two conditions. The results will improve our understanding of how the brain's innate immune response to soluble $A\beta$ oligomers in Alzheimer's disease is affected by environmental enrichment.

Identification and characterization of transient upper layer callosal projection neuron white matter synapses in the developing mouse cerebral cortex

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Brain circuits, networks of neurons connected through synapses, are a key functional feature of the central nervous system, enabling it to receive, process, and transmit information. Previous research has suggested that early temporary connections between developing neurons facilitate the formation of mature circuitry. My project on work spearheaded by my mentoring postdoc, Alex Pouloupoulos, established a novel generalizable approach that allows the identification and characterization of early synaptic connectivity forming between subtype-specific neuron populations within the developing mouse cerebral cortex. Targeted synapses are identified by the spatial apposition of fusion proteins produced by genetic constructs of presynaptic synap-

tophysin and postsynaptic PSD-95 fused to fluorescent proteins of different colors. In my project, I introduced these constructs into mammalian cell lines to optimize image acquisition by confocal microscopy. In order to apply this method to the developing brain, and to obtain specificity to upper layer neurons of the cerebral cortex that connect across the two hemispheres (callosal projection neurons), I delivered the genetic constructs to the mouse brain via *in utero* electroporation at embryonic day 15.5 and 16.5. Using this *in vivo* approach, I used confocal microscopy to identify transient synapses at postnatal day (P) 9 occurring in the corpus callosum. Unexpectedly, unilateral electroporation revealed both putative presynaptic and postsynaptic puncta, or protein clusters, in the white matter. Moreover, the distribution of these puncta indicates unusual white matter axo-axonal excitatory reciprocal synapses of callosal projection neurons that do not exist at P4, form by P9, and persist at P16. By P16, fewer synaptic puncta were observed, suggesting that the time window for the formation of these synapses occurs between P4 and P16. Bilateral electroporation will reveal whether neurons from opposite sides of the brain interact during this time period. This experimental approach allows us to discover whether synapses form between callosal projection neurons from the same brain hemisphere or different hemispheres during development. These initial findings will guide the design of experiments to interrupt synaptic activity in order to identify the potential developmental role of these transient synapses.

Longitudinal analysis of neurocognitive function in men with and without HIV infection and heavy cocaine use

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Up to 50% of HIV+ patients are affected by neurological disorders, despite the availability of highly active antiretroviral therapy (HAART). These disorders are collectively labeled HIV-Associated Neurocognitive Disorders (HAND). Substance abuse is a common comorbidity among HIV+ patients that has been associated with exacerbated neurocognitive decline. Especially as HAART enables patients to live longer, the neurocognitive effects of cocaine on the aging HIV+ brain are increasingly important to study. However, clinical studies of the combined effects of heavy cocaine use, HIV infection, and aging remain sparse and limited to cross-sectional studies.

In this longitudinal study, we characterize the neurocognitive trajectories of men with and without HIV infection and heavy cocaine use over 11 years (1996-2007). Three hundred sixty-four participants were selected from the Multicenter AIDS Cohort Study (MACS), an ongoing multicenter study that began in 1983 and has enrolled 6,972 HIV- and HIV+ homosexual men in the United States. Every 6 months, participants underwent physical examinations, provided blood for laboratory testing, and responded to a questionnaire about sexual behavior, medical conditions and treatments, and substance use. All subjects had at least two visits with neurocognitive data between 1996 and 2007, and data was limited to visits from ages 30-60. Cocaine users were defined as heavy cocaine users who reported daily and/or weekly cocaine use for at least 2 visits in the study.

Four groups matched for race, baseline age, HCV status, and education level were compared for performance on 34 neurocognitive variables: HIV- non-drug users (n=96), HIV+ non-drug users (n=134), HIV- cocaine users (n=53), and HIV+ cocaine users (n=81). We use latent class analysis to identify subgroups of subjects with similar neurocognitive trajectories for each tested variable. Then, we identify the baseline demographic, behavioral, and clinical variables that are associated with class membership and predict a declining neurocognitive trajectory.

Control of adenovirus replication in carrier stem cells improves GBM tumor therapy

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Despite recent advances in molecular understanding, standard therapy methods, including resection, radiation, and temozolomide chemotherapy are all ineffective at repressing glioblastoma multiforme (GBM) growth due to the tumor's characteristic invasiveness and radio-chemo resistance. Oncolytic viral therapy using conditional replicating viruses and human mesenchymal stem cell carriers to specifically target tumor cells in the brain has emerged as a promising solution for GBM treatment. Nevertheless, one of the main limitations of this strategy is the toxicity of the viral progeny to the cellular vehicles and the fact that the stem cells are killed before sufficiently delivering the viruses to the tumor site. This project focused on engineering and testing inducible oncolytic adenoviruses whose replication can be repressed in the stem cells to allow for adequate delivery, distribution,

and ultimately reactivation of the viruses at a later time. To do so, the therapeutic gene for the antitumor agent S-TRAIL (soluble tumor necrosis factor receptor apoptosis inducing ligand) or a bimodal fluorescent and bioluminescent marker, GFP-Fluc (GFI), flanked with FRT sequences, was incorporated into the oncolytic adenoviral genome between the promoter CMV and the early adenoviral gene E1a Δ 24. A hypoxia promoter driving FRT-recombinase allowing for the excision of the transgene in hypoxia conditions was then expressed in the stem cells to reactivate viral replication. This strategy thus allowed for control over viral replication, real time monitoring of the activation of the oncolytic adenoviruses in real time by loss of the Fluc signal, and enhancement of the antitumor effect using S-TRAIL before virus activation.

Identification of reward and punishment inputs to the ventral tegmental area.

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Dopamine neurons in the ventral tegmental area (VTA) of the brain display firing signals that convey reward prediction error, or the difference between expected reward and actual reward. How and where the VTA receives its value-coded signals remains a mystery, however. Through analysis of the electrophysiological signals of monosynaptic inputs to the VTA in lab mice, a better understanding of the mechanisms underlying reward prediction may emerge. One particular input region, the rostromedial tegmental nucleus (RMTg), is known to exhibit inverse reward prediction error signals that precede the conventional error signals we see from the VTA. Furthermore, the RMTg receives a major excitatory input from the lateral habenula, which processes aversive (punishing) stimuli. Considering the RMTg is heavily GABAergic (and thus sends out many inhibitory signals), our research tests the hypothesis that reward and punishment dependent signaling is sent from the RMTg to the VTA.

Through the transgenic expression of channelrhodopsin-2, a light-sensitive cation channel, in neurons, we can “tag” input neurons to the VTA from the RMTg. After classically conditioning mice to associate specific odors with reward (or punishment) delivery, we surgically implant electrodes by which we can conduct extracellular recordings of the tagged neurons in vivo. By analyzing the firing patterns of VTA inputs from the RMTg during odor-associated tasks, we hope to characterize the type(s) of neurons that mediate

signaling from one region to another. In addition to the RMTg, we hope to investigate other related regions such as the pedunculopontine nuclei and ventral striatum in the near future.

Exploring the Relationship between Movement Speeds and Motor Learning Rates

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When we first learn to perform a task, such as playing a sport, we usually begin with slow movements to make the task easier to achieve. However, do slower movements necessarily improve our learning capability? The goal of this experiment is to determine how the speed of the movement being learned impacts the motor learning rate.

Our experimental design required human participants to move their arms towards a target at fast and slow speeds while holding a robotic manipulandum. A computer gave appropriate feedback for movement speed: too fast, too slow, or just right. We first trained subjects to move at the correct speed on cue in a baseline period. Next there were randomly alternating fast and slow 7-trial blocks, in which the robot perturbed subjects' movements by exerting lateral forces on the arm, proportional to the movement velocity. We monitored how quickly subjects adapted to the force field (FF) to restore a straight reaching trajectory toward the target. Each block was preceded and followed by non-FF trials to “wash out” learning from the previous block, allowing for repeated and reliable measurements for learning rates. Error clamps, which exert a restoring force that cause subjects to move straight, allowed us to measure the force exerted by the subjects at three stages of learning: before the FF trials, “early” (after the first FF trial), and “late” (after 7 FF trials).

Subjects were able to consistently modulate movement speeds on cue, and demonstrated learning for both fast and slow movements. We quantified learning by calculating an “adaptation coefficient” by regressing measured force on ideal force. Analysis reveals that fast movements significantly improve late learning versus slow movements, while there was no significant inter-speed difference for early learning. These results are surprising because they counter the intuition that slow movements improve learning. This research can potentially lead to the development of new motor training techniques.

Screening of Compounds to Enhance Neuroprotection and Neurite Growth in Retinal Ganglion Cells

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Retinal ganglion cells (RGCs) reside in the inner layer of the retina and receive information generated by photoreceptor cells. RGCs convey that information to the brain through the optic nerve, which consists of the axons of the RGCs. RGCs are damaged in a variety of eye conditions, such as glaucoma, which is the world's second-leading cause of blindness, as well as in other conditions such as optic neuritis and brain injury. Like many other types of neurons in the central nervous system (CNS), RGCs do not regenerate in adult mammals, making the treatment of these conditions difficult.

My project this summer was screening for compounds that can enhance survival and neurite growth of RGCs *in vitro*, using RGCs obtained from P10 mouse pups and compounds identified by a collaborating laboratory at the Gladstone Institute in California. In order to do this, we first isolated the retinas of the mouse pups and then extracted RGCs before culturing the cells with the different compounds we were testing in an incubator. After a three-day incubation period, we stained each of the two sets of cells exposed to identical compounds using two different methods. We stained one set with a fluorescent marker that labeled surviving and dead RGCs (a Live/Dead staining kit), allowing us to quantify RGC survival rates, while for the other set we used an antibody against Beta-III-Tubulin, an RGC marker, which allowed us to assess neurite outgrowth and neurite lengths. Our goal is to identify a compound that enhances both RGC survival and neurite growth, and to eventually be able to validate our results *in vivo* in animal models of optic nerve injury. A candidate compound could present a drug candidate for treating conditions that damage RGCs. These treatments could potentially be useful not only for RGCs but also for a wide variety of neurons in the CNS.

Connectomic Analysis of the Structural Dynamics of Neighboring Astrocytes in the Mammalian Cortex

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The star of the brain is the neuron, an information-transmitting cell whose electrochemical activity holds much of the responsibility for the sum of human experience: from memories to emotion, sensation to cognition. Most neuroscience research investigates the activity of neurons and neuronal circuits. Consequently, far less is known about non-neuronal cells called glia. Until recently, glia, the most numerous brain cell-type, were simply considered to be latticework holding the brain physically together. A subtype of glia called astrocytes have been found to be closely associated with synapses. Light microscopy experiments have suggested that astrocytes form non-overlapping spatial domains that contain such that synapses within these domains are modulated by the surrounding astrocyte. The structural nature of these domains, and whether astrocytes interact at their boundaries, have not been fully elucidated.

This project aims to trace the structures of four neighboring astrocytes in mouse cortical tissue through the analysis of serial-section scanning electron microscopy images. This state-of-the-art method delivers 10 billion pixel images of brain tissue slices 30 nanometers thick. When stacked, these images allow 3-D reconstruction of tissue and give insight to the structure of the brain at the cellular level. So far, I have discovered a junction where all four astrocytes come together, and touch at points. Further work will investigate the nature of their boundaries, possibly by triangulating the points at which the astrocytes touch, and attempt to describe the nature of synapses near these boundaries and how they are affected by the interactions of neighboring astrocytes.

Digital novel object recognition as a visual assessment for rats

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Novel object recognition (NOR) is a robust and oft-used trial in the field of behavioral neurobiology. In most literature, the test involves giving the subject, a laboratory animal, a pair of objects to explore. The animal is then moved from the testing area while one of the objects is switched out with a new one. Whether or not the animals, on average, correctly identify the novel object when reintroduced to the testing area—determined by heightened time spent interacting with the object—is often an assessment of the effect of surgeries, drugs, or other memory- or behavior- affecting stimulants. Classically, these objects have been physical ones, such that the animals can investigate them using the full spectrum of

senses. For animals such as rats, this is crucial, as rats rely heavily on smell and touch to interact with the world around them.

This particular NOR project aims to explore purely the visual sense by using digital objects presented on a screen rather than physical ones. It has been shown that laboratory rats' visual systems have a rather high-level capacity and can recognize digital images as objects, given extensive training. This study investigates whether these rats can also, given exposure to two identical images initially with no prior training, be able to generally recognize a novel image later switched out on one of the screens. The results of a series of these assessments has the simple goal of elucidating the extent of the rats' visual capabilities, and to measure the effectiveness of a purely visual NOR assay as a way to supplement further studies.

The Role of Nap-dependent Auditory Reactivation on Salient Memory Consolidation

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How does our brain determine which memories are retained and which are forgotten? Previous studies have shown that covertly reactivating memories during sleep may selectively influence the retention of stored memories. Ken Paller's study in 2013 tested the effect of targeted memory reactivation of object-location associations during sleep and wakefulness. Auditory cues of specific object-location associations during sleep rescued memories from being forgotten. In the present study, we plan to test the effect of covert reactivation of emotional and neutral memories with Paller's learning task. Participants were first assigned to a computerized learning task where they learned fifty emotional or fifty neutral object-location associations, each of which was paired with auditory stimuli. All participants were monitored via EEG to measure their brain activity during the task, sleep, and quiet wake. Because the benefit of auditory cueing during sleep may depend on when these memories are stimulated, we reactivated memories either during slow-wave sleep (SWS) or rapid eye movement sleep (REM). Participants who were not assigned to the nap group rested for approximately 90 minutes, and nap participants were given a 120-minute nap opportunity. We expect participants who receive auditory reactivation during the nap to show improvement on those triggered memories during re-test. We also expect reactivation of the emotional and neutral memories to improve memories

of object-location association when triggered during REM and SWS, respectively. To test the role of auditory reactivation on long-term memories, participants were re-tested on the same learning task one week after their first visit. If memories selectively triggered during the nap show improvement during immediate and delayed re-test, these results would suggest the potential role of sleep-dependent reactivation on learning and memory consolidation.

Expression of MeCP2 in PV cells of the brainstem is linked to respiratory function in Rett syndrome

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Rett syndrome (RTT) is a neurodevelopmental disorder caused by de novo mutations in the MECP2 gene, which codes for a transcriptional repressor called methyl-CpG binding protein 2 (MeCP2). Patients experience a variety of symptoms, including autistic behaviors, impaired vision, and respiratory problems, including breath-holding and apneas. Approximately 25% of patients die prematurely of cardiorespiratory failure, and since no treatments are currently available, further study of this respiratory dysfunction is crucial.

Previous research in other symptoms, like visual regression, has focused on a class of inhibitory interneurons called parvalbumin cells (PV). Loss of MeCP2 in the visual cortex leads to hyperconnectivity in PV cells, which causes a neurological deficit in the visual system. Since PV cells are also highly expressed in areas of the brainstem that control respiration, we are currently studying expression of MeCP2 in PV cells in respiratory nuclei. We are working to determine whether only expressing MeCP2 in PV cells has a positive effect on respiratory symptoms.

We used mice bred with the Loxstop-Cre recombinase system, a genetic engineering tool that uses the viral enzyme Cre recombinase to express certain genes in only certain cells, allowing us to work with mice that only express MeCP2 in PV cells. Using whole body plethysmography, which involves placing a mouse in a sealed chamber in order to measure its respiration, we aim to study the effects of only expressing MeCP2 in PV cells on various respiratory parameters, including the frequency and duration of apneas, in order to determine whether targeting PV cells is an effective mechanism for rescuing respiratory dysfunction.

The role of Twist-1 in venous angiogenesis.

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Blood vessel development occurs in a two-step process. The first step, vasculogenesis sees mesodermal cells differentiate into endothelial cells which coalesce to form primitive arterial and venous structures. The second step, angiogenesis is a process by which new blood vessels grow and remodel from primitive arteries and veins. Conceivably, arterial and venous angiogenesis are independently regulated to ensure that aberrant connections do not form between functionally distinct neighboring blood vessels. In diseases such as hereditary hemorrhagic telangiectasia (HHT) arteriovenous malformations can lead to seizures, strokes, and in some cases, death. In 2011, Wiley et al. identified signaling cues in zebrafish that were specifically necessary for the regulation of venous angiogenesis. However, evidence in support of this hypothesis has yet to be reported in mammals. Previous experiments done in the Engle lab indicate that the transcription factor Twist-1 may play a role in modulating venous angiogenesis. I hypothesized that mice which lacked expression of Twist-1 in the mesenchyme surrounding the blood vessels in the head would exhibit defects in the development of the major head veins, but not in arteries. Twist-1 was conditionally knocked out in the head mesenchyme using mice that express Cre-recombinase under the control of the platelet derived growth factor receptor beta (Pdgfrb) promoter. From mid to late embryogenesis, the Twist-1FLX/FLX;Pdgfrb-Cre mutants were analyzed for vascular phenotypes using whole-embryo immunohistochemistry with endomucin, and smooth muscle actin, antibodies that specifically recognize veins and arteries, respectively. The Twist-1FLX/FLX;Pdgfrb-Cre mutants mice did indeed demonstrate defects in venous angiogenesis. Furthermore, although the growth and remodeling of the major head veins was appreciably perturbed, arterial sprouting appeared to be relatively normal, suggesting that Twist-1 is part of a pathway that regulates venous angiogenesis independently of arterial angiogenesis. The results of this study have begun to illuminate a heretofore undescribed concept in the field of mammalian vascular development.

Intrinsic Firing Patterns of Somatosensory Neurons

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The brain perceives the sensory world from patterns of action potential (AP) spikes in somatosensory neurons. Previous functional classification of small-diameter somatosensory neurons, those sensing pain, itch, and temperature, have been based mostly on morphology and biomarker expression. Meanwhile, firing patterns have already been used to classify neurons into functional subtypes in other areas of the nervous system, such as the neocortex. The goal of this project was to determine whether subgroups of small-diameter somatosensory neurons also have distinct intrinsic firing patterns, and, if so, to characterize their patterns.

To achieve this goal, we exploited the recently developed technique to measure and induce APs called Optopatch, in contrast to traditional patch clamp. Cultured mouse dorsal root ganglion (DRG) neurons were transfected with Optopatch plasmid, which contains a voltage actuator (optimized channelrhodopsin) and sensor (Arch). The neurons were activated by exposure to blue light in time intervals of 0.5s to open the channelrhodopsin, and Arch fluorescence was measured using a 1-photon laser microscope.

To classify intrinsic firing patterns that likely reflect functional neuronal subtypes, I compiled data collected with Optopatch and evaluated the data along parameters with physiological significance, such as firing frequency and the distribution of AP spikes during a stimulus. MATLAB was used for all image-processing and data analysis. Preliminary results suggest clustering of neurons based on differences in rate of reactivation and adaptation. Future work will apply cluster analysis algorithms like K-means to the parameters to attempt a rigorous classification. The intrinsic firing pattern data for DRG neurons will also be compared to DRG responses to a variety of sensory ligands, as well as immunohistochemical characterizations. Correlation between intrinsic firing pattern and ligand binding classifications would suggest that a neuron's intrinsic firing patterns can predict cellular function and yield a deeper understanding of the mechanisms of physical sensation.

Using Functional Connectivity to Understand Memory System Communication During Off-line Learning

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As humans learn different facts and skills each day, the ability to retain this new information is essential and often reliant on different types of memory systems. Consolidation is a process that cements a memory after it is first obtained. While different memories share this process, they differ in neural architectures and can be divided into two types: declarative (fact and list learning) and non-declarative (skill and motor learning). Evidence has traditionally suggested that the neural circuits of these categories were separate. Recent functional imaging studies have found, however, that activity in declarative memory regions is negatively correlated with that of non-declarative regions. Furthermore, previous work has shown that declarative learning can cause interference (i.e. inhibit consolidation) of a motor skill. These results suggest communication and competition between the two systems.

While many of the previous studies on memory consolidation and interference have been behavioral, this research seeks to study the direct biological mechanisms involved in interactions between declarative and motor memories. This project specifically looks at how resting-state connectivity changes after learning a competitive declarative task versus a non-competitive task immediately following a motor skill. Using BOLD signals from fMRI, we have performed region of interest functional connectivity analysis to examine network differences resulting from consolidation (or interference) in the two groups. By investigating changes in functional connectivity, we will be able to better understand how respective memory systems affect each other and the specific connectivity and biological mechanisms that underlie them.

Electrophysiological and Behavioral Development of Spatial Memory

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Spatial memory, a function of declarative memory, is more specifically divided into two categories: egocentric and allocentric spatial memory. While subjects use

egocentric spatial memory to locate an object in relation to him/herself, subjects use allocentric spatial memory to locate an object in relation to his/her environmental landmarks. Although we understand from previous literature that both the hippocampus and parahippocampal cortex are distinct markers for allocentric and egocentric spatial memory respectively, more specific neuroimaging and behavioral analysis is required for the development of spatial memory. Currently, we have developed a spatial memory testing tool by placing 3 different objects onto 1 of 8 different places on a table separately in order to "encode" participants with the object positions. Then, subjects are presented with one of the original objects in the familiar location with another identical object in an unfamiliar position. We expect that subjects will look at the novel stimulus object longer if they have accurately encoded the original object locations. We then move participants to the opposite end of the room and test them again in order to include allocentric spatial memory processing. In addition, we are using electrophysiological analysis of ERP in conjunction with behavioral data in order to determine the electrophysiological effects of spatial memory encoding, particularly within the parietal scalp region. Having tested adults and 9-month old infants in an earlier portion of the study, we are currently testing 4-year-old children in order to place when egocentric and allocentric spatial memory encoding comes online and expect significant results of both types of spatial memory encoding in 4-year-olds.

Analyzing the Bi-Phasic Reaction of Astrocyte Bone Morphogenetic Proteins in an Optic Nerve Crush Model of Glaucoma

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Though bone morphogenetic proteins (BMPs) were initially identified as osteogenic factors, their critical roles in patterning and differentiation during embryonic development and in maintenance of tissue homeostasis throughout adult life have become increasingly apparent. Their diverse functions make BMPs prime targets for clinical intervention research in a myriad of disorders. In the pathogenesis of glaucoma, retinal ganglion cells are damaged and die, causing vision loss. The optic nerve head is the likely site of injury to retinal ganglion cells in this disease. Using an optic nerve crush (ONC) glaucoma model, our group previously observed that white matter astrocytes in the optic nerve head react bi-phasically to such injury. First, astrocytes become

amoeboid in shape with reduced spatial coverage; the second phase is characterized by process re-extension and glial scar formation, which prevents regeneration of damaged axons. Quantitative PCR analysis of BMP expression levels after ONC revealed that BMP1 and BMP2 are upregulated three days after injury, while BMP4 and BMP5 show upregulation three weeks after the same insult.

We hypothesize that BMP1 and BMP2 play a role in the first protective phase of astrocyte reactivity, whereas BMP4 and BMP5 govern the second, more detrimental phase. We are performing immunohistochemical analysis of BMP expression levels in tissues that have undergone ONC, at time points of one, three, seven, and twenty-one days after injury. Concurrently, we seek to test whether BMP2 overexpression induces astrocyte reactivity in the optic nerve head. Having recently observed that adeno-associated virus (AAV2/9) efficiently transfects optic nerve head astrocytes, we designed a synthetic BMP2 gene and inserted it into an AAV vector backbone. The resulting virus will overexpress BMP2 and a red fluorescent protein and will be intravitreally injected into the eyes of wildtype C57BL/6 mice, allowing us to observe the effects of BMP2 on the morphology of transfected astrocytes.

Investigating High-Level Vision Using a Rodent Model

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Human visual systems are able to recognize objects with such ease that we often overlook how impressive a feat this is. This ability to recognize objects despite tremendous variation in view, size, lighting, etc. is known as invariant object recognition. With seemingly no effort, humans are able to identify many distinct objects in spite of the infinite number of images each object can cast upon the retina. Even though this aspect of our visual system is critical to the way we perceive the world, the computational structures are still poorly understood. In studying invariant object recognition in rats, the Cox lab has found that rats are able to spontaneously generalize to previously unseen transformations of learned objects. Their ability to recognize these objects in spite of significant variation in appearance demonstrates that rats possess more advanced visual abilities than previously appreciated.

In order to fully establish the rat as a model system for the study of high-level biological vision, we aim to

determine what the visual capabilities of rodents are. Using highly parallel, computer-controlled behavioral rigs, we are able to run many experiments simultaneously. Pigmented rats are trained to perform visual tasks that require them to recognize objects in the face of real-world image variation. So far, these high-throughput experiments have provided strong evidence for high-level visual abilities in these rodents. Although the brains of rats are clearly less advanced than those of non-human primates, this may be an asset as we try to seek out the simplest system that demonstrates properties of interest. The availability of these simpler systems might provide us with an additional window onto the computational problem of object recognition.

A Genetic Screen to Identify Novel Regulators of Neurotransmitter Release Kinetics

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All processes in the brain are encoded by temporal patterns of neural activity. Even the most minute changes in signal timing can lead to large cognitive and developmental differences, so elucidating the fundamental cellular mechanisms that shape kinetics has significant implications. Today, the pre-synaptic neuron's role in kinetics is a key area of interest and scientists are studying how quickly neurotransmitter vesicles can fuse with the cellular membrane. Using the worm *C. elegans* as a model organism, it is currently thought that there exist two populations of vesicles with distinct kinetics—fast-release and slow-release. In addition to differing spatially—fast-release vesicles are proximal to the cell membrane and slow-release vesicles are found more distally—they are unique in the set of proteins involved in vesicle fusion. One such fundamental player is UNC-13. While one isoform, UNC-13L (long), promotes fusion of fast-release vesicles, the short isoform, UNC-13S, is involved primarily in slow-release. Moreover, in opposition to the slow-release mechanism exclusively, Tomosyn (TOM-1) protein inhibits UNC-13S.

In order to understand other factors that regulate release kinetics specifically in the slow-release pathway, I will use the mutagen ethyl methanesulfonate (EMS), to perform a genetic screen on an *unc-13* mutant strain (*e1091*) that specifically disrupts UNC-13L but leaves UNC-13S intact. Because these worms have severe movement defects, I will screen for mutations that restore locomotion by decreasing TOM-1 activity or enhancing

UNC-13S functionality. Among these candidates, I expect to find mutations that may increase the quantity of UNC-13S, decrease the binding affinity of TOM-1, or improve locomotion through other means. Ultimately, I hope identify and characterize novel components that regulate the kinetics of neurotransmitter release.

Characterizing Dorsal Horn Interneurons in the Deeper Lamina of the Spinal Cord

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The intricacy of our somatosensory system has allowed us to perceive the richness of the tactile world. Receptors in our skin are innervated by sensory neurons that help carry information to the spinal cord and the brain so that we can detect and interpret innocuous and painful stimuli accordingly. The spinal cord dorsal horn is the center for the integration and processing of tactile input, and it has been shown that the interneurons in the superficial lamina (I/II) of the spinal cord are predominantly responsible for pain, thermal, and itch perception, while the interneurons in the deeper lamina (III-V) are responsible for innocuous perception. While some work has already been done to characterize the interneurons in the superficial lamina of the spinal cord, very little is known about the interneurons in the deeper lamina.

We are using mouse molecular genetics to uncover the diversity of deep dorsal horn interneurons. The first part of my project involves the characterization of three lines of interneurons: Cadherin3-GFP, Igfbp5-GFP, and Htr6-GFP. I am quantifying the overlap of these three lines with other known dorsal horn molecular markers and the percentage of the deep dorsal horn that they represent in order to better understand the neural circuitry underlying the perception of innocuous touch. The second part of my project focuses on Cadherin3, a protein that plays an important role in the development of epithelial cells and synapse formation in the spinal cord. We found these interneurons to be largely inhibitory, suggesting that Cadherin3 may help mediate touch and prevent feeling pain in response to innocuous stimulus. First, by staining for neuronal endings in the skin of mice, we can see which types of sensory neurons innervate Cadherin3. Second, by examining behavioral deficits of knockout mice, we can learn more about how Cadherin3 affects the perception of touch.

Climbing the Evolutionary Tree: An Investigation of Morphological and Behavioral Adaptations to Arboreality in Forest Deer Mice

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Adaptation by natural selection is the process by which organisms adapt different traits to best suit their environments. These changes can occur rapidly with different populations of the same species often becoming locally adapted to different habitats. This is true for two subspecies of *Peromyscus maniculatus*, *nubiterrae* and *bairdii*, which have differences in tail length and foot size in accordance with their habitats, forest or prairie. The forest variety *P. m. nubiterrae* have longer tails that have more vertebra and vertebra of longer length, as well as larger feet when compared to the ancestral prairie mice, *P. m. bairdii*. To better understand how forest mice have adapted to a more arboreal lifestyle, we studied the subspecies from cellular and behavioral perspectives. To understand what in development leads to differences in bone length between forest and prairie mice, the bones of developing mice are studied. We looked at the growth plates of bones in the tail and feet for cells called hypertrophic chondrocytes which are the final stage in the cell progression to bone formation that occurs directly before ossification. Comparing the area of these cells gave insight into how differences in bone growth produce differences in adult morphology. The different morphologies of the subspecies could account for one subspecies having a higher aptitude for arboreal locomotion and climbing. From experiments in the past, it is known that arboreal species perform better at balancing tasks than terrestrial species. To find out if this is also true for *P. m. nubiterrae* and *P. m. bairdii*, tasks were developed to test which subspecies performs better on two artificial branch balancing tasks and how they use their tails to maintain balance. *P. m. nubiterrae* showed an ability to maintain balance more often than *bairdii* and used their tails with better efficiency and effectiveness.

Quantitative analysis of positive selection in microbial species

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The role of positive darwinian selection in the evo-

lution of the natural world has been well documented, but is still not firmly understood in its mechanisms nor its distribution among organisms. How does the “rate” of evolution vary among species, and why do some species seem to evolve more stochastically (i.e. less “goal oriented”) than others? This project examines such selection on a microscopic scale, studying the difference in rates of selection among several microbial species by comparing their variations in genetic code. A robust quantitative method known as the McDonald-Kreitman test as well as over a million sequences of DNA retrieved from public genetic banks has allowed for the calculation of selection rate of genes for near entire genomes of species. With this data in hand, selection rate can be compared amongst species and correlated with factors like population size, genome size, and gene expressivity to gain new insight into what influences the rate of positive selection among species, in turn giving insight into how those species function and evolve. Furthermore, such understanding of what determines the rate of selection may allow for improvement of the McDonald-Kreitman test and other current methods by shoring up inadequacies in assumptions about the nature of adaptive evolution or by in fact developing new methods. Though this work is restricted to small bacteria, applying it in conjunction with past literature on larger species can increase its scope to include even humans.

Evolution of Paternal Behavior in *Peromyscus*

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Parental behavior is highly variable across species. Paternal care, in which the father significantly invests in the care of the offspring, occurs predominantly in monogamous species and very rarely in promiscuous species. While species differences in parental behavior have been heavily documented, the genetic basis of its evolution remains unknown.

To study this question we examined two species of *Peromyscus*, the deer mice genus, that differ in their mating system: *P. polionotus*, which is highly monogamous, and *P. maniculatus*, which is highly promiscuous. The parental behavior of these two species has not been directly compared. Here, we studied the parental behavior of these two sister species as a basis to understand the underlying genetic architecture. First, we characterized and quantified their parental behavior through behavioral assays. Behaviors measured included the latencies to approach, lick, handle, huddle, and retrieve a pup. Apart

from retrieving, *P. polionotus* fathers were as parental as *P. polionotus* mothers. In contrast, *P. maniculatus* fathers behaved significantly less parentally than *P. maniculatus* mothers and both *P. polionotus* fathers and mothers.

To determine the heritability of parental behavior, we conducted interspecies cross-fostering experiments. A newborn litter from one species was exchanged with a litter from the other species. Later, we evaluated the parental behaviors of these cross foster pups when they became parents. Minimal differences between cross-fostered and non-cross-fostered individuals suggest a strong genetic component to parental behavior.

To further investigate the genetic basis of parental behavior, we performed an F2 intercross between the two species, measuring the parental behaviors of the hybrid offspring and the F2 generation. Together, these findings will elucidate the parental behaviors of these two sister species and are a preliminary step towards understanding the genetic underpinnings of parental behavior.

Adaptation and the evolutionary advantage of sex

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The purpose of my project is to elucidate at what rate sex affects adaptation in populations. Using four different lines of yeast, we try to determine how the rate of adaptation depends on the mutation rate and recombination. To assess the fitness consequences of genetic mixing, we directly compare the fitness of sexually and asexually derived genotypes in our experimental populations. Sexually derived genotypes are more fit than asexually derived genotypes when adaptive pressures are strong because in sexual populations, the process of genetic recombination allows the genomes of the progeny with fewer mutations to be generated from more mutated parental genomes by putting together mutation-free portions of parental chromosomes with deleterious mutations. To measure this, we first mutated genes that code for proteins implicated in key repair pathways of the yeast. Mutating each of these regions will cause the populations to evolve with a high rate of mutation; however, disabling these two different DNA repair mechanisms cause the yeast to evolve at different rates of mutation. Using serial dilutions, we evolve four different yeast strains that span three orders of magnitude. We evolve the populations by replicating them in parallel sexually and asexually, and we genetically mix the sexual genotypes by crossing them every 75 generations. We

will measure the fitness increase every 300 generations. After experimentally evolving the lines of populations, mating them and putting them through sporulation in a regular fashion, we will have the data to measure the adaptation rate of the populations. With this data, we will be able to determine how the rate of adaptation depends on the mutation rates in the population and the rate of recombination.

Maneuvering and Anatomy in Cichlids

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There are about 32,000 fish species, yet most of them have one of three types of bodies. It is thought that each body type is specialized for a certain type of swimming: accelerating, cruising, or maneuvering. Accelerators have flexible, muscular bodies with high-area fins, allowing them to generate strong thrust to either ambush prey or escape predators. Cruisers' stiff, torpedo-shaped bodies reduce drag, lowering the energetic cost of swimming. Their crescent-shaped tails act as sideways wings to create propulsive forward thrust. Maneuverers have round, flat bodies, which means that their fins are positioned far from the center of their bodies, allowing them to make sharp turns through complex habitats. We seek to determine how differences in anatomy affect the ability of suspected accelerators, cruisers, and maneuverers to move through complex habitats. When comparing distantly related species, many different factors, including behavior and physiology, can result in differences in swimming performance. To minimize such confounding factors between distantly related fishes, we study closely related species in the family *Cichlidae*, each with different specialized swimming anatomies. *Crenicichla saxatilis* has a body shape associated with acceleration, *Cichla ocellaris* with cruising, and *Symphysodon aequifasciatus* with maneuvering. To mimic movement through a complex habitat, we stimulate the fishes to swim through a tank filled with vertical obstacles. We used high-speed videography to measure variables that reflect maneuvering ability, including angular acceleration, path length, maximum body curvature, and time to course completion. Future research will replicate this study in other lineages within *Cichlids*, to examine the evolution of body shape and swimming performance in this group. Understanding the connection between anatomy and swimming style will help biologists understand how species with different anatomies forage and escape predators.

A Fungus Among Us: The Hidden Truffles of Harvard's Arnold Arboretum

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Trees are often characterized as being strong and solitary, capable of thriving without intervention from other organisms. However, beneath the soil the roots of a diverse range of trees, including some of the most successful families, are coated in fungal mantles that provide nitrogen, phosphorus, and other nutrients to the plants. Pines, oaks, beeches, and even some orchids are all dependent on these symbiotic partnerships known as *ectomycorrhizae*. There is significant experimental evidence suggesting that *ectomycorrhizae* are essential for healthy tree growth and development, in fact the health and diversity of a tree's ectomycorrhizal community is a strong indicator of the tree's overall health. These fungi are difficult to study because of their subterranean nature and their inconsistent, unpredictable fruiting patterns. Because of these challenges, many species of ectomycorrhizal fungi have not yet been described.

Research on *ectomycorrhizae* has substantial economic and gastronomic repercussions as well as ecological, as the genus *Tuber*, which includes a number of important edible truffles, including the prized black Perigord and white Piedmont varieties, is ectomycorrhizal. I spent this summer gathering data about the ectomycorrhizal community of Harvard's Arnold Arboretum, focusing particularly on the genus *Tuber*. I have found some fruiting bodies of an undescribed species of *Tuber* that is widespread throughout the arboretum and has been documented on tree roots throughout the northeast. My mentor, Dr. Rosanne Healy, and I are currently in the process of describing this species, which appears to be a strong competitor in ectomycorrhizal communities. Knowledge of this species will allow for a better understanding of the forests of the northeast, a valuable resource, and also will further research into truffle cultivation, a new industry in North America that is often hindered by native *Tubers*, such as our species, out-competing the European truffles that are the target product.

Improving on the Most Accurate Measurement of the Electron's Magnetic Dipole Moment

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A single electron, exhibiting a quantum mechanical "spin," produces a miniscule magnetic field. The strength of this field is characterized by the electron's magnetic dipole moment, known as $g/2$ when measured in Bohr magnetons. It is one of the most accurately measured properties of an elementary particle. The experimental measurement of $g/2$ and its comparison with its theoretical value serves as the most stringent test of quantum electrodynamics, which describes how light and matter interact via photons. It also provides a method for determining the experimental value of the fine structure constant α , which characterizes the strength of electromagnetic interactions. The measurement of the magnetic dipole moment is carried out by confining a single electron in a cylindrical Penning trap. This artificially replicates the energetic structure of a weakly bound atom. Microwave excitation and spectroscopy are used to determine the separations between the energy levels, which can be related to $g/2$. Gabrielse (2008) measured $g/2$ with a record-breaking accuracy of 0.28 parts per trillion and α at 0.37 parts per billion. Future work aims to refine this measurement even more. My work involved designing and building an aluminum support structure for the Penning trap and the Faraday cage that surrounded it. This structure had to be strong, movable, and stable to ensure both safety and ease of use.

Time limitations on wavepacket transfer via stimulated Raman adiabatic passage in the production of ultracold molecules

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Stimulated Raman adiabatic passage (STIRAP) is a well documented technique for the spectroscopic transfer of a wavepacket between long-lived initial and target states via a lossy intermediate state without ever populating the latter. This is necessary in systems where direct transfer from initial to target state is impossible or inefficient. Complete transfer via STIRAP is theoretically possible, but significant differences in the shape of the potential surfaces is expected to limit the efficiency at

short time scales. This is because the light selectively promotes a portion of the wavepacket matching the upper surface eigenstates, leaving a hole of similar shape which has insufficient time to heal if the excitation occurs too quickly.

By programming an implementation of the split-operator method to numerically solve the time-dependent Schrödinger equation, the rate of hole digging and healing can be investigated for various potentials with the intention of observing behaviour on experimentally determined surfaces for NaCs molecules. This will help facilitate the production of ultracold NaCs molecules in experimental groups where the use of STIRAP is planned to lower the vibrational state of the molecules.

Preliminary experiments on a two level harmonic system have identified wavepacket hole digging and show a fixed deviation from Rabi cycling as the light intensity is decreased to zero. This is likely to be a result of time evolution of the promoted wavepacket on the upper surface where it is not an eigenstate. It is expected that similar behaviour will be observed on the full three state STIRAP system.

Aligning the Magnetic Field Inside a Proton Penning Trap

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In a Penning trap, single particles can be trapped and detected using the superposition of an axial magnetic field, which leads to circular motion of the particle in a transverse plane, and a quadrupole electrostatic field, producing axial harmonic oscillations. The electric field is harmonic only in the central region of the trap. Any misalignment of the magnet with respect to the axis of the trap leads to particles getting away from the center and, as a consequence, to loss of control over their position and trajectory. Therefore, a precise alignment of the magnetic field is necessary for particle detection. The aim of this project is to improve the precision in aligning the magnet inside the proton trap by using inductive sensing to control its distance from the radiation shield inside it. In order to achieve this, several sensors will be mounted at different points around the radiation shield. Each sensor contains a coil and a capacitor which form an oscillating circuit. When a conductive target is placed in the vicinity of the sensor, eddy currents are induced in the target and the magnetic fields produced by these currents change the inductance of the circuit. Thus, by measuring the inductance, the values for the distance between the

magnet and the radiation shield at different points can be compared. We have studied the behavior of the sensors and the dependence of their response on factors such as temperature, the wires used to connect them or their position on the trap, in order to find a feasible way to mount and calibrate them and to determine how much this method can improve the precision.

Electro-optic phase modulation for magneto-optical trapping with lithium niobate

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Ultracold atoms are a versatile tool for a range of quantum computation and quantum optics experiments. Typical cold-atom experiments involve a sequence of cooling and trapping steps to isolate single atoms at temperatures lower than one millikelvin. The initial step, called magneto-optical trapping, involves irradiating a gas of neutral atoms in vacuum with circularly polarized laser light tuned slightly below an atomic transition. Introducing a magnetic field gradient induces Zeeman splitting in the energy levels of atomic orbitals, which interact with the laser light and create a resorting force towards the center of the trap. Moving atoms perceive the laser frequency Doppler-shifted towards the transition frequency and absorb more photons than stationary atoms, which has a net cooling effect on the sample.

Modulating a laser by a sinusoidally-varying phase shift creates sidebands in the laser power spectrum, separated from the carrier frequency by the modulation frequency. Around an absorption feature like an atomic transition, differential sideband absorption can be used to lock a laser to a frequency that enables laser cooling and magnetic trapping.

Certain crystals, including lithium niobate, exhibit the Pockels effect, where an applied voltage changes the refractive index of the crystal and the phase of incident light. I designed and built a phase modulator using gold-coated lithium niobate crystal and a high-Q resonant RLC circuit. I constructed a Mach-Zehnder interferometer to test the device and observed the predicted frequency sidebands. I soon hope to use the electro-optic modulator for the magneto-optical trapping of sodium.

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Neutralization of Charged Particles Passing through Graphene

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In the last decade, graphene has been the subject of a surge in scientific interest. As a hexagonal, monatomic layer of carbon, graphene exhibits unique optical, electrochemical, and thermal properties that have exciting implications for material science and electrochemistry. In particular, graphene has important applications in commercial electronics, drawing special attention from the semi-conductor industry.

One specific property of graphene that is of interest is its response to a beam of charged particles. Classical scattering theory suggests that an incoming charged particle should either pass through or bounce off of the carbon atoms in a graphene sheet. Experimentally, however, we are unable to detect any charge passing through. While classical physics fails to explain this phenomena, quantum mechanics suggests that electrons can move between materials, neutralizing charge. Charge neutralization has not been adequately described for graphene, but it would explain why we do not detect charged particles.

Our work tests this charge neutralization hypothesis. Graphene is created by chemical vapor deposition on copper. Silicon chips are coated in a thin layer of silicon nitride which is milled away with a focused ion beam to create one micron square pores. In a liquid transfer process, the graphene is transported to the surface of the chip where it is suspended over the pore. Using a 3kv Argon beam, I dose the suspended graphene with charged particles and count which are detected. Over time, the graphene is incapable of neutralizing all the charged particles and we begin to see them. Matching these detected particles with our predicted model will help fill an important gap in graphene literature.

Semi-supervised and unsupervised classification of defects in amorphous solids

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Locating regions of rearrangement in amorphous solids is a difficult task. Localized particle rearrangements are usually determined by a metric called D_{min}^2 , in which local non-affine transformations over a small time interval are characterized as rearrangement. A cutoff of the bimodal D_{min}^2 distribution introduces the notion of “soft spots”, or neighborhoods susceptible to structural rearrangements, to aid in predicting rearrangements. While the phonon method is an established way of determining these soft spots, it is not very accurate. Machine learning on structural information of neighborhoods provide a new set of approaches to predict rearrangements with a higher degree of accuracy.

Taking in data from simulated Lennard-Jones glass undergoing thermal fluctuations, we can train the machine learning model to identify local structural information from symmetric features of the neighborhoods around the particles. These approaches treat the soft spots as a standard binary classification problem in which support vector classification algorithms make statistical inferences from a training set of “soft” and “hard” spots based on the cutoff from D_{min}^2 . One inherent problem with this dichotomy is that only positive (“soft”) results can truly be identified, so neighborhoods we train our algorithms to be “hard” can be false negatives and may still rearrange. With this in mind, we show that with semi-supervised methods — using only some positively labelled data — and unsupervised learning — using completely unlabeled data — we can achieve better prediction accuracy since the information we input into machine learning algorithms is more accurate about the nature of the spots.

Preliminary results show that unsupervised learning yields very cross-validated clusters after principal component analysis (PCA) for both $k=2$ and $k=3$ in k -means cluster analysis. Alas, these clusters do not appear to correlate with our labels, such as the D_{min}^2 , meaning the clusters we found are unphysical. But it does pose the question of whether the working assumption of binary classification is even an adequate model for rearrangement. This research is about developing a toolbox to predict the plastic behavior in systems like lithiated amorphous silicon, which is important in improving the durability and other macroscale properties of lithium-ion batteries.

Investigating the role of leflunomide on transcription elongation in zebrafish

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Dihydroorotate dehydrogenase (*dhodh*) is a gene important for neural crest cell differentiation and melanoma formation. Inhibition of *dhodh* gene function with the chemical leflunomide reduces melanoma and neural crest cell formation. Evidence has suggested that by blocking *dhodh*, leflunomide affects transcription elongation. Thus, the creation of homozygous mutants for *dhodh* and proteins involved in transcription elongation will elucidate leflunomide’s mechanism of action. We used a CRISPR-Cas9 system to create a *dhodh* mutant with a nonfunctional form of the protein, and identified heterozygous fish for a frameshift mutation resulting in an early stop codon in *dhodh*. We then performed an incross with these heterozygotes and did not observe any abnormal phenotype in the offspring. To exclude the possibility that the homozygous mutation was toxic to the embryos, we verified the presence of homozygous mutants by genotyping single embryos. The next step will be to confirm that this frameshift mutation truly affects protein translation by Western Blot analysis for *dhodh* on single *dhodh* $-/-$ embryos. In addition, we aim to generate maternal zygotic mutants, as the maternal contribution of the gene could be sufficient to allow for normal embryonic development.

Lipid Metabolism in Endodermal Derivatives of Zebrafish

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In the last twenty years, nonalcoholic fatty liver disease (NAFLD) rates have nearly doubled in both adults and children. In NAFLD, hepatocytes accumulate excess fat, leading to inflammation and scar tissue formation that obstructs normal liver function. There is currently no cure besides transplantation and, to a limited degree, diet and exercise. To address this problem and learn more about disease mechanisms, we studied endocannabinoids, using zebrafish as a model organism. Endocannabinoids are lipid-signaling molecules that bind to the cannabinoid receptors CB1 and CB2, which are encoded by the *cnr1* and *cnr2* genes. These receptors are abundantly present in the brain and in several peripheral organs, like the liver

and gut, and are conserved in zebrafish. The receptors have previously been implicated in mediating different aspects of liver disease and peripheral metabolism, but it is unclear how the CB receptors function in the development of endodermally-derived organs such as the intestines and liver.

We use zebrafish embryos and adult zebrafish to assess the impacts of mutating *cnr1* and *cnr2*. First, we exposed wild type and mutant zebrafish embryos to ingestible 2% ethanol or 3% egg yolk solutions to induce metabolic injury, and then stained lipids using Oil Red O. We found the mutant intestines began to collect lipid droplets in vast quantities compared to wildtype intestines. Using *in situ* hybridization, we also saw that the endoderm was unchanged earlier in development in our mutants when analyzing *foxA3* expression. Thus, early in development, these mutant fish endoderm develop similarly to wildtype endoderm. However, *ifabp*, which marks the differentiated gut, showed a significantly smaller pattern of expression in mutants compared to wildtype fish. We conclude that between 48 hours post fertilization (hpf) and 72 hpf CB receptor mutations impact endodermal development. Thus, we are currently investigating the genes and pathways responsible for these aberrations to clarify how disrupting endocannabinoid signaling affects these organs.

Adeno-Associated Virus Mediated Muscle Satellite Cell Transduction

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Muscle satellite cells are unipotent adult stem cells largely responsible for skeletal muscle maintenance and regeneration. While these mononuclear cells generally adopt a quiescent state, they become active in the event of muscle injury or disruption. Once activated, satellite cells proliferate rapidly and generate differentiated myoblasts capable of fusing to form new muscle fibers or repairing existing fibers. Additionally, muscle stem cells are capable of self-renewal in order to replenish the pool of satellite cells.

The importance of satellite cells in normal muscle function is most apparent in individuals with muscle degenerative diseases such as Duchenne's Muscular Dystrophy (DMD). DMD patients harbor a genetic mutation in the dystrophin gene. Dystrophin is an important structural protein that links the cytoskeleton of the myofiber to the extracellular matrix and stabilizes

the muscle. Consequently, the muscles of individuals with DMD exhibit a greatly increased susceptibility to contraction-induced muscle damage. Chronic muscle damage induces persistent satellite cell activation that ultimately exhausts the stem cell pool, leaving the muscle unable to regenerate and instead allowing fat or fibrotic tissues to replace the muscle fibers, leading to muscle wasting.

One of the most promising therapeutic approaches to muscle degenerative diseases is gene therapy. This method bypasses difficulties associated with other therapies, such as immune system rejection or the limited ability of satellite cells to proliferate *ex vivo*, by directly introducing exogenous DNA to either supplement or correct genetic mutations that underlie these conditions. However, most attempts at genetically altering muscle satellite cells *in vivo* have relied upon electroporation to deliver the desired DNA constructs, which poses the problems of inducing further muscle damage, random genomic integration, and limited translational applications.

An alternative delivery method can be found in viral delivery, specifically adeno-associated viruses (AAVs) which have shown great potential given their lack of pathogenicity, low immunogenicity, and non-integrating nature. While AAVs have been shown to transduce a wide range of different tissues and cell types, there have been little to no reports characterizing the viability of AAVs as a vector to deliver exogenous genetic material to muscle satellite cells, which could represent an attractive and applicable alternative to electroporation. In order to study AAV-mediated satellite cell transduction, a viral vector carrying a reporter transgene will be compared against other gene delivery techniques, including electroporation, based upon criteria of systemic transduction efficiency, transgene expression, tissue damage, and immune response.

Modeling Cortical Development Using Human Embryonic Stem Cells

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For mammals, the neocortex is an extremely important structure responsible for controlling several key functions, including cognition, sensation, and movement. The development of this six-layered structure of the brain involves a diverse array of neural and glial progenitors, all of which are ultimately specified to particular cortical layers and neural subtypes. Although the different types

of cells have been characterized in human and other mammalian brains, the developmental programs controlling fate specification of each cell have yet to be completely elucidated. Furthermore, most of the current knowledge on cortical development is limited to inferences drawn from observations in mouse and primate development.

Therefore, this project aimed to use directed differentiation of cortical neurons from human embryonic stem (hES) cells as a way to recapitulate key events during human cortical development. Using an established dual-SMAD inhibition protocol for differentiation, with the addition of various small molecules to accelerate the neural patterning process, the current experiments seek to differentiate these pluripotent stem cells to a deep layer (V/VI) dorsal forebrain (PAX6+, FOXG1+, FezF2+) fate. Future goals involve the ability to pattern cells to any cortical subtype and layer. Gene expression of the developing cortical cells was studied using immunohistochemistry staining and also quantified with qRT-PCR and fluorescence assisted cell sorting (FACS). This study is unique in its use of Hes5:GFP and FezF2:GFP reporter lines in combination with cell surface markers identifying progenitor and neural states to characterize the fate specification from progenitors to specific cortical projection neuron subtypes.

By analyzing and retracing the transcriptional profiles of these different cortical types, this study hopes to shed some more light on this still unclear area of developmental neurobiology. Moreover, establishing these *in vitro* models and protocols of generating different neuronal types can be applied to the study of various neurodegenerative diseases based in the cortex, such as Amyotrophic Lateral Sclerosis (ALS).

***Cbln1* is a novel molecular control over corticospinal motor neuron subtype specification and axon extension**

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Corticospinal motor neurons (CSMN) are a neuronal subtype in the neocortex that make synaptic connections to motor output circuitry in the spinal cord and brainstem and control voluntary movement. CSMN are of particular clinical significance because they are selectively vulnerable to degeneration in “motor neuron diseases”, most prominently amyotrophic lateral sclerosis (ALS). Also, damage to CSMN in spinal cord injury is the principal cause of loss of voluntary motor control. Thus, further understanding of controls over CSMN development might

contribute to future strategies for repairing damaged neural circuitry.

CSMN can be further classified based on their axonal targets. Some CSMN extend their axons to proximal targets in the hindbrain and the cervical region of the spinal cord (termed collectively as CSMN_C), while other CSMN extend their axons distally to the lumbar spinal cord (CSMN_L). We are currently investigating molecular mechanisms underlying this segmental specificity. This project investigates the role of one particular control, cerebellin-1 (*Cbln1*), in directing CSMN_L axon outgrowth. Previous studies in the Macklis lab have shown that *Cbln1* is specifically expressed by CSMN_L during development. Mis-expression of *Cbln1* in CSMN_C (from the earliest time when they are born) can re-direct their axonal projections toward caudal targets in the spinal cord.

Building on these findings, I am working with Vibhu Sahni, a postdoctoral fellow, to investigate whether mis-expression of *Cbln1* in CSMN_C, once their axons have reached the spinal cord, can still result in re-directing their axons caudally toward thoracic and lumbar targets. We mis-expressed *Cbln1* by injecting adeno-associated virus (AAV) particles, engineered to express *Cbln1* and a GFP reporter, in the neocortex of newborn pups. I am currently analyzing how far these labeled CSMN extend their axons, using GFP immunohistochemistry. In parallel with these over-expression studies, I am also investigating whether *Cbln1* is necessary for normal long axon extension by CSMN_L. The lab had already obtained *Cbln1* loss-of-function mutant mice. Vibhu had injected these mice with the neuronal tracer biotinylated dextran amine (BDA) in the neocortex where CSMN_L reside. I am analyzing whether labeled CSMN_L extend axons to their normal lumbar targets in *Cbln1* mutant mice. Together, these studies will advance our understanding of the possible function(s) of *Cbln1* as a molecular control over CSMN_L axonal targeting, and might contribute toward potential use of *Cbln1* in future approaches targeted toward CSMN regeneration and repair.

Development of luciferase assay for glucose-stimulated insulin secretion from pancreatic β -cells

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Affecting 382 million people worldwide in 2013, diabetes is a widespread disease in which patients are unable to regulate their blood glucose levels due to the

malfunctioning or death of insulin-producing pancreatic β -cells. The Melton Lab aims to use human embryonic and induced pluripotent stem cells to provide a source of functional β -cells for diabetics. For β -cells differentiated from stem cells to be useful *in vivo*, it is essential that they exhibit a proper glucose-stimulated insulin secretion (GSIS) response. Currently, ELISA is employed for assaying insulin gene expression in β -cells, but it is expensive, difficult to automate and run, and insensitive. The goal of my project is to develop a new luminometric assay for monitoring β -cell GSIS, using a luciferase reporter. If the system is successful, it can be used to search for ways to turn on insulin production in β -cells; to test the effects of perturbing β -cells with sugars, fats, or small molecules; and to assay β -cells of different patients to study why people differ in their capabilities of making and secreting insulin. The tagging technology may also be applied to a variety of future genes of interest.

VEGFA: A possible factor in the initiation of cardiac regeneration

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Although the human heart can form new cardiac muscle cells during its lifespan, the efficiency of this process and the human heart's regenerative capacity in general are very limited. As a result, heart disease alone accounts for 1 in 4 deaths in the U.S. every year. In this study, we aimed to identify molecular factors that play a role in heart regeneration using a comparative genomics approach. Three models of cardiac regeneration already exist: resection of the apex of the left ventricle in the axolotl, zebrafish, and neonatal mice. With the idea that evolutionary conservation of certain genes suggests function, we studied the common molecular signals during the initiation of cardiac regeneration in these species. In all three models, we performed apical resection of the hearts and isolated them for RNA sequencing at three different time points. Using several computational pipelines, hundreds of specific cytokines and growth factors have been identified to be possible common upstream factors. Our preliminary data suggests that vascular endothelial growth factor (VEGFA) may be an especially important factor in this process, and it is now necessary to functionally test this candidate's role in heart regeneration.

Differentiating Hematopoietic Stem Cells into YFAK-Specific Regulatory T Cells

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The OP9-DL1-IAs cell line is a murine stromal cell line which serves as an *in vitro* system for the differentiation of bone marrow derived hematopoietic stem cells isolated from SJL mice into YFAK-specific regulatory T cells. YFAK is a random amino acid copolymer shown to be more effective than the copolymer YEAK (Copaxone) in inducing regulatory T cells and suppressing the autoimmune disease Multiple Sclerosis. Preliminary results from our lab show that retroviral vectors containing YFAK-specific T cell receptors (TCRs) can be used to transduce hematopoietic stem cells for the differentiation of YFAK-specific regulatory T cells *in vivo*. The aim of the OP9-DL1-IAs cell line is to provide an *in vitro* system that optimizes differentiation of regulatory T cells with YFAK-specific TCRs from the IAs background. The addition of the IAs Major Histocompatibility Complex Class II protein will increase the effectiveness of the OP9-DL1 system of T cell differentiation. The ability of the YFAK-specific T cells to produce cytokines, induce T-cell activation marker expression, and fully differentiate will all be analyzed to test the efficiency of the OP9-DL1-IAs *in vitro* system. The *in vitro* system will also provide the means for analyzing IL-10 cytokine secretion of YFAK-specific T cells from SJL mice with the IAs background, and the manipulation of this system will further reveal information about the effect of the YFAK copolymer on increasing T cell stimulation and lessening Multiple Sclerosis' flairs.

Elucidating the Role of *TGF β 2a* in Heart Morphogenesis

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Over 1,000,000 babies are born with developmental heart defects annually worldwide, making congenital heart defects a leading cause of birth-defect related deaths. The prevalence and impact of these diseases requires further investigation to elucidate the underlying mechanisms that cause such heart defects to arise. Although the TGF β family of proteins has been shown to play a key role in heart development, the role of *TGF β 2a* in heart morphogenesis remains elusive. Therefore,

the goal of the proposed project is to define the role of *TGF β 2a* during heart morphogenesis using zebrafish as a model. Heart development in zebrafish, similarly to mammals, occurs by the sequential differentiation of an early and late differentiating pool of progenitor cells, i.e. the first and second heart field progenitor pools. Second heart field progenitors give rise to cells from the ventricle and outflow tract in zebrafish. My overall hypothesis is that *TGF β 2a* knockout fish will display significantly impaired development of their second heart field, manifested as reduction in ventricular size and absence of smooth muscle cells in the outflow tract. In order to address this hypothesis my first aim is to generate *TGF β 2a* knockout zebrafish. Fish were previously injected with a *TGF β 2a*-specific TALEN (transcription activator like effector nuclease) to generate frameshift deletions or insertions in *TGF β 2a*. I am currently mating *TGF β 2a* TALEN-injected fish and screening their progeny for *TGF β 2a* mutations by PCR. Once I identify fish with a *TGF β 2a* mutation, I will breed these fish for two successive generations to generate heterozygous and homozygous *TGF β 2a* knockout fish. My second aim is to directly address the role of *TGF β 2a* during heart morphogenesis. In a two-fold approach, I will first follow heart morphogenesis in *TGF β 2a* knockout and wildtype clutchmate embryos by *in situ* hybridization for the cardiac progenitor marker *NKX2.5*, and the differentiated cardiomyocyte marker *CMLC2*. Second, and independently of the success of generating *TGF β 2a* knockout fish, I will use the pan-TGF β inhibitor LY-364947 to inhibit TGF β expression in wildtype fish before the onset of second heart field progenitor differentiation. I will use immunofluorescence to visualize the heart and look for reduction of ventricle size and absence of smooth muscle cells in the outflow tract. The results of this project could contribute to future development of gene therapies for congenital heart defects as well as techniques to promote human heart regeneration.

Tapping into Blood's Full potential: A Look at the Interactions Between Runx1, Creb, and Pge2 to Understand Hematopoietic Stem Cell (HSC) Formation in Zebrafish.

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Past work has shown that Prostaglandin E2 (Pge2), a lipid signaling molecule in developing embryos, increases the number of hematopoietic (blood) stem cells in zebrafish. This was shown to be conserved in mammals

and is already in stage 2 of clinical trials in cancer patients undergoing bone marrow transplantation as it offers a powerful therapy to increase stem cell number in chord blood and thereby limit complications of graft versus host. The targets and mechanistic function of Pge2, however, has not yet been fully identified. A recent study coupled with bioinformatic analysis suggests that Pge2 works through cyclic AMP, another small signaling molecule, to activate the Creb transcription factor. Preliminary data suggests that Creb binds to super enhancer regions on DNA and increases the expression of genes that, in turn, may help transform normal epithelium cells into HSCs.

To study this our group inhibited Creb while treating with Pge2 and observed stem cell formation using an mRNA based visualization assay. This we hope will allow us to verify Creb's downstream location in the Pge2 pathway. In a related project we also studied Runx1, a gene that was found to be necessary for stem cell formation in mice, using a transgenic fish line that overexpresses the gene and performing a similar inhibitory experiment. Runx1, has not yet been shown to directly interact with Pge2 but we believe that it may be a target of Creb. These studies will illuminate the changes necessary for HSC formation in zebrafish that will further translate to a deeper and more thorough understanding of human blood development.

Characterization of the phenotypic expression of long non-coding RNAs in normal development.

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Many recent studies point to the noncoding genome as a potential factor in human health and disease such as cancer. One emerging element of the noncoding genome is thousands of lincRNAs, which are long intergenic noncoding RNAs that are transcribed from DNA but are not translated into protein products. Although some lincRNAs have been identified and their molecular function has been characterized, there remain many more lincRNAs whose function is unknown. Our lab studies these lincRNAs by observing the phenotypic effects of lincRNAs in knockout mouse models. We generated knockout mouse models by replacing the lincRNA gene-coding region with a lacZ reporter cassette. We have observed that linc-Kantr knockout mice have had tremors characteristic of neurological/behavioral defects, suggesting that it may play a role in such diseases as epilepsy. We have also seen various phenotypic defects

in the linc-Pint knockout mice, specifically infertility. Similarly, we observed an abnormal clasping reflex in linc-Trp53cor knockout mice when we picked them up by the tail, indicating a muscle defect.

This summer, I worked on characterizing this defect of linc-Trp53cor knockout mice and the expression pattern of linc-Pint in heterozygous adult mice. We sectioned the tibialis anterior muscle of adult linc-Trp53cor knockout mice and performed succinate dehydrogenase staining on the sections to quantify the mitochondrial count compared to wildtype muscle. I also extracted organs from two adult male Trp53cor heterozygous mice for lacZ staining to analyze the expression of the linc in adult organs. No differential expression was found in comparison with wildtype organs. For linc-Pint characterization, I extracted organs from linc-Pint male heterozygous mice and stained for lacZ. All organs showed high expression of linc-Pint. Further work will involve sectioning the brain and reproductive organs to better analyze the expression patterns and identify any potential histology differences via hematoxylin and eosin staining.

Pericytes as a Platform for a Cell Based Continuous Glucose Monitoring System

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Every year, as the incidence of type-1 diabetes increases globally, so too does its negative impacts of vascular disease and hypoglycemia. This particularly affects children due to their fluctuating levels of activity and blood glucose. In order to track blood glucose levels more closely, we aim to create a cell-based glucose monitoring system. The system will use a specially engineered glucose binding protein which fluoresces when bound to glucose, allowing for real time glucose detection with a scanner. The optimum cell type to express this sensor must be established. It is necessary to target a subpopulation of cells that can be easily collected, cultured, manipulated, and then reinserted into the patient. The candidate target cells have been identified as pericytes, commonly known as Rouget cells or mural cells, which are intimately associated with the microvasculature and have connections with endothelial cells.

For preliminary experiments, we are using the mouse as our model system. Although pericytes have been well characterized in human tissues and mouse brain and retina, they have not been well studied in the mouse skin. As a result, we aim to identify the native cells in

mouse skin and characterize their marker expression and relationship to the vasculature using immunofluorescence. Commonly used pericyte markers as determined from the literature such as CD146 and PDGFR will be utilized. Antibodies for markers such as CD31 and CD34 will also be used to differentiate pericytes from endothelial cells and other cell types in the vasculature. In addition, we will conduct flow cytometry on the mouse skin cells to determine what percentage contains pericyte markers. Lastly, the optimal culturing conditions for pericytes will be investigated by comparing the difference in marker expression when pericytes are plated on plastic dishes versus an extracellular matrix enhanced with growth factor. Results of these experiments will inform us on how to proceed with the isolation and culture of mouse pericytes.

Identifying Surface Markers to Purify Human Embryonic Stem Cell-Derived Motor Neurons

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HDRB
Class of 2017

Lee Rubin
Harvard University - Stem Cell and Regenerative Biology

The ability to differentiate human embryonic stem cells (hESCs) into motor neurons creates enormous potential for stem cell therapy and *in vitro* modeling of neurodegenerative diseases such as Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS). However, when stem cells are differentiated, only a fraction (<10-30%) of the final product are actual motor neurons. Extraneous cell types pose safety barriers to stem cell therapy and compromise accuracy of disease models. Furthermore, there are no identified surface markers that can be used to isolate motor neurons from a mixed culture. Currently known motor neuron markers, such as transcription factors ISL1 and HB9, are all intracellular, which requires fixing, and thus killing, cells in order to sort them. Thus, the goal is to determine over- or under-expressed surface proteins that can be used to isolate live motor neurons from a heterogeneous culture.

To identify potential surface markers, motor neurons differentiated from a reporter hESC line using retinoic acid and sonic hedgehog agonist were sorted by fluorescence activated cell sorting (FACS), based on a motor neuron marker HB9 GFP reporter. RNA sequencing was conducted to evaluate protein expression in HB9 positive cells. Surface proteins identified in RNA sequencing were further investigated using quantitative polymerase chain reaction (qPCR) to compare expression between HB9 positive and negative populations. Antibodies for

proteins that demonstrated the significant increase or decrease in expression in motor neurons were then used to tag and sort differentiated cells. Antibodies that tagged the highest percentage of motor neurons can be used for positive selection, while antibodies that tagged the highest percentage of extraneous cells can be used for negative selection. The identified proteins serve as a first step to creating a motor neuron purification “kit” that can increase the feasibility of stem cell therapy and accuracy of *in vitro* disease modeling for drug development.

Uncovering the roles of novel small proteins in the development of insulin-producing beta cells

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Diabetes is becoming an increasingly prevalent global health issue characterized by inadequate levels of insulin production and/or response. beta cells are responsible for secreting insulin in the pancreas in order to maintain proper metabolism of glucose. Cell replacement therapy offers promising treatment opportunities for diabetics provided that we can make beta cells *in vitro* from stem cells. However, current directed differentiation protocols do not fully recapitulate the function of mature beta cells *in vivo*. We seek to improve the directed differentiation of stem cells into insulin-producing cells by uncovering the roles of small open reading frames in beta cell specification and function. Because this RNA space has not been thoroughly characterized, a better understanding of its biological significance may lead to the discovery of novel small RNAs—in particular, ones that encode peptides secreted by insulin expressing cells. We have further characterized two human embryonic stem cells lines that either express GFP constitutively or only in insulin-producing cells. By isolating small RNAs (<500bp) from the endoplasmic reticulum via sub-cellular fractionation, we specifically enrich for small secreted proteins. In later stages of the study, we will use RNAseq analysis to compare the transcription levels of small coding RNAs in insulin expressing and non-expressing cells. Differentially expressed and highly abundant small RNAs will be tested in gain-of-function screens. The combined use of these cellular and molecular tools will help us identify novel small proteins—and potentially, novel hormones—involved in key functional processes or developmental transitions of beta cells. Proper application of these biomolecules can take us a step closer to a cure for diabetes.

SHARP

Syncretism and Symbolism in The Princess and the Frog

Ali Zimmerman
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Folklore and Mythology
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Maria Tatar
Harvard University

Folklorists have long been interested in the origins of things. As people migrate, decades pass, and walls crumble, cultures change, and the resulting syncretism proves a veritable treasure trove of traditions and tales. Disney’s *The Princess and the Frog* is a masterpiece of syncretism, drawing from European, American, African American, and Caribbean cultures to create a creolized tale set in the diverse city of New Orleans. In order to successfully combine disparate cultural elements into a cohesive narrative, Disney distills the folklore and folktales from which it draws into salient symbols that convey information efficiently, appeal to emotions, and play with viewers’ previous assumptions. The syncretism of *The Princess and the Frog*, Disney’s first full-length animated film to feature an African American princess, parallels the amalgamation of traditions that can be found in contemporary African American culture. Meanwhile the reliance on symbols eliminates nuance, creating a reductive narrative that resists interpretation. The story ultimately encourages viewers to fill in the story’s gaps with their own experiences, offering ‘something for everyone’ via a reliance on syncretism and symbolism.

Theory in Practice: The Emerging Field of Publicly Engaged Humanities Scholarship

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WGS
Class of 2017

Doris Sommer
Harvard University

In efforts to remain relevant and effective, many humanities scholars and programs across the country have committed themselves and their institutions to the pursuit of public scholarship initiatives. These initiatives serve to bring the humanities of the academy into dialogue with humanists and non-humanists of the public sphere. We sought to identify trends in publicly engaged scholarship and programming and “hotspots” of public engagement. These trends are represented in a profiling project that analyzes about a dozen public scholarship programs. The “hotspots” are represented in a mapping project that physically and thematically locates hundreds of public arts and

humanities projects (university and otherwise). Both of these projects assess the current state of the public humanities. Using these assessments, we can infer the general direction of humanistic public scholarship and ascertain how Cultural Agents Initiative (the organization founded by Professor Sommer, which promotes the arts and humanities as impetuses for social change) can contribute to and alter the arc of public scholarship.

Our profiling initiative, primarily conducted through interviews with center directors at the institutions, highlights the challenge of maintaining academic rigor in publicly engaged work. Most programs reflect a desire to expand the accepted forms of scholarship in the academy to encompass public work as well as traditional publication. It is also of increasing importance for programs to prepare their students to engage their humanistic training outside of the academy, resulting in mutually beneficial community partnerships. The culmination of the mapping project is a dynamic, online map interface which will consolidate university and non-university programs under the headings “Centers, Institutes, and Degree Programs”; “Municipalities and Communities”; “Private Associations”; and “Publications.” Moving forward, the Cultural Agents Initiative looks to develop the notion of rigorous, engaged scholarship through partnerships and collaborations formed during our discussions with leading scholars in the field.

Crossing the Analog-Digital Divide

Brianna MacGregor
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English
Class of 2016

Professor Jeffrey Schnapp
metaLAB

With the recent rise of science and technology as new frontiers of learning, the role of the humanities in our everyday lives has been placed under increasing scrutiny. At metaLAB, a self-described “research and teaching unit,” we strive to explore networked culture in relation to projects dealing with the arts and humanities. metaLAB is currently working on a variety of projects at the intersection of technology and the humanities, and constantly exploring how the two interact.

At metaLAB, I have worked on a variety of projects and become acquainted with several high-tech pieces of equipment. For our summer workshop entitled “Beautiful Data,” in which we invited participants to examine the new challenges that the modern era brings to museum collections, I explored the possibilities and limitations of a 3D scanner and gave demonstrations on my findings in relation to the analog-digital divide, a line that many museums are exploring and pushing in their collections today. I found that the, though technology can be a useful tool

for education purposes, there are aspects of an object that cannot be captured in digital form – such as its feel – that provide an essential part of a person’s interaction with that object.

For metaLAB’s interactive documentary on the Harvard Depository, I did archival research and sifted through records dating from the depository’s opening in 1986. I went through photographs, correspondences, blueprints, and other archival records to help paint the picture of the milieu in which the Harvard Depository built, and around which its purpose was envisioned. I also helped think about how to present this information in a visually engaging way in digital format, encapsulating my summer spent combining classical humanistic thinking with new ideas about networking and technology.

African American Folktales

Rebecca Panovka
Quincy House

English
Class of 2016

Maria Tatar
Harvard University

Compiling Norton’s new anthology of African American folktales, Professor Maria Tatar aims to expand the existing folkloric canon to afford African American tales the recognition they have long been denied. I worked with Professor Tatar to survey and select slavery tales, original African tales, and tales collected by Zora Neale Hurston. After reading hundreds of tales and recommending several for inclusion, I researched a few favorites and wrote introductions and annotations to accompany them. In addition to working on select tales that may be included in Professor Tatar’s volume, I conducted independent research into the history of African American folktales and particularly their appearance in literary works. I located and interpreted the use of folktales in African American novels and discovered that their seeming innocuousness belies a history of politically charged debate. From their earliest inclusion in written literature, African American folktales have been recruited (by coercion or design) to promote causes as wide-ranging as nostalgia for slavery and plantation life, white social liberation, cultural assimilation, segregation, and an organic African American literary tradition. In a volume of folktales, it might be too easy for a reader to come away with an appreciation for the inventive, funny, and often beautiful stories—but entirely ignorant of their complex history. My work seeks to contextualize the folktales so that readers can experience them with a full understanding of their contested background.

The Semitic Museum at Harvard special exhibition: “From the Nile to the Euphrates: David Gordon Lyon and the Creation of the Harvard Semitic Museum”

Ozdemir Vayisoglu
Eliot House

Economics
Class of 2016

Peter Der Manuelian
The Semitic Museum

Founded in 1889 by Prof. David Gordon Lyon, the Semitic Museum now houses a rich collection of over 40,000 ancient artifacts that is dedicated to the study of Near Eastern archaeology, history, and culture at Harvard. Just like the artifacts in its collections, the museum itself has a rich and curious history. This summer I have had the pleasure of working with Prof. Peter Der Manuelian and Dr. Joseph Greene, who serve as the museum’s current director and deputy director respectively. I helped their curatorial team with the preparation of a special exhibition highlighting the museum’s history and its founding director, Prof. David Gordon Lyon. This exhibition, which is scheduled to open in December 2014 on the second floor gallery, aims to tell the story of the Semitic Museum through Prof. Lyon’s early acquisitions for the museum as well as some of the photographs that he took during his exploratory travels in the Middle East. As a SHARP intern, my primary task was to conduct archival research about these objects and photographs. While working in the archives, I traced the history of the Semitic Museum through primary sources, such as object registration cards, Harvard’s annual reports, the museum’s correspondence with antiquities dealers and benefactors, excavation reports, and most importantly, Prof. Lyon’s sixty-five years of daily diary entries. Over the summer, in addition to conducting background research for the exhibition, I have also helped our architectural consultant with the preparation of the layout of the gallery installation. Next steps will include writing the gallery labels, and eventually positioning the objects and visual materials in their assigned cases.

Staging the Civil War

Rachel Gibian English and Comparative Religion
Eliot House *Class of 2015*

Prof. Timothy Patrick McCarthy
Harvard University

In early 2015, the American Repertory Theater (ART) will premiere four plays commissioned as part of the National Civil War Project, a multi-year collaboration between four universities and five performing arts organizations from across the country to commemorate the 150th

anniversary of the American Civil War. By bringing together academic research and the arts, this project aims to explore how ostensibly disparate areas of inquiry can inform each other, and bring new interpretations of history to light. This summer, I worked with Professor Timothy Patrick McCarthy on a new spring course focusing on these plays: “Staging the Civil War”. The primary objective of this course is to analyze each work’s unique way of telling history through the interpretive lens of theatre. In particular, this course places significant emphasis on the importance of archival research in the playwright’s craft. “Staging the Civil War” connects research and interpretation to adaptation and creation, by moving from historical documents to performance. I helped design the class by devising assignments, and by working to develop a coherent and engaging structure for the course. As for assigned readings, my main task was to identify the most salient archival holdings in the Houghton and Schlesinger collections at Harvard. I also assisted Prof. McCarthy in the conception and writing of “Four Harriets”—one of the plays commissioned by the ART. By researching the connection between the play’s protagonists in their time as well as organizing informal readings of the work, I was able to observe how significant research can be in informing the creative process, and in building the world of a play.

Maps and Meaning

Rachel Cheong History of Art and Architecture
Adams House *Class of 2016*

Jessica Martinez
Harvard Art Museums

What’s out there and how we can understand and navigate through it? This summer, I’ve been working with the staff of the Harvard Art Museums on a project about mapping, and the different ways that people have tried (and are still trying) to answer this question. We carry maps in our smartphones, see them come alive on the news, and know that we live in a world ordered and structured by their precise and definite logic. Maps surround us in our every day life and we allow ourselves to take their efficacy and accuracy for granted. We assume that the world is as maps show it to be. And yet, as philosopher Alfred Korzybski noted, the map is not the territory. Inevitably, certain aspects of reality are repressed, distorted, compressed, and re-arranged through the process of map-making. Subjectivity churns hotly just beneath the flat surface of the cartographer’s creation. Map-making is layered with serious political, artistic, informational, and philosophical implications. This summer, under the guidance of DAPP head Jessica Martinez, I did research on the use and creation of maps throughout history, both in the traditional sense and also more broadly, thinking about the nature of semiotics

as a whole. I benefitted from the expertise and guidance of a diverse array of specialists at the Harvard Art Museum, who in addition to putting their knowledge at my disposal, also provided art supplies, well-considered advice, and the occasional peach pie. The products of my research include over 25 maps, inspired by what I learned over the summer.

What musical careers can tell us about migration

Samantha Heinle
Pforzheimer House

Music and Literature
Class of 2016

Professor Kay Kaufman Shelemay
Harvard University

Since the 1960's, there has been a wave of emigration from the African Horn to locations throughout the world. Compelled by natural disasters, political conflicts, or the desire for greater educational or economic opportunity, a large population from the African Horn has migrated elsewhere, creating a large and widespread diaspora. Included among this population of emigrants were many musicians of varying ethnic groups, including Ethiopians, Oromos, Eritreans, and Somalis. This project seeks to construct an overview of the lives and musical careers of these musicians living in the diaspora by compiling data from oral histories gathered by Professor Shelemay. We also observed how these musicians use social media, such as Facebook, Twitter, Instagram, YouTube, webpages, and Listservs, to portray and publicize themselves and their music, as well as their use of social media as an important tool for communication with those who remain in the homeland. The data collected during this project will be used as material for two books about musicians from the African Horn living in the diaspora. In examining these musicians' lives and musical careers, we hope to better understand their experiences of migration, both shared and individual, and to see what their musical careers can inform us about the migration process.

Indigenous Navigation

William Looney
Quincy House

History
Class of 2015

John Huth
Harvard College

In conjunction with Professor John Huth and the Harvard Museums of Science and Culture, I have spent the summer exploring the various strategies people used to find their way without modern technological advances. Such strategies include using the wind, waves and stars

to navigate across land and sea. My research has been geared toward the opening of a museum exhibit on indigenous navigation at Harvard's Collection of Historical Scientific Instruments in the Science Center. Professor Huth has given me themes he plans on incorporating into the exhibition and it is then up to me to conduct background research on that topic. My research provides him with information that can be used in write-ups to accompany each artifact and can help further educate the staff that will ultimately work in the exhibition when it opens in March 2015. In conducting my research I have engaged with a number of texts (some that are centuries old), spoken with some of the most highly regarded Anthropologists studying this field, and studied many artifacts including a fifteenth century wind compass and two Marshallese stick charts found in the Peabody Museum. Aside from the background research, I have also spent considerable time working out various multi-media outlets that can be used in the exhibit, including a wave tank applet. My work coupled with the extensive work of Professor Huth and the other museum curators will culminate with the opening of a museum exhibit that will inform its guests of various navigation techniques in an interesting and interactive manner.

A Network of Cultural Agents: Mapping The Public Humanities

Jesse Adam Shulman
Mather House

Social Studies
Class of 2016

Prof. Doris Sommer
Cultural Agents Initiative, Harvard

A burgeoning field of the academy, the public humanities, also called "engaged scholarship", develops ties between arts and humanities and the surrounding world and local communities. Professor Sommer has led the drive for public humanities at Harvard, and directly through her own program, Pre-Texts, which engages children to generate enthusiasm for learning and literature through workshops on classic texts. However, as a new field of the Academy, many of the public humanities institutes and programs had little access to information of who else was at work in the same arena at other institutions. No accurate map of public humanities programs existed, or analytic profiles of other public humanities initiatives so that a common understandings of "public" and "humanities" could be reached among the diversity of the various programs. Working together with my research partner, Josh Stallings, Dr. Lisa Crossman, and Professor Doris Sommer, we created a map of the diverse public humanities centers and programs at nearly one hundred academic institutions around the country, as well as their sources of funding, partner cities, and publications. In

the process of conducting in-depth profiles on twelve particularly noteworthy programs, we also began productive one-on-one conversations with directors at those institutions from Brown, Iowa, and UT Austin to Yale, creating a network of leaders of this new field in the academy which had previously lacked communication and worked independently. While challenges of maintaining academic rigor while engaging in public programs remain, partnerships between academic institutions and local organizations showed benefits to both parties. Moving forward, the Cultural Agents Initiative looks to develop the notion of rigorous, engaged scholarship through partnerships and collaborations formed during our discussions with leading scholars in the field, and create several new programs across institutions as well as at Harvard. With these maps and profiles, as well as other research, Cultural Agents Initiative, founded by Professor Sommer, which promotes the arts and humanities as catalysts for social change, continues to learn about the current state of the publicly engaged arts and humanities and the opportunities for development and collaboration it provides.

Harvard Reconstruction Unit

Katherine Skipper
Quincy House

Romance Lang. & Lit.
Class of 2015

Mary Clare Altenhofen
Harvard Fine Arts Library

In marking the 100-year anniversary of the beginning of WWI, we are reminded of the devastating aftermath that followed this conflict. The countries involved suffered great losses of life, livelihood, urban fabric, and cultural property. The “Destruction and Recovery” project specifically focuses on the war’s impact on France and the United States’ response. In the wake of the war, Americans recognized the great need abroad and began to organize relief efforts. Among responses by organizations across the nation, student groups in particular showed admirable initiative and compassion. In 1920, a group of Harvard undergraduates expressed a desire to aid in the reconstruction of France. The team, known as the Harvard Reconstruction Unit, was composed of students and recent alumni of the College and the Graduate School of Landscape Architecture. They joined members of other colleges to form an effective alliance that would greatly impact the country of France during the summers of 1920 and 1921. Three locations in particular were the focus of the Harvard Reconstruction Unit: Reims, Clermont-en-Argonne, and Somme-py. The extent of the reconstruction varied among these areas. For example, in Somme-py the team completely redesigned the water and sewage systems for the town. Meanwhile, in Reims the main project of the

team was to restore the damaged cathedral, which served as a symbol of strength to the French people. Rebuilding did much more than restore architecture; it was instrumental in reviving hope that had been lost in the war. Harvard’s primary source collections offer a wealth of information on the events following the war and Harvard’s role in the reconstruction. By gaining a better understanding of the significance of the actions of the Reconstruction Unit, we might come to acknowledge our potential to impact the world even as current college students. The “Destruction and Recovery” project will culminate with the presentation of findings by means of an online exhibit.

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