

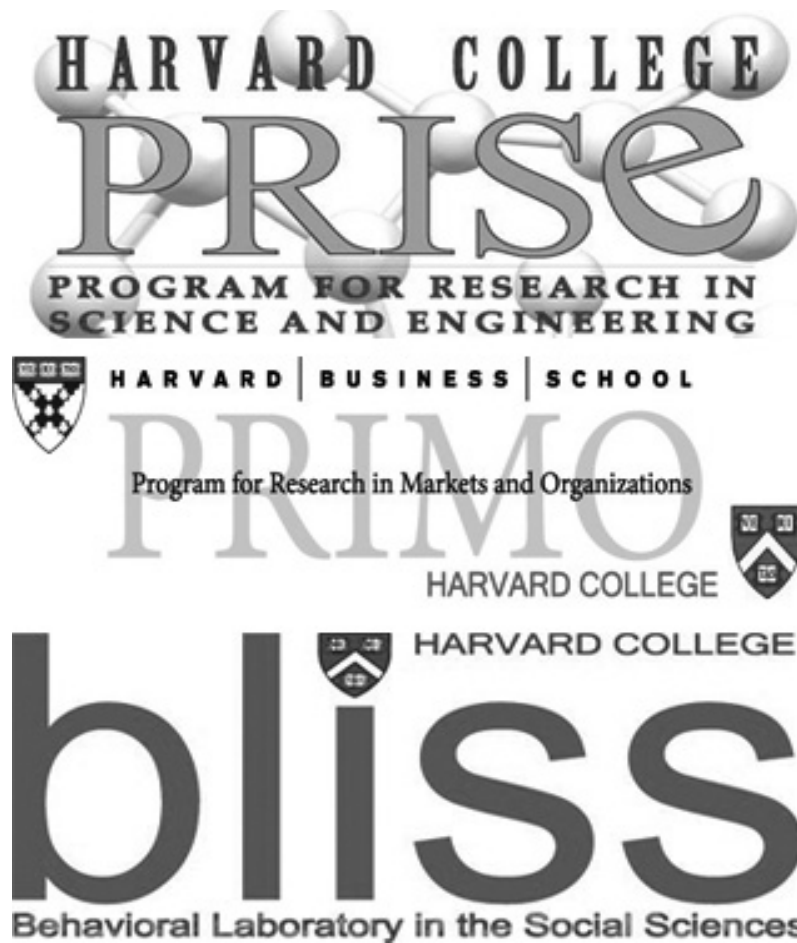
## 2012

# BLISS . PRIMO . PRISE



A word cloud graphic with the word "data" as the central, largest element. Other words include "APP", "without", "normal", "made", "time", "low", "functional", "very", "database", and "point". The words are arranged in a circular pattern around "data".





# ABSTRACTS

## 2 0 1 2

[prise.fas.harvard.edu](http://prise.fas.harvard.edu)

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## Letter from the Director

With great pleasure I write to introduce this outstanding collection of research abstracts from the 180 Harvard College undergraduates participating in the 2012 Summer Undergraduate Research Village. 2012 is the seventh year of the Program for Research in Science and Engineering (PRISE) and the second of the Behavioral Laboratory in the Social Sciences (BLISS) and the Program for Research in Markets and Organizations (PRIMO), which is co-sponsored by the Harvard Business School. By all accounts, this has been a banner summer: the largest community to date, the widest range of academic disciplines ever covered in the summer across the schools and research enterprises of the University, the most robust and creative schedule of activities, and a roster of incredibly talented, enthusiastic, and engaged fellows.

Having established a lively and energetic residential environment at Winthrop House, the Summer Undergraduate Research Village experience once again is further testimony to the compelling value of developing community and fostering student-faculty interaction, both intellectually and socially, through research. I would be remiss if on this page I didn't thank the all-star students and recent graduates who made up our staff of program assistant fellows and residential proctors, as well as Jennifer Shephard and Marais Young, my BLISS and PRIMO colleagues, and of course, staff assistant Jamie Romine. In addition, I would like to thank the group of PRISE, BLISS, and PRIMO fellows who designed, edited, and published this historical record, as well as the fellows who organized our fellow-initiated activities throughout the summer. The Summer of 2012 has been deeply collaborative and inclusive, as well as inspiring, productive, and fun.

It has been nothing short of a terrific summer, which passed far too quickly. To each of you PRISE, BLISS, and PRIMO fellows, I wish the best of success going forward, and hope that the relationships you built over these ten weeks last long into the future.

Yours truly,

Gregory A. Llacer  
Director, *Harvard College Office for Undergraduate Research Initiatives*  
Director, *Harvard College Program for Research in Science and Engineering*

## Letter from the Editors

Dear PBP Fellows,

What was once the PRISE, BLISS, and PRIMO communities is now simply the PBP community. Despite being three distinct programs, we set off together as one, diving into the intriguing questions of our respective fields. We shared in the excitement that makes research worthwhile, but also in the frustration we feel when things don't go according to plan- times spent toiling over programs that did not run or long experiments that did not yield useful data. Despite the ups and downs of our individual research, the support of the PBP community was consistent and strong. For every eureka and disappointment, there was someone in the PBP community who could share in the joy or frustration.

While our weekdays were spent in labs scattered across Cambridge and Boston, we had the wonderful opportunity to get to know one another through our weekend escapades and evening gatherings. We bonded over spectacular adventures and new experiences - from getting drenched in the rain during our Six Flags trip to scaling White Mountain in New Hampshire to learning how to salsa dance. Though the summer has come to an end, the friendships we have made this summer will carry on.

The abstract book you hold in your hands reflects that diverse yet cohesive community we built this summer. Between the covers of this book lies the culmination of our determination and hard work, bound together by our common curiosity and compulsion to always ask, "Why?". We hope that you will enjoy delving into the many projects showcased here and come to appreciate both the work put into each one and the diversity among them.

Sincerely,

Olive Tang '15, Jen Guidera '15, and Salena Cui '15  
*Editors-in-Chief*

*The PRISE 2012 Abstract Book Editorial Staff:*  
Caleb Cañas '14 • Melissa Chan '15 • Jennifer Cloutier '13  
Kuo-Kai Chin '15 • Francisco Galdos '15 • Margaret Ho '15  
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Fox Morone '14 • Radhika Rastogi '15 • Katrina Williamson '15



# BLISS

Meg Barrow  
Dunster 2013

## The role of executive function in the emergence of theory of mind

Professor Susan Carey,  
Psychology,  
Harvard College

Many of our social interactions every day rely on the ability to put yourself in someone else's shoes and understand that other people have beliefs, desires, and goals that may not be the same as your own and may or may not be in accordance with the true state of affairs. This understanding is known as a theory of mind, and it includes the understanding of others' preferences, desires, thoughts, and beliefs. While explicit reasoning about one aspect of theory of mind, namely false belief understanding, doesn't usually develop until around the age of four, three-year-olds can learn this concept through a two-week training. Additionally, executive function, which includes skills such as working memory and inhibition, develops throughout the preschool years. Studies with both adults and 5-year-olds have shown that it is resource that can be depleted: if you do a task that requires a lot of executive function (for 5-year-olds, waiting for a 5 minutes before being allowed to open a box of toys), performance on a subsequent task requiring executive function (such as an "opposite game" where you must counter-intuitively name shapes) gets significantly worse. Correlational studies have provided evidence for a connection between theory of mind understanding and executive function development, and this study aims to investigate the role executive function plays in the emergence of the ability to understand others' minds. Based on the evidence that theory of mind can be taught and executive function can be depleted, we will deplete executive function before teaching theory of mind to see if the training is still successful. We hypothesize that 3-year-olds who have had executive function depleted will not successfully learn the concept of false belief understanding during training. This summer we have been trying to find a method to deplete executive function in three-year-olds, which has previously been done with five-year-olds and adults.

Salena Cui  
Mather 2015

## Legal ambiguity and dual process reasoning

Professors Mahzarin Banaji and Yuval Feldman,  
Psychology,  
Harvard College

Laws can be written with different levels of specificity, with some being very rigid and others offering room for interpretation. Legal ambiguity and legal specificity both have advantages and disadvantages in terms of promoting ethical behavior. One line of research suggests that when laws are vague, people will interpret them in such a way as to maximize self-interest. Existing literature also suggests

*Psychology*

that when given more time to consider their options, people are able to override initial selfish impulses and act more ethically.

The aim of our research is to determine the optimal specificity of the law. In particular, this project examined how people interpret vague instructions and if the aggressiveness of their interpretation would change under different conditions. In our study, participants were instructed to answer a series of 20 math questions and were allowed to choose how many easy and hard questions to answer. Most participants were given an incentive (money, assurance of competence) to answer more easy questions, but were instructed to answer a "reasonable mixture" of easy and hard questions. We were interested in seeing how participants, under this conflict of interest, would interpret the word "reasonable", and if the interpretation would change under different conditions. The conditions manipulated include time constraints, ego-depletion, wording of the instructions, accountability, incentives, and the criteria for obtaining bonuses.

We were also interested in seeing how other aspects of the participants' performance (such as amount of time spent per question and accuracy rate in answering questions) would change under different conditions, and whether different patterns of performance could be found for different personality types.

Medha Gargeya  
Adams 2014

*Government*

## The politics of genomics

Professor Jennifer Hochschild,  
Government,  
Harvard College

This summer, I have been lucky to work on a multitude of projects related to genomics and politics, under the supervision of Professor Jennifer Hochschild. We have focused on public opinion pertaining to genomics research, working with data from a Genomics: Knowledge, Attitudes, and Politics (GKAP) survey conducted in May 2011. The GKAP includes a series of questions to gauge willingness towards genetic testing in the medical and legal realms, and respondents' explanations for their level of willingness. We found that in both contexts, roughly 60% of respondents were willing to undergo genetic testing. Some of the more interesting open-ended responses included, "We all should be equally be screened as humans not a race" and "Knowledge is power." We also examined the interest in genomics study with optimism toward technology. For the project on probing whether technology appears beneficial or harmful, we wanted to learn whether people with a vested interest in genomics research, who have a certain genetically inherited disease or are affiliated with those who do, had a distinct view from those who do not. To study this question, we had to take a step back to learn which diseases people found to be genetically inherited or which individuals thought to be acquired through life events using an online MTurk survey. We found some results contradictory to our hypothesis, such as our respondents narrowly choosing cancer to be mainly acquired through life events and heart disease a product of genes. We also studied the effects of race on genomics research.



Véronique Irwin  
Mather 2013

*Sociology*

### **SECURE research team**

Professor Stephanie Jones,  
Prevention Science and Practice,  
Harvard Graduate School of Education

SECURE (Social, Emotional, and Cognitive Understanding and Regulation in education) is a social-emotional learning intervention, which was piloted in three elementary schools this past year for children from kindergarten to third grade. The goal of the program is to teach students the non-academic skills necessary to become more productive and conscientious members of their peer groups, schools, and communities. SECURE focuses on the development of cognitive regulation and executive function through the implementation of school-wide signals and routines, weekly lessons, and “Brain Games,” which put these tools into practice in a way that engages children. The primary cognitive skills targeted by SECURE are the ability to focus, exercise self-control, be flexible, and access and manipulate information through working memory. The importance of empathy and emotional expression and regulation is also addressed, in addition to other social skills.

Data were collected as part of a randomized pilot evaluation of SECURE in which schools were matched and randomly assigned to implement the program (3 schools) or to a control condition (3 schools). The data collected include student assessments and teacher reports (about themselves and their students), as well as information about implementation of the program itself. Analysis of the data is now underway to determine preliminary outcomes of SECURE. Readyng the data for analysis has been a major component of my work this summer and consisted of tasks which ranged from marking student assessments to preparing a codebook describing the range of data collected. Next steps include a national-scale trial and extending the curriculum to encompass pre-K and grades four and five.

Jillian Jordan  
Lowell 2013

*Psychology*

### **The development of third party punishment of cooperative norm violations**

Professor Felix Warneken,  
Psychology,  
Harvard University

In many human societies, there exist strong social norms prescribing costly cooperative behavior. Empirical evidence demonstrates that third party adults frequently pay costs to punish norm violators, and such third-party punishment is thought to be an important mechanism for promoting cooperation. However, the development of third-party punishment remains poorly understood. The present study seeks to fill this gap by studying costly and non-costly third-

party punishment in five and six-year-old children. In this study, children make decisions to accept or reject equal or unequal distributions of candy between two absent peer children: an actor and a recipient. Children are told that the actor proposed the distributions. Thus, selfish unequal distributions constitute a violation of the norm to share resources fairly, and rejection of these distributions is punishment because it imposes a cost on the actor. By illustrating the developmental timeline of costly and non-costly third-party punishment, this study will contribute to our understanding of these behaviors as important pieces of the puzzle of human prosociality.

Cote Laramie  
Pforzheimer 2014

*Psychology*

### **Preventative health technologies experiment**

Professor Gunther Fink,  
Global Health and Population,  
Harvard School of Public Health

The possibility of improved global health has driven many organizations to spread the word about preventative health technologies. These technologies are things like bed nets, public bathrooms, and contraceptives. While people may adopt these technologies over the short term, they frequently do not adopt them over the long term. This problem persists despite adequate education on the technologies. Perhaps there is something else going on besides lack of information. One factor in this problem might be the stochastic or random nature of a person's health outcome. People fall sick despite preventative measures. When this happens the real effectiveness of the technology comes into question. If one trusts personal experience after negative health outcomes, then one might stop using the technology. One might also spread the word about one's negative experience and advise others to stop using the technology. This hypothesis (the spreading of negative information) and the former hypothesis (stochastic health outcome) were tested in the experiment I worked on this summer. We used a game in which subjects had the option of investing or not investing in a cheap preventative health technology each period with 15 periods in a game. The technology would reduce the chances of getting sick that period. At the end of a game the subjects rated the effectiveness of the technology in preventing sickness. The subjects played three rounds of the game with the effectiveness of the technology varying in each. In the third game the subjects could pay to send messages to the other three members of their group. In line with the first hypothesis, we expected that subjects would rate the effectiveness of the technology based upon their own stochastic health outcome. In line with the second hypothesis, we expected that subjects would spread the word about their negative health outcomes influencing others in their group to not invest in the health technology. We are still analyzing the results.

Brendan Maione-Downing  
Kirkland 2013

*History*

### **Geospatial analysis of patterns of third-century coin deposition**

Professor Michael McCormick,  
History,  
Center for Geographic Analysis

The introduction of GIS (Geographic Information Systems) into the fields of archaeology and history in recent years has given historians new quantitative tools to ask fundamental questions about the human past. Particularly in the field of numismatics, the ability to efficiently and flexibly analyze large data sets over space and time provides the opportunity to ask spatially motivated questions of historical material culture. I focused my work on a comprehensive database of 1776 third-century coin hoards found in the territory of Roman Gaul with terminus post quem deposition dates ranging from 180-300. I used ESRI ArcMap to perform a spatial frequency and clustering analysis using absolute and quantile frequencies as well as local z-scores obtained using the Getis-Ord  $G_i^*$  statistic. Statistically significant results at the  $\alpha = 0.05$  level suggest that we can observe (1) the occurrence of clustering in regional patterns of coin deposition in third-century Gaul and that (2) these areas of clustering are spatially differentiated over time. Further work will focus on developing historical arguments to explain these observed patterns and searching for correlates in other spatially documented historical phenomena, as well as expanding this study of coin deposition in temporal and spatial dimensions. The methodology developed in this project has implications both for numismatists and for scholars seeking to understand the economic history of the Roman period.

Anja Nilsson  
Currier 2015

*Social Studies*

### **Understanding the roots of policy and political change**

Assistant Professor Stephen Kosack,  
Ash Center for Democratic Governance and Innovation,  
Harvard Kennedy School

In an effort to facilitate the study and understanding of mass movements aimed at achieving policy and political change, Professor Stephen Kosack's team is developing the first comprehensive database of mass movements. Previously the study of political mass movements has been mostly through case studies, which has made it difficult to test hypotheses and understand the origins and workings of these movements. With recent mass movements such as Occupy and the Arab Spring making headlines, it is important that we understand how these movements originate, organize and affect political institutions and political change.

When finalized, the database will only include mass movements

that involve over 1,000 individuals committing 'costly action' over a sustained amount of time in the past two centuries. One of the most important parts of the research is determining whether a movement requires coding as some movements only last for a couple of days or involve a couple of hundred people, no matter how significant the outcome. 'Costly action' is determined by the context as voting is not costly in the United States but elsewhere voting could land you in jail.

This summer I was on the team of coders working on Brazil. Each week we independently code movements and then have a meeting to discuss discrepancies within the coding. The key variables usually up for discussion are the starting and ending date of the movement, funding, the organizational structure, primary tactics employed and whether preferences flowed from the periphery to the center or whether the movement was more "top-down" in nature. Lastly, we examine how the government responds to the movement and its demands and record any policy and institutional change.

Radhika Rastogi  
Adams 2015

*History of Science*

### **Aspects of social cognition**

Professor Jason Mitchell,  
Psychology,  
Harvard College

I have been involved with projects researching aspects of mentalizing, or thinking about others' thoughts and emotions, at the Social Cognitive and Affective Neuroscience Lab. Using behavioral paradigms with fMRI techniques, we hope to identify neural architecture associated with these thought processes.

The first project investigates how mentalizing ability changes as people age. We asked participants older than 65 to evaluate individuals on personality traits based on their behavior, determine emotions through a face-morph animation, and rate people on characteristics based on just their photos. In keeping with prior research, we hypothesized that elderly participants would be more likely to internalize positive information and emotions and thus rate the individuals more positively than younger participants would. This effect, called the positivity bias, is part of the socioemotional theory that proposes that as people age, the motivations behind their interactions with others shifts from knowledge-seeking to taking pleasure in their company.

A second project researched the role of others' perceptions on self-conception. While there have been studies concluding that society contributes to the formation of self-image, the role of close others on self-image has not been elucidated. First, we had participants rate themselves on personality traits. Afterwards, we showed the participants others' ratings and asked them to re-rate themselves while in the MRI machine. To control for others' ratings, we substituted in computer-generated variations of the participants' original ratings. We hypothesized that upon presentation of others' perceptions, participants would change their own ratings in the direction of the other ratings. We can then use fMRI data to determine which brain regions might be responsible for participants' changes in their ratings of themselves.

Zachary Sogolow  
Kirkland 2015

*Psychology*

### **Cultural influences on the development of fairness**

Professor Felix Warneken,  
Developmental Psychology,  
Harvard University

Research has shown that, as early as age four, children develop such a sense of fairness— or perhaps more aptly put, a sense of inequity aversion— that they are willing to give up a free reward and get nothing rather than allow someone else to get more than them. Yet, by age eight, children in the United States seem to develop a more social view of fairness which leads them to frequently reject distributions of rewards that would actually give them more than another child, which can be considered advantageous inequity aversion. Our lab has been examining various factors that affect the development of a sense of fairness in children at these different ages.

I have been assisting with the part of the study examining how cultural influences effect the development of fairness. We have children between ages 4 and 15 make decisions about accepting equal and unequal distributions of both a high value treat and a low value treat, such as Skittle candy and peanuts. This difference in the reward offered is to examine whether the value of a reward will effect inequity aversion, or if the social norms of fairness in a culture will dictate behavior regardless of value. While my work has been done in parks in Boston, the study is also in the process of being run in Uganda, Senegal, and Mexico, and our goal is to see if any social trends, such as Uganda's reputation as an egalitarian culture, might affect the development of fairness in children raised in these cultures. Such findings could be valuable for the fields of developmental psychology, evolutionary biology, and other social sciences as well.

Aleksandra Topczewska  
Winthrop 2015

*Government*

### **Racial Threat and Perceptions of Immigration**

Professors Ryan D. Enos and Dustin Tingley,  
Government,  
Harvard Faculty of Arts and Sciences

This summer I worked with Professor Ryan D. Enos in the Government Department on a project about racial threat and perceptions of immigration. Specifically, we wanted to see whether repeatedly exposing people living in predominantly racially White neighborhoods to phenotypically Hispanic people would affect their views on immigration policy and immigrants. The study was conducted as a field experiment. Native Spanish speakers were hired as confederates to travel along the MBTA Commuter Line along the same route for 10 consecutive workdays. They were instructed to wait at certain stations to catch the train, thus making it seem like they had moved into the neighborhood. Commuters were surveyed using an online interface before and after exposure to determine their attitudes toward minorities, their political views, and their opinions on immigration. A link to the survey was distributed half a week before

treatment began. Commuters who responded to the initial survey received a follow-up survey after exposure, allowing us to calculate a change score and reduce external variation. We hypothesized that exposure to the native Spanish speakers would shift commuters' views in a conservative direction.

Linda Zhang  
Winthrop 2015

*History of Science*

### **Chinese transnational diaspora**

Professor Nicole Newendorp,  
Social Studies,  
Harvard College

This summer, I've been learning how to do field research via participant observation, a methodology that involves immersing oneself in the interviewee's everyday life to transcend from the position of interviewer into witness. This method enables us to understand more about the lives of Chinese senior migrants who have immigrated to the US after retirement. Participant observation, as the name suggests, means joining in all the activities the seniors at the community centers we visit engage in. This has ranged from waltzing across a dance floor to doing tai-chi, and of course chatting with them about their day-to-day lives. After a day's worth of fieldwork research, I return to a quiet space and relive all the interactions yet again so I can construct a detailed narrative that captures all that we've seen and learned so far. In anthropologist-speak, this is known as taking ethnographic field notes.

Ultimately, we hope to gain a richer and more contextualized understanding of the unique and intricate threads that weave into the larger portrait of Chinese senior immigrants. Why did they choose to settle here? What drew them to America, and what are the challenges that stand in their way of adaptation? How do they feel about raising and nurturing a grandchild in a Western environment? What are they doing to enrich their own lives in a foreign world, and what can we learn from them? Our research endeavors to shed light on a long-overlooked cohort of immigrants who are changing the demographics of America's aging population.

# PRIMO

Jamie John Ashton  
Adams 2014

*Social Studies*

## Decision making and behavioral economics

Professor Francesca Gino, Michael Norton, and Leslie John,  
Marketing,  
Harvard Business School

By cultivating creativity amongst its individual members, the GiNorton Lab strives to unlock intricacies of mind through imaginative studies of human psychology. Dissonances in intuition, clandestine erosions of morality, the subconscious licentiousness of us all—each of these topics, along with hosts more, has recently engrossed the GiNorton Lab in its fundamental mission to employ psychological rigor to the study of human decision-making. Through a meticulous—and occasionally iconoclastic—debunking of classical economics’ homo economicus, the behavioral research performed at the GiNorton Lab ushers in an exciting and profound new era of economics in which humans no longer appear as merely utility-maximizing agents of rationality but rather as impossibly complex and unpredictable actors in a commensurately muddled world. The implications of this work are, of course, profound and far-reaching. Freed from their traditional shackles and the burdensome etiology of classical economic myth, humans acquire an intoxicatingly intriguing nature, the understanding of which is as important as it is daunting. Indeed, though signaling but a beginning in this turning tide economic thought, the research performed by the GiNorton Lab nonetheless holds the power to explicate foundational mysteries of human behavior, organization and choice.

Charlotte Chang  
Adams 2014

*Psychology and Economics*

## Innovation for sustainability in the built environment: Understanding smart cities

Professors Bob Eccles and Amy Edmondson,  
Innovation, Organizational Behavior,  
Harvard Business School

As urbanization intensifies around the globe, sustainable urban growth has risen to be an increasingly important issue. Sustainable urban growth refers to the city’s potential for continuous growth in economic, environmental, social, and governance dimensions. Based on this premise, the first part of my research project focuses on understanding the key metrics by which one can measure a city’s sustainability performance. Through surveying an array of sustainable reports on global cities, I extrapolate a framework for an integrated reporting scheme that city planners can reference and adopt. The second part of my research project focuses on innovation - specifically, how to maximize collaboration and minimize conflict when professionals from various disciplines join efforts on an innovative project. To answer this question, I use qualitative research methods to analyze publication materials targeted specifically at profession-

als within each industry (e.g., architecture, IT, and government). Through understanding the priorities and challenges people within each profession face, researchers can subsequently develop insights for how to facilitate interdisciplinary collaborations in the future.

Irene Chen  
Cabot 2014

*Applied Math*

## Racial and gender bias in online markets

Professor Benjamin Edelman,  
Negotiations, Organizations & Markets,  
Harvard Business School

Online rental marketplaces such as Airbnb.com connect guests seeking short-term accommodations with hosts renting spare rooms or entire properties. These services offer widely-publicized benefits including convenience, efficiency, and cost-savings; however, the services also present some downsides. For one, there are serious trust problems on both sides of the market: some properties aren’t as described, and some guests have even robbed and vandalized hosts’ property. In response, Airbnb established verifications, site visits by paid staff, and photos of both guests and hosts. While photos add accountability, they can create further problems: some users discriminate based on sensitive characteristics including gender and race. To explore the scope of this problem, we categorize images of hosts and guests (employing low-cost image sorters found via Amazon Mechanical Turk). We then harness publicly-posted reviews in search of patterns in who books where. We expect to be able to measure the amount of bias that is occurring, identify where it is most pronounced, and identify the extent to which system features such as reputations and reviews help to attenuate discrimination.

Tom Dan  
Leverett 2013

*Economics*

## Innovation in media

Professor Bharat Anand,  
Strategy,  
Harvard Business School

Newspapers, magazines, and other forms of media are facing considerable challenges as they confront numerous threats to their existing business models. These threats are diverse and include changes in technology, the development of new mediums, and changes in the preferences of readers and advertisers. While discouraging for some publications, others are seizing these developments to create innovative publications with sustainable business models. Over the summer I’ve gotten the chance to explore the changes faced by media organizations and how some organizations are transforming these threats into opportunities. Most of my work was dedicated to helping draft a chapter in my Professor’s book that analyzes and



examines economic models, empirical research and case studies of media bias and media slant. Overall this project has been an incredible experience that taught me not only about the news market, but more broadly about various research methodologies in business and economics. I am certain that these tools will prove priceless as I continue onward with my academic studies.

Zachary Fogelson  
*Dunster 2015*

*Computer Science*

### **Competition in global wireless telecommunications: Industrial organization, management & development topics in wireless technology, from start to saturation**

Professors Juan Alcacer and Susan Perkins,  
Strategy,  
Harvard Business School, Sloan School of Management

As the global economy expands and private participation increases in global markets, firms will continually be faced with the challenge of learning how to adapt to idiosyncratic institutional environments that differ from their home country's institutional norms. The laws, regulatory environments, cultures and governmental structures have differing implications for firms' ability to organize, generate profits, sustain a competitive advantage and compete with their industry peers. The global wireless telecommunication team's agenda addresses the imperatives of understanding these factors of globalization. The data our team has collected captures most of the economic movement in mobile telephony on the planet. With our expansive, unprecedented, global dataset we hope to explore a broad range of research questions related to how markets evolve, how firms compete and how firms respond strategically to the institutional environment. This summer I have spent time analyzing countrywide telecommunications infrastructure and multinational telecommunication companies. Additionally, I have leveraged my programming skills to help automate data collection. Finally, through econometric modeling our team is building an understanding of important firm wide factors which determine growth in the telecom industry.

Glynis Healey  
*Cabot 2015*

*Statistics*

### **Research in family businesses**

Professor John Davis,  
Entrepreneurial Management,  
Harvard Business School

This summer, my research focused primarily on the unique nature of family businesses and the factors that lead to their success. The project looked at the growth (or decline) of wealth over generations, and will attempt to find patterns among the most successful fam-

ily businesses as well as those that experienced serious declines in wealth.

Before the summer, family businesses in the United States had already been examined, so I focused primarily on international family enterprises. For data, I used the Forbes Billionaires list, which has been published since 1987. The database now includes every billionaire appearing on the list for ten years between 1987 and 2011, their net worth, and their generation. We are just now beginning to analyze the data to discover whether or not there is a difference in wealth growth between generations, as well as possible differences between different regions of the world. We are also looking at the effect of regional economic events on the growth of wealth in those regions and, finally, examining in particular those families that managed to survive from 1987 to 2011. As some of the most successful international families, we are looking at both the data and at the stories of these families to determine if a clear pattern emerges.

K.C. Jaski

*Adams 2013*

*History of Science*

### **How star women succeed**

Professor Boris Groysberg,  
Organizational Behavior,  
Harvard Business School

In the twenty first century, whether women can "have it all" and achieve success in high profile positions continues to pervade public consciousness. Anne Marie Slaughter's article "Why Women Still Can't Have It All" published in the July/August 2012 Atlantic went viral, breaking readership records for the Atlantic's web site. While women have actively sought leadership positions such as corporate board positions, women only held 15.7 percent of Fortune 500 corporate board seats in 2010, a figure that has increased only 1.1 percent in the past five years (Catalyst.org). In addition, a study that revealed differences in how "star" men and women navigate their careers designed by Professor Boris Groysberg incited a new project that aims to more closely examine how star women succeed.

The How Star Women Succeed project includes interviews from more than 250 women globally. Compiling and updating a database of these individuals from corporate, nonprofit, NGO, and government sectors, tracking their career shifts, education, marital statuses, number of children, positions on corporate boards, and recognition by Forbes and Fortune, provide quantitative data to profile this population and their career trajectories. In addition, analysis of qualitative data obtained from interview transcripts will further reveal insights into these women's leadership styles, approaches to organizational management, "work life balance," and the contextual factors that contributed to their success.

This research has broad implications of illuminating infrastructures that build and retain women's talent. It can also help inform women's and men's future career decisions and will contribute to existing theories of human capital, allocation of talent, labor market competition, and human research management studies.

Sandesh Kataria  
Winthrop 2014

*Applied Mathematics*

### **Humanitarian supply chain mapping for time sensitive materials**

Professor Douglas Fearing,  
Technology and Operations Management,  
Harvard Business School

This summer I worked on a project to model the delivery of humanitarian goods via air cargo to a region affected by a natural disaster. I worked with Ozlem Ergun, a visiting faculty member in SEAS and Douglas Fearing, Assistant Professor at Harvard Business School on developing this model. Our goal was to create a model such that when a natural disaster strikes, corporations, governments, and NGOs would be able to assess the demand for humanitarian goods in the affected area, and determine how much would need to be delivered to the affected area by air. To support this effort, I did a substantial amount of research focusing specifically on Haiti, mainly because it had the best available data, and mapped out the humanitarian supply chain for time-sensitive materials - shelter kits, perishable goods, vaccines, and medical supplies to prevent a disease outbreak. The result of this project will be a mathematical model describing the demand for humanitarian goods over time, which should allow air-freight service providers to allocate their resources more efficiently.

Kristiana Laugen  
Currier 2013

*Psychology*

### **Consumer review websites**

Professor Michael Luca,  
Negotiation, Organizations and Markets,  
Harvard Business School

Technological advances over the past decade have led to the proliferation of consumer review ranging from Yelp.com to movie review websites such as Rotten Tomatoes where consumers can share experiences about product quality. With the click of a button, we can now acquire information from countless other consumers about products ranging from restaurants to movies to physicians. My research this summer investigates the way consumers use this information, how this information varies depending on the type of reviewer, how this affects markets, and the motivations that drive people to leave reviews.

Janet J. Lu  
Winthrop 2014

*Applied Mathematics – Economics*

### **The Basel Capital Accords and banks' asset distributions**

Professors Victoria Ivashina and Bo Becker,  
Finance,  
Harvard Business School

The Basel Committee on Banking Supervision, an international group based in the Bank for International Settlements, published the first Basel Capital Accords in 1988 to standardize minimum capital requirements for banks across countries. Since then, the committee has issued numerous versions of the accords, each building on the last: Basel I, Basel 1.5, Basel II, Basel 2.5, and Basel III. We are primarily interested in Basel 1.5 and II. Before the publication of Basel II, a complete revision, the Basel Committee made numerous amendments to Basel I, the combination of which is referred to as Basel 1.5. These changes include the refinement of weight categories, inclusion of market risk, and possibility of using internal models to calculate risk rather than the committee's standardized approach. Basel II includes three pillars, providing guidelines for capital requirements, supervision, and disclosure. For the first pillar, banks must factor credit risk, market risk, and operational risk into the calculation of their capital requirements. For the second and third pillars, regulators and banks must follow standard procedures for enforcing the first pillar and providing information to the market. Since Basel I did not account for market risk, banks may have decreased the credit risk of their investments while increasing their market risk; a parallel may be drawn with Basel 1.5 and operational risk. We are interested in analyzing the effects of the Basel Capital Accords on banks' asset distributions, as well as the differences between countries, particularly between the United States and Europe.

Mary Reed  
Currier 2014

*Social Studies*

### **Competition in global industries: Multinationals and the development of international strategy**

Professor David Collis,  
Strategy,  
Harvard Business School

As the volume and scope of business activity across borders has increased over the past several decades, examining and developing an effective international strategy has become a key concern for many of the world's largest companies. Given the wide and often unpredictable range of differences that exist among countries and regions along economic, cultural, political, and geographic lines (to name a few), the development of theoretical frameworks and case-based methods of analysis to determine where and how a company can succeed has emerged as a principal area of research in the field of strategic management. Detailed investigations of critical issues such as what product a company should offer, where they should locate



key activities, where they should compete, and how they should structure their organization as a whole—examined through the lens of today’s dynamic business environment and the experience of industry leaders like Coca Cola, Unilever, General Motors, General Electric, Cemex, Proctor and Gamble, and more—will form the backbone of an upcoming text summarizing the bases of strategic decision-making in the international sphere as well as insights into the conditions under which certain generic strategies prove most effective. By employing an approach grounded in both grounded quantitative data analysis and a more holistic evaluation of company circumstances, the text and the ongoing research supporting it aim to provide a clear guide for both executive practitioners and students of strategy hoping to navigate the murky waters of multinational expansion and operation.

Patrick Rooney  
Lowell 2014

Economics

### **Valuation and the Foxconn-Sharp Deal**

Professor Mihir Desai,  
Finance,  
Harvard Business School

By introducing the fundamentals of corporation and equity valuation, my principal investigator and I were able to develop a case study that analyzes the implications of the set of acquisitions between the Asian technology companies Sharp and Foxconn that occurred in March 2012. Over the past decade, Foxconn has become one of the world’s largest destinations for outsourced labor and the largest original manufacturer partner of the California-based Apple Inc. The process of assigning correct value to the deals is not purely scientific; rather it is one that involves threading various facets together to present a well-founded prediction of the companies’ prospective joint success. Attributes found to hold special importance in this case include the release of future product lines, research and development strengths and weaknesses, and worker health and safety. The case is expected to be used in MBA pedagogy at the Harvard Business School in the coming years and be disseminated to other schools and programs in the near future.

Gabriel Rosen  
Cabot 2015

### **Venture capital**

Professors Paul Gompers and Yuhai Xuan,  
Business Administration,  
Harvard Business School

Autism is a neurological disorder characterized both by impaired coOver the summer I have been researching under professors Paul Gompers and Yuhai Xuan at the Harvard Business School. Initially, our project was finalizing a paper entitled The Cost of Friendship that explores the consequences of similarity biases among Venture Capitalists when they syndicate in their funding of portfolio companies. Affinity based on education, race and employment history were shown not only to be significant but to have adverse affects on the outcome of the companies. Beyond simply showing the damage of affinity, our research showed that the majority of the harm came not from inferior selection of companies but from less skilled management of the companies in the periods after funding. After we succeeded in cleaning up various aspects of the data for the paper, our next task was to discover new uses for the tremendous amount of data we had collected for the previous project. The second project we worked on was exploring the creation and consequences of Forbes Midas list, which ranks the top 100 venture capitalists every year. In addition to recreating the approximate formula used by Forbes in creating the list, we are trying to discern the concrete affects that being on the list has on the deal offers and success rates of the individuals. Some of the things we intend to study about these “All-Star” venture capitalists are the quality of the deals they are offered, their affect on their peers, and the transferability of their success when they switch firms.

Hee Kwon Seo  
Currier 2013

Applied Mathematics

### **Two development projects on informational frictions and transmissions in India**

Professor Shawn Cole,  
Finance,  
Harvard Business School

1. Preliminary results from analyzing a field experiment that provides low-cost, mobile-phone-based agricultural advice to farmers in Gujarat, India show the service has important impacts in affecting farmers’ sources of information and farming practices. Treated farmers are more likely to use appropriate pesticides and invest in new crops. Work also involves analyzing the social networks of these farmers, to understand how external information is transmitted throughout these community. 2. Many Indians choose life insurance policies that appear attractive, but are much more expensive than simpler alternatives. This study tests for behavioral biases that drive these decisions, and develops interventions designed to debias consumers. The interventions are tested via online experiments and in cooperation with several leading Indian employers.

Alastair Su  
Mather 2014

History

Joseph Richard Zorn III  
Lowell 2014

Economics

### The etiology of fraud

Professor Eugene Soltes,  
Accounting and Management,  
Harvard Business School

This summer I analyzed fraud and its related causes. While popular accounts tend to ascribe fraudulent behavior to “greed” or the moral failure of individuals, research suggests a much more complicated picture where variegated motivations and organizational culture are prominent factors. In addition to surveying theories of fraud in popular and academic literature, my research focused on high-profile cases of fraud committed in the last decade or so, such as Enron, Tyco International and Computer Associates.

James Sun  
Leverett 2014

Economics

### Identifying high-value hospitals

Professor Anita Tucker,  
Technology and Operations Management,  
Harvard Business School

The U.S. health care system is in crisis. Costs are high and unsustainable: at 18% of GDP, U.S. health care spending is higher than that of any other country and is predicted to reach almost 20% of GDP by 2020. Yet quality is surprisingly average: the U.S. ranks 27th in the OECD in life expectancy and 31st in infant mortality. If the system is to be rescued from crisis, increasing value in health care delivery—outcomes achieved per dollar spent—must become the central goal of all stakeholders. Indeed it is the only goal in which all stakeholders, including providers, payers, and most importantly, patients, benefit. The process of increasing value requires the rigorous identification of high-value hospitals so that best value-enhancing practices can be learned and shared throughout the system.

Much has been written on high-value hospitals, but the literature lacks a robust methodology for their identification. The IOM recently released a discussion paper entitled, “A CEO Checklist for High-Value Health Care.” Similar to previous work, the checklist describes in detail the cost-saving, outcome-improving methods used by organizations like Mayo Clinic, Intermountain Healthcare, and Cleveland Clinic. But these organizations, while famous for delivering high-quality care, do not necessarily deliver high-value care. We contend that many other U.S. hospitals and health care systems should be considered exemplary models of high-value care, although no empirical work exists to support this notion. Using data from the AHA annual survey, the Hospital Compare database, and the MedPAR database, we seek to identify high-value hospitals by measuring value delivery at over 3,000 U.S. hospitals, taking into account care quality, patient satisfaction, and cost.

### Changing behavior: Cheating, voting, feedback, and Shirley Temples

Professors Francesca Gino, Michael Norton, and Leslie John,  
Decision Making and Behavioral Economics,  
Harvard Business School

Working under Harvard Business School Professors Francesca Gino, Michael Norton and Leslie John, I have spent this summer contributing to research in the fields of decision-making and behavioral economics. Early on, I helped design an experiment to determine how giving advice affects the morality of the advice giver by having subjects give either ethical advice, general advice, or no advice and then giving the subjects an opportunity to cheat on a mathematical matrix task, hypothesizing that those in the ethical condition would be less likely to cheat than others. In a different, voting experiment, I looked at whether voting on something, even something small or inconsequential, makes someone more likely to label oneself a voter and more likely to vote on more important issues in the future. Later, I assisted in a collaborative experiment with Professor Michael Norton from HBS and Professor Todd Rogers from the Harvard Kennedy School of Government by providing positive and negative feedback to high school parents about their child’s performance in summer school to determine what type of feedback best increased student performance. Finally, I helped Professor Ryan Buell from HBS with an experiment that explored how organizational service affects consumer preferences by manipulating whether or not subjects could see researchers make a Shirley Temple (those who could not see it made only hoped it was a Shirley Temple) before being asked to drink it and indicate how well they liked it.

# CHEMISTRY AND BIOCHEMISTRY

Jolie Berg  
Adams 2014

*Chemistry*

## Characterizing the albicidin biosynthetic pathway

Chemistry  
Balskus Lab  
Chemistry and Chemical Biology,  
Harvard University

The small molecule albicidin is produced by the sugarcane pathogen *Xanthomonas albilineans*. Although initially discovered as the cause of the devastating disease leaf scald in sugarcane, albicidin was subsequently shown to possess potent bactericidal activity through inhibition of prokaryotic DNA gyrase by a mechanism distinct from known gyrase inhibitors (i.e. quinolones and aminocoumarins). Despite the promise albicidin holds as an antibiotic, a lack of structural knowledge has impeded its development into a pharmaceutical. In addition to producing a compound with intriguing biological activity, the genes involved in albicidin synthesis potentially encode for enzymes with unusual activities, e.g. a non-ribosomal peptide synthase (NRPS) that may utilize aryl amino acids as extender units and a second NRPS enzyme that may catalyze the dehydration of an asparagine amide into a nitrile. In this project, we aim to study the enzymes from the albicidin biosynthetic pathway by heterologous expression in *E. coli*, purification via affinity chromatography, and characterization using a variety of biochemical techniques. Using these methods, we hope not only to characterize enzymes that catalyze novel enzymatic transformations but also to aid in the structural elucidation of the albicidin molecule as a potential new anti-bacterial compound.

Matthew Condakes  
Winthrop 2014

*Chemistry*

## Developing novel chiral silicon protecting groups

Myers Lab  
Chemistry,  
Harvard College

In organic synthesis, it is crucial to be able to control when and how different functional groups in a molecule react. Oftentimes, it is necessary to keep certain functional groups from undergoing undesired reactions by attaching protecting groups to them. These protecting groups are small molecules and, when used for alcohols, commonly silicon-based. Once the danger of an unwanted reaction passes, the protecting group can then be removed, returning the original functionality unchanged. Ideally, it would be possible to selectively protect any functional group in a molecule; however, if a molecule is densely functionalized, such a task can be quite formidable.

In particular, prochiral 1,3-diols prove intractable to selective mono-protection, as the two hydroxyl groups are chemically identi-

cal. To address this challenge, we have been investigating chiral silicon protecting groups. These groups give rise to selective protection via a two-step process. First, a single protecting group is applied to both hydroxyl groups, forming a cyclic siloxane. Then, owing to the chirality of the protecting group, it is possible to singularly deprotect the molecule selectively, leaving the desired mono-protected alcohol in great diastereomeric excess. It is our hope that this method will see applications in total synthesis, allowing for the straightforward attainment of previously elusive compounds.

Katherine Ebright  
Cabot 2015

*Undeclared*

## Effects of polycomb group proteins on chromatin structure

Zhuang Lab  
Chemistry and Chemical Biology,  
Harvard University

Transcriptional silencing is crucial to the development and maintenance of different cell types, tissues, and organs. Polycomb group (PcG) proteins modulate chromatin structure to mediate transcriptional silencing in multicellular organisms. Previous research shows that PcG proteins function by trimethylating histone H3 on lysine 27 (H3K27). However, previous research does not explain how trimethylated H3K27 (H3K27me3) interacts with PcG proteins to achieve transcriptional silencing. The objectives of this work were to determine whether H3K27me3 PcG protein interactions reconfigure local chromatin and to determine the structure of silenced chromatin. The approach used in this work was to image histones at specific gene loci in *D. melanogaster* embryos. Gene loci, including sites in the Antennapedia complex and sites in the Bithorax complex, were tagged with biotin- and digoxigenin-labeled probes through fluorescence in situ hybridization. Antibodies labeled with Atto 488, Alexa Fluor 568, DyeLight 750, and Alexa Fluor 647 photoswitchable dyes were used to tag biotin, digoxigenin, all histones, and H3K27me3, respectively. Stochastic Optical Reconstruction Microscopy (STORM) was used to achieve super-high resolution three-dimensional images of chromatin in nuclei of interest (~30nm resolution in the lateral direction; ~60nm resolution in the axial direction). Acquired images were used to determine whether H3K27me3 is a sufficient causal factor for transcriptional silencing, to identify when instances of H3K27me3 first arise, and to analyze the effects of H3K27me3 on local chromatin structure. The findings of this research have the potential to further the fields of epigenetics, stem cell biology, and cancer biology.

Richard Ebright  
Cabot 2014

*Chemical and Physical Biology*

### A novel target for beta-catenin cancers

Schreiber Lab  
Chemistry and Chemical Biology,  
Broad Institute of MIT and Harvard

Small molecules have all-but-eliminated a handful of cancers, most notably the successful treatment of CML by the small molecule imatinib. Thus far, all such often-successful (as opposed to chemotherapy), cancer-treating drugs have targeted the oncoprotein, the mutated protein responsible for driving tumor formation. However, it has proven difficult to specifically target oncoproteins, and effective anti-cancer drug development has been limited.

Instead of targeting the oncoprotein itself, it may be possible to identify and target other, non-mutant proteins upon which the cancerous cell relies for survival. As such, the Cancer Target Discovery and Development team of the Schreiber lab seeks to identify and characterize non-oncogene co-dependencies – wildtype proteins upon which an oncoprotein depends to survive and proliferate.

We have identified connections between the oncoprotein  $\beta$ -catenin and the anti-apoptotic protein Bcl-xL.  $\beta$ -catenin is a transcription factor that signals for cell proliferation, and mutations in  $\beta$ -catenin preventing its degradation are known to cause intestinal cancers. Bcl-xL is a previously unconnected protein that inhibits apoptosis (programmed cell suicide). We found that in cancers driven by mutations in  $\beta$ -catenin, there often is up-regulation of Bcl-xL, protecting the cell from apoptosis.

This reliance on Bcl-xL indicates it as a novel drug target in  $\beta$ -catenin cancers. Indeed, we found that  $\beta$ -catenin cancers show increased sensitivity to Bcl-xL inhibitors. In addition to serving as a basis for drug tests of Bcl-xL inhibitors in  $\beta$ -catenin-driven cancers, these data indicate that it may be possible to alter the sensitivity of non- $\beta$ -catenin cancers by increasing  $\beta$ -catenin levels, forcing reliance on Bcl-xL.

A thorough understanding of the relationship between  $\beta$ -catenin and Bcl-xL will allow research and drug development that may be able to effectively treat  $\beta$ -catenin cancers.

Tara Jain  
Eliot 2015

*Chemical and Physical Biology*

### Improving the geometry of interaction-dependent PCR: A rapid method of discovering ligand-target pairs

Liu Lab  
Chemistry and Chemical Biology,  
Harvard College

The identification of ligand-target pairs is currently achieved using high throughput screening, by testing the activity of one small molecule at a time on one disease-associated protein. The understanding of the interaction of small molecule modulators with these proteins has proven to be useful in studying various diseases. Interaction-Dependent PCR (IDPCR) is a novel, faster

method of drug discovery in which an entire library of compounds can be tested concurrently with multiple protein targets. Each small molecule and target protein in the library is linked to tagged DNA, so that ligand-protein binding brings the DNA into close proximity and results in the annealing of complementary regions on the two DNA tags. DNA polymerase will extend the annealed region, forming a longer product corresponding to the activity of the small molecule on the target protein. The tagged region on the DNA allows us to identify the specific ligand-target pairs for potential pharmacological use. We are continuing to improve IDPCR by studying the effect of the geometry of the DNA-protein conjugate on the facilitation of the annealing of complementary regions. To do so, we created eight carbonic anhydrase II (CAII) mutants, on which we could attach the DNA tag to the protein at variable site-specific distances from the active site. By performing IDPCR with four small molecules biotin, desthiobiotin, carboxybenzenesulfonamide (CBS), and gly-leu-CBS (GLCBS), two negative and positive controls with each CAII mutant, we can determine the optimal DNA tag position for IDPCR.

Won Ryan Lee  
Winthrop 2015

*Undecided*

### A novel platform for the selective chemical labeling of cellular RNAs

David R. Liu Lab  
Chemistry and Chemical Biology,  
Harvard College

The discovery of ribozymes and a rapidly growing number of non-coding RNAs, both appearing to perform diverse cellular functions, has catalyzed much investigation into RNA structure and function. However, platforms and tools for studying RNAs and their function are lacking in comparison to other biomolecules. This project works towards the development and application of a novel method for the selective chemical labeling of a specific RNA of interest, in order to establish a platform for both *in vitro* and *in vivo* study of RNA. We utilize a nucleophilic ribozyme sequence, attached to the 3' end of the RNA of interest, which binds to an epoxide probe specific for the ribozyme. Attaching a desired chemical tag or functional group to the epoxide then covalently links the RNA of interest to this tag. We investigated optimal methods of cloning and expression of the epoxide-labeling ribozyme sequence using 5S rRNA as a model RNA of interest. Moreover, a multiribozyme sequence was synthesized through oligomerization by T4 ligation of ribozyme 'monomers', which resulted in a statistical distribution of various length multiribozyme oligomers, and a comparison of labeling efficiency between expression of the single ribozyme and multiribozyme was conducted. We are exploring live-cell experiments on the feasibility of labeling specific RNAs in cells for both functional and real-time imaging purposes, through the cationic transfection of the 5S rRNA and ribozyme on a single mammalian plasmid. In doing so, we hope to construct a general and versatile platform through which the fluorescent imaging, selection, and other biochemical studies on cellular RNAs can be easily conducted.



Alison Liou  
Kirkland 2014

*Organismic and Evolutionary Biology*

### Testing different activated RNA monomers in template-directed nonenzymatic RNA replication

Szostak Lab  
Molecular Biology and Center for Computational & Integrative Biology,  
Massachusetts General Hospital

The RNA world hypothesis claims that a RNA-dominated world preceded our current world of DNA, RNA, and proteins. Support for the hypothesis is founded on the discovery of RNA-based enzymes called ribozymes. An important example is the ribosome, which not only demonstrates that RNA has catalytic ability, but also indicates that RNA must have come before protein enzymes. RNA would have been able to catalyze reactions necessary for life, carry genetic information in its base sequences to be passed down to subsequent generations, and eventually provide the blueprint for translation. RNA could have, alone, performed the tasks that DNA, RNA, and proteins carry out together.

There are several models of early RNA replication, most of which are centered around ribozyme-catalyzed mechanisms. My work, however, explores an earlier model based on template-directed nonenzymatic RNA replication. In order for RNA to replicate based on this model, a continuous supply of activated nucleotide monomers is necessary for the energetically favorable polymerization of a complementary strand of RNA onto a template strand. Activation of nucleotide monomers is achieved by attaching a leaving group to the phosphate of a ribonucleotide monophosphate. Although partial copying of short RNA strands has been achieved with leaving groups such as 2-methylimidazole, the final goal of efficiently and accurately replicating arbitrary RNA template sequences has not yet been attained. 2-methylimidazole, the leaving group that currently works best in nonenzymatic RNA replication, also could not have existed prebiotically. My project involves testing new leaving groups to determine if different activated ribonucleotide monomers allow for more efficient and accurate template-directed nonenzymatic RNA replication.

Richard Liu  
Pforzheimer 2015

*Chemistry and Physics*

### Catalytic C—H activation with high-spin iron complexes

Betley Lab  
Chemistry and Chemical Biology,  
Harvard University

Protein folding, involving the formation of secondary structures and the conversion of unactivated carbon-hydrogen bonds into heteroatom-bearing functional groups is an important area of active study in synthetic chemistry. Potential applications include the conversion of common, cheap hydrocarbons into high-demand feedstock chemicals, and potentially improved efficiency in the synthesis of complex natural products. Biologically, the enzyme Cytochrome

P450 is thought to catalyze such functionalization reactions through intermediates with metal-ligand multiple bonds. Previously, iron(II) dipyrromethene complexes have been shown to be simple, effective synthetic analogues capable of catalytically inserting nitrenes, among other small organic groups, into C—H and C=C bonds at room temperature. In this project, the reaction mechanism of iron-catalyzed amination was probed through kinetic experiments involving substrates of varying electronic inductive effects. Evidence was obtained in support of a radical mechanism involving hydrogen-atom abstraction followed by radical recombination. Subsequently, reactivity was demonstrated among an expanded substrate scope, including strong primary, secondary and allylic C—H bonds in linear and cyclic hydrocarbons. Studies were focused on increasing the yield and optimizing the reaction to avoid destructive intramolecular attack of the catalyst. Finally, we targeted the synthesis of an effective asymmetric catalyst capable of activating C—H bonds with chiral selectivity. These continuing investigations aim to explore and expand the power and synthetic utility of iron-catalyzed activation of organic molecules.

Peggy Walenda Mativo  
Lowell 2013

*Chemistry*

### Carbon nanotubes and electrochemical water filtration

Vecitis Lab  
School of Engineering and Applied Sciences,  
Harvard College

Point-of-use methods of water treatment are increasingly needed to supplement other centralized methods of water processing. Both in developed and developing countries, water quality drops and contamination rises after centralized treatment due to handling or transportation in aging or underdeveloped infrastructure. Carbon nanotubes, because of their desirable electrical and mechanical properties, can offer a potential solution to the water quality degradation that is associated with centralized transportation and handling infrastructure. Carbon nanotube (CNT) mats are porous and have the ability to conduct electricity, so they can participate in water filtration not only as physical barriers, but also as sites of electrochemistry. Electrochemistry serves to transform the pollutants in water via oxidation at room temperature and pressure. Through adding CNT mats in different conformations to filter-casings that were created in the Vecitis lab, we explored the effects of flow rate, applied voltage, concentration and electrolyte differences on the efficacy of this system of combined water filtration and electrochemical treatment. The nature of these effects was characterized using analytical techniques including electrical impedance spectroscopy, chronoamperometry and cyclic voltammetry.

Manuel I. Fox Morone  
Mather 2014

Chemistry

### Unprecedented tridentate ligands for first-row transition metal catalysis

Ritter Lab  
Chemistry and Chemical Biology,  
Harvard College

The overarching goal of our research was to develop a catalytic reaction to produce silafluorene derivatives, which are coveted as electron transporters in field-effect transistors and optical materials such as light emitting diodes (LEDs). While processes to synthesize silafluorenes are known, this class of molecule has not become commonplace in LED electronics because silafluorene synthesis is not cost-effective. Current syntheses involve substrates that are difficult to make and commercially unavailable. Other syntheses employ intramolecular carbon-hydrogen bond functionalization—a direct and simple synthetic pathway—but utilize catalysts containing rhodium or iridium, both of which are rare metals and cause material manufacturers to steer away from their use.

Our research focuses on developing an efficient method to functionalize carbon-hydrogen bonds using common and inexpensive first-row transition metal catalysts. Ligand screens have attracted our interest to rarely used tridentate phosphine-carbene ligands, and the development of these ligands has been my personal research goal for the summer. Conventional methods of developing these ligands fail for this ligand for reasons unknown at this time. Thus, for most of the summer I have been exploring synthetic pathways that involve late phosphination making use of known methods of synthesizing functionalized N-heterocyclic carbenes that can then be subjected to some electrophilic or nucleophilic aryl phosphine reagent.

Brandon K. Sim  
Kirkland 2015

Applied Mathematics – Physics

### Calculation of biologically relevant binding sites and energies of drugs using functionalized ensemble chemical annealing for rational drug design

Dr. Alex Kentsis  
Oncology,  
Dana-Farber Cancer Institute, Boston Children's  
Hospital, Harvard Medical School

A major unsolved problem in chemical biology and drug design is the de novo determination of affinities and sites of drug binding. Ligand docking using scoring empirical functions is computationally efficient, enabling high-throughput virtual screens, but cannot be used to calculate binding free energies. This in turn precludes the analysis of effects of ligand binding on target conformation and functional activity, both of which are necessary for drug design. The use of free energy or pathway perturbation methods can be used to calculate free energies of drug binding but is complicated by limited configurational space sampling and the need to assign starting poses, both of which preclude their general use. In addition, discrimination of biologically relevant binding sites using free energy

perturbation methods is particularly difficult for drugs with relatively low binding affinities, such as lead compounds, which are ostensibly the ones with the greatest need for such studies. To overcome these limitations, we have taken advantage of recently developed generalized ensemble molecular mechanics algorithms to sample the configurational space of drug targets as well as grand canonical Monte Carlo simulations of binding to calculate drug binding sites and free energies. Comparison of ensembles of active and inactive configurations allows for discrimination between sites with different functional activities. Here, we implement and test this approach using the recently described KRAS inhibitor as a model system. The developed methodology is amenable to large-scale simulations of macromolecular drug binding. Accordingly, we have implemented this approach as a set of facile programming scripts, which should be widely useful for lead optimization and de novo design in drug discovery and computational chemistry.

Justin To  
Cabot 2014

Chemistry

### Development of a Palladium-catalyzed C-H fluorination of arenes

Ritter Group  
Chemistry and Chemical Biology,  
Harvard College

The practical formation of carbon-fluorine bonds has remained a longstanding challenge for chemists, and the need to develop new routes to form the C-F bond is compounded by its massive importance in pharmaceuticals and positron emission tomography (PET) tracers. Due to the unique abilities that it confers onto molecules as a result of its high electronegativity, fluorine is found in 20% of all pharmaceuticals, including Lipitor and Prozac.

Until recently, conventional methods for fluorinating arenes (aromatic compounds like benzene which are ubiquitous in pharmaceuticals) require high temperatures and harsh conditions that greatly limit substrate scope. Consequently, fluorine must be introduced early on in the synthesis of a molecule, which may require complete redesigns of synthetic routes. Alternatively, new methods must be developed in order to add fluorine to existing drug structures with “late-stage fluorination” methods, e.g., labeling PET tracers with the fluorine-18 isotope to image in vivo processes, especially in oncology.

Newer metal-catalyzed fluorination reactions for arenes have been developed, but the vast majority requires preexisting groups such as halogens, boronic acids, or stannanes to already be installed. While these methods enable late-stage fluorination, the ability to selectively functionalize carbon-hydrogen bonds (C-H functionalization or activation), which are available in almost all pharmaceuticals, would allow for generation of aryl fluorides easily from existing compounds without additional modifications. A handful of metal-catalyzed C-H fluorinations of arenes exist, but they also require pre-existing directing groups that participate in the reaction. These studies look into the possibility of using and optimizing the reactivity of high-valent palladium complexes (metals that are highly electron deficient or oxidized) to functionalize C-H bonds into C-F bonds without directing groups.



Emily Unger  
Quincy 2013

*Organismic Evolutionary Biology*

### **Non-enzymatic RNA replication and the chemical origins of life**

Szostak Lab  
Molecular Biology,  
Massachusetts General Hospital

The ability to self-replicate is one of the key features of life. Although we have a thorough understanding of how modern cells reproduce, it remains largely mysterious how this ability could have developed in a pre-biotic world. Before life existed on Earth, there were no enzymes, no ribosomes, no mitotic spindle — none of the machinery that allows cells to reproduce. How could self-replicating life have originated in the absence of these tools?

One hypothesis is that the earliest organisms' genetic material was replicated by entirely chemical processes, relying on base-pairing and the slow ligation of short pieces of RNA. My work this summer explores this process of non-enzymatic RNA replication. I have been working on new ways of replicating RNA, such as using nucleotide dimers rather than just single nucleotides and replicating templates without using a matching "primer" strand of RNA to initiate the reaction. In addition, I have been looking at the fidelity of non-enzymatic replication, measuring the frequency with which nucleobases pair incorrectly and cause replication errors.

The goal of these experiments is to gain a greater understanding of the ways in which RNA can be reproduced non-enzymatically, and the rate and accuracy with which this replication can occur. This will let us learn what processes would have been feasible in a pre-biotic world and how an early proto-cell might have functioned. Understanding how a simple chemical system such as this can become self-replicating will help us solve the ultimate chicken-and-egg problem: how life can originate from non-life.

Afoma Umeano  
Currier 2014

*Chemistry*

### **Organic synthesis in the presence of living organisms**

Balskus Lab  
Chemistry and Chemical Biology,  
Harvard College

We sought to perform a series of organic synthesis in the presence of living organisms (in this case *e. coli*). We have termed this kind of chemistry "biocompatible chemistry." Biocompatible chemistry is chemistry that produces non-enzymatic reactions that are capable of chemically modifying small molecules in the presence of living systems. In my case, through each reaction I was creating an essential nutrient needed for mutated strains of *e. coli* to grow.

Lucy Zhong  
Currier 2014

*Chemistry and Physics*

### **Characterization of Endogenous Metabolite-Protein Interactions for the Orphan Nuclear Receptor Nurr1: A Potential Target of Parkinson's Disease**

Saghatelian Lab  
Chemistry and Chemical Biology  
Harvard University

Nuclear receptors (NRs) are a family of well-conserved transcription factors that function to regulate essential physiology and their dysfunction is associated with a variety of disease states. Lipids, vitamins, and hormones can regulate the transcriptional activity of nuclear receptors by binding to the ligand-binding domain (LBD) of these receptors. To date there are many NRs that don't have identified natural (endogenous) ligands; these are referred to as orphan receptors. Our goal is to identify endogenous ligands for certain members of the NR4A orphan nuclear receptor family using an untargeted metabolomics approach and to characterize the effect of ligand binding on receptor activity.

The particular orphan nuclear receptor of interest is Nurr1, a protein widely expressed in energy demanding tissues (such as brain and liver), where it regulates metabolic pathways involved in the development and maintenance of dopaminergic neurons. These neurons are the main source of dopamine in the midbrain; depletion of dopamine is a characteristic of Parkinson's Disease. After recombinantly expressing the Nurr1 LBD, we used an untargeted metabolomics strategy to identify a number of polyunsaturated fatty acids (PUFAs, from mouse brain extracts) as candidate ligands for Nurr1. We then used targeted biochemical screening methods to determine whether these candidate ligands induced a conformational change upon binding to Nurr1. Some of these assays included ANS displacement, circular dichroism (CD), internal tryptophan fluorescence, and a thermal stability shift assay.

We further plan to determine the conformational changes associated with ligand binding by co-crystallization of the Nurr1 LBD and candidate ligands. This research will elucidate previously unknown regulatory pathways and resolve the molecular mechanism of ligand-dependent regulation of the NR4A family.

# COMPUTER SCIENCE

Jao-ke Chin-Lee  
Currier 2015

## Modeling termite construction as a distributed system for use by autonomous robots

Professor Radhika Nagpal  
Self-Organizing Systems Research Group,  
Wyss Institute for Biologically Inspired Engineering

Termites are often associated with destruction, but certain species are extremely constructive, working millions together and building towering mounds over one story in height from the ground and made even more impressive due to their being built without any centralized command. As part of the TERMES project, we seek to discover exactly how these tiny termites raise structures millions of times their size as “autonomous agents,” without hierarchical command and control, and then use this knowledge to develop an analogous system for autonomous robots to raise structures themselves, in a similarly decentralized system. The greatest advantage to such a setup is robustness: without a centralized control, there is no single articulation point, no single point of failure. Instead, there are many individual agents which can be put out of commission with no adverse effect on construction. We quantify this inspiration from termites by developing a model for termite behavior: where and how they move, and under what social and environment conditions. For instance, how do termites react to different types of soil? Are they more or less attracted to wetter soil or soil with which other termites have already built? Do they tend to move towards other groups of termites? By answering these questions we can understand better how to construct autonomous robots that not only build collaboratively, but also build structures that are adapted to the environment. A complete model for termite behavior is extremely complicated, so we focus on aspects of their behavior—regional attraction, velocity with time, etc.—assuming independence, and also make preliminary explorations into their behavior without the assumption of independence—how termites react to each other and to the collective.

Edward Gan  
Dunster 2013

*Computer Science and Mathematics*

## Typeclasses in a language with Affine Types

Professor Greg Morrisett  
Computer Science,  
Harvard SEAS

In many programming languages, “Types” are a tool used to classify the data that a program works with. For example, the type of a function  $f(x)$  might specify that  $f$  takes an integer input and returns an employee record. This project aims to simplify the use of “Affine Types”, which are an extension of standard types to support controlling not just data, but consumable resources.

Data classified by normal types can be reused, but data classified by affine types can only be used once. Clever use of this property

*Applied Math*

of affine types allows programmers to specify policies for resources such as locks or files, and protocols such as for internet sockets.

The difficulty with using affine types is that allowing programmers to use both affine and normal types simultaneously usually greatly complicates the type system. The goal of this research project is thus to better integrate affine and normal types by using the framework of “Typeclasses.” With typeclasses, types by default could be affine, and normal types would just belong to a typeclass defined by an operation that allows a value to be duplicated.

By modifying an existing language with affine types to use typeclasses, and examining the mathematical consequences of mixing typeclasses with affine types, we hope to evaluate the effectiveness of managing affine types in this way.

Victoria Gu

*Applied Math – Computer Science*

Kirkland 2015

## rRNA depletion technique for RNA-seq analysis of tissue samples with partially degraded RNA produces data of comparable quality to the standard microarray assay

Professor John Quakenbush  
Biostatistics and Computational Biology,  
Dana Farber Cancer Institute

The convenience of archiving tissue samples using the Standard Protocol for Formalin-Fixed, Paraffin-Embedded (FFPE) tissue samples comes at the cost of partial degradation of RNA, and new techniques are needed to improve the quality and amount of data that can be extracted from FFPE tissue samples. The standard technology used is the array-based Illumina DASL assay, but RNA-seq, a sequencing-based assay, has many advantages over array-based assays, including greater resolution, sensitivity, and dynamic range for genome expression and association studies. We made adjustments for low input to the Epicentre Ribo-Zero Magnetic Gold protocol in conjunction with the rRNA removal kit and then prepared the cDNA library and sequenced it on the Illumina 1.9 pipeline. Osteosarcoma tumor tissue samples embedded in 2004 and 2008 were run on both techniques, and Spearman correlation analysis of the data showed high correlation between data obtained using our technique and the DASL assay data. On samples run under our technique, SNP (single-nucleotide polymorphism) analysis revealed an average of 1050 nonsynonymous (causing amino acid changes) SNPs per sample. A large number of the statistically significant, quality-score-filtered SNPs detected were validated against published osteosarcoma literature and the public SNP database, dbSNP. SNP-based pathway enrichment analysis on our data showed that there were potentially important nonsynonymous SNPs in pathways related to transcription and transport in cells. Larger studies will be needed to verify this. Our technique is a viable alternative to the DASL assay, offering the benefits of both a one-third cost reduction for RNA-seq analysis of FFPE tissue samples and the greater power RNA-seq technology holds for characterizing transcriptomes.

Abiola Lanionu  
Lowell 2013

*Computer Science and Mathematics*

### **Developing efficient differentially private algorithms for statistical analyses**

Professor Salil Vadhan  
Computer Science,  
Harvard College

Society benefits when individuals aggregate their personal information, like medical records, in datasets which are then analyzed by researchers to gain insights in a population. However, this process may result in harm to an individual who includes personal sensitive information in the dataset if the data is released in raw form. Techniques designed to render data entries anonymous by removing personally identifying attributes prior to the release of the dataset have proven vulnerable to attacks involving auxiliary information that identify particular individuals and reconstruct their entries.

Differential privacy provides a provable guarantee of privacy by mandating that any one individual's decision to participate or not participate in the dataset will have at most a negligible impact on the probability that any possible result occurs. We seek to design a more efficient algorithm to release a differentially private summary of relevant statistics of a dataset. We focus on the problem of releasing  $k$ -way marginals, which describes what percent of the entries in a database have a particular setting of up to  $k$  attributes for all possible groups of  $k$  attributes. We seek to combine techniques from function approximation and other areas to achieve more efficient results for this particular class of statistical queries than have been achieved by algorithms designed to provide differential privacy for arbitrary queries. We also seek to implement efficient differentially private algorithms for logistic regression and other procedures as modules in Zelig, a statistical software package, to allow researchers in the social sciences to perform analyses on real world datasets while simultaneously protecting the privacy of survey participants.

Jenny Liu  
Pforzheimer 2015

*Computer Science with Mind Brain Behavior*

### **Designing culturally adaptive user interfaces**

Professor Krzysztof Gajos  
School of Engineering and Applied Sciences,  
Harvard University  
Ken Nakayama, Edgar Pierce Professor of Psychology  
Department of Psychology,  
Harvard University

The recent proliferation of the Internet is accompanied by a chasm between software designers and their audience, as the majority of software industries are from market-dominating countries such as the United States. Different cultures perceive information in different ways, resulting in differing preferences for user interfaces. To target this issue, this project explores the interface preferences of a diverse sample of cultures through online studies for the purpose of creating culturally adaptive user interfaces.

Past research has shown cultural differences in aesthetic preferences such as color. However, very little has been done to study these preferences with regard to user interfaces. One of the tests developed

in this project asks participants to rate a pool of webpage screenshots on a nine-point scale. Based on the participants' responses and demographics, we will determine which correlations exist between aesthetic preference and cultural background.

Another online study in development is based on emotional categorization, or the phenomenon that people do not view facial expression of emotion on a continuum, but rather with distinct boundaries between emotions. Participants will take a new, interactive test which measures their accuracy and response time. Across cultures, the results of this test could provide insight on cultural differences in sensitivity to emotion. This new knowledge can help web-designers present more suitable facial emotions in pictures.

These findings will promote a greater understanding of cultural interface preferences and encourage more engaging and accessible designs. Culturally adaptive interfaces hold potential to transform the Internet through a new consideration for a global audience.

Max Lu  
Mather 2014

*Undeclared*

### **The ADS All-Sky Survey**

Professor Alyssa Goodman  
Astrophysics,  
Harvard College

The Astrophysics Data System (ADS), an online collection of astrophysics literature, has become a powerful research tool. This project aims to extract data from ADS papers, thereby creating a data repository that consists of an interactive heatmap that visualizes the distribution of objects' references in literature and a historical data-layer that overlays images from literature onto sky maps.

To accomplish this, we extract all images that can be plotted onto the sky. Images are extracted using an algorithm that identifies image data within the paper and trends within its pixel histogram. Those images are then tagged with their corresponding location and time-stamped. An astrometric calibration algorithm uses established indexes of stars to identify the coordinates of the images. Alternatively, optical character recognition algorithms search surrounding text to find images' locations and other metadata. When astrometric calibration and text-mining fail, we will export the image to Zooniverse, a "social-media" approach to citizen science that asks the general public to tag these images.

The All-Sky Survey utilizes powerful methods to discover novel uses for existing literature. The interactive map introduces a faceted visual search that can enable data discovery better than current text-based search engines. Areas of the sky of interest to a specific sub-field of astrophysics may also be well studied in another sub-field. Visualization of the search process allows users to share relevant data between sub-fields. Moreover, the timestamp on each image allows users to track motions of celestial objects and recognize patterns between astrophysical events. By integrating literature and data into a single source, the ADS All-Sky Survey provides a seamless tool that significantly simplifies and optimizes research in astrophysics.

Yiren Lu  
Adams 2013

*Mathematics*

### **Classifying Quora questions using hidden topics from Quora answers**

Professor Stuart Shieber  
Computer Science,  
Harvard College

Q&A sites such as Quora and StackExchange have long relied on crowdsourcing to assign topics to questions and posts, but the potential for redundancy and contentiousness makes this method less than ideal. One solution is automatic text classification. A site feature that suggests a topic to the user after he inputs his question would reduce ambiguity and result in cleaner topic ontologies. However, since questions are usually short and sparse, traditional methods of text classification struggle to attain high accuracy rates. A framework that adds external knowledge to the question text is used in this paper to address the issue. Specifically, we use LDA (Latent Dirichlet Allocation) to uncover hidden topics in Quora answers. These hidden topics are then integrated into the labeled question training and test sets. A classifier is built using the enriched features that maps questions to six predetermined topics: Politics, Music, Movies, Books, Travel, and Science. Various experiments are performed to test the robustness of hidden topics as classification features, and the robustness of Quora Answers as a universal dataset, using the popular learning methods Naive Bayes and SVM. Results show significant improvements in accuracy and the possibility of using drastically fewer features.

Amy Tai  
Leverett 2013

*Computer Science and Mathematics*

### **Playing with an in-memory database**

Professor Eddie Kohler  
Computer Science,  
Harvard SEAS

It is well known that `\emph{data}` is now a key word in many technical circles; because of technological advances, but especially because of the Internet, we are capable of collecting data from pretty much anywhere. There are two main problems with this deluge of data: how to store it and how to interpret it. This project focuses on storing that data, because storage is a necessary precedent to interpretation. In particular, this summer I worked on an in-memory database, which are becoming more popular because memory is becoming much cheaper, and memory is much faster to access than disk. In-memory data structures differ vastly from on-disk data structures, which have been traditionally used as back-ends to databases. Thus not only does this research have practical implications, but it is also a very compelling thought exercise.

This summer I tested and added a robust logging system to the in-memory database we are working on. I first swapped out the on-disk backend for SQLite and replaced it with our database; this exercise was to show that our in-memory database could perform as well as the SQLite database, which is a standard database. Having such a SQLite integration is useful for introducing our database as a standard, high-performing database. I also made the logging system more efficient and robust by adding log truncation and checksumming, two indispensable qualities of any logging and recovery system. We are now interested in model-checking the correctness of the database, which requires more detailed specifications of the behavior of our database.

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# EARTH AND PLANETARY SCIENCES

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Diana Powell

*Physics and Astrophysics*

*Lowell 2014*

## **Planet formation signatures around young stars**

Professor Catherine Espaillat

Astrophysics,

Harvard – Smithsonian Center for Astrophysics

T Tauri stars (TTS) are a type of young variable star. This study of TTS focused on type II stars that still have their protoplanetary disks. Within the type II subclass there are stars with full, pre-transitional, and transitional protoplanetary disks. Pre-transitional and transitional disks have gaps or holes while full disks do not. It is thought that planet formation sweeps out material from the disks, leaving behind these gaps and holes.

Type II TTS have specific signatures that can be analyzed to determine the rate at which mass is being accreted from the surrounding disk onto the star. One signature of an accreting disk is excess emission in the ultraviolet wavelengths due to an accretion shock. The other two signatures are broadened H $\alpha$  spectral features and stronger CaII features due to free-falling gas traveling along the star's magnetospheric field lines. In this study, all three forms of mass accretion rate calculation were utilized to provide the most accurate picture of the sample.

Through the analysis of over 110 TTS in the Chamaeleon I star forming region I have found that stars with pre-transitional and transitional disks have lower accretion rates than stars with full disks. The physical mechanism behind this observation is that planets may be forming or already existing in the transitional and pre-transitional disks and they are thus accreting material from the outer disk and lowering the stellar mass accretion rate.



# ENGINEERING & BIOENGINEERING

Godwin Abiola  
Quincy 2014

*Biomedical Engineering*

## Design of naturally derived hydrogels for growth and regeneration of neuronal cells

Bhatia Lab  
School of Engineering and Applied Sciences,  
Harvard College

Despite the versatility of the brain, the central nervous system lacks the ability to regenerate neurons after severe trauma. This often leads to permanent detrimental problems, such as reduced cognitive or motor functions, and paralysis. The central nervous system's lack of regrowth, particularly in adults, can be attributed to several factors, such as proliferation of astrocytes after injury resulting in scar tissue, lack of growth factors and adhesive substrates to stimulate growth and extension, as well as few neurons present with the capability to divide further. Several biomaterials and therapy techniques have been created to attend to and overcome the short comings of the central nervous system environment, and facilitate the regeneration and replacement of damaged neurons.

The goal of the project is to design a biocompatible, conductive hydrogel that would serve to improve growth and regeneration of neuronal tissue, and possibly extend to application in the regeneration of tissues. The hydrogel will address several of the issues that inhibit growth and regeneration of damaged neurons in the central nervous system. Previous work has shown that mild electrical stimulation can help facilitate neuron growth. For this reason, the hydrogel to be designed will incorporate carbon nanobrushes, tubes made of interconnected carbon molecules that previously been used as conductive wiring in nanodevices. Hydrogel spheres were created from alginate, a sugar derived from algae, are to be suspended within another hydrogel. The dual hydrogel system will not only inhibit astrocyte proliferation, and provide support for growth and regeneration of damaged cells, but also serve as a transport system of stem cells to the site of injury.

Abel Arwaga  
Quincy 2015

*Physics*

## Single photon emitters in nano-diamonds

Hu Group  
School of Engineering and Applied Sciences,  
Harvard College

Diamond is well known for its exceptional physical, thermal and optical properties that manifest in its bulk form. Some of these properties extend down to the nano-scale. Its large band-gap makes it ideal for optical work as there will be minimal reabsorption of light emitted from inside the lattice structure. This in turn means we can externally collect emitted light for study and also for other possible future applications.

Color centers are defects that occur in a lot of crystal structures

that modify the energy diagram of the lattice locally and thus result in distinct optical properties such as fluorescence. These defects can come in the form of vacancies in the lattice, dopants in the lattice (either nodal or irregular), or a combination of the above. Only a few of the 500 or so color centers in nano-diamond are well understood. One possible path the study of color centers may lead to is the discovery of single photon emitters. These are sources of light that can provide a low fluctuation stream of individual photons on demand. Their place in the nano-scale engineering cannot be overemphasized and their practical applications range from bio-marking and random number generation to basic research in the study of quantum systems.

My project focuses on a specific dopant, Europium, and its incorporation into the diamond structure through growth with chemical vapor deposition. We use a unique method of introduction that may be extended to other more interesting color-centers and even single photon emitters. The main goal is to see if we can control the amount and distribution of deposition easily so we can generalize the approach to multiple color centers.

Maria E. Bendana  
Elit 2014

*Engineering Sciences (SB)*

## Development of a haptic user interface for use in micromanipulation

Wood Lab  
School of Engineering and Applied Sciences,  
Harvard University

Human inaccuracy in performing manual micromanipulation tasks may result in damaged tissues or nerves in microsurgery and broken components in the micro-assembly of small structures. Haptic technology can aid humans in performing tasks requiring high accuracy and precision, such as microsurgical procedures and micro-assembly tasks, by providing force feedback and contact location information to the user. While such technologies exist, their high cost and unlikeliness to current micromanipulation tools present barriers to their widespread acceptance. This summer, a haptic interface was developed to control a seven degree of freedom robotic micro-manipulation system. The haptic interface is compatible with the six degree of freedom PHANTOM Omni haptic device from SensAble technologies and includes an added degree of freedom, pinching motion, to control a micro-gripper at the working end of the system. Computer Aided Design software and rapid prototyping methods were used to develop the haptic interface, which is modeled after tweezers currently used in micromanipulation in order to facilitate adaptation to this system. Bend sensors were used to measure the angle change at the interface and to map the angle change to the micro-gripper jaws. Future work for this project includes experimental testing of the micromanipulation system for lab tasks and clinical procedures, as well as adding further functionality to the system such as incorporating an added pinch-roll degree of freedom.



Lukas Bielskis  
Currier 2014

*Engineering Sciences (SB)*

### ***Dexterous micromanipulation project***

Harvard BioRobotics Lab, Robert Howe; Harvard Microrobotics Lab, Robert Wood  
School of Engineering and Applied Sciences,  
Harvard College

Microsurgery and microassembly are two fields where robotic grippers can significantly improve manipulation capabilities by allowing precise and safe handling of objects on a scale much smaller than humans can accommodate manually. Operating on small blood vessels in particular is a challenge for microsurgeons as it requires both small-scale manipulation as well as the ability to accurately modulate the gripping force in order to avoid any damage to biological tissues. As part of the dexterous micromanipulation project in the Harvard BioRobotics and Microrobotics Labs we wish to solve these challenges by enhancing the problematic small scale to a much more comfortable level by creating an accurate remote-controlled microgripper as a substitute for the manually operated forceps.

The main objectives for my project are to use three-dimensional engineering design software and plastic 3D printing technology to create a microgripper that is simple, scalable and cheap and to enable accurate measurement of the gripping force. Once this goal is achieved, we will integrate the designed microgripper with the other components of the dexterous robotic micromanipulation platform currently being designed by researchers in the Harvard BioRobotics and Microrobotics Labs and experimentally validate its functionality.

Brian Boursiquot  
Pforzheimer 2014

*Biomedical Engineering*

### **Synthesis and characterization of peptide based nanoparticles for drug delivery**

Joshi Lab  
School of Engineering and Applied Sciences,  
Wyss Institute for Biologically Inspired Engineering, Harvard University

Nano-scale structures are increasing in popularity as drug carriers because they can prolong the circulation of drugs in blood and sustain their release over longer periods of time. Specifically, structures called carbon nanocapsules have been shown to improve the delivery of a blood-clot busting drug called heparin in mice, and are effective due to their small size and long-term mechanical stability. However, one concern with many carbon nanostructures is that their permanence may result in toxicity when placed in humans. To solve this problem, we aim to develop a safer, biocompatible alternative composed of peptides. By cyclizing 8 specific types of amino acids, we create self-assembling nanotubes in which the peptide rings are stacked on top of one another with a hollow core. As a crucial part of reaching our goal, we explore the relationship between different amino acid sequences and the final assembled structure, as well as the process of assembly. To functionalize our nanotubes, we incorporate specific chemical groups which will allow us to easily attach

other molecules to their surface. We envision that this property will be useful for a variety of purposes, including the creation of safe, versatile, and appropriately sized drug carriers.

Stephen Burke  
Winthrop 2014

*Engineering Sciences*

### **Image processing with a robotic system for the efficient production of a malaria vaccine**

Howe Lab  
School of Engineering and Applied Science,  
Harvard College

Malaria causes roughly one million deaths each year around the world. When a mosquito becomes infected with this disease, the Malaria parasites are carried in the mosquito's salivary glands. Therefore, extracting the glands from an infected mosquito is an effective method for collecting these parasites, which can then be processed and turned into potential vaccines against the disease. While these vaccines are still undergoing trials, the goal of this project is to work on parts of a robotic system to automate the extraction of the glands, so that the vaccines can be made efficiently.

One of the challenges of the project is to take pictures of mosquitoes located on a petri dish with a microscope camera and then use image processing techniques to identify the exact locations of the mosquitoes. This algorithm combines auto thresholding and feature-detection techniques and must work for numerous different orientations of mosquitoes on the dish. The next challenge is to program the movement of a positioning table that can be used to move the petri dish on a path so that the microscope camera can sequentially take images of the entire dish. Once the images are processed and each mosquito's location is known, the table can once again be used to position each mosquito under a tool which can extract the salivary glands. Ideally this automated system will allow for thousands of extractions every day.

Gary Carlson  
Leverett 2013

*Engineering Sciences (SB)*

### **Plantar pressure measurement insole using MEMS barometric sensors**

Harvard Biodesign Lab  
School of Engineering and Applied Sciences,  
Wyss Institute for Biologically Inspired Engineering

Gait measurement systems enable clinicians and researchers to perform better diagnosis and evaluation of patients with neuromuscular disorders. In particular, biomechanical analyses with plantar pressure sensing instruments are very valuable as they quickly help determine areas of high pressure on the plantar surface.

Previous studies suggesting that inflammation leads to the metastasis of melanoma, lead us to believe non-steroidal anti-inflammatory drugs may hold potential in stopping the spread of cancer. For both its potential as an anti-cancer agent as well as its wide availability and inexpensiveness, we focus on the drug commonly known as ibuprofen. Ibuprofen loaded hydrogels additionally may be suitable for the localized treatment of pain and inflammation. By manipulating the weight percentage of pluronic, affecting the viscosity of the resulting gel, or the weight percentage of the ibuprofen loaded inside the gel, we are able to affect the release profile of the ibuprofen, alter both the rapidness of drug release and the percentage of total drug released.

Ruth Choa  
Eliot 2014

*Biomedical Engineering*

### **Chemotaxis and recruitment of mesenchymal stem cells**

Mooney Lab  
School of Engineering and Applied Sciences,  
Harvard College

Adult bone marrow derived mesenchymal stem cells (MSCs) represent an important source of cells for bone tissue regeneration. Identification and characterization of MSC chemoattractants would enable development of methods to recruit these cells to an injury site and aid regeneration. This project aims to identify and characterize potent chemoattractants for MSCs and optimize release systems for these chemokines.

The two potential chemoattractants we study in this project are growth factor Thymus Chemokine 1 (TCK-1) and small molecule AMD 3100. To compare chemokine potencies, a 3D migration assay is used: MSCs are seeded into collagen gels and exposed to different concentration gradients of chemokine. Cell movement is then tracked over a 24-hour time period using timelapse. Chemokine potency is measured via several chemotaxis parameters: velocity in the direction of interest (V), center of mass (Mend), forward migration indice (YFMI), and directionality (D). To confirm the TCK-1 and AMD 3100 pathways in rat MSCs, we stain for the CXCR2 and CXCR4 surface receptors respectively.

Since there is a ten fold difference in size between TCK-1 and AMD 3100, different release systems are used to optimize the release kinetics of these two molecules. We study the release kinetics of TCK-1 in a two-phased hydrogel system composed of oxidized alginate microspheres encapsulated in nondegrading bulk alginate. Once the oxidized microspheres have been degraded through hydrolysis, the gel becomes macroporous. For AMD 3100, we are designing a combination release system of polylactic-co-glycolic acid (PLGA) microspheres encapsulated in a bulk alginate matrix. The results of this research can enable the further development of methods and biomaterials for MSC recruitment.

Jennifer Chen  
Quincy 2015

*Human Developmental  
and Regenerative Biology*

### **Optimizing expression of chimeric antigen receptors (CARs) for immunotherapy**

Silver Lab  
Department of Systems Biology,  
Harvard Medical School

Adoptive T-cell therapy represents an exciting way of enhancing the immune system's ability to pinpoint and destroy cancer cells. T cells play an important role in cell-mediated immunity, from activating other immune cells and signaling pathways to directly destroying malignant cells in the body. Our research focuses on expressing chimeric antigen receptors (CARs) in T cells, enabling them to recognize and subsequently redirect their activity toward tumors that might otherwise elude the existing immune system. Several clinical studies have yielded promising results in treating leukemia and melanoma patients.

The architecture of a CAR has several key components, including a tumor-associated-antigen-binding region, an extracellular hinge, a transmembrane domain, and intracellular signaling elements. Due to the modular nature of CAR structure, we can mix and match these parts to determine the optimal design of constructs for expression and subsequent characterization. Our current array of CARs recognizes several markers for B-cell malignancies, but previous studies indicate that constructs recognizing one marker express better than those recognizing another. We are also interested in identifying new combinations of hinge and transmembrane domains that express well and can be paired with various antigen-binding regions. I am therefore building CAR variants with different components for each of these domains and testing their surface expression levels in immortalized T cell lines. These results will hopefully inform our design of future CARs, especially as we assemble a panel of CARs that can be expressed in combination to enable multiple-antigen recognition in T cells.

Brandon Gerberich  
Cabot 2014

*Engineering Sciences (SB)*

### **Dendritic crystal patterning for tissue scaffold engineering**

Bhatia Lab  
Biomedical Engineering,  
Harvard College

Polymer scaffolds represent the primary platform for cell growth in soft tissue engineering. Past studies have shown that selective topography patterning improves cell growth and can even determine stem cell differentiation independently of chemical stimuli. Despite the rapid advances in scaffold patterning research, many designs are not suitable for medical implants because they only utilize one flat surface contrary to natural three-dimensional tissue growth.

To address this problem, a highly reproducible method has been discovered for creating 3-dimensional porous network patterns in hydrogel scaffolds. Calcium chloride was chosen for creating the crystals inside of an algae-based biopolymer, sodium alginate.

Dendritic crystals represent a special group of branched fractal-like structures that resemble the branching patterns of body tissues such as the vascular system. These crystals were grown inside of alginate microspheres and then washed away to creating a porous internal network that resembles natural tissue vascularization. Crystallization offers a low-cost method for 3-dimensional patterning of alginate hydrogels for tissue engineering.

Creation of a reproducible dendritic crystal network within hydrogels has biomedical applications impacting tissue scaffold patterning and drug delivery techniques. Furthermore, high reproducibility of the crystals provides a controlled platform for physicists and mathematicians studying fractal geometry. Finally, alginate crystals may even reveal a possible explanation for an age-old question in evolutionary biology regarding the origin of terrestrial plant life.

Lili Jiang  
Kirkland 2015

*Chemistry and Physics*

### **Optimizing anatase-TiO<sub>2</sub> thin film deposition for low-loss wave guides**

Mazur Lab  
Applied Physics,  
Harvard School of Engineering and Applied Sciences

Recent advances in laser and fiber-optic technology have expanded the capacity of existing communications networks. Electronic switching and routing becomes very inefficient at future data rates, leading us to ask if we can design photonic devices capable of switching and routing data completely in the optical domain. Among the candidate materials for photonic devices, titanium dioxide (TiO<sub>2</sub>) combines a high optical nonlinearity with extended transparency from 400 nm to the infrared and low two-photon absorption for wavelengths longer than 800 nm. As nonlinear optical devices require high intensities to function, the critical challenge this project focuses on will be sustaining high optical intensities within TiO<sub>2</sub>-based devices.

My project explores TiO<sub>2</sub> deposition parameters to understand the dominant source of propagation losses in our films and achieve higher quality, lower-loss films. The Mazur Group currently deposits anatase-TiO<sub>2</sub> films with planar optical propagation losses down to 4 dB/cm using reactive sputtering of titanium metal in an oxygen environment. The resulting films are polycrystalline and display differing grain sizes and orientations, depending on deposition parameters. We study the effects of changing the oxygen flow rate, deposition pressure, power, temperature, and cleaning procedure on the physical and optical properties of our films.

After depositing using reactive sputtering, we characterize the physical and optical properties of our films. We use ellipsometry and prism coupler to measure the thickness and planar optic losses of the resulting films. Raman spectroscopy provides information on the crystalline phase and scanning electron microscopy (SEM) is used to image the films and estimate granularity. By correlating film morphology with waveguiding properties for various deposition parameters, we identify an optimal deposition procedure for optics devices that causes minimum optic losses while maintaining a reasonable deposition rate.

David Liu  
Currier 2014

*Engineering Sciences*

### **Synthesis and characterization of peptide cross-linked hydrogels as a means for on-demand drug delivery**

Joshi Lab  
Wyss Institute for Biologically Inspired Engineering,  
Harvard University

Hydrogels (molecular networks that expand greatly in water) loaded with therapeutic drugs have been shown to be effective materials for sustained drug release and an alternative to systemic drug delivery. Most hydrogels use non-specific interactions to encapsulate the target drugs, limiting our control of release rates. In order to circumvent these limitations, this project seeks to introduce specific interactions to the network via structure-dependent binding. Specifically, by utilizing novel amino acid sequences that can selectively bind to a certain drug, we will craft a system wherein the peptide and drug will be attached tightly to the hydrogel until the peptide's 3-D structure is mechanically deformed by an external force (such as light, temperature, or magnetism). Our group aims to show that one such peptide—shown to selectively bind to vascular endothelial growth factor (VEGF), an important protein for directing blood vessel growth—can be incorporated into hydrogels. In order to do so, we are currently working on synthesizing the required peptides and hydrogels, and characterizing their mechanical and functional properties (such as how well VEGF binds to the peptide, and the elasticity of the gel) to better predict how they would act in vivo. In the future, these hydrogel systems could see many applications such as on-demand drug release to treat a variety of diseases.

Morgan Paull  
Cabot 2013

*Engineering Sciences*

### **Bacteria-mediated gene therapy**

Silver Lab  
Systems Biology,  
Harvard Medical School

This project seeks to use harmless bacteria to transfer any genetic material desired into immune cells in the intestines. The genes transferred could code for proteins whose absence has caused disease, or whose presence in greater quantities can promote health. The genes transferred can even encode a means to turn off other genes already within the cell. As a first target, we seek to express proteins which tune the immune response to the presence of normal, healthy, bacteria in the gut. When defective, these proteins can cause immune disorders such as Crohn's disease or Ulcerative Colitis, and we hope to restore normal function to patients with these diseases using the simple, non-invasive and non-permanent intervention of simply drinking a culture of innocuous bacteria modified to carry our gene of interest.

Once inside the gut, some of these bacteria will be eaten by im-

mune cells. Once inside, we have prepared a genetic circuit which replicates the genes in question many times over, and then bursts the carrier cell to release the DNA into the mammalian cell. The DNA has been experimentally observed to migrate to the nucleus where it will be expressed, creating the behavior desired. After a period of as yet unknown length, the DNA will be lost with no permanent alterations made to the patient. The treatment can be repeated as desired.

Katrina Ann Williamson  
*Eliot 2014*

*Engineering Sciences*

### **Hydrogels for optimizing delivery of non-steroid anti-inflammatory drugs**

Bhatia Lab  
School of Engineering and Applied Sciences  
Harvard University

Several considerations must be taken into account when choosing an optimal method of drug delivery. For treatments in which sustained release and localization of a drug is preferred, hydrogels provide an attractive option. Hydrogels consist of a meshwork of hydrophobic polymer chains and, as the name suggests, great quantities of water. In this study, we choose to work with poloxamer gel made from pluronic f-127 due to its reverse phase transition property. When cooled, the pluronic mixture remains a liquid, while at room or body temperature the mixture hardens into a gel. Poloxamer-based gels loaded with a drug are thus easily injectable if chilled, but, as a gel in the body, lend us a greater ability to dictate where and for how long a drug persists inside the body. The specific target region of a hydrogel is especially attractive for treating cancer, for which existing therapies often decimate healthy and malignant cells throughout the body indiscriminately.

Previous studies suggesting that inflammation leads to the metastasis of melanoma, lead us to believe non-steroidal anti-inflammatory drugs may hold potential in stopping the spread of cancer. For both its potential as an anti-cancer agent as well as its wide availability and inexpensiveness, we focus on the drug commonly known as ibuprofen. Ibuprofen loaded hydrogels additionally may be suitable for the localized treatment of pain and inflammation. By manipulating the weight percentage of pluronic, affecting the viscosity of the resulting gel, or the weight percentage of the ibuprofen loaded inside the gel, we are able to affect the release profile of the ibuprofen, alter both the rapidness of drug release and the percentage of total drug released.

Matthew Yarri  
*Currier 2014*

*Mechanical Engineering*

### **Achieving safer, smaller, and better surgeries with laser origami**

Walsh Lab  
School of Engineering and Applied Sciences,  
Wyss Institute for Biologically Inspired Engineering

Over the past few decades the medical world has witnessed an explosion of innovation in the field of human surgery. With advances in micromachining, computing power, and general surgical practice, surgeons are able to accomplish feats once thought unthinkable: the reattachment of severed limbs, the ability for a patient to return home one day after having reconstructive knee surgery, the first remote-controlled “Lindbergh surgery”, and many other advancements that are nothing short of medical marvels.

At the forefront of this surgical innovation are “minimally invasive procedures.” Traditionally, surgeons would make very large incisions into the body, cutting through large amounts of bone and tissue to gain access to the area of the body they were repairing - leading to high probabilities of infection and a very long recovery period for the patient. Minimally invasive surgery solves this problem by using thin tools that the surgeon can insert through very small incisions, and with the aid of an inserted video camera, can perform the same surgery in a much cleaner and less destructive way - drastically reducing surgical complications, patient recovery time, and allowing surgeons to do things that traditional surgery never could.

The growth of minimally invasive surgery has brought with it a demand for smaller, cheaper, and more complex micro-surgical tools. At this “mesoscale” of 1-10 millimeters, conventional manufacturing becomes very challenging, if not impossible. This summer I have worked to overcome this “mesoscale gap” by exploring ways to use micro-laser machining to create “pop-up”, origami-like surgical devices that allow surgeons to perform surgeries that push the envelope of patient care.



# MATHEMATICS AND STATISTICS

Eric Larson  
Dunster 2013

*Mathematics*

## Maximal rank for curves and their hyperplane sections

Professor Joseph Harris  
Mathematics,  
Harvard College

One basic goal of algebraic geometry is to understand algebraic curves in projective space. An  $n$ -dimensional projective space  $\mathbb{CP}^n$  is intuitively an  $n$ -dimensional complex space  $\mathbb{C}^n$  with some extra points added at infinity for each direction in which we can go off to infinity. An algebraic curve is something that looks like a one-dimensional subset of projective space that can be specified by polynomial equations. Here, one-dimensional means one complex dimension, which would be two real dimensions; so topologically, an algebraic curve is a surface.

Given an algebraic curve  $C$  in projective space  $\mathbb{CP}^n$ , it is natural to ask for the dimension of the space of polynomials on  $\mathbb{CP}^n$  of a given degree that evaluate to zero on  $C$ . My research concerns understanding the typical behavior of these dimensions when we choose the curve (and then its embedding into projective space) “at random.”

As a stepping stone towards understanding this, I have proved a formula for a similar family of dimensions, when we replace the curve  $C$  by its intersection with a “random”  $(n-1)$ -dimensional plane  $H$ . Namely, the points of intersection impose independent conditions on polynomials of a given degree --- or in other words, the dimension of the space of polynomials of degree  $k$  on  $H$  evaluating to zero on the intersection equals the dimension of the space of polynomials of degree  $k$  on  $H$ , minus the number of points of intersection (or 0 if that is negative), except for some exceptions that occur when  $k=2$ .

Keli Liu  
Winthrop 2013

*Statistics*

## “You can’t please everyone”: The impossibility of objective science?

Professor Xiao-Li Meng  
Statistics,  
Harvard College

Three friends drool over your blueberry pie. To be fair, you serve up  $1/3$  of the pie to each. But suppose you’re quite popular i.e. you’ve got infinite friends (at least on Facebook). One divided by infinity is zero. In your misguided attempt to please everyone, no one receives any pie! This pie sharing problem shows how bias necessarily leaks into scientific analyses. Rather than apple filling, suppose our pie is stuffed with probability, and instead of friends, we need to divvy up the probability among the possible answers to a question. To exclude bias, one must give equal probability (i.e. equal consideration) to all possible answers—an impossible task when the possibilities are infinite!

Trying to please everyone creates catastrophe when you’ve got too many friends. What we need is a “fair way” to unfriend some people/exclude possible answers. For scientific experiments, the key to this fairness lies in recognizing that given only a finite amount of data, some answers are so similar that they cannot be distinguished. Can you really tell apart a coin with probability 0.10 of heads from a coin with probability 0.11 of heads with only one flip of the coin? The lack of “resolution” forces us to collapse highly similar answers together into “distinguishable subsets,” so named because the data allows us to discriminate between subsets but all answers within a fixed subset are equally supported by the data. Even though the number of possible answers may be infinite, the number of distinguishable subsets will often be finite, allowing us to give equal probability to each.

Arpon Raksit  
Eliot 2015

*Mathematics*

## Representations of Lie groups and Lie algebras

Professor Joseph Harris,  
Department of Mathematics,  
Harvard University

Lie groups are mathematical objects with rich algebraic and geometric structure; precisely, a Lie group has the structure of both a group and that of a smooth manifold, and moreover these structures are compatible (in a relevant sense). Lie groups arise naturally, e.g. in problems dealing with continuous symmetries—like those of the sphere—and in theoretical physics. Thus, understanding the structure of Lie groups is of inherent interest. Representation theory studies algebraic objects by analyzing the ways in which they can act as linear maps on vector spaces; these actions are called representations of the object. Since linear algebra is well-understood, this method of reducing general algebraic problems to linear-algebraic problems can be very powerful. The goal of this project is to understand Lie groups by studying their representations.

While the rich structure of Lie groups is (partially) what motivates this study, it also makes Lie groups quite complicated objects to deal with. Hence, our approach to the problem is to strip away some of the structure by passing to simpler objects related to, and containing valuable information about, the Lie group. We can associate in a natural way to any Lie group a purely algebraic object called a Lie algebra. It turns out that we can learn a great deal about the representations of a Lie group by analyzing the representations of its Lie algebra. Moreover, by a classification of Lie algebras, it suffices to study semisimple Lie algebras, whose representation theory is particularly nice. In this project we thus focus on classifying the representations of semisimple Lie algebras.

# MICROBIOLOGY AND IMMUNOLOGY

Olivia Angiuli  
Pforzheimer 2015

*Chemical and Physical Biology*

## Controlling HIV

Walker Lab,  
Microbiology and Immunology,  
Ragon Institute of MGH, MIT, and Harvard

Human Immunodeficiency Virus (HIV) is a virus that hijacks the host machinery of key cells in the human immune system (mainly CD4+ T cells) in order to replicate. Curiously, less than 1% of people who become infected with HIV (called “elite controllers”) can maintain undetectable levels of virus in their plasma, whereas most untreated HIV-infected patients (“chronic progressors”) have active viral replication with thousands of viral copies per milliliter of plasma.

This summer, under the supervision of Dr. David Shasha, we have been comparing how effectively HIV-infected CD4+ T cells are killed by CD8+ T cells isolated from elite controllers, chronic progressors, and HIV negative patients. We use viral inhibition assays (VIAs), in which CD8+ T cells are co-cultured with HIV-infected CD4+ T cells in order to test the CD8+ T cells’ ability to kill HIV-infected cells.

Previous studies demonstrate that CD8+ T cells of elite controllers showed stronger inhibition of the HIV virus than did CD8+ T cells from chronic progressors. Our preliminary results suggest that this difference in the two populations of CD8+ T cells is only present when CD8+ T cells rest for three days without any exposure to the virus. CD8+ T cells from chronic progressors that do not undergo a three-day rest period may, in fact, exhibit equal abilities to kill HIV-infected cells. This may suggest that elite controllers’ CD8+ T cells are not necessarily more effective at killing HIV-infected cells, but rather may merely survive longer or exhibit better functionality after prolonged incubation *in vitro*.

Melissa Chan  
Kirkland 2015

*Chemistry*

## Colony dwarfing of *Escherichia coli* in response to carbon starvation

Mitchell Lab,  
School of Engineering and Applied Sciences,  
Harvard University

Bacteria are constantly subjected to environmental stresses such as heat, pH, antibiotics, and starvation. *Escherichia coli* has been shown to survive well in extremely nutrient poor conditions, and is thus a good model for studying starvation response. *E. coli* stress responses to carbon starvation include formation of smaller spherical cells, development of more rigid cell envelopes, repression of aerobic metabolism, reduction in protein synthesis, and initiation of programmed cell death. While previous studies have focused on the

effects of starvation on individual cells, my research aims to investigate the effect of carbon deprivation on colony formation. I devised experiments in which *E. coli* was grown on Davis Minimal Media with glucose as the only carbon source, at concentrations ranging from 0.0313 g/L to 1 g/L. Initial results show that colony sizes diminish in response to reduced glucose concentration. Cell cultures from the lowest and highest glucose concentration plates were switched to establish that the variations in colony sizes are simply a reversible physiological response. Further studies are ongoing to investigate the molecular mechanisms underlying colony size reduction in response to reduced carbon.

Diego B. López  
Mather 2013

*Molecular and Cellular Biology*

## Inhibition of T-Cell migration to the intestine as a possible treatment for Crohn’s disease

Von Adrian Lab  
Microbiology and Immunology,  
Harvard Medical School

Inflammatory bowel diseases such as Crohn’s Disease are characterized by chronic inflammation of the intestine and a large influx of leukocytes into the gastrointestinal tract. Novel therapeutic approaches have focused on inhibiting adhesion molecules involved in the migration of leukocytes toward sites of inflammation in patients with autoimmune disorders such as Crohn’s disease. One of the targeted adhesion molecules is the  $\alpha 4$  integrin, expressed in gut-homing T-cells as an  $\alpha 4\beta 7$  heterodimer. The treatment of Crohn’s disease patients with antibodies against  $\alpha 4$  integrin has shown clinical efficacy. However, a small portion of treated patients suffers from opportunistic infections of the central nervous system, presumably because  $\alpha 4$  inhibition affects immune surveillance in the central nervous system as well as in the gut. Other approaches have targeted chemokine receptors such as CCR9 – also expressed by gut-homing T-cells. The treatment of patients suffering from Crohn’s disease with CCR9 inhibitors has shown greater specificity (no opportunistic infections in the central nervous system) but lower clinical efficacy. We hypothesize that a combinatorial blockade of  $\alpha 4$  integrin and CCR9 chemokine receptor, by only partially blocking  $\alpha 4$  but completely blocking CCR9, may be able to achieve complete inhibition of T-cell migration to the gut without affecting immune surveillance in the central nervous system. Such an approach could have broad implications for the treatment of patients suffering from Crohn’s disease and other autoimmune disorders.



Joshua Ra  
Cabot 2013

Molecular and Cellular Biology

Olive Tang  
Currier 2015

Chemical and Physical Biology

### **PD-1 expression after recombinant adenovirus vaccination**

Barouch Lab,  
Viral Pathogenesis Division,  
Beth Israel Deaconess Medical Center

T cell exhaustion is a feature of chronic viral infections that likely plays a significant role in ineffective viral control. While memory CD8 T cells generated from acute viral infections can rapidly reactivate effector functions and have high proliferative potential, antigen-specific CD8 T cells during chronic viral infections undergo a phenomenon of “exhaustion” that eventually leads to impaired homeostatic proliferation and loss of effector functions. PD-1, an inhibitory receptor, has been reported to play an important role in T cell exhaustion during chronic viral infection. It has been shown that blocking the PD-1/PD-L1 pathway during infection *in vivo* increases virus-specific CD8 T cell responses, enhances effector function, and decreases viral load. However, T cell exhaustion has not been fully examined in the context of recombinant adenovirus (rAd) vector vaccinations. Engineered as replication defective virus particles expressing a transgene product, rAd vectors have been favored for vaccination due to their induction of potent humoral and cellular immune responses. In particular, the human adenovirus serotype 5 vector (Ad5) has been widely used, but a failed Merck HIV vaccine clinical trial cast doubts on using Ad5 in populations with pre-existing anti-Ad5 immunity due to a lack of protection to HIV infection in such populations. New alternative serotype vaccine vectors - most notably Ad26, Ad35, and Ad48 - have been reported to be more viable than Ad5 as vaccine vectors due to considerably lower pre-existing anti-vector immunity in various populations. My research question seeks to examine the expression of PD-1 as a marker of T cell exhaustion in SIV antigen-specific CD8 T cells after common and alternative serotype rAd vaccinations in mice.

### **Roles of topoisomerases in chromosome organization and segregation in *Bacillus subtilis***

Rudner Lab,  
Microbiology and Immunology,  
Harvard Medical School

Central to all life processes is the faithful replication and transmission of genetic material from one generation to the next. Although mitosis in eukaryotic cells has been visualized and studied for over 100 years, until recently, little was known about the organization and segregation of the bacterial chromosome.

Most bacteria have a single circular chromosome, which is compacted approximately 1000-fold within the bacterial cell to form a highly ordered structure known as the nucleoid. Chromosome replication initiates from a unique origin and proceeds bi-directionally to a site opposite the origin called the terminus. In eukaryotic cells, chromosome replication, segregation and cell division are temporally separated. However, in bacteria, these processes overlap during the cell cycle. Although the underlying mechanisms of DNA replication are very well studied, an understanding of how the bacterial chromosome is organized and segregated is only now emerging.

Chromosome compaction is essential for cell viability and plays a crucial role in chromosome segregation. One principle mechanism of chromosome compaction is through DNA supercoiling: the under- or over-winding of the DNA duplex, which is generated and maintained largely by topoisomerases. These enzymes catalyze the passage of single or double strands of DNA through each other. This project focuses on the role of topoisomerases in organizing and segregating the chromosome *in vivo* using *Bacillus subtilis* as a model organism. We will perform genetic screens to identify temperature-sensitive mutations in the subunits of DNA gyrase and topoisomerase IV, which are essential for cell viability. We will then use these mutants in combination with live-cell imaging of the whole chromosome and individual chromosomal loci to define how these enzymes impact chromosome organization and segregation.

# MOLECULAR AND CELLULAR BIOLOGY

Leandra Barnes  
Currier 2013

*Chemical and Physical Biology*

## Investigating the mechanism of SpoIIIE mediated end-loop resolution in sporulating *Bacillus subtilis*

Burton Laboratory,  
Molecular and Cellular Biology,  
Harvard Faculty of Arts and Sciences

Faithful chromosome segregation is necessary for the growth and development of all living organisms. During sporulation in the bacterium *Bacillus subtilis*, transmembrane protein SpoIIIE is required for proper chromosome segregation; it transports 70% of the chromosome that is destined for the forespore, but trapped in the mother cell (Wu and Errington 1998). It is proposed to form two independent channels, one for each arm of the circular chromosome, to transport the two-thirds of the chromosome that remain in the mother cell into the forespore. However, since the DNA is circular, there remains a loop of DNA at the division plane, presenting a topological problem that must be overcome by the cell in order to form a viable spore. Burton et al. (2007) suggest that this loop is resolved via one of two possible mechanisms: (1) linearization of the circular DNA that is later rejoined or (2) changes in the oligomeric state of SpoIIIE to form a single, larger channel that allows the terminal loop to be transported across the asymmetric septum without being cleaved. To discover the mechanism by which this topological problem is overcome in the cell, I am investigating end-loop resolution in *Bacillus subtilis* via three specific aims: (1) investigating whether linearizing the end-loop of the chromosome using yeast HO endonuclease will improve DNA transport efficiency, (2) investigating whether varying the frequency of dimers of the chromosome via *ripX/codV/recA* null deletions will affect the level of terminal DNA transport efficiency, (3) investigating if the native topological state of the *Bacillus subtilis* chromosome is transiently linearized at different stages of sporulation using pulsed-field gel electrophoresis.

Caleb Cañas  
Leverett 2014

*Molecular and Cellular Biology*

## The characterization of DUB activity in cancer proliferation

King Lab  
Cell Biology,  
Harvard Medical School

The addition of ubiquitin to proteins is a reversible process that is involved in the regulation of their stability and, consequently, various cellular functions such as cellular proliferation and protein degradation by the proteasome. Deubiquitinating enzymes, or DUBs, are an essential component of the Ubiquitin/Proteasome system because of their ability to remove ubiquitin from a target protein. About one

hundred different DUBs are encoded by the human genome and they display a variety of mechanistic functions, domain structures, and may have dynamic roles in the regulation of cellular processes. Proper DUB activity is crucial for protein stability, various signaling pathways, and overall cellular homeostasis. Recent studies have shown that alteration in DUB function correlates with the onset of diseases, including cancer. However, only a few human DUBs, notably Cyld and A20, have been well-characterized and have known oncogenic roles. In-depth analysis of human DUB activity can open up new molecular therapies against cancer.

In this project, I attempt to further characterize the activity of DUBs in the cellular proliferation of cancer. To examine the role of DUBs we conducted siRNA, or short interfering RNA, screens on various breast and colorectal cancer cell lines. siRNA facilitates the knockdown of a gene by targeting mRNA for cleavage. The screen tested what effect the knockdown of 102 DUBs would have across eleven cell lines. Each DUB had seven siRNAs with distinct seed sequences. DUBs were ranked based on various factors such as percent inhibition and siRNA activity. The top ranking DUBs were visually analyzed to help understand the phenotype that arose upon gene knockdown. For strong and prominent phenotypes, further experiments were performed to characterize the phenotype.

Kuo-Kai Chin  
Eliot 2015

*Chemical and Physical Biology*

## An RNA interference-based screen of potential arginine demethylases

Shi Lab  
Division of Newborn Medicine,  
Boston Children's Hospital

Epigenetics concerns heritable phenotypic changes that do not involve alterations of the underlying DNA sequence and one common mechanism of epigenetic control utilizes modifications to histone proteins, which bind and package DNA. Such modifications, which add various molecules to histone tails, include acetylation, methylation, and phosphorylation, and they can all affect gene transcription and expression. In particular, multiple arginine methyltransferases add methyl groups to arginine residues and are known to be critical for neuronal outgrowth as well as dendritic spine maturation and proliferation, partially through histone modification. However, the reversibility of this modification is uncertain. With that knowledge, this project seeks to identify an arginine demethylase capable of removing methyl-marks from modified arginine residues using RNA interference in *C. elegans* to degrade messenger RNAs of interest and thereby knock down candidate demethylases. If successful, this screen will identify long sought-after enzymes which can reverse arginine methylation on chromatin, and thereby provide a mechanism to dynamically control the epigenetic landscape.

Lawrence S. Chiou  
Cabot 2014

Chemistry and Physics

### ***A multi-type branching process model for cancer dedifferentiation and mutation***

Dr. Benjamin Allen  
Program for Evolutionary Dynamics,  
Harvard University

The cancer stem cell paradigm posits that only a relatively small subpopulation of tumor cells, termed cancer stem cells, has the ability to generate the entire tumor cell population and drive enlargement of the tumor. While certain aspects of this view are disputed, it is clear that in most cancers there is some rough hierarchy of stem-like and differentiated cells. As opposed to cells in many typical tumors and tissues, however, cancer cells in certain tumors can be especially plastic. In particular, in some cases cancer progenitor cells may frequently transition back to the stem cell type.

To investigate the significance of this dedifferentiation on tumor progression, we model a system of cancer stem and progenitor cells as a multi-type branching process, a Markov process in which each cell type has a set of fixed rate parameters for death, symmetric division, and asymmetric differentiation (or dedifferentiation). In addition, we consider the case in which resistance mutations occur at cell divisions with a given mutation rate parameter. This represents the first stochastic model for cancer stem cells to consider dedifferentiation.

Based on both simulations and theory, we compute the survival probability of a system of sensitive cells, subcritical (limiting survival probability of zero) under treatment, as well as the probability that a system of sensitive cells escapes extinction via mutation to a system of supercritical (nonzero limiting survival probability) resistant cells.

Christine Choi  
Cabot 2013

Molecular and Cellular Biology

### **The role of MELK over-expression for the maintenance of the tumorigenic phenotype of ovarian cancers**

Zhao Lab  
Biological Chemistry and Molecular Pharmacology,  
Harvard Medical School

Ovarian cancer is one of the most common causes of cancer-related deaths in woman. They are difficult to detect, and most diagnosed patients present with advanced disease and face poor prognoses. However, the vast majority of high-grade serous ovarian cancers present with a specific set of mutations in well-known tumor suppressors, including p53, BRCA1, and BRCA2. Incidence and median survival rates have improved in the past few decades, but the need for novel therapeutic options is high, especially due to resistance to chemotherapy and cancer recurrence.

Maternal embryonic leucine zipper kinase (MELK) has been associated with cell division and is over-expressed in many different cancer types, including ovarian cancers. There is very little data, however, characterizing the role and importance of MELK for ovar-

ian cancer cell growth and survival. In my project, I am studying the potential of MELK as a potential therapeutic target in ovarian cancer. First, I am examining the effects of MELK knockdown on the proliferation of ovarian cancer cell lines. I am also studying the ability of the cells to grow in an anchorage-independent manner, a hallmark of cancer, in the absence of MELK. The hypothesis is that MELK over-expression is necessary for the maintenance of the high proliferation rate of the cells as well as their ability to grow in an anchorage-independent manner. In addition to the *in vitro* experiments, I will be conducting *in vivo* work in mice to determine whether MELK knockdown *in vivo* can reduce tumor growth and proliferation.

Aisha Lee  
Mather 2015

Chemistry

### **Understanding malaria invasion pathways: The search for erythrocyte receptors**

Duraisingh Lab  
Immunology and Infectious Diseases,  
Harvard School of Public Health

Malaria, to this day, is one of the biggest global health challenges the world faces. With about 300 million reported cases and over 600,000 related deaths in 2011 alone, the disease continues to rapidly spread in developing nations across the globe. Growing resistance to existing treatments in addition to the parasite's general ability to efficiently evade host immune responses has led to a need for newer, cheaper treatments that will hopefully lead to the complete eradication of malaria.

Malaria is caused by five species of single-celled obligate intracellular parasites in the genus *Plasmodium*. The parasite undergoes a complex life cycle with a sexual stage in female *Anopheles* mosquitoes and two asexual stages in humans. In humans, there is a liver stage, in which injected sporozoites from mosquitoes develop into merozoites, and then the blood stage in which the released merozoites invade erythrocytes (red blood cells) and divide - the stage of infection where one sees the physical manifestations of the disease. In my lab, we are focused on the blood stage of *Plasmodium falciparum* - the species of parasite that causes the most severe and lethal strain of malaria. We are attempting to understand the specific pathways of invasion between the merozoite and the human erythrocyte. Invasion specificity is determined by the binding between a specific parasite surface protein and a cognate erythrocyte surface protein (known as a receptor), thus forming the basis of an invasion pathway. Although many of the parasite invasion ligands have been identified, there are still some complementary receptors have yet to be found. In addition, as *Plasmodium falciparum* is capable of utilizing different invasion pathways based on the availability of host receptors, a full understanding of these interactions is key to developing future therapeutic agents. Therefore to further study binding specificity, our approach is to clone and express individual parasite ligands and use these to identify each unique erythrocyte receptor by performing various knockdown assays. By assessing the binding affinities of six different parasite proteins (RH1, RH2, RH4, EBA 175, EBA 181, and DBP) in the presence or absence of certain erythrocyte surface receptors, then we can confirm what target exactly these proteins are binding to - leading to a better understanding of the disease and much better chances of ultimately creating a cure.

Reshma Lutfeali  
Adams 2013

*Molecular and Cellular Biology*

### **Characterizing the impact of protein translation on mitotic spindle morphology**

Blower Lab  
Molecular Biology and Genetics,  
Massachusetts General Hospital

The mitotic spindle is a critical structure needed for the proper progression of cells through mitosis. Although conventional wisdom once held that protein translation halts during mitosis in order to conserve cellular energy, more recent evidence suggests that some translation does indeed occur via the Internal Ribosomal Entry Site (IRES) initiation mechanism, the implications of which have yet to be fully determined. Additionally, RNA has been shown to localize to the mitotic spindle, and localized translation may help regulate cell cycle checkpoint factors. In order to better understand the dynamic conditions of mitosis, it is of great interest to study the interaction between translation and the mitotic spindle.

In order to study mitotic spindles, particularly during metaphase, a model system is required that does not affect spindle morphology; however, traditional treatments for inducing metaphase arrest function by depolymerizing microtubules and triggering the spindle cell cycle checkpoint. In *Xenopus* cytostatic factor-arrested (CSF) egg extract, however, metaphase arrest is induced through inhibition of the Maturation Promoting Factor, thus leaving the spindle intact and providing an ideal vertebrate model system for this study. Using the translation elongation inhibitor puromycin as my primary treatment, I am comparing the cells that are actively translating to cells that are not. Through quantitative analyses of spindle and nucleus characteristics, I am studying the impact of protein translation on spindle morphology and chromosome alignment. Preliminary results suggest that inhibition of translation may affect the uniformity of DNA alignment along the metaphase plate and the ability of RNA to localize to spindle poles.

Ann Maurine Morgan  
Dunster 2013

*Chemistry*

### **Effect of pigment on production of reactive oxygen species**

Fisher Lab  
Cutaneous Biology Research Center,  
Massachusetts General Hospital

Of all pigmentation types, individuals with pale skin, red hair and freckles—“redheads”—are at the greatest risk of developing melanoma. While redhead melanoma risk has been historically attributed to poor shielding from genotoxic solar UV radiation, recent work has led to the striking conclusion that the “red” pigment pheomelanin may be carcinogenic independent of UV radiation. Based on the structure of pheomelanin, we have hypothesized that

pheomelanin propagates DNA-damage-inducing reactive oxygen species. In this study, we have used protein carbonylation, lipid peroxidation, and oxidative purine modification as indicators of oxidative stress in order to compare baseline oxidative stress in the skin of “redhead” mice to mice of other pigmentations. Specifically, we have found that oxidative stress in the skin of “redhead” mice is higher than that in the skin of “albino-redhead” mice, which are genetically “redhead” but also carry an inactivating Tyrosinase mutation and thus produce no pigment and appear albino. This finding indicates that pheomelanin itself, or the synthesis thereof, increases basal oxidative stress in the skin independent of UV radiation, which may contribute to redhead melanomagenesis.

Robert Edward Powers  
Kirkland 2014

*Chemical and Physical Biology*

### **Towards a structural study of a positively selected variation in protocadherin-15**

Gaudet Lab  
Molecular and Cellular Biology,  
Harvard University

The sensation of hearing involves the transformation of sound into electrical signals by stimulation of inner-ear hair cells. These specialized cells feature bundles of hair-like stereocilia that are arranged in order of increasing height. Each stereocilium is connected to the next longest stereocilium by a filament comprised of the proteins Cadherin-23 (CDH-23) and Protocadherin-15 (PCDH-15). This complex, called a “tip-link”, is essential for hearing because it conveys sound-induced forces and pulls open mechanosensitive ion channels that generate the electrical signal involved in sound perception. CDH-23 and PCDH-15 are part of the larger family of cadherins that typically adhere cells together in a calcium-dependent manner and contain extracellular cadherin (EC) repeats.

Recent research has identified an aspartate to alanine variation (D435A) within the linker region between extracellular repeats 3 and 4 of PCDH-15 that is positively selected for in East Asian populations. Such a substitution is particularly interesting because it occurs in a putative calcium-binding region, thereby removing a charged residue that could coordinate calcium ions. Given PCDH-15’s calcium dependence, my research focuses on characterizing the impact that this variation has on the architecture and calcium binding affinity of the EC3+4 fragment using x-ray crystallography, NMR, and various biochemical assays. The ultimate goal of my project is to understand why such a variation could be evolutionarily advantageous.



Ana Rivera  
Pforzheimer 2013

*Human Developmental  
and Regenerative Biology*

### **The role of p53 in cellular response to DNA damage in human embryonic stem cells**

Lahav Lab  
Systems Biology,  
Harvard Medical School

In response to various types of cellular stress, including DNA damage, the transcription factor p53 has the ability to trigger a variety of cell fate responses such as repair, cell cycle arrest, senescence, and apoptosis. Previous work in the Lahav lab has demonstrated that pulses of p53 in response to damage cause somatic cancer cells to undergo cell cycle arrest. Interestingly, embryonic stem cells respond to the same stress by undergoing apoptosis. The goal of my project was to compare different cell types to discern how distinct cellular outcomes can be regulated by the same protein network. We began by comparing pluripotent stem cell and differentiated, non-pluripotent cell responses to double-stranded DNA breaks. After differentiation due to retinoic acid treatment, fewer stem cells died. We also established that two separate stem cell lines, the H1 and HUES9, reacted similarly to damage. We have shown using p53-knockdown cell lines that responses in both cell lines are p53-dependent. Finally, we investigated the relative roles of cytoplasmic and nuclear p53 in cell fate decisions. Using standard molecular techniques such as Western blots and qPCR, we tracked the induction of p53 and its downstream targets such as p21 and PUMA on the mRNA and protein level. We also investigated other possible sources that could be responsible for the apoptotic fate, such as novel interacting proteins and priming of the mitochondria with pro-apoptotic proteins. The unique response of these cells to DNA damage allows us to study how different cell types can respond differently to the same stimulus, helping to answer other questions such as why certain cell types are more responsive to cancer therapies than others.

Michael Silva  
Currier 2012

*Molecular and Cellular Biology*

### **Autism-associated Ube3a conditional knockout**

Anderson Lab  
Neurology,  
Harvard Medical School

Triplication of the maternal 15q11-13 region of chromosome 15 is responsible for 1-3 % of autism cases in humans and tripling the gene dosage of Ube3a alone within 15q11-13 is sufficient to reconstitute autism-related behavioral deficits in transgenic mice. In an effort to understand whether this behavioral disorder results from an irreversible defect in brain development or instead an ongoing defect in brain function, we developed a conditional inactivatable Ube3a gene construct using BAC recombineering. We have flanked exon 2 of the Ube3a gene, a gene of interest within 15q11-13, with loxP sites such that the excision of exon 2 by the enzyme Cre, which

recognizes loxP sites and removes the sequence between them, would cause a frameshift mutation and inactivate Ube3a. The construct will be used to generate transgenic mice so that the excision of exon 2 (and, hence, the inactivation of the duplicate or triplicate copy of Ube3a) can be temporally controlled. By crossing to existing mice that carry a tamoxifen-inducible Cre recombinase, we will be able to expose these mice to tamoxifen at early postnatal ages or in adulthood to shut off the extra copies of Ube3a. Postnatal exposure to Cre would bring expression levels of an idic15 (three copies of Ube3a) mouse back to normal if the extra copies consisted of our construct. If behavior does not improve, this tells us that the Ube3a mutation probably takes its toll during development and causes permanent damage, decreasing the hopes for a therapeutic solution in humans. On the other hand, if behavior improves, this tells us that the mutation is an ongoing expression problem and can hopefully be solved therapeutically in humans.

Constantine Tarabanis  
Winthrop 2015

*Molecular and Cellular Biology*

### **Investigating the LPS-mediated signaling pathway leading to proteinuria**

Greka Lab  
Nephrology,  
Massachusetts General Hospital, Harvard Medical School

In our time, one of the most urgent health problems is the emergence of diabetes secondary to obesity and the metabolic syndrome, which many have described as an epidemic. The first sign of kidney damage related to diabetes is the presence of protein in the urine, termed proteinuria. The progression of this failure of the kidney filtration barrier leads to kidney failure.

Early podocyte injury is characterized by dysregulation of Ca<sup>2+</sup> homeostasis followed by disruption of the contractile apparatus and increased motility, leading to proteinuria. Ca<sup>2+</sup> homeostasis is maintained mainly by the antagonistic action of Transient Receptor Potential Channels (TRPC) 5 and 6. Recent work has also shown that lipopolysaccharide (LPS) induces proteinuria in mouse models.

TRPC5-mediated Ca<sup>2+</sup> influx induces Rac1 activation, thereby promoting podocyte migration, a phenotype known to correlate with proteinuria *in vivo*. The mentor has shown that TRPC5-mediated degradation of synpo and actin fibers can also be rescued by Cyclosporine (CsA), placing TRPC5 upstream of synaptopodin-mediated signaling in podocytes. Since LPS has been previously shown to also mediate podocyte migration, our hypothesis is that LPS induces proteinuria by enhancing the activity of TRPC5 channels.

In order to test this hypothesis, TRPC5 will be knocked down in podocytes through lentiviral delivery of TRPC5 specific shRNAs. Also, lentiviral TRPC5 constructs will be over-expressed in podocytes. We anticipate that LPS-treated TRPC5 knock down podocytes will be protected from the maladaptive migratory phenotype, whereas TRPC5 overexpressing cells will show increased migration. The podocyte specific actin regulator synaptopodin is also expected to be intact and present on a western blot of lysates of TRPC5 knockdown cells, and degraded in TRPC5 overexpressing podocytes.

Elizabeth Wang  
Lowell 2014

*Chemical and Physical Biology*

### Characterization of SID-1 homologs

Hunter Lab  
Molecular and Cellular Biology,  
Harvard College

RNA interference (RNAi) is initiated by dsRNA and has crucial roles in cellular protection against viral infections and transposons, the regulated development of organisms, and potential gene therapies. In *C. elegans*, SID-1 is a transmembrane protein that is essential for the import of dsRNA into the cell. SID-1 has been found to be an energy-independent, ligand gated channel that probably functions as a multimer. The fact that SID-1 has a homolog in humans (SIDT2) has significant implications for the use of RNAi in drug therapies.

Sid-1 has five homologs (Sid-like genes) in *C. elegans* that have not yet been characterized. Research in these homologs could shed light on the improvement of RNAi-based therapies in humans. We performed enhanced double knockdowns on *C. elegans*, in which we fed Sid-like gene silencing dsRNA to mutants lacking a competing endogenous RNAi pathway. We found that knockdowns of two of the Sid-like genes are significantly RNAi-deficient, suggesting a possible role of these genes in the RNAi process.

We plan on using *Drosophila* S2 tissue cultures to characterize the mechanisms of dsRNA transport in the Sid-like genes. SID-1 transfected into S2 cells has been shown to greatly increase the amount of dsRNA taken up from the environment. Luciferase assays in these cell lines have demonstrated that optimal silencing occurs with 500 bp dsRNA. We have replicated these experiments, and plan on conducting them with Sid-like transfected cells to investigate the substrate preference and silencing abilities characteristic of these proteins. Through radioactive uptake assays, we can also demonstrate the retention dynamics of these putative transmembrane proteins.

Jeffrey Bond Wang  
Eliot 2015

*Applied Math - Biology*

### The influence of promotor architecture on targeted gene activation by complex transcription factor signaling

Professor Erin O'Shea  
FAS Center for Systems Biology,  
Harvard University

The cell maintains an arsenal of genes which are activated by transcription factor (TF) proteins only in the presence of the proper stressor. Upon stress, the eukaryotic cell activates certain TFs, which then translocate to the nucleus, where they can bind to promoter sequences and induce expression of the appropriate genes. How the cell responds to these changes in transcription factor levels in the nucleus is less obvious however. Our studies focused on Msn2, a TF in budding yeast responsible for mediating the response to a number of stresses, such as oxidative stress and starvation. Based on

the identity of the stressor, Msn2 enters the nucleus with different patterns, such as entering and leaving the nucleus rapidly or periodically. Our project's goal was to elucidate how the positioning of histones within promoter sequences allowed genes to be differentially activated by these various signals. We selected the DDR2 gene promoter, which possesses Msn2 binding sites both in and out of its well-defined nucleosome binding positions. Then, we systematically modified the position of its binding sites relative to the nucleosomes and utilized a fluorescent reporter that allowed us to quantify relative expression levels. We focused on how the promoter processes three aspects of the incoming Msn2 signal: the duration (how long Msn2 is present in the nucleus), the intensity (the maximum amount of Msn2 within the nucleus), and the frequency of oscillations (how quickly we move Msn2 in and out of the nucleus). We then fit these results to a set of differential equations describing how transcription factor binding can lead to protein production. With these results, we hope to identify how all of these binding sites cooperate to analyze complicated Msn2 signaling.

Bonnie Wong  
Mather 2013

*Organismic Evolutionary Biology*

### The reciprocal activation between natural killer (NK) cells and dendritic cells (DC)

Strominger Lab  
Stem Cell and Regenerative Biology,  
Harvard College

Dendritic Cells (DC) are crucial to both innate and adaptive immunity. Immature DC patrol the circulatory system in search of stress signals; upon recognition of a stress, the maturation of DCs is initiated. Mature DCs display components of their original environment on MHC molecules triggering specific responses, for example, enhancing the cytotoxic function of Natural Killer (NK) cells. NK cells eliminate pathogen-infected cells without antibody-specific recognition; their secreted pro-inflammatory cytokines and chemokines serve to prime the adaptive immune system, and include IFN- $\gamma$ , which prevents the survival of pathogens, and TNF, which prevents the growth and spread of tumors.

Previous studies have shown that the activation of NK cells triggers the maturation as well as lysis of DCs, giving evidence to a complicated bidirectional crosstalk between DC and NK cells. While the mechanism of DC-mediated activation of NK cells is more delineated, the NK-mediated lysis and maturation of DC is not well understood. Examination of this reciprocal crosstalk between DC and NK cells is threefold. First, we seek to better understand the process of DC-mediated NK-activation, by analyzing the individual heterogeneity of NK IFN- $\gamma$  secretion induced by both syngeneic and allogeneic DC. Second, we hope to illuminate the processes of NK-induced DC activation; and lastly, to determine the nature of NK-induced DC apoptosis, in regards to the ratio of activated NK and immature DC as well as the nature of induction.

William Zhang  
Mather 2015

Undecided

### Investigating a sensor for NAD<sup>+</sup> levels in mammalian cells

Sinclair Lab  
Genetics,  
Harvard Medical School

Calorie restriction (CR) is a diet that involves a 40% decrease in calorie consumption compared to normal intake. It has been well established in many animal models that CR can slow down aging and increase lifespan. CR is thought to work by increasing the activity of sirtuins, longevity genes that appear to be major players in life span extension, thus delaying the aging process. NAD<sup>+</sup>, a common cofactor, activates sirtuins, which then alter metabolism and turn on a variety of cell defense mechanisms against aging. Thus, it is important to know the concentration of NAD<sup>+</sup> to determine sirtuin activity levels.

One such system to measure NAD<sup>+</sup> levels in yeast has already been built. Currently, a similar sensor is being developed for mammalian cells. I have been working with this system, which consists of three plasmids, to examine its potential. The first plasmid functions as an on-off switch. It is activated in the presence of a drug, doxycycline. When it is turned on, it activates the second plasmid, which transcribes for the NadR protein. NadR activity is dependent on NAD<sup>+</sup> levels. Higher concentrations of NAD<sup>+</sup> result in greater activity of NadR. NadR activates the third and final plasmid, which expresses GFP. Thus, more NAD<sup>+</sup> increases NadR activity, which causes higher expression of GFP.

My experiments are performed with 293T cells. Based on the construction of the system, cells that have been transfected with all three plasmids and have been treated with doxycycline should be the only ones that emit a green glow under the microscope. If this sensor is successful, it can be a very useful tool in measuring NAD<sup>+</sup> concentrations in mammalian cells.

Xinrui Zhang  
Leverett 2014

Molecular and Cellular Biology

### Mitochondrial prohibitin-2 mutation stimulates drug detoxification in *C. elegans*

Ruvkun Lab  
Molecular Biology, Genetics,  
Massachusetts General Hospital, Harvard Medical School

As with all organisms, the soil-dwelling nematode *Caenorhabditis elegans* faces an environment with finite resources that drive interspecies conflict. It has been proposed that, to defend against toxic compounds and virulence factors released by its microbial co-inhabitants, *C. elegans* has evolved astute molecular surveillance pathways to recognize damage to core cellular components and subsequently launch immune and detoxification responses to counter such xenobiotic invasion. To better understand the effect of lesions to core cellular components on xenobiotic stress response, which holds immense implications for not only developmental biology but also human drug therapeutics, we sought to elucidate the pathways by which perturbation to one mitochondrial protein, prohibitin-2

(PHB-2), results in resistance of the nematode to drugs of a variety of chemical nature. Because PHB-2 is not enzymatically involved in drug detoxification, we hypothesized that the drug resistance sprang from broad-spectrum up-regulation of metabolic survival pathways triggered by mitochondrial stress in phb-2 mutant nematodes. Using quantitative real time PCR, we found five cytochrome P450 genes known to respond to xenobiotics whose expression was drastically up-regulated in phb-2 mutant in the absence of foreign toxins, substantiating our mitochondrial stress model for drug detoxification. Ongoing research includes creating five reporter lines with cytochrome P450 promoter regions fused with GFP in phb-2 mutant background to monitor detoxification activity, with the ultimate goal of using such reporters in reverse genetic screens to find genes that are part of the pathway for relaying signal from mitochondrial dysfunction to drug detoxification.

Eric B. Zheng  
Mather 2015

Chemical and Physical Biology

### Investigating the effect of sirtuins on Friedrich's ataxia

Gaudet Lab  
Molecular and Cellular Biology  
Harvard University

To survive, an organism must be able to sense and avoid harmful conditions, like freezing temperatures or toxic chemicals. Eliciting a protective response after exposure to such harmful stimuli is the biological function of pain. The ion channel TRPA1 (transient receptor potential channel, ankyrin subfamily member 1) plays a critical role in the sensation of pain. TRPA1 serves as a temperature sensor: specifically, it senses extreme cold in mammals and warmth in insects. TRPA1 also senses pungent chemicals like those found in wasabi, mustard, and cinnamon and has been implicated in protective responses such as coughing and regurgitation. TRPA1 is therefore polymodal; that is, it is activated by multiple stimuli. Such polymodal function poses a challenge in terms of specificity; organisms must distinguish signals resulting from different stimuli to respond appropriately. In insects, this is accomplished through alternative splicing. One isoform, expressed in the proboscis, lacks temperature sensitivity, allowing it to be specific for potential toxins; the other isoform, expressed in the head, and thus removed from chemical exposure, acts specifically in response to heat. Intriguingly, these two isoforms differ only at a short region at the N-terminal end of the protein, implying a critical role for the N-terminus in determining the sensory functions of TRPA1.

We seek to understand the structural basis for this functional modulation using both biochemical and structural approaches. Techniques such as multi-angle laser light scattering and cross-linking experiments may uncover possible multimerization interactions, while circular dichroism and X-ray crystallography can reveal structural details key to the modulatory process. Understanding the molecular mechanism of N-terminal modulation of TRPA1 could also help explain the reversal of temperature sensitivity between insects and mammals.



# NEUROSCIENCE

Opeyemi Alabi  
Pforzheimer 2013

*Neurobiology*

## Examining the connective principles of axons that synapse on a basal dendrit

Lichtman Lab  
Molecular and Cellular Biology,  
Harvard College

The central nervous system is a veritable labyrinth of synapses and cell types, an enigmatic matrix of neural connections, which somehow function together to produce what we perceive as behavior. In the human brain alone, there are hundreds, if not thousands, of classes of neurons, each with distinct properties and functions. These individual classes are coordinated to form webs of connections, or circuits, which collectively function to control aspects of behavior. While this web of connections may seem inscrutable now, scientists are escalating efforts to understand the fundamental underpinnings of basic brain processes. The goal of this project was to elucidate a specific element of the fundamental organizing principles of connectivity within the neocortex. To do this, I digitally reconstructed axons that synapsed on a basal dendrite and built a matrix describing their synaptic connections with neighboring dendrites in a defined volume. By analyzing this matrix, I hope to answer whether or not there is a difference in connectivity between the axons that synapse on the basal dendrite and those that synapse on its neighbors.

Namrata Anand  
Adams 2014

*Chemical and Physical Biology*

## Studying synapses via optical imaging

Cohen Lab  
Chemistry and Chemical Biology; Physics,  
Harvard University

Optogenetic tools can greatly advance the understanding of circuit-level and system-wide activity in neuroscience research. In mammalian neurons, single action potentials have been simultaneously initiated and recorded through the use of Optopatch: a blue light-gated ion channel used in junction with a voltage-sensitive, endogenously fluorescent microbial rhodopsin protein Archaeorhodopsin-3 (Arch). The tandem actuation and recording abilities of the Optopatch system can be utilized to analyze synaptic activity, variability, and transmission at the local level—that is, at the junction between pre-synaptic and post-synaptic neurons—a regime that is inaccessible to classical electrophysiology techniques. This tool can be used to map the functional connectivity of neural networks and to characterize synapse-affecting diseases.

While optogenetic pH sensors have been used to resolve

single synaptic vesicle exocytosis and endocytosis events, we believe that optical highlighter proteins whose photoconversion rates demonstrate local pH sensitivity have the potential to record synaptic activity at a global level. Photoconvertible, switchable, or activatable proteins are capable of changing fluorescent states upon stimulation at specific wavelengths of light. We are currently searching for proteins whose photophysical properties ensure photoconversion is minimal within the acidic environment of the vesicle and increases with exposure to neutral pH. Targeting these proteins to synaptic vesicles will allow us to take a light-activated snapshot of the global state of synaptic activity in the brain at a given moment.

Asante Badu  
Leverett 2013

*Neurobiology*

## Memory retention of emotionally charged events in an extended audiovisual narrative

Kreiman Lab  
Neurobiology,  
Boston Children's Hospital

The project the Kreiman Lab is working on has three dimensions: (1) creating computational models for the neural circuitry involved in visual processing, (2) exploring the neurophysiology that underlies object recognition and learning/memory, and (3) gaining a better understanding of the psychophysics that underlie the transition of visually presented stimuli from short to long term memory. The aspect I am pursuing is the psychophysical dimension of creating long term memories—what determines the transformation of the stream of images presented during a movie into long-term memories? A problem with many studies conducted by presenting people with a series of images of isolated objects flashed on a screen is that it does not accurately simulate the visual stimuli we are realistically presented in life which occur in a continuous stream, in the presence of complex clutter and background and can change rapidly. The long term aim is to use the more realistic medium of movies to explore the interplay between emotion and memory and to tease out any differences that may exist in the retention of scenes in which emotions are simply observed versus scenes in which emotions are elicited. A lot of my summer research has been focused on establishing a more objective system for characterizing emotion with the goal of incorporating this system into the future experimental design. The Kreiman Lab has the unique opportunity to examine neural activity in epileptic patients in whom electrodes have already been implanted for clinical purposes and the hope is to pair the results of this psychophysical experiment with neurophysiological recordings from these patients as they watch the movies to explore memory and emotion centers in the brain.



Rupak Bhuyan  
Winthrop 2013

Neurobiology

### Disruption of synaptic plasticity in hippocampal CA1 area by soluble amyloid beta

Murthy Lab  
Molecular and Cellular Biology,  
Harvard College

Alzheimer's disease (AD) is a progressive disorder that eventually results in dementia, a nonspecific mental illness syndrome caused by gradual brain cell death. One region of the brain that exhibits extensive damage in AD is the hippocampus, which controls the encoding and retrieval of declarative memories, and mediates the consolidation of short-term memories into long-term ones. It is currently believed that hippocampal plasticity underlies learning and memory. Plasticity in neuroscience is defined as a change in the strength of a synapse, or junction, between two neurons due to prior activity of that synapse. Using electrophysiological techniques, one way to observe plasticity involves measuring changes in the amplitudes of electrical potentials for a given synapse. A recent hypothesis proposes that an abnormally high concentration of the soluble form of the amyloid beta protein (A $\beta$ ) is associated with memory loss and synaptic injury in AD. It has been demonstrated that soluble A $\beta$  oligomers disrupt plasticity. My lab planned to confirm this effect of soluble A $\beta$  on one mechanism of plasticity called long-term depression (LTD), and then test a novel hypothesis about the molecular basis of this disruption. Whole-cell patch clamp electrical recordings were conducted on hippocampal CA1 neurons in mice that were 8 or more weeks old. Changes in synaptic strength in hippocampal neurons before and after induction of LTD were measured with an intracellular recording electrode. LTD was observed in control neurons, whereas preliminary data indicated that LTD was not observed in CA1 neurons that were bathed in soluble A $\beta$ . These results are in agreement with previous studies, and we are now undertaking studies examining the mechanisms underlying this disruption.

Jimmy Bohoslav  
Currier 2013

Neurobiology

### Food preference in larval zebrafish

Engert Lab  
Neurobiology,  
Harvard College

According to the CDC, more than 35% of Americans are considered obese. In addition, more than 8 million Americans have eating disorders such as anorexia or bulimia. Therefore, it is of critical importance to understand the brain circuitry involved in our desire for food. I developed a behavioral assay for the food preference of larval zebrafish. Using zebrafish as a model system allows for high-throughput experiments with powerful genetic, molecular, and opti-

cal tools. I built a fish tank that allows fish to move freely throughout, but has food only on one half of the tank. This offers the fish a choice between eating and not eating, depending on its location in the tank. I track their coordinates automatically with an infrared camera. Fish consistently swim on the side of the tank that contains paramecia, small protozoa that are natural prey for the larval zebrafish. Many animals use the neurotransmitter serotonin (5-HT) to signal the desire for food, or as a reward upon consuming food. Exposing larval zebrafish to serotonin antagonists abolishes their preference for food. This is the first hint of the mechanisms of food desire and reward in larval zebrafish. Further studies will elucidate the role of the dopaminergic and opioid systems on food desire and reward. Eventually I will be able to ablate individual neurons in the fish's brain to assess their role in computing food desire and reward.

Ian Boothby  
Mather 2014

Molecular and Cellular Biology

### Patterns of synapse elimination in the levator palpebrae superioris muscle

Lichtman Lab  
Molecular and Cellular Biology,  
Faculty of Arts and Sciences

Determining the basis for learning remains one of the greatest unsolved problems of neuroscience, and synaptic plasticity—the remodeling of wiring and synaptic strength between neurons—is thought to play a major role. One possible model for synaptic plasticity in the central nervous system (CNS) is synapse elimination in the neuromuscular junction (NMJ). At birth, the mammalian NMJ contains excessive wiring, with multiple axons innervating each muscle fiber, but throughout early postnatal life, these axons are pruned such that adults have only one axon innervating each muscle fiber. As the simplest, most accessible, and best understood type of synapse, the NMJ is a useful model for studying the CNS, and research on synapse elimination may be applicable to synaptic plasticity in the CNS.

The aim of this project is to use confocal microscopy to gain insights into the progression of synapse elimination in the mouse levator palpebrae superioris (LPS), a muscle responsible for raising the eyelid. Determining the exact wiring patterns of NMJ can be difficult because of the density of axons, so this project uses Brainbow mice, which have easily distinguishable neurons that randomly express differently-colored fluorescent proteins. The LPS is particularly interesting because its synapse elimination is delayed, taking over two months (as compared to two weeks for other muscles). This property makes it easier to observe intermediate stages of synapse elimination, and hopefully to develop a model of how the order and timing of the process.

Shaunte Butler  
Currier 2014

Neurobiology

### **Cranial nerve development in TUBB3 R380C mutant**

Engle Lab  
Neurobiology,  
Boston Children's Hospital

Congenital fibrosis of the extraocular muscles type 3 (CFEOM3) is a disorder characterized by restricted eye movements due to dysinnervation of the cranial nerves. CFEOM3 has been linked to mutations in the TUBB3 gene, which encodes for beta-tubulin isotype III which is specific to the nervous system. The R380C TUBB3 mutation is a dominant mutation characterized by drooping of the eyelids (ptosis), Marcus Gunn jaw-winking syndrome, and agenesis of the corpus callosum. In this project, we look to characterize the development of the cranial nerves in the R380C homozygous and heterozygous mutant and contrast it to the development of the cranial nerves in the wildtype mouse by performing whole mount neurofilament staining in embryonic day 11.5 mice that will allow us to look at the trajectory of the cranial nerves. Based on the symptoms in human patients we predict that cranial nerves III(oculomotor), IV (trochlear), and V (trigeminal) will be affected in the mutant and heterozygous mouse.

Herbert Castillo  
Kirkland 2014

Neurobiology

### **Identification of specific genes and potential gene regulatory mechanisms by which Ube3a loss (AS, Ube3a<sup>am</sup>-) or increase (Idic15 Autism, Ube3a<sup>2xTg</sup>) alters gene expression in cortex and cerebellum**

Anderson Lab  
Department of Pathology and Neurology,  
Beth Israel Deaconess Medical Center

Autism is a neurological disorder with complex genetic origins. It is characterized both by impaired communication and social interactions and by repetitive and stereotyped behaviors. Studies have shown that duplication of the maternal 15q11-13 region is associated with ASD, while maternal deletion causes Angelman Syndrome, a closely linked neurological disorder. The 15q11-13 duplication is the most common copy number variation (CNV) in ASDs, responsible for 1-3% of all cases. UBE3A is an imprinted gene. In the brain only the maternal copy of the gene is normally active, suggesting its role in 15q ASDs. After successfully creating mouse models with one or two extra copies of Ube3a by bacterial artificial chromosome recombineering, these subjects displayed autism-like behaviors measured by behavioral analysis of social interaction, stereotyped behaviors, and communication. We are now interested in the effects of deletion and duplication of Ube3a on gene expression. Cortex and cerebellum RNA from wild type, Ube3a<sup>am</sup>-, and Ube3a<sup>2xTg</sup> assayed by Affymetrix DNA chip hybridization and confirmatory transcript qRT-PCR show differences in gene regulation by Ube3a gene dosage. We are

currently analyzing the gene regulation results and producing annotations of each of the genes. Performing transcriptome profiling can ultimately help us formulate an explanation on how extra copies of Ube3a create an autism phenotype.

Michael Drumm  
Pforheizer 2015

Undecided

### **Examining dreams and performance in a 3-D spatial learning task and examining music as a trigger for dreams and for improved memory consolidation**

Stickgold Lab  
Center for Sleep and Cognition,  
Harvard Medical School

It is generally known that sleep is good for you, but why this is true is still not perfectly clear. The lab that I am working in attempts to dissect the mechanisms underlying sleep-dependent memory consolidation. Currently, my lab hypothesizes that dreaming of a newly learned spatial memory task at sleep onset leads to prioritized memory processing later in the night. To explore this idea further, we currently have subjects complete a Virtual Maze Task before they go to bed and also in the morning, and we collect EEG data and dream reports at night. Specifically, this experiment attempts to discover if the reward component or the auditory feedback component of the VMT, or both, drive the increased incorporation of dreams as well as increased performance.

The second experiment that I am involved in also utilizes the virtual maze as its spatial memory task, but instead attempts to examine the role of music in increasing memory consolidation during a post-learning nap. My lab hypothesizes that music played during sleep increases coherent gamma band oscillations in key areas of the brain, and music that is played both when the subject is learning the task and when asleep will act as a reactivation trigger of task imagery. Both of these things will lead to increased sleep-dependent memory consolidation. In fact, in a pilot study, my lab showed that subjects that heard music during both the task and during sleep reported almost tenfold more dream reports related to the task and performed better on the retest than did a control group. This current experiment is designed to explore this area further.

Nicole Golbari  
Dunster 2013

Neurobiology

### **Behavioral cues as triggers for aggression in *Drosophila melanogaster***

Kravitz Lab  
Department of Neurobiology,  
Harvard Medical School

Aggression is a behavior present in almost every complex organism. Understanding aggression is key to understanding social dominance, successful reproduction, and evolution. *Drosophila melanogaster* is an ideal species to study when analyzing the neurobiology of aggression. A completely sequenced genome, short generation time, an easily manipulated nervous system, and specific sexually dimorphic behaviors make *Drosophila* an excellent species to use for behavioral analysis and genetic manipulation.

In a previous study, the Kravitz lab discovered that aggression is not a default behavior in wild type males, but that aggression is stimulated by pheromonal and behavioral cues. When masculinizing the female pheromonal profile, the researchers found that wild type males attacked the females that expressed male pheromones. However, they also found that in female flies with masculinized nervous systems (ie: females that express female pheromones, but exhibit male-like aggressive behavior), the male initially courted the female, but eventually, the masculinized behavior was sufficient to stimulate the wild type male's aggression.

I perform genetic crosses to generate masculinized female *Drosophila*. By manipulating a splicing factor named transformer, I am able to switch the sexual differentiation of the nervous system. I pair wild type males with masculinized females to try to understand why the males attack the females. There is likely a learning process, involving the recognition of threatening behavioral cues from the female, by which a male realizes or decides that the female is an opponent and chooses to retaliate and attack. By scoring certain parameters, such as the frequency that a masculinized female performs a male specific lunge, I will hopefully find a correlation between a specific cue and the onset of *Drosophila* male aggression.

Kyle Green  
Kirkland 2014

Neurobiology

### **Age related changes in gene expression of photoreceptors in the mouse retina**

Sanes Lab,  
Molecular and Cellular Biology,  
Harvard College

As the nervous system ages cognitive functions such as memory decline, reflexes and mobility deteriorate, and the brain becomes more susceptible to disease. However, little is known about the molecular causes of these alterations. To begin to uncover these molecules, we have focused our analysis on the mammalian retina. The retina is an ideal system to undertake such studies as it is composed

of identifiable populations of neurons whose circuitry underlies the first stages in visual processing. In addition, an aged retina recapitulates many changes observed in an aged brain, including alterations in neuron connectivity. Our studies have shown that photoreceptors, the light sensing neurons in the retina, are especially vulnerable to age-related changes. With age, the connections between these neurons rewire and become mislocalized, which may contribute to decreased visual function in the elderly. To uncover the molecules responsible for these processes, we are undertaking a series of studies using both microarrays and RNA-seq to compare the gene expression profiles of photoreceptors from young and old mice. In addition to elucidating the underpinnings of neuronal aging, these studies may identify pathways that could potentially aid in preventing or reversing neuronal miswiring with age.

Margaret Ho  
Cabot 2015

Chemical and Physical Biology

### ***Analysis and rescue attempt of autism-like behaviors in OGAD65 knockout mice***

Hensch Lab,  
Molecular and Cellular Biology, Neurobiology,  
Harvard College

Autism is a largely enigmatic disorder, with patients that suffer from an Autism Spectrum Disorder (ASD) exhibiting a broad range of deficits of varying severity. Nevertheless, there are three defining diagnostic criteria of ASD: repetitive and obsessive behaviors, impairments in language and communication, and aberrant social behaviors. While many genes have been found to be associated with ASD, the etiology of the disease remains unknown.

Mouse models are an important tool for discovering the neuronal changes underlying ASD. One unifying hypothesis that has emerged from studies of both animal models and humans is that a disruption of the excitatory/inhibitory (E/I) balance in the brain may underlie the disorder.

To test directly whether disruption of E/I balance throughout the entire brain may lead to the manifestation of autistic traits, we investigated autism-related behaviors in GAD65 knockout (KO) mice. These mice were genetically engineered from the normally highly social strain of C57BL/6J mice to lack one of the two primary enzymes that synthesize the inhibitory neurotransmitter GABA ( $\gamma$ -aminobutyric acid). Remarkably, we found that GAD65 KO mice exhibited behaviors reported in other mouse models of ASD, such as abnormally high grooming and decreased social interactions compared to wild type C57BL/6J mice.

Using the finding that diazepam triggers critical period plasticity in the visual cortex of GAD65 KO mice, which do not enter this phase until an inhibitory threshold is reached (Fagioli & Hensch 2000), a rescue experiment was formulated. We hypothesize that diazepam may also reestablish proper E/I balance in neuronal circuits implicated in the expression of autistic behaviors by increasing GABA inhibition. The investigation of the behavioral consequences of this rescue attempt is currently ongoing.

Saheela Ibraheem  
Quincy 2013

Neurobiology

### **Signs of old in young: How apolipoprotein E affects cortical thickness and functional connectivity in young adults**

Buckner Lab  
Psychology,  
Harvard University

Apolipoprotein E, commonly referred to as ApoE, is a gene that has been identified as the strongest predictor of risk for Alzheimer's disease. There are three allelic variants of the gene, namely e2, e3, and e4. While the e2 allele is shown to have protective effects against Alzheimer's, the e4 allele is associated with greater risk for the disease, with the chance of e4 homozygotes developing Alzheimer's being up to fifteen times the probability for e2 homozygotes. We want to determine if the divergent effects of the e2 and e4 alleles develop in young adulthood. Thus, we respectively use magnetic resonance imaging, MRI, and functional connectivity magnetic resonance imaging, fMRI, to determine how the ApoE variant affects cortical thickness and functional connectivity, or the strength of connections, of brain regions in subjects between the ages of 18 and 35. Since the default network, the connection of brain areas that is most active during rest, is affected in Alzheimer's patients, regions of this network, including the posterior cingulate, the medial orbitofrontal, and the rostral anterior cingulate, in addition to the hippocampus, are analyzed. The differences in cortical thickness and functional connectivity of these structures between e4 homozygotes and e2 carriers, specifically e2e2 homozygotes or e2e3 heterozygotes, are then quantified. While systematic differences do not guarantee a link to the disease, if results prove significant, Alzheimer's risk in old age could be observed in youth, with MRI and fMRI, compared to genotyping for ApoE, more easily incorporated into medical procedure. Consequently, different methods may be used to determine the underlying causes of the association between these anomalies and Alzheimer's risk, aiding in early protection against this disease.

Frank Maldonado  
Lowell 2013

Neurobiology

### **Eye tracking as a predication of emotional states**

Kreiman Lab,  
Neurobiology,  
Boston Children's Hospital

The Kreiman lab deals with visual object recognition and understanding how subjects interpret various emotional and physical stimuli. This summer, we aimed to connect emotional qualities of movies and TV episodes with memory and visual eye tracking data. Primarily, we asked whether subjects were better able to remember clips with high emotional content that was either elicited in the viewer or observed in the clip itself. For example, often there may exist a mismatch between the emotions a viewer feels and those observed in the

clip. To validate our interpretation of emotions, multiple researchers spent time annotating clips for characters, movement, emotions, and objects in the scene. In terms of emotional mismatch, oftentimes, during an interrogation scene, the interrogator may not express any emotions, but viewers would legitimately be disgusted or anxious.

Using Eyelink, a device that tracks eye movements, we are able to note where subjects tend to gaze in each frame of the TV show 24. Previous research by Borod et al. has demonstrated that subjects tend to look significantly more to the left than the right to emotional stimuli, a derivative of increased right hemisphere involvement in the emotional processing. Building on this understanding, we aim to help illuminate whether congruency across subjects in terms of eye movements can be informative of the emotions presented in the clips. Since emotionally laden stimuli tend to lead to greater memory recall, a natural extension of this hypothesis is whether eye movements, in turn, could be correlated to recall and recognition of clips.

Rachel Moda  
Eliot 2013

Neurobiology

### **Characterizing transcriptional regulation of the DYT6 dystonia gene, THAP-1**

Dr. Christopher Bragg  
Neurology,  
Massachusetts General Hospital

Dystonia is a movement disorder characterized by sustained, involuntary muscle contractions, thought to result from aberrant signaling in brain regions controlling movement. DYT6, a hereditary form of primary dystonia, is linked to many different mutations in THAP-1, which encodes the THAP-1 DNA binding protein. The majority of DYT6-related THAP-1 mutations lie within the coding sequence. However, four single nucleotide polymorphisms (SNPs) have been identified in the putative 5' promoter region, which appear differentially enriched in DYT6 versus control individuals. These SNPs are -236\_237 GA>TT, -42 C>T, -40 T>C, and -32 C>T. The importance of the promoter region in the ultimate regulation and transcription of THAP-1 makes these SNPs significant for further investigation as potential disease modifiers.

Efforts to understand the THAP-1 promoter region have been directed in two main areas. First, to analyze the effects of the four SNP variants on THAP-1 expression, mutagenesis is used to introduce the polymorphisms into THAP-1 cDNA clones. These cDNAs, driving a firefly luciferase gene, are employed in luciferase reporter assays to determine the relative effect the SNPs have on THAP-1 expression. Second, bioinformatics analysis has identified nine transcription factors that may bind to the promoter region of THAP-1. These transcription factor cDNAs, along with three controls, have been obtained for use in the luciferase reporter assays to analyze subsequent modifications in THAP-1 expression. The results of this experiment will aim to identify previously unknown transcription factor binding sites on THAP-1 that may indicate pathways by which THAP-1 is regulated.



Abdullah Nasser  
Cabot 2013

Neurobiology

George Plummer  
Lowell 2013

Neurobiology

## **RalA drives dendritic spines formation in the hippocampus**

Schwarz Lab,  
Neurology and Neurobiology,  
Boston Children's Hospital

RalA, a small GTPase, is a member of the Ras family of proteins. It has been shown to participate in exocyst assembly regulation, increase folding in sub-synaptic reticulum in the *Drosophila* neuromuscular junction, and play a vital role in supporting tumorigenic transformation in human cells. In the hippocampus, RalA has been shown to increase neuronal branching, yet its role in dendritic spines formation is not well understood. Dendritic spines are important because they have been previously implicated in memory formation and experience-dependent plasticity. Our work shows that RalA, through its interaction with Sec5 of the exocyst complex, increases dendritic spines density in 20 day-old hippocampal neurons by about 30%. However, 48-hour expression of constitutively active RalA does not change the length or width of dendritic spines, nor does it significantly impact the morphology of neurons.

Akhilesh Pathipati  
Quincy 2011

*Organismic and Evolutionary Biology*

## **Predictability of Human Movements**

Assad Lab,  
Neurobiology,  
Harvard Medical School

Humans possess an incredible ability to see and understand movements around them. If I reach towards a basket that has apples in it, you understand that I am reaching for an apple long before my hand actually makes contact. When a quarterback launches a football into the air, the receiver is able to predict the trajectory of the ball even if he loses sight of it while the ball is in the air.

Despite the relevance of such skills, researchers have only recently begun to understand the cognitive underpinnings that allow us to make such predictions. One question that has remained unanswered is how perception may vary for different types of movement. For instance, is our predictive power better for human motion or for the movement of objects (like a ball)? Intuitively, one may guess that we are evolved to perceive biological motion. However, biological motion follows rigid empirical laws that constrain the relative velocity and curvature of motion, as described by the two-thirds power law. As such, it may be that our predictive power for human movements declines if we see movements that do not comply with that law.

My research investigates this phenomenon by evaluating how perception varies for different types of stimuli. More specifically, I am comparing how well subjects predict the movement of human avatars compared to more abstract stimuli, including point-light stimuli (dots arranged in the outline of a human form) and dots. The results will shed light on the cognitive phenomena that underlie action perception.

## **Axonal morphologies of individual retinal ganglion cells**

Engert Lab,  
Molecular and Cellular Biology,  
Harvard Faculty of Arts and Sciences, Harvard College

Retinal Ganglion Cells (RGCs), transmit sensory information from the photoreceptors and interneurons in the eye to the brain. To better understand the transmission of this information, the morphological inputs and outputs must be uncovered. Many studies have looked into the inputs of RGCs, by studying the dendrites. We hope to gain a deeper understanding about this visual circuitry, by studying the axonal morphologies of individual RGCs.

To study the morphology of the individual axons in RGCs, we designed zebrafish with photoactivatable green fluorescent protein. This protein can be converted to fluoresce when UV light is shone on the fish. By photoactivating individual RGCs in the eye (identified by expression of red fluorescence in neural cell bodies of RGCs), we attempted to trace the axons and identify their terminals. This method has had issues, so we are currently designing new fish with the same protein, which will get actively transported to axon terminals.

In the meantime, we have also undertaken a different method, using a way to transiently randomly induce expression of three different fluorescent proteins in neurons. Current finding suggest that individual RGCs project to individual regions in the brain, called arborization fields.

As a side project, I have also undertaken the study of neurons that receive input from the RGCs, by photoactivating arborization fields known to receive innervations from the RGCs. The methodology again need to be perfected; however, pilot studies show some promise.

Laura Polding  
Winthrop 2014

Neurobiology

## **Automaticity in object recognition in *rhesus macaques***

Livingstone Lab,  
Neurobiology,  
Harvard Medical School

Distinct regions of the inferior temporal lobe (IT) in macaque monkeys respond selectively to different categories of visual objects, providing primates with the ability to recognize and differentiate between complex visual stimuli. Previous studies in our lab have shown that intensive early experience can influence the development of specialized modular organization in macaque IT. Early experience allows for more fluent processing of visual objects and the development of a high degree of automaticity, defined here as the ability to rapidly recognize images in a visual discrimination task and the inability to override this automatic response. It remains unknown how factors such as age-of-learning, relative order of learning and differences in low-level visual features of stimuli affect automaticity in primates. I trained two rhesus monkeys to recognize and discrimi-

nate between exemplar images using a delayed match-to-sample task presented via an in-cage touchscreen system. For each trial, the monkey was presented first with a sample stimulus image on the touchscreen monitor, followed by a one-second delay prior to the side-by-side appearance of two choice stimuli, one of which identically matched the sample. The monkey received a fluid reward for correctly matching the choice stimulus to the sample in each of four scenarios in which the two choice stimuli were identically rotated 0°, 90°, 180°, or 270° to investigate the degree to which macaque object recognition is orientation-invariant. Analyzing reaction times and percentage of trials correct will allow comparison of differences in automaticity between earlier- and later-learned symbol sets. This research will yield further insight into the functional organization and selectivity of IT and may contribute to understanding of object recognition and symbol processing pathways in humans.

Kelly Shim Robinson    *Neuroscience (Mind, Brain, and Behavior)*  
Adams 2013

### Meditate to Create

Lazar Lab,  
Psychiatry and Neurobiology,  
Massachusetts General Hospital

Creativity is an extremely complex human behavior that requires a multitude of approaches to understand; yet it can be seen as one of the fundamental elements defining humans as it allows us to flourish throughout our lives. Likewise meditation is equally as difficult to scientifically define, as there are hundreds of methods.

Theoretically, meditation should be able to induce states of higher creativity, as meditation is known to reduce levels of anxiety, fear, and judgment while increasing internal and external awareness, thus allowing for higher probability of new connections. However, humbly accepting the idea that there is still no set psychological or neural mechanism fully explaining both, I approach them not as a whole, but focus on particular, well-defined meditations and subcomponents of creative performance.

In the Lazar Lab at MGH, we are working to establish pre- and post- structural and functional neuroimaging for subjects participating in an 8-week meditation program. The 30-year-old program (Mindfulness Based Stressed Reduction) requires the students to practice a combination of open-monitoring and focused-attention mindfulness meditations. We are administering several psychological tests and surveys including the TTCT, a figural and verbal test that can determine a base line of comparison for divergent thinking skills (vs. convergent thinking).

Through neuroanalysis of the data, we hope to show that there may be a connection between creativity and meditation. In particular, we are focusing on the temporo-parietal junction, which has been shown to change in neural density following the MBSR (along with changes in the amygdala, hippocampus, insula, and prefrontal cortex).

Lynn Shi  
Leverett 2013

*Neurobiology (Mind, Brain, and Behavior)*

### Tracing the brain's connections to dopamine neurons

Uchida Lab  
Molecular and Cellular Biology,  
Harvard College

The midbrain dopamine system is central for movement, learning, and motivation. Malfunction of this system can result in disease states such as Parkinson's disease and schizophrenia. Developing a better understanding of the specific neuronal connections provides critical insight into how circuits underlie behavior and various disease states. In order to identify specific inputs to dopamine neurons, we combined the Cre/loxP expression system with rabies virus-based transynaptic retrograde tracing to allow our starter cells to be restricted to a certain neuron type and control level of transynaptic spread. Using mice as a model, my project involves mapping di-synaptic inputs to dopamine neurons via various brain regions, including ventral pallidum, ventral striatum, lateral hypothalamus, along with anterograde tracing from the olfactory region to understand the nature of sensory processing to the dopamine system. These circuit-tracing experiments complement data acquired from electrophysiological techniques, and lays a foundation to study how neural circuits that regulate dopamine neuron activity underlie mental activities and pathological states associated with dopamine dysfunction.

Christine Shrock  
Pforzheimer 2013

*Neurobiology*

### The role of ionic zinc in neuronal cell death after optic nerve injury

Benowitz Lab,  
Neurosurgery,  
Children's Hospital, Harvard Medical School

Retinal ganglion cells (RGCs), the projection neurons of the eye, play a crucial role in the transduction of visual information from photoreceptors to the brain. It is known that under normal conditions, RGCs, like most other adult neuronal cells in the central nervous system, are unable to regenerate axons after injury, but instead undergo cell death. As a result, victims of traumatic brain injury or neurodegenerative diseases such as glaucoma are often left with permanent visual loss.

At present, the molecular events that underlie the death of RGCs after axonal injury are still not well understood. However, preliminary data from the Benowitz Lab has shown that ionic zinc, which is toxic to neurons, is dramatically elevated in the retina shortly after optic nerve injury, and that blocking this increase can promote neuronal survival and regeneration. We hypothesize that Zn<sup>2+</sup> may be a trigger for the cell death pathway and study this effect in mouse models, using fluorescent sensors and other markers to determine the location of zinc in the retina, as well as how zinc levels change at different time points after injury, with and without treatment. Our current data has yielded exciting results, showing that zinc elevation occurs as early as one hour after injury, making it the earliest detectable marker. In addition, multiple different staining methods

have produced similar patterns of zinc localization in the retina. We hope our findings will provide further insight into the specific role that zinc plays in causing cell death, and the mechanism by which it acts, so that we can intervene and reverse the damage caused by nerve injury.

Greta Solinap  
Currier 2013

*History and Science*

### **Behavioral and physiological phenotypes in Rett syndrome mice models**

Fagiolini Lab,  
Neurobiology,  
Boston Children's Hospital, Harvard Medical School

Rett Syndrome (RS) is a neurological disorder that reverses the normal development of various cognitive and motor functions in females, with symptoms beginning at around 6-18 months of age. They typically lose their ability to walk and speak, eventually becoming fully intellectually disabled and manifesting cardiovascular and autonomic impairments. RS is caused by a mutation in the X-linked gene methyl-CpG-binding protein 2 (MeCP2). Mice models with a loss-of-function mutant allele recapitulate many of the features of RS, and are pivotal in elucidating the neural and physiological mechanisms underlying the pathogenesis of the disease. This summer, my research consisted of studying a variety of behavioral and physiological characteristics in two mouse models of RS.

In RS, abnormalities like social behavior deficits and autistic features are prominent. To study this phenotype in mice, several anxiety tests such as the open-field and elevated plus maze tasks were conducted. Unlike anxiety, cardiovascular autonomic dysfunction has been minimally investigated in mouse models. From patient data, it is implicated that the high incidence of sudden, unexpected deaths in RS has a cardiac origin. To study certain autonomic and cardiovascular functions, an electrocardiogram (ECG) device designed specifically for mice was used to gather a variety of data, including autonomic properties using a power spectrum analysis program.

The better scientists can characterize the phenotypic profiles of certain mice models, the more information doctors will have on treating RS patients, eventually transitioning that knowledge from bench work to clinical therapeutics. In this light, our project collaborates with clinical researchers, including the Nelson lab, a lab of Cognitive Neurosciences, to compare our mice data to patient databases.

Gaynel Cordero Taveras  
Currier 2013

### **Candidate-based search for APP ligands that modulate APP-dependent neurite outgrowth**

Selkoe Lab,  
Center for Neurologic Diseases,  
Harvard Medical School

Retinal Ganglion Cells (RGCs), transmit sensory information from Alzheimer's disease (AD) affects about 5.4 million people in the United States. AD causes memory loss, the inability to interpret ones surroundings, communication problems, and can lead to behavior changes. AD is pathologically characterized by the buildup of plaques composed of the amyloid-beta peptide (A $\beta$ ) and neurofibrillary tangles composed of the Tau protein. The A $\beta$  peptide is generated by proteolytic processing of the Amyloid Precursor Protein (APP) during normal cell metabolism. Several therapeutic strategies for AD, some of which have already entered patient trials, aim to inhibit APP processing to prevent A $\beta$  generation. To understand the potential effects of reducing APP processing to treat AD, it is important to decipher the normal functions of APP and to understand the molecular pathways through which APP executes these functions.

Several functions of APP during neuronal development have been reported including neurite outgrowth. Multiple candidate ligands have been proposed to interact with the ectodomain of APP and modulate APP processing and/or APP function. From our studies of these candidate ligands, Reelin has emerged as a top candidate for a protein that modulates APP processing. The goal of my research is to determine if Reelin is a key regulatory factor of APP-dependent neurite outgrowth. I tested several strategies to investigate the effects of Reelin and APP on neurite outgrowth, including treatment with recombinant protein, transfection, co-culture, and utilizing neurons from Reelin knock-out mice. I performed immunohistochemistry and microscopy to measure neurite lengths of rodent cortical neurons in response to each of these treatments.

Audrey Young  
Currier 2013

*Neurobiology (Mind, Brain, and Behavior)*

### **The effect of early experience on emotional face-processing**

Nelson Lab  
Division of Developmental Medicine,  
Boston Children's Hospital, Harvard Medical School

Facial expressions play an important role in human social communication, providing information about the gender, age, focus of attention, and emotional state of another individual. Face-processing abilities begin to develop in the first few months of life, within a distributed network of brain regions. In addition to biological systems, however, the development of face perception appears to be dependent upon exposure to social stimuli, including infants' early experience with faces. Dr. Charles Nelson and colleagues have proposed that the development of face perception is an "experience-expectant, activity dependent process" (2001 in Moulson et al., 2009). To explore the role of early exposure in the development of emotion pro-

cessing abilities, my research project includes typically-developing children as well as others from two special populations: children with autism spectrum disorders and children who spent their early childhood in Romanian institutions. Though affected by different factors— inherited disorders versus adverse experiences— both groups show similar profiles of psychopathology following early underexposure to social stimuli. These populations can therefore provide important insights into the mechanisms that underlie neural facial processing. While individuals from these groups complete an emotion-processing task, we use electroencephalography (EEG) to record and study electrical activity in the brain. Specifically, we examine event-related potentials (ERP) that are embedded within the EEG recordings. Variations in the amplitude (size) and latency (timing) of ERP components, such as the P1 and N170, will contribute to the identification of group differences in face processing. Focusing on the institutionalized population, I also hope to identify a sensitive period in the acquisition of face-processing abilities and to examine the effect of foster-care placement on social development.

Lingjin Zheng  
*Cabot 2014*

*Neurobiology*

### **Neuron type specific tracing from Dopaminergic and GABAergic neurons in the Ventral Tegmental Area**

Uchida Lab,  
Molecular and Cellular Biology,  
Harvard College

The Ventral Tegmental Area (VTA), part of the mesolimbic pathway in the brain, is thought to be involved in reward, learning, and addiction. The VTA has both GABA neurons and dopamine neurons. These types of neurons use different neurotransmitters and have different functions. Dopamine neurons fire in response to rewarding stimuli. GABA neurons fire when the animal expects upcoming reward, but the mechanisms that generate these responses are unknown. My interest is in finding direct input to GABA and dopamine neurons in the VTA. I inject an adeno-associated virus (AAV) into the VTA that causes neurons to express the Tva receptor and the rabies glycoprotein. Then I inject a modified rabies virus that expresses a fluorescent protein. The modified rabies virus only infects neurons previously infected by the AAV virus and expressing the Tva receptor. These neurons also express the rabies glycoprotein, which the rabies virus needs in order to spread to other neurons. Rabies hops retrogradely (backwards) through the synapses of the infected neuron, and infected cells are seen by looking at the fluorescence. This type of tracing is special because it is neuron type specific. It not only projects to the VTA, but also to a dopamine or a GABA neuron in the VTA. In addition, I use transgenic mice that express GFP in GABA neurons or glutamate neurons in the entire brain. This allows me to determine the neuron type of each labeled input neuron are. These experiments allow for a more a detailed understanding of neural connections involved in processing rewards.



# ORGANISMIC AND EVOLUTIONARY BIOLOGY

Martha Farlow  
Quincy 2013

*Human Evolutionary Biology*

## Unintended consequences: The effects of endogenous and exogenous estradiol on insulin sensitivity

Lipson Lab,  
Human Evolutionary Biology,  
Harvard College

Hormonal contraception (HC) generally consists of a dose of estrogen and progesterone, and is intended to mimic pregnancy, where levels of these ovarian hormones rise and ovulation is therefore prevented. During pregnancy, women become less sensitive to insulin, retaining glucose in their bloodstreams for longer. Some mothers develop an extreme form of insulin insensitivity known as gestational diabetes, which subsides after parturition. There is evidence suggesting ovarian hormones, particularly estrogen, may be responsible for this shift in insulin sensitivity during pregnancy.

My experiment consists of 60 healthy, young women, half of whom are using hormonal contraception, and half of whom are not. The women each complete two overnight fasts (dinner to breakfast): one on day 1 of their menstrual cycle, and one on day 14. After a fast, the body should have low levels of insulin. In a normal, unmanipulated cycle, day 1 is the estrogen nadir, and day 14 is the peak. I am looking at the estrogen and insulin (via c-peptide) levels in samples given by the women just after their fast on both these days. A high level of insulin indicates insensitivity, as the subject had to over-produce it and saturate cells to get glucose absorbed. I predict the lowest levels of insulin will be in the non-HC users on day 1, the next lowest in the non-users on day 14, and the highest in the HC users, as I believe estrogen levels negatively affect insulin's function in a normal biological range.

Emily Groopman  
Kirkland 2014

*Human Evolutionary Biology*

## Food and fertility: The impact of diet quality on male reproductive health

Wrangham Lab,  
Human Evolutionary Biology,  
Harvard College

Humans have long increased the "quality" (available energy content) of their diets through a variety of methods, including grinding, pounding, and cooking (heating). Given the importance of energy in both survival and reproduction, these practices directly impact our evolutionary fitness. Though people today face less challenging energetic environments than those of their ancestors, human reproductive physiology remains acutely sensitive to energy balance. Yet, the impact of energy deficit on male fertility has been largely ignored.

While males do not shoulder the burdens of gestation, processes such as spermatogenesis, growing and maintaining muscle tissue, and producing testosterone represent substantial metabolic investments. Thus, it is likely that energy balance plays some role in male fertility. The low diet quality of raw foodism, abstention from food heated above 115°F, and caloric restriction, limiting intake to remain at 75-80% of natural body weight, directly impacts this relationship. Male practitioners of both exhibit not only low body weight, but decreased libido and sexual performance.

This summer, I investigated the link between diet quality, energy balance, and male fertility via a mouse model. Mature male mice were calorically deprived on either restricted, cooked (CR) or unlimited, uncooked (RF) rations, or given unlimited, cooked portions (CF), of tubers, a food consumed by humans for over 2 million years ago. Feces were collected daily, and, after 5 days of feedings, tissues were collected. Preliminary data strongly supports an energy-dependent model of male reproductive fitness. The CR and RF mice showed lower weights, relative testes mass and testosterone levels compared to the CF subjects. Immunostaining of testes section will also be done to look for histological effects. My findings emphasize the importance of diet quality – via both gross caloric content and food processing – to reproductive and overall health.

Elizabeth Harvey  
Pforzheimer 2014

*Human Evolutionary Biology*

## The effect of cooking on the ratio of isotopes in meat

Tuross Lab,  
Human Evolutionary Biology,  
Harvard College

The question of when humans began cooking is one that has long been of interest to evolutionary biologists. However, no one has pinpointed when cooking started, because it is difficult to find convincing archaeological remains of the fires that would have been used to prepare the food. This summer, I have been working on experiments that could help researchers determine when cooking began.

The goal of this experiment is to determine if there is a detectable change in the natural abundance of the isotope ratios of carbon, nitrogen, oxygen, or hydrogen in cooked meat. To test this, we developed an experimental protocol that cooks meat under controlled temperatures for varying amounts of time. The meat is then freeze-dried, and homogenized before being weighed and analyzed in the isotope ratio mass spectrometer.

After establishing that the process of cooking meat changes the ratios of the isotopes present, we investigated whether these experimentally induced changes are incorporated into animal tissue. We use an unusual animal model: dermestid beetles. For one month, these beetles are fed meat that is either raw, or cooked, and tissues are prepared for mass spectrometry.

We also use ELISA assays to determine the amount of heterocyclic amines that can be found in the cooked meat, and prepare these extracts to determine if the observed isotopic changes caused by cooking are concentrated in this group of combustion compounds. These high temperature molecules are products of cooking meat, and their presence in soils can be seen as evidence of cooking.

Tess Linden  
Currier 2015

*Organismic and Evolutionary Biology*

### Genetic basis of behavioral traits in the cavefish *Astyanax mexicanus*

Tabin Lab,  
Genetics,  
Harvard Medical School

The Mexican tetra *Astyanax mexicanus* is a fish species that exists in multiple forms: a river-dwelling surface form (“surface fish”) and several cave-dwelling forms (“cavefish”). The selection pressures of a cave habitat have caused independent cavefish populations to evolve a set of convergent morphological and behavioral traits that distinguish them from their surface relatives. Morphologically, adult cavefish lack functional eyes due to optic degeneration during development. Cavefish also have altered jaw morphology and greater numbers of cranial neuromasts (sensory organs that detect movement) and taste buds than surface fish. Behaviorally, cavefish display decreased aggression, lack a schooling instinct, and when searching for food, adopt a feeding posture at a lower angle to the ground compared to that of surface fish.

The goal of this project is to study the evolution of behavioral traits in cavefish using quantitative trait loci (QTL) analysis. QTL analysis is a method of locating one or multiple genes for which differences between the alleles of the cave and surface populations cause a particular phenotypic difference between the populations—in this case, a difference in a behavior. The process involves genotyping F2 fish from a cross between cave and surface fish, quantifying the behavioral phenotypes of the F2 fish, and searching for an association between phenotype and genotype across the genome. Separately, the same F2 population will be phenotyped for related morphological traits, such as taste bud and neuromast number, to detect potential correlations between morphological and behavioral traits. Ultimately, identifying the genetic basis of behavioral traits in *Astyanax* could give insight into the genetic processes that underlie the evolution of animal behavior, an area of evolution that remains to be well understood.

Amanda Lu  
Winthrop 2013

*Organismic and Evolutionary Biology*

### Recent evolution of *Mycoplasma gallisepticum* in house finches

Edwards Lab  
Organismic and Evolutionary Biology,  
Harvard Faculty of Arts and Sciences

Infectious diseases can mutate rapidly to evade host defenses following introduction to a new host. *Mycoplasma gallisepticum* is an avian bacterial pathogen that affects poultry and wild songbird populations through conjunctivitis, which can be lethal. Since 1994, *M. gallisepticum* has spread to house finches in much of the United States causing substantial population declines. Although the disease is now endemic among eastern populations, the lower disease prevalence of conjunctivitis in eastern populations suggests a dynamic host-parasite relationship. Previous characterization of *M. gallisepticum* isolates in house finches was analyzed from samples taken during 1994–2007. An exceptionally fast nucleotide substitution rate was reported and functional loss of the genes, which control viral and phage infection.

One of the objectives of our research will be to characterize genetic changes in *M. gallisepticum* isolates (MG) from house finches since 2007 in twelve isolates. With a substitution rate of  $0.8 - 1.2 \times 10^{-5}$  per site per year, we expect to find new variation within the four year time period. After DNA extraction and purification from samples, Illumina library construction, and sequencing of the samples using NextGen, we will incorporate bioinformatics to conduct a comparative analysis with early strains of MG. Further work on this project will seek to clarify gaps in the MG house finch sequence. Of particular interest is the loss of clustered regularly interspaced short palindromic repeats (CRISPR) in house finch MG from poultry strains, which plays an important role in defense against bacteriophages. Although the reason for functional loss is unknown, studying the origin and consequences of CRISPR loss could help determine if it played a role in the expansion of MG into house finches.

Anita Murrell  
Adams 2013

*Organismic and Evolutionary Biology*

### Energetic costs of bumblebee ascending and horizontal flight

Combes Lab,  
Organismic Evolutionary Biology,  
Harvard College

Flight is an energetically costly endeavor for small insects. Bumblebees (*Bombus impatiens*) fly out to flowers of varying distances from their hive in search of nectar and pollen that they can collect and bring back to the hive. During these foraging flights, bees expend different amounts of energy as they forage vertically into the canopy and horizontally over a field. Within the bumblebee colony of closely related sisters, some bees are relatively large while others are much smaller, and these size differences affect the energetic cost of flight. To explore the connection between bumblebee body

size and cost of vertical or horizontal flight, we have built a testing area for a bumblebee colony that simulates aspects of foraging flight while allowing us to take relevant measurements of flight. Using high speed cameras, wing beat frequency and stroke amplitude are recorded and measured for a bee as it travels toward a patch of desirable pollen. Comparing this data during primarily vertical or horizontal flight shows differences in energetic costs between bumblebees of different sizes.

Additionally, larger bumblebees may prefer horizontal foraging flight to vertical foraging flight because of higher vertical energetic foraging costs. Further exploration into the preferential foraging patterns of bees of differing body sizes may also support correlations found in the previously explained biomechanics and wing kinematics of bumblebee flight.

Neil Patel  
Pforzheimer 2013

*Human Evolutionary Biology*

### **The self domestication hypothesis: Using domesticated animals to understand the basis of complex traits in primates**

Ruvolo Lab  
Human Evolutionary Biology,  
Harvard College

Artificial selection against aggression in animals can have dramatic effects on their physiology, morphology, and behavior. Human evolutionary biologists have proposed that selection against aggression in wild species, namely in bonobos and humans, could operate in a similar way, a hypothesis that has been termed the “self-domestication hypothesis”. The bonobo is less aggressive, has a smaller skull, and has shorter canine teeth compared to the chimpanzee, its closest living relative. Many of these features, commonly referred to as the “domestication syndrome,” are also seen in humans.

This summer, I have been testing the domestication hypothesis by searching for signals of convergent evolution amongst humans, bonobos, and domesticated animals. Initially, genes were identified in domesticated animals, such as dogs, sheep, and cattle that are implicated in the domestication syndrome. After producing alignments of orthologous DNA sequences from the genes of interest in primates and other mammals, models of codon sequence evolution using maximum likelihood estimation are employed to test for selection. These models estimate the ratio of nonsynonymous to synonymous mutation rates,  $dn/ds$ , along the different lineages. A  $dn/ds$  ratio greater than one is indicative of positive selection. Within this framework, a signal of positive selection for a domestication gene along the lineages of humans, bonobos, and domesticated animals lends support to the self-domestication hypothesis. I have focused on *CHRNA*, a gene that has been selected during the domestication of sheep and cattle. The protein is important in early development in signaling between nerve and muscle cells. In phylogenetic analyses, it shows an unusual amount of amino acid change along the human lineage.

Elaine Tran  
Adams 2013

*Organismic and Evolutionary Biology*

### **Single Genome Amplification to Study Population Diversity of *Plasmodium falciparum***

Wirth Lab,  
Immunology and Infectious Diseases,  
Harvard School of Public Health

The eradication of malaria requires the combined efforts of people from multiple sectors of the community to confront the epidemic from several directions. Amongst many strategies such as targeting the vector, designing vaccines, and distributing drugs, it is also necessary to study the impact of these efforts, in order to understand how to best combat the spread of the disease. One way to do this is to look at the diversity of the parasite population. Successful interventions should be marked by a decrease in transmission paralleled by a decrease in the number of parasite genomes in patient samples. But there is yet to be a technique that allows deconstruction of clones in multiclonal infections and that accurately and efficiently identify the complexity of infection in a patient sample. Single genome amplification, in reducing template concentration as well as the number of cycles in the standard PCR reaction, has been found to decrease chimera formation which leads to improved accuracy. Using single genome amplification, DNA of individual parasites in multiclonal infections can be sequenced and their haplotypes determined. This technique can be applied to samples from both low transmission and high transmission regions where malaria is endemic, revealing more about the complexity of infections in both regions, and ultimately, how eradication efforts have affected the malaria parasites.

# PHYSICS AND BIOPHYSICS

Christian Anderson  
Kirkland 2012

*Mathematics and Physics*

## The physics of *C. elegans* behavior

Levine Lab  
Physics,  
Harvard College

The *C. elegans* is a 1 millimeter nematode (roundworm) that is used by biologists as a model organism. Before each of its four moltings, the *C. elegans* enters a state of “lethargus” that is characterized by an overall lack of movement. If stimulated, by a beam of light for instance, it might begin moving. My project is to use Fluctuation Response Theory, a tool from theoretical physics, to predict its reaction to these stimulations.

Fluctuation Response Theory (FR theory) is a branch of statistical mechanics that studies the response of systems to small perturbations. It begins with a system that is in thermodynamic equilibrium or with a system that has Markovian dynamics and is in a nonequilibrium steady-state. If the system is perturbed by a small external force, the expectation values of its observables may change. FR theory describes this “response” in terms of correlation functions (“fluctuations”) of the unperturbed system. This analysis holds in very general situations, and it is the source of central theoretical results such as the Fluctuation Dissipation Theorem.

*C. elegans* lethargus constitutes a statistical system: we measure certain observables for the unperturbed worm such as the duration and severity of its occasional twitches. We can combine this data with a theoretical model to predict its response to stimulation. If successful, this will be the first application of this general physical theory to the study of organismic behavior.

Eric Bersin  
Kirkland 2014

*Biomedical Engineering, Chemistry and Physics*

## Towards room-temperature magnetic sensing of a single electron spin in biological systems

Lukin Lab  
Physics,  
School of Engineering and Applied Sciences

A great number of biological mechanisms occur via radical pathways, and being able to detect single electron spins would give great insight into these processes. However, localized room-temperature detection of spins situated outside of the measurement substrate has yet to be accomplished. The nitrogen-vacancy system in diamonds has shown the potential to detect small numbers of electrons spins.

Nitrogen vacancy (NV) centers consist of a missing carbon atom adjacent to a nitrogen impurity in the diamond lattice. Using green light ( $\lambda=532$  nm), we can control the spin state of the NV electrons and measure their interactions with external magnetic fields. Our first experiment is a proof-of-principle demonstration of the detection capabilities of our system. We attach gadolinium (III) to the sur-

face of a bulk diamond in various concentrations and measure the external magnetic field surrounding our NV; this shows how we can detect the concentration of external spins down to the resolution of a few electrons. Our second experiment is an application of these principles in organic systems. We immerse nanodiamonds in a solution of an organic spin label, again detecting varying concentrations of these free radicals. After successfully demonstrating detection of a spin label, we will attach equivalent spin traps to our nanodiamond surface. Inside cells, these nanodiamonds allow us to detect superoxide and other native radicals to nanometer resolution.

Once successfully applied, this system can be used for a wide variety of biological applications. Nanodiamonds can be tagged with antigens and other labeling compounds to target various cell components, allowing measurement of local magnetic and electric fields. This is particularly useful for measuring ion channel action across cell membranes, looking at neuron action potentials, as well as investigating mechanisms of drug delivery.

Irineo Cabrerios  
Pforzheimer 2013

*Mathematics and Physics*

## Structural Color

Amir Lab  
Optics,  
Harvard College

Structural color refers to a broad range of physical phenomena that produce color in the absence of pigment. Objects displaying structural color are characteristically composed of transparent materials with no intrinsic color. Color therefore emerges as the result of various structural properties of the objects. Examples of structural color are ubiquitous in nature. The color of the sky, rainbows, the sheen of a thin film of gasoline on the road, mother of pearl, the human iris, as well as many birds and insects all display structural color.

We made one- and two-dimensional numerical models mimicking the exoskeletal structure of beetles that display structural color and compared our results to experimental data. These models were successful in reproducing some of the general features of the observed beetle spectra. We are currently beginning to explore various questions of optimality: what physical parameters have been optimized to produce a specific appearance and ensure biological “robustness” to variation?

The effects of disorder in these optical systems lead to an unexpected intersection between our research and a topic of interest in quantum mechanical systems known as Fano interference. The effects of high disorder in our models are characteristic of Fano interference, which generally results from a coupling between discrete states and a continuum. One confounding effect is the transformation of a peak in the modeled spectrum with low disorder to a pronounced trough in the presence of high disorder. Though preliminary research has revealed suggestive analogues between classical Fano physics and our systems, determining whether or not a true connection exists will require further study.



Lucy Chen  
Eliot 2015

Physics

### **Plasmonic transfection substrate optimization by finite-difference time-domain simulations**

Mazur Lab  
Physics,  
Harvard University

The quest for a gene transfer method with high efficiency, high throughput, low cytotoxicity, and wide applicability continues to be a difficult goal. Engineered viruses have limited use, while cellular barriers constrain non-viral techniques.

Plasmonic poration has recently been introduced as a new technique to directly introduce DNA in a cell. The basic technique uses a short-pulse laser to illuminate a thin metal substrate, upon which cells are attached. The illumination excites collective free electron oscillations (plasmons), which enhances locally the electric field and leads to localized transient poration and subsequent transfection. Using nanostructured plasmonic substrates, we attempt to optimize optical transfection by varying nanostructure geometry. Proof-of-principle experiments with gold-coated nanopillar arrays and HeLa cells have shown that the surface is nontoxic to cells and a DNA plasmid encoding the green fluorescent protein (GFP) gene has been taken up and expressed by the cells.

Our project has a few related goals—identifying promising nanostructure geometries, fabrication of the good candidates, and the eventual poration experiments. We will model the field enhancement with finite-difference time-domain (FDTD), a computational technique that models the electromagnetic field propagation in different substrates and geometries. Fabrication of the substrates involves creating a negative mold of silicon, thermally evaporating metal onto the mold, and template stripping the metal off to form the substrate. We are experimenting with different labeling dyes and microscopies to find a good technique to monitor the poration with fast, high-resolution images.

The use of laser-excited plasmons enables achieving high spatial selectivity, and in the long run, our project seeks to scale up the plasmonic poration process and advance our understanding of light-mediated transfection.

Hemi Gandhi  
Leverett 2013

Physics

### **Mid-infrared invisibility cloak through manual rolling**

Mazur Lab  
Applied Physics,  
Harvard University

Over the last decade, there has been a tremendous increase in understanding of how light propagates and interacts with micro and nanostructured materials. Metamaterials, materials with optical properties that are determined by their sub wavelength internal structures in addition to their chemical composition, have generated particular

interest due to their non-naturally occurring characteristics. Invisibility cloaks have perhaps become the most famous class of metamaterial devices. Although many designs for invisibility cloaks have been proposed, very few have been demonstrated due to fabrication challenges. The major difficulty is construction of required three-dimensional metamaterial structures with sub-wavelength features. We investigate a novel and simple cloak fabrication method, which leverages 2D photolithography to achieve 3D structures through rolling. Meta-atoms are patterned on polymer sheets, which can be rolled into an Archimedean spiral geometry. To facilitate the rolling process, thin film polymers are floated onto a water basin and manually rolled around an optical fiber. High rolling fidelity is achieved. We present FDTD simulations and metrology characterizations of a mid-IR cloak composed of split ring meta-atoms, fabricated through this rolling method. The ease, simplicity, and low cost of this new fabrication method may enable the realization of previously theorized cloak designs.

Mark Hagemann  
Visiting Fellow

Physics

### **Transferring cold atom clouds for Bose-Einstein condensate formation**

Hau Lab  
Applied Physics,  
Harvard College

Bose-Einstein Condensates (BECs) are currently an area of intense research with applications in information storage and quantum entanglement. A BEC consists of a group of atoms that all occupy the same atomic ground state, and have overlapping wave functions, which makes them indistinguishable from one another. This means that a group of hundreds of thousands of atoms all behaves as a single very large coherent particle, which makes them a very interesting subject to study. My project this summer has focused on one part of an ongoing experiment involving BECs. The purpose of the project is to make a microchip that can magnetically confine a cloud of cold atoms, which can then be further cooled to make a BEC. My part in this project has been focused on optimizing a transfer from the Magneto-Optical Trap (MOT), which is where the cold atoms are originally captured, to the microtrap, where a BEC will be formed above the microchip. This transfer is necessary because a low pressure chamber is needed to extend the BEC's lifetime, while the MOT needs comparatively higher pressure. I have worked to optimize this transfer through modeling in BiotSavart, which is a program for simulating magnetic fields generated by current configurations. With an optimized transfer, more atoms will reach the microchip for BEC generation. I have also worked in the optics lab on the experimental system itself, as well as programming the transfer. After helping to construct power supplies and circuits for the system and changing the simulation so it more closely matched experimental data, use of the new transfer process has helped lead to the highest count of atoms transferred so far.

David Kersen  
Eliot 2014

*Chemistry and Physics*

### Reptation in *C. elegans*

Samuel Lab,  
Physics,  
Harvard College

The mathematical theory of entangled polymer dynamics is centered on the concept of reptation, originally developed by P.G. de Gennes. The key insight was that, at sufficiently high densities, polymers would only move past one another with snakelike movements as thermal fluctuations would be able to drive longitudinal but not transverse movements. de Gennes dubbed the dynamics “reptation” after the Latin word “reptare”, which means to crawl or creep. The description of microscopic dynamics inspired by the reptation theory led de Gennes directly to the first convincing explanation of the macroscopic dynamics of the viscous flow of polymer melts.

Here, we propose to develop a new dynamical model to further explore the basic ideas behind entangled polymer melts. Instead of thermally driven polymers, however, we will use self-driven thread-like objects, i.e., the slender nematodes that literally crawl. We will use the nematode *C. elegans* that, at sufficiently high numbers in its environment, prefers to aggregate into tightly packed colonies to avoid atmospheric levels of oxygen, behavior which reflects the worm’s tendency to burrow in soil in pursuit of microbial food. For our purposes, the worm has an intrinsic preference to form polymer melts.

Though most behavioral analysis of *C. elegans* is carried out by tracking individual worms in isolation, here, we propose quantitative behavioral analysis of individual worms within dense clusters of other worms. Our expectation is that, to first order, the dynamics will bear a strong resemblance to de Gennes’ theory of reptation. Beyond this, our ability to quantify the whole trajectories of worms navigating within these dense colonies should allow us to explore new mathematical descriptions of entanglement in polymer melts.

Alex Krolewski  
Mather 2015

*Physics and Astrophysics*

### Improving the Pan-STARRS outer solar system data-processing pipeline

Holman Lab  
Astronomy,  
Harvard-Smithsonian Center for Astrophysics

When Pluto was discovered in 1930, some astronomers speculated that it did not stand alone, but in fact represented the first of a new class of trans-neptunian objects (TNOs). Improved telescope technologies in the 1990s allowed the first non-Plutonian TNOs to be observed, and today ~1200 such objects have been discovered. However, this represents just a small fraction of the total number of

bodies believed to exist, and continuing advances in telescope technology should dramatically increase the number of known TNOs over the next decade.

The Panoramic Survey Telescope and Rapid Response System (Pan-STARRS) project is primarily intended to find hazardous near-Earth asteroids, but its wide field of view and observing cadence makes it ideal for the discovery of TNOs. Because of the massive quantity of data produced (4.4 million potential objects), we use a computer algorithm (the “data-processing pipeline”) to identify all transient objects whose motion can be described by a trans-neptunian orbit. While some of these detections are actual TNOs, at very low signal-to-noise ratios (i.e., very dim potential objects), noise spikes, image defects and other spurious detections dominate real point sources by ratios of several to one. Culling these false detections is thus the logical next step in the TNO discovery process, and is the primary objective of our current research. Our approach is to use Source Extractor, a software tool that identifies point sources and returns various parameters of those point sources (e.g. the total flux from the source). This approach has the potential to reduce our consideration set by 90% and cut our false positive rate to 50% or less, a significant winnowing that will be greatly helpful to the TNO discovery process.

Rolando La Placa  
Cabot 2014

*Physics and Mathematics*

### Extraction Efficiency of Spontaneous Emission of NV centers in Diamond using Photonic Crystals

Loncar Lab,  
School of Engineering and Applied Sciences,  
Harvard College

Technology developments rely on our understanding of material properties. For example, the transistor, which revolutionized the field of electronics, is a direct result of our knowledge of semiconductor physics and the conducting properties of different materials. Recently, people have started thinking about the possibility of controlling optical properties of matter by constructing photonic devices - an example of which is the fiber-optic cable. The focus of this project is the study of the behavior of light inside a so-called “photonic crystal” (PC), an optical analog of the semiconductor. Some of the optical phenomena related to a PC are: confinement of light to a small region of space, guidance of light through a material without significant loss of energy, and the enhancement and inhibition of light. Another unique quality of some PCs is that light of certain frequencies cannot be transmitted through the PC, a concept known as photonic band gaps. The main goal of the project is to design a PC that enhances light in a highly directional beam. Such a PC could be used in the development of photonic circuits in which high extraction efficiency of light from an LED is needed.

Elisabeth Meyer  
Cabot 2015

*Chemistry and Physics*

### **Investigating Euler buckling in double-stranded DNA**

Cohen Lab  
Chemistry and Chemical Biology,  
Harvard University

Double-stranded DNA is a surprisingly stiff polymer – “surprisingly” considering that a single human cell contains a few meters of DNA. In the nucleus, DNA is compactly packaged, twisted and wrapped around histones, but retains its chemical integrity. Investigating DNA stiffness will expand our understanding of DNA’s interactions and reactivity in the cell and might also pave the way for using the polymer in nanotechnology.

The best current model to explain DNA’s stiffness describes DNA as a “worm-like chain” (WLC): a uniform, flexible rod that requires energy to bend. This model, however, does not take into account potentially significant effects at the level of nucleotides and atoms. Based on a mathematical WLC model, we expect a straight section of duplex DNA to experience Euler buckling when compressed inwards. As is characteristic of Euler buckling, the DNA should remain straight until a large enough force is applied, at which point it will suddenly buckle.

We study the buckling of double-stranded DNA by applying Förster resonance energy transfer (FRET) to a hairpin DNA structure. Instead of varying the force applied, we vary the length of the double-stranded region being compressed. A pair of fluorophores in the stem of the hairpin allows us to deduce the shape of the double-stranded DNA at a particular length, and therefore to pinpoint the length at which buckling occurs. It has been shown that particular base pairings, mismatches, and nicks in the DNA heavily influence the buckling transition. We now study another crucial factor, ion species and concentration. To examine the difference between buckled and kinked DNA, we also use endonucleases that should cleave the hairpin at any single-stranded regions.

Daniel Ranard  
Kirkland 2014

*Physics and Mathematics*

### **Measuring optical binding forces on a piezoelectric surface**

Golovchenko Lab  
Physics and Applied Physics,  
Harvard College

Light is an important tool in the manipulation of nanoscale objects. When laser light illuminates nano- or microscale metallic spheres, the light exerts a force on them. The spheres re-scatter the laser light and may, in turn, exert forces on each other. These forces are called optical binding forces, and the binding force between two spheres oscillates with the distance between them, varying with a spatial period equal to the optical wavelength. When laser light illuminates multiple spheres suspended in a fluid, they may self-organize into

a periodic array and become optically bound. With a better understanding of optical binding, we may use light to assemble micro-objects in new and interesting structures.

We are developing an experiment to measure optical binding forces by using sphere-like metallic objects, 100-300 microns in diameter, rigidly arranged on the surface of a piezoelectric crystal. Laser light illuminates the surface and induces optical binding forces between the metallic objects. The laser is pulsed on and off at radio frequency, generating vibrational waves on the crystal surface. The deformation of the crystal produces electrical voltages, and these voltages are detected by electrodes placed on the crystal surface. The strength of the electrical signal will indicate the magnitude of the optical binding forces, and we hope that this set up will allow us to investigate the forces on multiple configurations of metallic micro-objects.

Leah Weiss  
Dunster 2013

*Physics*

### **A biophysical approach to understanding photosystem II**

Hau Lab  
Physics,  
Harvard College

Photosystem II (PSII), a protein complex in green plants and algae, is unique in its ability to split water to form oxygen gas and hydrogen ions. The electron transfer process in PSII allows plants to use the excitonic energy of the surrounding light harvesting system to drive charge separation. The water splitting and electron transfer process further serves to build a pH gradient that powers the production of ATP. This process enables effective storage of solar energy in chemical bonds as sugars. Understanding PSII on the molecular level could therefore provide insight into methods of solar energy storage. Past studies have used large sample population and statistical analysis of light-stimulated oxygen gas emission to understand oxygen evolution in PSII. In order to understand this system in detail we will instead study a single PSII monomer and integrate this complex into a solid-state nanoscale system. To achieve this goal it is necessary to compile and test methods of purification of PSII and understand the theory and methods of measuring redox potentials. We report the results of purification attempts and review redox potential theory and measurements.

Lewin Xue  
Currier 2015

*Computer Science*

### **Study of the effect of physical stress on mutations of alpha-actinin 4 proteins**

Weitz Lab  
Soft Condensed Matter,  
Harvard College

Crosslinks formed between filamentous actin proteins play crucial roles in establishing physical properties in eukaryotic cells. These crosslinks are formed with the aid of  $\alpha$ -actinin 4 (Actn4) binding proteins, which bind the actin proteins together to create the crosslinks. Various mutations of the Actn4 protein interfere with the cellular ability to cope with physical stress. By studying four strains of the Actn4 protein, the wild type, the K255E mutation, and the wild type and K255E mutations with QT mutation, we will attempt to determine the relation between the binding affinity of Actn4 to actin and varying amounts of physical stress. An increased binding affinity will indicate an increased stiffness of the cell. This relationship can reveal how stiffness in the cell changes with increased applied stress. We will measure the binding affinity through the application of the Fluorescence Recovery After Photobleaching (FRAP) process. By tagging Actn4 with green fluorescent proteins (GFPs) and transfecting these mutations into Madin-Darby Canine Kidney Epithelial Cells (MDCKs), we can use FRAP to observe and measure the recovery rates of the fluorescent Actn4. We grow MDCKs on Polydimethylsiloxane (PDMS) gels with varying stiffness and apply further external physical stress through the use of an indenter. The mutations of Actn4 may explain the underlying mechanism in inherited focal segmental glomerulosclerosis and various other kidney diseases.



# STEM CELL AND REGENERATIVE BIOLOGY

Jennifer Cloutier  
Quincy 2013

*Human Developmental  
and Regenerative Biology*

## **The role of the miR302/367 cluster in cellular reprogramming and development**

Hochedlinger Lab,  
Stem Cell and Regenerative Biology,  
Mass General Hospital / Harvard Stem Cell Institute

In 2011, induction of the miR-302/367 cluster was implicated as an alternative method to OKSM (Oct-4, Sox2, Klf4, c-Myc) mediated cellular reprogramming to pluripotent stem cells (Anokye-Danso et al). Although its role in reprogramming remains contested, the miR-302/367 cluster has recently been reported as an epiblast stem cell (EpiSC) marker. Furthermore, data from the Hochedlinger laboratory demonstrates miR302/367 expression briefly spikes late in reprogramming intermediates along with other known epiblast markers (i.e. Fgf5) (JM Polo, unpublished data). This summer I aimed to shed light on the role of miR302/367 in murine cell reprogramming. I hypothesized that the expression profile of miR302/367 points to a conserved mechanism of reprogramming mimicking early developmental stages in reverse. In order to elucidate the validity of this hypothesis, I proposed a series of reprogramming and transdifferentiation experiments. Over the next academic year, I also hope to develop the means of studying the role of miR302/367 in the adult and development through *in vivo* models. These experiments may enhance our knowledge of the conversion of putative 'primed' EpiSC cells to a more 'naïve' embryonic stem (ES) or induced pluripotent (iPS) cell state. As current human ES (hES) cell cultures are postulated to be 'primed' and thus in a less developmentally potent state, understanding the relationship between murine EpiSCs and ES cells could be salient for future therapeutics.

Sayantan Deb  
Adams 2014

*Human Developmental  
and Regenerative Biology*

## **iPSC-derived neuronal transplantation for Parkinson's disease: *In vivo* application of a new differentiation protocol**

Isacson Lab,  
Harvard Stem Cell Institute,  
Harvard Medical School

Parkinson's Disease (PD), characterized by rigidity, tremor, slowness in initiating voluntary movement, and a disturbance in gait and posture, is associated with a loss of dopamine signaling in the striatum of the brain accompanied by the degeneration of dopaminergic (DA) neurons in the substantia nigra. A cell therapy

approach to treating PD has thus focused on restoration of dopamine signaling in the striatum, specifically using the A9 group of DA neurons in the substantia nigra pars compacta (SNpc), while trying to avoid immune rejection. To this end, DA neurons differentiated from patient-specific induced pluripotent stem cell (iPSCs) lines were transplanted into rodent models of PD. The xenograft model showed survival of the graft; however, the graft was not rich in the correct subtype of DA neurons (A9). A protocol using floor plate (FP) precursors differentiated from human embryonic stem cells (HESCs), had a much higher concentration of the A9 DA neurons. The FP-derived grafts also resulted in a significant reduction in motor asymmetry in rodent models of PD. The next step, therefore, towards clinical applications, was to examine the functionality of DA neurons differentiated using the FP-based protocol, but with macaque iPSCs in lieu of HESCs in a xenograft model. Short-term assays using the modified protocol in the xenograft model showed surviving macaque A9/A10 DA neurons in the rat striatum. Further behavioral tests are currently being conducted to analyze functional recovery in rat models of PD.

Emmanuel Figueroa  
Mather 2015

*Human Developmental  
and Regenerative Biology*

## **Designing a system to rapidly create TALENs to facilitate genome editing of human pluripotent stem cells**

Cowan and Musunuru Labs,  
Stem Cell and Regenerative Biology,  
Harvard College

In order to further our understanding of biological mechanisms, it is important to accurately target and modify specific DNA sequences in the genome. The plant pathogen *Xanthomonas* produces transcription activator-like effectors (TAL effectors) that can accurately target select DNA sequences. Using the TAL effectors as motivation, we can create DNA binding proteins that are sequence specific for the genome, and fuse them with an endonuclease. This would effectively make a TAL effector nuclease (TALEN) that selectively induces DNA double strand breaks and mutations. Even though the technology seems extremely promising for research in the field, it is difficult and time-consuming to create a variety of TALENs primarily because of the multitude of repeat domains that they possess. Therefore we have tackled on a project that will expedite the process of producing TALENs by creating reserves of repeat domains that make up the component part of TALENs. By using the Golden Gate cloning strategy for multi-piece DNA ligation and PCR, we aim to produce a library of all possible repeat combinations so that user defined TALENs can be created faster and single gene targeting made possible.

Francisco Galdos  
Currier 2015

*Human Developmental  
and Regenerative Biology*

### **Small molecule screen to identify novel molecular pathways required for pharyngeal arch artery formation in zebrafish**

Burns Lab,  
Cardiovascular Research Center,  
Massachusetts General Hospital

Defects in the continuity or conformation of the great arteries result in a range of common congenital defects, the genetic basis of which remains largely undefined. In air-breathing vertebrates, the great arteries are remodeled from six pairs of bilaterally symmetric pharyngeal arch arteries (PAAs). Extensive efforts have described the genetic pathways responsible for the remodeling aspects of this process, yet those essential for their initial establishment remain largely undefined. Zebrafish produce large numbers of embryos and develop their PAAs similarly to their mammalian counterparts, which allows for both unparalleled real-time and forward screening approaches for studying PAA development. A recent zebrafish study revealed that the PAAs arise via vasculogenesis through the differentiation of *tie1*+ angioblast "islands" in the pharyngeal mesoderm that then expand and sprout by angiogenesis. Our goal is to identify the molecular programs involved in the formation of these *tie1*+ clusters, as a means to further understand PAA development.

To this end, we are conducting a small molecule screen from a library of 2080 FDA approved compounds provided by the Harvard Institute of Chemistry and Cell Biology. Wild-type embryos are treated with chemicals and processed by *in situ* hybridization for *tie1* expression. Compounds that disrupt *tie1* angioblast island formation will be retested and identified as true hits through a 3 pronged approach that: (1) evaluates embryo health (2) determines the potency of the drug and (3) analyzes the specificity of the drugs in targeting the *tie1* angioblast islands. The culmination of these experiments will identify and characterize novel determinants required for the earliest steps of PAA specification. Identification of new molecular programs that regulate PAA formation may inform the creation of improved preventative and therapeutic approaches for cardiovascular malformations.

Rachel Gladstone  
Cabot 2014

*Human Developmental  
and Regenerative Biology*

### **Investigating the molecular mechanism of cardiomyocyte dedifferentiation and proliferation**

Lee Lab,  
Cardiology,  
Harvard Medical School, Brigham and Women's Hospital

Heart failure is a major health risk worldwide, thus the need to pursue cost-effective treatment strategies is great. The heart has a finite ability to repair itself after injury because mature human cardiomyocytes have limited proliferative capabilities. Recently, it was shown that neonatal mice could regenerate the heart following resection,

and cell dedifferentiation appears to be an important process. However, by 7 days of age, this regenerative capability is lost, suggesting that between day 1 and day 7, mammalian cardiomyocytes lose the potential to dedifferentiate and proliferate. Understanding the molecular cues that guide cardiomyocyte differentiation will allow us to harness these factors for future regenerative therapies. It has been demonstrated that tissue specific decellularized matrix (DCM) used as a cell culture substrate induces cell maturity. We hypothesized that heart DCM encourages differentiation in cardiomyocytes in culture. To test this hypothesis, we plated neonatal rat cardiomyocytes onto wells coated with either rat DCM or with fibronectin, a well-documented component of the DCM, as well as in non-coated wells. We expected that the expression of certain factors marking cell maturation would be expressed in opposite directions in cells plated on DCM-coated wells versus those grown on non-coated wells, because cardiomyocytes cultured on non-coated plates show a less differentiated phenotype. We compared gene expression in cells after the various treatments and observed expression changes in DCM-plated cells compared to cells from non-coated or fibronectin-coated wells. These results suggest that there is one or more factor other than fibronectin in the DCM that regulates differentiation in cardiomyocytes. Future work includes validation of gene misregulation at the protein level and development of an assay to test cardiomyocyte differentiation in culture.

Jennifer Guidera  
Adams 2015

*Neurobiology*

### **Is SMN located at the synapse of mammals?**

Rubin Lab,  
Stem Cell and Regenerative Biology,  
Harvard College

The neurodegenerative disease Spinal Muscular Atrophy (SMA) is the leading genetic cause of death in infants. SMA is characterized by the death of the motor neurons in the spinal cord and subsequent muscle atrophy. The disease is caused by a mutation in *SMN1*, a gene that encodes a protein called Survival of Motor Neuron (SMN) protein. This mutation leads to lower levels of SMN protein in all cell types, yet only motor neurons in the spinal cord degenerate as a result. This observation suggests that SMN might play a special role in the survival of motor neurons. However, neither the role that SMN plays in motor neuron survival nor the location of SMN within motor neurons is currently known.

A recent study looked at SMN location in the model organism *Drosophila*, and found that SMN is localized at the synapses of motor neurons. The goal of my project is to determine whether SMN is localized at the synapses of motor neurons in mammals as well. I am using immunohistochemistry to visualize SMN at two different types of synapses affected by the disease. The first type of synapse is between proprioceptive sensory neurons and lower motor neurons in the spinal cord. The second type of synapse is between lower motor neurons and muscle in the diaphragm. In addition to visualizing SMN at the synapses of mice, I will also determine whether levels of SMN vary throughout spinal cord.

Gunsagar Gulati  
Adams 2014

*Human Developmental  
and Regenerative Biology*

### **Effect of small molecule kinase Inhibitors on the survival of wild-type and SOD1G93A motor neurons**

Rubin Lab,  
Stem Cell and Regenerative Biology,  
Harvard College

Amyotrophic Lateral Sclerosis (ALS) is a late-onset, progressive, neurodegenerative disease of the upper and lower motor neurons. Currently, the only drug approved to treat ALS, Riluzole (Rilutek), extends life only by months and is marginally effective in treating advanced cases, necessitating research to identify novel and effective therapeutics for ALS.

One way to find new therapeutics is to carry out a high throughput small molecule survival screen using motor neurons derived from two types of embryonic stem cells: wild-type and those carrying the ALS G93A mutation of human superoxide dismutase 1 (SOD1). In such a screening performed earlier in the lab, 14 overlapping hits were identified and classified into six categories based on their annotations and mechanisms of action. This summer, I am working on one of the six categories, a class of small molecules that inhibits a particular kinase. My project involves testing a wide array of compounds from this class of kinase inhibitors on wild-type and mutant SOD1G93A motor neurons to validate the effectiveness of this class of inhibitors. The experiment involves differentiating embryonic stem cells into motor neurons, growing them in trophic factor-rich media for four days, and then, simultaneously, removing the trophic factors and adding the compounds to the culture. After another three days, the culture is scanned to measure motor neuron survival by count and the results are compared to a negative control (no trophic factor/compound) and a positive control (trophic factor). Our results show that most drugs from this class increase survival significantly.

Seungjun Kim  
Cabot 2013

*Human Developmental  
and Regenerative Biology*

### **Heterogeneity in regenerative support among reactive astrocytes in the mouse neocortex**

Zhou Lab,  
Stem Cell and Regenerative Biology,  
Harvard University

The adult mammalian central nervous system (CNS) has limited regenerative capacity after injury. This limited regenerative ability is partly due to the inhibitory effects of reactive astrocytes that form a glial scar in response to severe injury. Although reactive astrogliosis occurs in the neonatal mouse CNS in response to injury, neonatal reactive astrocytes are more supportive of neuron survival and axon regeneration than adults. Differences in functionally distinct sub-

populations of reactive astrocytes may help explain the improved regeneration in neonatal mice. There is growing evidence for heterogeneity in reactive astrocytes, and that progenitor genes are up-regulated in some reactive astrocytes in the injury site. Given that the number of neural progenitor cells in the forebrain is known to decrease with increasing age, it seems plausible that an immature reactive astrocyte subpopulation expressing progenitor genes could mediate a beneficial response to CNS injury. Through *in vitro* overexpression and neuron co-culture, immunohistochemistry and gene expression profiling, and *in vivo* overexpression, I test whether there is a direct correlation between the immature, progenitor marker-expressing subpopulation of reactive astrocytes activated upon injury and functional capacity to support neuron survival and regeneration.

Garrett Kingman  
Cabot 2013

*Human Developmental  
and Regenerative Biology*

### **The role of WDR62 in neuronal migration**

Walsh Lab,  
Genetics,  
Harvard Medical School, Boston Children's Hospital

Many complex neural disorders result from simple mutations in genes critical to brain development. Mutations in the gene WDR62 have recently been identified as causing the development of an abnormally small brain with additional structural deficits. This double phenotype suggests that WDR62 not only plays a role in regulating cell proliferation, but also influences neuronal migration. I have sought to clarify its role in cell migration by studying its interactions with other proteins through protein complex immunoprecipitation and mass spectrometry. Protein complex immunoprecipitation (Co-IP) uses an antibody against the protein of interest, in this case, WDR62, to extract it and other proteins binding to it. In mass spectrometry, the samples are then broken down and ionized before being processed and analyzed to identify the proteins pulled down by the Co-IP. Future steps involve a more detailed study of several promising interactions and the direct test of WDR62's role in cell migration through RNAi expression knockdown, both *in vitro* and *in vivo*.

Jonathan Li  
Currier 2015

*Undeclared*

### **Studies of the regulation of a novel liver-specific gene controlling pancreatic $\beta$ -cell replication**

Melton Lab,  
Stem Cell and Regenerative Biology,  
Harvard University

Diabetes mellitus is a rapidly growing threat to global human health, with approximately 346 million humans worldwide afflicted with the disease. Diabetes, characterized by high blood sugar (hyperglycemia) and relative insulin deficiency, is classified into two types. Type 1 diabetes is caused by an autoimmune attack



on insulin producing  $\beta$ -cells, while type 2 is due to peripheral insulin resistance. In insulin resistant environments, a compensatory increase in  $\beta$ -cell mass is often observed. The activity of a recently discovered gene has been correlated with the  $\beta$ -cell replication, making it an exciting candidate to study. The novel gene, expressed specifically in the liver, shows a 5 to 6 fold activity increase in the insulin-resistance condition. In this work, we isolate the minimal promoter of the candidate gene by measuring activity of variable promoter-reporter constructs in *in vivo* and *in vitro* environments to find the regulatory elements that control liver specific expression and the upregulation during insulin resistance. Afterwards, we will establish a stable cell line by transfecting the minimal promoter-reporter complex. Next, we will perform an expression screen using a cDNA library derived from the liver undergoing insulin resistance to look for factors controlling gene transcription. We will also use a chemical genetic approach to determine the signaling pathways that control the novel gene's expression. Finally, we search for a potential drug which can upregulate the gene, thereby increasing insulin production in diabetic patients.

Letitia Li  
Mather 2015

Undecided

### Stabilization of *in vitro* pancreatic $\beta$ -cell phenotype by the extracellular matrix

Lee Lab,  
Department of Cardiology,  
Harvard Medical School, Brigham and Women's Hospital

The pancreas is composed of many different cell types, one of which, the  $\beta$ -cell, is responsible for regulation of glucose concentration in the bloodstream through secretion of insulin, scientifically termed glucose-stimulated insulin secretion (GSIS). Diabetes ensues when  $\beta$ -cells are either destroyed or rendered unable to function properly leading to chronically elevated blood sugar levels. Extensive scientific inquiry currently focuses on discovering methods to either replace lost  $\beta$ -cells through new stem cell techniques or restore lost  $\beta$ -cell insulin secretion function. One of the main obstacles hindering such research is that  $\beta$ -cells, once isolated *in vitro*, lose some function. Understanding how to maintain the phenotype of these cells could enable better transplantation approaches.

We hypothesized that  $\beta$ -cells dedifferentiate *in vitro* due to a loss of their natural extracellular environment. To address this hypothesis, we decellularized pancreatic tissue and cultured primary  $\beta$ -cells in the resulting decellularized matrix (DCM). We posited that factors within the pancreatic DCM could potentially maintain  $\beta$ -cell phenotype. Our preliminary studies show that mRNA levels of various genes such as, MafA and PDX1, known regulators of insulin expression, Insulin (Ins2) itself, and Ucn3, a marker for mature insulin secretion capability in  $\beta$ -cells, are increased in  $\beta$ -cells cultured in DCM compared to negative controls, suggesting a stabilization of  $\beta$ -cell phenotype. Presently, we are in the process of screening for relevant individual factors through systematic fractionation and reconstitution of rat DCM fractions. In addition, we plan to confirm our initial findings on a translational (protein) level and functional (GSIS) level. Our research may uncover future applications for islet cell stabilization for transplantation into diabetic patients and clues on how to improve differentiation of induced pluripotent stem cells (iPS) into  $\beta$ -cells.

Stephanie Lim  
Lowell 2014

Neurobiology

### Selective labeling of CSMN using enhancer elements of transcription factors

Macklis Lab  
Human Development and Regenerative Biology  
Harvard College

The neocortex is a six-layered structure of the mammalian brain that plays an essential role in motor control, sensory perception, and association. Many subtypes of neurons exist within the cortex, including corticospinal motor neurons (CSMN), which send their axons to the spinal cord, and control voluntary movement. CSMN are a clinically significant population of neocortical projection neurons because they degenerate in diseases such as amyotrophic lateral sclerosis (ALS), and are damaged in spinal cord injury. These conditions lead to irreversible paralysis of voluntary muscles. A more thorough understanding of CSMN biology might add to the understanding of CSMN degeneration, and might enable strategies for repair, regeneration, or replacement of diseased neurons.

This summer, I aimed to identify enhancer elements, which are stretches of DNA that enhance the transcription of a gene, in the genomic regions upstream of the coding sequences of two transcription factors. One transcription factor, retinol-binding protein 4 (Rbp4), is expressed specifically by CSMN, and the other transcription factor, empty-spiracles homolog-1 (Emx1), is expressed in the neocortex more broadly. I am identifying enhancer elements by selecting from evolutionarily-conserved regions (ECRs), which are regions of DNA that are conserved among different species. The enhancer elements were tested for specific activity using *in utero* electroporation (a method used to introduce plasmid DNA into cortical neurons and express a reporter gene), perfusion (a method of fixing the brain tissue), and immunocytochemistry (a method using antibodies to label the reporter protein for visualization). The enhancer elements I am aiming to identify will be used to generate tools for selective labeling and genetic manipulation of CSMN. Although no such tools are currently available, they would be extremely valuable for studying CSMN development, degeneration, and regeneration.

Eden Liu  
Winthrop 2013

Human Developmental  
and Regenerative Biology

### The effect of exercise on angiogenesis

Wagers Lab,  
Stem Cell and Regenerative Biology,  
Harvard College

Sarcopenia, the age-acquired loss of muscle mass and function, has significant clinical implications in the elderly population. Patients with sarcopenia experience a progressive decline in tissue function and muscle regeneration after injury. Currently, exercise is believed to be the most effective and safest interventional strategy for slowing sarcopenia (Jang et al. 2011). Though the underlying mechanisms are not yet known, scientists posit that one of the ways through which exercise attenuates sarcopenia is by promoting



angiogenesis, the formation of blood vessels. Pro-angiogenic factors improve myogenic function and contractility by protecting tissue from hypoxia and necrosis. As vessels are essential for the transport of growth factors, cytokines, and nutrients to energy-utilizing tissues, signaling molecules that regulate oxidative metabolism could also play a role in angiogenesis (Potente et al. 2011). Recent studies found that moderate levels of swim training increases coronary blood flow and myocardial capillary-to-fiber ratio in murine and swine models (Roque et al. 2011; da Silva et al. 2012; White et al. 1998). Thus, changes to metabolism through exercise influence the vasculature (Potente et al. 2011).

My experiment will test the hypothesis that the crosstalk between signaling pathways regulating metabolism and angiogenesis is critical for improving muscle function in aging skeletal muscle. To induce increased levels of oxidative metabolism, five young mice ran for four days a week at 15 meters per minute on a 15° incline. After four weeks, I performed a Western blot for four proteins: CD31, an endothelial cell marker, VE-cadherin, an endothelial adhesion molecule, cytochrome C, a mitochondrial protein, and myoglobin, an oxygen-binding molecule in muscle. Changes in protein levels are confirmed with frozen section immunohistochemical staining.

Samita Mohanasundaram  
Quincy 2014

Environmental Science &  
Public Policy

### **Evaluation of the leukemogenic potential of agricultural pesticide, Mancozeb**

Wagers Lab,  
Stem Cell and Regenerative Biology  
Harvard University,

Every day you are surrounded by pesticides - on your lawn, in your flower pots, and even in your food. A recent report by the Environmental Protection Agency (EPA) shows that over five billion pounds of pesticides are used annually around the globe. Previous studies reveal that mancozeb, a widely used agricultural pesticide that can be easily purchased in department stores, is correlated with a higher incidence of leukemia and other cancer types in field workers. Leukemia has been shown to result from the oncogenic transformation of hematopoietic progenitor cells (HPCs), which are precursor cells with the ability to give rise to all blood cell types. In accordance with prior studies, we have found that mancozeb induces DNA damage. We therefore hypothesize that DNA damage by mancozeb could cause the oncogenic transformation of HPCs, leading to diseases such as leukemia. I will be taking two different approaches, one *in vitro* and the other *in vivo*, to assess whether HPCs treated with mancozeb are more prone to oncogenic transformation. Our results will achieve a better understanding of how exposures to certain environmental chemicals can impact our health.

Kabungo Mulumba  
Winthrop 2015

Human Developmental  
and Regenerative Biology

### **Non-canonical hedgehog signaling activation of Gli-transcription factors**

Humphreys Lab  
Harvard Stem Cell Institute  
Harvard Institute of Medicine

Following injury, the kidney has the ability to regenerate damaged tubular cells and ultimately recover its normal structure and function. However, if the kidney injury is repeated, as seen in cases of chronic inflammation and diabetes, then this triggers a maladaptive repair process. The pathological hallmark of all chronic kidney disease is the presence of fibrotic matrix, or scar tissue. The Humphreys lab has shown that interstitial pericytes are the major scar-producing cells in the kidney, as they proliferate and differentiate into myofibroblasts following injury. In human chronic kidney diseases increased fibrosis results in decreased kidney functioning and can ultimately lead to end stage renal disease (ESRD) and the need for renal replacement therapy. Therapies targeted to pericytes/myofibroblasts may hold promise in preventing or reversing kidney fibrosis. The role of signaling pathways and growth factors in fibrosis is still being determined, but one pathway suspected to increase fibrosis is the hedgehog-signaling pathway, Hh (Fabian et al., 2012). It is suspected that prolonged injury is associated with continuously elevated Hh signal activation that can trigger pericyte proliferation and differentiation into myofibroblasts. Gli1 is a major hedgehog downstream gene, as activation of the pathway will increase transcription of Gli1 itself. Therefore, it is considered a bona fide readout of canonical hedgehog pathway activation. My project this summer is to identify potential non-canonical signals that activate Gli factors – i.e. are there extracellular ligands that can activate Gli; and are there intra-cellular signaling pathways (MAPK/ERK, PKA, cAMP) that may positively or negatively modulate Hh activity. We are using shh-light II cells that have been stably transfected with a Gli-responsive firefly luciferase reporter. We then study Gli-activity using luciferase assay by quantifying the amount of fluorescence released when Gli transcription is active; and also by RT-PCR.

Yucheng Pan  
Currier 2015

Undecided

### **miRNAs as mediators of local protein regulation in growth cones of callosal projection neurons**

Macklis Lab,  
Stem Cell and Regenerative Biology,  
Harvard College

The mammalian neocortex is a highly organized six-layered structure that is progressively established as distinct subpopulations of neurons target their axons specifically and precisely to other regions of the central nervous system. Within the neocortex, projection neurons extend their axons over remarkably long distances to intracortical, subcortical, and subcerebral targets.

Callosal projection neurons (CPN), a subtype of neocortical

projection neurons, are characterized by their extension of an axon through the corpus callosum to target areas of contralateral cortex, functioning to integrate information between the two cerebral hemispheres. Located at the distal end of extending axons, growth cones enable projection neurons to detect and interpret extracellular, spatiotemporal information such as molecular gradients and ligands expressed on other axons.

Tight regulation over proteins in the growth cone is, therefore, essential to precise navigation. However, because growth cones function far from their cell body and nucleus, local autonomy is critical in their ability to make navigating decisions. MiRNAs have been identified as regulators providing posttranscriptional control over protein synthesis. These short non-coding RNA sequences preferentially bind to 3' untranslated regions of target mRNAs and facilitate mRNA degradation and translational repression. During axon navigation, changes in the growth cone miRNA profile can regulate the growth cone protein complement and thus the ability to respond to spatiotemporal cues. A critical step towards understanding the function of miRNA in axon navigation involves the development of a technique to isolate miRNAs localized to the growth cone.

In this project, we describe a novel technique to affinity-purify miRNAs localized to the growth cone. Once candidate miRNAs are identified, their translational regulation over mRNA stability and protein synthesis, and thus ultimately CPN navigation, may be further elucidated.

Daniel Park  
Mather 2015

*Human Developmental  
and Regenerative Biology*

### **Directed differentiation of dopaminergic neurons from human induced pluripotent stem cells to model Parkinson's Disease**

Rubin Lab,  
Stem Cell and Regenerative Biology,  
Harvard University

Parkinson's Disease (PD) is a neurodegenerative disease characterized by the progressive loss of motor functions including shaking, rigidity and difficulty walking. Symptoms are caused by the death of dopaminergic (DA) neurons in the substantia nigra, a region of the midbrain. These DA neurons generate the neurotransmitter dopamine, which is important in regulating motor control, reward-seeking behavior and learning.

By the time of death, 50% to 80% of PD patients' DA neurons have died, posing a challenge to studying the disease. Establishing a human *in vitro* model of PD would allow study of the progression of the disease and, in the future, enable accelerated screening of drug candidates. The first goal of this project is to establish a protocol for differentiating human induced pluripotent stem cells (iPSCs) into DA neurons with high viability. Studer et al. have already established a differentiation protocol for creating neural progenitor cells (NPCs) and terminally differentiating them into DA neurons, and we will adapt this protocol to our lab conditions. The second goal of the project is to establish appropriate conditions for the overexpression of transcription factors in the NPCs generated using the Studer

protocol. Several different populations of DA neurons exist in the midbrain so in order to study the progression of the disease we must be able to produce the mature nigral DA neurons that die in PD. To this end we will overexpress certain candidate transcription factors as a method of programming our neurons towards a particular population of DA neurons. My project will set up the conditions for the overexpression of these transcription factors so that we can produce the DA neurons affected by PD.

Giuliana Repetti  
Lowell 2013

*Human Developmental  
and Regenerative Biology*

### **Characterizing a heterogeneous population of neural progenitor cells**

Rubin Lab,  
Department of Stem Cell and Regenerative Biology Department,  
Harvard College

Embryonic stem cells (ESCs) have the potential to differentiate into neurons, which can be useful for modeling or treating neurodegenerative diseases such as Parkinson's disease. In the differentiation of ESCs into neurons, the cells first pass through an immature neural progenitor cell (NPC) identity. Although previously these progenitor cells were considered identical, recent evidence supports the idea that this population of NPCs may experience varying neurogenic potentials. My thesis aims to characterize this heterogeneous population of NPCs, and determine their neuronal fates. Enriching the culture at an early stage in differentiation could drastically increase the overall efficiency of differentiation.

Carlos Rodriguez-Russo  
Pforzheimer 2013

*Human Developmental  
and Regenerative Biology*

### **A functional and structural analysis of the HCELL homing ligand in human and mouse models**

Sackstein Lab,  
Dermatology,  
Harvard Medical School

A great deal of therapeutic promise has been ascribed to the use of stem cell therapeutics, since these cells hold the capacity to repair or replace damaged or cancerous tissues within the human body. Indeed, the intravenous transplantation of hematopoietic stem cells from bone marrow is already a part of the standard repertoire of patient care for chronic myeloid leukemia. However, the expansion of this therapeutic model into other organ systems is hampered by the lack of understanding of how best to administer progenitor cells specifically so that they only incorporate into the tissues where they are needed, minimizing the risk of uncontrollable growth or differentiation of the therapeutic cells in other parts of the body.

Previous studies by Sackstein et al. have produced a cellular engineering technique known as Glycosyltransferase-Programmed Stereosubstitution (GPS), which can enforce the expression of the homing ligand HCELL on mesenchymal stem cells by enzymatically altering the sugars decorating the native membrane glycoprotein CD44 such that it replicates HCELL homing function; this technique has successfully employed with the enzyme fucosyltransferase VI (FTVI) to increase trafficking of mesenchymal stem cells to bone tissue in mice.

Before such a technique can become a truly feasible therapeutic option in humans, however, the structure of the homing ligand must be fully characterized and the molecular specificity of the enzyme must be assessed. I seek to remedy this deficiency by determining whether the homing-relevant glycans on HCELL are N-linked (conjugated to CD44 via an asparagine residue), as well as by assessing the specificity of FTVI-mediated fucosylation on the membrane proteins of human and murine mesenchymal stem cells. This work will serve to advance the scientific community's understanding of the biochemical basis of engineered stem cell localization within the body, providing a platform for translation of GPS technology into the clinical arena.

Jane Suh  
Mather 2014

*Human Developmental  
and Regenerative Biology*

### **Runx1-mediated hematopoietic stem cell transgene expression and Cre-based recombination for lineage tracing of blood development in zebrafish**

Zon Lab  
Hematology/Oncology  
Howard Hughes Medical Institute, Boston Children's Hospital

Stem-cell based therapies for the hematopoietic system require an important understanding of how hematopoietic stem cells (HSCs) choose their fate and differentiate into many blood cell type lineages. In order to understand the mechanisms that control lineage differentiation, the zebrafish model has been shown to be very useful in this field. Zebrafish models help us to understand human blood development because these hematopoietic programs in mammals and zebrafish are conserved. A critical regulator for the generation of the first definitive hematopoietic stem cells (HSCs) in early development of hematopoiesis is the transcription factor Runx1/AML1. Since runx1 is such an important transcriptional regulator for HSC formation, tracing the cells that express runx1 in early development will provide a useful tool for studying blood lineages from HSCs.

This project therefore aims to apply the discovery of the runx1+23 enhancer elements to zebrafish transgenesis to establish stable transgenic lines of a runx1+23 driving a Cre/loxP recombination system as a powerful tool to lineage trace HSCs in early hematopoietic development. The F0 generation founder lines have been made by injecting the runx1+23:Cre-ERT2 (cmlc2-GFP) into the one cell stage eggs of AB zebrafish embryos. Positive F0s were isolated and outcrossed to wildtype TL fish. These F1s were then crossed to various

switch fish including fish with the ubi:loxP-EGFP-loxP-mCherry gene construct and the efficiency of the cre-ERT2 reporter line was determined through 4-OHT (tamoxifen) induction in order to examine the switching efficiency.

Establishing these stable transgenic lines that contain the runx1+23:Cre/Cre-ERT2 constructs will provide a powerful tool for studying lineage differentiation of hematopoietic stem cells *in vivo* and lead us to better understanding of how blood diseases develop.

Alexander Tang  
Winthrop 2014

*Human Developmental  
and Regenerative Biology*

### **The effect of ANGPTL3 expression on LDL cholesterol level in humans**

Cowan and Musunuru Labs,  
Stem Cell and Regenerative Biology,  
Harvard College

Callosal projection neurons (CPN), a subtype of neocortical projection neurons, are characterized by their extension of an axon through the corpus callosum to target areas of contralateral cortex, functioning to integrate information between the two cerebral hemispheres. Located at the distal end of extending axons, growth cones enable projection neurons to detect and interpret extracellular, spatiotemporal information such as molecular gradients and ligands expressed on other axons.

Tight regulation over proteins in the growth cone is, therefore, essential to precise navigation. However, because growth cones function far from their cell body and nucleus, local autonomy is critical in their ability to make navigating decisions. MiRNAs have been identified as regulators providing posttranscriptional control over protein synthesis. These short non-coding RNA sequences preferentially bind to 3' untranslated regions of target mRNAs and facilitate mRNA degradation and translational repression. During axon navigation, changes in the growth cone miRNA profile can regulate the growth cone protein complement and thus the ability to respond to spatiotemporal cues. A critical step towards understanding the function of miRNA in axon navigation involves the development of a technique to isolate miRNAs localized to the growth cone.

In this project, we describe a novel technique to affinity-purify miRNAs localized to the growth cone. Once candidate miRNAs are identified, their translational regulation over MST1/2 knockout animals after sulfur dioxide injury in the small airways. Future studies will be conducted to define the downstream effectors of MST1/2 in the hippo pathway that cause the changes in proliferation and differentiation.

Jonathan Tran  
Adams 2014

*Human Developmental  
and Regenerative Biology*

### **Effect of Mst1/2 Knockout in Small Airway Epithelium During Regeneration**

Rajagopal Lab  
Pulmonology  
Massachusetts General Hospital

The Hippo tumor suppressor pathway has been shown to regulate the growth and organ size in both *Drosophila* and mammals via regulation of cell proliferation and apoptosis. The upstream protein kinase Hippo (MST1/2 in mammals) acts to phosphorylate and negatively regulate the downstream transcription co-activator Yap1, which is assumed to be an oncogene in multiple systems. The roles of MST1/2 have been studied in multiple systems including the liver, intestine, skin, and hematopoietic system; however, no studies have been performed to elucidate their role in the airway.

My project over this summer is to characterize the functional role of MST1/2 in the small and large airway epithelium during homeostasis and after injury. We took a genetic approach to delete both MST1/2 specifically in the airway epithelium to characterize the phenotypic outcomes. Our focus lies in characterization and differentiating the expression patterns of cell proliferation, differentiation and cell death markers in epithelial progenitors and differentiated cells. We used immuno-fluorescence stains to identify and quantify the relative proportion of different cellular populations and subpopulation of epithelial cells that are undergoing proliferation/apoptosis. Our preliminary studies show that there are more epithelial progenitors that undergo cell proliferation in MST1/2 knockout animals after sulfur dioxide injury in the small airways. Future studies will be conducted to define the downstream effectors of MST1/2 in the hippo pathway that cause the changes in proliferation and differentiation.

Radovan Vasic  
Winthrop 2013

*Human Developmental  
and Regenerative Biology*

### **Bone and fat: Remodeling of the hematopoietic bone marrow niche mediated by peroxisome proliferator-activated receptor- $\gamma$ inhibition in the context of bone marrow transplantation**

Scadden Lab,  
Stem Cell and Regenerative Biology,  
Harvard Stem Cell Institute

For over 60 years, the transplantation of Hematopoietic Stem and Progenitor Cell (HSPC) transplantation has been used as a therapy for patients suffering from bone marrow malignancies, as well as a viable treatment option for patients with a variety of autoimmune disorders (Korbling & Freireich 2011). Successful transplant depends heavily on the interactions of HSPCs with the bone marrow microenvironment, or the bone marrow 'niche' in which they classically reside. Cells of the mesenchymal lineage

play key roles in the niche: osteoblastic ('bone') cells are known to support functional hematopoiesis, while adipocytes ('fat') have recently been characterized as negative regulators of hematopoiesis. Based on our knowledge of mesenchymal lineage fate decisions we attempted to pharmacologically inhibit PPAR- $\gamma$ , a nuclear hormone receptor and master regulator of hematopoiesis, following HSPCs transplantation in mice. By our rationale, inhibition of PPAR- $\gamma$  would decrease the fat content of the niche while fostering bone development, thus creating a healthier niche for HSPCs to settle in to following transplantation. We successfully demonstrated that inhibition of adipogenesis can produce differential survival effects post-transplantation, and have begun characterizing the underlying biological mechanism of these effects.

Stephanie Wang  
Eliot 2013

*Chemical and Physical Biology*

### **Uncovering a pathway of aging: The Role of HSP72 and IL-6 in the Regeneration of Skeletal Muscle in Aged Mice**

Wagers Lab,  
Stem Cell and Regenerative Biology,  
Harvard College

As the elderly population continues to expand, elucidating the mechanisms behind aging becomes necessary in order to treat the disease conditions that arise with it. A key characteristic of aging is sarcopenia, a decline in muscle mass, strength and coordination. In my project, I propose a novel mechanism for the insufficient muscle regeneration that occurs during sarcopenia. I hypothesize that chronically elevated levels of inflammation in the elderly, as exhibited by higher systemic levels of IL-6, result in an activation of the NF- $\kappa$ B pathway. I also predict that these age-related changes alter the levels and activity of HSP72, a heat shock protein, in skeletal muscle. By utilizing a murine model, I define the relationship between IL-6, HSP72, and the NF- $\kappa$ B pathway in the decreased muscle regeneration that accompanies old age.



Amy Wann  
Kirkland 2014

*Human Developmental  
and Regenerative Biology*

### **Modeling fatty liver and cardiac dysfunction using ATGL-knockout human embryonic stem cell lines**

Cowan and Musunuru Labs  
Stem Cell and Regenerative Biology  
Harvard College

Adipose triglyceride lipase (ATGL), highly expressed in the fat tissue of both humans and mice, is involved in the catabolism of triglycerides in various metabolic tissues. Patients with various ATGL mutations suffer from lipid storage disease, diabetes, and cardiovascular complications. Previous studies performed on mice have shown that ATGL knockouts result in cardiac dysfunction, excessive buildup of lipids and glycogen, and premature death. My project aims to utilize genome editing with TALENs to create a knockout stem cell line, which I will differentiate into relevant cell types like cardiomyocytes and hepatocytes. TALENs, transcription activator-like effector nucleases, are a class of plant pathogens that can be customized to target and mutate a specific sequence of DNA in the genome. I plan to design TALENs that target ATGL in the stem cells, developing homozygous knockout cell lines. I will differentiate the knockout cell lines into hepatocytes and cardiac muscle cells. Characterization of the differentiated cells will likely result in a very clear phenotype – fatty liver and fatty heart. The generation of the mutant cell line and the subsequent differentiation and phenotypic characterization is significant for many reasons. First, it validates the system of TALEN design as an effective tool to model disease. In addition, this project will be the first to study ATGL in relevant human cell types rather than mouse models. The significance of humanized models lies in the fact that mice often do not provide a perfect model of disease pathology in humans. Extended study of ATGL  $-/-$  hepatocytes and cardiomyocytes will allow for efficient drug screening and elucidation of the disease pathway, as well as potential *in vivo* transplantation studies.

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Finally, PRISE 2012 would not have been possible without contributions from the following people:

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