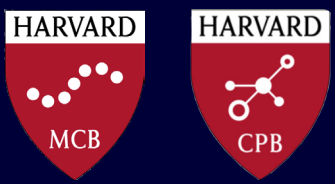
MOLECULAR & CELLULAR BIOLOGY

CHEMICAL & PHYSICAL BIOLOGY

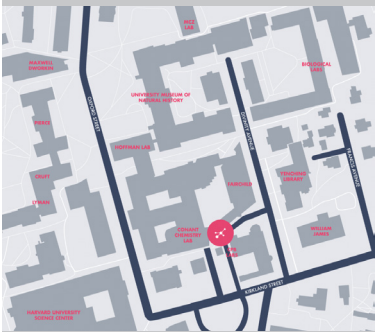
Concentration Handbook



WHERE WE ARE

The CPB-MCB Undergraduate Office is located at:

7 Divinity Avenue, Fairchild 095, Cambridge




CPB
Chemical and Physical Biology
MCB
Molecular and Cellular Biology
7 Divinity Avenue
Sherman Fairchild 095

WHO WE ARE

Adam Cohen
Co-Head Tutor of CPB
Professor of Chemistry and
Chemical Biology and of Physics

Rachelle Gaudet
Co-Head Tutor of CPB
Professor of Molecular and
Cellular Biology

Vlad Denic
Head Tutor of MCB
Professor of Molecular and
Cellular Biology

Dominic Mao
Assistant Director of
Undergraduate Studies

Irina Cashen
Program Coordinator

MCB

The Molecular and Cellular Biology (MCB) concentration emphasizes the intersection of modern cellular biology research with medicine and society. It is rooted in the investigation of biological processes based on the study of molecules and their interactions in the context of cells and tissues, and how the genome orchestrates cell behavior. MCB is therefore ideally suited to students who wish to study molecular and cellular processes at the heart of both normal physiology and disease. MCB concentrators explore contemporary subjects spanning genomics, systems biology, immunology, cancer biology, the microbiome, global health, and infectious disease.

CPB

The Chemical and Physical Biology (CPB) concentration provides students with a broad foundation in the physical and life sciences. This concentration is designed for students interested in applying quantitative tools, physical concepts, and chemical principles to the study of biology. CPB graduates will be able to supplement the traditional arsenal of biological techniques with advances in chemical and physical methods in fields as diverse as engineering, biomedicine, and mathematics.

Tutorial

The Board of Tutors in Biochemical Sciences, established in 1926, runs the tutorial program for MCB and CPB concentrators.
The objective of the program is to enable concentrators to think critically about problems and experiments in modern biological sciences. The focus is on careful reading and analysis, not on a broad coverage of a particular field. Thus, tutorial complements and expands upon the formal course curriculum. In addition, the tutorial provides an important opportunity to meet with a member of the faculty and/or a senior scientist on a regular basis. Mentoring on career choices, research opportunities, and other academic issues are logical extensions of the tutorial.

MCB
CONCENTRATION REQUIREMENTS

REQUIREMENTS	SELECTIONS		
Foundational courses 2 half courses	LS 1a (or LPS A) and LS 1b		
Intermediate biology 2 half courses	MCB 60 and either MCB 63, 64, 65 or 68		
Upper level biology 2 half courses	2 courses, at least one of which must be an MCB 100-level course. Visit *mcb.harvard.edu/undergraduate for* a full list of courses that fulfill this requirement.		
Chemistry 1 General chemistry 1 Organic chemistry	General chemistry: PS1, PS10, PS11, or Chem 40 Organic chemistry: Chem 17 or Chem 20		
Math and computation 1 or 2 half-courses	Math 19a (or higher) or Statistics 110 or Statistics 111	**OR**	Math 1b and Math 19a or Statistics 102 or CS50 (or higher)
Physics 1 half course in mechanics	PS2, PS12a, Physics 15a or 16, or Applied Physics 50a		
Physics 1 half course in electricity and magnetism	PS3, PS12b, Physics 15b or Applied Physics 50b		
Research 1 semester	At least one chosen from: LS 100r, MCB 91, MCB 99, or approved summer research experience. For more information on getting started in research, visit *mcb.harvard.edu/undergraduate.*		
HONORS 1+ Advanced* 1+ Organic Chemistry Thesis	1 additional course from the list posted at *mcb.harvard.edu/undergraduate.* 1 additional organic chemistry (Chem 27 or 30) Thesis: Required for highest honors eligibility *One semester of MCB 99 (thesis research) counts as one of the 3 advanced courses required for honors eligibility.		

CPB
CONCENTRATION REQUIREMENTS

REQUIREMENTS	SELECTIONS
Foundational courses 2 half courses	LS 1a (or LPS A) AND LS 1b
Intermediate biology 2 half courses	MCB 60 AND MCB 63, 64, 65 or 68
General or Inorganic Chemistry 1 half course	PS1, PS10, PS11, Chem 40, or Chem 160
Physical Chemistry 1 half course	MCB 65*, MCB 199, CHEM 60, or CHEM 161
Organic Chemistry 2 half courses	Chem 17 AND Chem 27 OR Chem 20 AND Chem 30
Mathematics 1 full course	Math 19a AND 19b **OR** Math 21a AND Math 21b **OR** Applied Math 21a AND Applied Math 21b
Physics 1 half course in mechanics	PS 2**, PS 12a, Physics 15a or 16, or Applied Physics 50a
Physics 1 half course in electricity and magnetism	PS 3**, PS 12b, Physics 15b, or Applied Physics 50b
Upper level natural sciences 3 half courses	3 courses in the natural sciences, engineering, and/or math (e.g., 100-level CHEM, MCB, or Physics) Visit *mcb.harvard.edu/undergraduate for a* list of courses that fulfill this requirement.
Research 1 semester	At least one upper level project lab course chosen from: LS 100, CHEM 100, CPB 91, and CPB 99. For more information on getting started in research, visit *mcb.harvard.edu/undergraduate.*

*MCB 65 cannot double-count as both an intermediate biology course and as a physical chemistry course

**Students who do not take at least one course at the level of Physics 15 or 16 or Physical Science 12 must take a computational course as one of the upper level courses chosen from CS 50 or 109; Applied Math 111, 115 or 126; MCB 111, 112, 131, or 199; or other computational class approved by the Head Tutor.

INTERMEDIATE BIOLOGY COURSES

The courses below will fulfill the intermediate course requirement, with all students taking MCB 60 and at least one other course within this selection. Two courses focus on biochemistry (MCB 63 and MCB 65) while the other two courses tackle cell biology (MCB 64 and MCB 68). Furthermore, two courses have a perspective closely linked to human health (MCB 63 and MCB 64), while the other two are more singly focused on fundamental science concepts (MCB 65 and MCB 68). Note that spring courses MCB 64, MCB 65 and MCB 68 do not require MCB 60, allowing students to start an intermediate course sequence in the spring. Students who have completed LS50ab have the option of taking any two of the five 60-level courses.

MCB 60. Cellular Biology and Molecular Medicine (Gateway Course)
Dominic Mao and Vlad Denic (fall course)

This course provides an introduction to the principles of molecular and cellular biology and their connections to biomedicine. We explore how medical syndromes provide insights into biological processes and how biological mechanisms underlie human disease and physiology. Topics range from DNA repair, protein folding and vesicle transport to metabolism, cell migration, and cancer. Lectures focus on the experimental evidence for key concepts, and the weekly sections comprise a semester-long discovery-based laboratory research project on DNA damage response using yeast as a model organism.

MCB 63. Biochemistry and Molecular Medicine
Alain Viel (fall course)

The course integrates an introduction to the structure of macromolecules and a biochemical approach to cellular function. Topics addressing protein function will include enzyme kinetics, the characterization of major metabolic pathways and their interconnection into tightly regulated networks, and the manipulation of enzymes and pathways with mutations or drugs. An exploration of simple cells (red blood cells) to more complex tissues (muscle and liver) is used as a framework to discuss the progression in metabolic complexity. Students will also develop problem solving and analytical skills that are more generally applicable to the life sciences.

MCB 65. Physical Biochemistry: Understanding Macromolecular Machines
Rachelle Gaudet and Monique Brewster (spring course)

The course aims to develop fundamental concepts of biochemistry as they apply to macromolecules, including protein and nucleic acid structure, thermodynamics and kinetics, ligand interactions and chemical equilibria. The course will also emphasize how these concepts are used in studies of the structure and function of biological molecules, including examples from metabolism. In the weekly section, students will undertake a discovery-based laboratory research project in which they will apply these concepts toward understanding the structure and function of the ATPase domain from the ABC transporter associated with antigen processing (TAP).

MCB 64. The Cell Biology of Human Life in the World
Robert Lue (spring course)

This course teaches fundamental concepts in cell biology in the context of individual life histories drawn from different parts of the world. Each life case focuses on key aspects of human development, growth, aging and disease while providing a nuanced view of the interplay between the life sciences, geography and culture. For example, a comparative discussion of aging in the United States and Japan is used to explore diet, cellular metabolism and its relationship to protein damage and turnover, while the Human Immunodeficiency Virus and AIDS in South Asia is used to explore mucosal immunity and the basis for estimating relative infection risk. Each case delves into the cell biology of major biological events across the life history of the human organism.

MCB 68. Cell Biology Through the Microscope
Ethan Garner and Jeff Lichtman (spring course)

MCB 68 explores three fundamental fields of eukaryotic cell biology: chromosome segregation, cell motility, and neuroscience. Each topic is approached from a historic and technical perspective. Students will discover these systems as the scientific field did, learning how each successive advance in microscopy revealed new biological details. Students will come away with a theoretical and hands-on understanding of microscopy as well as a grasp of the biological findings each technology revealed.

THESIS ABSTRACTS

CPB and MCB concentrators have the option of pursuing a senior thesis with any Harvard-affiliated faculty member. Below are a few thesis abstracts from 2018, illustrating the range of research interests within the life sciences covered by our senior thesis writers.

Naomi Asimow
Iron Tetraphenyl Porphyrin as a Formate-Selective CO2 Reduction Catalyst
PI: Daniel Nocera, The Patterson Rockwood Professor of Energy, Department of Chemistry and Chemical Biology, Harvard University
Concentration: CPB '18

As atmospheric CO2 levels continue to climb due to excessive use of fossil fuels, it is increasingly important that humanity shift towards carbon neutral energy sources. There is great scientific interest in mimicking nature's solution to energy storage, photosynthesis, by storing energy from the sun in the bonds of a reduced form of CO2. The guiding principle of these technologies is that CO2 can be sequestered and electrochemically reduced into an energy storing form that can later be combusted to produce CO2 creating an overall carbon neutral cycle. Iron (Fe) porphyrins have been shown to electrochemically catalyze the reduction of CO2 to CO in non-aqueous solvents. Selective reduction of CO2 to CO is accomplished with the addition of a weak Brønsted acid to drive catalysis with 100% faradaic efficiency. In the presence of a strong Brønsted acid, Fe porphyrins can also catalyze the reduction of H+ to H2. These two processes beg the question: can the dual nature reactivity of Fe porphyrins be exploited to accomplish new reactivity? Formate (HCO_2^-) is a desirable product of CO2 reduction for its industrial uses and potential usage in novel biofuels because it provides a soluble form of hydrogen. In this thesis, I show that in the presence of a strong acid, iron tetraphenyl porphyrin (FeTPP) can catalyze the reduction of CO2 to formate with high faradaic efficiencies. Selectivity for this process can be controlled and is highest in proton-depleted environments. In acid rich environments, evolution of protons to H2 gas is the only observable process. This is an exciting and novel result in CO2 reduction chemistry and the work presented here puts forward the opportunity for follow-up studies.

Alan Gao
Mechanisms of DNA-Protein Crosslink Proteolysis During DNA Replication
PI: Johannes Walter, Harvard Medical School, Howard Hughes Medical Institute
Concentration: CPB '18

DNA-protein crosslinks (DPCs) are DNA lesions that result from the covalent attachment of proteins to DNA. Once formed, DPCs are potent obstacles to chromatin processes such as DNA replication. Previous experiments demonstrated that DPCs encountered during DNA replication are repaired via proteolysis of the crosslinked protein, which promotes replisome progression past these lesions. Recently, the metalloprotease SPRTN was identified to degrade DPCs in vertebrates. However, there is also evidence that the proteasome is involved in DPC removal, and a unified understanding of how DPC degradation occurs is lacking. By monitoring the repair of site-specific DPCs during DNA replication in Xenopus egg extracts, I demonstrate that SPRTN and the proteasome are independent proteases each capable of degrading DPCs. During DNA replication, DPCs are rapidly polyubiquitylated, which is essential for recruitment and activity of the proteasome. In contrast, SPRTN recruitment and activity is independent of DPC ubiquitylation. In total, these findings outline two different pathways of DPC proteolysis during DNA replication.

Julian Braxton
Capsule remodeling in Klebsiella pneumoniae ST258
PI: Deborah Hung, Massachusetts General Hospital, Harvard Medical School
Concentration: CPB '18

Carbapenem-resistant and hypervirulent Klebsiella pneumoniae pose a grave and immediate threat to public health. In this study, a diverse set of K. pneumoniae ST258 isolates collected from hospitals in Boston, MA and Irvine, CA was characterized, revealing many mutations that alter the production of capsule, a major virulence factor in this species. Engineered isogenic capsule mutants revealed advantages and disadvantages of various levels of capsule production in infection and led to the conclusion that strains that do not produce capsule are hyperurovirulent, i.e. more able to establish urinary tract infections, while classically hypervirulent strains that produce excess capsule were impaired in urovirulence, which helps explain why a clinical isolate appeared to revert from producing excess capsule. These findings demonstrate that capsule remodeling is a major driver of hypervirulence in K. pneumoniae ST258.

Brittany Petros
The pursuit of mechanism: Computational approaches to infer the biological basis of differential response to therapeutics treatment in cancer cell lines
PI: Paul Clemons, Chemical Biology and Therapeutics Science Program,Broad Institute
Concentration: CPB '18

High-throughput cancer cell line (CCL) viability assays conducted after exposure to small molecules or genetic knockdown reagents have the potential to uncover novel cancer therapeutics. By studying these data with the genomic, transcriptomic, and proteomic features collected on the same group of CCLs, one can establish links between "-omics" data and heightened cell death upon treatment with a particular reagent. Via the development of bioinformatics pipelines, we used genomic and gene-expression data to derive functional phenotypes present in the CCLs. By comparing groups of CCLs possessing aberrant functional phenotypes to groups of CCLs with heightened sensitivity to treatment, we uncovered novel signatures that predict treatment efficacy. Some of these signatures recapitulated known biomarkers, shedding light on known cellular processes. Others were false inferences, in which a confounding variable was responsible for both the functional signature and heightened sensitivity to treatment. Finally, some signatures offered novel links between cellular processes and sensitivity. Importantly, these functional signatures offered mechanistic hypotheses—that is, that heightened cell death upon treatment is caused by the aberrant functional phenotype. One of the aberrant phenotypes that our analyses uncovered is the loss of a phosphorylation site in ERBB4 that mediates signaling between ERBB4 and Ras. This phenotype predicted the sensitivity of breast CCLs to genetic knockdown of NRAS. Preliminary in vitro verification experiments are underway to study the cellular state underlying this connection. The results of one such experiment are included here.

Aniket Zinzuwadia

An Investigation of the Encoding of Molecular Properties into Odor Perception using Gaussian Processes

PI: Venkatesh Murthy and Alan Aspuru-Guzik, Departments of Molecular and Cellular Biology and Chemistry and Chemical Biology, Harvard University
Concentration: CPB '18

The encoding of molecular properties at different stages of olfactory processing is not well understood. Multiple studies have supported the idea that odor-chemical space can be reasonably predicted with random forest and regularized linear models using molecular features like Morgan fingerprints and eDragon descriptors. Despite these positive results, a study with a variety of molecular features and more complex nonlinear models like Gaussian processes (GP) could elucidate the role of various molecular properties in odor perception via odorant receptor activation. The study and use of vibrational descriptors can provide evidence regarding the controversial vibrational theory of smell. In this project, we used electronic structure calculations and GP models to investigate potential vibrational descriptors in predicting determined molecular properties like lipophilicity (LogP) and drug-likeness (QED). We found that a histogram representation of vibrations outperformed prior kernel estimation-based methods in predicting these properties. Furthermore, while GP calibration suggested that a vibrational representation of a molecule added molecular information to predictions made by structural descriptors, it was clear that vibrations can directly convey information about the presence and absence of specific functional groups. Thus, when making predictions on the DREAM Challenge and Good Scents data using vibrational and structural descriptors, it was impossible to make any conclusion about the vibrational theory of smell as vibrations directly conveys information about chemical structure. Despite this inconclusive result, we found that GP had high relative performance compared to other successful machine learning methods in making regression and classification predictions on odor perceptual data. For example, we determined that DREAM Challenge predictions with GP achieve reasonably high r and R 2 values with MACCS and eDragon descriptors. Likewise, GP showed strong predictive performance for classification of Good Scent data across most molecular features. These results suggest that while it is difficult to pinpoint individual molecular properties as key in odorant receptor activation, GP can leverage the similarity between molecular features to distinguish perceptual qualities of an odorant. The high performance of nonlinear GP models support the theory that feature-specific patterns of odorant receptor activation can sum nonlinearly when determining an odorant's perceptual attributes. This result regarding olfactory system processing speaks to the growing intersection between machine learning and human behavior.

Emilia Gonzalez
Exercise Induces the Birth of New Cardiomyocytes in the Adult Mammalian Heart
PI: Richard Lee, Department of Stem Cell and Regenerative Biology, Harvard University
Concentration: MCB '18

Heart failure is a leading cause of death around the world. The adult heart has a limited capacity to generate new cardiomyocytes of 0.76-1% per year, yet, there is little known about what factors can stimulate this endogenous mechanism. Studies have demonstrated that exercise induces cardiac hypertrophy and cardiac remodeling Recent reports show that some proliferation markers also increase with exercise. Despite these initial findings, whether exercise induces cardiomyogenesis, or the birth of new cardiomyocytes, remained unknown. Here, we use quantitative multi-isotope mass spectrometry (MIMS) in conjunction with fluorescence in situ hybridization (FISH) and Period acid Schiff (PAS) staining to identify new cardiomyocytes and quantify exercise induced-cardiomyogenesis. We show that after eight weeks of voluntary running, there is at least a 4-fold increase of diploid/mononucleated cardiomyocytes when compared to the sedentary control. Furthermore, we performed a myocardial infarction followed by eight weeks of voluntary running, and then quantified the rate of cardiomyogenesis. We show a significant increase in cardiomyogenesis in the extended border zone for the exercised group compared to the sedentary control group. Together, these results indicate that exercise stimulates the endogenous potential of cardiomyogenesis which may contribute to the beneficial role of exercise.

Connor Horton
Towards higher standards for quality control and analysis of single-cell Hi-C data
PI: Peter Park, Massachusetts Institute of Technology
Concentration: MCB '18

Chromatin conformation capture methods have enriched our understanding of chromatin structure, providing novel insight into how gene expression and disease pathology are affected by the conformation of the genome in the nucleus. Single-cell Hi-C, a newer chromatin conformation capture technique, has the potential to elucidate cell-to-cell variability in chromatin structure and thereby uncover new structure-function relationships in the nucleome. Despite the promising potential of single-cell Hi-C, little work has been done to ensure proper quality control of these data. Thus, I present GiniQC, a novel quality control metric, which quantifies noise by measuring inequality in the distribution of trans contacts per bin. I also present a pipeline for uniformly processing single-cell Hi-C data generated by different protocols. In constructing this pipeline, I also examine the effect of various data filters on data quality, as measured by GiniQC and the percentage of contacts in cis. I find that these data filters have contradictory or negligible effects on these quality control metrics, suggesting that these filters may not improve data quality as intended. Finally, I sought to use these tools to investigate cell-to-cell variability in chromatin loops. However, because I was unable to reproduce prior work on chromatin loops this aim was not completed within the thesis timeline. With these results, I hope to move towards higher standards for quality control and analysis of single-cell Hi-C data, thereby contributing to a more accurate and complete understanding of chromatin organization in the nucleus.

Emma Keteku
The Role of IdrE in an Effector/Immunity System of Proteus mirabilis
PI: Karine Gibbs, Department of Molecular and Cellular Biology, Harvard University
Concentration: MCB '18

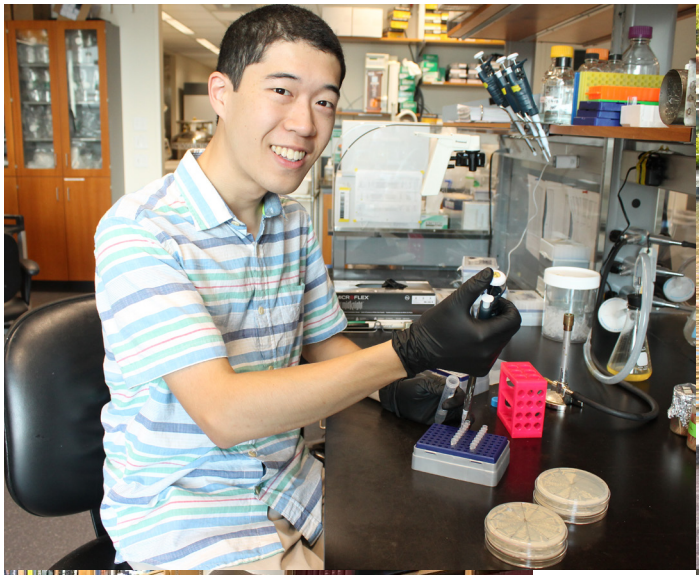
When two different strains of Proteus mirabilis are grown together, the strain expressing one gene, idrD, consistently overtakes the strain that lacks this gene in competition during swarming. Isolated expression of idrD in P. mirabilis and E. coli has also been shown to induce cell death (Sirias, data unpublished). Introduction of a separate gene from the same locus, idrE, leads to a reversal of the competition phenotype and rescues cell death. Further analysis has revealed that the idrD gene shares homology to a family of toxic proteins shown to play a role in bacterial competition. I am interested in determining the role of the idrE gene in relation to the apparent toxic function of the idrD product. Does the IdrE protein function as the immunity partner to the IdrD protein? To address this question, I used P. mirabilis and E. coli to assess the effect of idrE on growth inhibition and performed biochemical assays to assess protein dynamics and interactions between IdrD and IdrE. We found that idrE induced the expected immunity phenotype when co-expressed with idrD. Unexpectedly, coproduction of the IdrD and IdrE proteins led to reduced levels of IdrD detected. From our time course experiments, we found a time point at which IdrD protein levels were stable and, using this time point, detected an interaction between IdrD and IdrE in co-immunoprecipitation experiments. We conclude from these experiments that the IdrE protein serves as the immunity protein to the IdrD effector. We propose a model in which the IdrE protein accomplishes immunity function by interacting with proteases to induce the degradation of IdrD. While we were unable to isolate a specific protease responsible for the loss of IdrD in the presence of IdrE, our data suggest that the mechanism by which IdrE accomplishes its immunity function is atypical.

Richard Ng

Discovery and Modulation of the IRF3-dependent Type I Interferon Response to Myocardial Infarction

PI: Ralph Weissleder, Center for Systems Biology, Harvard University
Concentration: MCB '18

Myocardial infarction (MI) induces ischemic heart disease (IHD), which is the most common cause of death in the world3. Following MI, the innate immune system is strongly activated. With the recent exception of the canakinumab anti-inflammatory thrombosis outcome study (CANTOS), attempts to achieve cardioprotection by modulating immunity have been largely unsuccessful4,5,6,7. The majority of studies examining immune responses in the context of MI to date, including CANTOS, have focused on the role of the nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) inflammatory response pathway and the inflammasome in the context of MI8,9,4,5,6. In contrast, relatively little research has seen performed to investigate the role of the interferon regulatory factor 3/type I interferon (IRF3/type I IFN) antiviral response pathway in the context of MI. This thesis investigates the role of the IRF3/type I IFN pathway in the context of MI and identifies a therapeutic strategy for achieving post-MI cardioprotection. First, we collected heart tissue samples from wild type (WT) mice before and after MI and analyzed our samples by performing western blots, ELISAs, and RTqPCR assays. Our results demonstrate that MI induces the activation of the IRF3/type I IFN pathway. Next, we compared the infarcted hearts of WT mice to the infarcted hearts of mice lacking critical components of the IRF3/type I IFN pathway using RTqPCR assays to measure the expression of interferon stimulated genes (ISGs). Our results demonstrate the necessity of several components of the pathway for ISG expression after MI including: cyclic GMP-AMP synthase (cGAS), a cytosolic DNA sensor; the stimulator of interferon genes (STING), an adaptor protein; and the interferon alpha/beta receptor (IFNAR), a type I IFN receptor. Next, we performed survival studies on WT mice and genetic knockout mice. Our results demonstrate that genetic inhibition "6 of the IRF3/type I IFN pathway achieves post-MI cardioprotection, which is measured as a dramatic increase in the survival rate after coronary artery occlusion. Based on these results, we set out to develop an anti-interferon therapy to phenocopy the cardioprotection achieved by genetic inhibition of the IRF3/type I IFN pathway. First, we used single cell RNA sequencing (scRNAseq) to identify the key cell type(s) responsible for the post-MI activation of the IRF3/type I IFN pathway. Our results demonstrate the presence of interferon responsive neutrophils in the infarct on day 2 post-MI and the presence of interferon responsive macrophages in the infarct on day 4 post-MI. Next, we developed an in vitro model of DNA induced interferon signaling in bone marrow derived macrophages (BMDMs) to investigate the effectiveness of pharmacologic inhibitors at preventing signaling through the IRF3/type I IFN pathway. RTqPCR assays demonstrate that the treatment of the BMDMs with an anti-IFNAR antibody results in dramatic inhibition of IRF3/type I IFN pathway, and survival studies demonstrate that the treatment of mice with this antibody results in significant post-MI cardioprotection. Taken together, these findings demonstrate that MI induces IRF3 and type I IFN signaling through a DNA-sensing mechanism; that this pathway is mediated by interferon responsive myeloid cells; and that genetic or pharmacologic inhibition of the pathway is cardioprotective. This thesis motivates future studies that investigate the IRF3/type I IFN pathway's role in human MI and explore the therapeutic cardioprotective potential of anti-interferon therapy.



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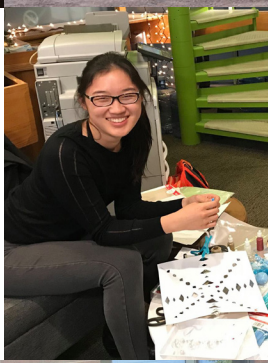

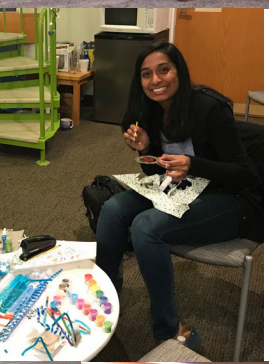

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