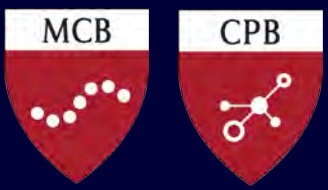
MOLECULAR & CELLULAR BIOLOGY

CHEMICAL & PHYSICAL BIOLOGY

Concentration Handbook



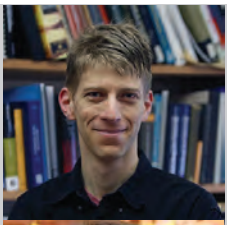
WHERE WE ARE

The CPB-MCB Undergraduate Office is located at:

7 Divinity Avenue,
Fairchild 095, Cambridge


CPB
MCB

WHO WE ARE



Adam Cohen
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Professor of Chemistry and
Chemical Biology

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Professor of Molecular and
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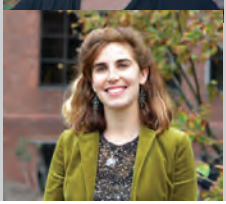


Irina Cashen
Program Coordinator

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, 65, 66, 68, or 80**		
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* more info on 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 upper level course. 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, 65, 66, 68, or 80**
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 more info on 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 three courses tackle cell biology (MCB 66, MCB 68, and MCB 80). Furthermore, two courses have a perspective closely linked to human health (MCB 63 and MCB 66), while others are more singly focused on fundamental science concepts (MCB 65, MCB 68, and MCB 80). Note that spring courses MCB 65, MCB 66, and MCB 68 do not require MCB 60, allowing students to start an intermediate course sequence in the spring.

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 Mchines
Monique Brewster and Maxim Prigozhin (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 66. Pathological Cell Biology
Sam Kunes (spring course)

Pathological cell states are at the heart of human disease: in this course, we view cell pathology as a window into the normal state of the cell; the robustness of its homeostatic mechanisms and the alternative modes a cell may adopt in order to contribute to multicellular structures as precise as a nervous system and as chaotic as a malignant tumor. The curriculum draws upon foundational courses in genetics and cell biology (e.g. LS1A, LS1B, MCB60 and related coursework) and supports further understanding of normal cell states through exploration of cell's pathological states. The curriculum emphasizes advanced experimental approaches and current findings in oncogenic transformation and other pathologies.

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.

MCB 80. Neurobiology of Behavior
Jeff Lichtman and Kathleen Quast (fall course)

An introduction to the ways in which the brain controls mental activities. The course covers the cells and signals that process and transmit information, and the ways in which neurons form circuits that change with experience. Topics include the neurobiology of perception, learning, memory, emotion, and neurologic disorders. This year we are combining interactive, didactic lecture videos with live Tuesdays and Thursdays featuring guest lectures, hands-on demonstrations, and review sessions in addition to small discussion sections.

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 2020-2022, illustrating the range of research interests within the life sciences covered by our senior thesis writers.

Yi Hua Chen
Investigating the Role of the G1 Phase of the Cell Cycle in Genetic Instability in S. cerevisiae
PI: Andrew Murray, Department of Molecular and Cellular Biology
Concentration: CPB '20
Winner of 2020 Hoopes Prize

Almost two decades ago, the Nobel Prize in Physiology or Medicine was awarded to Leland Hartwell, Paul Nurse, and Tim Hunt for their discovery of the fundamental principles that govern the cell cycle. However, the implementation of our understanding of the cell cycle in treatment of diseases related to the cell cycle, namely cancer, has been limited. To date, only one FDA approved cell cycle drug exists for cancer treatment. The challenges in the clinical application of cell cycle research highlight the gaps that remain in describing the relationship between the cell cycle and biological processes such as the maintenance of genomic integrity and viability. Though it is known that cell cycle misregulation can induce genetic instability, which is a hallmark characteristic of cancer defined as the heritable increase in mutation rate, a mechanistic relationship between the two features remains unclear. Most studies have examined the S phase, the site of DNA replication, to study the causes of genetic instability, but, interestingly, genes encoding the regulators of the G1 phase of the cell cycle are among the most frequently mutated genes in most human cancers. In this thesis, I investigate the relationship between the G1 phase of the cell cycle and genetic instability. I show that many factors, including the level of B type cyclin activity in G1, the length of the G1 phase, and cell size, can influence whether a cell gains or loses genetic instability. My results highlight that genetic instability is a complex phenomenon whose rules remain ill-defined, despite the wealth of knowledge available about the cell cycle.

THESIS ABSTRACTS

Ralph R. Estanbouleh
Deep Learning Models for Variant Pathogenicity Prediction
PI: Arjun K. Manrai, Harvard Medical School, Boston Children's Hospital
Concentration: CPB '21
Winner of 2021 Hoopes Prize

Technological advancements in DNA sequencing have made it a mainstay in the clinic in the form of targeted genetic testing as well as whole exome and whole genome sequencing (WES andWGS, respectively). With increased use comes a growing need to interpret the abundance of data being generated and the myriad variants being discovered. Many computational methods have been developed to address this issue, with varying levels of success. My goal in this thesis is to build on such methods by altering the underlying the models, the learning algorithms, and the data being used, and then apply them to the task of clinical-grade variant pathogenicity classification. To do so, I first review and compare the methods that have been developed so far, trying to identify a common pattern of strengths, weaknesses, and aspects to account for. Then, I reproduce a foundational method developed for the interpretation of hypertrophic cardiomyopathy-related disease, PolyPhen-HCM. Finally, using the insights learned from both the comprehensive review and the redesigning and in-depth analysis of PolyPhen-HCM, I introduce deep learning models that address, through their improved architectures and data, some of the most salient issues that methods in variant interpretation have to deal with.

THESIS ABSTRACTS

Christie Hung
Cyclophilin E Selective Inhibition Through Lysine Covalent Modification
PI: David Liu, Department of Chemistry and Chemical Biology, Broad Institute
Concentration: CPB '22

Cyclophilins are a family of ubiquitous cellular proteins that contain a peptidyl-prolyl isomerase domain (PPIase). They play a variety of roles in biological and disease pathways. For example, cyclophilin A (CypA), cyclophilin B (CypB), and cyclophilin D (CypD) have been implicated in viral infection, cell signaling, and mitochondrial-mediated cell death, respectively. However, the roles of the other cyclophilins are still being elucidated. While cyclophilins are attractive targets as biological probes and potential therapeutics, there have been no subtype-selective cyclophilin inhibitors reported in the literature. Recently in the Liu lab, novel CypD subtype-selective inhibitors were developed from inhibitors discovered using an in vitro selection of a DNA-templated library for 256,000 macrocycles for CypD affinity. Their work demonstrated that engineering specific electrostatic, steric, and hydrogen bonding interactions within CypD's unique S2 pocket can achieve sub-type cyclophilin selectivity.

In this thesis, we designed a synthetic scheme to generate a series of macrocycles that places an aryl boronic acid carbonyl warhead, which has previously been demonstrated to modify non-catalytic lysine residues, on a promiscuous cyclophilin inhibitor in the vicinity of the lysine residues in the S2 pocket of several cyclophilins. We hypothesized that these macrocycles could preferentially target an S2 pocket of a lysine- containing cyclophilin through covalent modification. We tested these newly designed inhibitors against a panel of cyclophilins for inhibition and binding, and subsequently developed a cyclophilin E (CypE)-selective inhibitor with an IC50 of 13 nM for CypE and 30-to-750-fold selectivity over the other tested cyclophilins. We then verified its reversible covalent binding mode by mass spectrometry analysis. The work presented provides the first CypE selective inhibitor and further supports a generalized model to design cyclophilin selective inhibitors.

THESIS ABSTRACTS

Stephen Freeman
Exploring the Effects of Raising cAMP on Cellular Ubiquitination
PI: Alfred Goldberg, Department of Cell Biology, Harvard Medical School
Concentration: CPB '21

The ubiquitin proteasome system (UPS) is responsible for the degradation of the majority of intracellular proteins, including misfolded proteins as well as regulatory proteins crucial to cellular health. Impairment of proteasome activity can lead to the accumulation and aggregation of toxic proteins associated with neurodegenerative diseases including Alzheimers, Huntington's, and Parkinson's diseases. Recent research has found that raising the levels of the second messenger molecule cyclic AMP (cAMP) in cells can lead to a rapid increase in the activity of the proteasome. Moreover, it has been shown that raising cAMP promotes the degradation of short but not long-lived proteins in cells, which is critical as this short-lived fraction includes the misfolded proteins whose accumulation is associated with disease. The effect of raising cAMP on the other aspects of the UPS, such as protein ubiquitination, however remains uncharacterized. Understanding how raising cAMP affects cellular ubiquitination is critical to understanding how extracellular signals could selectively promote the degradation of particular proteins. This thesis presents evidence indicating that raising cAMP levels in HEK 293A cells with forskolin, a direct activator of cAMP synthesis, leads to a rise in short-lived ubiquitinated proteins within minutes. These observations motivate further studies into the many remaining questions about the effect of heightened cAMP levels on cellular ubiquitination. This thesis highlights a number of these key questions and proposes strategiesto investigate them in the future.

THESIS ABSTRACTS

Edward Lee
Determining the Metal Transport Features of the Eggerthella lenta Nramp-like Proteins
PI: Rachelle Gaudet, Department of Molecular and Cellular Biology
Concentration: CPB '22
Winner of 2022 Hoopes Prize

All organisms import transition metals using transporters for a variety of biological functions. A family of such transporters are the natural resistance associated macrophage proteins (Nramps). The metal transport features of several Nramps are understood, including those of a model bacterial Nramp from Deinococcus radiodurans (DraNramp), which transports the divalent transition metals Mn2+, Fe2+, Cd2+, Co2+, and Zn2+ but excludes alkaline earth metals. However, two groups of bacterial homologs closely related to the Nramps, termed Nramp-like proteins, remain poorly studied. I investigated metal transport by two Nramp-like proteins from the bacterium Eggerthella lenta, EleNrmT and EleNrampG, using a proteoliposome-based transport assay. With this assay, I tested the ability of EleNrmT and EleNrampG to transport Mg2+, Ca2+, Mn2+, Fe2+, Cd2+, Co2+, and Zn2+ in vitro at different membrane potentials. In the conditions I tested, EleNrmT transported Mn2+, Fe2+, and Mg2+ under high membrane potentials, while EleNrampG did not transport any of the tested metals. Furthermore, EleNrmT required a higher membrane potential than DraNramp to transport Mn2+ and Fe2+. These results suggest differences in the physiological role of bacterial Nramps like DraNramp, and Nramp-like homologs like EleNrmT and EleNrampG. To probe the biological function of EleNrmT, I used bioinformatic analyses and AlphaFold predictions to identify a potential interaction between EleNrmT and a co-operonic protein homologous to the regulatory region of MgtE, a Mg2+ transporter. The MgtE homolog, EleMgtE-like, may alter metal transport by EleNrmT. My results motivate further research into EleNrmT, EleNrampG, and EleMgtE-like to reveal their physiological role while opening future study into more examples of these divergent proteins.

THESIS ABSTRACTS

William Stainier
The Natural Viral Environment of Caenorhabditis elegans: Interactions Between RNA Interference, the Dauer State, and Orsay Virus Infection
PI: Craig Hunter, Department of Molecular and Cellular Biology
Concentration: CPB '21
Winner of 2021 Henderson Prize and Hoopes Prize

While best known and studied within a laboratory environment, C. elegans originally evolved in the context of its natural environment. One particularly potent source of selective pressure is host-pathogen interactions, including interactions between the nematode and viruses. Here, I use the recently discovered C. elegans specific Orsay virus (OrV) to investigate how two prominent features of C. elegans biology, RNA interference (RNAi) and the dauer state, influence viral infection. RNAi mutants have previously been reported to display a reduced ability to defend against viral infection, though it is notknown how the lack of the RNAi pathway influences the spread of OrV through a C. eleganspopulation. I focused my study on viral infection at an individual worm level as well as on a population scale in order to understand how both the cell-autonomous and systemic RNAi pathways influence the population dynamics of OrV infection. In addition, while the dauer state is a prominent feature of C. elegans in its natural environment, its ability to harbor and transmit OrV infection has not been studied. In order to study the influence of the RNAi pathways on disease spread, I first developed a group testing assay for C. elegans. My results suggest that RNAi does not protect against the establishment of OrV infection through a liquid infection protocol. Additionally, my results indicate that dauer larvae are competent hosts of OrV infection; they also provide further evidence for the previouslyhypothesized oral-fecal transmission route of the virus.

THESIS ABSTRACTS

Hannah Cole
Characterizing the Role of Stromal Cells in T Cell Infiltration of a Zebrafish Melanoma Model
PI: Leonard Zon, Department of Stem Cell and Regenerative Biology
Concentration: MCB '22

Melanoma is the deadliest form of skin cancer. While immunotherapies, which harness the body's immune defenses to fight the cancer, have been effective for many melanoma patients, these therapies are not effective for all patients. One known predictor of immunotherapeutic response is the degree of T cell infiltration in a tumor. As the reasons for variations in T cell infiltration of tumors is not well understood, my research aims to elucidate the reasons for variability in T cell infiltration by studying the role of stromal cells in regulating T cell infiltration of tumors in a zebrafish model of melanoma. In this thesis, I hypothesized that stromal cells critically regulate tumor development by affecting the ability of T cells to infiltrate a tumor. I tested the effect of T cells on tumor dynamics in a zebrafish model of melanoma and found a significant decrease in survival rate but insignificant differences in rates of development of tumors and pre-tumorous lesions in immunodeficient zebrafish. I developed a method to inducibly ablate cxcl12a+ stromal cells and showed its effectiveness in zebrafish embryos and adults. Finally, I used single-cell RNA-sequencing to identify six candidate genes, including two positive control genes, for stromal regulation of T cell infiltration in a zebrafish melanoma model. This work paves the way for understanding how stromal cells inhibit or promote T cell infiltration and which stromal genes regulate this interaction. This work has implications for determining which tumors would best be treated by immunotherapies and suggesting new therapeutic co-targets to increase the proportion of responders to immunotherapy.

THESIS ABSTRACTS

Sreekar Mantena
Model-based Exploration Algorithms for Diagnostic Probe Design
PI: Pardis Sabeti, Department of Organismic and Evolutionary Biology, Department of Immunology and Infectious Diseases, Harvard School of Public Health
Concentration: Statistics and MCB '22
Winner of 2022 Henderson Prize

Designing and deploying accurate diagnostic assays is critical to effectively responding to emerging viral pathogens. Nucleic acid-based diagnostic technologies are widely considered the gold-standard and rely on diagnostic probes to detect viral pathogens in a sensitive and specific manner. Although sequencing of viral pathogens has grown substantially in the last decade, there are a lack of computational methods which can leverage this sequence data to generate optimal diagnostic probe designs for several well-defined tasks across genomic variation.

To overcome the limitations of previous approaches, we develop model-based exploration algorithms, a set of computational methods that pair a machine-learned predictive model of diagnostic probe activity with exploration algorithms to search through a landscape of candidate probe sequences and design optimal probes.

We first apply these algorithms to design diagnostic probes that have maximal activity in expectation across genome sequence variation. Focusing on 15 genomic sites in 5 highly-diverse viral pathogens, we experimentally demonstrate that the probes designed by our methods can detect a greater percentage of sequence diversity down to a lower limit of detection than probes designed by state-of-the-art methods.

Next, we apply these algorithms to design diagnostic probes that can optimally distinguish viral lineages down to the single nucleotide level. We design probes for 6 clinically-important single nucleotide mutations in malaria, SARS-CoV-2, and Zika virus and experimentally demonstrate that the probes designed our model-based exploration algorithms achieve superior specificity and sensitivity than those designed by current approaches.

These results indicate that our model-based exploration algorithms can design probes for any well-defined task across known genomic variation, and have significant potential to advance the performance of both point-of-care diagnostic assays and lab-based genomic surveillance technologies.

THESIS ABSTRACTS

Luz Ramirez-Ramirez
Identifying Genomic Changes to Evolutionary Pressures in Babesia Parasites
PI: Manoj Duraisingh, Department of Immunology and Infectious Disease, Harvard School of Public Health
Concentration: MCB '22

Babesia are apicomplexan parasites that are responsible for infecting cattle with bovine babesiosis. Given its global distribution, bovine babesiosis can have devastating economic consequences, thereby making Babesia crucial to understand. An important tool in understanding the biology of parasites is our ability to propagate the organisms in a laboratory setting. However, much of its genome is still uncharacterized due to a lack of adequate culturing methods that make it difficult to grow and experiment on in the lab. Previous research on Plasmodium, another genus of apicomplexan, has suggested that understanding culture adaptation is key to the process of developing experimental models for such parasites. This study aims to develop a pipeline of analysis that can identify conserved genetic changes resulting from evolutionary pressures present in the laboratory in Babesia parasites with high confidence. Impacts of evolutionary pressures such as drug resistance to imidocarb and diminazene, the two most widely used drugs to combat bovine babesiosis, is not yet well-understood. Thus, I first set out to develop a pipeline using data gathered from drug resistant clonal lines sequenced for B. divergens and B. bovis. Next, this pipeline was used to analyze data in a defined series of in vitro and in vivo propagated Babesia spp. lines to determine the genetically conserved mechanisms for adaptation to in vitro culture. Lastly, I aimed to develop an episomal expression plasmid capable of stably transfecting Babesia spp. as a tool for future gene validation studies. The development of this pipeline revealed a defined target for diminazene resistance in B. bovis, a cyclin, N-terminal domain containing protein whose potential mechanism has previously been implicated in drug resistance in P. falciparum.

THESIS ABSTRACTS

Palak Shah
The Role of Mitochondrial Metabolism in Peripheral and Intestinal CD8+ T Cell Dysfunction in People With HIV
PI: Douglas Kwon, Massachusetts General Hospital, Ragon Institute
Concentration: MCB '22

CD8+ T cells constitute a major effector population essential for the cellular immune response and control of viral infections. During HIV infection, these cells become persistently activated and dysfunctional in mucosal tissues such as the gastrointestinal (GI) tract, despite suppressive antiretroviral therapy (ART). Impairment of GI mucosal CD8+ T cells is believed to be central to HIV pathogenesis and disease progression, yet the mechanisms inducing this dysfunction are unknown. Mitochondrial metabolism directly impacts CD8+ T cell effector function. Therefore, a complete understanding of peripheral and GI mucosal CD8+ T cell mitochondrial properties in people living with HIV (PWH) may reveal both intrinsic mitochondrial defects and compartmental differences in mitochondrial responses to provide a more detailed understanding of immune dysregulation during HIV infection.

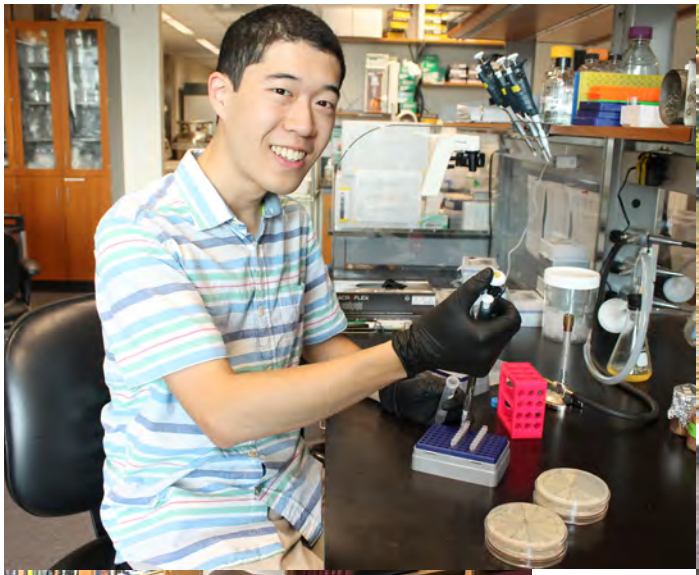
This thesis examines the influence of HIV on peripheral and GI mucosal CD8+ T cell mitochondrial characteristics and function. Peripheral blood mononuclear cells (PBMCs) and GI mucosal lymphocytes were isolated from HIV uninfected donors and ART-treated and ART-naïve PWH. Flow cytometry analysis was used to quantify mitochondrial mass and membrane potential in CD8+ T cells, while real-time mitochondrial metabolic analysis was used to measure mitochondrial respiration in CD8+ T cells.

We found that the mitochondrial membrane potential (MMP) of peripheral CD8+ T cells was significantly hyperpolarized in ART-naïve compared to uninfected donors. ART treatment reversed this MMP hyperpolarization in peripheral CD8+ T cells. In contrast, GI mucosal CD8+ T cells from PWH exhibited significant MMP hyperpolarization irrespective of ART status. Mitochondrial mass did not differ between HIV uninfected and infected donors in both the periphery and GI mucosa. However, mitochondrial respiration was significantly diminished in GI mucosal CD8+ T cells from PWH relative to autologous peripheral CD8+ T cells, independent of ART treatment. These findings indicate that mitochondrial metabolic dysregulation of intestinal CD8+ T cell in PWH persists despite ART and that MMP is predictive of mitochondrial function in CD8+ T cells from PWH.

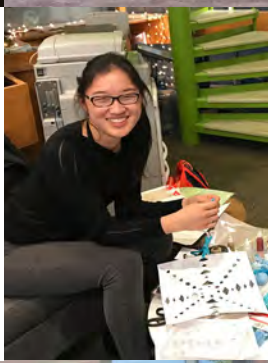
THESIS ABSTRACTS

Sophia Tang
Dissecting and Targeting a Bcl-w/IP3R1 Signaling Axis for the Treatment of Chemotherapy-Induced Peripheral Neuropathy
PI: Rosalind Segal and Loren Walensky, Dana Farber Cancer Institute
Concentration: MCB '21

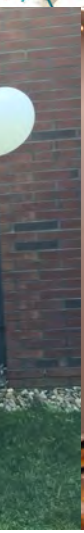
Chemotherapy-induced peripheral neuropathy (CIPN) is a painful and often long-lasting sequela for many cancer patients treated with specific categories of chemotherapies. There is currently no effective therapy to treat or prevent CIPN. Paclitaxel is one of the microtubule- targeting chemo-drugs that causes severe peripheral neuropathy. Paclitaxel disrupts axonal transport which leads to axonal Bcl-w depletion followed by IP3R1-dependent Ca2+ dysregulation. Reintroducing Bcl-w, a specialized anti-apoptotic Bcl-2 family member, or a synthetic helix or "SAHB" (stabilized α-helix of Bcl-2 domains) modeled after its BH4-domain, into the distal axon is sufficient to prevent paclitaxel-induced degeneration, providing a potential pathway to develop a therapeutic agent. This study seeks to determine the key structural components of the BH4 domain in Bcl-w that give rise to its efficacy in preventing degeneration. This project provides quantitative assessments of interactions with IP3R1 and cell permeability for a generated library of Bcl-w BH4 SAHB peptides. These measures allow the identification of the most critical structural components in order to develop the most potent, selective, and deliverable SAHB constructs that can be further tested in vivo for validation and introduced to induce a neuroprotective pathway. This study also provides a valuable screening platform for discovering new therapeutic approaches for CIPN treatments.



MCB



CPB



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