MD/PhD

Sample Essays

Attached are sample responses for the AMCAS "MD/PhD Essay" and "Significant Research Experience" from three past applicants. Please note that the "Significant Research Experience" samples are shown in two different formats (numbered list/essay format), though both types explain research experiences in chronological order.

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MD/PhD Essay (Sample 1)

I entered Hopkins intent on pursuing a PhD. I have always found the pathways and molecular mechanisms fascinating and benchwork has been a prominent part of my life since high school. Now, with my current work schedule resembling that of a scaled-back physician scientist's schedule, in the clinic one day a week and the rest in the lab, I have seen first-hand how the interplay between science and medicine can make you both a better researcher and physician, leading me to pursue a combined MD-PhD.

In the clinic I realized that working as a physician will center my research, helping me develop questions that probe the true knowledge and treatment gaps in the field. My research has always been basic science research, working in S. Cerevisiae to investigate basic mechanisms, but as I began working clinically I started to conceptually frame my science translationally. My first research project was investigating the processes behind telomere elongation and cellular senescence. As I worked, I found myself striving to develop hypotheses relating specifically to my projects applications to constitutive telomerase activation in cancer. Now in my current project I investigate cell signaling in hypoxia; where, again I have mentally framed my project around the hypoxic microenvironments seen in cancer in which G Bodies may promote survival.

In addition to helping me view my work translationally, my volunteering work has helped personify the diseases that previously were just descriptions in textbooks. Now, when I think of cancer, instead of reciting facts memorized in my courses, I reflect upon the patients I have seen in the Pediatric Clinical Research Unit who have had their lives drastically changed by the disease. This sobering reality has further motivated me to pursue research to uncover the mechanisms behind cancer to inform future treatments. Though I may at times get frustrated with my experiments, when I am in the clinic it reminds me of the big picture, how research helps real people with real lives and real diseases.

Lastly, working in the lab will make me a better doctor. Through research, I will become more familiar with the molecular mechanisms behind the disease than possible otherwise. Scientists know the ins and outs of their field, which will mean I know the ins and outs of my patients' diseases more thoroughly than I would without my research. This will aid me in recommending the best possible course of treatment for my patients.

Though I have no naive notions about the difficulty to come as I progress into my career as a physician scientist in Pediatric Oncology, my current work has served to confirm that as a physician scientist I will have the best of both worlds. My research will make me a better doctor and my clinical work will make me a better researcher--that I am passionate about both is an added benefit.

Significant Research Experience (Sample 1)

Research Experience 1: Intern at Segan Industries
June 2014-August 2014, 40 hours a week

My first significant research experience was an internship in the industrial chemical company, Segan Industries. I worked under Hans Ribi in investigating novel color former and developer complexes to be used in color changing products produced by the company. I had applied for the position hoping to complete a long-forgotten project investigating the use of biodegradable plastics in their products. So,

when I arrived and began the actual project I was somewhat discouraged by both my lack of intellectual interest, and ironically the vast amount of plastic waste we would produce in the course of the project. Despite the early setbacks, I worked intently and by the end of it, I had independently established the framework to synthesize a novel high-temperature color changing plastic. This is now a product that is found in fancy cooking stores. I took away from this experience the knowledge that I had the patience and determination to persist through difficult projects, as well as a more clear direction for future research I would pursue.

Research Experience 2: Research Assistant for Dr. David Zappulla
September 2015-May 2016 10 hours a week
July 2016-August 2018 30 hours/week
Winter and Summers Full-Time

I spent the first three years at Johns Hopkins working under Dr. David Zappulla in the Molecular Bio Genetics (MBG) program. The lab's main focus was investigating the composition of telomeres and the components involved in their elongation in Saccharomyces cerevisiae. Prior work in the lab had established that there are 112 long non-coding RNAs that are differentially regulated as cells senesce and then escape senescence. My project was to systematically knock out each lncRNA and analyze its effects on the cells.

Over the year that I worked on this project, I established a strong foundation in yeast biology and mastered various yeast and E. coli cloning techniques. Additionally, the strains and the data that I generated have informed future projects that the lab is currently pursuing.

I later worked alongside another graduate student to develop a novel method, CRISPR-assisted RNA/RBP yeast (CARRY) two-hybrid (https://doi.org/10.1101/139600). CARRY two-hybrid is a technique that uses deactivated Cas9 (dCas9) to investigate RNA binding proteins robustly in S. cerevisiae. The system works as follows: dCas9 is directed to the DNA by a guide RNA fused to our RNA of interest. The protein of interest was in turn fused to a Gal-Activating protein. If the protein bound the mRNA, the galactose promoter would be activated and the downstream His3 gene would be transcribed. This allowed us to easily assay binding through spot assays on -Histidine plates.

I performed the system's secondary validation and characterization by applying the technique to replicate the results of a recent paper which claimed that three components of the RNAse MRP complex: Pop1, Pop6, and Pop7 bound the Est1 arm of telomerase RNA (Laterreur et al. 2016). I first encountered issues with cloning Pop6. Although I had successfully performed several similar reactions, the PCR for Pop6 did not work. I attempted touchdown and gradient PCRs, different enzymes, new primers, and various different preparations of gDNA. After nearly a full semester of PCRs, we ordered a G-Block DNA for the protein and the science continued.

As I then began assaying the binding of the proteins with the Est1 Arm, the second major roadblock arose. One of the positive controls, Est1 protein, which is known to bind the Est1 arm, did not show protein-RNA binding. I predicted that the RNA was not folding correctly, or that the protein being assayed may be too large. First, I tested various versions of the RNA including one where all nonessential regions were removed, as well as the full length transcript, neither of which improved binding. Then,

knowing the tertiary structure of the mRNA, I clamped the base of the hairpin to promote proper folding. Although this did slightly improve binding, it was still highly variable and lower than expected.

Next, I hypothesized that the protein may be large enough that binding to the mRNA was not positioning the Galactose activating protein properly to allow Binding and activation. To test this, I began investigating the various domains of the Est1 protein, our positive control. I predicted that if I fragmented the protein, the putative RNA binding domain would show activation of the transgene. Unfortunately, at this point my PI did not receive tenure and the project was terminated as he left the university.

Although the three years I spent in Dr. David Zappulla's lab did not result in any significant results or publications, I have taken away a great deal from the experience. My work began in a well populated lab where I was able to learn a great deal from seasoned graduate students regarding benchwork, the world of academia, as well as their tips for surviving graduate school. I participated in lab meetings through which I gained a better understanding of genetics and yeast biology. Additionally, as I became the sole member of the lab, I learned how to work independently on a research project by developing my own hypotheses, designing experiments, troubleshooting and analyzing my data. Finally, by working and communicating directly with Dr. Zappulla, and presenting my results to the faculty in poster sessions, I learned to communicate my results effectively and professionally--mastering the "elevator speech" of which Dr. Zappulla hounded the importance.

Research Experience 3: Research Assistant for Dr. John Kim
September 2018-December 2018 20 hours a week,
January 2019-Present Full time

As I entered my Senior year, I joined Dr. John Kim's lab, also in the molecular bio genetics program. Dr. Kim's lab focuses predominantly on the regulation of small RNAs in Caenorhabditis Elegans; however, a small subset of the lab works in S. Cerevisiae investigating non-canonical RNA binding proteins that phase separate into puncta, termed Glycolytic (G) Bodies, in hypoxia. This allowed me to continue working in S. Cerevisiae, while also serving to diversify my research experiences.

G Bodies have been shown to form in cancer derived HepG2 cells (Jin et al. 2017) and are potentially involved in hypoxic survival and the Warburg effect. This provided me with the opportunity of transforming a very fundamental observation into translational research. I am in the process of performing a drug screen to determine which drugs inhibit formation of G Bodies in hypoxia. As the loss of G bodies negatively impacts cell survival in hypoxic conditions that are similar to those present in the interior of tumors, drugs that I identify will have ramifications in cancer treatment. Through my preliminary optimizations for the drug screen I discovered Rapamycin as a potent G Body inhibitor.

As an additional advantage, the drugs that I am screening are inhibitors of known molecular pathways. Following up on the identification of Rapamycin, I am working to fully characterize Torc signaling as a regulator of G Body formation. By genetically manipulating factors upstream and downstream of Torc activation, I can identify other proteins involved in this pathway, as well as the mechanism of action. I am currently cloning constitutively active Tor1, as well as phosphomimetic downstream effectors.

To find other factors that regulate G body formation, I will perform two separate high throughput screens. The first is an overexpression screen in normoxia as well as hypoxia, through which we hope to discover pathways that promote G Body formation. I expect that the candidates that I identify may correlate with oncogenic pathways. To perform this screen, I will be traveling to and working with a collaborator in Stanford, where I will be trained on a liquid handling robot allowing the systemic transformation of thousands of S. Cerevisiae strains very rapidly. In the second high throughput screen, I am testing a library of strains in which individual genes are degron tagged so that they can be degraded in an inducible manner. This will complement the deletion screen already completed in the lab, now allowing us to assay the loss of previously untested essential genes. I have liaised with the microscopy and imaging experts at Johns Hopkins to successfully establish a platform to perform this, and the other screens, in an efficient manner. In the preliminary optimizations of the degron screen I have discovered a novel phenotype which I am actively pursuing and I suspect that many of the other essential genes important for hypoxic survival may replicate this phenotype.

I am excited to unravel the role of the Torc signaling pathway as a regulator of G bodies during my gap year. We have outlined plans for a first author publication discussing my results and I plan to submit the manuscript before I leave for medical school. Integrating the results from the two high throughput genetic screens and additional drug screen will inform the future directions of the G Body research and phase separation as a whole in the lab.

After joining the lab, I quickly decided to graduate a semester early so that I could work full time on my project. I currently work independently on my project, designing my own experiments and developing my own hypotheses. I meet with Dr. Kim every week to discuss my results and participate in journal clubs and present lab meetings alongside the graduate students. My time in Dr. John Kim's lab has given me insight into what life will be like as a graduate student and has given me confidence that I will be able to work successfully as a researcher.

MD/PhD Essay (Sample 2)

I entered college with a raw but unrefined passion for science and medicine. I explored different disciplines as a freshman but quickly realized that the questions addressed in neuroscience were the ones that intrigued me most. I was drawn to the subject of the diseased nervous system and, when given the opportunity to take a course about that exact subject my junior year, I felt that it had been designed for me. Each lecture focused on a unique disease or disorder and was taught by a specialist from the School of Medicine. The speakers repeatedly left us with the daunting and inspiring message that there is still so much we do not understand about what underlies neurological conditions, meaning questions remain that I can help answer. The particular subset of talks that resonated most with me were the ones given by lecturers who had opted for a unique path that bridged medicine and research. Until this point, I thought I had to choose between science or medicine. My passion for patient interaction made me question a research-only future yet I was hesitant about treating patients, especially those afflicted with neurologically related conditions, with a limited therapeutic arsenal. Suddenly, there was this incredibly enticing third possibility where clinical observations inform research

questions and lines of inquiry in lab can be translated into therapeutic interventions. These physician-scientists also addressed our concerns about splitting their time between two fields to which many people singularly dedicate themselves. They helped me understand that their goal is not to be a full-time physician or scientist. Rather, they have the unique opportunity to work directly with a specific group of patients, identify knowledge gaps and then chase down those questions in lab.

This class motivated me to join a lab where I could become deeply immersed in a research project to learn about a career in science. I demonstrated curiosity and dedication, so I was given the opportunity to experience all aspects of research: designing an experiment, collecting and analyzing data and presenting at a poster session. Concurrently, I started to volunteer in the pediatric oncology unit at Johns Hopkins and felt this field's allure. Observing and experiencing first-hand the frustrations that physicians face when treating children with cancer motivated me to pair my clinical and scientific interests through the Pediatric Oncology Education program at St. Jude where I worked on a developmental neurobiology project seeking to understand how misregulation of a protein complex in cerebellar granule neurons can lead to medulloblastoma, the most common pediatric brain tumor. The physician-scientists with whom I interacted at St. Jude, who often chose to specialize and subspecialize as a way to focus the questions they explored in their labs, showed me how to successfully occupy both realms. This experience confirmed that a career as a physician-scientist is right for me.

Significant Research Experience (Sample 2)

Dr. Akira Omaki's inclusion of his lab's research comparing language processing in children to adults into his Language and Mind course motivated me to join his lab. From January to July of my sophomore year, I worked on a project studying active gap filling as a learned comprehension mechanism. Previous work in the lab found that five-year-old (5yo) children did not actively fill the gap location in an adult-like way when asked a wh- question about a story they watched on a screen. For instance, if they heard a story about a girl who built a sandcastle with a shovel and were asked "What was the girl building the sandcastle with?," they did not predict sandcastle as the answer when they heard the verb "build." Eye fixation, tracked using an EyeLink 1000 remote eye-tracker, was the metric used. Conversely, the adult cohort reliably fixated on the object of the verb during the wh- question. Data analysis revealed a confounding variable in the study design, though, so I helped redesign and run an expansion of the project that included 6yo and 7yo cohorts to address the hypothesis that as children age they gradually become more adult-like when interacting with filler-gap regions. We also measured whether children with more mature vocabularies process sentences in an adult-like way using the PPVT-4 standardized vocabulary assessment. Preliminary analysis indicated that 7yo children fixate more reliably on the object during the wh- question than 6yo children, who fixate more reliably than 5yo children. Vocabulary size was not a predictor of adult-like gap filling. We discussed a follow-up study to test if priming before the experiment would increase performance in all cohorts by increasing familiarity with ambiguous sentences since active gap filling is a learned comprehension skill. I enjoyed my dive into linguistics, but this experience helped me recognize a stronger desire to pursue research that investigated neural mechanisms underlying brain function.

I then joined Dr. Daniel O'Connor's lab, which studies the neural circuitry underlying touch perception from the periphery up through primary and secondary somatosensory cortices, in January of 2016. I worked on a project exploring how the behavioral relevance of sensory stimuli affects the firing of primary somatosensory (S1) neurons as initial results were obtained from head-fixed mice trained in a novel cross-modal (CM) attention task, which consists of interleaved trials of either a weak single-whisker stimulus or a weak visual stimulus presented in a blocked trial structure: mice lick in response to a whisker stimulus for a water reward on one lickport in touch blocks and in response to a visual stimulus for a water reward on a second lickport in visual blocks. This challenging task takes mice about 3 weeks to learn. Once they reach a performance level of 70% or better, we begin neural recording. Prior to training, a 32-channel tetrode microdrive for extracellular recording of neural activity with an attached optic fiber is implanted into S1 and is then advanced from superficial to deep layers of cortex over 16 days. After each recording session, the cortex is optogenetically stimulated with a 473nm laser. Because we use Ai32 transgenic mouse lines that express channelrhodopsin-2 in one of three interneuron types (somatostatin, parvalbumin or vasoactive intestinal polypeptide), interneurons active in the task can be identified by matching their waveform to those of neurons that spike in response to the laser, which interests us since cortical interneurons have been shown to encode behavioral relevance in other model systems. The initial results suggested three subpopulations of neurons: those that fired to the stimulus, to the licking or in the period between. After a comprehensive literature review, I helped design and pilot a new delay task with a no lick period of 1.25s between the stimulus and reward to temporally isolate the middle epoch of neural activity to determine if this enhanced firing was attention-related. Over the next 6 months, we refined the protocol to establish the most efficient training strategy: we introduced an auditory tone while increasing the delay in 0.2s increments to 1.25s but found that mice were trying to anticipate the stimulus rather than respond to it and that they were responding to the auditory cue rather than the visual or touch stimuli. We also introduced a punishment where the intertrial interval increased if mice licked within the delay period. It still took mice months to learn so we adopted a new method: we trained mice fully on the CM task then immediately introduced a 2 second delay. That was more successful but data collection was ongoing when my senior year ended.

In the summer after graduation, I traveled to St. Jude to gain research experience in a field that interests me clinically. I worked in Dr. David Solecki's developmental neurobiology lab, which studies the polarization and migration of cerebellar neurons during development. These processes, which are critical for the maturation and migration of granule cell precursors from the transient external germinal layer to the inner granule layer, are driven by the PAR polarity complex. In the Sonic Hedgehog subtype of medulloblastoma, the most common pediatric brain tumor, dysfunction of PAR complex activity causes an accumulation of precursors in the EGL. My project explored the functional relationship between Zeb1, a transcription factor that represses the expression of Par3 and Par6 mRNA, and Siah2, an E3 ubiquitin ligase that targets Par3 for degradation, since they are upstream regulators controlling PAR complex activity. I performed a knockdown of Zeb1 and Siah2 and a simultaneous knockdown of one paired with an overexpression of the other to see if Zeb1 and Siah2 function in the same or parallel pathways. Using an ex vivo cerebellar pulse-chase assay, I electroporated P7 mouse cerebella with appropriate shRNA constructs for four conditions: a control, a Zeb1 only knockdown, a Siah2 only

knockdown and a double knockdown. The plasmid solution for each condition contained the nuclear marker, H2B-mCherry. I then sectioned the cerebella, incubated the slices at 37 C for 48 hours, fixed them to prevent further cellular migration, imaged them using a confocal microscope and analyzed them to measure distances that each cell migrated. The slight increase in migration produced by the Siah2 knockdown was not as robust as previously observed in the lab. The Zeb1 knockdown results were even less consistent with previous findings. We believe that this in part stemmed from the use suboptimal shRNA concentrations; I reached the upper limit to how much plasmid can be safely introduced because I electroporated with Zeb1 shRNA, Siah2 shRNA and H2B-mCherry. 48 hours may also have been a long enough period for the cells in the individual knockdowns to "catch" the control. The double knockdown produced a clear increase in migration that exceeded the results observed in either of the individual knockdowns, which suggests that Zeb1 and Siah2 function independently in parallel pathways. The decreased shRNA concentrations were ultimately a sensitive enough test to report this functional interaction. The robust decreased migration phenotype in both experimental conditions of the simultaneous gain and loss of function experiment again suggested functional independence. Alternatively, these results could be the outcome of using suboptimal shRNA concentrations, meaning I did not truly knockdown the repressors of migration. With more time, I would have liked to run replicates to assess the minimum effective shRNA concentrations and to vary the fixation time points. This experience helped confirm my interest in matching my clinical interest with scientific inquiry in the future.

Once back in Baltimore, I transitioned into my new role as a joint research fellow for Dr. Daniel O'Connor and Dr. Jeremiah Cohen. In the O'Connor lab, I primarily resumed work on the project with which I was previously involved. The project's focus has shifted to understanding the late epoch of neural activity since papers from the Deisseroth and Svoboda labs reported last May that activity of premotor area, ALM, ramps up and spreads throughout cortex from the time of stimulus presentation so we are now trying to determine if this ALM activity can account for the enhanced spiking of some neurons in S1 in our CM task. I have also been able to work on a project looking at the recurrent circuitry between S1 and S2, through which I have learned new skills like viral injections and intrinsic signal imaging.

In the Cohen lab, which studies the neural circuitry underlying reward and decision making, I am working on a project exploring the encoding of decision variables, such as reward history, in medial prefrontal cortex. In a dynamic foraging task, head-fixed mice choose between two alternatives with non-stationary reward probabilities after the presentation of an uninstructive olfactory go cue. With reversible muscimol inactivation of mPFC, a region involved in abstract decision making, mice once expert in the task show a strong bias to one side and slowed response times, demonstrating that mPFC is necessary for successful performance. Extracellular neural recordings acquired through a 32-channel tetrode microdrive throughout this task showed the persistent encoding of decision variables during the intertrial intervals. I worked on mapping this activity onto a relevant circuit. We looked at prefrontal projections to dorsal medial striatum, an area responsible for goal-directed behavior, to see if any connections were enriched. Through extracellular recordings and optogenetic stimulation of corticostriatal neurons that expressed Chronos, an opsin with temporal resolution superior to

channelrhodopsin, we found that 83% of identified neurons indeed showed persistent activity that correlated with decision variables.

MD/PhD Essay (Sample 3)

When I was little, I could always be found huddled in an igloo of books. Their themes changed constantly, for I frenetically cycled through obsessions—begging my mother to read me chapters from dusty medical tomes one week, probing my grandmother for her take on "Jabberwocky" the next. It was as if each bit of knowledge I gained was one piece of a vast puzzle etched into the nooks and crannies of my brain. Then, I had no idea what picture these pieces would form. When a close friend and my high school debate coach were both diagnosed with aggressive brain tumors five years ago, I began to feel that my previously undirected pursuit of knowledge had found a purpose.

The two passed away within two weeks of one-another, and I coped with loss in the way that felt most natural. Having been raised on a steady regimen of science fairs and academic competitions, I immersed myself into studying cancer—scrutinizing textbooks, devouring academic papers—hoping for a clue as to how the disease works. Around then, I began an independent study of viruses as cancer immunotherapy agents at Schmahl Science Workshops, a California nonprofit dedicated to offering research opportunities to students. Encouraged by the belief that my efforts could one day positively impact the field of oncology, I continued exploring at the Haussler lab at UC Santa Cruz the next year. There, while searching for candidate genes that may drive pediatric cancers, I began to see an eerie beauty emerge from the web of connections spanning genes, proteins, and across cells.

I have since investigated compounds potentially rich in insights about patient prognosis, crafted tools for analyzing cells' transition from healthy to malignant, and developed databases of analyses by scientists globally. These experiences have cemented my goal of leading efforts to comprehensively characterize tumors.

As a physician-scientist, clinical practice will help me identify technological gaps that can be addressed in the lab; conversely, researching biological processes will inspire therapies that I can help bring to patients. I have been reminded of the inextricable bond between clinical and research realms while working with clinicians to build breast biopsy devices and to devise sensors of blockage in hydrocephalus shunts. Seeing research enterprise coupled with clinical immersion has cemented my desire to straddle the two. It has awakened me to the reality that factors that often extend beyond the science, such as cost and compatibility with existing workflows, can make or break the translatability of an innovation—most apparently in the context of medical device development but no less true of biomarker and therapeutic target discovery, where I intend to make my mark. I aim to identify healthcare needs first-hand, using these to motivate my research. Thus, I see MD-PhD training as integral to my vision of a future at the fore of medical innovation, developing and delivering effective, accessible care.

Significant Research Experience (Sample 3)

Research has long been a part of my life—participating in science fairs and summer camps when I was little made it fairly easy to envision a future for myself in STEM. After losing a close friend and my debate coach to glioblastomas, cancer research became a personal mission. When I subsequently began a study of the M13 bacteriophage as a cancer treatment, I was introduced to the tumor microenvironment's role in immune evasion. This research—as well as my work the next summer, identifying hotspot mutations in pediatric central nervous system tumors at the Haussler lab at UC Santa Cruz crystallized my desire to make sense of the vast complexity of cancers and ultimately drew me to pursue a biomedical engineering degree.

Immediately upon arriving at Johns Hopkins University, I joined Dr. Kristine Glunde's lab in the Department of Radiology and Radiological Science at the School of Medicine, where I began work on several projects revolving around metabolic changes accompanying cancer. This work has led to the completion of two manuscripts—one, a first-author paper, is under review, while the other is in press (Sonkar, et al.)—and eight abstracts, presented (or to be presented) at national or international conferences.

My primary goal as member of the Glunde lab has been to uncover a role for aberrant creatine (Cr) and phosphocreatine (PCr) metabolism in breast cancer. Cr and PCr provide a dynamic reserve of phosphate for ATP synthesis. While several cancers exhibit altered Cr metabolism, the genetic and molecular changes that impart these altered profiles are not established. My hope is that, since Cr and PCr can be imaged using magnetic resonance-based approaches, finding a role for these compounds in oncogenesis and tumor progression may be useful for cancer diagnosis, patient stratification, and treatment monitoring.

In light of our lab's previous discovery of decreased Cr and PCr in metastatic breast cell lines, I hypothesized an association of levels of Cr compounds in cells with the expression of enzymes associated with Cr metabolism. To first assess potentially relevant genetic changes, I analyzed a microarray dataset comparing primary and metastatic tumors and found that metastatic samples displayed downregulation of CKMT1, which encodes ubiquitous mitochondrial creatine kinase, a candidate prognostic indicator in several cancers. After confirming these in silico results using qRT-PCR and immunoblotting, I was encouraged to find a strong correlation of CKMT1 expression with levels of PCr, as detected by proton magnetic resonance spectroscopy (1H MRS). The latter result lends credence to the exciting prospect of eventually using PCr as a biomarker of CKMT1 status.

While working on the project, I have appreciated the opportunity to flex my creativity and design my own studies. Having identified CKMT1 as potentially responsible for malignant Cr metabolite profiles in breast cancer, I sought to examine the effects of CKMT1 overexpression, using lentivirus-based transfection to engineer two breast cancer cell lines overexpressing CKMT1. Using 1H MRS, I found that CKMT1 overexpression resulted in increased Cr and PCr levels, confirming that CKMT1 drives Cr metabolite profiles in breast cancer. I was also curious about the possible impact of CKMT1 overexpression on cells' energy generation, given that cancer cells are known to exhibit mitochondrial dysfunction and upregulated glycolysis. Since CKMT1 is a mitochondrial membrane protein, I hypothesized that its expression might be coupled to oxidative phosphorylation. While I did identify an overall increase in energy metabolism among CKMT1-overexpressing cells, I was surprised to find that

CKMT1 overexpression increased the ratio of metabolites associated with glycolysis to those associated with the TCA cycle, as detected by 1H MRS. In the future, using dynamic assays of metabolism (such as 13C MRS-based flux analysis) and further molecular studies of CKMT1 overexpression and knockdown, I plan to probe the simple explanation that CKMT1, by increasing the availability of phosphate for ATP synthesis, just facilitates increased flux through cancer cells' preferred glycolytic mode of energy generation.

Throughout my time in the Glunde lab, I have sought to complement my molecular work with computational analyses to gauge the ability of my findings in cells to translate to patient populations. To understand transcriptional programs occurring alongside low and high CKMT1 expression, I performed functional annotation of genes (from the TCGA and METABRIC datasets) whose expression correlated with that of CKMT1 in patients. I found that CKMT1 expression correlated positively with expression of genes associated with proliferation and negatively with expression of genes associated with cell migration and adhesion. These findings accord with assays of CKMT1-overexpressing cells, and I am now performing studies on murine models of breast cancer to confirm these results. Although I have stepped away from the lab for the summer, while I investigate metabolic biomarkers of TERT promoter mutation in glioblastoma in Dr. Sabrina Ronen's lab at the UCSF Department of Radiology and Biomedical Imaging, I look forward to applying the techniques that I am learning, such as measuring metabolism in real-time with NMR-compatible bioreactors, when I return to the lab in the fall.

Broadly, my aim of understanding altered metabolism in cancers has led me to connect cellular energy generation to diverse processes in cancer progression including autophagy and the epithelial-mesenchymal transition. My results underscore the biological variability that distinguishes cancer and highlight the value of imageable biomarkers that can guide patient prognosis and treatment monitoring. This has led me to explore the use of data science to study and predict patterns that cut through cancer's heterogeneity. Projects completed through coursework—for example, building deep Q-learning-based solvers for NP-hard discrete optimization problems—and extracurricularly—using binary integer programming to generate schedules for umpire crews and minor league baseball teams—have only fueled this growing interest. In January 2019, I began collaborating with Dr. Ishan Barman's lab in the Johns Hopkins University Department of Mechanical Engineering to develop deep learning tools for segmentation and classification of quantitative phase images of white blood cells from pediatric patients with acute lymphoblastic leukemia. This has provided me with a tremendous opportunity to teach myself machine learning and computer vision techniques, and I am currently completing a manuscript detailing our use of a random forest model that uses features learned by a neural network.

My foray into computational research did not begin here, though. In January of 2018, I joined Dr. Anthony Leung's lab (jointly affiliated with the Johns Hopkins Department of Molecular Biology and the School of Public Health) to help build—and subsequently, to analyze—a database of proteins that undergo ADP ribosylation, a protein modification produced by mitochondrial metabolism. I had been studying post-translational regulation of CKMT1 and was thus already intrigued by the phenomena that build proteome from genome. When I read one of many recent papers that describe sensitizing glioblastomas to chemotherapies by inhibiting ADP ribosylation, I felt called to study the phenomenon further. My bioinformatics-based study of ADP ribose-mediated ubiquitination (PARdU), a recently-

discovered phenomenon described in our review (Vivelo, et al.), explores the hypothesis that PARdU regulates low-abundance proteins that are rate-limiting factors within their respective biological processes. This complements my work in the Glunde lab—studying cancer metabolism has helped me to understand specific changes that accompany malignant transformation; my study of ADP ribosylation investigates regulatory events that enable these changes, as is highlighted in our recently-accepted manuscript (Kalesh, et al.). In the future, I seek to characterize processes like metabolism, not only in terms of their immediate effect on cells, but also in terms of their influences across biological networks. I aim to leverage this understanding to address the root of how cancers form and how they progress.

I should mention that, for all of my interest in basic sciences, I have an immense desire to contribute to innovation that immediately and directly impacts patients. At Johns Hopkins, I have enjoyed working alongside my peers to engineer solutions to real clinical challenges, from instrumentation-focused work for interventional radiology to an electrical/computer-engineering project on hydrocephalus management. Most rewarding has been the experience of working to design a breast biopsy device intended for use in low-resource settings. Accepted devices for core needle biopsy (CNB) are either disposable devices, expensive over the long-term, or reusable devices, which are susceptible to contamination and thus require laborious and time-consuming cleaning procedures. As member of a team of eight undergraduates, I helped develop a novel CNB device attachment that interfaces with reusable biopsy drivers to prevent internal contamination. The device was awarded a provisional patent, and our technology is currently employed in reusable CNB devices now being piloted in Peru and South Africa.

Ultimately, I envision myself as a medical oncologist and researcher at an academic institution. As a scientist, my goal is to use molecular imaging techniques and systems-biology analyses to debug tumors' faulty genetic code, to translate communications among cells, and to use this information to guide individualized cancer treatments for patients. As a clinician, I dream of bringing improved diagnostic and treatment technologies to underserved populations and low-resource settings.