MD/PhD Sample AMCAS Essays

including: 1) “Personal Comments,” 2) “MD/PhD Essay,” and 3) “Significant Research”

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Applicant 1 SAMPLE ESSAYS:

PERSONAL COMMENTS---Tensions were already high after the American and Chinese doctors argued over the proper distribution of antibiotics, only to be exacerbated by the case of this little boy. I noticed the boy and his parents when they arrived two days ago, and assumed that, they, like everyone else, had come for the surgeries provided by Operation Smile. But unlike others waiting in line for screening, they sat on the side of the room. As the mother looked distressed, I approached her to ask if I could help, introducing myself as a medical translator. She revealed that her son had been deemed ineligible for the cleft palate surgery because he had been sick and feverish for the past few days. She was quite distraught as Operation Smile was her only hope of getting her son this expensive corrective surgery that he desperately needed. I tried to reassure her and promised that I would work to present and advocate their case. As the family had come a long way, the doctors decided to have the boy stay for observation. However, things came to a head two days later when they were at an impasse over how to proceed. The Chinese doctors were worried about the risks while the American doctors were more optimistic. Concerned that the argument was getting heated, I consulted the senior American doctor, who suggested that I refrain from translating some of the less tactful comments from one particular physician to avoid offense. But one of the Chinese physicians caught on and demanded that I translate everything word for word. Stuck between two opposing perspectives, I tried to balance competing demands by focusing on the patient, centering the debate around the boy's latest test results, his current condition, and what his future might be like without the surgery. I also tried to explain the cultural context, for example, in China, there is considerable fear of vigilante retaliation against doctors when surgeries go wrong. By bridging the cultural gap, each side was able to see the other's perspective and came to an agreement. The boy got a new smile, and I had the joy of translating the parents' thanks as the doctors deemed him ready to go home.

In college, I was keen to engage in more of the personal interactions with patients that I had experienced as a volunteer by engaging in clinical research. I began working with Dr. Bodurtha, a geneticist, and Dr. Feliciano, an oncologist, to understand the views of lung cancer patients on how doctors could better address their concerns. As my work entailed talking with the patients and their families, I learned how to discuss sensitive matters like stopping treatment. I was reminded of my grandma who, despite coughing blood for months, refused to seek treatment as she did not trust doctors. Her illness had progressed to a late stage by the time she sought help, and she died from the disease. I heard countless stories like hers while working on clinical research: one man showed symptoms for a year but kept delaying testing; another woman undergoing treatment could not discuss it with her family. Seeing this, I led focus groups to better understand patient experiences and hosted workshops to talk about family health histories. I heard patients speak about how distrust of doctors and a lack of communication prevented them from getting vital care: a bridge was needed to close the communication gap between doctors and patients. I saw how physicians could remedy this by being a resource for patients. Dr. Feliciano contextualized treatment so patients could understand the hospital's plan for care; Dr. Bodurtha went to local organizations to speak on new health initiatives.

It was Dr. Bodurtha who told me that it was never too early to start closing the gap. Inspired, I joined the MERIT program to teach Baltimore high schoolers interested in medicine. One weekend, the conversation turned to family health, and some of them expressed their frustration at the limited health outreach efforts available in their neighborhoods. Stirred by the discussion, we collectively figured out how they could take part in a community health forum that would inform public health initiatives and jumpstart neighborhood engagement. My mentorship experience taught me how to connect with people and to ensure that they can get the resources they need to succeed, which is something I hope to do for my future patients.

Looking back on the uncertainty I felt when navigating the conflict between the American and Chinese doctors, I better understand why the boy's mother looked so worried. Patients are often in uncharted territory when they seek care. But through communication, doctors can serve as guides to help them through some of the most difficult times of their lives. Each of my experiences has bolstered my desire to close communication gaps between the healthcare system and the individual: to be a physician with the necessary scientific expertise and cultural awareness to put patients at ease. I can think of no better way to serve others than to bring their voices into the conversation. I want to be a physician that will build the bonds of trust that are so crucial to helping patients in need, like the little boy who just needed a smile.

MD/PHD ESSAY-- As a child, I believed that lung cancer was a disease that only affected people who smoked. I was shocked when my health-conscious grandma was diagnosed with this disease. To understand what happened, I started doing research on the causes of cancer, which led me to apply for my first internship at a biochip lab at National Taiwan University. Here I learned that genetics was the primary cause of lung cancer in many Taiwanese women with no history of smoking, just like my grandma. Research opportunities at Hopkins further opened my eyes to how science could be applied to solve real problems in the clinical setting.

In college, I joined the Rong Li lab to continue to look for answers about diseases that seemingly struck from nowhere. My research focused on protein aggregates in cells, which are associated with diseases like cancer and Alzheimer's. My project aimed to identify a new pathway of protein dissolution, which gave me the opportunity to think creatively about a problem as we tried to winnow down the thousands of possible answers. Witnessing the results of the time and effort we spent in the lab sparked my passion for research. However, I wasn't ready to discard my interest in a clinical career. It was around this time that I invited Dr. Andrew Cameron, Chief of Transplantation at Johns Hopkins Medicine to speak at an event in my role as Chair of the Conversations In Medicine Symposium. Dr. Cameron is an M.D./Ph.D. who specializes in developing new immunosuppressant implants to help solve the problem of liver transplant patients needing to take numerous drugs after surgery. He talked about his successful and fulfilling career that allowed him not just to invent, but also play a key role in putting his invention into action in a clinical setting. His talk opened my eyes and helped me understand how I could meld my interests in both clinical work and research by seeking dual degrees, that I would not need to forego one interest in order to pursue the other.

My desire to be both physician and researcher comes from wanting to find cures in the lab without giving up the opportunity to work with patients. When I was shadowing an oncologist, I remember how one patient, a man with stage III lung cancer, was given new hope as a new clinical trial became available. Scientists create new drugs, and physicians bring them into the clinic in the context of patient treatments. Physician-scientists can play a unique role acting as leaders that set the course of the research, using patient experiences to inform and accelerate their progress. I want to pursue an MD-PhD because I want to become such a leader. Pursuing a dual degree program will help me grow as a researcher and give me the skills to help push the boundaries of medicine. Doing research work at Hopkins for the past four years has cemented my commitment to this career path and fueled my strong desire to help patients, not just one at a time, but by the thousands or more.

SIGNIFICANT RESEARCH EXPERIENCE

Research Experience 1: Research Assistant for Professor Eric Y. Chuang, National Taiwan University June 2014 to August 2014, 60 hours a week. I assisted in research to investigate the role of microRNAs in regulating triple-negative breast cancer. MicroRNAs are short non-coding RNA molecules that help regulate genes associated with cancer. My work primarily consisted of quantitative reverse transcription PCR of cell samples to examine microRNA expression profiles, in addition to the use of western blots in validation experiments to examine gene expression effects.

Research Experience 2: Research Assistant for Professor Pan-Chyr Yang, Academia Sinica June 2015 to August 2015, 60 hours a week. This project focused on the experimental testing of DNA aptamers as potential therapies for MRSA (Methicillin-Resistant Staphylococcus Aureus). DNA aptamers are 3-D structures made from oligonucleotides. The systematic evolution of ligands by exponential enrichment (SELEX) usesrandomized libraries of DNA aptamers to screen candidates based on their binding affinity to a specific protein. With the rising threat of antibiotic resistance, my project focused on testing a collection of MRSA PBP2a protein-targeted ligands for potential therapeutic capabilities in disabling the protein responsible for Staphylococcus aureus bacteria being resistant to beta-lactam antibiotics. Through the use of growth assays and PCR of the aptamer libraries, we identified two aptamer sequences with a high binding affinity for protein PBP2a.

Research Experience 3: High School Senior Thesis Research, Dulwich College Beijing September 2016 to March 2016, 10 hours a week. Previous studies have indicated that air pollution resulted in severe reductions in plant growth in polluted native environments. My study aimed to examine the effect of air pollution on crop plants in controlled environments, to study the impact of increasing air pollution on a global scale on food production. By building two greenhouses with controlled airflow I grew Glycine max soybeans in two different environments, one polluted and one clean.

I presented the final results of my study at the Intel Science and Engineering Fair Greater China regional in Sichuan and published the results as part of my senior thesis. The project showed a

47.4% reduction in dry biomass and a 52.3% reduction in stomatal density in new leaves but no significant difference in older leaves at the bottom of the plant, indicating a potential epigenetic response to particulate pollution stress.

Research Experience 4: Medical Tutorial Student Researcher for Professor Joann Bodurtha and Professor Josephine Feliciano, Johns Hopkins University September 2017 to May 2018, 10 hours a month. The barriers to treatment and diagnosis that lung cancer patients face include a scarcity of screening resources, financial constraints, and lack of access to primary care. My work consisted of conducting focus groups to explore common themes among lung cancer patients and their families at Johns Hopkins Bayview Medical Center. I helped to recruit participants into the study, lead focus groups, organize digital records, transcribe recordings, and assisted with IRB approval. My research was published in Supportive Care in Cancer in May 2019 (DOI: 10.1007/s00520-019-04839-5), where I was listed as the second author.

Research Experience 5: Research Assistant for Professor Rong Li, Johns Hopkins University January 2017 to March 2020, 20 hours a week from September to May during the semester, 60 hours a week from June to August during the summers of 2017, 2018 & 2019. As an undergraduate researcher in the Center for Cell Dynamics, I first started working on studying a cellular pathway called MAGIC (Mitochondria As a Guardian In the Cytosol), a novel pathway for maintaining protein homeostasis. Discovered by Professor Li's lab, the pathway is distinct from the ubiquitin-proteasome system and autophagy-lysosome system. Loss of protein homeostasis underlies aging and neurodegenerative diseases, hence identifying the different pathways involved in maintaining protein homeostasis is essential for understanding and developing possible treatments. I initially started by working on a whole-genome screen using an endogenous misfolded protein (LSG1) as a reporter, testing if certain gene knockouts would disrupt its import or degradation in mitochondria. The system we applied for studying the import of misfolded LSG1 into mitochondria in live cells was the split-GFP system. The green fluorescent protein (GFP) is engineered into two parts and each part by itself does not fluoresce. When two parts encounter each other in the same compartment, they will form the fully functional GFP. We expressed the first part of GFP (GFP1-10) in the mitochondrial matrix and linked the second part of GFP (GFP11) with LSG1. Only when the misfolded LSG1 enters mitochondria upon proteotoxic stress, can the two parts be brought together inside the mitochondria and allow us to observe the GFP signal that results from our misfolded LSG1 co-localizing with the mitochondrial marker. This allows us to examine the import of misfolded proteins into mitochondria through a fluorescence-detection based approach.

Our lab used a high-throughput technique to transform the split-GFP reporter system into the yeast whole-genome knockout collection. My job was to screen the resultant reporter library for abnormally high or low fluorescent signals pre- and post- proteotoxic stress, which would imply that the gene affects the MAGIC pathway. By using flow cytometry, we screened over 4500 genes and identified different groups of genes of interest. These genes were then examined with a secondary screen via confocal live cell imaging and biochemistry assays such as sucrose gradient centrifugation separation of protein aggregates. This experience not only allowed me to master

many lab techniques such as gene manipulation, flow cytometry analysis, imaging, biochemistry, and high-throughput study, but also helped improve my critical thinking as we developed hypotheses regarding a novel pathway and analyzed large datasets. Early difficulties with our high-throughput transformation protocol gave me valuable experience in how to troubleshoot an experiment. As we were seeing decreasing transformation efficiency in our strains, I systematically adjusted different parts of the transformation process to identify the problem in one particular batch of primers and put us back on track. This opportunity was a learning lesson on how to break down research problems efficiently and effectively. The results from this project are currently in the manuscript stage in preparation for publication.

The second study I participated in involves understanding the consequences of the MAGIC pathway. It has been shown that many cytosolic misfolded proteins are detected in the mitochondria of patients with age-related diseases, which may be the key to understanding degenerative diseases that arise as the body grows older. We discovered that excess misfolded proteins in the mitochondrial matrix are organized at specific sites, which we named DUMP (Deposits of Unfolded Mitochondrial Protein). Subsequent experimentation by others in the lab showed that these DUMP sites were associated with ER mitochondria encounter structures (ERMES). My work primarily focused on using inducible expression and degradation systems to test the formation dynamics of DUMP and manipulate genes that are essential to ERMES function, which eventually led us to discover that genes associated with cardiolipin synthesis such as TAM41 were essential to the formation of DUMP sites. Inducible systems use the addition and removal of beta-estradiol and auxin to growth media to selectively promote protein synthesis or target them for degradation. Yeast strains are transformed to express Z3EV transcription factor and to have the Z3EV-responsive promoter upstream of our genes of interest. When beta-estradiol is added, it binds to the estrogen receptor in Z3EV, which disrupts its interaction with Hsp90 and causes rapid nuclear import of Z3EV. The Z3EV responsive promoter is then activated, conditionally expressing the gene downstream of the promoter. Auxin-inducible degradation (AID) systems operate by having constitutive expression of TIR1. A protein of interest is genetically modified to express an auxin-dependent degron sequence derived from IAA17.

In the presence of the plant hormone auxin, the hormone mediates the interaction of TIR1 and the degron domain, leading to ubiquitylation of the target by the recruit of an SCF-type ubiquitin ligase, which leads to proteasomal degradation. Combining these two systems gave us the protein expression equivalent of an on-off switch. Unlike the first project which was an unbiased high-throughput study, this project focuses on dissecting the mechanistic details of a particular process. During the process, I learned a lot about how to develop a project and how to focus on the relevant evidence through the critical analysis of data. I am a co-author of an article on this project and its findings detailing the mechanisms for DUMP site formation, which has been submitted for publication and is under review.

Research Experience 6: Junior Specialist for Professor Manish Aghi, University of California San Francisco. May 2020 to May 2021, 60 hours a week. I have now been offered a position at UCSF as a Junior Specialist for the next year, starting right after graduation. This position provides the chance for me to conduct research in cancer metastasis, thus furthering my interest in the study of degenerative diseases. My work will include intra/extravasation assays, western blots, and immunoprecipitation. I am excited to have this opportunity to gain valuable experience working with cell culture and mouse models while acquiring the skills needed to do more independent research.

APPLICANT 2, SAMPLE ESSAYS:

PERSONAL COMMENTS-- "La familia es todo, mija" means "Family is everything, my daughter." I was told that these were the first words my father whispered to me as he kissed my tightly shut eyes, wrapped me in a pink, semiprecious serape and handed me to my mother for the first time. Eighteen years prior to that moment, my parents, both children of Mexican immigrants, fell in love as they worked their way through medical school to fulfill their shared American Dream of becoming doctors. Now, a physician-scientist at the XXX School of Medicine, and the other a gastroenterologist in Santa Monica, they both recognize how far they have come. My parents still reflect on their early days quizzing each other under the flickering light of the two-bedroom San Fernando house my mother and five others called home. I have always quite literally walked in my parents' footsteps.

At five, I'd strut down the halls of my father's lab wearing his white coat that would trip me every so often and his goggles that would quickly find their way around my shoulders. At seven, I pushed my mother's stethoscope into my ears, parading around her endoscopy center trying to listen to the heartbeat of any nurse willing to indulge me. These are the anecdotes shared by my relatives when I tell them I am pursuing a career in medicine. While all these events may be true, they are certainly not the memories at the forefront of my mind that have fueled my passion to pursue a career as a physician-scientist. On my thirteenth birthday, I remember the taste of stale hospital juice on my lips, staring blankly at the generic botanical paintings on the walls of the XXX Radiation Oncology unit. I was anxiously waiting to kiss my father's hairless head after he completed his first of many rounds of treatment.

My hero, a man who dedicated his life to caring for his patients, became a patient himself: fearful, feeble, and relying on the strength of others. He needed a caregiver. For two years, I would hold the bloody tissues, the pill bottles, and Ensure shakes in one hand, and his hand in the other. But his was not the only hand I had to hold. Panicked, at age fourteen, I held my mother's clammy hand as she lay sprawled on the cold linoleum floor of our kitchen, praying the ambulance would arrive sooner than it had the times prior. While I do not understand the mind of an addict, I know that the stress and profound sadness of my father's illness had taken its toll. My mother was broken. Alcohol seemed, at the time, to be her only haven.

For seven years, I would listen to her sorrows, brush the tears off her face, align my smaller body next to hers for support when she couldn't stand on her own two feet, and change her soiled clothing before tucking her into bed to sleep off the pains of that day. However, her pain was not all that consumed my mind at the time. I recall the harsh buzz the door would make of the inpatient facility in which my brother lived for months at a time.

At age fifteen, my face would tighten to that sound, just as my parents would to the sound of physicians telling them that their son suffers from schizophrenia. At the time, I felt like I had lost the only brother I had known. He was an extraverted teenager, the type who would sweep up our mother and salsa dance through the kitchen or tease my father just to get him to chuckle after a long day of work. My brother, the one with the warmest soul and loudest laugh had become plagued by haunted thoughts and subdued by antipsychotics. I held his hand and sang for him on his bad days and stayed up watching his favorite movies on his good ones. While my family put their faith in me, I put my faith in medicine. I put those I love the most, amidst their darkest hours, in the hands of those who valiantly practice medicine. It is because of medicine that my father is now in remission, my mother is one year sober, and my brother has a job he loves and hasn't exhibited symptoms of psychosis for over a year now. I am ready to pursue what I put my faith in for all those years. In every waiting room, every doctor's office, and after every night of tucking my mother in, I would study. Even far from home, I would continue to study until the lights turned off in the Johns Hopkins University library and the calluses on my fingers formed a topographic map of my future. Now, a scientist at the Broad Institute of Harvard and MIT, conducting groundbreaking research in schizophrenia, I have not stopped studying. And I intend to dedicate my life to just that in hopes that one day it will make an impact on the lives of others. "La familia es todo" is the saying by which I live.

Family is my first love, it is my home, it is my drive, and it is the reason that I know medicine is my path. Every patient is someone else's mother, father, daughter, or son. The challenges I've faced have taught me what it means to care unconditionally. However, when I earn the privilege of putting on that white coat, I want to know my hands are capable of doing more than holding the hands of others. I want to know that they are capable of helping the family of the anxious little girl staring at the generic botanical painting in the waiting room. Because, she knows, and I know, that family is everything.

MD/PHD ESSAY-- I was always a curious child. There was no subject I didn't profoundly enjoy. I was privileged to be raised in a household in which education came first. My parents had infinite patience for my questions and encouraged my imagination. At six I'd show my mother my hands, always stained with some variation of the rainbow, saying, "I'm going to be an artist mamá. I know it." But at seven, I'd blush to the feeling of my hands resting on the ivory keys. It didn't take long before I told her, "A musician is what I will be." And yet, at ten, my fingers would become as stiff as the wooden yellow pencil I clenched for days at a time. As she'd massage them, I whispered to her, "I'm a writer, mamá". It wasn't until I was thirteen that I noticed my mother's hands. How they would brush the blood off my father's lips after radiation. Or the way they aged a decade in the two years-time my brother had three psychotic breaks. But most of all, I noticed how they

would tremor and sweat as she attempted to control her withdrawal symptoms and the reality of those she cared about most. It is because of this realization that I found a new passion. One that stimulated my mind more than any other had before. One that stemmed from fear, necessity, and a drive to keep my family safe. That passion was medicine. Not yet capable of helping patients, I would do what was possible. I would read.

Most nights, I would turn my desk-lamp on until the sun caught up with it, as I'd chicken scratch my way through scientific articles. I would absorb the research written on the pages regarding the effects of Clozapine, the reward pathways relevant to addiction, or the biological underpinnings of metastasis formation. With the realization that there is still so much to be discovered about the fields that kept me up at night, I felt an urgency to contribute to the science. Now, in my seven years of conducting medical research, I see that medicine and science are complex disciplines for the very reason that the two are intertwined and complement each other in ways that are both daunting and yet fascinating. As the world's health issues become increasingly challenging, I believe that I will be the most qualified to affect positive change if I do what I have always done; follow my inquisition and efforts to have an in-depth understanding of both disciplines. To enter the clinic and assess patients' symptoms will influence how I design cellular and biochemical inquiries at the bench. The treatment options of my patients will be shaped by the therapeutic discoveries I make in the lab. I have known I would pursue medicine and science since the day I turned thirteen. I yearn to be the best equipped to understand and cure complex diseases and disorders and an MD-PhD would supply me with that capability. But most of all, I choose MD-PhD, because I want to hold my mother's hands knowing that my own can heal some of the pain that hers have endured, as I say to her, "I'm a physician-scientist, mamá."

SIGNIFICANT RESEARCH EXPERIENCE-- Research has always been a part of my life. As a child, I would listen to my father's teleconferences and eagerly wait until dinner to ask him the string of questions that lined my sketchbook. At the table, I tripped over my words asking, "Papi, what's gastrointroljy or malsorption? What's immu, immunohisto…?". My father would chuckle, help me sound the words out properly then draw diagrams to clarify his explanations. After he'd put me to bed, I would remain wide eyed for hours, thinking back to what I had just learned. By the time these diagrams filled every surface of my bedroom walls, I had begun middle school and my father finally gave in to my countless requests to help in the lab after school. I began by conducting menial tasks then progressed to mouse genotyping and running PCRs. During high school, I continued those endeavors but I knew I needed to expand my knowledge by working in a lab with a different model system and a different focus.

Dr. Leanne Jones of XXX provided that opportunity. Her lab utilized Drosophila melanogaster as a model system to examine alterations in stem cell behavior in senescence. I was tasked with managing the fly stock. In the process, I observed her team devise numerous experiments, and learned the practical applications of the genetic concepts I had studied in the classroom. I grew more intrigued as each day in the lab progressed. At this point, I knew research would be a big part of my life because, to me, there is nothing more astounding than to witness a known theory become a practice and to have that practice provide new knowledge that advances an entire field

of study. In college, I remember losing sleep as I attempted to grasp a field of research that helped me understand my family's potential outcomes. That field was health services.

Dr. Carol Mangione, the division chief of general internal medicine and health services research at XXX, saw my will to learn and chose to mentor me for 3 years. I had conducted research in a cluster-randomized and intention to-treat trial that utilized an extensive academic healthcare system to test the efficacy of utilizing pharmacists in the primary care setting to deliver a shared decision-making intervention to prediabetic patients for diabetes prevention. I actively participated in every aspect of that study. From the study's documentation, to patient recruitment and engagement. I also analyzed large datasets and articulated the findings of the study in a first authorship paper. This experience taught me how to collaborate with others, effectively write scientific articles, and how to construct well-devised experimentation that is scalable, thorough, and unbiased. These are tools I have utilized to this day as I work at the lab bench.

In my second year, I committed myself to studying neuropsychiatric disease; the field that I spent so many of my nights in my adolescent years trying to understand. Still the same wide-eyed little girl, only this time, stimulated by both curiosity and by fear of the uncertainty that my family's future holds. I began my research in this field at the Lieber Institute of Brain Development where Dr. Brady Maher played a pivotal role in my career as a scientist. Here, I was able to not only aid in completing experiments, but to construct them myself. I researched a mutation in Transcription Factor 4 (TCF4), a gene that is highly correlated to schizophrenia and autism spectrum disorder (ASD). Monoallelic point mutations of TCF4 cause a truncation of Tcf4, rendering the protein non-functional. A mutation in this gene is the genotypic source of Pitt Hopkins Syndrome (PTH), a syndromic form of ASD. The purpose of the first project was to understand the phenotypic changes in neuronal morphology that occur due to this mutation. Tcf4 aids in the structural organization of layer 2/3 pyramidal neurons present in the medial prefrontal cortex (mPFC).

Using an in-utero electroporation (IUE)-based Supernova technique on wildtype and PTH model mice, we obtained sparse labeling of the mPFC. At postnatal day 22 the brains were sliced and imaged using a high-resolution confocal microscope and traced computationally. This discovered phenotypic changes in the length of the dendrites, the size of the soma and the pattern of branching of both the dendrites and the axons. This project provided me with the skills to perform mouse surgeries, brain slicing, confocal microscopy, and computational data analysis. But most importantly, it led to more questions that encouraged me to pursue my own project in the lab only this time using a new model system: induced pluripotent stem cells (iPSCs).

A postdoctoral fellow, Dr. Davis and I chose to investigate differences in transcriptional regulation, synaptic activity, homeostatic plasticity, network activity, and neuronal cell fate in human cortical neurons derived from iPSCs. iPSC cultures were grown from five PTH patient lines and five control lines. Cells were treated with two experimental conditions, picrotoxin (PTX) or tetrodotoxin (TTX), and a control condition. The conditions assess homeostatic plasticity of synaptic downscaling or upscaling of neuronal populations. Treating neurons with PTX, a GABA inhibitor, leads to global disinhibition in excitatory neurons. Chronic disinhibition in these cultures

causes synaptic downscaling—an effect mediated by both significant decreases in presynaptic vesicle release as well as quantal decreases in postsynaptic AMPA receptors. TTX, a Na+ channel blocker that halts synaptic transmission, instead leads to synaptic upscaling—an effect mediated by both significant increases in presynaptic vesicle release and quantal increases in AMPA receptor number or synapse number. Both Ca2+ transients and electrophysiological measurements of miniature excitatory postsynaptic currents were used to compare and contrast changes amongst the cell lines and all conditions. RNA-seq was analyzed to visualize transcriptional changes among the various populations and the various conditions.

Moreover, to assess the effect mutations in TCF4 have on neuronal fate, an assay was constructed on the same iPSC lines in monolayer and organoid cultures. Mitotic arrest at various time points during maturation, using AraC was initiated in order to perceive changes in cell fate over time. Cells were stained using immunofluorescence for specific cortical layer markers and a distinct cell fate phenotype was discovered. I found this research to be so engaging because I was attempting to understand disease in its most fundamental and yet incredibly complex state: at the cellular and biochemical level.

After completing my degree and my research at Johns Hopkins University, I felt an urgency to commit to an area that resonated with me personally and would challenge me further: molecular and biochemical neuropsychiatric research. For that reason, I chose a two year position at the Broad Institute of Harvard and MIT under Drs. Kevin Eggan and Kasper Lage. I play a key role in a project that seeks to understand how diverse genetic perturbations converge onto functional pathways by investigating protein-protein interaction (PPI) networks of proteins encoded by genes strongly associated with schizophrenia, ASD, and PTSD in iPS-derived human excitatory neurons (hENs); a cell type strongly incriminated in neuropsychiatric disease. In more detail, GWAS studies indicate genes implicated in these three diseases. Single-cell RNAseq from six human brains allows identifiesthe cell type in which the genes of interest are most expressed: hENs. Bulk RNA-seq data and western blot analysis of hENs pinpoint an optimal time frame for PPI assessment. hENs are then differentiated at a very large-scale due to the substantial material required for proteomics.

The cells are processed for immunoprecipitations (IP) of all proteins of interest (POI) and subsequently liquid chromatography mass-spectrometry (LCMS). An IP allows one to isolate not only the POI from the cell lysate, but also the proteins that interact with that POI. The interactors are labeled using LCMS. Lastly, a bioinformatic algorithm soon to be published in Nature Methods, GENOPPI, assesses the quality of the proteomics data, incorporates the data with pre-existing genetic datasets, identifies biological relationships between the POI and their interactors, and predicts a plausible PPI network relevant to these neuropsychiatric diseases. PPI networks of risk genes for complex multigenic diseases derived from incriminated cell types can be interrogated to elucidate molecular pathways; predict significance in sub-GWAS loci, and discover new biology relevant to therapeutics and patient stratification.

My initial involvement consisted of all wet-lab tasks. I performed the tissue culture and biochemistry directly implicated in the study. I also conducted CRISPR knockdown experiments, ChIP seq, Appex, and a plethora of other experiments for PPI network validation and scientific inquiries investigated due to the findings of this pipeline. Yearning to be a part of every aspect of the project, I helped in the bioinformatic analysis of the RNA-seq data as well as the proteomics data. Lastly, I am spearheading my own project in the lab that constructs and optimizes a novel protocol for the culturing of iPSC derived endothelial cells. This project aims to create a protocol that is brain specific, easy to maintain, cost effective, and scalable to the magnitude that is required for proteomics research. Given my past scientific experience and the continued passion I have for advancing medical knowledge, I can confidently say that pursuing an MD-PhD is the right path for me. I will always be the wide-eyed girl with the endless stream of questions that keep her up at night, but with this degree, I will be empowered to develop solutions. To me, the beauty of science is that with every answer comes an array of new questions and the possibilities are endless.

APPLICANT 3, SAMPLE ESSAYS:

PERSONAL COMMENTS-- I built on this interest in medicine and the brain as an undergraduate at Johns Hopkins University. I majored in neuroscience and was fascinated that the brain is not only involved in motor skills, but also in cognition and memory, and even in maintaining homeostasis in the digestive system. Through my coursework, I studied the nervous system at the molecular and patient care levels. My research interests involved small molecules called long non-coding ribonucleic acids (lncRNAs) and their role in brain development and disease states, such as Alzheimer's disease. Medical school will enhance my understanding of the nervous system along with other fields of biology and will give me the skills to apply what I have learned to effectively treat patients. In parallel with my interest in medicine, I also sought out ways to learn about other cultures and to celebrate diversity.

Before my undergraduate years, I had taken Spanish classes and hosted an exchange student from Mexico in high school. I continued with Spanish classes while in college and enrolled in a medical Spanish course, which introduced me to the healthcare challenges that can affect Hispanic communities, especially those that are underserved. This class also provided me with a strong foundation in medical terminology. To learn more about the medical profession and the importance of cultural aspects for healthcare, I volunteered as a Spanish-English interpreter and patient advocate. I communicated with individuals about their medical problems and developed a trusting relationship between our doctor and his patients. I observed our staff physician's effort to learn about patients, their cultures, and other factors such as their income. He used this information to design realistic treatment plans that respected patients' situations and beliefs and took into account their socioeconomic status.

Currently as a postbaccalaureate research fellow at the National Institutes of Health (NIH), I have seen that biomedical research of all types can play a crucial role in guiding diagnoses and patient

care. My research focuses on the role of ATP-binding cassette (ABC) transporters in the efflux of anti-cancer drugs. These transporters are expressed at high levels at the blood-brain barrier and are important to understand for the treatment of central nervous system cancers. In this way, our research is helping to advance not only the field's understanding of drug resistance, but also medicine and care for cancer patients. I continue to learn more about patient access to treatments for conditions like cancer by participating in a health disparities program for future clinicians and public health workers called the NIH Academy.

Our weekly discussions have shown me the challenges that doctors face in eliminating disparities in mortality rates for diseases like cancer across different ethnicities. I am eager to face these challenges and will use basic science, clinical, and translational findings to treat all patients and work towards eliminating healthcare inequities. In my future studies and as a physician, I will draw on current literature and my research findingsto better understand human models of disease. My experiences advocating for underserved individuals and engaging with NIH physicians have given me insight into the importance of celebrating diversity and treating patients with respect and kindness. I want to take on a leadership role in patient treatment and to mentor others to improve their academic knowledge and patient interaction skills.

MD/PHD ESSAY-- I first learned that biomedical research can be an important foundation for understanding diseases and their treatment as I transitioned from high school to college. I worked with a gastroenterologist who studied chronic disorders that involve the nervous system and the digestive tract. Meeting with patients and listening to their symptoms and medical history was crucial for her to design a treatment that improved their quality of life. During my freshman year at Johns Hopkin University, I joined a neuroscience lab that studied neural microcircuits involved in the processing of biological stimuli along with development of the nervous system. My mentor and principal investigator was an MD-PhD who chose to pursue a career in basic science research.

Throughout the 3.5 years I worked in the laboratory, I observed that our findings were important for advancing the knowledge of disease mechanisms as well as their treatment. While investigating the role of small molecules called long non-coding ribonucleic acids (lncRNAs) in brain development using animal models, I learned that these molecules can be associated with conditions such as Alzheimer's disease and epilepsy. Medical school training, including human anatomy, pathology, and patient care, will allow me to build on my basic science knowledge to better understand human models of disease.

As a postbaccalaureate research fellow at the National Institutes of Health (NIH), I see the benefits of the bench-to-bedside approach every day. I shadow a physician who studies neurodegenerative conditions such as motor neuron disease (ALS). Dr. Grunseich and his team use patient data, including skin biopsies and exam observations, to map out disease characteristics. His lab uses patientskin cells to generate stem cells, which are then in turn differentiated into motor neurons. Analyzing these motor neurons can aid in the diagnosis of motor neuron disease in which molecular signaling pathways have changed. I want to apply my knowledge from medical school on disease states to design basic science or translational experiments. Caring for patients and

improving their health is rewarding to me, and analyzing their cases and data will be crucial for shaping my research questions.

Dr. Grunseich's work motivates me to explore the clinical and translational aspects of my research. Pursuing and obtaining a PhD will give me the depth of knowledge in my field needed to design studies and ask questions about topics like brain structure and disease states. Together with my graduate school training, medical school will allow me to bridge these areas of interest to care for patients and further the knowledge of their conditions.

SIGNIFICANT RESEARCH EXPERIENCE-- Throughout my time as an undergraduate student at Johns Hopkins University and as a postbaccalaureate research fellow at the National Institutes of Health (NIH), I have developed a broad interest in understanding the underpinnings of neurological development and disease. The brain is capable of integrating a vast array of biological stimuli ranging from touch to taste through the actions of neural circuits.

Along with processing stimuli, it is fascinating that the brain can be involved in wideranging activities from motor control to the regulation of other organs such as the kidneys. My ultimate goal is to combine my interests in neuroscience and medicine to become a leader in the field of neurooncology as a physician-scientist. I first became curious about neuroscience after shadowing a physician who studied how the brain maintains digestive homeostasis. I wanted to know more about the ways in which stimuli like the sensation of fullness or touch were processed by the brain.

With these interests in mind, I joined the laboratory of Dr. Solange Brown at the Johns Hopkins School of Medicine as an undergraduate research assistant. During the 3.5 years I spent in her lab, my first project focused on how the visual and somatosensory cortices were involved in processing biological stimuli. My aim was to elucidate the role of cortical layer six (L6) in sensory processing. Specifically, I hypothesized that a region of L6 called L6a was comprised of an upper and lower sublayer, each of which had its own unique set of inhibitory neurons and distinct axonal targets. To address this hypothesis, I used histology and microscopy and studied the morphology of neuron subtypes called parvalbumin (PV)-positive inhibitory interneurons (INH INs) and corticothalamic neurons (CThNs) located in L6. My detailed observations revealed two key patterns: almost all PVpositive INH INs located in the upper sublayer had interlaminar axons that could span cortical layers L5 up to L2, while most PV-positive INH INs in the lower sublayer had axons that branched locally within L6 and into L5b. These results have important implications for our understanding of neurological circuits and the development of neurodegenerative and neuropsychiatric diseases.

My contributions to this study were included in a paper published in September 2019, and I was an author on this publication. Following my project on circuit organization in the somatosensory cortex, I became interested in how neuronal connections were formed during brain development. In particular, I sought to understand how the long non-coding RNA (lncRNA) Pantr1 interacts with transcription factors during cortical development. Building on my experience with cellular morphology, I designed a study to measure the width of each cortical layer in wild type and Pantr1 knockout mice. The measurements I obtained suggest that Pantr1 could promote neural progenitor

cell differentiation over proliferation through its interaction with POU3F3, a transcription factor involved in cortical development. lncRNAs have been associated with brain disorders such as Alzheimer's disease, and understanding the role of Pantr1 in modulating transcription factor activity may elucidate novel treatment options for this and other related conditions.

Throughout my 3.5 years in the Brown lab, I learned the importance of being detail-oriented as I gained skills distinguishing one cell type from another. I also learned to write a compelling narrative to justify my research questions. In recognition of this, I received the Johns Hopkins Provosts' Undergraduate Research Award to fund my lncRNA project. These experiences solidified my desire to pursue a career in research, where I can continue to ask interesting questions and interrogate the molecular mechanisms underlying the brain. While my experiences up until this point were impactful in supporting my desire to pursue research, I wanted to gain more experience conducting full time research to prepare for the rigors of a dual degree program.

After graduating from Johns Hopkins, I accepted a position as an Intramural Research Training Award (IRTA) fellow in the lab of Dr. Ariel Levine at the National Institute of Neurological Disorders and Stroke (NINDS). In the year that I worked in her lab, my research project focused on changes in protein expression that follow spinal cord injuries. I used immunofluorescence to identify and locate protein markers of interest that were in healthy and injured spinal cords. Understanding the distribution of such markers may improve our knowledge of cellular changes that occur after spinal cord injury. During my time in the lab of Dr. Levine, I was also able to shadow a number of physicians at the NIH Clinical Center. It was during these shadowing experiences that I realized I was becoming interested in the cellular mechanisms underlying neurological cancers.

To further explore this topic, I joined the laboratory of Dr. Michael Gottesman at the National Cancer Institute (NCI) in the spring of 2019. My current project in the Gottesman lab focuses on identifying genes involved in drug resistance in cancer cells. Our hypothesis is that resistance is mediated by active efflux of the anti-cancer drugs. To address this hypothesis, I am using the CRISPR/Cas9 gene-editing tool to either inhibit or activate expression of genes in the ATP-binding cassette (ABC) transporter family, a protein family known to be important for multi-drug resistance. My preliminary results suggest that overexpression of the ABC transporter gene ABCB1 can confer resistance to the anti-cancer drug paclitaxel in lung cancer cells. In the future, I also hope to leverage my interest in nervous system cancers by performing screens using glioblastoma cell lines. Because the ABC transporters are expressed at high levels in specific regions of the body, including at the blood-brain barrier, my findings may be an important first step in overcoming drug resistance during the treatment of these cancers.

As the first person in Dr. Gottesman's current laboratory group performing CRISPR screens, I have been responsible for testing my own hypotheses as well as establishing new protocols. I have gained resilience and confidence to troubleshoot experimental setbacks and push the project forward. Furthermore, I quickly became a leader in the lab as graduate students and postdocs interested in performing their own CRISPR screens sought my advice. Finally, through

departmental seminars and campus-wide poster sessions, I have also gained experience in communicating my data to those who are unfamiliar with the growing CRISPR field. My research experiences have taught me to be curious about every aspect of my work, from the detailed classification of cell morphology in Dr. Brown's lab to the bioinformatic analysis of sequencing data in Dr. Gottesman's lab. I have learned to be intellectually accountable for my research, whether it is designing new experiments or troubleshooting new protocols. I am committed to exploring basic, translational, and clinical research to better understand human models of disease. In my future career, I will use my skills to bring together biomedical research and patient treatment to answer questions at the intersection of neuroscience and cancer biology.