Jim L. Zhang - Personal, Background, and Future Goals Statement

I hesitated in my decision to immediately pursue a college education. I spent most of my high school career as the sole caretaker of my family, providing for a younger sibling who, at the time, was only in middle school. Leaving for university meant finding a new home for both of us. As the first person in my family to attend college, these circumstances resulted in significant self-doubt and guilt during my initial semesters. I spent my freshman year balancing time between class, checking in on things at home, and working to financially support both myself and my brother.

Despite these personal challenges, I discovered a passion for biology – more specifically, proteins. Twenty amino acids are all it takes, yet proteins exhibit a remarkable diversity in structure and function – forming not only gates and chemical catalysts, but the motors and turbines that ultimately power life itself. I was thrilled to finally have the opportunity to study them upon arriving at Rice University. My goals remained constant: to lead a research lab and classroom as a structural biology professor. To do so, I will obtain a Ph.D. in biology followed by a postdoctoral fellowship, allowing me to begin pursuing tenure-track faculty positions.

These aspirations motivated me to contact prospective labs on campus by the end of my first semester. Despite having no prior research experience, my advisor Dr. Yizhi Jane Tao welcomed me into her lab, guided me through my first semester of wet-lab work, and provided an opportunity for independent research. The support I received was valuable encouragement for me to continue as both a student and scientist, reaffirming my interests in an academic career. As a result, I applied and enrolled in an accelerated, thesis-based B.S.-M.S. program by the end of my freshman year. This allowed me to take graduate-level courses in advanced biochemistry and biophysics, in addition to specialized classes on scientific research ethics and proposal writing. As a part of my thesis requirements, I have also presented in yearly departmental seminars and defended progress reviews with a faculty-led thesis committee.

Intellectual Merit: My initial project in the Tao Lab focused on developing a native-condition culture and purification scheme for Orsay, the only virus known to infect *Caenorhabditis elegans*. To support this work, I applied and was ultimately accepted to the National Science Foundation's REU in Multi-Scale Biomolecular Networks, allowing me to remain at Rice the summer following my freshman year and receive additional training in research ethics, computational data modeling, and molecular biology. Purifying Orsay would provide a key reagent for structural characterization, supporting its growing role as a tool to identify conserved genetic elements required for eukaryotic viral infection. As the lead researcher responsible for this project, I learned to successfully apply techniques in nematode culture and ultracentrifugal density-based protein purification to obtain pure samples of the infectious virion. With these samples, I was able to demonstrate that Orsay incorporates a spike protein into its capsid structure via immunoblotting and transmission electron microscopy. I presented these findings in a co-authored publication in the *Journal of Virology*, where I was also responsible for major revisions to the manuscript.[1] These samples were then analyzed with collaborators at Harvard Medical School via single-particle cryo-EM, resulting in a high-resolution structure of the infectious virion — which I interpreted to reveal that the spike protein is covalently incorporated into a unique vertex about the viral capsid. I presented these preliminary findings at the 2020 Cellular and Molecular Biophysics Conference where I was the only undergraduate selected as a speaker. Subsequent assays I performed *in vivo* demonstrated this spike protein is ultimately essential for viral infection and entry. I recapitulated these findings in my proposal to the Goldwater Foundation, where I was selected as a Scholar for the 2020-2021 cohort. In addition, I am currently preparing a first-author manuscript describing the composite Orsay virion structure and function of the incorporated spike protein.

My present work centers around expressing and purifying the ectodomain of a putative host-cell receptor for the Orsay spike protein via eukaryotic insect cell culture. Upon purification, I will conduct *in vitro* binding assays to confirm the expected interactions between a viral protein and its

receptor and determine a co-structure of the two interacting proteins. I will defend this work along with previous results in my master's thesis by the end of this upcoming academic year.

Alongside my graduate research project, I am also purifying and structurally analyzing an additional novel virus through cryo-EM for my undergraduate honors thesis. The virus, discovered in 2017, is unique in that it contains a double-stranded RNA genome yet has a filamentous capsid. Determining the structure of the capsid and how the virus compartmentalizes double-stranded nucleic acid into such a complex will enable a structure-based analysis of viral capsid proteins. Such analysis would provide exciting clues towards the evolutionary relationships between single- and double-stranded RNA viruses, which remain ambiguous. Currently, I have cloned and expressed the recombinant capsid protein in *Escherichia coli* for purification and analysis. Once again using ultracentrifugal density-based protein purification, I demonstrated that the recombinant capsid protein successfully forms filamentous virus-like particles upon analysis with transmission electron microscopy. The resulting samples present another promising target for single-particle cryo-EM, which I am currently receiving training in for in-house analysis. These results were ultimately shared in a presentation at the 2021 Rice Institute of Biosciences and Bioengineering Research Symposium, where I won an award for Outstanding Poster Presentation.

From my overall time in the Tao Lab, I've gained significant experience in conducting independent research and practical wet-lab skills, working with multiple model organisms and biophysical techniques for the expression, purification, and analysis of proteins. My enrollment in the accelerated B.S.-M.S. program provided me with early exposure to graduate study — pushing me to professionally communicate my work and reaffirming my interests in an academic career. All the while, the support my advisor provided inspired a personal commitment to outreach and mentorship.

Broader Impacts: As a result, I applied to become a Student Ambassador for first generation, low-income students. As an ambassador, one of my responsibilities was to host lunches where members of the community could gather and socialize. From conversations at these lunches, I learned that my initial hesitancy to pursue opportunities in research was not an isolated incident. Many felt similarly unprepared, hindered by extenuating circumstances, or were unsure of where to begin.

Hoping to leverage my personal experience with adjusting to college and navigating research, I hosted student-led research and career panels, forming partnerships with university offices to promote resources available on-campus. These advertised dedicated services for academic and career advising, faculty within each department capable of referring students to prospective labs, and fellowships within the university that provided financial compensation for first-time researchers — all to increase the accessibility of scientific opportunities around campus.

After this, I began to recognize the impact I could make as a peer who understood first-hand the unique circumstances first generation, low-income students often face. Thus, I sought to extend my efforts across multiple leadership positions. During my time as an Orientation Week Leader, I developed and administered training campus-wide to student volunteers on social and academic advising for all matriculating undergraduates, with a particular emphasis on first-generation students. As a Peer Academic Advisor, I held yearly "Introduction to Research" events for freshmen students on how to look for and contact prospective laboratories. Across each of these positions and events, I aimed to demonstrate the accessibility of lab work to students of all research backgrounds — sharing my personal experience with adjusting to campus and finding a lab to do so. In the process, I discussed strategies for balancing research positions with other personal, financial, and academic commitments. Many of my peers, for instance, were not aware that most laboratory positions could offer compensation at a rate comparable to a part-time job, providing money they may need to support their own families — or that research could be taken for course credit to meet the full-time student requirement, which is necessary for financial aid eligibility. Overall, by sharing my personal experiences and knowledge of available resources, I hoped to encourage any aspiring or curious researchers to pursue their scientific interests — discovering my passion for mentorship in the process.

Since then, I have begun directly mentoring researchers in the wet-lab and on behalf of the Department of Biosciences. For the past two summers, I've assisted as a student mentor for the Rice Summer Research Institute, a departmental program offering crash courses in scientific conduct and journal club presentations for undergraduate summer researchers. As a student mentor, I provided guidance and feedback on presenting primary scientific literature, in addition to serving as a discussion leader during the ethics course. This past summer, I was also entrusted by my advisor with teaching a visiting student basic scientific techniques and presentation skills. It was an incredibly fulfilling experience to introduce a first-time researcher to the laboratory. Their assistance was ultimately greatly beneficial for our research and served as a valuable learning opportunity for both of us.

In addition to scientific and research mentorship, I have also applied my passion for teaching in the classroom. The summer before my freshman year, I was accepted as a Teaching Fellow in Biology and Department Chair of Science for the Breakthrough Collaborative, a national organization that hosts six-week courses in math, science, and English for high-performing underserved middle school students. There, I received professional training in classroom management and communication, which I ultimately applied to carry out independent instruction and curriculum planning. I've since continued teaching at Rice, where I taught as a Teaching Assistant for undergraduate courses in biochemistry, organic chemistry, and graduate courses in virology. In addition, I provide free tutoring to undergraduates as an Academic Fellow, hosting review sessions for courses in introductory biology, biochemistry, and cell biology. Within these positions, I strive to share personal study and note-taking strategies in addition to reviewing course material. I believe these additional efforts are especially beneficial for first generation, low-income students such as myself, a demographic that generally has lower retention rates in STEM-associated fields. To further address this, I have begun working with the Dean of the Wiess School of Natural Sciences, providing student perspective and feedback in a pilot program aiming to incorporate new teaching practices to support high-risk student populations in introductory STEM courses.

Future Goals: By pursuing a Ph.D. and post-doctoral fellowship, I will gain the practical and theoretical knowledge necessary to become an independent researcher in the field of structural biology. I will apply these skills to lead a laboratory and classroom as a tenure-track faculty member. Training in biophysical techniques, particularly single-particle cryo-EM, is key to this objective. Through the support offered by the NSF-GRFP, I can continue to develop my practice and understanding of structural biology while shifting towards the study of cellular protein complexes. I am especially interested in working with nuclear and transmembrane proteins which, despite their fickle behavior *in vitro*, facilitate some of the most incredible physical and chemical transformations within cells. With the critical role played by these proteins, any dysfunction renders them key causative agents of disease. Structural analysis, in turn, provides a means to enable the development of novel therapeutics while contributing to our fundamental understanding of biological function.

However, I recognize that professors and scientists have additional responsibilities beyond research, namely in the education and empowerment of the next generation of students. To that end, I will continue advocating for students from unconventional and underserved backgrounds as I have throughout my undergraduate career. Whether through bench mentorship or continuing to volunteer in outreach programs, I will actively increase the accessibility of research and scientific careers by providing opportunity, education, and encouragement. I believe these efforts are an important component in addressing the ongoing struggle for accessibility and inclusion in science, of which includes first generation, low-income students — a group that ultimately encompasses multiple underserved demographics. I intend for these efforts to continue well into the classroom, where I will serve as a professor who directly supports underserved student populations through active mentorship and a first-hand understanding of the unique experiences we are frequently faced with.

References: (1) Guo, Y.R. *et al*. (2020). Orsay Virus CP-δ Adopts a Novel β-Bracelet Structural Fold and Incorporates into Virions as a Head Fiber. Journal of Virology *94*, 15.