SPONSOR'S TRAINING PLAN

1. Current research in the Deiters Lab. My research program comprises a multidisciplinary team working in the field of Chemical Biology. We develop new chemical tools that interface with biological systems both to probe and to control cellular function. Specifically, much of my group's work has focused on engineering proteins with unnatural amino acids and engineering nucleic acids with novel nucleotides, often with the overall goal to achieve conditional control over biological processes. Furthermore, we are developing novel small molecule inhibitors, with a focus on the microRNA pathway. We leverage organic, medicinal, and organometallic chemistry to prepare molecular probes, and we test them in cell culture and vertebrate animals.

My group has developed many chemical tools that respond to triggers (e.g., light or specific chemicals) and that interface with biomolecules in live cells and organisms. I have had a long-standing research interest in small molecules that respond to oxidative stress—specifically, to hydrogen peroxide (see Govan et al., *Angew. Chem.* **2012** and Hanna et al., *J. Am. Chem. Soc.* **2016**). This work sets the stage for Josh to expand the scope of our approach by investigating therapeutics for ischemia-reperfusion (I/R) injury in myocardial infarction in this proposal. This is an excellent project for a dual-degree student and since the scientific foundation for the project is strong, the chance of success is high.

2. Training plan. Josh and I have worked closely to tailor a training plan that will prepare him for a career as a physician-investigator in cardiology at a major academic medical center. The plan builds off of Josh's talents as a chemist that he developed in college and as a post-baccalaureate Eyler Fellow while synthesizing ganglioside GM3, a complex natural product that could treat GM3 Synthase Deficiency in the Amish. This resulted in several conference presentations, and F&M is seeking IP protection for this work with publication as a secondary goal. Josh joined my lab as a medical student in the University of Pittsburgh-Carnegie Mellon University Medical Scientist Training Program (MSTP), an integrated MD/PhD training program designed to train physician-scientists. Josh had a productive rotation in my lab in which he made substantial progress toward synthesizing a nucleic acid linker molecule to develop light-activated gene knockdown in zebrafish. Since joining my lab, he has worked on several projects centered around conditional control of molecules. He is now preparing two manuscripts on small molecule control of (1) protein SUMOylation, and (2) gene knockdown in zebrafish embryos. Josh's experience synthesizing and testing small molecule-triggered bioactive compounds lays a strong foundation for his proposed work.

My trainees routinely synthesize complex molecules for use in biological systems and can assist Josh if any difficulties arise. Beyond the synthesis, Josh will be testing the molecules he prepares in cell culture and in animal models. Josh developed expertise in cell culture in a rotation with Dr. Patrick Pagano, an expert on Nox enzymes. He has further developed his abilities by mastering difficult genetic code expansion experiments using a variety of cultured cells (manuscript under preparation). Our lab has a history of putting new chemical tools into animal models, and Josh has assembled an impressive network of mentors and collaborators through both the chemistry department and Pitt's Vascular Medicine Institute (VMI) who will work with him to guarantee success on the animal experiments. Josh has been involved in mouse studies of the cardiovascular system in his previous work with Dr. Pagano and with Dr. Vladimir Muzykantov at UPenn, and this project provides a hands-on opportunity for him to design animal experiments, become proficient with the models, troubleshoot, and understand the capabilities and limitations of the techniques. Overall, Josh's broad research experience, extensive training in biomedical science, and network of mentors have positioned him for success.

Josh will continue presenting all experimental designs, results, analysis, and future next steps to all lab members at our weekly meetings – in addition to discussing and reviewing pertinent literature. I have set aside Monday afternoons at 4p to meet with Josh (and also maintain an open-door policy). Further, our group has also set aside Tuesdays from 12-2p for literature reviews and annual progress updates. I will arrange a meeting with Josh, Dr. Weber, and Dr. Dutta every 6 months to discuss the project as Josh moves forward. Outside of my group, Josh will continue to attend and to present annually at a departmental Chemical Biology seminar series. For networking and career development, Josh is expected to attend the VMI's Basic Translational Research Conferences, which focus on research in pulmonology, cardiovascular biology, hematology, and immunology. Further, he will present his work at VMI Research in Progress meetings and the annual MSTP Retreat. Outside of our institution, Josh will submit abstracts to two conferences each year, including an American Chemical Society national meeting, the AHA Scientific Sessions, and the 2020 Nox Family (NADPH Oxidases) Gordon Research Conference. I expect Josh to publish two first-author papers in high-impact journals, in addition to collaborative papers with his colleagues. Josh will draft all manuscripts (he already started two of them) and posters and we will work together extensively on revisions.

3. Other related training. Josh worked with the Graduate Student Advising Committee to design a streamlined, personalized course of study, which he completed with straight A's. To supplement his training in vascular biology, he will take "Angiogenesis: Molecular Pathways and Pathophysiological Functions" through the Cellular and Molecular Pathology and Angiopathy Training Programs. He now has the opportunity to develop his clinical acumen through the Medical Scientist Training Program (MSTP) Longitudinal Clinical Clerkship (LCC) program. Each of his two LCCs will be one half-day a week for 20 weeks. Josh will complete an LCC with John Pacella, MD, MS, an accomplished interventional cardiologist and researcher. Additionally, Josh will continue to meet semiannually with his MSTP career advisor (Don DeFranco, PhD), to attend monthly MSTP workshops, and to attend the annual MSTP Scientific Retreat.

Josh will continue to learn several new techniques from other groups for this project. Josh will work with Dr. Stephen G. Weber, a chemist who has published extensively on new methods for inducing I/R and probing for changes in living tissue, to learn to use the superfusion model for cell culture experiments. For the animal experiments, Josh will be trained in Dr. Partha Dutta's lab by post-doctoral fellow Sathish Vasamsetti, PhD and with the two full-time animal surgeons in the VMI's Small Animal Hemodynamics Core (Jeff Baust, BS and Jian Hu, MD, PhD).

4. Relationship of Training to Career Goals and Role of Applicant in Developing the Proposal. Josh is in training for a three-pronged career where he will carry out research at the (surprisingly) underdeveloped intersection of chemistry and vascular biology, care for patients as a cardiologist, and teach at an academic medical center. The proposed research and training plan will prepare him for a research-heavy residency in internal medicine followed by a fellowship in cardiology. Josh will further develop his skills in organic synthesis that will serve him well as a unique talent for a translational researcher in cardiology. Additionally, Josh will learn cutting-edge approaches for probing redox biology with Dr. Weber's group. Lastly, Josh's work with Dr. Dutta on a mouse model of I/R injury will provide him with skills in experimental design, animal surgery, and data analysis that will round out his already impressive abilities. The LCC with Dr. Pacella will keep Josh focused on the clinical ramifications of his results and give him one-on-one experience treating MIs with an outstanding clinician-scientist.

Josh creatively conceived of the idea for this proposal when several lines of thinking from his research experiences coalesced. His work with Dr. Muzykantov exposed him to selective delivery of therapeutics to sites of vascular injury based on chemical cues. A rotation with Dr. Pa-

gano prompted an immersion into the Nox field, revealing that these enzymes act as double-edged swords. In my lab, Josh has been working on spatial control of biologically-active molecules, and realized that the proper caging group could allow him to construct exactly the sort of selective Nox inhibitor we need to address the gap in reperfusion injury treatment. He realized that our lab's longstanding work using boronic esters to respond to H_2O_2 was just the caging group he needed. Josh then wrote the research plan entirely by himself and forged a network of collaborators for training in the techniques.

5. Assessment of Applicant. I met Josh when he first interviewed for Pitt's MSTP and I was immediately impressed by his grasp of scientific principles, his enthusiasm, and his maturity. Overall, Josh is an exceptional student and I would rank him in the top 2% of all early-stage graduate students that I have interacted with (>100, including 41 trainees in my lab). This is based on his academic track record (see biosketch), his enthusiasm for research (he started to read key papers and reviews months before he started in lab), his diligence at the bench (he always includes all necessary controls in his experiments and always systematically screens experimental parameters), his creativity (he constantly offers new ideas for the projects he is involved in, including direction-changing "big picture" ideas), his work-ethic (he regularly works 60-70 h weeks), and his ability to communicate (his weekly progress reports are excellent and his final summer report after his initial lab rotation was one of the best that I had seen).

Josh had a nearly perfect academic record at Franklin & Marshall College, despite the institution's reputation for grade *deflation*. This is all the more impressive given his challenging course of study (a double major in chemistry and economics with a minor in applied math). His MCAT score was a 37S, which is at the 98th percentile, and he capped off the first two years of medical school with a 257 on the U.S. Medical Licensing Exam, qualifying him for the most competitive residencies in the country. In graduate school, Josh maintains a perfect GPA. Josh upheld this exceptional performance as a varsity athlete in college (and club cross-country team member now) and leads a variety of committees (MSTP Welcoming, Workshop, and Retreat Committees), proving himself to be a well-rounded student. Just as he has always been a great team player as a scholar-athlete, he has been a team player in the lab too, always willing to take on extra duties and to help out with tasks to keep the lab running, even if they are completely unrelated to his own work. Despite him only being in the early stage of his graduate career, he is a well-respected lab member who other students seek out for advice and support.

In summary, Josh is an exceptional applicant who possesses all the qualities and skills to become an independent physician-scientist. Few students are as well rounded as he is: great scientific knowledge, excellent experimental skills, and an outstanding communicator/writer; however, his strongest assets are his razor-sharp intellect and his phenomenal drive! Josh is a highly qualified candidate who shows great potential even at this early time in his career and is on a steep upward trajectory. Given his keen scientific ability and exemplary personal attributes, Josh is the kind of candidate we want to train as a future physician-scientist and highly deserving of this prestigious award.

6. Funding Support. I have adequate financial resources to support Josh's project during the entire fellowship term. Currently, I have R01 GM112728 (till 7/31/2019), R21 HD085206 (till 8/31/2018), and R21 AI130815 (till 08/31/2019). I am a co-investigator on R24 OD023046 (till 5/30/2021) and R43 GM121129 (till 8/31/2018). Through the NSF, I have CBET-1603930 (till 7/31/2019), CCF-1617041 (till 6/30/2019), and CHE-1404836 (till 7/31/2018). Additionally, I have unrestricted internal funds at the University of Pittsburgh, including start-up funds from moving in 2013. Josh's salary support currently comes from R01 GM112728.