Senior Project Proposal

Sofia

12/17/25

I. Title of Project:

A Cureless Killer- Exploring the Mechanisms of Glioblastoma

II. Statement of Purpose:

We live in a world where medicine is ever evolving. Yet there still exist countless unanswered questions in the medical world, such as with glioblastoma. Glioblastoma is a grade 4 brain cancer that to many is considered a death sentence. The lack of a cure in the field of brain cancer raises a multitude of questions. What mechanisms allow brain cancer to resist radiation? Why do ultimately all patients relapse after trials of treatment? How do glioblastoma cancer cells manipulate immune systems? Why does the body's first line of defense phagocytosis not occur?

Through working with a lab whose ultimate objective is to uncover a cure for glioblastoma, I will gain clinical research experience and make an impact on uncovering the mechanisms of glioblastoma. With my research question, I seek to understand how glioblastoma confuses the immune system and induces an inflammatory environment. Due to a myriad of known and unknown factors, there still exists no cure for glioblastoma. Ultimately, this clinical research will uncover the unknowns of the mechanisms of glioblastoma, allowing for further clarity for scientists developing a cure.

III. Background:

By taking a leap across continents, I found a place where I belonged. "You're going all the way to China?!" they exclaimed in surprise, as I announced I had been chosen for an international research program at Westlake University. Little did I know the 3 week experience would open my eyes to new possibilities. By working with CRISPR/Cas 9 technology with pGLO bacteria in the lab every morning, interacting with students who had similar goals as me, and exploring China, I developed a love for biological research driven by the medical world's unanswered questions, particularly in oncology.

A year after my Italian grandfather's Stage 4 lung Cancer diagnosis, I watched him jump in a lake with me. "L'ho fatto!" (I did it!) he exclaimed. A new immunotherapy unexpectedly brought life back into his eyes and energized him to swim, something he couldn't do since the diagnosis. Just as the therapy unexpectedly revived my Nonno, by going to China and blazing my own trail, I gained new found admiration for the unknown. From that moment on, I knew I wanted to become a researcher and medical doctor who dives into medical mysteries. My unexpected experiences fostered my passion not just for curing diseases, but more about improving quality of life.

For my senior project, I hope to gain invaluable experience in clinical research, a blend of medicine and research. I want to make a lasting impact on others lives, through oncology and cancer treatment. As the glioblastoma research lab I will be working in is nearing the end of their projects, I hope my final project and presentation will give new insights on the mechanisms of glioblastoma, both scientifically and phenotypically. This senior project would not only allow me to further uncover my passions and the possibilities in clinical research, but would allow me to be involved in making a long-lasting impact in medicine and progress in the field of brain cancer research.

IV. Prior Research:

Glioblastoma (GBM) also named glioblastoma multiforme is a rare and very aggressive cancer developing from glial cells of the brain and spinal cord. There does not exist a current cure or preventative measures for GBM. GBMs are hard to treat for many reasons. They are fast-growing and invade nearby brain tissue, making 100% removal nearly impossible [1]. The blood brain barrier [1] makes GBM especially difficult for certain treatments to reach. They have many different types of tumor cells that can evolve over time [1]. Patients with GBM have a dismal prognosis, with short survival rates even when they receive conventional treatment. The cause of most GBMs is not yet known. All cancers, including glioblastoma are related to DNA mutations resulting in uncontrolled cell growth (tumors). GBM starts in the brain's astrocytes, which are cells that provide structure and support for neurons [2]. Although the exact cause of most GBMs is not yet known, researchers believe that inherited DNA defects, chemical exposure, and ionizing radiation exposure are involved in the development of GBM[2].

Focusing on my research question of how GBM manipulates the immune system, there exists prior research on the idiosyncrasies of this aggressive cancer. Dr. Baskin, Dr. Sharpe, and students at Research Center at Houston Methodist claim that by producing proteins that are usually reserved for the testicles, semen and placenta, GBM deceives the immune machinery into protection rather than attack [3]. The group found some of the tumors were acting like fetuses by expressing pregnancy-related proteins to evade the immune system [3]. In hiding, GBM suppresses T-regs (immune cells) by activating seminal proteins and drawing attention away from the cancer cells. Others argue GBM tumor cells sometimes downregulate major histocompatibility complexes (MHC) expression in order to avoid neoantigen presentation [4]. MHC's play a critical role in the immune system as they present antigens to T-regs (neoantigen presentation). Mutated GBM cells also trick the immune system into failing to register as presenting 'self' antigens by circulating natural killer (NK) or CD8 T cells [4]. NK cells kill stressed cells, and GBM utilizes NK to fatally weaken the body. Ultimately, there exist many theories on how GBM aggressively manipulates the human immune system. Through my research, I hope to uncover how placenta and sperm proteins,

MHC deregulation, and NK activation cooperate to manipulate the immune system.

As for the second half of my research question, I want to understand how GBM facilitates an inflammatory environment. The inflammatory microenvironment is of importance in cancer cells as it is a general signature of tumors that accelerates epigenetic changes in GBM and helps tumors avoid immunological surveillance [5]. GBM tumor cells produce abundant Interleukin-1 (IL-1) and Interleukin-6 (IL-6) through activating various pathways including STAT3, RAS, NFκB, NLRP3, and HIF-1a pathways, thus creating a chronic inflammatory environment, which benefits GBM growth [5]. IL-1 and IL-6 are signaling proteins and primary mediators of inflammation in the body. When the GBM activates IL 1 and 6 inflammation occurs in the brain ultimately creating ideal conditions and space for uncontrolled cell growth and for a tumor to form. IL-33 expression has also been linked to increased GBM tumor growth. Fluid from the tumor microenvironments (glioma and host-derived interstitial fluid) of two distinct patient-derived brain tumor-initiating cells (BTIC) orthotopic animal models (BT25 and BT147) that differ in abundance of tumor-associated macrophages (TAM) [6]. These fluids were from the initiating cells of GBM tumors which hold different amounts of TAM which are cells that have been reproprogrammed by the tumor microenvironment. In the results, IL-33 was one of the most abundantly secreted factors, and based on its ability to act on a range of innate and adaptive immune cells [6]. In my research, I expect to study the Interleukin signaling proteins that create unique GBM inflammatory environments.

I will be working with Dr. Krishna Bhat's team, who have extensive past findings in relation to the context of my research question. In particular in the context of inflammation, well established Bidirectional biomolecular transfer between platelets and other cells allows for the increased activation of platelets in patients with GBM which may benefit the tumor by allowing the transfer of RNAs to and from platelets [7]. Bidirectional bimolecular transfer is a form of dynamic regulation in which molecules move against each other in opposing directions. This transfer allows for further RNAs reaching the tumor, mRNA is commonly used to drive the rapid cell division of tumors. Dr. Bhat has also tested triggering receptors expressed on myeloid cells 2 (TREM2) in correlation with immunosuppressive pathways. TREM2 is important to test in the context of GBM as it is a receptor on immune cells primarily in the brain. The study found TREM2 is not associated with immunosuppressive molecules in GBM and TREM2 is associated with phagocytosis in both human and mouse gliomas [8]. TREM2's association with phagocytosis, an important immune protection method, suggests the potential of TREM2 as an immunotherapy for brain tumors. Ultimately there still exist many questions in the field of GBM yet to be discovered. GBM represents a truly urgent unmet need for both clinical

practice and research.

V. Significance:

As already emphasized, there exists no cure for Glioblastoma (GBM), only treatments that slow cancer growth and reduce symptoms. GBM is the most common malignant brain tumor, accounting for about 48% of all cases [9]. GBM causes an estimated 10,000 deaths per year in the United States and 200,000 deaths worldwide [9]. GBM's median survival rate for adults is 14.6 months [10]. Researching the specific mechanisms of GBM is of great importance in order to better the scientific world's understanding of this cancer and better developing treatments.

Through this project, I hope to learn further lab techniques such as micropipeting, PCR, and microscope utilization. I also hope to develop and expand my understanding of glioblastoma, the brain, and moreover cancer research. Our group's research efforts seek to add knowledge on radiation resistance of GBM and immune system responses to GBM. Through this research, we strive to add on to the existing research on GBM, allowing for the creation of further effective treatments.

Through my final presentation I hope to share our GBM research with the greater scientific community. I hope my presentation can bring GBM to light within the general public. I hope to share progress we have made in the field. By showcasing the power of important research, I hope to garner further support for brain cancer research among scientists and the general public. Once our studies are complete we hope to publish literature which I will share through my presentation. Ultimately GBM is a field of science that has yet to be answered and through further public support and awareness hopefully an answer will arise sooner.

VI. Description:

For this project, I will be conducting scientific research in a lab at Mayo clinic. I expect to be observing glioblastoma (GBM) in vitro and in vivo. As for in vitro, I expect to study GBM cancer cells and proteins utilizing microscopes and petri dishes. By studying GBM, I hope to understand its genomic cancerous and inflammatory mechanisms. As for in vivo, I expect to study GBM is donated human tissues and organs of someone affected by GBM. I also will be performing this research as our team induces GBM into mice models and studies the effect on the brain pre and post mortem. For my final project, I plan to produce a poster or book that explains our research results in a comprehensible manner and engages the general public's attention on GBM.

VII. Methodology:

Over the course of the three months, I will be working in the lab weekly. First, from December to January, I will be reading multiple research papers on immunology and past GBM research to prepare myself to understand the known mechanisms of cancer specifically in GBM. In early February, I will be trained in the lab by graduate students on lab safety and procedures as a high school student. After training and until May, I will be conducting weekly research. I plan to drive to Mayo clinic once a week and stay in Phoenix at my grandmother's house, while I perform research for 2 or 3 consecutive week days. While performing research, I will be mentored by Tyler Johnston, one of Dr. Bhat's PhD students. I plan to work in the lab each day for multiple hours. After my research period ends, I will work on my final project.

VIII. Problems:

Over the course of my research, I may encounter issues with transport. Since I will be driving down to Phoenix on a weekly basis, I may encounter issues of car malfunctions, weather issues, or lack of an available vehicle which may stop me from performing in person research that week. If this issue does arise, I plan to read existing papers and study our results so far.

Time took to start

Issues with transduction of cells, EVs added to validity, Delay on dye shipping, had to alter schedule

IX. Bibliography:

(1)Yu, J. American Brain Tumor Association. American Brain Tumor Association. https://www.abta.org/tumor_types/glioblastoma-gbm/.

(2)Glioblastoma Causes & Risk Factors. moffitt. https://www.moffitt.org/cancers/glioblastoma/diagnosis/causes/.

(3)Masters of disguise: Glioblastomas trick the immune system by masquerading as reproductive tissue. Methodology | Houston Methodist. https://read.houstonmethodist.org/masters-of-disguise-glioblastomas-trick-the-immune-system-by-masquerad.

(4)Himes, B. T.; Geiger, P. A.; Ayasoufi, K.; Bhargav, A. G.; Brown, D. A.; Parney, I. F. Immunosuppression in Glioblastoma: Current Understanding and Therapeutic Implications. Frontiers in Oncology 2021, 11, 770561. https://doi.org/10.3389/fonc.2021.770561.

(5)Chen, N.; Peng, C.; Li, D. Epigenetic Underpinnings of Inflammation: A Key to Unlock the Tumor Microenvironment in Glioblastoma. Frontiers in

immunology 2022, 13. https://doi.org/10.3389/fimmu.2022.869307.

(6)De Boeck, A.; Ahn, B. Y.; D'Mello, C.; Lun, X.; Menon, S. V.; Alshehri, M. M.; Szulzewsky, F.; Shen, Y.; Khan, L.; Dang, N. H.; Reichardt, E.; Goring, K.-A.; King, J.; Grisdale, C. J.; Grinshtein, N.; Hambardzumyan, D.; Reilly, K. M.; Blough, M. D.; Cairncross, J. G.; Yong, V. W. Glioma-Derived IL-33 Orchestrates an Inflammatory Brain Tumor Microenvironment That Accelerates Glioma Progression. Nature Communications 2020, 11 (1), 4997. https://doi.org/10.1038/s41467-020-18569-4.

(7)Karp, J. M.; Modrek, A. S.; Ravesanker Ezhilarasan; Zhang, Z.-Y.; Ding, Y.; Graciani, M.; Sahimi, A.; Silvestro, M.; Chen, T.; Li, S.; Wong, K.-K.; Bhama Ramkhelawon; Bhat, K. P. L.; Sulman, E. P. Deconvolution of the Tumor-Educated Platelet Transcriptome Reveals Activated Platelet and Inflammatory Cell Transcript Signatures. JCI Insight 2024, 9 (19). https://doi.org/10.1172/jci.insight.178719.

(8)Peshoff, M. M.; Gupta, P.; Trivedi, R.; Shivangi Oberai; Prashanth Chakrapani; Dang, M.; Milam, N.; Maynard, M. E.; Vaillant, B. D.; Huse, J. T.; Wang, L.; Clise-Dwyer, K.; Bhat, K. P. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Regulates Phagocytosis in Glioblastoma. bioRxiv (Cold Spring Harbor Laboratory) 2023. https://doi.org/10.1101/2023.04.05.535792.

(9)Binaytara.org. https://binaytara.org/cancernews/article/what-to-know-about-glioblastoma-awareness-day-2025.

(10)What is the average glioblastoma survival rate? Glioblastoma Research Organization. https://www.gbmresearch.org/blog/glioblastoma-survival-rate.