Manipulating DREADDs to Develop a Novel Therapeutic Platform for Drug Delivery Through the Blood-Brain Barrier

Employing Technological Momentum to Analyze how Chemotherapy has Contributed to Cancer Care Inequalities in Rural America

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

By developing cancer treatment technologies, researchers have helped treat cancer patients and reduce deaths from cancer. However, these technologies require frequent, expensive in-person treatments. As a result, patients can struggle to afford and receive cancer care, especially if they live in a rural area (*Brain Tumor - Coping with Treatment*, 2012). These technologies, including chemotherapy and focused ultrasound (FUS), have led to inequalities in cancer treatment. To improve the current state of cancer care, I aim to develop an effective therapeutic platform that is more accessible and less debilitating for patients. For this technical project, the patient would easily self-administer the therapy at home, resulting in drug delivery to the brain.

Both technical and social factors have influenced how cancer treatments, such as chemotherapy, have advanced and impacted society. I will utilize the science, technology, and society (STS) framework of Technological Momentum to characterize how the social and technical factors of chemotherapy have contributed to cancer care inequalities in rural America. Additionally, I will assess which factors would have to change, and how, to redirect the technological momentum of chemotherapy. Cancer care is sociotechnical in nature; it requires attending to both its social and technical factors. Attending to the network actors, without accounting for how the sociotechnical system has changed over time, would leave the healthcare barriers only partially understood.

In the following, I elaborate on two related research proposals: first, a technical project that aims to develop a novel therapeutic platform for drug delivery to the brain, and, second, an STS project that examines the technological momentum of chemotherapy. Ultimately, I will apply insights from the STS research to inform the development of the technical project. I will take into consideration all social and technical factors necessary for the therapeutic platform to be affordable and available for all patients, including those living in rural areas.

Technical Project Proposal

Currently, brain cancer treatment technologies are highly demanding and inconvenient for the patient. During chemotherapy, chemicals are inserted into the body and attack all fast-growing cells, such as cancer cells. Yet, chemotherapy cannot target specific areas and unnecessarily attacks healthy cells (Amjad et al., 2023). Chemotherapy is an invasive treatment that can have severe adverse effects (Barlow & Tee-Melegrito, 2022). During FUS, an ultrasound machine aims beams of ultrasound energy directly at the tumor. At the site of convergence, the beams heat up and destroy the tumor (Foley, 2023). However, there is a risk of damaging nearby healthy tissue (Malietzis et al., 2013). Beyond their technical limitations, both therapies necessitate expensive in-person treatments. FUS is rarely covered by private or public insurance (Foley, 2023). Additionally, FUS is often only available at specialized centers, which are difficult to access for those who do not live nearby or have the means to travel for treatment (Sullivan, 2022).

To address the deficiencies of these technologies, this technical project aims to develop a precise, effective therapeutic platform that is noninvasive and accessible. To accomplish this, we will utilize designer receptors exclusively activated by designer drugs (DREADDs). DREADDs are engineered molecules that contain genes to encode for specific protein receptors. After the receptors are assembled, a drug can be sent through the blood to bind with the receptors; due to this coupling, cellular pathways are activated or inhibited. Each DREADD type can induce a specific cellular activity.

For this project, we aim to deliver drugs to the brain, which is challenging due to the blood-brain barrier (BBB). The BBB is a complex network of vasculature that regulates the movement of molecules between the brain and blood, preventing harmful substances in the blood from reaching the brain (Daneman & Prat, 2015). Endothelial cells line the BBB; between these cells is the interendothelial cleft, where molecules can travel. To limit circulation, tight junctions seal this interendothelial cleft (Stamatovic et al., 2008). As a result, the tight junctions resist any drug particles from being delivered to the brain, especially relatively large particles (Pardridge, 2012). Therefore, we will utilize a DREADD that is capable of opening tight junctions. (*Addgene: Chemogenetics Guide*, n.d.). By increasing BBB permeability, drugs will be able to enter and successfully perform their designated function in the brain, such as targeting a brain tumor.

To achieve this, we will fulfill three subprojects. First, we will test the ability of DREADDs to alter the permeability of the BBB. We will culture endothelial cells and introduce DREADDs. Then, we will determine the size and duration of tight junction openings through tools to measure the downstream effects of the DREADDs. Simultaneously, we will develop a computational model in Microsoft Excel to simulate the effects of DREADDs. By optimizing parameter values, we will guarantee the DREADDs properly alter cellular activities and pathways. If these preliminary results are promising, we will design a safe protocol to test our therapy in mouse models. We will send a blue dye to the brain, representing drug delivery. Then, we will assess BBB permeability by harvesting the mice's brains and visualizing the dye through fluorescent imaging.

Our therapeutic platform will be more convenient and less burdensome for patients. We plan to have an initial in-person treatment to administer the DREADDs, which are cost-effective

(Smith et al., 2016). For following treatments, the patient would apply our therapy through oral consumption, then take their medication as directed. Our treatment would open the tight junctions, allowing the succeeding drug access to the brain. By self-administering the affordable treatment at home, less time and money would be required for treatment. Through the noninvasive and accessible design, our therapy would be less debilitating for patients.

STS Project Proposal

During World War I, the use of mustard gas as a weapon accidentally led to the discovery of chemotherapy. In exposed patients, the amount of white blood cells had decreased significantly. White blood cells are capable of rapidly dividing, similar to cancer cells. Accordingly, researchers pursued the idea that mustard gas and other chemicals could kill cancer cells. By the late 1960s, a greater number of patients experienced remission from cancer due to a combination of chemotherapy agents (DeVita & Chu, 2008).

Although treatment has improved and death rates have decreased, equal access to cancer care remains a challenge (Sullivan, 2022). Millions of Americans delay, avoid, or stop their medical treatment due to the high costs, especially in rural areas (Sainato, 2020; *The Costs of Cancer in Rural Communities*, 2022). Barriers to quality cancer care more often affect people with fewer financial resources and people who live in rural areas or underserved communities (*Brain Tumor - Coping with Treatment*, 2012).

In 2022, Emily Gebel, a mother of two, was diagnosed with breast cancer; as a resident of Juneau, she experienced accessibility issues while receiving treatment. Initially, Gebel opted for treatment in Seattle, believing a bigger city would have better care. Eventually, Gebel was exhausted by the weekly flights to Seattle; she started receiving her chemotherapy regimen in Juneau instead. At the hospital in Juneau, the cost estimate was $7,500 per weekly infusion, more than 4 1⁄2 times what Gebel had been charged in Seattle. Fortunately, Gebel's insurance covers most of the cost, but she still has to pay thousands of dollars for treatment (Zionts, 2023).

Authors have identified how technology is both a cure for and a cause of inequalities related to cancer care. Applying technology to treat cancer has mixed impacts on society due to socioeconomic differences. The patients who can access chemotherapy will experience improved health, while outlying patients experience declining health. Current discourse addresses how cancer treatment can benefit or harm society, based on the involved actors. Authors have applied Actor Network Theory (ANT) to consider the factors involved with inequalities in cancer treatment; however, they have not yet employed Technological Momentum (Montgomery & Little, 2011). By analyzing this case through ANT, writers overlook how the power of technology, including chemotherapy, has grown significantly. Authors fail to recognize how the relationship between chemotherapy and society has changed over time.

By examining this relationship, we will more fully understand how chemotherapy has contributed to cancer care inequalities in rural America. Initially, social factors shaped chemotherapy. Before chemotherapy, there were limited treatment options and low chances of curing cancer. There was a strong demand for cancer research, which, supplemented by the mustard gas discovery, led to the creation of chemotherapy (*History of Cancer Treatments*, 2014). Afterward, chemotherapy began influencing society. Chemotherapy changed the perception of cancer treatments, allowing for cancer to be conceived as a curable disease for the first time (Godoy, 2014). Overall death rates from cancer have declined in the United States. Yet, chemotherapy is only available to patients who have the resources. The treatment requires frequent, in-person treatments, which takes people away from work and demands extra money for lodging. In the United States, chemotherapy treatments are highly expensive and completely unaffordable without insurance, as revealed in Gebel's case. If chemotherapy continues to only be accessible to a select group, then cancer care will only become more and more exclusive (Ruff et al., 2016).

Therefore, to frame my analysis of chemotherapy, especially Gebel's case, I will draw on the STS framework of Technological Momentum. Developed by STS scholar Thomas Hughes, Technological Momentum claims that social and technical factors interact thoroughly in technological systems, exerting influence on each other. Hughes argues that people initially direct the development of new technology. Over time, these sociotechnical systems exert a stronger influence on society. Due to the investment of money, effort, and resources, the systems are resistant to any attempt to change or abandon them. In addition, Hughes asserts that, although sociotechnical systems develop rigidity over time, their momentum is not irresistible. I will also utilize the claim that, if a variety of system components are subjected to change, a system with technological momentum can be changed (Dyson et al., 2021; Hughes, 2005). To support my argument, I will draw on evidence from news media articles, scientific and historical literature, and first-hand interviews with patients, physicians, and researchers.

Conclusion

By developing a novel therapeutic platform for drug delivery to the brain, the technical project has the potential to improve the quality of life for patients with various brain-related diseases. If unsuccessful, our work will still provide insight into the ability of DREADDs to alter BBB permeability as a drug delivery tool. The computational model could be employed for future DREADD applications. The STS project will issue a greater understanding of how chemotherapy has been partly responsible for cancer care inequalities in rural America. Drawn from Technological Momentum, the STS project will outline which social and technical factors are involved, how these factors have influenced each other, and how the dynamics of these factors have changed over time. From my STS research, I hope to analyze the technological momentum of chemotherapy, determining how the system could increase its accessibility. I will apply these insights to design my technical project intentionally. To conclude, the technical and STS projects address how the influences of social and technical factors can contribute to the technical momentum of a technological system. To break down barriers to cancer care, both projects aim to change the technological momentum of chemotherapy.

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