Manipulating DREADDs to Develop a Novel Method to Non-Invasively Disrupt the Blood Brain Barrier
(Technical Project)

Investigating the Role of the Economic and Political Environment Surrounding the FDA Approval of Biogen's Alzheimer's Drug
(STS Project)

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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

According to the World Health Organization, the United States healthcare system is ranked at 37 out of 191 countries (World Health Organization, 2000). The Commonwealth Fund reported that "people in the United States experience the worst healthcare outcomes overall for any high-income nation" (Gunja et al., 2023). To make matters worse, when compared to wealthy and equally developed countries, the US ranks the lowest in life expectancy at birth, has the largest mortality rates from treatable conditions, and has some of the steepest suicide rates (Gunja et al., 2023). Despite spending "a higher portion of its gross domestic product than any other country [on healthcare]," the current system falls short (World Health Organization, 2000). In 2006, the National Institutes of Health, or the NIH conducted a survey and found that 32% of Americans were "very worried about not being able to afford the health care services they thought they needed," with these percentages jumping to 52% for low income households (Blendon et al., 2006, pg. 633). These concerns are well-founded, given that 66.5% of all personal bankruptcies in the US stem from the burden of medical bills, causing Americans to be left grappling with financial hardship and uncertainty (Fielding, 2023).

Neurological conditions, such as Alzheimer's disease and brain cancer, are amongst the top five most expensive health conditions (Murtha, 2023). In particular, Alzheimer's disease is the most expensive condition to treat in the United States, costing $321 billion dollars per year (USC Price, 2023). Given that 1 in 6 people are affected by brain diseases, targeted drug delivery systems are seen as a treatment option for many of these conditions. These systems enable treatment with minimal side effects and high therapeutic efficacy (Sousa, 2022). American medical companies are constantly developing new therapies with the hope that their design will be approved by the Food and Drug Administration, or the FDA.

The FDA is “responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices” (FDA, n.d.). Federal law mandates rigorous evaluation by the FDA of all new drugs, in order to ensure safety and effectiveness before becoming accessible to the general public. However, in the last ten years there were over 14,000 drug recalls, averaging to about four every day (Shmerling, 2023).

My technical project will focus on creating a targeted drug delivery platform for diseases and disorders in the brain, including Alzheimer's disease. This designed platform will be safe, cost effective, and accessible to the public. My STS topic aims to investigate the inner workings of the FDA and uncover the decisions that lead to market approval of ineffective and inaccessible drugs. I will examine the relationship between social factors and technological development through the lens of a recent case study about an Alzheimer's drug. My STS topic and my technical project will work together to address the need for innovation and change in the United States healthcare system, and ensure that patients receive the care they deserve.

Technical Topic

Scientists are constantly seeking new methods to deliver pharmaceuticals to the human body. Targeted drug delivery allows for enhanced efficiency, faster recovery periods, and overall improved effectiveness (Tewabe et al., 2021). The field of nanopharmaceutics focuses on developing technologies that allow for drug delivery to the brain by penetrating the blood brain barrier, or the BBB. The BBB is formed by a network of capillaries that construct a shield over brain tissue, only allowing for small molecules and gasses to pass through (Kadry et al., 2020). The endothelial cells that make up these capillaries severely limit permeability due to their selective tight junctions. Typically, scientists view the BBB as an asset as it acts as a safeguard

against toxic substances in the bloodstream (Zheng et al., 2003). However, the BBB becomes an obstacle to overcome when attempting to deliver a drug to the brain.

Current methods for nanopharmaceutics are lacking. Viral vectors, which allow for infecting cells with various nucleic acids, are used as a common drug delivery strategy. However, these vectors have numerous safety concerns, have a high production cost, struggle to bypass the BBB, and are administered directly into the brain (Dong, 2018). Invasive techniques, such as these viral vectors, pose a danger to patients as risks include brain trauma, surgical complications, and amiss targeting (Fang et al., 2017, p.). One of the newest non-invasive techniques for BBB opening is focused ultrasound, or FUS which utilizes microbubbles in combination with ultrasound (Rohani & Fasano, 2017). When considering FUS treatment, there are limitations that patients must accept in terms of comfort and treatment compliance. FUS requires chronic exposure, meaning that the patient must attend in person treatments regularly where they are under anesthesia. These treatments also require a shaved head which can create insecurity as, for many of us, our hair is an important part of our self-identity (Dhami, 2021). The demand for a safe, cost effective, and accessible drug delivery platform is established, and we aim to address this need.

For our technical project, we plan to develop a platform using DREADDs, or Designer Receptors Exclusively Activated by Designer Drugs, that allows for non-invasive targeted drug delivery to the brain. DREADDS are proteins that are taken up by endothelial cells and encodes for a designer receptor. These receptors only recognize and are activated by CNO, or clozapine-N-oxide (Thomas, 2019). When DREADDs are transfected into brain endothelial cells, and its resulting receptor is activated by CNO, the production of cyclic adenosine monophosphate, or cAMP is inhibited (Campbell & Marchant, 2018). The downstream effects of

this inhibition decrease tight junction resistance, therefore increasing permeability of the BBB (Viña et al., 2021). When CNO is injected into the body, designer receptors encoded by DREADDs will recognize the CNO and increase endothelial cell permeability, allowing for a selected drug to pass through. Conceptually, we are punching a temporary hole in the brain's shield.

Our proposed solution offers a non-invasive strategy with lower costs than existing treatments, fewer patient hospital visits, and a regime that would boost treatment compliance. Our platform would require only one round of FUS initially to deliver the DREADDs to the brain, preventing constant shaving of the head. Our treatment platform not only eliminates the need for weekly hospital visits, but also establishes a manageable treatment plan, with patients only required to take a pill periodically. Although the cost of our platform is unknown, the NIH has found that DREADDs are highly cost effective when compared to other treatments (Smith et al., 2016). The price of a periodic pill will most likely be inexpensive compared to regular hospital visits for invasive surgery.

Our designed platform seems logical, yet there are many challenges to our approach. First, DREADDs have never been utilized for this purpose meaning that it might not work, despite research indicating that it *should.* Additionally, the success of our proposal is highly dependent on the size of the openings in the BBB that we are able to observe. If the modulated cAMP levels do not open holes large enough for most drugs to pass through, the treatment will not be effective.

Although there will be many challenges to overcome, conducting research to find a non-invasive method for drug delivery is imperative. Patients deserve treatment options that are affordable, safe, accessible, and effective. Our project has the potential to target a wide range of

diseases such as Parkinson's, Alzheimer's disease, brain cancer, and even mental disorders such as OCD and depression. We plan to deliver a non-invasive and targeted drug delivery platform that can aid researchers and doctors around the world so that they can best help their patients.

STS Topic

In 2012, 5.5 million Americans and 24 million people worldwide had Alzheimer's disease (Mayeux & Stern, 2012). In 2021, it was declared as the seventh leading cause of death among older adults in the United States (NIH, n.d.). Although over 10% of Americans age 65 and older have Alzheimer's disease, not every community is affected equally (Alzheimer's Association, n.d.-a). Individuals with Alzheimer's in rural areas have a higher mortality rate than those in metropolitan areas (Kulshreshtha, 2021). According to Ho and Franco (2022), "health care and long-term care services needed by individuals with ADRD [Alzheimer's Disease and Related Dementia] are much scarcer in rural areas than in urban areas" (Ho & Franco, 2022, pg. 1). Furthermore, an increased number of hospitals and nursing homes in rural areas have closed, in part, due to the physician shortage. In addition to morbidity rates, the cost of memory care can range from $13,740 to $115,007 per year, prompting extreme financial hardships (Alzheimer's Association, n.d.-b). An affordable, effective, and accessible treatment plan for Alzheimer's patients is desperately needed.

In June of 2021, against the approval of their advisory committee, the FDA granted accelerated approval for an Alzheimer's drug developed by Biogen known as Aduhelm. Approval of Aduhelm was granted despite failure to produce statistically significant data to support that it improves patient's cognitive function (Glymour et al., 2022). After persistent media backlash, a scandal involving FDA advisory committee members quitting, allegations of "inappropriately close relationship[s] between the FDA and the industry", and the refusal from

large insurance companies, including Medicare, to cover Aduhelm, the FDA had to re-evaluate (Belluck & Robbins, 2021; Gleckman, 2022; U.S. Department of Health and Human Services, 2021). Biogen halted Aduhelm marketing, withdrew European approval applications, and is in the market for a new CEO (Langreth, 2022). Nonetheless, the FDA has not recalled or withdrew Aduhelm from patient access.

In order to understand how the economic and political environment led to the approval of Aduhelm, I will utilize the Actor Network Theory, or ANT, framework. The ANT framework provides a method to comprehend how human and non-human actors shape technology as well as social networks (Jallinoja, 2000). When analyzing the events leading up to and after the approval of Aduhelm, it is important to understand how the development of this drug evolved through diverse actors interactions. The ANT framework might underestimate the role of individuals' motivations, as it primarily focuses on relationships. Prior work utilizing this framework with respect to medical technology can be used to overcome this challenge. Through the use of the ANT Framework, I will identify the primary actors and contextualize Aduhlem's approval by utilizing heterogeneous networks.

According to a prominent developer of the ANT framework, Michael Callon, actors are "entities that serve as intermediaries between other actors. Actors can be humans, but also include technology, text and organizational groups" (Uden, 2012). It is crucial to identify the primary actors in order to understand how they interact. These actors can be Biogen, the company that developed Aduhelm, the FDA, the government agency that approved Aduhelm, clinical trial data that was used to make informed decisions, and even patient advocacy groups that pushed for Alzheimer's treatments accelerated approval. In Law's words, "All are actors. All are strategists and tacticians. All seek to enroll others in their schemes" (Law, 2016), pg. 41).

Each actor contributed to Aduhelm's approval, and by investigating their interactions, I will be able to understand how these actors have shaped the technical and social.

A core idea in the ANT framework is heterogeneous networks, which revolves around the desires and agency each actor holds. Human and non-human actors together shape a network. Each actor holds power in the process of translation, and their interactions contribute to the overall construction of a system. For example, Biogen desired the approval of Aduhelm for monetary gains, while the FDA sought to ensure drug efficacy and user safety. The clinical trial data was used to translate evidence between the FDA and Biogen, even though the interpretation of this data was up to the FDA advisory committees. Public advocacy groups pushed for accelerated approval for any Alzheimer's drug, which translated to political pressure on the FDA.

Once the primary actors are identified and the heterogeneous networks are examined, I will be able to learn about the economic and political power dynamics in place during Aduhelm's drug approval. This work will be useful in further investigations of how outside influences can shape the future of Alzheimer's research. Further research exploring the power of patient advocacy groups, as well as the interpretation of data used to advise the FDA, will be useful when applying the ANT framework to my STS topic.

Research Question and Methods

The research question I will investigate is: How did the economic and political environment, in the years leading up to 2021, impact the approval process of Aduhelm? In order to answer this question, I hope to interview members of the FDA advisory committee that rejected Aduhelm. I will reach out to the three members of the advisory committee that resigned because of the approval. I will prepare questions about how the committee works, why the approval process failed, and the power dynamic between the FDA and its advisory committee. In

parallel, I plan to get into contact with at least three Alzheimer's disease experts at UVA to discuss how the approval can impact future developments in biopharmaceutics. Additionally, I plan to conduct extensive research to establish how the FDA acts as a politically motivated agency, understand how public advocacy groups had social power when pushing for accelerated approval, examining how economic factors influenced decision making, as well as investigate the inappropriate relationships between the FDA and industry.

Conclusion

In my technical project, I plan to develop a targeted, cost effective, and safe drug delivery platform that can be utilized in the future to treat a wide variety of brain diseases and disorders. My STS project aims to investigate how a controversial Alzheimer's drug was FDA approved due to the intricate interplay between political and economic factors. This investigation can guide policymakers to understand how complex relationships shape the future of healthcare. Through the parallel production of a medical platform and dissecting the forces that shape FDA approval, we can better develop innovative technologies that enhance the quality of life for those affected by brain diseases while prioritizing safety and efficacy.

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