Prospectus

Evaluation of Caffeic Acid Diffusion in a Simple 3D Model of Hepatocellular Carcinoma

(Technical Topic)

The Inherent Politics That Impact Access to Hepatitis C Treatment

(STS Topic)

By

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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:

Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. In the same year, liver cancer was the third most deadly form of cancer, causing 830,000 deaths and in 2018 alone the National Cancer Institute spent over 95 million dollars in research funding (*2019 NCI Budget Fact Book - Research Funding - National Cancer Institute*, 2021; *Cancer*, n.d.). Based on this data, it is clear that cancer treatment as a whole, and liver cancer in particular, is a major issue within the medical field. This is a proposal to address the challenging question of how to reduce liver cancer incidence through the development and improved access to innovative treatment methods. To address the technical aspect of this problem, my team and I will design and manufacture a tissue model that closely resembles the tumor microenvironment of hepatocellular carcinoma (HCC), a common form of liver cancer, to evaluate the release kinetics of a new drug at various concentrations and rate of cellular uptake to optimize the current therapeutic procedures.

However, this technical aspect alone is insufficient to accomplish my overall goal of addressing how to reduce liver cancer incidence. Treatment options must be paired with effective access strategies to maximize success. If only a purely technical solution is developed, those currently without liver cancer will not benefit from learning about the preventable causes of this fatal disease and organizations will not understand the impact of healthcare policies on the treatment of said disease. By simply improving treatment options for liver cancer patients, the impact of each factor on access to cancer prevention and treatment will be entirely missed.

To best reduce liver cancer incidence, the social and technical aspects of the problem must both be analyzed. The technical component of this project is addressed through engineering improved HCC treatment options. To address social implications, I will analyze the inherent

politics associated with curative Hepatitis C (HCV) treatment after its initial release using the technological politics framework. This will allow me to better answer the question of how to reduce liver cancer incidence through the completion of a technical aspect that will improve alternative therapeutics and an increased understanding of the obstacles to initial HCV treatments, which is a critical step to prevent the development of liver cancer.

Technical Problem:

Hepatocellular carcinoma (HCC) is a common form of liver cancer, accounting for 70-85% of total liver cancers, and is the fifth most commonly diagnosed tumor worldwide (Jemal et al., 2011; Raza & Sood, 2014). HCC is becoming one of the most prevalent causes of cancer deaths and its increasing incidence can be linked to the aging population and prevalence of cirrhosis due to hepatitis (Jemal et al., 2011; Mittal & El-Serag, 2013). Current treatment options include liver transplantation, surgical resection, and various locoregional therapies such as transarterial (chemo)embolization (TA(C)E). Liver transplantation is considered the best therapeutic option due to its curative properties. However, most HCC cases are too advanced by the time of diagnosis, causing patients to be unsuitable for transplant and directed toward therapies like TA(C)E. Image-guided TA(C)E aims to restrict tumor blood flow by delivering particles to obstruct arterial blood supply. The overall objective of this treatment is to downstage HCC, thus increasing the chance for transplant eligibility (Raza & Sood, 2014). Unfortunately, results from clinical trials show high rates of tumor recurrence after TA(C)E, which causes patients to continue to be ineligible for curative liver transplant (Porrett et al., 2006). This presents a need for the development of a more effective treatment as the HCC patient population continues to grow.

Recently published research shows that natural phytochemical caffeic acid (CA), in combination with small particles to block blood flow to tumors in TA(C)E procedures, has the ability to cause extensive regression of HCC tumors in rat models. This regression is attributed to CA disruption of tumor metabolism and an increase in programed cell death (Wilkins et al., 2017). Although the mechanism in which CA causes cell death has been determined, very little is known about the local kinetics of CA within the tumor microenvironment. For this reason, there is a current need for a reliable model in order to optimize a TA(C)E + CA clinical approach.

The ultimate goal of this technical project is to design and manufacture a tissue surrogate that mimics the HCC tumor microenvironment to evaluate the kinetics of CA distribution at various concentrations and rate of cellular uptake to optimize the TA(C)E + CA procedure. In order to accomplish this goal, my team will begin by conducting an extensive literature review of methods for surrogate tissue growth and determine how to mimic the HCC tumor microenvironment. My team and I will also balance the reproducibility, scalability, and cost-effectiveness of the surrogate through careful material and method selection. We will then design the tissue surrogate to replicate the clinical application as much as possible. Next, we will culture the simple tissue surrogate in a laboratory. A Trypan Blue stain will be used to test cellular viability, a Lucifer Yellow assay will assess model permeability, and Doxorubicin (a common drug in TACE procedures) will be used to validate the diffusion of the model. Once the method of development for the tissue surrogate has been perfected, CA will be released into the surrogate with its release kinetics carefully measured. In order to complete this task, my team and I will review current literature to select an appropriate method of specifically imaging CA within the tissue surrogate over a period of time. We will then establish a protocol of mapping the selected imaging technique to CA concentration. Next, we will conduct the imaging protocol for CA at

multiple concentrations and time points. Lastly, the data will undergo thorough analysis which will be used to ultimately characterize the CA release kinetics within the overall surrogate system.

The completion of this technical project will provide valuable information that characterizes the local drug diffusion and release kinetics of CA within a simple tissue surrogate that resembles an HCC tumor. Consequently, the TA(C)E + CA protocol can be better understood, allowing for continuous parameter optimization until desired results are achieved. This data will then provide a solid foundation for further animal and human testing and eventually, implementation into clinical practice to improve prognoses and extend lives of HCC patients.

STS Problem:

Hepatitis C (HCV) is a viral infection that causes liver inflammation, sometimes leading to serious liver damage (*Hepatitis C*, n.d.-a). The virus spreads through blood contamination and symptoms can take decades to appear, resulting in about half of people with HCV to not know they are infected. People generally realize they have the condition once the virus has damaged the liver enough to cause signs and symptoms of liver disease (*Hepatitis C - Symptoms and Causes*, n.d.). It is essential to evaluate HCV treatment access because patients with the untreated infection have a significantly increased risk of developing HCC (Axley et al., 2018).

Due to a variety of factors, there is an unfortunate stigma around patients with HCV. Risk of contracting HCV increases if a person is positive for human immunodeficiency virus (HIV), has injected illicit drugs, is part of the Baby Boomer generation (born in 1945 to 1965), has received a tattoo with unsterile equipment, is a healthcare worker that has been exposed to

infected blood, or has received a blood transfusion or organ transplant prior to 1992. Although people develop HCV through a variety of means, it is stigmatized the most for its association with intravenous illicit drug use. This stigma causes patients with HCV to feel marginalized and makes it harder for them to advocate for their treatment in healthcare settings where they may face discrimination (Marinho & Barreira, 2013).

Prior to 2013, the best method of treatment was a combination of pegylated interferon-α, administered once weekly, plus daily oral ribavirin for 24 to 48 weeks. In patients with HCV genotypes 2 and 3, this therapy led to the absence of HCV RNA in a patient's blood 6 months after treatment in 80-90% of patients treated. However, it was only successful in 50% of patients with genotypes 1 and 4 and came with numerous side effects (Rong & Perelson, 2010). In 2013, Sovaldi was approved by the FDA as an oral therapy taken as a tablet in combination with other drugs (depending on HCV genotype). It was the first drug to be taken without an interferon component and was immediately more effective. However, it came with a massive price tag. Gilead's Sovaldi came to the market at a cost of $1,000 per pill, which translates to $84,000 for a 12-week treatment cycle that cures most patients (*Hepatitis C*, n.d.-b).

State Medicaid budgets are simply not large enough to cover treatment for everyone with HCV due to the price of Sovaldi. Most state Medicaid programs have dealt with this shortfall by limiting treatment to people who meet their predetermined criteria. In the state of Louisiana, this meant a liver damage requirement that ensured those in the worst condition got treated first. Additionally, Louisiana Medicaid programs also implemented a sobriety restriction that required all eligible patients to be substance-free for 12 months prior to treatment approval, even though most new HCV infections in the US are the result of drug use ("Hepatitis C," n.d.-c). These requirements made it nearly impossible for patients in Louisiana like Lisa Gray who eventually

had to rely on alternate means to seek generic HCV medications from other countries once she lost Medicaid coverage after beginning to receive disability compensation for her failing liver (*Hepatitis C Patients Are Being Forced Into Underground Buyers' Clubs*, 2018). These conditions for treatment seem to further perpetuate financial divides and reduce access to HCV treatment among the poor.

The drug Sovaldi is currently understood to perform the solely technical function of curing HCV infection in patients. However, the drug also does significant political work due to its high price and the nature of the virus primarily impacting poorer communities because those are the ones with the most unlawful drug usage (Omland et al., 2013). If we continue to think that Sovaldi only does technical work, we will miss how it works to shape power relations along financial lines. I propose that the exorbitant price of Sovaldi within the context of the Medicaid system in Louisiana expresses power relations by privileging some and marginalizing others based on their financial status and illicit drug usage. Technological politics is a framework that emphasizes the inherent political qualities of certain technologies. Although the situational context of a technology is essential to consider, the properties of some technologies are strongly linked to particular institutionalized patterns of power (Winner, 1980). Using this framework, I will describe how the Sovaldi drug has inherent political qualities that perpetuate power relations in the state of Louisiana. To complete this analysis, I will utilize information regarding Medicaid policies and their coverage of HCV treatment at the time, first-hand accounts from HCV patients on their diagnoses and treatment journeys, data concerning HCV patient demographics in the US, and medical information on the pathogenesis of the infection. This evidence will allow me to draw a conclusion on the impact of politics associated with Sovaldi and how it was unsuccessful in providing access to curative HCV treatment to all vulnerable populations.

Conclusion

The completion of my technical project will provide valuable information that characterizes the local drug diffusion and release kinetics of CA within a tissue surrogate that closely mimics HCC tumor conditions. My STS research paper will determine why the initial release of direct-acting antivirals, such as Sovaldi, did not have more success in curing HCV positive patients in the US. This will be accomplished by applying the technological politics framework to analyze the impact of the inherent qualities of the medication that influenced access to HCV treatment and perpetuated power relations along financial status. The combined results of this report will address the issue of reducing liver cancer incidence from a sociotechnical lens, through the improvement of alternative therapeutics and an increased understanding of the obstacles to initial medical treatments.

Word Count: 1910

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