Design of an Improved Imaging System for Ultrasound-Guided Microbubbles in Tumor Vasculature

Analysis of the Development of a Colorectal Cancer Vaccine

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By
Anand Kanumuru

December 8, 2022

Technical Team Members:
Akbar Ali, Gabriel Villarroel

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.

Anand Kanumuru

ADVISORS

Benjamin Laugelli, Department of Engineering and Society

Richard Price, Department of Biomedical Engineering

Introduction

For decades, scientists and researchers have been searching for effective ways to cure colorectal cancer. The American Cancer Society estimates that the disease caused over 52,000 deaths in the United States in 2020, which would make it the second most common form of cancer death (Siegel et al., 2020). Although current treatments like surgical procedures and chemotherapy have vastly improved survival rates throughout the years, these methods often come with extensive side effects and complications. However, recent studies have shown that promising colorectal cancer vaccines that can target healthy people at high genetic risk may be closer than initially expected. Lynch syndrome is a disease that is caused by mutations in key genes responsible for DNA repair (Bhattacharya & McHugh, 2022). Unfortunately, this results in a 70% lifetime risk of cancer probability (Kaiser, 2022). To combat this risk, researchers have developed a vaccine that targets special molecular markers present on the surface of colorectal tumor cells named antigens. This vaccine is currently going through clinical trials and could potentially be available to patients before 2030 (National Cancer Institute (NCI), 2022). Analogously, I aim to develop an improved imaging system that will allow for better visualization of tumor vasculature to address the deficiencies in cancer treatment. When combined with focused ultrasound and lipid-based microbubbles, this can lead to more efficient chemotherapeutic drug delivery.

In addition to the technical factors that have impacted the development of the aforementioned cancer vaccines, it is also important to consider other factors. A viable solution must be able to adequately prevent cancer while accounting for FDA approval, development costs, and more. For example, a technically flawless cancer treatment cannot impact lives if it is

not affordable and accessible to the patient population. To design a successful cancer treatment, all aspects of the issue must be addressed.

Below, I propose a technical solution to improve chemotherapeutic drug delivery to tumors by improving tumor vasculature imaging. I also use the Actor-Network theory to analyze the various factors that have played a role in the development of an effective colorectal cancer vaccine for patients with Lynch syndrome.

Technical Project Proposal

Initially developed to enhance ultrasound scans, lipid-based microbubbles have recently been shown to be an important tool in noninvasive drug and gene delivery to specific tissues (Tsutsui et al., 2004). Microbubbles are gas-filled bubbles whose minuscule size of 0.5-10 μm allows for delivery mechanisms to easily navigate the body (Jangjou et al., 2021). When these microbubbles are injected into tumor models, they can traverse the tumor's blood vessels and image the vasculature with the aid of contrast-enhanced ultrasound. Anti-angiogenic drugs are able to restore a more functionally and structurally normal vasculature in tumors (Vafopoulou & Kourti, 2022). Together, microbubbles and anti-angiogenic drugs are able to normalize a tumor's vasculature which allows for improved delivery of subsequent chemotherapeutic drugs (Jain, 2005).

Imaging processes to capture microbubbles interacting within the tumor's vasculature have been developed in MATLAB and other similar platforms. However, these methods are not very efficient, quick, or adaptable. If the program cannot quickly provide high-quality images of a tumor's vasculature, it will not be useful in interpreting the effects of microbubbles with anti-angiogenic drugs. By developing a more efficient and adaptable program, I will be able to make

the analysis of ultrasound-based microbubble delivery more robust. Eventually, improved chemotherapeutic drug delivery could lead to lower drug doses and reduced drug toxicity (Veselov et al., 2022). Additionally, the current program I have been working with is specific to a certain project at the Price Lab at the University of Virginia. It is not currently adaptable to other similar projects that could benefit from this technology. A more versatile program would be able to add value and impact other research in cancer and more. This would lead to innovation in ultrasound-based medicine, which has the potential to be expanded to other fields of medicine. Lastly, images generated by the ultrasound output different two-dimensional tumor cross-sections. This does not allow for optimal visualization and understanding of a tumor's anatomy. A more comprehensive overview of a tumor's appearance would be greatly valuable due to its ability to inform decision-making regarding medications and treatment.

This technical project aims to design an improved imaging program that is able to analyze ultrasound-based microbubbles in tumor vasculature. The Price Lab has provided us with their current rendition of an imaging program, which will serve as the basis for our scale-up. This program will be able to identify microbubble signals under ultrasound as the signal of interest. It will also be able to measure the rate of microbubble movement through tumor vasculature and the percentage of a tumor that the microbubble signaling covers. Furthermore, we will aim to take two-dimensional tumor cross-sectional imaging provided by the Price Lab to develop a program that is able to compute three-dimensional models. We will achieve these aims by working with researchers at the Price Lab to gather real data.

To develop our designs, mice will be injected with 4T1 breast cancer cells which are allowed to grow for two weeks under treatment with an anti-angiogenic drug named DC101. 4T1 is a transplantable tumor cell line that is highly potent (Pulaski & Ostrand-Rosenberg, 2000).

There will also be a control group whose 4T1 breast cancer cells are treated with a neutral protein. Once microbubbles are injected into these samples, they will cavitate and burst under focused ultrasound. The signal that appears will serve as the baseline. Lastly, bubbles will be injected again to restore blood flow to the tumor and generate new signals that will be compared to the baseline. The gathered data will be incorporated into an improved imaging program on MATLAB. MATLAB was chosen for both its computational power and extensive documentation. Two-dimensional images gathered from the ultrasound will be input into AutoCAD to create a three-dimensional model that maps out tumor vasculature. These tasks will be completed as a team of three students over the course of two semesters in BME 4063 and BME 4064. Data collection, program optimization, and three-dimensional modeling work will be divided equally among the team members.

STS Project Proposal

Although technology and treatments in medicine are constantly evolving at a rapid rate, these innovative solutions are not always able to impact patients to their full potential. In this case, the development of an effective vaccine against colorectal cancer has seen limited progress. Animal trials and preliminary human trials have seemed promising in vaccines built around the same technology as this one, but most fail to halt tumor growth because the antigens being attacked can also be present on normal cells. Furthermore, chemotherapy and similarly harsh treatments can weaken the immune system that the vaccine aims to utilize to eliminate cancer cells. Even if these technical issues did not exist, heavy government regulations and exorbitant funding requirements have hampered the development of this product.

According to *Nature Medicine*, some of the regulatory hurdles involved in cancer research include patent restrictions, material transfer agreements, and Health Insurance Portability and Accountability Act (HIPAA) regulations ("Roadblocks to Cancer Cures," 2004). Since human sample information is required to be deidentified, researchers lose valuable medical information. In addition, patients with a particular diagnosis cannot be directly recruited for new therapies that require clinical trial volunteers. This obstruction of research increases costs and prevents patients from seeking treatment options. In relation, developing therapeutic solutions for cancer is an extremely expensive task. In 2017, the median cost of developing a single cancer drug was $648 million (Prasad & Mailankody, 2017). It is also important to note that most drugs take more than a decade to develop, which would increase the costs as well. Since so many resources are put into research and development, the costs to receive cancer treatment are not viable for a majority of patients. Sipuleucel-T, a vaccine used to treat prostate cancer, came with a cost of $93,000 in 2010 (Geynisman et al., 2014).

Previous writers have examined how regulatory burdens and demanding costs can play a massive role in the development and administration of a cancer vaccine. However, they have not yet adequately addressed how medical mistrust and aversion to vaccines have impacted the development of an effective cancer vaccine. If these factors are not also considered, it is impossible to gain a comprehensive understanding of what needs to be addressed to maximize the impact of a technically proficient colorectal cancer vaccine. This is especially true in current times, where these factors are having an increasingly substantial impact on healthcare in general. While the other factors that have been thoroughly documented by experts are integral to the development of a colorectal cancer vaccine, they don't demonstrate how the attitudes of patient populations are extremely important to the process.

I argue that previously mentioned regulatory and financial factors in conjunction with medical mistrust and a general fear of vaccinations have substantially hindered the development of the colorectal cancer vaccine for patients with Lynch syndrome. To frame my analysis, I will draw on the Actor-Network theory which examines how a system of "actors" associate together for a common purpose. In the design process, there is a network builder who identifies a problem and the actors that are needed to solve it. Human and non-human actors can be technical, social, economic, and more. Through the process of translation, the network builder must form and maintain a network consisting of actors. Importantly, all actors must be accounted for and successfully associated together for a network to function properly. To analyze the actors in the network, I will utilize information from research studies that have documented the impact of medical mistrust on cancer treatment. In addition, I will look at how vaccine hesitancy stemming from COVID-19 may have impacted the patient population's willingness to partake in cancer vaccines and other novel treatment plans.

Conclusion

For the technical problem discussed in this paper, the final deliverable will be a revamped MATLAB imaging program that is able to visualize ultrasound-mediated microbubbles in tumor vasculature with improved efficiency and versatility. The STS research paper will aim to understand how medical mistrust and fear of vaccinations have hampered the development of a colorectal cancer vaccine targeting those with Lynch syndrome. I will accomplish this by utilizing the Actor-Network theory to explore how the actors in the network have shaped the design process. The insights from my STS research paper will facilitate an understanding of what actors have contributed to the underwhelming development of a new cancer treatment

technology, which will allow me to optimize the design of my technical project. Together, the combined results will serve to address how an effective cancer vaccine can be developed from a socio-technical point of view.

Word Count: 1,777

References

Bhattacharya, P., & McHugh, T. W. (2022). Lynch Syndrome. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK431096/

Geynisman, D. M., Chien, C.-R., Smieliauskas, F., Shen, C., & Tina Shih, Y.-C. (2014). Economic evaluation of therapeutic cancer vaccines and immunotherapy: A systematic review. *Human Vaccines & Immunotherapeutics*, *10*(11), 3415–3424. https://doi.org/10.4161/hv.29407

Jain, R. K. (2005). Normalization of Tumor Vasculature: An Emerging Concept in Antiangiogenic Therapy. *Science*, *307*(5706), 58–62. https://doi.org/10.1126/science.1104819

Jangjou, A., Meisami, A. H., Jamali, K., Niakan, M. H., Abbasi, M., Shafiee, M., Salehi, M., Hosseinzadeh, A., Amani, A. M., & Vaez, A. (2021). The promising shadow of microbubble over medical sciences: From fighting wide scope of prevalence disease to cancer eradication. *Journal of Biomedical Science*, *28*(1), 49. https://doi.org/10.1186/s12929-021-00744-4

Kaiser, J. (2022, April 7). *New generation of cancer-preventing vaccines could wipe out tumors before they form*. Science. https://www.science.org/content/article/new-generation-cancer-preventing-vaccines-wipe-tumors-form

National Cancer Institute (NCI). (2022). *A Phase Ib/II Clinical Trial of Nous-209 for Recurrent Neoantigen Immunogenicity and Cancer Immune Interception in Lynch Syndrome* (Clinical Trial Registration study/NCT05078866). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT05078866

Prasad, V., & Mailankody, S. (2017). Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Internal Medicine*, *177*(11), 1569–1575. https://doi.org/10.1001/jamainternmed.2017.3601

Pulaski, B. A., & Ostrand-Rosenberg, S. (2000). Mouse 4T1 Breast Tumor Model. *Current Protocols in Immunology*, *39*(1), 20.2.1-20.2.16. https://doi.org/10.1002/0471142735.im2002s39

Roadblocks to cancer cures. (2004). *Nature Medicine*, *10*(10), 1003–1003. https://doi.org/10.1038/nm1004-1003

Siegel, R. L., Miller, K. D., Goding Sauer, A., Fedewa, S. A., Butterly, L. F., Anderson, J. C., Cercek, A., Smith, R. A., & Jemal, A. (2020). Colorectal cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(3), 145–164. https://doi.org/10.3322/caac.21601

Tsutsui, J. M., Xie, F., & Porter, R. T. (2004). The use of microbubbles to target drug delivery. *Cardiovascular Ultrasound*, *2*, 23. https://doi.org/10.1186/1476-7120-2-23

Vafopoulou, P., & Kourti, M. (2022). Anti-angiogenic drugs in cancer therapeutics: A review of the latest preclinical and clinical studies of anti-angiogenic agents with anticancer potential. *Journal of Cancer Metastasis and Treatment*, *8*, 18. https://doi.org/10.20517/2394-4722.2022.08

Veselov, V. V., Nosyrev, A. E., Jicsinszky, L., Alyautdin, R. N., & Cravotto, G. (2022). Targeted Delivery Methods for Anticancer Drugs. *Cancers*, *14*(3), 622. https://doi.org/10.3390/cancers14030622