The Additive Cytotoxic Effect of BMS754807 and BMS599626 on the Head and Neck Cancer Proteome

(Technical Paper)

The Impact of Telemedicine on Antimicrobial Resistance During the COVID-19 Pandemic

(STS Paper)

A Thesis Prospectus Submitted to the

Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements of the Degree

Bachelor of Science, School of Engineering

Sarah Hall

Fall, 2020

Technical Project Team Members

Sarah Hall

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

Signature ______________________________________ Date __5/5/2021________

Sarah Hall

Approved ______________________________________ Date __________

Dr. Daniel Gioeli, Department of Microbiology, Immunology, and Cancer Biology

Approved ______________________________________ Date __________

Sean Ferguson, Department of Engineering and Society

Introduction

The technical portion of this prospectus delves into a mechanism of Head and Neck Squamous Cell Carcinoma (HNSCC) drug resistance. The main objective will be to apply computational and mathematical analysis in order to develop a model that illustrates relevant protein signaling pathways. The sociotechnical portion will focus on the evolving issue of antimicrobial resistance (AMR) during the COVID-19 pandemic. I will explore telemedicine as a vehicle for this growing problem due to the inability for doctors to physically examine their patients. This topic is of interest because eventually, our society runs the risk of being immune to all antibiotics that are in current use.

While targeted therapy is an attractive treatment option for various types of cancer, drug resistance is extremely common. An understanding of the mechanism behind the drug combination of interest is needed in order to guide development, determine dosing, and aid in the creation of new drugs. With assistance from Daniel Gioeli, Ph.D. in the Department of Microbiology, Immunology, and Cancer Biology of the University of Virginia School of Medicine, the effect of the drug combination on the HNSCC proteome will be visualized via Python and a mathematical model will be derived. This model will explain how the two drugs essentially inhibit cell growth when used in combination.

The sociotechnical portion focuses on a different yet still pertinent type of drug resistance. This topic is motivated by the current pandemic, in which many patients have been prescribed antibiotics without the necessary tests to validate that prescription. I will explore the reason behind this assertion, looking into telemedicine as a seemingly attractive technology that contributes to the growing

AMR crisis. As I transition into a career focused on discovering safe and effective treatment methods for cancer, the outcomes of these projects will help me gain the relevant knowledge to contribute to the biomedical research field.

Technical Topic

Head and neck cancers are the sixth most prevalent cancer worldwide and the 5-year survival rate is ~65%. These types of cancers can occur in the nose, oral cavity, tongue, tonsils, and the sinuses (Pulte & Brenner, 2010). Most of these cancers are squamous cell carcinomas (SCC), which develop in epithelial cells usually due to tobacco/alcohol use (Argiris et al., 2008). These cancers affect roughly 14.97 men and 6.24 women per 100,000 (Pulte & Brenner, 2010). Treatment for head and neck squamous cell carcinoma (HNSCC) includes radiation, chemotherapy, and surgery to remove tumors. Major problems can arise from these treatments, including loss of speech or the inability to swallow; thus, new and safer treatment methods are needed. Single-agent therapy is not enough to effectively treat these aggressive tumors. Resistance to any single drug is likely, which is why using combinations of targeted therapies is a promising approach.

Epidermal growth factor receptor (EGFR) is a potential therapeutic target for HNSCC, being overexpressed in more than 90% of HNSCCs (Jameson et al., 2011). EGFR family receptors play a major role in processes needed for HNSCC growth and metastasis (Roskoski, 2014). Previous work has shown that insulin-like growth factor 1 receptor (IGF1R) signaling is a resistance mechanism to EGFR inhibition in HNSCC (Jameson et al., 2011). To combat resistance, the effect of BMS754807 and BMS599626 on HNSCC will be investigated, which inhibit IGF1R and EGFR respectively.

The objectives for my Capstone project are to identify functional signaling components inhibited by the drug combination and to understand the mechanism behind the combination's effect. I will be analyzing reverse phase protein array (RPPA) data that quantifies expression of 145 epitopes across five cell lines at five time points. The conditions are control, BMS599626, BMS754807, and BMS599626 + BMS754807. Working with the Jameson lab in the Department of Otolaryngology and Daniel Gioeli, Ph.D. in the Department of Microbiology, Immunology, and Cancer Biology at UVA, I will be using Python to create heatmaps and run statistical tests in order to discover key epitopes inhibited by the drug combination. Following this discovery, I will be working with systems biologists to develop a model that describes the mechanism behind the combination's robust cytotoxic effect.

I have already generated heatmaps that display log fold changes in expression for the combination and the drugs individually compared to the control group. These heatmaps have allowed me to visualize trends across time points and cell lines, illustrating the additive, if not synergistic, effect on EGFR/IGF1R signaling pathways. In addition, I performed t-tests and derived Benjamini-Hochberg False Discovery Rate (FDR) adjusted p-values. An FDR threshold of 5% was used for this test. T-tests were performed for 5 comparisons at every time point, for every epitope, and for every cell line. The 5 comparisons were as follows: combination to control, BMS599626 to control, BMS754807 to control, BBMS599626 to combination, and BMS754807 to combination. A heatmap of corrected p-values was produced to highlight only statistically significant comparisons. Unsurprisingly, the EGFR/IGF1R pathways demonstrated significance.

For the remainder of this semester, I will be conducting literature searches to find methods for creating this model and finding a UVA faculty member that can assist with the systems biology component. In the spring semester, I will be focused on development of the model, which will likely involve R software and the use of differential equations.

STS Topic

AMR is an increasingly prevalent problem worldwide. Physicians often prescribe antibiotics to treat patients suffering from symptoms that align with bacterial infections without confirming the type of illness. Running additional tests costs more money, which leads to doctors prescribing medications prematurely. During the COVID-19 pandemic, this problem has been exacerbated. With social distancing and quarantining, patients no longer physically go into a doctor's office. Thus, there has been a rise in the utilization of telemedicine. Patients are no longer receiving in-person examinations, so the only information that a doctor can use for diagnosis is communicated verbally. This research paper explores the potential for contactless interactions between doctors and patients to increase drug resistance and threaten human survival.

At least 700,000 people die each year worldwide due to bacterial infections that cannot be treated due to AMR, and it is projected that 10 million people will die per year by 2050. In the United States, there are over 2.8 million cases of multidrug-resistant bacterial infections per year, resulting in $20 billion in health care spending (Strathdee et al., 2020). Antibiotics are relied upon for many different aspects of healthcare, including chemotherapy for cancer treatment, organ transplantation, hip replacement surgery, and intensive care for pre-term newborns. Scientifically, AMR occurs when a small population of bacteria that are naturally resistant to the antibiotic survive and multiply. Eventually, this population grows large enough such that the drug can no longer effectively kill the bacteria and the patient cannot overcome their illness (Prestinaci et al., 2015).

Medical professionals put pressure on the AMR landscape. With the emergence of the coronavirus, experts have a growing concern for the health of our society. A CDC senior science advisor stated, "The resulting increased exposure to healthcare settings and invasive procedures, along with expanded antibiotic use, amplifies the opportunity for resistant pathogens to emerge and spread" (Hsu, 2020). Additionally, a study conducted at two hospitals in Wuhan found that 95% of COVID-19 patients were treated with antibiotics while only 21% were treated with antivirals ("Antimicrobial Resistance in the Age of COVID-19," 2020). These figures demonstrate the lack of diligence put into patient care due to the stress that the pandemic is putting on health care systems. Ultimately, the human immune system will lose the ability to fight bacterial infections if doctors continue to prescribe antibiotics in such a haphazard manner.

Telemedicine emerges as a niche that has impacted the regime of modern medicine. This technology is defined as providing health care services by exchanging information via information and communication technologies (ICT). While distance was typically the reason for using telemedicine prior to 2020, the pandemic has provided a unique opportunity for utilization. There are many benefits to this method of interaction, including the freedom of location, safety for the patient and for the physician, and time efficiency (Monaghesh & Hajizadeh, 2020). However, overly cautious physicians may be prescribing antibiotics without providing a diagnosis. For example, a study was conducted that involved children who had acute respiratory infections (ARIs). Researchers found that antibiotics were prescribed in 52% of telemedicine visits, 42% of urgent care visits, and 31% of primary care visits (Ray et al., 2019). This evidence supports the claim that telemedicine appointments result in more antibiotic prescriptions, and thus contributes to AMR. Essentially, this research paper will be utilizing multilevel perspective to analyze the relationships between AMR, conventional modern medicine techniques, and telemedicine technology in the midst of a global pandemic.

I intend on finding more evidence to develop solid reasoning for why telemedicine has increased antibiotic prescriptions. I will be surveying physicians as well as interviewing patients to get a better understanding of how telemedicine appoints operate. Do physicians prescribe because it takes more effort to test a patient? Are tests avoided for financial reasons? Are physicians being overly cautious like some evidence suggests, or are they being careless/need better training to adjust to the new technological environment? Why are physicians not more concerned about AMR as they continue to prescribe antibiotics? I will need to expand upon the claims made in this prospectus after synthesizing new information. There is also a counterargument that I have discovered in my research, claiming that telemedicine has actually decreased the spread of AMR because patients are isolated in their homes, not exposing others to their illness in an effort to go to a doctor’s office. I hope to disclaim this argument by the end of my exploration.

Next Steps

The evidence discussed in this prospectus supports the claim that telemedicine has increased the prescription of antibiotics during the COVID-19 pandemic. For the remainder of the fall semester, I aim to gather more literature/textual evidence to confirm these initial findings, as well as expand my knowledge on existing scholarship supporting the counterargument. In the spring, I will be conducting interviews with physicians and patients, reaching out to pharmacies to see if the distribution of antibiotics has increased, and looking into resources for physicians to see if and how the framework of medical education has changed due to the current pandemic. Examples of these resources would include literature, physician blogs, and seminars.

References

Antimicrobial resistance in the age of COVID-19. (2020). *Nature Microbiology*, *5*(6), 779–779. https://doi.org/10.1038/s41564-020-0739-4

Argiris, A., Karamouzis, M. V., Raben, D., & Ferris, R. L. (2008). Head and neck cancer. *Lancet (London, England)*, *371*(9625), 1695–1709. https://doi.org/10.1016/S0140-6736(08)60728-X

Hsu, J. (2020). How covid-19 is accelerating the threat of antimicrobial resistance. *BMJ*, *369*. https://doi.org/10.1136/bmj.m1983

Jameson, M. J., Beckler, A. D., Taniguchi, L. E., Allak, A., Vanwagner, L. B., Lee, N. G., Thomsen, W. C., Hubbard, M. A., & Thomas, C. Y. (2011). Activation of the insulin-like growth factor-1 receptor induces resistance to epidermal growth factor receptor antagonism in head and neck squamous carcinoma cells. *Molecular Cancer Therapeutics*, *10*(11), 2124–2134. https://doi.org/10.1158/1535-7163.MCT-11-0294

Monaghesh, E., & Hajizadeh, A. (2020). The role of telehealth during COVID-19 outbreak: A systematic review based on current evidence. *BMC Public Health*, *20*. https://doi.org/10.1186/s12889-020-09301-4

Prestinaci, F., Pezzotti, P., & Pantosti, A. (2015). Antimicrobial resistance: A global multifaceted phenomenon. *Pathogens and Global Health*, *109*(7), 309–318. https://doi.org/10.1179/2047773215Y.0000000030

Pulte, D., & Brenner, H. (2010). Changes in survival in head and neck cancers in the late 20th and early 21st century: A period analysis. *The Oncologist*, *15*(9), 994–1001. https://doi.org/10.1634/theoncologist.2009-0289

Ray, K. N., Shi, Z., Gidengil, C. A., Poon, S. J., Uscher-Pines, L., & Mehrotra, A. (2019). Antibiotic Prescribing During Pediatric Direct-to-Consumer Telemedicine Visits. *Pediatrics*, *143*(5). https://doi.org/10.1542/peds.2018-2491

Roskoski, R. (2014). The ErbB/HER family of protein-tyrosine kinases and cancer. *Pharmacological Research*, *79*, 34–74. https://doi.org/10.1016/j.phrs.2013.11.002

Strathdee, S. A., Davies, S. C., & Marcelin, J. R. (2020). Confronting antimicrobial resistance beyond the COVID-19 pandemic and the 2020 US election. *Lancet (London, England)*, *396*(10257), 1050–1053. https://doi.org/10.1016/S0140-6736(20)32063-8