Developing EGFR-Targeted Nanoliposomal Therapeutics in Head and Neck Squamous Cell Carcinoma

(Technical Paper)

The Impact of Biosimilars on the Provision of Value-Based Healthcare

(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

Abhishek Karkar
Spring, 2020

Technical Project Team Members
Patrick Beck
Sally Greenberg
An Smith

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

Introduction

The rise of biosimilars in the biologics market has drastically transformed the delivery and affordability of healthcare across the world. Biologics, or biopharmaceuticals, have been identified as one of the major forces behind increasing healthcare costs across the globe (Cohen, Faden, Predaris & Young, 2007). Manufacturers of biopharmaceuticals continue to charge exorbitant prices for biopharmaceuticals needed to treat a variety of high-risk medical conditions such as diabetes and various forms of cancer (Blackstone & Fuhr, 2007). Producers of pharmaceuticals often justify the gouging of prices by claiming that costs of research and development as well as future research into more effective drugs need to be recouped and financed, respectively (DiMasi, Grabowski & Hansen, 2016). However, with the introduction of biosimilar drug variants to the biopharmaceuticals market, patients have access to alternative options for a variety of drug therapy treatments (Blackstone & Joseph, 2013).

The cost of biopharmaceuticals have created a dilemma of unaffordability in healthcare across the world and even more so within the United States. Consequently, accessibility to healthcare for middle- and low-income populations has been severely obstructed with the primary obstructing factor being cost (Simoens, 2009). Biosimilars offer an affordable alternative for a variety of drug products and enhance access to these products for the entire healthcare market and the millions of patients in critical need of life-saving biologic drug products (DiMasi et. al, 2016). Furthermore, this more affordable relationship between patient and treatment allows physicians and care-givers to shift their model for providing care from one that is solely focused on “quality no matter the cost” to one that is more cognizant of the overall value that a given treatment option may provide (Patel, Arantes, Tang & Fung, 2018). This

"value" would not just consider quality of care, but would factor in and evaluate the optimum balance between quality and cost of care, hence termed as a value-based healthcare model (Gray, 2017). The issue of affordability affects millions of people across the United States, and the integration of biosimilars into the healthcare market with governmental or private regulation could potentially be a viable solution to this grand dilemma. The use of biosimilars has the potential to ameliorate the burden of affordability that is faced in healthcare and with this burden removed, healthcare provision can follow a value-based model rather than a volume-based model. To assess this issue and the potential for its solution, the STS study aims to investigate the impact of biosimilars on the biopharmaceuticals industry and how its impact may be coupled with the use of value-based healthcare models to bring affordability to healthcare.

Consequently, the focus of the technical study on developing an EGFR-targeted therapeutic for Head and Neck Squamous Cell Carcinoma (HNSCC) is also driven by the principle of discovering a treatment that is not only of greater efficacy, but one that is also more affordable compared to current treatments. The need for more effective and affordable therapeutics that can specifically target rarer forms of cancer is prevalent in healthcare. To this end, the technical study aims to investigate the effects of known HNSCC therapeutics and to develop a targeted drug delivery system that allows the current therapeutics to work more effectively in smaller doses.

Technical Topic

With approximately 600,000 new cases diagnosed each year, Head and Neck Squamous Cell Carcinoma (HNSCC) is the seventh most common form of cancer worldwide. Patients diagnosed with HNSCC exhibit a 61% 5-year survival rate, which drops to 50% at the 10-year

mark (Mao et al., 2004). Despite the large volume of cases and poor outcomes for patients, only one targeted therapy has been developed specifically for patients with HNSCC, underscoring the need to develop new treatment options. The only major druggable target that has been identified in HNSCC is the Epidermal Growth Factor Receptor (EGFR), which has been shown to be overproduced in 40-80% of HNSCC tumors according to data from the Tissue Cancer Genome Atlas (TCGA). Cetuximab (Erbitux), the only FDA-approved therapy for patients with HNSCC, is an antibody that inhibits EGFR signalling activity by blocking the receptor's ability to bind Epidermal Growth Factors (EGF). Cetuximab alone has shown some success in treating HNSCC; however, the development of drug resistance has been common and its efficacy has been inconsistent (Stanam et al., 2016). The apparent shortcomings of Cetuximab highlight the need to develop new targeted therapies for patients with HNSCC.

The Kester Lab at the University of Virginia has developed a therapeutic called the Ceramide Nanoliposome (CNL), consisting of a pro-death form of the lipid ceramide encapsulated inside a spherical, lipid-bilayer delivery system, which is currently in Phase I clinical trials for treating several different cancers (Stover and Kester, 2003). In addition to showing strong efficacy as a single agent in treating HNSCC *in vitro*, the CNL has also been shown to have strong, synergistic effects when combined with other chemotherapeutics, enhancing their effectiveness (Adiseshaiah et al., 2013; Jiang et al., 2011; Myrick et al., 1999; Sok et al., 2006). Currently, a capstone team at the University of Virginia has discovered a novel synergistic effect between the CNL and two EGFR inhibitors in HNSCC, both of which had previously failed HNSCC clinical trials as individual agents (Perez et al., 2012; Soulieres et al., 2004). In addition, this discovery provides a strong rationale that the combination of the CNL

with Cetuximab may produce a similar effect. This project aims to develop two separate drug delivery devices in preparation for testing the above synergistic drug combinations in HNSCC mouse models.

Both EGFR inhibitors will be encapsulated in nanoliposomes of their own, serving to improve *in vivo* circulatory system retention time, aid in shielding the drugs from host immune system detection, and facilitate the delivery of each drug to the acidic HNSCC tumor microenvironment (Lu et al., 2006; Ranson and Wardell, 2004). Employing the molecular properties of Cetuximab, a second delivery system will be developed by linking Cetuximab to the surface of the CNL. The addition of this Cetuximab targeting mechanism will more efficiently promote drug delivery to HNSCC cells rather than healthy cells, as HNSCC cells have higher surface quantities of EGFR, while taking advantage of Cetuximab's properties as an antibody to mobilize an immune response against the cancerous tissue (Pozzi et al., 2016). Additional funding will be secured to test both delivery systems in HNSCC mouse models. By the conclusion of this project, the team aims to have laid the groundwork on producing two novel drug delivery systems for patients diagnosed with HNSCC.

STS Topic

Biosimilars are a scientific breakthrough in that they are near identical copies of original biologic medical drug products. However, biosimilars require an extensive series of regulatory standard approval and clinical experimentation to ensure that the physiological effects of the biosimilar are comparable to the original biologic medical product (Reinisch & Smolen, 2015). Biosimilars are also prohibited from manufacturing and production until the patent for the original biologic medical product has expired (Muller et. al, 2014). When biosimilars do

eventually enter the market they are often sold at a substantially reduced price to patients. This pricing introduces a level of competition in the biologics market that could not exist without cheaper alternatives to original biologic drug products (Nabhan & Feinberg, 2017). In turn, the access to necessary medical drugs increases for middle- and low-income patients since affordability becomes less of a barrier with cheaper alternatives available (Hirsch & Lyman, 2014).

Consequently, the value-based model for healthcare is strongly supported when competition exists within the biologics market. Biologics are one of the largest contributors to the high cost of healthcare in the United States and the introduction of competition in this market allows patients and clinicians the opportunity to weigh both the quality and the cost of care (Erstad, 2016). The value-based model for healthcare is defined as a system in which care providers are compensated based on the health outcomes of their patients rather than the quantity of care that is provided (Gray, 2017). This model has been introduced in a variety of hospital systems and healthcare groups over the past decade and has seen astounding results for patient health outcomes (Kenney, 2016). By focusing compensation for clinicians based on patient health outcomes, the direction and provision of care is no longer tied to the administering of the most expensive forms of care and drug products (Kenney, 2016). This form of healthcare practice, defined as "volume-based," was the preferred model of choice for healthcare provision, until recently (Gray, 2017). In a value-based model, patients can receive more affordable treatment and regulatory policies that reward clinicians for using this model of care have begun to be instituted by the U.S. government.

In the evaluation of the impact of biosimilars on the provision of value-based healthcare, it is important to note the key stakeholders and entities involved in the relationship between these two complexly connected items in the context of healthcare. The key stakeholders include patients, clinicians, the biopharmaceuticals industry, producers of biosimilars, and the U.S. government in an overarching regulatory context. These stakeholders are connected through a variety of complex relationships and interactions that surround the key entities or artifacts. The key artifacts consist of biosimilars, biopharmaceuticals, and the two healthcare models currently utilized in the field, which are the value-based and volume-based models. The stakeholders and artifacts interact cohesively to determine the background upon which the current system of healthcare is built upon. Understanding how these stakeholders and artifacts interact also provides insight into how value-based model of healthcare can succeed (Kenney, 2016). Every stakeholder and artifact contributes a key component of the integration of biopharmaceutical drugs, corresponding state of affordability, and subsequent access within U.S. healthcare (Simoens, 2009).

In order to demonstrate a clearer perspective on this complex web of connections and interactions, actor-network theory (ANT) will be utilized. ANT is a Science, Technology, and Society (STS) studies theory that is often used to profile socio-technological systems or processes by defining all the relationship or "networks" that exist between the defined "actors" in the corresponding system or process. While ANT serves as a useful technique for a user to break down and define a complex system, the nature of ANT allows it to yield a different outcome or different web of networks between various actors involved in the system (Cressman, 2018). Variation in the outcomes of applying ANT to any system or process can become highly

dependent on the background, experiences, or requirements of the user. Additionally, ANT is often limited in its use due to its focus on case studies and empirical observations, leading to situations where a researcher or user of the theory simply reports observations and fails to identify intangible values or norms in a system (Cressman, 2018). On the other hand, ANT allows the user to focus on a portion of a system via the use of a blackbox as a restriction on the scope of a system or its accompanying relationships that the user may want to analyze. Given the complexity of the interactions between the biopharmaceuticals industry, biosimilars, and the U.S. healthcare system, ANT serves as a useful overarching STS framework to build an analysis of the system.

Overall, this research can contribute towards a more holistic understanding of the complex relationship between the biopharmaceuticals industry and healthcare. Understanding this relationship in the restricted contexts of biosimilars and the value-based healthcare model can provide a more fruitful insight into the affordability concerns that plague the lower end of the socioeconomic spectrum. Understanding these relationships in depth will provide valuable insight into how biosimilars and value-based healthcare can potentially be fused together to mitigate the issues of overbearing cost in the biopharmaceuticals industry and the current unaffordability of biologic therapeutics (Erstad, 2016).

Research Questions and Methods

How can the use of biosimilars increase the affordability of healthcare and consequently shift the current healthcare provision model towards one that is value-based?

Research for the investigation of this question will be performed using network analysis. Network analysis is useful due to its nature of identifying and understanding relationships in a

complex socio-technical network such as the network that exists between the various stakeholders and artifacts mentioned previously (Wang, Srinivasan, Uddin & Chawla, 2014). Both quantitative and qualitative information will be compiled through a literature review to obtain a complete understanding of the contributions to this network made by each of these stakeholders and artifacts. This information will consist of longitudinal and statistical reports on pharmaceutical use and cost and how shifts in healthcare models have affected the market or been affected by the market. Additionally, research into the relationship of clinical outcomes with respect to both biosimilar use and value-based healthcare models compared to volume-based healthcare models will be utilized. With this information in hand, the possibility for the use of biosimilars as a mitigating factor towards affordability of healthcare as a general concept can be investigated. Moreover, the relationship between biosimilars and the provision of value-based care can be established and investigated based on current literature and statistical research. Network analysis is the most proper approach for delving into the complexities that are presented in healthcare when all of these stakeholders and artifacts act on and with each other (Wang et. al, 2014). Ultimately, network analysis is the most rational and systematic method that will provide a wide web of associations from which the relevant networks may be identified to formulate an understanding to the complex question at hand.

Conclusion

The goal of the technical project in this study is to establish a more physiologically and cost effective treatment for HNSCC by utilizing *in vitro* and *in vivo* studies to test a new form of targeted drug delivery for existing drug therapeutics. The primary objective is to use CNLs, in combination with existing drug therapeutics, to act as an inhibition mechanism for the EGFR

pathway, which is overexpressed in HNSCC. This synergistic targeted drug delivery therapeutic system has the potential to not only change treatment of HNSCC but also treatment of all EGFR overexpression exhibiting forms of cancer in the human physiology. In conformity with the overarching objectives of the technical project, the STS study aims to identify the role of biosimilars in healthcare and investigate the possibility that they may shift the structure of healthcare delivery towards a model that is value-based rather than volume-based. The potential exists for biosimilars to mitigate the affordability and cost difficulties that are associated with healthcare provision and it is the goal of this study to discover how this may be achieved.

References

Adiseshaiah, P.P., Clogston, J.D., McLeland, C.B., Rodriguez, J., Potter, T.M., Neun, B.W., Skoczen, S.L., Shanmugavelandy, S.S., Kester, M., Stern, S.T., et al. (2013). Synergistic combination therapy with nanoliposomal C6-ceramide and vinblastine is associated with autophagy dysfunction in hepatocarcinoma and colorectal cancer models. Cancer Lett. 337, 254–265.

Blackstone, E. A., & Fuhr, J. P. (2007). Biopharmaceuticals: The Economic Equation. Biotechnology Healthcare, 4(6), 41–45.

Blackstone, E. A., & Joseph, P. F. (2013). The Economics of Biosimilars. American Health & Drug Benefits, 6(8), 469–478.

Cohen, J., Faden, L., Predaris, S., & Young, B. (2007). Patient access to pharmaceuticals: An international comparison. The European Journal of Health Economics, 8(3), 253–266.

Cressman, D. (2018). Actor‐Network Theory. 1–2.

DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47, 20–33.

Erstad, B. L. (2016). Value-Based Medicine: Dollars and Sense. Critical Care Medicine, 44(2), 375.

Gray, M. (2017). Value based healthcare. BMJ, j437.

Hirsch, B. R., & Lyman, G. H. (2014). Biosimilars: A cure to the U.S. health care cost conundrum? Blood Reviews, 28(6), 263–268.

Jiang, Y., DiVittore, N.A., Kaiser, J.M., Shanmugavelandy, S.S., Fritz, J.L., Heakal, Y., Tagaram, H.R.S., Cheng, H., Cabot, M.C., Staveley-O'Carroll, K.F., et al. (2011).

Combinatorial therapies improve the therapeutic efficacy of nanoliposomal ceramide for pancreatic cancer. Cancer Biol. Ther. 12, 574–585.

Kenney, J. T. (2016). Value-Based Care Must Be Linked to Improved Clinical Outcomes. American Health & Drug Benefits, 9(Spec Issue), 22.

Lu, J.-F., Eppler, S.M., Wolf, J., Hamilton, M., Rakhit, A., Bruno, R., and Lum, B.L. (2006). Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. Clin. Pharmacol. Ther. 80, 136–145.

Mao, L., Hong, W.K., and Papadimitrakopoulou, V.A. (2004). Focus on head and neck cancer. Cancer Cell 5, 311–316.

Müller, R., Renner, C., Gabay, C., Cassata, G., Lohri, A., & Hasler, P. (2014). The advent of biosimilars: Challenges and risks. Swiss Medical Weekly, 144(2728).

Myrick, D., Blackinton, D., Klostergaard, J., Kouttab, N., Maizel, A., Wanebo, H., and Mehta, S. (1999). Paclitaxel-induced apoptosis in Jurkat, a leukemic T cell line, is enhanced by ceramide. Leuk. Res. 23, 569–578.

Nabhan, C., & Feinberg, B. A. (2017). Behavioral Economics and the Future of Biosimilars. Journal of the National Comprehensive Cancer Network, 15(12), 1449–1451.

Patel, K. B., Arantes, L. H., Tang, W. Y., & Fung, S. (2018). The role of biosimilars in value-based oncology care. Cancer Management and Research, 10, 4591–4602.

Perez, C.A., Song, H., Raez, L.E., Agulnik, M., Grushko, T.A., Dekker, A., Stenson, K., Blair, E.A., Olopade, O.I., Seiwert, T.Y., et al. (2012). Phase II study of gefitinib adaptive dose escalation to skin toxicity in recurrent or metastatic squamous cell carcinoma of the head and neck. Oral Oncol. 48, 887–892.

Pozzi, C., Cuomo, A., Spadoni, I., Magni, E., Silvola, A., Conte, A., Sigismund, S., Ravenda, P.S., Bonaldi, T., Zampino, M.G., et al. (2016). The EGFR-specific antibody cetuximab combined with chemotherapy triggers immunogenic cell death. Nat. Med. 22, 624–631.

Ranson, M., and Wardell, S. (2004). Gefitinib, a novel, orally administered agent for the treatment of cancer. J. Clin. Pharm. Ther. 29, 95–103.

Reinisch, W., & Smolen, J. (2015). Biosimilar safety factors in clinical practice. Seminars in Arthritis and Rheumatism, 44(6, Supplement), S9–S15.

Sekhon, B., & Saluja, V. (2011). Biosimilars: An overview. Biosimilars, Volume 1, 1–11.

Simoens, S. (2009). Health economics of market access for biopharmaceuticals and biosimilars. Journal of Medical Economics, 12(3), 211–218.

Sok, J.C., Coppelli, F.M., Thomas, S.M., Lango, M.N., Xi, S., Hunt, J.L., Freilino, M.L., Graner, M.W., Wikstrand, C.J., Bigner, D.D., et al. (2006). Mutant Epidermal Growth Factor Receptor (EGFRvIII) Contributes to Head and Neck Cancer Growth and Resistance to EGFR Targeting. Clin. Cancer Res. 12, 5064–5073.

Soulieres, D., Senzer, N.N., Vokes, E.E., Hidalgo, M., Agarwala, S.S., and Siu, L.L. (2004). Multicenter Phase II Study of Erlotinib, an Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Patients With Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck. J. Clin. Oncol. 22, 77–85.

Stanam, A., Gibson-Corley, K.N., Love-Homan, L., Ihejirika, N., and Simons, A.L. (2016). Interleukin-1 blockade overcomes erlotinib resistance in head and neck squamous cell carcinoma. Oncotarget 7, 76087–76100.

Stover, T., and Kester, M. (2003). Liposomal Delivery Enhances Short-Chain Ceramide-Induced Apoptosis of Breast Cancer Cells. J. Pharmacol. Exp. Ther. 307, 468–475.

Wang, F., Srinivasan, U., Uddin, S., & Chawla, S. (2014). Application of network analysis on healthcare. 2014 IEEE/ACM International Conference on Advances in Social Networks Analysis and Mining (ASONAM 2014), 596–603.