

**Developing EGFR-Targeted Nanoliposomal Therapeutics in Head and Neck
Squamous Cell Carcinoma**
(Technical Report)

Music Streaming Services: The Soundtrack to our Future
(STS Topic)

A Thesis Prospectus in STS 4500
Presented 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 in Biomedical Engineering

Author
Sally Greenberg
October 30, 2019

Technical Project Team Members
Patrick Beck
Abishek Karkar
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

Signature _____ Date _____

Approved _____ Date _____

Rider Foley, Department of Engineering and Society

Head and Neck Squamous Cell Carcinoma

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 5-year survival rate of 61% and a 50% survival rate at the 10-year mark (Mao et al., 2004). Despite the large volume of cases and poor outcomes for patients, only one drug has been identified to help develop targeted treatments for patients with HNSCC. This target 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 (also called Erbitux) is an antibody that inhibits EGFR signaling activity by blocking the receptor's ability to bind Epidermal Growth Factors (EGF) and is the only FDA-approved therapy for patients with HNSCC. Cetuximab alone has shown some success in treating HNSCC, however, it is common for patient cells to develop a resistance to the drug and its efficacy has been inconsistent (Stanam et al., 2016).

In 2016 and 2019, respectively, two new drugs, nivolumab (Opdivo) and pembrolizumab (Keytruda), were approved for use on patients with HNSCC. However, it is important to acknowledge that both of these drugs were designed to primarily treat other types of cancer and have been applied to HNSCC versus being specifically developed for HNSCC (Center for Drug Evaluation and Research, 2019; National Cancer Institute, 2011). These shortcomings of Cetuximab, with addition to the development of non-targeted therapies such as nivolumab and pembrolizumab, highlights the need to develop new efficacious therapies that exploit molecular targets specific to patients with HNSCC.

New Therapy Development: Procedure & Results

In addition to the FDA approved drug treatments, there are multiple different therapies being developed that target HNSCC. One of these therapies is known as Ceramide Nanoliposome (CNL) and was developed in the Kester Lab here at the University of Virginia. This therapy, which consists of a pro-death form of the lipid ceramide encapsulated inside a spherical, lipid-bilayer delivery system, shows a strong efficacy as a single agent in treating HNSCC *in vitro* and has also been shown to have strong, synergistic effects when combined with other chemotherapeutics, enhancing their effectiveness (Adisheshaiah et al., 2013; Jiang et al., 2011; Myrick et al., 1999; Sok et al., 2006). Currently, the Kester lab has discovered a novel synergistic effect between CNL and two EGFR inhibitors, Erlotinib and Gefitinib. This discovery provides a strong rationale for the assumption that the combination of CNL with Cetuximab may produce a similar effect (Perez et al., 2012;). This project aims to develop two separate drug delivery devices in preparation for testing the above synergistic drug combinations in HNSCC-positive mouse models.

Using resources provided by the Kester lab, both EGFR inhibitors will be encapsulated in nanoliposomes of their own, which will serve 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 the Cetuximab targeting mechanism will more efficiently promote drug delivery to HNSCC cells rather than healthy cells, which is due to HNSCC cells having a greater quantity of EGFR at the cell surface. This also takes advantage of Cetuximab's properties as an antibody to mobilize an immune

response against the cancerous tissue (Pozzi et al., 2016). Additionally, by developing these new drug delivery methods, the aim is to increase the amount of time the drug can stay active within a patient's body and to reduce the number of cells that become drug resistant. Funding to test both delivery systems in HNSCC mouse models is being sought. By the conclusion of this project, the team will have laid the groundwork for producing two novel drug delivery systems for patients diagnosed with HNSCC and by describing them in a published research article.

The Evolution of Music Listening

While my technical thesis focuses on developing two new drug delivery devices, my STS research paper will focus on the evolution of how individuals listen to music and how this impacts the music industry and the ideal of sharing. Over the past two centuries, the role of music in our everyday life has shifted drastically. Starting in the 19th century, individuals could only listen to music in two locations: a public concert site, like a tavern or a theater, or at home on a phonograph or by playing instruments. However, no matter where it happened, listening to music in the 19th century was mostly a public experience or shared with family, friends, and even strangers at times (North, 2004).

Due to the limited options for listening, music in the 19th century was viewed as a more prized and valued commodity because not everyone could afford to partake in the experience. The 20th century brought change with concern to how music was enjoyed and viewed. With the development of mass media, e.g. radio and television, and the development of music listening devices, music became less of a commodity and more of an everyday resource (North, 2004). Additionally, music itself became a much more private matter. With the invention of technology, like the Sony Walkman, listeners no longer had to share their music experience, having the

option to experience it individually or surrounded by others. Released in 1979, the Walkman provided users with the opportunity to make music mobile due to its small frame and lack of weight. Furthermore, the Walkman is credited as being the first personal music device and the first object to change music enjoyment, with concern to music listening devices, music sharing, and the music industry (Du Gay et al., 2013).

With how important the Walkman is to the development of music listening devices, music sharing, and the music industry, it is hard to believe that its development was an accident. In 1978, the tape recorder division of Sony was faced with the possibility of a department shutdown, so they developed a brilliant idea to take a device they had already invented (the tape recorder), convert it to a normal stereo recorder, and resell it to teenagers as a “portable stereo recorder”. The device ended up being a huge success (Du Gay et al., 2013). Not only did the Walkman provide the user with newfound freedoms, but more importantly, it also established a “new” way for users to control their music selection, which was known as home-taping. Home-taping is the action of taking a blank tape and copying something onto it, whether it be music, a radio show, or even a concert. While the action of home-taping itself was not a new practice in the 1980s, the amount of times it occurred increased dramatically after the release of the Walkman (Bottomley, 2015). Furthermore, this action of home-taping is considered by some to be the first form of music piracy. It was such a common practice, that record companies released a campaign against home-taping titled ‘Home-Taping is killing music — and its illegal!’ in order to try to prevent people from conducting this action. However, the campaign was not very successful (Bottomley, 2015). Luckily for the record companies, technology progressed and the Walkman gave way to the Discman, however, when technology evolves, society does as well. Therefore, home-taping did not go away, it instead gave way to CD burning, which then gave

way to a file-sharing service called Napster, which was another instance where the future of music listening devices, music sharing, and the music industry was impacted (David, 2016; McCourt & Burkart, 2003).

Creating Connections Through Co-Production

In order to properly discuss this topic, I will be using the co-production framework. Sheila Jasanoff introduced the idea of co-production in order to use a more non-linear approach in understanding how technology and society evolve. This model is a shift from the more extreme ideals of technological determinism and social constructivism, which focus on either the technological aspect or the societal aspect as the driving force in change. In co-production, Jasanoff states that it isn't one or the other that drives change, but that they both co-produce each other in a non-linear fashion (Jasanoff, 2004). Co-production serves as a very effective framework to explore this idea because music streaming services or not developed linearly or independently of one another or of societal changes. They are constantly evolving and adapting with and impacting the shifts in music listening technology and the social norms surrounding sharing music. A perfect example of this is Napster. Napster was developed because the music listening technology had progressed from a Walkman to MP3s and individuals wanted an easy, cheap and efficient way to get and share music files (David, 2016; McCourt & Burkart, 2003). Then, Napster paved the way for legal music streaming services, like Spotify, by being shut-down due to copyright issues and by changing the social ideal surrounding music downloading (David, 2016; LaRose et al., 2005 McCourt & Burkart, 2003).

The Importance of Napster

Napster is credited for being the first independent peer-to-peer file sharing service that allowed their users to share music over the internet. This new technology is important for two key reasons. First, Napster revolutionized how and with who individuals shared music. Since all Napster required was an internet connection, individuals were no longer limited to sharing music with close friends and family (David, 2016; McCourt & Burkart, 2003). Not only did this allow individuals to form new connections with people they had never met before, it also provided individuals with the opportunity to express their true selves in a judgement free environment, which helped promote the importance of music to personal growth and development (Kennedy, 2014; LaRose et al., 2005). Second, in 2001, only 3 years after its creation, Napster provided the music industry, specifically record companies, the opportunity to successfully challenge and defeat a form of music piracy which was free peer-to-peer file sharing (David, 2016; McCourt & Burkart, 2003). While the destruction of Napster did not end music piracy, it did pave the way for new music streaming services, some of which, like Spotify, are currently still in use. This begs the question, how is the music industry responding to these new music streaming services and how are these new services impacting how users share music with one another?

Research Question: The Answer is with the People

The question I aim to address is: How are current legal and free music streaming services affecting the music industry and the norms of sharing? I will approach this by conducting a case study comparison between Spotify, Apple Music, SoundCloud, and Pandora, which are four different legal and free music streaming services available in the US. In this context, the term “free” means that users can create an account and access the service without having to directly

pay. Services that require payment, but provide a free trial period were not considered. In order to determine which legal and free music streaming services I was going to utilize in my comparison, I first narrowed it down to services that had a free option. Then, I removed all radio streaming services, like iHeartRadio or SiriusXM, because, from my experience, they operate in a different manner from non-radio music streaming services. My next step was removing all music streaming services that I did not recognize, like Earbits and Anghami, because I believe this will provide the best results for my case study comparison. Finally, I then compared the monthly active users (MAUs) and subscribers of each remaining platform and chose the four platforms with the highest MAUs and/or subscribers, which also happened to be the four platforms that I believe are most well-known.

In order to determine how these four platforms impact the music industry and the ideal of sharing, I plan on creating a survey and distributing it to around 150-200 individuals ranging in age, education level, race/ethnicity, and profession. The purpose of trying to reach such a large diverse group of individuals is because music is a universal resource that impacts everyone, not just college students ranging from 18-22. If I were to only target one section of the individuals using these streaming services and sharing this music, I would only be getting part of the story. This survey will be conducted through google forms, which I believe is an easy and straight-forward survey tool that everyone will be comfortable using, and will contain a variety of questions that focus on what music streaming services they use, how they share music, and how much they know about the service itself. The data will then be condensed and looked at with concern to gender and age. Furthermore, I plan on comparing each platforms music distribution policy and looking into any lawsuits/legal rulings that involve each music streaming platform, primarily focusing on those that involve the streaming platforms and the music industry in some

way, like record companies or artists. Then, by using the co-production framework, I will be able to look at how current music streaming services impact and are impacted by the ideal of sharing between users and the music industry, which includes the user, the record companies and the artists.

Timeline & Expected Outcomes

By conducting this research, I plan to learn more about how my current music listening habits affect the world around me and affect how I interact with the world. I am interested to see how music is shared today and how that impacts individuals. Furthermore, I plan gain insight as to which streaming service is most popular among users and why, and to then determine how norms of sharing have evolved with the technology and legal structures. This information could be very useful to the music industry, as well as to the streaming service platforms, because it can update them on what their users like and dislike about their platform and it can help them prepare for what is yet to come. I will pursue this research in the following twelve weeks, see Table 1 below.

Gantt Chart by Sally Greenberg for STS Timeline (Weeks)	1	2	3	4	5	6	7	8	9	10	11	12
Create Music Survey & Distribute (Aiming for 150 students - number subject to change)	█	█										
Research into legal action taken against or by Spotify, Pandora, SoundCloud, & Apple Music	█	█	█									
Research into distribution policy and patent applications for Spotify, Pandora, SoundCloud, & Apple Music	█	█	█									
Analyze data from Survey			█	█								
Compare & Contrast information gathered to determine how Spotify, Pandora, SoundCloud, & Apple Music vary			█	█	█							
Meet with STS advisor to discuss information collected and if there is anything else missing			█	█	█							
Write first draft					█	█	█					
Edit & meet with STS advisor to iterate and improve								█	█			
Write final draft										█	█	█

Table 1. Research Timeline

References

- Adisheshaiah, 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 Letters*, 337, 254–265.
- Bottomley, A. J. (2015). ‘Home taping is killing music’: the recording industries’ 1980s anti-home taping campaigns and struggles over production, labor and creativity. *Creative Industries Journal*, 8(2), 123-145.
- Center for Drug Evaluation and Research. (2019). FDA approves pembrolizumab for first-line treatment of head and neck squamous cell carcinoma. FDA. Retrieved from <http://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-first-line-treatment-head-and-neck-squamous-cell-carcinoma>
- David, M. (2016). The legacy of Napster. In *Networked Music Cultures* (pp. 49-65). Palgrave Macmillan, London.
- Drugs Approved for Head and Neck Cancer [CgvArticle]. (2011, July 12). Retrieved October 30, 2019, from National Cancer Institute website: <https://www.cancer.gov/about-cancer/treatment/drugs/head-neck>
- Du Gay, P., Hall, S., Janes, L., Madsen, A. K., Mackay, H., & Negus, K. (2013). *Doing cultural studies: The story of the Sony Walkman*. Sage.
- Jasanoff, S. (Ed.). (2004). *States of knowledge: The co-production of science and the social order*. Routledge.
- 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.
- Kennedy, J. (2014). *Sharing in networked culture: Imagination, labour and desire* (Doctoral dissertation, PhD dissertation). Swinburne University, Melbourne).
- LaRose, R., Lai, Y. J., Lange, R., Love, B., & Wu, Y. (2005). Sharing or piracy? An exploration of downloading behavior. *Journal of Computer-Mediated Communication*, 11(1), 1-21.
- 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.

- McCourt, T., & Burkart, P. (2003). When creators, corporations and consumers collide: Napster and the development of on-line music distribution. *Media, Culture & Society*, 25(3), 333-350.
- 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.
- North, A. C. (2004). Uses of Music in Everyday Life. *Music Perception: An Interdisciplinary Journal*, 22(1), 41–77. <https://doi.org/10.1525/mp.2004.22.1.41>
- 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.
- 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.
- 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.