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

(Technical Paper)

Best Practices of Information Gathering for At-Risk Patient Populations

(STS Paper)

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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

Introduction

For most students of UVA, access to medical help is never too far away. With the UVA Medical Center less than a 5 minute walk from the Corner and the Elson Student Health Center open 5 days a week, it would be easy to assume that most residents of Charlottesville have this same access. In reality, this is not the case. With the vast improvements being made in medical research that have made treatments more effective, it is important to ensure that everyone has access to them. The technical portion of this paper will address the development of nanoliposomal therapeutics that intends to increase the efficacy of existing FDA-approved drugs for Head and Neck Squamous Cell Carcinoma. The research portion of this paper will address how to best identify populations of Charlottesville who are at-risk for various medical issues and are in need of medical intervention.

Technical Report

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 signaling 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 Thesis

Introduction

The Universal Declaration of Human Rights states "Everyone has the right to a standard of living adequate for the health and well-being of himself and his family including … medical care". This fundamental human right is not being granted to everyone, as disparities in healthcare have persisted for decades and are still apparent across the country. For example, in 2010, African Americans were 30% more likely than whites to die prematurely from heart disease and twice as likely to die prematurely from stroke (Office of Minority Health). Although often used to describe differences in racial or ethnic groups, these disparities can be also be attributed to gender, sexual orientation, age, socioeconomic status and many other patient characteristics. Several actions have been put into place to attempt to mediate healthcare inequities in racial or ethnic groups; however these methods often unwittingly cause harmful side effects. The Affordable Care Act intervened but was unable to ensure competition or price ceilings in many areas, causing many insurance premiums to increase dramatically (Weinstein, Geller, Negussie, & Baciu, 2017). This is the case in Charlottesville, where the sole ACA provider raised its premium costs by nearly 300%, making it the most expensive ACA insurance throughout the nation (Bluth, 2018).

It is evident that a better way to address the health disparities in Charlottesville is needed, one that is tailored to the community and makes healthcare accessible to more residents. To do so, I am going to attempt to **identify and understand the best methods to gather information on at-risk patients and other members of the Charlottesville community who require medical intervention.**

Literature Review

Electronic Medical/Health Records (EMR or EHR) first became implemented in the 1960s and have since become ubiquitous in healthcare organizations. These records were first used primarily in inpatient/outpatient centers and focused on gathering patient's billing and scheduling information. Now, they are used not only to track patient history but also for prescription orders, ordering procedures, and other clinical purposes. EMRs have also recently begun to be used as sources of data to make predictive analyses on patient populations, demonstrating the capacity for EMR data to be used in preventative measures. Data pulled from EMRs were used to construct a predictive model using metrics ranging from specific lab results to whether the patient had Medicare/Medicaid in order to predict the likelihood of readmission to

the hospital within a month (Amarasingham et al., 2015). Further, Healthcare organizations in Hawaii such as Hawaii Pacific Health have also recently adapted EMRs to include important information about social determinants of health in order to study their relationship with common acute care outcomes. One notable metric is the extent of a patient's social support and its effect on a patient's recovery of mobility. Physicians noted how much support a patient had in their home in addition to common metrics like level of physical activity while hospitalized and frequency of mobilizations, in order to gauge whether a caregiver would be given for post-discharge care (Trinacty et al.,, 2019). This adapted EMR system could similarly be modified to feasibly gather patient information for at-risk patients.

SCOT suggests that paying attention to relevant social groups and the way in which they define problems and solutions through technological intervention could be an effective way to alter EMR systems in such a way to identify risk in patients. In Charlottesville, relevant social groups include not only physicians, but emergency medical responders, nurses, and patients and their families. Preliminary interviews suggest that having in-depth conversations with members of each social group are an effective method to understand how these groups view at-risk patients and the factors that make them at-risk. An initial interview with a local emergency responder provided insight into his views on what the most prevalent emergency medical issues are (drug addiction, for example) and the values he believes should be emphasized in implementing any healthcare project (safety). This interview, among others, provides valuable insight into what information should be collected in this modified EMR system and how it can best be used to identify at-risk patients. Public outreach programs, such as the Hardy Drive Community Clinic in which Dr. Sharon Veith provides health screenings and support for chronic conditions in a low-income neighborhood, suggest that similar initiatives can provide information on at-risk patients by actively engaging with Charlottesville residents directly (Kueter, 2018).

Future work includes further refining the interview methodology. This involves conducting more interviews, specifically more with members of the Charlottesville community who have experience with at-risk patients and patients in order to refine our understanding of the realities of Charlottesville. In addition, we will look at more existing prototypes similar to Hawaii Pacific Health to learn more about what metrics are feasible to gather from patients to input into a modified EMR system. We will also look into more public outreach programs similar to the Hardy Drive Clinic to assess what medical issues are being addressed at these clinics and to which residents.

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.

Amarasingham, R., Velasco, F., Xie, B., Clark, C., Ma, Y., Zhang, S., … Halm, E. A. (2015). Electronic medical record-based multicondition models to predict the risk of 30 day readmission or death among adult medicine patients: validation and comparison to existing models. *BMC Medical Informatics and Decision Making*, *15*(1). doi: 10.1186/s12911-015-0162-6

Bluth, R. (2018, April 24). The City With the Most Expensive ACA Insurance in the U.S. *The Atlantic*. Retrieved from https://www.theatlantic.com/health/archive/2018/04/the-city-with-the-most-expensive-aca-insurance-in-the-united-states/558605/

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.

Kueter, C. (2018, September 18). Carrying on Edwards' Legacy, Nursing School Meets Patients Where They Are. *UVAToday*. Retrieved from https://news.virginia.edu/content/carrying-edwards-legacy-nursing-school-meets-patients-where-they-are

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.

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.

Office of Minority Health. (n.d.). Retrieved from https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlID=19.

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.

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.

Trinacty, C. M., LaWall, E., Ashton, M., Taira, D., Seto, T. B., & Sentell, T. (2019). Adding Social Determinants in the Electronic Health Record in Clinical Care in Hawai'i: Supporting Community-Clinical Linkages in Patient Care. *Hawai'i journal of medicine & public health : a journal of Asia Pacific Medicine & Public Health*, *78*(6 Suppl 1), 46–51.

Weinstein, J. N., Geller, A., Negussie, Y., & Baciu, A. (2017). *Communities in action: pathways to health equity*. Washington, DC: National Academic Press.