The Physiological Effects of Various Vasoactive Agents on Mouse Ear Microvasculature

(Technical Paper)

The Historical Significance of Viral Therapy and How it has Shaped the Current Field in Cancer Treatment

(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

In 2018 alone, 1,735,350 new cases of cancer were diagnosed in the United States and resulted in 609,640 mortalities ("Cancer Statistics," 2015). Cancer is one of the most common reasons for death in today's society. We have finally gotten to a point in civilization where technology has assisted us in living longer lives. However, as the average lifespan increases it results in increasing a person's chances of developing some form of cancer. Cancer occurs when cells do not follow a normal cell life cycle. Everyone has some degree of risk when it comes to cancer, though healthy lifestyle choices can minimize the risk. Unfortunately, for most cancers, the risk of development increases with age. Researchers are always taking steps to advance cancer treatment. Their efforts have paid off with the death rate due to cancer in the U.S. having dropped by 26% since 1991 ("The top 10 leading causes of death in the United States," n.d.). There are a multitude of cancer treatments—chemotherapy, radiation therapy, immunotherapy, antiangiogenetic therapy, and many more. All of these treatments come with their fair share of advantages and disadvantages. However, there is a new up-and-comer in cancer treatment—virotherapy. In laymen's terms, virotherapy uses biotechnology to convert viruses into therapeutic agents by reprogramming the virus to treat the disease ("History of Oncolytic Viruses: Genesis to Genetic Engineering—ScienceDirect," n.d.). Thus, giving patients a less toxic treatment plan than others like chemotherapy. It would also most likely be a onetime dose rather than all the other treatments that need multiple visits. Virotherapy has the potential of efficiently ridding the body of cancer, while also keeping patient suffering relatively low.

Much must be known about which virus would be best for oncolytic use before injecting a patient with it. However, in the plastic surgery field, they are constantly using vasoactive agents without knowing much more than whether or not the agent is vasoconstricting or

vasodilating. There is a clear need in this industry to know more about various vasoactive agents. It would be beneficial for the surgeons to know the base dosage, how long the drug stays in the system, if there should be multiple doses, physiological effects, and other side effects. A doctor would never just give you a random injection without knowing everything that it does; especially when concerning cancer treatments. So why are we allowing surgeons to use a vasoactive agent without knowing all the effects. A pair of UVA students will be studying the physiological effects of various vasoactive agents on mouse ear microvasculature. One of those students will also investigate the benefits of virotherapy over other treatments and potential obstacles to further advancement in this field.

Technical Topic

Plastic surgeons around the world use vasoactive agents multiple times a week for their procedures. Vasoactive agents are inotropes and or vasopressors. Inotropes are agents that increase adrenaline, dobutamine, ephedrine, and isoprenaline; leading to vasodilation. Vasopressors are agents that cause vasoconstriction (Hollenberg, 2011). Vasodilation widens the blood vessels due to the relaxation of the smooth muscle cells of the vessels. Arterial dilation leads to an immediate decrease in arterial blood pressure and heart rate ("Vasodilators—Mayo Clinic," n.d.). Vasoconstriction is the narrowing of blood vessels; thus, slowing the blood flow ("Vasoconstriction: MedlinePlus Medical Encyclopedia," n.d.). Both constriction and dilation of blood vessels have their places in this field. However, not much is known about these vasoactive agents outside of whether it is a vasodilator or vasoconstrictor; thus a surgeon using an agent may not truly known how long the drug stays in the system, whether or not there are other physiological effects outside of altering vasculature diameter, and the dosage depending on the procedure type.

Dr. Campbell and Dr. Cottler in the Plastic Surgery Department put forth a Capstone project focusing on the physiological effects of various vasoactive agents for Julia Riedy and Jill Bracaglia to pursue. The agents to be observed are nitroglycerin, diltiazem, papaverine, and lidocaine. These come in liquid forms as well as paste-like gel forms. First a model to replicate the physiological effect of each drug in the microvasculature of a mouse ear must be developed. A mouse ear is a well-established model for viewing and measuring skin microcirculation (Barker et al., 1994). It is also thin enough to image through and result in a high resolution in vivo imaging of blood vessel (Fu, Matthews, Ye, & Warren, 2008). The only difficulty of using a mouse ear, is finding a way to lay the animal for optimal imaging of the ear without too much pressure on said ear as to prevent disruption to the blood flow. Dr. Campbell uses vasoactive agents when transplanting tissue flaps amongst other reconstructive surgeries to ensure the success of reconstruction. A successful reconstruction depends partly on ensuring the vascular vessels, or pedicles, supplying the tissue are active and attached well ("Microvascular Lifeboats," n.d.)**.** Vasoactive agents can be directly applied to these pedicles to avoid spasming, kinks, or clots which can lead to thrombosis and ultimately failure of the reconstruction. Vasoactive agents are also applied topically to aid in healing after surgery followed by wrapping of the site. Nitroglycerin and diltiazem are more frequently used topically for tissue flaps, while papaverine and lidocaine are usually used for pedicle treatment (Zhang & Chen, 2016). However, currently there is not much known about the vasoactive agents he uses outside of whether they are vasoconstricting or vasodilating. It would be helpful to him and surgeons like him to know more about the other physiological effects on the microvasculature. It will also be useful for these doctors to know how long it stays in the system, base dosage, and cytotoxic dosage. Decisions of which drug to use also need to be based on patient specifics, such as

whether or not the patient has a history of smoking, or another condition that could negatively couple with a vasoactive agent to create a harmful effect to the patient. Deeper understanding of each of these vasoactive agents will aid doctors in making the right, informed decision that is best for their patient's specificities.

The project is currently using eight female, albino mice. They are all female to prevent male-to-male fighting within the cages. The mice will be albino mice because the produce the least amount of hair. The discussion of adding more mice has started; but it is dependent on the official experimental plan, and whether or not it follows clinical guidelines that Dr. Campbell sets forth. Doppler imaging technology will be utilized to image the ear. It does not simply take pictures of the mouse ear, but it examines the blood flow rate through the imaged vasculature. Once the mice have acclimated to the UVA vivarium setting, actual experimentation will begin. Followed by data analysis, possible reformatting of the project, development of a model of the microvasculature, true experimentation, true data collection and interpretation, and the development of a catalog to be used by other doctors and scientists.

By the end of the project, the goal is to create some sort of shared catalog. Various vasoactive agents and their physiological effects would be found here. Whether an agent was a constrictor or dilator, to what degree, base dose, how long it stays in the system, and other observations. Ideally, the developed model would be used by other doctors and scientist, so they can determine whether or not they want to use a certain vasoactive agent. These results would then be added to a catalog, to save another doctor or scientist the time of actually performing the experimentation.

STS Topic

Virotherapy uses biotechnology to reprogram viruses to treat diseases. In this case, the focus will be on using virotherapy as a cancer treatment. This field was discovered in the early 60's due to realizing some viruses have the capability of destroying tumors. At the moment, three oncolytic viruses, an echovirus, an adenovirus, and a herpes simplex-1 virus have passed governmental regulatory approval in Latvia, China, U.S., and EU ("The emerging role of oncolytic virus therapy against cancer—Russell—Chinese Clinical Oncology," n.d.). Oncolytic viruses are viruses that preferentially infect and kill cancer cells. As these infected cancer cells are destroyed via oncolysis, they release new virus particles to destroy the remaining tumor cells ("Oncolytic virus therapy for cancer," n.d.). This is initially why scientist began researching viruses for this purpose. A virus's only objective is to enter a cell, take control of the nucleus, stop all production of proteins, organelles, and other molecules and start producing more viral particles until the cell bursts releasing the newly made viruses ("Viral Oncolysis," n.d.). This sounds incredibly promising and an effective cancer treatment. However, only a few years after its discovery the field was abandoned for a few decades. Part of this was due to the limited technology of the time. But a larger component to the halt of research was the public's opinion and in turn funding of the field.

Back in the 70's and 80's, media was growing and becoming a large influence on the general public's outlooks (Turnbull et al., 2015). This was also when AIDS and HIV crisis was occurring and splashed across newspapers and the nightly news ("History of HIV and AIDS overview | Avert," n.d.). This was a period of fear not just of HIV, but of any virus. The public was terrified. And they could not accept the possibility of potentially contracting HIV or another deadly disease in the hopes of curing cancer. This led to the public turning against virotherapy due to fear. When the public turned its back, the funding also dried up. To better understand this

event, researchers in this field will be interviewed to see if they have any insight into the situation. It will also be beneficial to see how the situation transpired from the researchers' perspectives.

The Actor Network Theory will be extremely helpful in determining whether it was in fact the public's fear or the limitation of past technology that resulted in the gap in virotherapy progression. ANT tries to "open the black box" of science and technology (Cressman, 2009). It traces the relationships between governments, technologies, texts, money, and people. ANT is committed to examining the historical and social context and contingencies of scientific knowledge (Rodger, Moore, & Newsome, 2009). This is the perfect theory to utilize in examining the past research and societal views of it and comparing it to the present, to determine if there are any current day views or opinions that could be a potential obstacle for the advancement in virotherapy as a cancer treatment.

Research Question and Methods

It was in 1960, that scientist discovered that viruses were capable of destroying tumors ("A New Future: Gene Therapy," n.d.). At this time the technology was not quite advanced enough to pursue this as a treatment plan. Technology alone wasn't the only reason for halting further research in this field. The public and in turn the funding was not backing this field. This paper will be used to determine why the public was against virotherapy in the past and to see if there are any current day reasons that could potentially halt the research again. This will be done by analyzing public opinion through editorials, interviewing researchers in this field, and utilizing the Actor Network Theory (ANT).

Public opinion is essential to understanding why there was a two decade pause in virotherapy research. There are some present day editorials that show that not all of the general public is

onboard with the field of virotherapy. Ashley Bell wrote a piece entitled “Fighting Fire with Fire: Can Viruses Cure Cancer?” indicating that she is not that comfortable with this type of cancer treatment (health, Business, William, Mary, & Policy, 2014)**.** It also implies that she thinks this treatment plan would be dangerous to the cancer patients. Another author, David Gorski, made his stance on the topic very clear with the title of his article being “Rigvir: Another unproven and dubious cancer therapy to be avoided” (“Rigvir,” n.d.)**.** Luckily, most of the present day opinions are actually hopeful about this form of therapy and have relatively positive spins and outlooks when describing the field. Brian Vastag showed his support of the field by writing an article entitled “Cancer Therapy Goes Viral: Progress is Made Tackling Tumors with Viruses” (“Cancer Therapy Goes Viral: Progress Is Made Tackling Tumors with Viruses—Scientific American,” n.d.). Heidi Ledform wrote an article emphasizing the promise of using virotherapy to treat cancer and how there has been huge investments to the field recently (“Cancer-killing viruses show promise—And draw billion-dollar investment,” n.d.). Cardiff University has recently published an article discussing how this field as seen as a new hope for cancer patients (“Fully reprogrammed virus offers new hope as cancer treatment,” n.d.).

Interviewing researchers in this field would be incredibly beneficial to getting their perspective of why virotherapy experienced a lull in advancement for a couple of decades. They would be able to explain more fully how the field has changed and grown since its founding. These researchers could even point out some of the areas of virotherapy that may be concerning to the public.

Conclusion

With hundreds of thousands of Americans being diagnosed every year with some form of cancer, the scientific community must be dedicating huge portions of their funding, time, and

energy into pursuing treatments for this deadly disease. As there are dozens and dozens of different types of cancer and different stages of the disease, pursuing multiple treatment plans is ideal. One type of therapy may be a very efficient treatment for one type of cancer, but may have poor results when used on a different cancer. Every treatment plan comes with pro's and con's. Virotherapy is no different, as shown in this paper. However, it does have a promising future, and the possibility of working against various forms of the disease. Being able to understand why this research stopped for a couple of decades, allows scientists to prevent this lull of interest to happen again. Virotherapy has the potential of being a human changing field. By being able to cure multiple forms of cancer, it would ensure that humans live longer and better lives. It would also allow the scientific field to dedicate funding to other world issues like ending hunger, reversing the greenhouse gas effect, or discovering a more inexpensive form of desalinating salt water for public use. Virotherapy also has the ability to treat other forms of diseases, not just cancer. The public should be backing this field of research both financially and show public support as it will just improve patient treatments. Determining the physiological effects of various vasoactive agents will assist a surgeon's ability to effective treat a patient and minimize recovery time.

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