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

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Introduction Focusing on Virotherapy and Its Importance as a Cancer Treatment

In 2018, 1,735,350 new cases of cancer were diagnosed in the United States, resulting in 609,640 mortalities (*Cancer Statistics*, 2018). Cancer is one of the most common reasons for death in today's society. Unfortunately, for most cancers, the risk of development increases with age. As the average lifespan increases, so does a person's chances of developing some form of cancer. There are a multitude of cancer treatments; including chemotherapy, radiation therapy, immunotherapy, antiangiogenic therapy, and others. However, there is a promising cancer treatment called Virotherapy. All of these treatments come with advantages and disadvantages.

Virotherapy uses biotechnology to convert viruses into therapeutic agents by reprogramming them to treat the cancer giving patients a less toxic treatment plan than others, like chemotherapy (*History of Oncolytic Viruses: Genesis to Genetic Engineering—ScienceDirect*, n.d.). The Virotherapy treatment has the potential to become a one-time dose rather than all other treatments that need multiple doses. Ideally, Virotherapy can efficiently rid the body of cancer, while also minimizing patient suffering. This field was discovered in the late 1950s due to the realization that some viruses have the capability of destroying tumors. Oncolytic viruses 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.).

The oncolysis process is promising as an effective cancer treatment. However, only a few years after its discovery the field was abandoned for a few decades. Part of the reason why the field experienced a lull in advancement is due to the limited technology of the time, but a larger component to the halt of research is the public's opinion at the time and in turn funding of the

field. In the late 1970s and early 1980s, America entered a period of fear; not just of HIV, but of any virus (Turnbull et al., 2015). The general public was terrified and could not accept the possibility of potentially contracting HIV, or another deadly disease in the hopes of curing cancer. This cultivated fear led to the public turning against Virotherapy. When the public turned its back, the funding also dried up. In order to determine the reasons behind the lack of the public's support, public opinion is analyzed through review of editorials, interviewing researchers in this field, and utilizing Actor Network Theory (ANT).

Research Question and Methods:

Why was the field of Virotherapy abandoned after the 1960s until the early 1990s?

The field of Virotherapy was primarily abandoned in the late 1960s. However, there is uncertainty surrounding the reasons why this mass exodus occurred. There was limited technology at this time that may have prevented advancements within the field. There were also various cancer treatment plans that began vying for the federal research funding in the 1960s. In order to determine what led to the halt of advancements in Virotherapy, lead scientists within the field are interviewed for their unique perspective and intel. The funding of various cancer treatment research projects from the 1960s will also be reviewed. All the actants in this network will be analyzed using ANT. Delving into the funding of various cancer treatment projects in the 1960s will aid in determining where the majority of cancer research funding was going at the time. The House Committee of Science, Space, and Technology was in charge of delegating federal funds for scientific research (*History and Jurisdiction | House Committee on Science, Space and Technology*, n.d.). Media coverage regarding viruses, cancer, and potential treatments from the 1960s will be examined for negative connotations that may have influenced the general public against the field of Virotherapy. The UVA Virgo system in tandem with Google Scholar are

utilized to find said media coverage. Top scientists involved with oncolytic viral research are interviewed to give their unique perspective on how the field has grown since its founding. Dr. Timothy Cripe and Dr. Stephen Russell were asked if they were aware of the period of abandonment of the field of Virotherapy, if they believed the public had any influence on this halt in research, and what they believed led to this lull in field advancement. It is beneficial to ask the current day researchers about their mentors, as those were the people working in the field when it was abandoned. Actor Network Analysis is used to evaluate all of the findings and to determine what led to a halt in progress in Virotherapy research.

Background Information on Virotherapy, the Creation of the Field, and Its Subsequent Abandonment

Virotherapy is a treatment that manipulates viruses so they target and destroy cancer cells without harming healthy, noncancerous cells (Kirn, 2005). This field was discovered in the early 1960s when scientists realized that some viruses have the capacity to destroy tumors. (Turnbull et al., 2015). These viruses are known as oncolytic viruses. The virus's ability to induce oncolysis is the initial reason why scientists began researching viruses in the first place. As of today, only three oncolytic viruses have passed governmental regulatory approval in the U.S., the EU, China, and Latvia; an echovirus, adenovirus, and a herpes simplex-1 virus (*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.). 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

theoretically becomes a positive feedback loop, where the number of viral cells increases until eventually there are no more cancer cells for the aforementioned virus to target. While this process sounds like an effective cancer treatment, only a few years after its discovery, the field was abandoned for a few decades. The field most likely experienced this lull in advancement due to the limited technology of the time, however, a larger component to the halt of research in the field was the public's opinion turning negative due to media coverage of the HIV and AIDS epidemic in the late 1970s and early 1980s. The federal funding to this field diminished due to the negative connotation put upon the field from the general public.

After the 1950s, the media had successfully entered almost every household in the United States. Media just kept growing and becoming a greater influential force on the opinions of the general public (Turnbull et al., 2015). By the late 1970s, the nightly news was playing in practically every U.S. living room. At the same time, the HIV and AIDs crisis was gaining national attention and the nightly news and newspapers had cultivated a sense of crippling fear (*History of HIV and AIDS overview | Avert*, n.d.). This fear was no longer just associated with this one crisis. The general public was terrified of anything involving unknowns, especially surrounding the viral field. They were petrified of possibly contracting HIV, or any other deadly disease – even in the face of potentially curing cancer. This cultivated fear led to the public turning against the field of Virotherapy. With the public's negative outlook on the field, the funding began to dry up.

STS Framework Utilized to Analyze the Research Question

Investigating Virotherapy is a study for STS, as how the public and society at the time had an influence on the lull of advancement of the field is being reviewed. Both Politics of Technology and Actor Network Theory are being utilized to delve into this topic. Politics of Technology is applied to the analysis of the funding aspect, the House Committee on Science, Space, and

Technology, and the role both played in an abandonment of the field of Virotherapy for decades. ANT is employed to determine whether the public's opinion of the field or the limited technology of the time was a greater contributor to the lull in advancement of research into Oncolytic Viruses.

Politics of Technology studies how uncontrollable properties of certain technology are unavoidably linked to particular institutionalized power and authority (Winner, 1980). This theory shows how artifacts can be used to increase power of some over others. This theory is being applied to the House Committee of Science, Space, and Technology and those that were on the Science and Technology subcommittee during the late 1970s. I believe this displays how the bias of those on the subcommittee and their subsequent power over federal research funding led to the lull in advancement of the field of Virotherapy. Langdon Winner was a major contributor to the theory of Political Technology.

Actor Network Theory tries to "open the black box" of science and technology (Cressman, 2009). ANT 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). ANT 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. Bruno Latour and Michel Callon originally created this theory to consider all surrounding factors and show that no one truly works alone (Winner, 1980). Criticisms regarding this theory that must be taken into account when utilizing it are the absurdity of assigning agency to nonhuman actors, and that because it assumes all actors are equal, no accommodations for power imbalances can be made (Sayes, 2017). The latter being the more prevalent concern when analyzing the network surrounding Virotherapy in the late 1970s.

Results and Discussion

Virotherapy seemed to be a practically desolate research field in the late 1960s and 1970s. Virotherapy has exceptional promise as a cancer treatment; however shortly after its discovery, the field was abandoned. This abandonment is intriguing due to the potential of the field. However, the cause for this halt in advancement is not one clear cut cause; but due to two simple reasons: the limited technology of the time and the emergence of a "more effective" cancer treatment. Chemotherapy is a drug treatment that uses chemicals to kill fast-growing cancer cells. Chemotherapy was discovered in the 1940s by Sidney Farber (Miller, 2006). By the early 1960s – when the Virotherapy field was just beginning – metastatic cancer had been cured using a chemotherapy drug. Throughout this decade, chemotherapy was curing patients with Hodgkin disease, childhood acute lymphoblastic leukemia, and even testicular cancer (*Evolution of Cancer Treatments*, n.d.). This treatment plan was easier to develop than that of oncolytic viruses; especially in the 1960s with the limited technology. CRISPR Cas9, the gene therapy needed to accomplish the creation of an oncolytic virus capable of targeting specific cancer cells was not fully developed.

On February 18th, 2020, Dr. Stephen Russell, a M.D., Ph.D. at the Mayo Clinic, discussed the current state of the Virotherapy field, his research into Oncolytic viruses, and his perspective on the decades of lack of advancement (*Stephen J. Russell, M.D., Ph.D.*, n.d.). On February 19th, 2020, Dr. Timothy P. Cripe, a M.D., Ph.D. at The Ohio State University, was interviewed on his cutting edge research and his interpretation of the cause of the lull in the Virotherapy field in the late 20th century (*Dr. Timothy P Cripe—Cancer Researcher at OSUCCC - James*, n.d.). The specific questions asked during the interview can be found in the Appendix. Through the line of

questioning and the responses given it was determined that the limited technology in the field of Virotherapy and the successful alternative cancer treatment options led to the abandonment of the field of Virotherapy from the late 1960s to the mid-1980s.

Limited Technology

Dr. Timothy Cripe believes that the limited advancement of genetic engineering in the 1940s and 1950s led to a period of almost complete field abandonment in Virotherapy (Timothy Cripe, personal communication, February 19, 2020). The targeted properties that are associated with oncolytic viruses today, would not have been possible in the 1970s let alone when the field was first gaining ground in the 1960s. Genetic engineering is a cornerstone of the field of Virotherapy. CRISPR Cas9 is today's most common form of gene editing. The CRISPR technology allows genetic material to be added, removed, or altered at specific locations in the genome. This system is composed of short palindromic repeats and the CRISPR-associated protein 9. The CRISPR methodology was first published in 1987, and the first publication included the coined phrase of 'CRISPR-Cas9' was in 2002 (Doudna & Charpentier, 2014). Virotherapy has utilized this ability to force the evolution of viruses with greater tumor specificity (*History of Oncolytic Viruses: Genesis to Genetic Engineering—ScienceDirect*, n.d.). It wasn't until the employing of reverse genetics that brought a fresh wave of interest in Virotherapy. The reverse genetics done using CRISPR-Cas-9 allowed for a generation of more tumor-specific and potent oncolytics by the viruses. Thus, it is clear to see that in the 1960s until the late 1980s, the technology was not quite advanced enough to create oncolytic viruses that could target cancer. In the 1960s until the creation of CRISPR, oncolytic viruses were just viruses that happened to display some level of oncolysis. Virotherapy at this time was injecting humans, mice, rats, rabbits, and guinea pigs with viruses to determine if said virus was capable of causing some degree of

tumor regression (Southam, 1960). However, at the time medical ethics were not being considered with testing of Virotherapy; which will be further discussed in the 'Leader in the field of Virotherapy' section. Even though there was at best suggestive regression of tumors in a few of the very early clinical trials of the late 1950s and early 1960s, there were still many remaining questions that were unanswered. How many viruses have the capacity for oncolysis? What mechanisms does a virus use to cause tumor destruction? And the biggest question left unanswered until the 1980s – Can the capacity for oncolysis be induced or enhanced by manipulation? (*History of Oncolytic Viruses: Genesis to Genetic Engineering: Molecular Therapy*, n.d.; Southam, 1960).

Rise of Alternative Cancer Treatments

Dr. Stephen Russell believes that the abandonment of Virotherapy was due to the ease of using chemotherapy that helped alter the scientific world's attention away from treatment plans like Virotherapy and focus more on effective routes like radiation and chemotherapy (Stephen J Russell, personal communication, February 18, 2020). The capability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin's disease in the 1960s and early 1970s proved to the scientific world that drugs could cure advanced cancers (DeVita & Chu, 2008). The success of chemotherapy was occurring at the same time as scientists in the field of Virotherapy were simply injecting viruses into test subjects to determine if there was any degree of oncolysis occurring. Chemotherapy was successfully curing patients with advanced cancer; while oncolytic viruses were causing momentary regressions in the tumor advancement. Radiation therapy was also taking off in the 1960s. Radiation therapy is a treatment modality using high energy rays or radioactive substances to damage tumor cells and halt their growth and division. In the 1930s, the Westminster Hospital started telecurietherapy with the radium bomb from 1929. In May 1960, megavoltage therapy was introduced into medical practice using 20 MV and 4 MV

radiation. By 1963, discussion of the design of radiation therapy departments was well underway (*Radiotherapy in the 1960s—British Institute of Radiology*, n.d.). The 1970s and 1980s were characterized by the introduction of new medical devices delivering proton beams. Radiotherapy had become a recognized medical discipline and the first radiologist associations were being founded. The use of ion beams allows a controllability to the treatment, making radiation therapy a superior tool for cancer therapy due to its newly enhanced localization properties (Gianfaldoni et al., 2017). There were many more successful options for cancer treatment in the 1960s that took the spotlight and allowed Virotherapy to be placed on pause and the field to experience a period lacking progress.

Cancer Research Funding

In 1954, the Senate Appropriations Committee appointed $1 million to the National Cancer Institute (NCI) to develop a program and anticancer drugs. However, in 1955 philanthropist Mary Lasker, who worked closely with Sidney Farber, convinced the Senate Appropriations Committee to provide $5 million to NCI for the establishment of the Cancer Chemotherapy National Service Center (CCNSC) (DeVita & Chu, 2008). $5 million in 1955 is the equivalent of $48 million today (*Calculate the value of $1,000,000 in 1955. How much is it worth today?*, n.d.). This money was used for commercial discreet agreements with the industry, access to clinical testing facilities, and the establishment of contracts with organizations to produce mice and testing sites (DeVita & Chu, 2008). In the 1960s, the Senate Appropriations Committee was composed of John Pastore (D-RI), Spessard Holland (D-FL), John Stennis (D-MS), Lister Hill (D-AL), Chairman Carl Hayden (D-AZ), and Margaret Chase Smith (R-ME) (*U.S. Senate: Appropriations Committee*, n.d.). From the 1920s until the early 1970s, Senate appropriators reviewed agency submissions by holding meetings behind closed doors to protect them from outside lobbying pressures. However in 1974,

congressional appropriators supported the passage of the 1974 Congressional Budget and Impoundment Control Act which created the Senate and House budget committees, the Congressional Budget Office, and the requirement for annual budget resolutions ("A History of the Senate Appropriations Committee / U.S. Capitol History | USCHS," n.d.). By 1974, the CCNSC had grown into an annual budget of $68 million (DeVita & Chu, 2008). It is clear that Chemotherapy received a large amount of funding even before the discovery of the field of Virotherapy, and continued receiving this funding during the early years of Virotherapy and in the years following its abandonment. During the HIV and AIDs epidemic of the 1980s and the 1990s, Dr. Russell explained that funding for Virotherapy actually increased due to the public's fear of all things associated with viruses (Stephen J Russell, personal communication, February 18, 2020; Timothy Cripe, personal communication, February 19, 2020). A financial dump into research in HIV occurred to aid in the understanding and potential interruption of its life cycle (Green, 2011). This precedent of researching and manipulating viruses, helped with the revival of the field of Virotherapy.

Leader in the Field of Virotherapy

Chester Southam was a leading figure in immunology, oncology, and virology starting in the 1950s. Southam was a respected clinical investigator at the Memorial Sloan-Kettering Cancer Center (Lerner, 2004). From the mid-1950s to the mid-1960s, he conducted clinical research on people without their informed consent, in which he injected cancer cells into their skin to see the immune response (Langer, 1964). The word 'cancer' was never said to the patients injected. Southam believed that there was no risk that the cancer would develop and that the word 'cancer' caused "bizarre, defensive" reactions from the patients; which is why he omitted using the word 'cancer' for their sake (Lerner, 2004). In 1963, Southam was reported to the Regents of the

University of the State of New York which found him guilty of deceit, fraud, and unprofessional conduct. He was placed on probation for a year (Langer, 1964). In the 1950s, Southam tested a potential Virotherapy—West Nile Virus—by injecting it into over 100 terminal cancer patients. Some of the patients showed good results; however, some patients developed severe cases of West Nile fever. Even though his ethics are very questionable, he became the unwanted father of Virotherapy. After his West Nile Virus experiments, Southam researched if he could "train" the virus to only kill cancer cells and do so without the side effects of chemotherapy (Sepkowitz & M.d, 2009). Due to Southam's unethical experimentation and the media coverage, the field of Virotherapy took a hit to its image, reputation, and advancement of the field.

Public Opinion

Southam's research was conducted during a time when cancer research was closely followed in mainstream media. Southam's experiments and the case at the Regents were reported in the New York Times ("14 Convicts Injected With Live Cancer Cells," 1956; "Many Scientific Experts Condemn Ethics of Cancer Injection," 1964; "RULING IS UPSET ON CANCER TEST; Appellate Count Bars Data to a Hospital Director," 1964; "SCIENTISTS SPLIT ON CANCER TESTS; Some Back Use of Humans—More Humility Urged," 1964; Sepkowitz & M.d, 2009; Times, 1957). In 1964, Brooklyn's Jewish Chronic Disease Hospital (JCDH) was the location of Southam's experiments. The hospital's staff was being compared to Nazi physicians who had performed brutal experiments in concentration camps (Lerner, 2004). One of the JCDH's board of directors, William Hyman, termed Southam's experiments as "acts which belong more properly in Dachau" (*Experimentation with Human Beings | RSF*, n.d.; Lerner, 2004). However, according to both Dr. Russell and Dr. Cripe, the public was relatively unaware of the Virotherapy field (Stephen J Russell, personal communication, February 18, 2020; Timothy Cripe, personal

communication, February 19, 2020). While the public was disgusted by the experiments being conducted on patients without their informed consent by Southam, the public was more focused on the ethics and not the experiments themselves or the findings. Today, there is more media coverage of Virotherapy; both good and bad. Ashley Bell's piece entitled "Fighting Fire with Fire: Can Viruses Cure Cancer?" indicates that she is not comfortable with this type of cancer treatment (health et al., 2014). Bell's paper also implies that she thinks this treatment plan is dangerous for cancer patients. However, not everyone shares Bell's pessimistic views. Heidi Ledform emphasizes the promise of using Virotherapy to treat cancer and how there are huge investments in the field recently (*Cancer-killing viruses show promise—And draw billion-dollar investment*, n.d.). Both Dr. Cripe and Dr. Russell agree that today media coverage has more of an influence over the field of Virotherapy than it has in the past. Both are not that worried about public perception; but instead are more concerned with the data (Stephen J Russell, personal communication, February 18, 2020; Timothy Cripe, personal communication, February 19, 2020).

STS Framework

Politics of Technology is applied to the analysis of the funding aspect, the House Committee on Science, Space, and Technology, the Senate Appropriations Committee and the role they played in an abandonment of the field of Virotherapy. Politics of Technology studies how uncontrollable properties of a specific technology are unavoidably linked to a particular institutionalized power and authority (Winner, 1980). This theory shows how artifacts can be used to increase power of some over others. Almost everyone that was on the Senate Appropriations Committee in the 1960s was a Democrat making them politically more inclined to dedicate greater amounts of money to scientific research (*U.S. Senate: Appropriations Committee*, n.d.). This theory must be utilized when considering any scientific research, because funding is government

led. With the government controlling most of scientific research funding, then the government has a certain degree of control and say over the research being conducted.

Actor Network Theory is employed to determine whether the public's opinion of the field or the limited technology of the time was a greater contributor to the lull in advancement of research into Oncolytic Viruses. ANT tries to "open the black box" of science and technology (Cressman, 2009). ANT 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). ANT is used to examine 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. Bruno Latour and Michel Callon originally created this theory to consider all surrounding factors and show that no one truly works alone (Winner, 1980). In this system the actants mainly focused on are the interviewees, the government agencies, alternative cancer treatments and limited technology. Alone, the actants of alternative cancer treatments and limited technology would not have led to a period of halted progress in Virotherapy. It is together that these actants work together to cause the abandonment of the field seen in the late 1960s.

Limitations

In attempting to answer what caused the abandonment of Virotherapy from the late 1960s to the mid-1980s, a few limitations were run into. When researching the government funding of cancer research surrounding said time frame, it was difficult to find records indicating cancer treatments outside of chemotherapy. Many of the government records of funding are challenging to track down for the correct subcommittee, time frame, and cancer research field. Another limitation that must be taken into account are the biases held by the interviewees—Dr. Stephen

Russell and Dr. Timothy Cripe. The latter showed a prejudice against Chester Southam, while Dr. Russell held Southam in a slightly more positive light due to Russell pursuing his PhD in a London lab that was affiliated with Southam. The study may benefit from interviewing more of the leading scientists in the field, or potentially contacting their mentors as they would have been in the field prior to the period of abandonment. There are also limitations associated with Actor Network Theory. ANT assumes that all actors are equal however as this paper has shown that some actors—limited technology and alternative cancer treatments—affect a system more than others do. ANT makes no accommodation for this power imbalance. ANT also assigns agency to nonhuman actors; which can be difficult to account for in a system especially concerning the power imbalance that would be seen between human actors and nonhuman actors (Sayes, 2017).

Future Works

For those that wish to continue this research there is much that can still be analyzed. A deeper analysis of the government funding distribution in 1960s cancer research. Many of the documents that can be accessed by the public focus mainly on the funding surrounding the field of chemotherapy. It would be helpful to see how the funding is broken down across various cancer treatments. It may even be beneficial to see if the funding decreases after the media circus encompassing the Southam human experiments. If that is found to be true, it would support the claim that the public did have some degree of negative influence on the advancement of Virotherapy. There were also a few scientists that continued with their oncolytic viral research during the period of field abandonment, that could be researched further to deduce why they stuck with the field when most others did not, what research they were able to conduct with the limited technology, and what sort of funding they were receiving at this time (Ammayappan et al., 2016).

Conclusion

After interviewing leading scientists in the field of Virotherapy, Dr. Russell and Dr. Cripe, conducting research in historical leading figures, alternative treatments for cancer, the funding of cancer research, and analyzing with ANT, it can be concluded that the limited technology of the time and the success of alternative cancer treatment plans led to a period of abandonment in the field of Virotherapy. It is important to determine the leading causes of the halt to progress of Virotherapy because it explains why there are not more approved oncolytic viruses today, and why this promising field is not as advanced as one would expect. Knowing the reasons behind the abandonment of the field, can help scientists in Virotherapy prevent another mass exodus of the field. These findings may also offer other researchers an insight into potential threats to the progress of Virotherapy in the future.

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