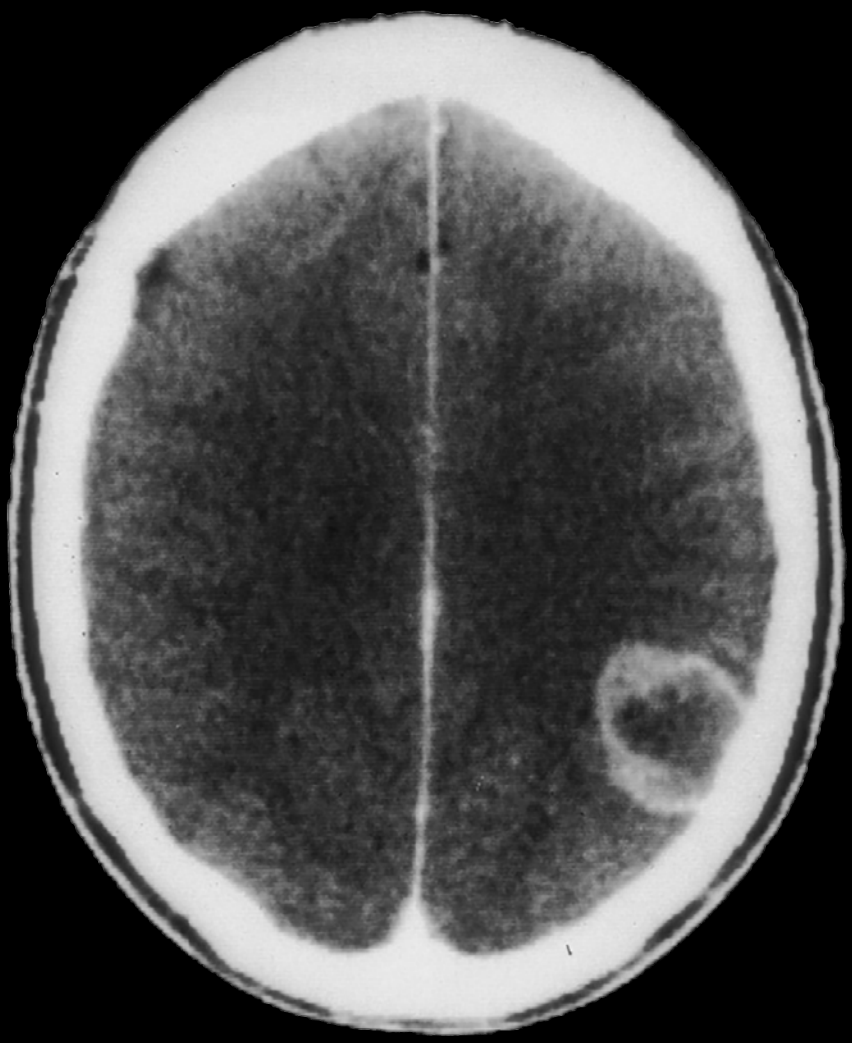
The Enemy of My Enemy is My Friend?

How Viruses Can Be Used to Treat Brain Cancer

by Kai Wilczewski-Shirai



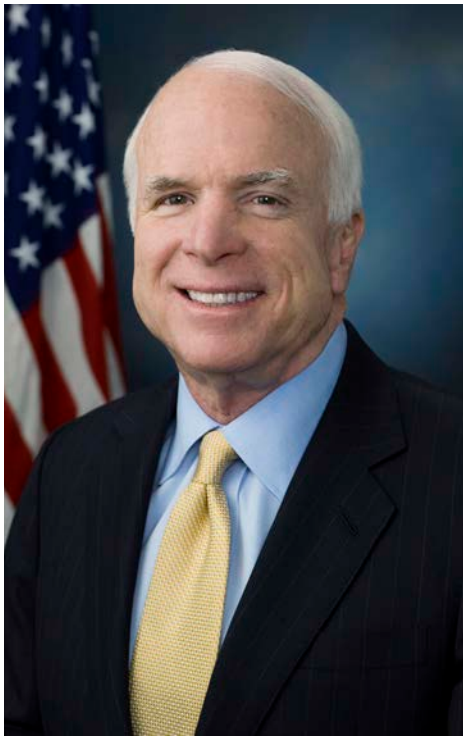
Glioblastoma tumor. Photograph by Sydney S Schochet, MD. MedPix.

Brain cancer: two words you never want to hear together. Even with all of the different kinds of cancer, brain cancers represent some of the deadliest cancers known to humanity, with an average 5-year survival rate of only 36%.[1] There are many different subtypes within brain cancer, but one of the most famous subtypes is glioblastoma multiforme (GBM). Although you may not have heard of it by that particular name, this cancer gained notoriety in 2018, as it is the cancer that claimed the life of the former United States Senator John McCain. GBM is the most commonly occurring primary malignant brain tumor, accounting for 80% of all primary brain tumors and 60% of all brain tumors.[2] It is also known for being one of the most lethal and aggressive forms of brain cancer, with only 5.5% of patients surviving more than 5 years from the time of diagnosis.[3] Still, there may be a glimmer of hope. Researchers have found that cancer patients who contracted certain viruses actually had increased survival. Even some of the deadliest viruses in the world have shown potential to help increase survival in patients that contracted them. Could our villains of yesterday be our saviors of tomorrow? Could it be that the enemy of my enemy is my friend?

Consequences of Glioblastoma

Although the poor survival rate of GBM is enough to darken anyone's day, the disease unfortunately comes with even more problems. Most, if not all, patients who somehow survive the disease are subject to debilitations that cripple them for life. Most long-term survivors of GBM have reported to suffer from crippling fatigue, which severely affected their quality of life. For adult long-term GBM survivors, many faced physical, psychological, and cognitive declines. Survivors suffer from impaired motor function, both in respect to coordination and speed. Also, sustained attention and the ability to maintain meaningful social relationships are found to be reduced in long-term surviving adults. For long-term GBM survivors that were children, there were very few of these negative effects. They displayed few, if any, cognitive deficiencies. Researchers believe that when the GBM tumor subsides more quickly, many of these negative impairments are avoided. There has been little evidence to suggest that a correlation exists between these effects and tumor location, leading researchers to believe that these consequences can arise regardless of the tumor location.[4]

Other than the direct effects of the tumor itself, patients also experience psychological problems from the knowledge of simply having a tumor residing in their brains. When notified about the length of treatment and the uncertainty of the treatment even working, patients frequently experience a downward trend in overall mood. The financial burden of the disease also affects the mental health of GBM patients significantly. This is considered exceptionally prevalent for GBM cases in Western countries, such as the United States, where social support for medical illnesses by friends and family is not as consistent as in countries like India, based on societal reactions to terminal diseases. Culturally in the United States, there is less of a desire for broader social networks, like friends and family, to constantly be in contact with patients who are in the hospital. In other places, it is more common for a wider range of friends and family to be invested in the health of the patient.



John McCain's official portrait. Public Domain.

There is also evidence to show that depression and GBM are linked directly to one another. Although psychological reasons for depression are prevalent, there are also mechanisms for the manifestation of depression based on the progression of GBM. Historically, the increase in depressive behaviors in GBM patients had been overlooked, as the depression of GBM patients seemed logical simply because it is a stressful disease.[5] Yet, depressive behaviors were found in GBM patients even prior to the patient learning of their diagnosis, suggesting that the emergence of both diseases are connected. Although there are many different ways that depression is caused in cancer patients, GBM is known mainly to cause depression by limiting the amount of serotonin in the brain. There are a variety of neurotransmitters—molecules that can induce responses in neural cells—and serotonin is the neurotransmitter that is essential for happiness and stabilizing the mood of healthy individuals. Serotonin

is also implicated in regulating sleep and hunger. It seems clear that having reduced serotonin in the brain would have serious consequences on the well-being of an individual, and GBM does just that. This is because GBM cells have increased activity of an enzyme called IDO.[6] IDO is responsible for converting tryptophan, a protein amino acid, into a molecule called kynurenine. This is problematic for one reason: tryptophan is also the precursor for serotonin. When IDO is highly active, like it is in GBM, there is not as much tryptophan available to be converted into serotonin, leading to a reduction in the serotonin produced.

To better illustrate the cause and effect of GBM causing depression, we will consider a pipe. Tryptophan is being put in one end of the pipe, and serotonin is coming out of the other side. When there is about as much serotonin coming out as the tryptophan that you are putting in, you are happy that there is sufficient serotonin being made and all is well. The increased IDO activity is like if there was a leak in that pipe, and some of the tryptophan you put in the pipe does not make it to the other side as serotonin. Instead, it is lost as something else (Figure 1). This reduced serotonin leads to unstable mood and depression. Depression has also been linked to significant decreases in GBM survival, so physicians must try to combat the two diseases at once.[7]

The Fight Against Glioblastoma

The poor prognosis of GBM does not reflect the amount of time and money put into researching therapies for it. Researchers have tried for many years to develop new therapies with the hope of improving the survival of patients diagnosed with GBM, yet they have had little success.[8] Currently, the standard of care treatment involves a combination of chemotherapy, surgery, and radiotherapy. In most cases, surgeons cut out as much of the tumor from the brain as possible before using radiation to try and kill off any remaining cancerous tissue. The patient is

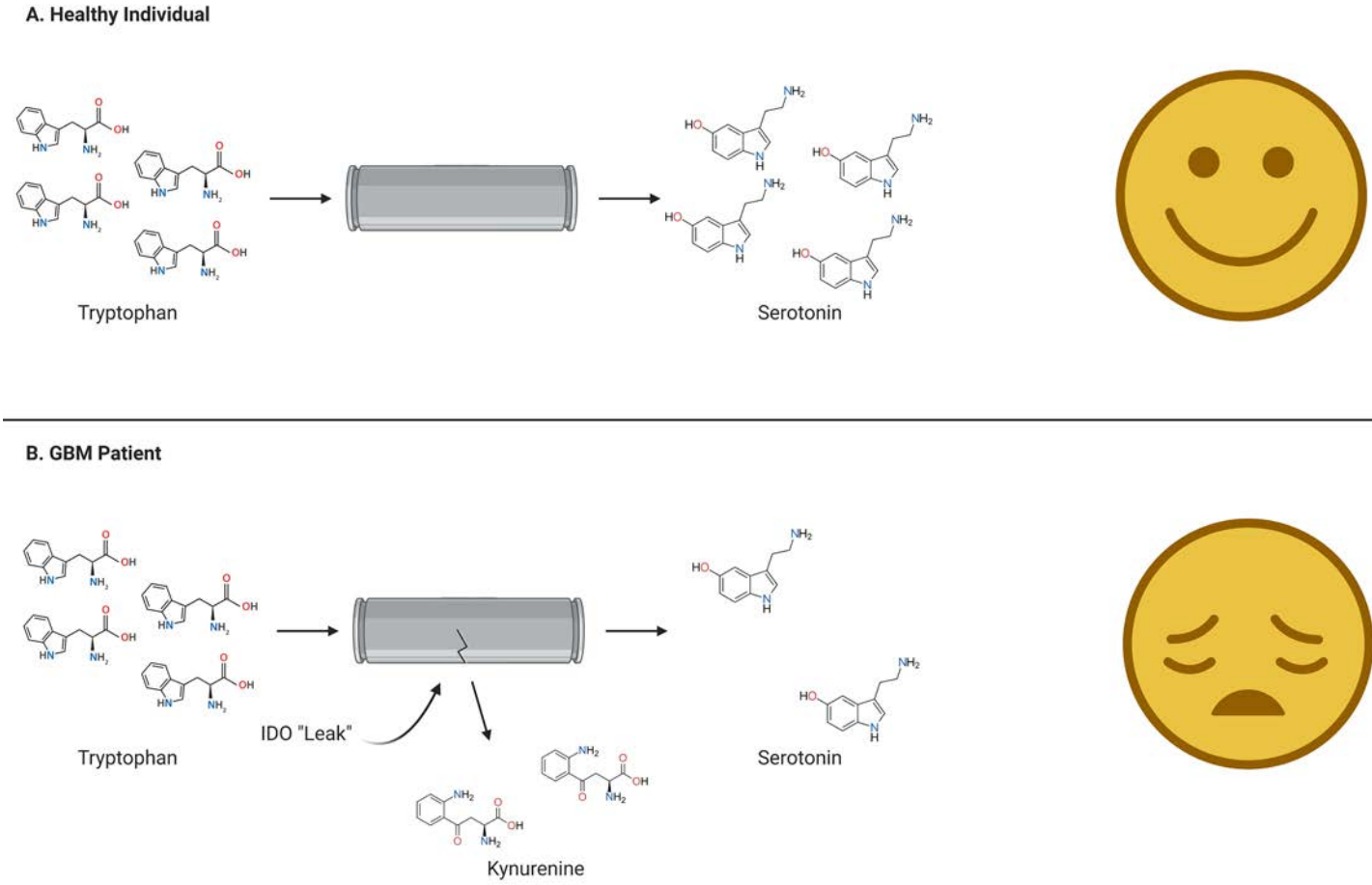
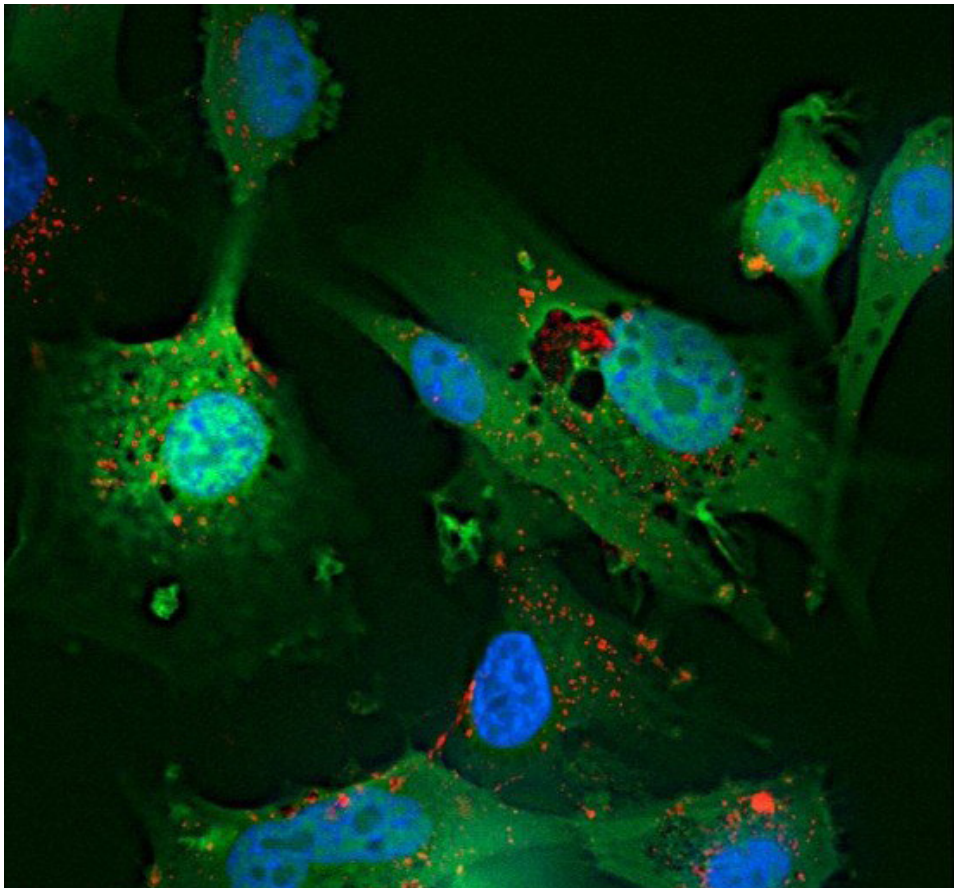


Figure 1. Mechanism of depression in GBM patients. A) Healthy individuals do not have the IDO "leak," and therefore can produce sufficient amounts of serotonin. The sufficient amounts of serotonin are enough to keep the individual happy and stable. B) GBM patients have increased activity of the IDO enzyme/leak, which causes some of the tryptophan to not be converted into serotonin. The insufficient production of serotonin causes depression in GBM patients. (Created with BioRender.com. Figure by Kai Wilczewski-Shirai, licensed under CC BY-NC-ND 4.0.)

then usually given a regimen of drugs to take in an attempt to stop the tumor from growing back. This approach has a multitude of problems. One of the reasons GBM is so deadly is because the tumor penetrates deep into healthy brain tissue, making it difficult to remove significant amounts of the tumor without doing significant damage to the rest of the brain. In fact, relapse occurs in 80% of patients after attempts to surgically remove the cancer, where the new tumor is found within 2 cm of the original. Radiation is also problematic since it indiscriminately destroys tissue, affecting healthy brain tissue as well as cancerous brain tissue.[3]

In addition to surgical removal and radiation, chemotherapy also comes with its fair share of limitations. Many drugs that can be used for other cancers are found to not be as effective in treating GBM. This is partially due to the blood-brain barrier (BBB), which prevents many drugs from reaching the target tumor in the brain. As the BBB prevents a large proportion of a drug dose from entering the brain, it is necessary to administer a high dosage so that an adequate amount of drug can reach the tumor. Otherwise, the drug may be ineffective against the brain tumor. However, these very high doses tend to be intolerable for the patient's body as a whole, causing harm in other areas of tissue. The most frequently used drug in chemotherapy is temozolomide, which damages the DNA in cancer cells, thus reducing their viability. This drug has still been found to be insufficient because many GBM cells express a protein called AGT, which can repair the DNA damage done by temozolomide.[3]

The current approach to treat GBM is a long and painful process by which the cognitive consequences are worsened, since treatment damages healthy brain tissue as well. To avoid long-term impairments in quality of life, it has been clear for some time that different treatment approaches are needed.



Glioblastoma cells transfected with green fluorescent protein in culture. Image by Alex Gray. Cell Image Library doi:10.7295/W9CIL38961

Viruses as Potential Therapy

The idea of using viruses as cancer therapies is not new to the medical world. While the use of viruses to treat cancer may sound like a crazy idea, the logic and evidence behind it is sound. In the early twentieth century, a viral outbreak in a cancer ward led to an unprecedented increase in the health and survival of those cancer patients.[9] Later, using data from the World Health Organization from 1955-2008, it was discovered that individuals with cancer who were also infected with the malaria virus had greater survival compared to their counterparts who did not have malaria.[10] Intrigued by this phenomenon, researchers began to suspect that something about viruses helped the body fight off cancer, perhaps by eliciting an immune response in the body. The researchers weren't wrong, but they were far from uncovering the full picture. After years of greater examination, it was discovered that viruses did indeed elicit an immune response, but were also the agent directly responsible for the destruction of cancer cells.

As viruses have evolved over millions of years, they have gained the ability to target specific types of cells while leaving most, if not all, other cells unaffected. Taking advantage of this natural selectivity has given researchers an exciting new way to make safe therapies for a variety of diseases.[11] As there are many different types of viruses that only affect certain tissues, there are many different types of cancers that have the potential to be treated this way.

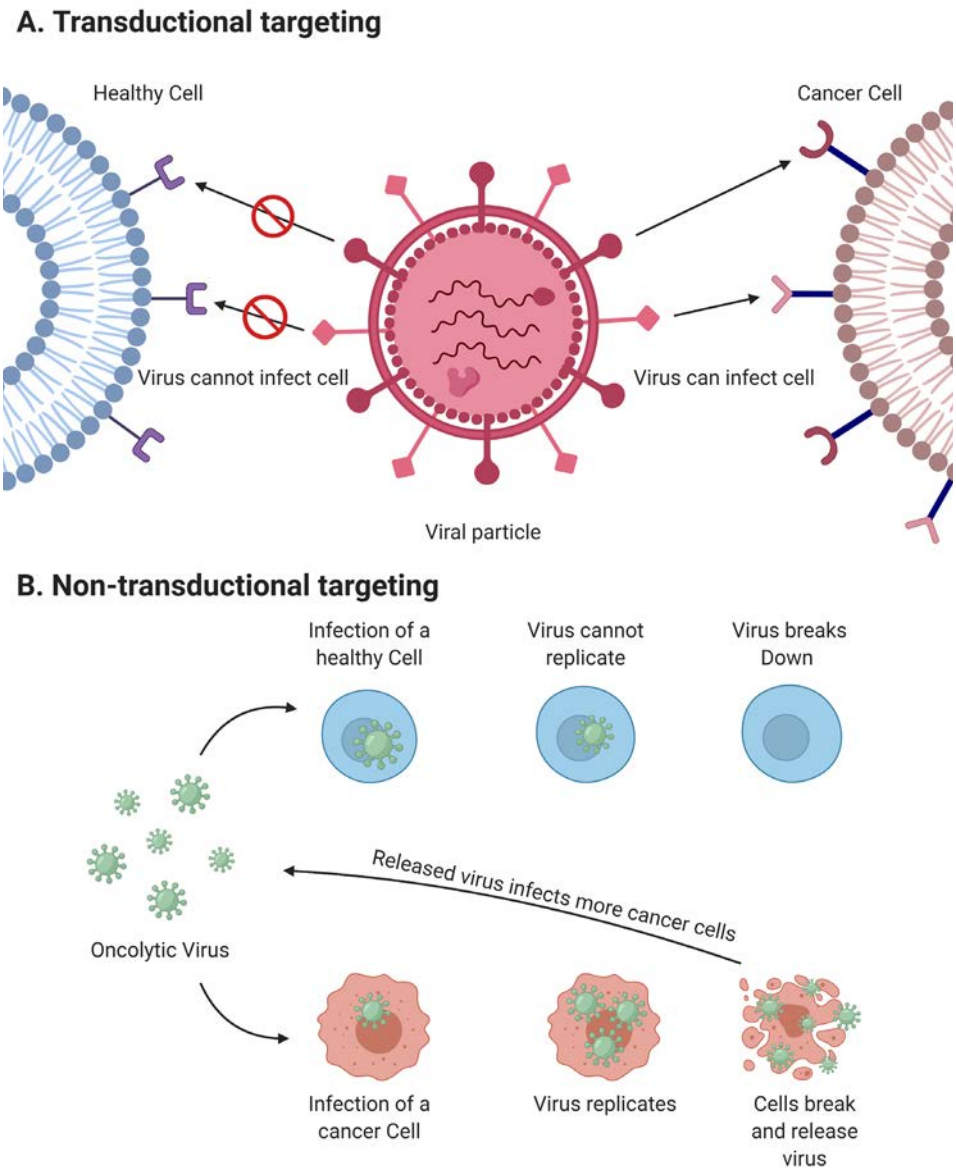


Figure 2. Common strategies for how viruses can be made to affect only cancer cells. A) The transductional targeting strategy involves using/making a virus that can only infect cancer cells due to having ligands that only interact with specific cell surface receptors. If the ligands on the virus correspond to the receptors, then the virus can infect the cell. If the ligands do not correspond to the cell surface receptors, then the virus cannot infect and harm the cell. B) The non-transductional targeting strategy involves giving viruses specific proteins and machinery, so that they can only replicate inside certain cells. In a healthy cell, the infection leads to an unharmed cell. In cancer cells, the virus can replicate and eventually lead to cell lysis, which releases more viral particles to kill more cancer cells. Original image by Kai Wilczewski-Shirai. Created in BioRender.

The specificities of viruses can overcome many of the obstacles that prevent most other therapies from being effective. As viruses can destroy specific cells while unharming other cells; they can exclusively destroy cancerous cells that penetrate deep into healthy tissue. The same specificity also eliminates the need for an abundance of therapeutic agents in order to reach the target tumor.[12] Viruses can multiply by destroying target cells, so a single viral particle can be sufficient to start the treatment of entire tumors. This is because once the virus multiplies, it can destroy even more cells, much like a domino effect.

In comparison to the previous methods of treating cancer, viral therapies have been found to be fairly fast acting, with significant improvements occurring to the patients' health within a month. This means that many individuals afflicted with GBM could be spared from the cognitive and physical after-effects of GBM by using viral therapies.[13]

How Are Viruses Engineered to Attack Only Cancer Cells?

Although there are viruses that have been found to naturally attack cancer cells, most of the time researchers must engineer viruses to ensure the harm of only the cancer cells. There are two main strategies that researchers use to achieve this. The most common approach is called transductional targeting. Viruses have components that bind to specific receptor proteins, which are located on the surface of cells, called ligands. These ligands can only bind to certain receptors, and if a virus cannot bind to these receptors, they cannot enter or infect the cell.[14] Therefore, by engineering viruses to have ligands that only bind to receptors found on cancer cells and not healthy cells, researchers can make viruses that do not harm healthy tissue (Figure 2A). To further explain this idea, imagine that the virus is a person with a key and that all of the cells are locked houses. The person cannot enter all of the houses because they don't have the correct key for each house, but the person can enter the house with the corresponding key. The ligands of the virus act like this key, and so researchers can make viruses target certain cells by only giving them the "keys" to certain houses/cells.

The second strategy is called non-transductional targeting. This strategy involves giving viruses special molecular proteins that are needed for the virus to replicate once they enter the cell. The virus is allowed to infect cells freely,

but the proteins these viruses have determine which cells will be harmed. These proteins can only be used inside specific cells, exclusively allowing the virus to replicate inside and kill those cells. If the virus is inside a targeted cell, like a cancer cell, the proteins in the virus will allow it to replicate.[14] Then, the cell will lyse, or break open, releasing the replicated viral particles and allowing them to infect additional cells.[15] Cells that are not compatible for the replication of the virus can be infected, but are ultimately unharmed (Figure 2B). To better understand this, let's go back to the house metaphor, except in this case let's imagine that the people/viruses are burglars. The burglars can get into all the houses, but while they are in the house, they encounter a security system. Depending on the equipment they brought with them, they can either continue the burglary or they are stopped by the security system. The specialized equipment can only work on certain security systems. Researchers can give the viruses/burglars special proteins/equipment that will allow them to kill/burgle certain cells/houses.

It is common for researchers to employ both of these strategies at the same time. By engineering the virus to only infect certain cells and to only replicate inside certain cells, we can be even more sure that the virus will selectively kill just the targeted cells. In this way, even the deadliest viruses can be turned into safe and powerful therapeutics to treat brain cancer.

Cases of Success

As of today, there has only been one viral therapy approved by the FDA to treat cancer, which is a modification of the herpes simplex virus to treat melanoma, or skin cancer. Regardless, there has recently been a lot of promise in the use of viruses to treat GBM.[16] One of the most well-known cases of this is the use of Zika to kill GBM cells. This virus, which causes birth defects, Zika fever, and Guillain–Barré syndrome, has shown promise as a potential therapy for GBM.[17] There are studies showing that Zika only infects GBM cells when added to a dish containing both GBM cells and healthy neural cells.[18] Although Zika has not gone through the rigorous clinical trial process that would allow it to be approved for widespread use, the preclinical results point strongly to the safety and efficacy of the virus as a tumor-busting therapeutic. At the very least, Zika has been shown to make cancer cells more sensitive to a variety of other cancer drugs, meaning that safer, smaller drug doses can be used to treat GBM when used with Zika.

In addition to Zika, Newcastle disease virus, a contagious viral disease known to mainly affect birds, has also been found to have some success in treating GBM. Although Newcastle disease virus is an avian disease, it is known to be able to affect humans and cause a mild fever, although almost all cases in humans are asymptomatic.[19] In 1999, researchers attempted to use a strain of Newcastle disease virus developed in 1968 to infect cancer patients. Researchers used the non-transductional targeting strategy for this virus, using a protein called interleukin 2 to limit the replication of the virus to only within cancer cells.[20] They found that the patients' tumors shrank while normal cells remained unaffected. This story of success led researchers to try using Newcastle disease virus in GBM. In a study published in 2020, four different patients diagnosed with GBM were infected with the virus. Three of the four patients in this study are still alive today, with one patient still surviving 15 years after diagnosis (Figure 3). Not only did this patient surpass the typical time frame of five years after diagnosis that usually only has a 5.5% chance

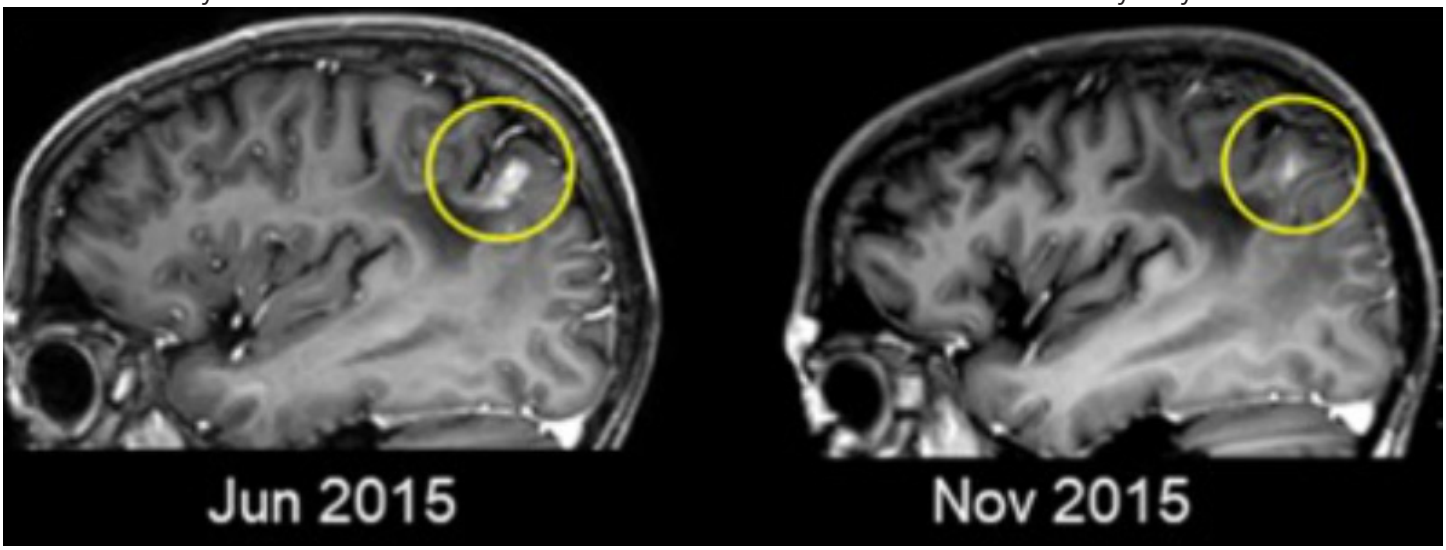


Figure 3. A GBM tumor shrinking from Newcastle disease virus therapy. The white area inside the yellow circle represents the tumor. (Adapted from Gesundheit, B. et al. (2020). Frontiers in Oncology, licensed under CC BY 4.0)

of survival, the patient lived three times as long as previously seen. Diagnosed at 33 years of age, this woman had suddenly lost her ability to speak and lost motor function in her left arm. She was treated with all the conventional therapies, but they were relatively ineffective. However, after receiving viral therapy she regained her speech and motor function, and later went on to give birth to a healthy baby. She currently lives almost as if she never had GBM in the first place. Stories of stability and happiness are also true for the other two surviving patients, who have been reported as enjoying a normal quality of life.[21]

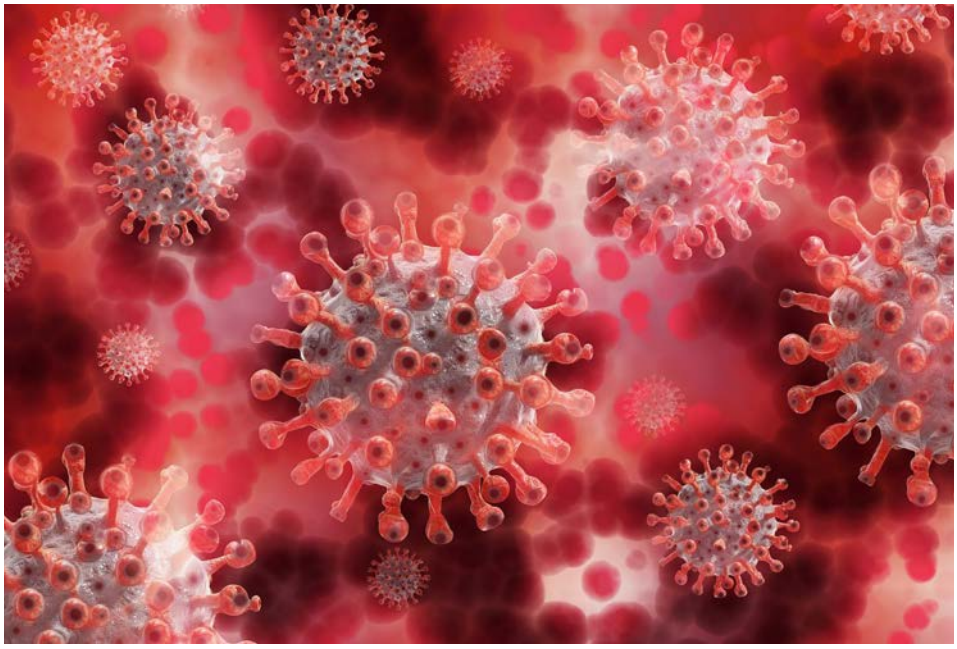
The patient who did not survive lived 6 years after diagnosis, which is amongst the highest percentiles for survival time, and the patient passed away after one year of stopping the therapy. Brain imaging showed that the tumors of the patient shrank at an incredible rate while being treated with the virus, while the rest of the brain remained unaffected.

Another virus that has been used to treat GBM is poliovirus. Poliovirus is commonly known as the virus that causes polio, which infects motor neurons and alters the central nervous system, resulting in muscle weakness and paralysis. Previous research has found that GBM cells overexpress the poliovirus receptor CD155, and poliovirus preferentially infects GBM cells because of this. In a study published in the New England Journal of Medicine, researchers infected 61 patients with an engineered strain of poliovirus. The patients experienced a 2-3 year increase in survival from the national average of less than a year.[22,23] All over the world, massive clinical trials are underway using an engineered poliovirus. Dr. Curry, who is the primary investigator of a poliovirus-GBM clinical trial at the Mass General Cancer Center, has stated that the early data gives much reason to be hopeful, and that he is optimistic that this will become an effective way to improve the outcome for those diagnosed with GBM.[24]

Why Aren't Viral Therapies More Common?

Nobody would blame you for asking why these therapies are not more common when they seem like medical miracles. Other than the difficulty for developing these viral therapies, there is significant public push back. As they do involve viruses, people fear that if these therapies are not properly contained, they will pose a public health threat. With the public's view of viruses primarily being one of fear, especially due to the COVID-19 pandemic, people are reluctant to trust viruses. This fear is especially bad for viruses like Zika or poliovirus, as they have also been viewed as especially harmful in our lifetime.[25] Yet, as Zika and poliovirus have been explored as viral therapies, it would not be unimaginable to have COVID-19 used as a potential viral therapy for cancer. Actually, this reality may not be as far into the future as one might think. A study shows that a patient who was diagnosed with lymphoma actually went into remission after contracting COVID-19, highlighting its cancer-attacking potential.[26]

Although some individuals fear their threat to public health, the safety of these viruses is thoroughly tested before they are even considered as therapies. Before any testing can be done on living beings, researchers are required to provide evidence that the engineered viruses do not harm healthy cells. Even with the safety of these viral constructs proven, researchers take great care in keeping the individuals who are being treated isolated. The patients are then kept until the virus leaves their body through waste. The patient is permitted to come back for another round of treatment later on if needed. The lack of trust in viral constructs prevents the development of a very safe and powerful therapy against one of the deadliest forms of cancer. Viral cancer therapies represent a glimmer of hope in a situation where everything seems to be at its darkest. ■



REFERENCES

1. Bondy, M. L., Scheurer, M. E., Malmer, B., Barnholtz-Sloan, J. S., Davis, F. G., Il'yasova, D., . . . Buffler, P. A. (2008). Brain tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium. Cancer, 113(S7), 1953-1968. doi:10.1002/cncr.23741
2. Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer Statistics, 2010. CA: A Cancer Journal for Clinicians, 60(5), 277-300. doi:10.3322/caac.20073
3. Thakkar, J. P., Dolecek, T. A., Horbinski, C., Ostrom, Q. T., Lightner, D. D., Barnholtz-Sloan, J. S., & Villano, J. L. (2014). Epidemiologic and Molecular Prognostic Review of Glioblastoma. Cancer Epidemiology Biomarkers & Prevention, 23(10), 1985-1996. doi:10.1158/1055-9965.epi-14-0275
4. Solanki, C., Sadana, D., Arimappamagan, A., Rao, K. V., Rajeswaran, J., Subbakrishna, D. K., . . . Pandey, P. (2017). Impairments in Quality of Life and Cognitive Functions in Long-term Survivors of Glioblastoma. Journal of Neurosciences in Rural Practice, 08(02), 228-235. doi:10.4103/0976-3147.203829
5. Lloyd-Williams, M. (2003). Depression--the hidden symptom in advanced cancer. Jrsm, 96(12), 577-581. doi:10.1258/jrsm.96.12.577
6. Young, K., & Singh, G. (2018). Biological Mechanisms of Cancer-Induced Depression. Frontiers in Psychiatry, 9. doi:10.3389/fpsyt.2018.00299
7. Mugge, L., Mansour, T. R., Crippen, M., Alam, Y., & Schroeder, J. (2018). Depression and glioblastoma, complicated concomitant diseases: A systemic review of published literature. Neurosurgical Review, 43(2), 497-511. doi:10.1007/s10143-018-1017-2
8. Rock, K., Mcardle, O., Forde, P., Dunne, M., Fitzpatrick, D., O'neill, B., & Faul, C. (2012). A clinical review of treatment outcomes in glioblastoma multiforme—the validation in a non-trial population of the results of a randomised Phase III clinical trial: Has a more radical approach improved survival? The British Journal of Radiology, 85(1017). doi:10.1259/bjr/83796755
9. Chernajovsky, Y., Layward, L., & Lemoine, N. (2006). Fighting cancer with oncolytic viruses. Bmj, 332(7534), 170-172. doi:10.1136/bmj.332.7534.170
10. Qin, L., Chen, C., Chen, L., Xue, R., Ou-Yang, M., Zhou, C., . . . Chen, X. (2017). Worldwide malaria incidence and cancer mortality are inversely associated. Infectious Agents and Cancer, 12(1). doi:10.1186/s13027-017-0117-x
11. Martinez-Quintanilla, J., Seah, I., Chua, M., & Shah, K. (2019). Oncolytic viruses: Overcoming translational challenges. Journal of Clinical Investigation, 129(4), 1407-1418. doi:10.1172/jci122287
12. Wollmann, G., Ozduman, K., & Pol, A. N. (2012). Oncolytic Virus Therapy for Glioblastoma Multiforme. The Cancer Journal, 18(1), 69-81. doi:10.1097/ppo.0b013e31824671c9
13. Martikainen, M., & Essand, M. (2019). Virus-Based Immunotherapy of Glioblastoma. Cancers, 11(2), 186. doi:10.3390/cancers11020186
14. Parato, K. A., Senger, D., Forsyth, P. A., & Bell, J. C. (2005). Recent progress in the battle between oncolytic viruses and tumours. Nature Reviews Cancer, 5(12), 965-976. doi:10.1038/nrc1750
15. Howells, A., Marelli, G., Lemoine, N. R., & Wang, Y. (2017). Oncolytic Viruses—Interaction of Virus and Tumor Cells in the Battle to Eliminate Cancer. Frontiers in Oncology, 7. doi:10.3389/fonc.2017.00195
16. Ohka, F., Natsume, A., & Wakabayashi, T. (2012). Current Trends in Targeted Therapies for Glioblastoma Multiforme. Neurology Research International, 2012, 1-13. doi:10.1155/2012/878425
17. Su, K. Y., & Balasubramaniam, V. R. (2019). Zika Virus as Oncolytic Therapy for Brain Cancer: Myth or Reality? Frontiers in Microbiology, 10. doi:10.3389/fmicb.2019.02715
18. Zhu, Z., Gorman, M. J., Mckenzie, L. D., Chai, J. N., Hubert, C. G., Prager, B. C., . . . Chheda, M. G. (2017). Correction: Zika virus has oncolytic activity against glioblastoma stem cells. Journal of Experimental Medicine, 214(10), 3145-3145. doi:10.1084/jem.2017109309122017c
19. Bai, Y., Chen, Y., Hong, X., Liu, X., Su, X., Li, S., . . . Li, Y. (2018). Newcastle disease virus enhances the growth-inhibiting and proapoptotic effects of temozolomide on glioblastoma cells in vitro and in vivo. Scientific Reports, 8(1). doi:10.1038/s41598-018-29929-y
20. Bai, F., Niu, Z., Tian, H., Li, S., Lv, Z., Zhang, T., . . . Li, D. (2014). Genetically engineered Newcastle disease virus expressing interleukin 2 is a potential drug candidate for cancer immunotherapy. Immunology Letters, 159(1-2), 36-46. doi:10.1016/j.imlet.2014.02.009
21. Gesundheit, B., Ben-David, E., Posen, Y., Ellis, R., Wollmann, G., Schneider, E. M., . . . Thaller, A. (2020). Effective Treatment of Glioblastoma Multiforme With Oncolytic Virotherapy: A Case-Series. Frontiers in Oncology, 10. doi:10.3389/fonc.2020.00702
22. Desjardins, A., Gromeier, M., Herndon, J. E., Beaubier, N., Bolognesi, D. P., Friedman, A. H., . . . Bigner, D. D. (2018). Recurrent Glioblastoma Treated with Recombinant Poliovirus. New England Journal of Medicine, 379(2), 150-161. doi:10.1056/nejmoa1716435
23. Duke Health News. (2018, June 26). Poliovirus Therapy for Recurrent Glioblastoma Has Three-Year Survival Rate of 21 Percent. Retrieved November 16, 2020, from https://tischbraintumorcenter.duke.edu/news/poliovirus-therapy-for-recurrent-glioblastoma-has-three-year-survival-rate-21-percent
24. Curry, W. T. (2020, August 19). Brain Infusion of Genetically Modified Poliovirus Is Used to Treat Glioblastoma. Retrieved November 22, 2020, from https://advances.massgeneral.org/neuro/article.aspx?id=1107
25. Olagnier, D., & Alain, T. (2020). Oncolytic viral immunotherapy in the time of COVID-19. Cytokine & Growth Factor Reviews. doi:10.1016/j.cytogfr.2020.10.009
26. Pasin, F., Calveri, M. M., Calabrese, A., Pizzarelli, G., Bongiovanni, I., Andreoli, M., . . . Rignanese, G. (2020, July). Oncolytic effect of SARS-CoV2 in a patient with NK lymphoma. Acta Bio Medica Atenei Parmensis, 13(91). doi:0.23750/abm.v91i3.10141