SASTA OLIPHANT SCIENCE AWARDS

SOUTH AUSTRALIAN SCIENCE TEACHERS ASSOCIATION

Prize Winner

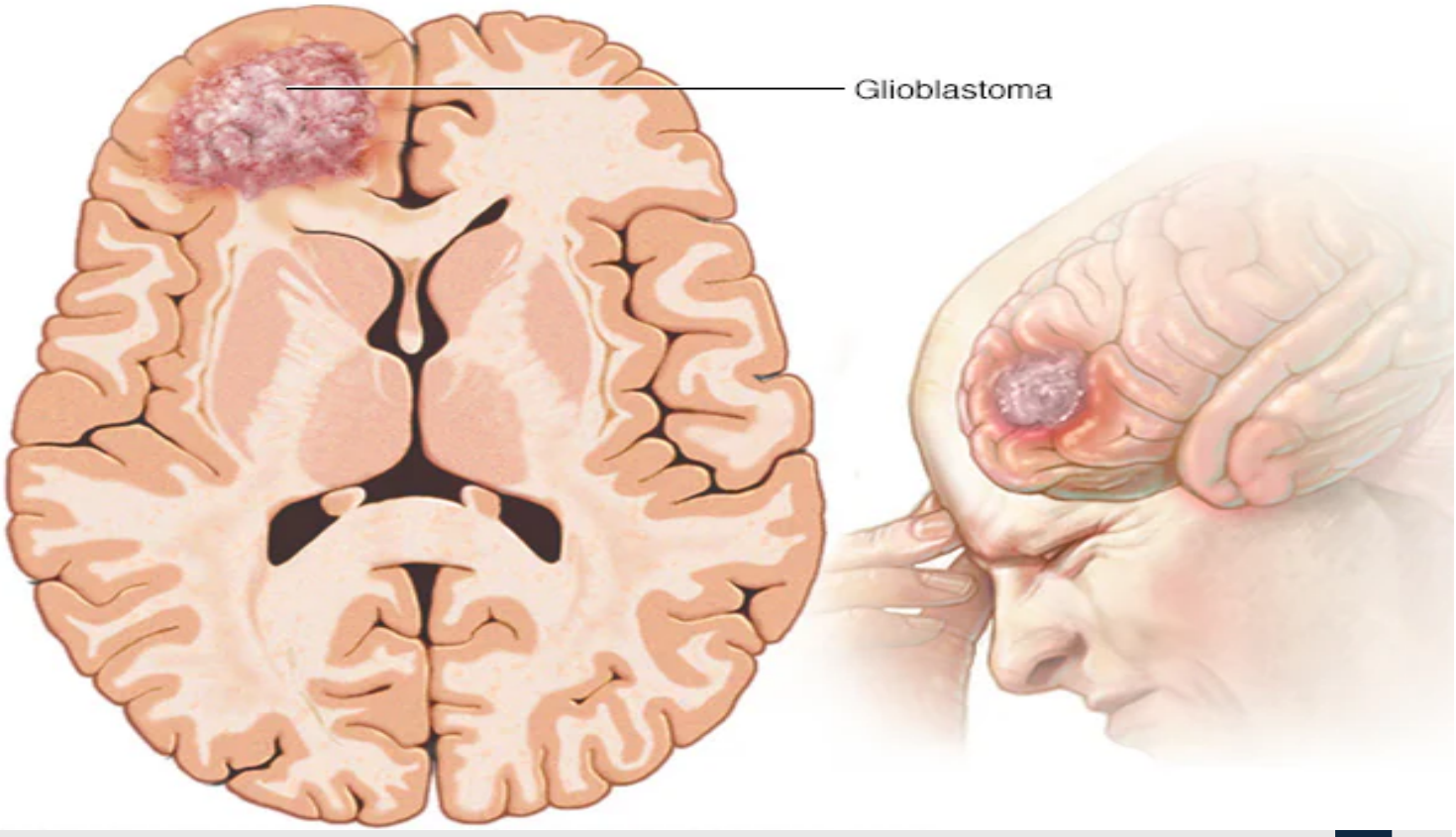
Science Writing

Year 11-12

Kreshma Razaqi

IQRA College

How is Oncolytic Viruses a Groundbreaking Advancement in Treating Patients with Glioblastoma?



Innovative cancer treatment that uses engineered or naturally occurring viruses to destroy cancer cells selectively while stimulating anti-tumor immune response (Santos Apolonio et al., 2021).

Linked to chapters 1.3 Genes, 1.7 Regulation of Gene Expression, 1.8 Mutations, 1.2 Biotechnology chapter 2 and chapter 3

SACE ID: 178578W

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

Introduction:

One of the most aggressive brain tumours, known as glioblastoma multiforme GBM, originates from glial cells and astrocytes, which support the spinal cord and nerve cells in the brain by providing structural support, regulating neurotransmitters and delivering nutrients. Glioblastoma GBM forms in the cerebral hemispheres, mainly in the temporal and frontal lobes of the brain (American Brain Tumour Association, 2024). It is categorised as a grade IV tumour, highlighting its fast growth and aggressive nature, making it the most common deadly brain tumour in adults, with an estimated 10,000 individuals dying from it per year in the US. This tumour has the shortest survival median of one year after diagnosis. (Mato Clinic, 2024; Cleveland Clinic, 2024; Cancer Research UK, 2023). Despite advancements in treatment options, this malignant tumour remains challenging to cure and resistant to treatment, making it a public health burden (Weingart, M.D., 2024). This has motivated researchers and scientists to develop oncolytic viruses OVs that produce anti-tumour immunity (Tian et al., 2022). This treatment offers a promising therapeutic application in today's society, and it has some societal influence. However, a few limitations are present.

Biological concept:

Traditionally, this aggressive tumour was thought to occur from glial cells, particularly astrocytes, which are star-shaped cells that protect neurons (Penn Medicine, 2024). However, scientists with ongoing research are still discovering the exact cellular origin of GBM.

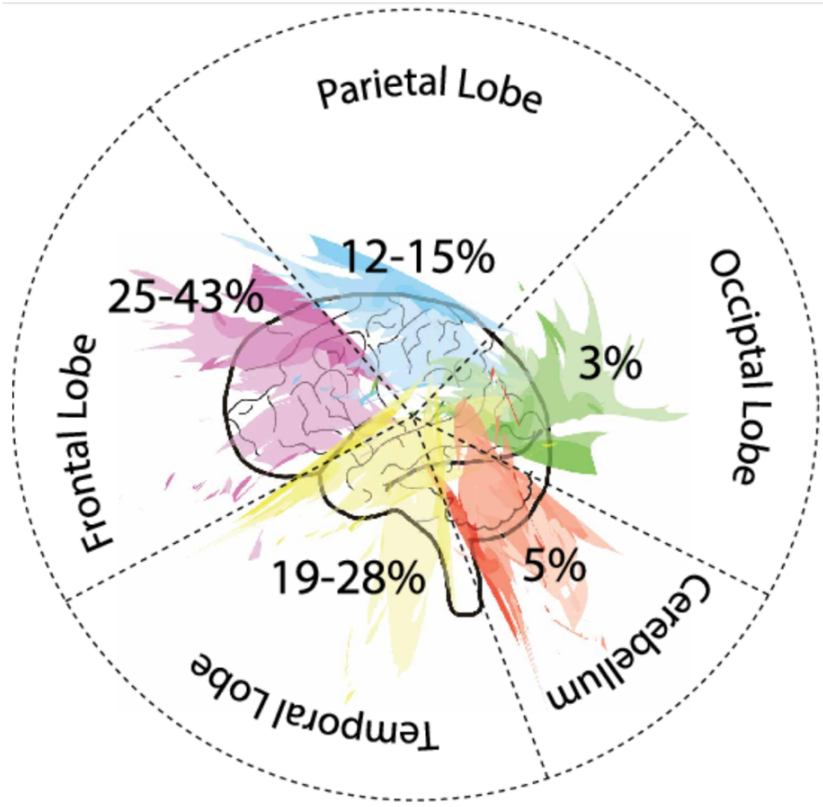


Figure 1: The diagrams show the incidence of GBM in the brain sub-region. The five different colours divide the human brain into five sub-regions. GBM multi-formed predominantly occurs in the frontal part (25-43%), highlighting a clear gradient in GBM occurrence, with the frontal region being the most affected part and the occipital Lobe being the least affected part, with only 3%. Overall, these percentages are the glioblastoma incidence by sub-region, highlighting the high topographical heterogeneity in the brain and with a predominance in the frontal lobes (Lee Perrin, 2019).

SACE ID: 178578W

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

GBM's complexity occurs from cellular heterogeneity and genetic diversity, including multiple molecular and cancer stem-like cells (CSCs) supported by the tumour microenvironment therapies (Becker et al., 2021; Han Bae et al., 2024; Valtorta et al., 2020). Genetically, GBM is determined by modifications in signalling pathways like RAS/PI3K affecting receptors such as EGFR and PDGFR, which are impacted by 88% of GBMs, P53 87% and RB pathway 78% (Hanif et al., 2017). The classical GBM subtype is characterised by EGFR mutation and amplification, especially in its extracellular domain, leading to increased growth. This mutation results in overactive EGFR proteins, leading to aggressive cancer growth and treatment resistance (Xu et al., 2017). GBM's heterogeneity is demonstrated by constitutive activation of proteins, like EGFR, that stimulate cell division without activation signals, resulting in the growth of tumours (Eskilsson et al., 2017).

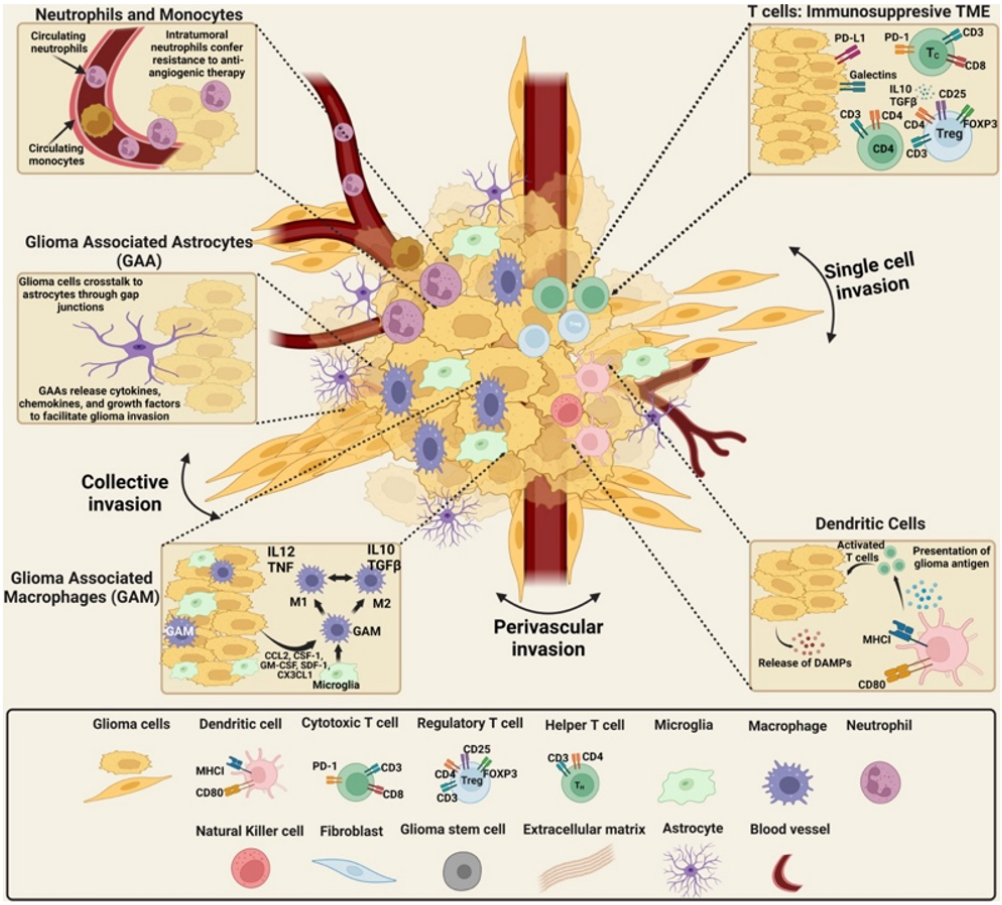


Figure 2: Diagram shows cellular components of brain tumour microenvironment. The gliomas consist of cell types. Malignant cells are known to be tumour cells, non-malignant cells, local immune cells, astrocytes, neurons, microglia, lymphocytes, and blood vessel cells. The presence of neutrophils in the GBM microenvironment is associated with resistance to anti-angiogenic therapy. Glioma cells release substances such as IL-10 and TGF,β which inhibit immune responses and alter the surrounding environment.
Tumour cell changes their environment by secreting chemokines such as CXCL8 and MIF to help neutrophils recruit. They travel along blood vessels by a process called streaming. This is where macrophages migrate, and tumour cells adhere to ECM fibres against endothelial cells. This activity helps intravasation, which is called TMEM, contributes to metastasis (Leung et al., 2017).
The interactions within the complex environment influence tumour growth.

SACE ID: 178578W

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

The proneural GBM subtype mutations in the PIK3R1 gene result in PI3K enzyme hyperactivity, uncontrolled cell growth without activation signals, highlighting GBM complexity and treatment therapies (Liu et al., 2016). The mesenchymal subtype is characterised by a mutation in the NF1 gene, a tumour-suppressor gene. These genetic changes result in hyperactivity of the RAS pathway, necessary for cell division (Marques et al., 2021).

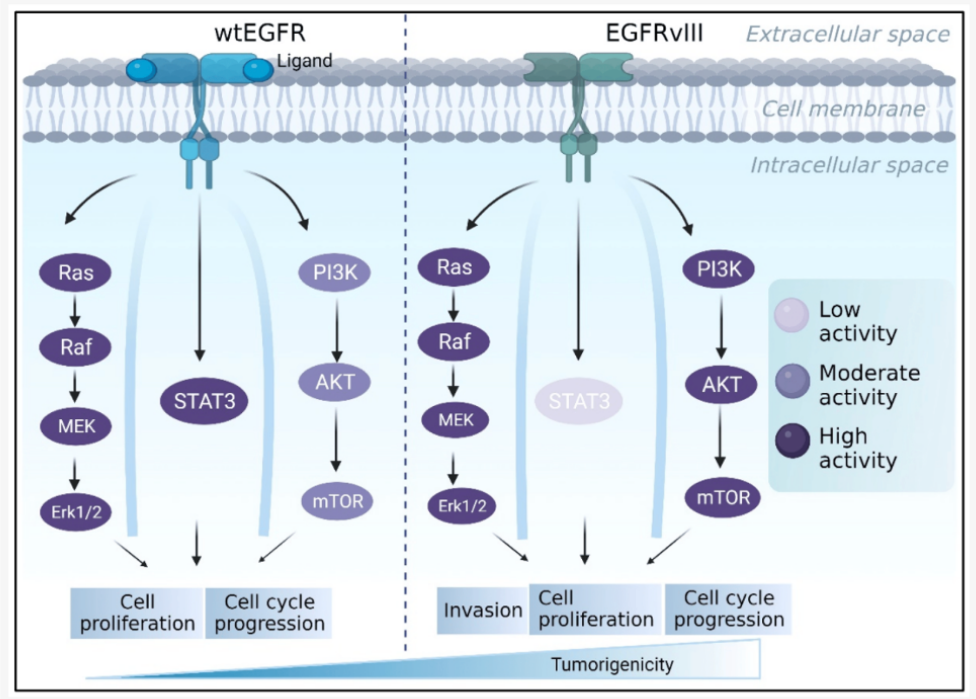


Figure 3: The diagram highlights how EGFR/EGFRvll pathways play a critical role in the growth and spreading of GBM tumors. EGFRvll is a mutated form of EGFR, which is mainly always active and turns on the PI3K pathway that supports the tumour in the nearby tissue and allows it to survive. EGFR mutation results in uncontrolled cell division by changing the function of the protein (Ellis, 2024). However, the mutated gene will constantly send growth and cell division signals, which lead to uncontrolled cell division, a danger for Cancer (O'Sullivan, 2022). RSA/PI3K pathways also play a key role in tumor growth and survival, as RAS proteins are the crucial pathway for cell survival, growth and differentiation. PI3KR1 and NF1 mutation result in further signalling, as this gene encodes a regulatory subunit of PI3K. Mutation can activate the PI3K pathway, leading to uncontrolled cell growth and survival (McCubrev et al., 2012).
In addition, EGFR primarily activates the MAPK and STAT3 pathways that lead to tumour growth (Rabah et al., 2023). Ultimately, this mutation contributes to uncontrolled cell growth as well as drug resistance, as this mutation can cause resistance to numerous therapies, leading to tumour cell survival. The increase in PI3K signalling causes metabolic changes that help tumour growth.

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

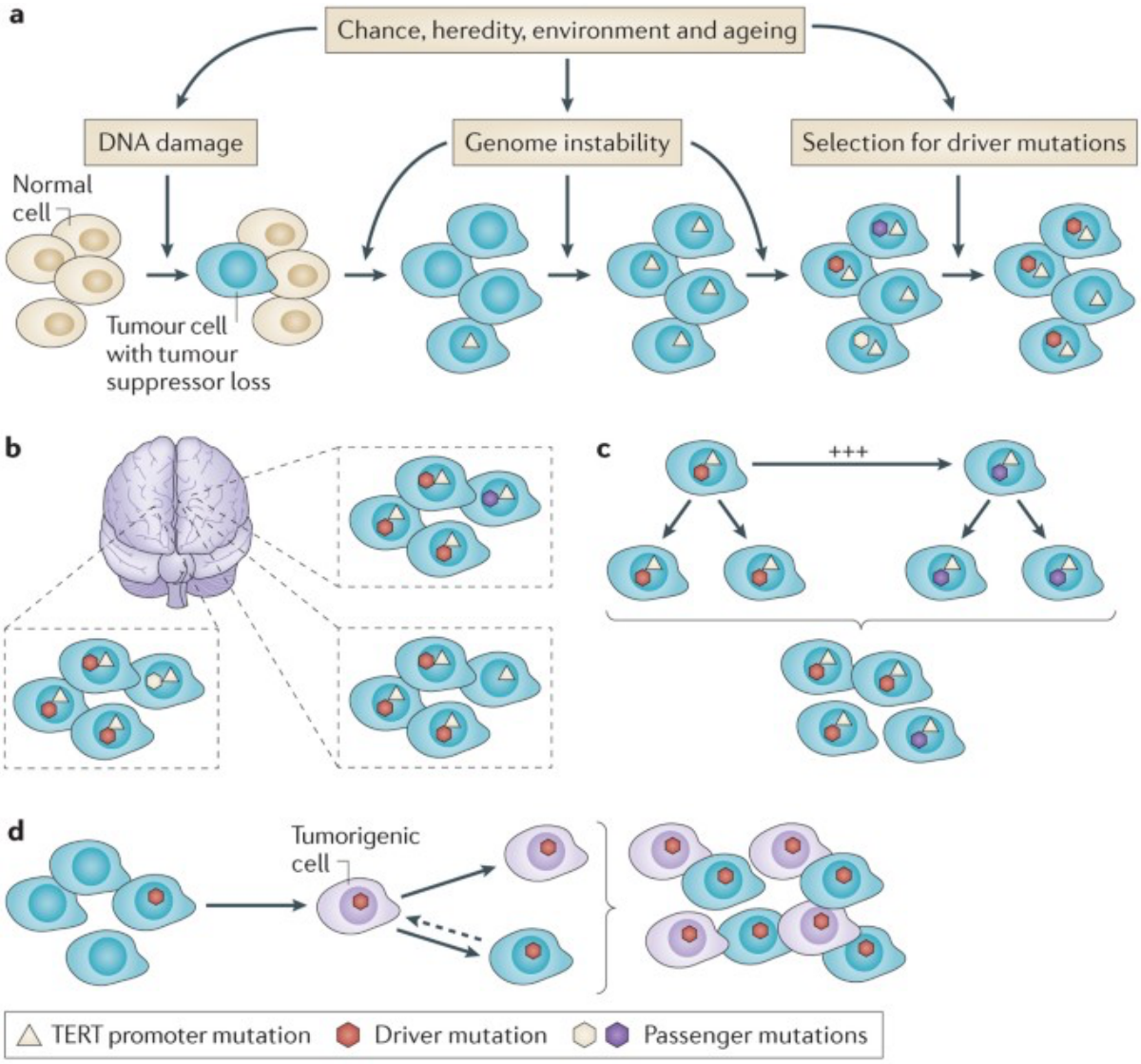


Figure 3: The diagram shows the heterogeneity of epidermal growth factor receptors' signalling networks in GBM.

CAN-3110 is a genetically engineered Oncolytic virus developed to treat GBM tumours. It retains the ICP34.5 gene under nesting promoter control, selectively fighting against cancer cells while stimulating the immune system and sparing healthy tissue (Ling et al., 2023). OVs work by virus replication in tumour cells; it makes them burst, releasing antigens and triggering an immune response and antitumor (GEN, 2023). This process converts the immunosuppressive GBM environment into a pro-inflammatory one, recruiting a different T cell repertoire.

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

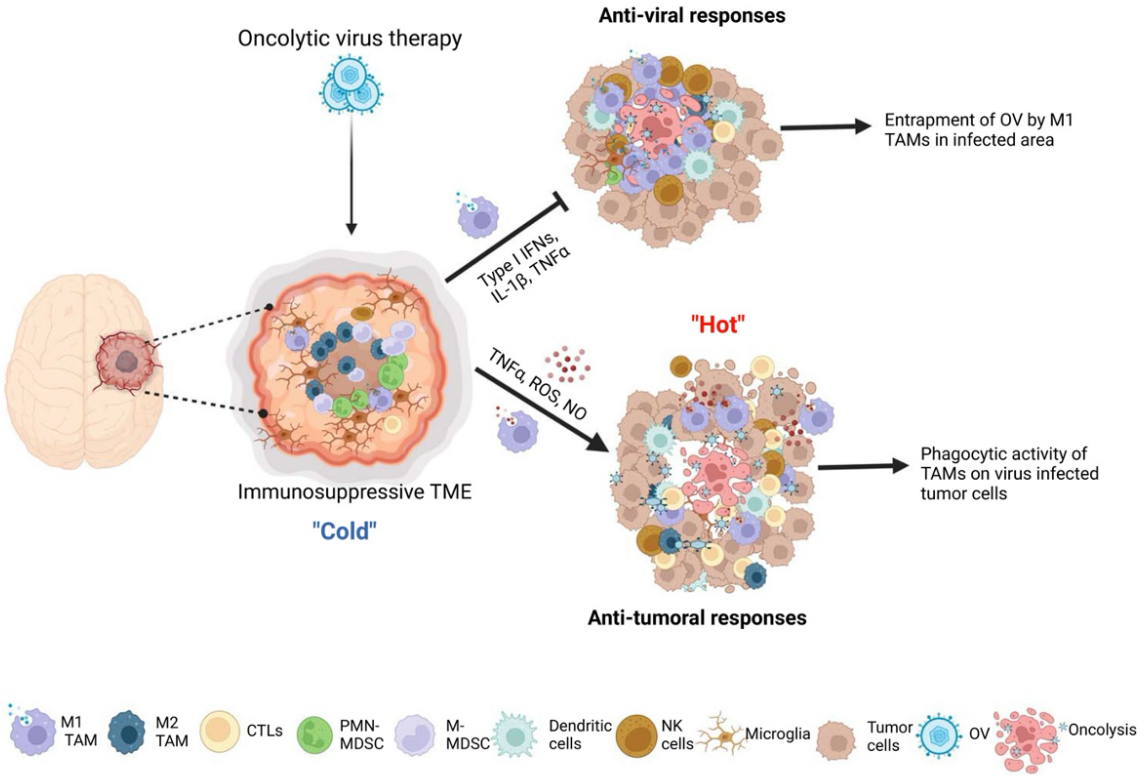


Figure 4: The diagram shows the interaction between Microglia and OVs in GBM. The OVs with infected glioma cells recruit peripheral macrophages and microglia to the OV delivery site, polarisation M2-type macrophages to M1-type tumour-related macrophages (TAMs). M1 TAMs build a barrier around the infected area, limiting virus spread, releasing anti-viral substances through the secretion of anti-viral cytokines,|and attracting other immune cells that fight against viruses. Additionally, M1 TAMs exert anti-tumor activity by producing tumor-killing factors, inducing other immune cells, like NK cells and dendritic to attack the tumor. Lastly, these cells act as antigens to elicit adaptive anti-tumor immune systems in the body (Frontiers in Cellular and Infection Microbiology, 2023)

Interaction Between Science and Society:

Influence:

The impact of OVs is revolutionising GBM treatment through enhanced immune stimulation and tumour lysis (Cristi et al., 2022), driving innovation in immunotherapy, bioengineering and healthcare, and improving treatment efficacy. OV treatment significantly impacts GBM treatment by selectively triggering tumour cells, stimulating immune responses, offering new hope for patients, and potentially improving survival rates (Asija et al., 2023; Askari et al., 2023). OVs therapy has shown positive results in improving the survival rate in patients with GBM, resulting in a positive influence on society as it improves the immune response by targeting GBM tumours, hence extending the survival rate. The standard GBM survival rate is a median of 14.6 to 20.5 months (Hamad et al., 2023). However, the survival rate after using CAN-3110 in the clinical trial has been shown to be a median of 11.6 months (95% CI=78-14.9 months) (Ling et al., 2023).

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

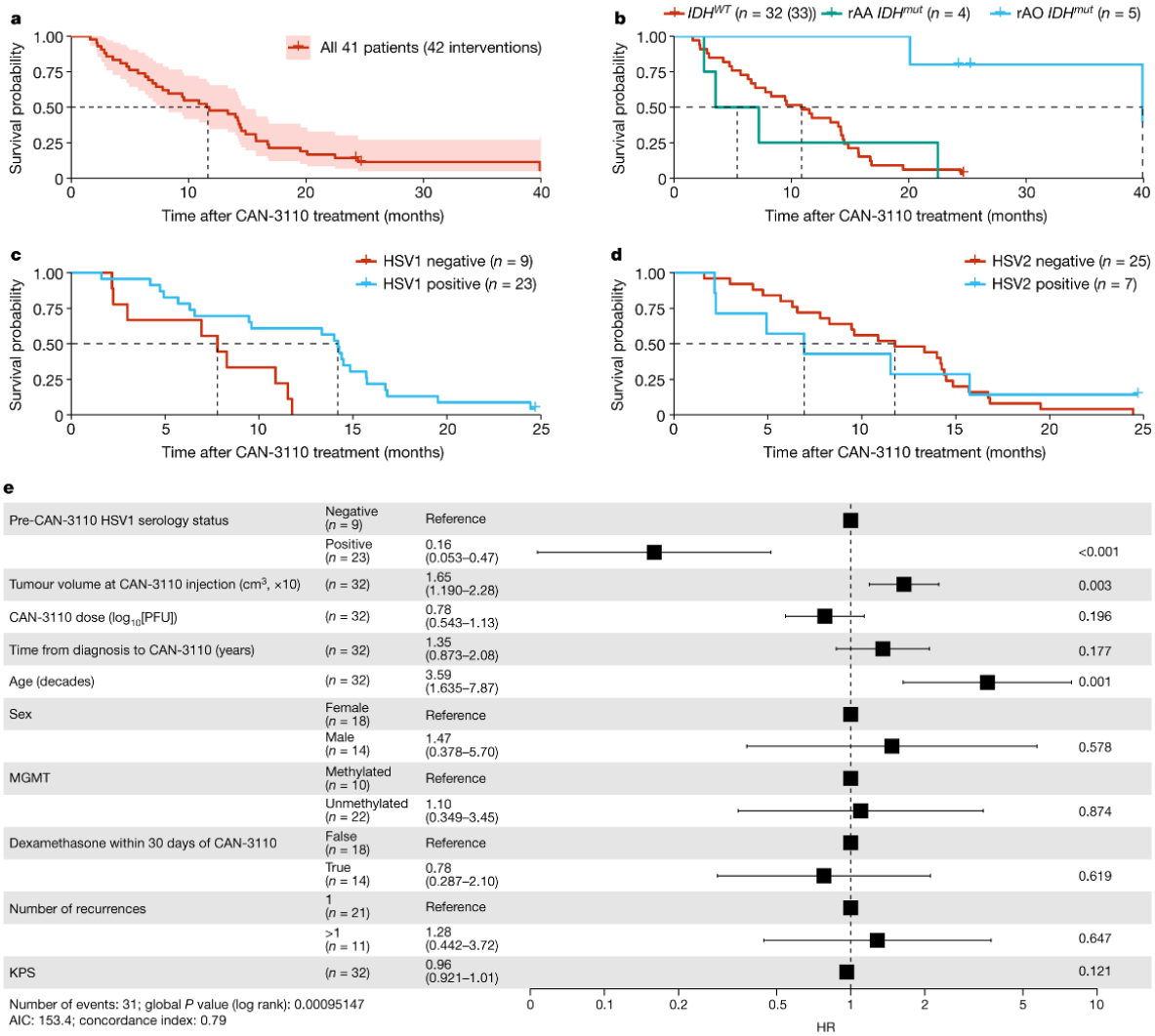


Figure 5: The diagram shows the study on the survival rates of patients with various types of brain tumors after receiving CAN-3110 treatment, highlighting how different characteristics of patients might affect the survival rate after CAN-3110 treatment. However, 41 patients with a high grade of GBM (rHGG) have a median survival of 11.6 months (95% CI=7.8-14.9 months) v after receiving CAN-3110 treatment. 33 patients with IDHWT (rGBM) have been shown to have a median survival of 10.9 months (IDHWTrGBM[95% CI=6.9-14.4 months), while patients with IDHmut (rAA) have a median survival of 5.4 months (IDHmutrAA; 95% CI=2.6-∞ months) and IDHmut (rAO) group 39.9 months (IDHmut rAO; 95% CI=39.9-∞ months) (Ling et al., 2023).

Additionally, while these data highlight its positive influence on society, it is essential to consider that the outcome can vary significantly among patients, and clinical trials should fully establish the positive effect of OV therapy in GBM treatment because it can reduce the burden on the healthcare system. Ongoing research has shown that OV therapy can reduce healthcare burden by minimising its side effects as it is significantly well-tolerated, reducing readmissions and complications. This therapy reduces the frequency of additional treatment and is more effective than traditional therapies, leading to a decrease in healthcare burden (Lauer & Beil, 2022).

The use of OVs in medical fields in treating GBM will influence clinical trial practices by necessitating expertise and specialised infrastructures for OV administration and monitoring. However, this therapy could significantly impact clinical trials by ensuring safe storage,

limiting the risks of contamination, simplifying treatment protocols, and improving efficiency (NCI staff, 2018). Current OVs are in the form of liquid, and proper frozen storage and following cold-chain protocols for transport are necessary for the healthcare system (Lin et al., 2023). The validity of OVs in evading the body's immune response and sustaining prolonged presence influences advancements in biomedical engineering and nanomedicine. This can have a positive effect on enhancing therapeutic and diagnostic practices since nanoparticles used in techniques such as MRIs and X-rays depend on biomarker recognition in distribution and clearance (Sim & Wong, 2021). However, the effectiveness and success of OVs may encourage scientists and engender an interest in improving this field, resulting in more accurate diagnostics for patients with GBM.

However, these bioengineering advances are not only considered academic practices but have profound effects and implications for solving real-world problems. Emerging specialised technology leading scientists address significant issues, such as developing sustainable energy solutions and creating personalised healthcare treatments, which are considered essential drivers of social progress and economic improvement (McKinsey & Company, 2023).

Implementing OVs to treat GBM may face public scepticism, mainly due to social, cultural and ethical considerations (Gupta et al., 2017). However, if OVs therapy proves successful, it can significantly influence society by necessitating improved healthcare practices. The use of OVs in clinical trials will have a positive economic impact. While OV therapy may initially increase costs, it has the potential for long-term cost-effectiveness compared to traditional treatments (NCI staff, 2018). OVs can prompt enduring immune responses, potentially reducing the need for hospitalisations and repeated treatments (Pohlmann et al., 2024). This could lead to prolonged cost saving, especially given that the current standard treatment for GBM costs between $50,600 and $92,700 per patient for surgery and radiation therapy (Raizer et al., 2014). However, the cost reduction will make the GBM treatment more accessible, mainly in low-income countries.

Application and limitation:

When applied, OVs highlight advantages over standard treatment, potentially by genetic modification to express immunomodulatory transgenes such as cytokines, which shows its effectiveness against GBM and other cancers. Cytokines are proteins that control immune responses. Genetic modification helps OVs by enhancing tumour-selective immunogenicity and replication efficiency (Cristi et al., 2022). Scientists can apply their knowledge as proof, including that OVs can be engineered to express interleukins such as IL-12 that help activate immune cells and prevent the formation of tumour blood vessels (Zhang & Liu, 2020). IL-12 significantly assists tumour destruction, stimulating T cells and natural killer cells, reprograms immunosuppressive tumour-presented macrophages and increases interferon-gamma production (Nguyen et al., 2020). The consequences of genetic engineering led to the customising of OVs therapy, which combines the virus's ability to kill tumour cells directly with improved stimulation of the immune system (Muthukutty & Yoo, 2023). The characteristics make OVs therapy unique compared to traditional treatments, as OVs combine direct tumour lysis with targeted immune stimulation.

The OVs treatment has shown promising and broad application beyond GBM treatment, demonstrating versatility among different types of cancer. This treatment has been effective

in melanoma, with T-Vec approved for treating various cancers (Fukuhara et al., 2016). OV therapy can reduce the burden on the healthcare system by offering adequate and targeted treatment and reducing prolonged hospitalisation and repeated treatment.

While this therapy offers significant advantages in treating GBM, it also faces several limitations and disadvantages in effectively achieving its goal. The blood-brain barrier (BBB) presents a significant disadvantage for OVs, limiting the ability to reach the tumour site when managed systemically, which needs local delivery that can be suboptimal for infiltrative disease (Samson et al., 2018). Its fit junction among specialised transport systems and endothelial cells stops large molecules, including viruses, from entering the brain, limiting its effectiveness in treating brain tumours (Gawdi et al., 2024). Furthermore, pre-existing or treatments-included (neutralising antibodies) can clear OVs, which reduces their efficacy. However, addressing these limitations of OVs is essential for enhancing the efficacy of these OVs in treating GBM. This happens by binding onto viral protein, which limits cell infection, and forming antibodies-virus for faster immune removal (Suryawanshi & Schulze, 2021).

However, ongoing research and innovations aimed at addressing these limitations by using intertumoral injections bypass the BBB that provides more OV concentration at the sites of the tumour (Li et al., 2020), significantly improving cancer treatment outcomes, enhancing patients' quality of life and possibly reducing healthcare costs.

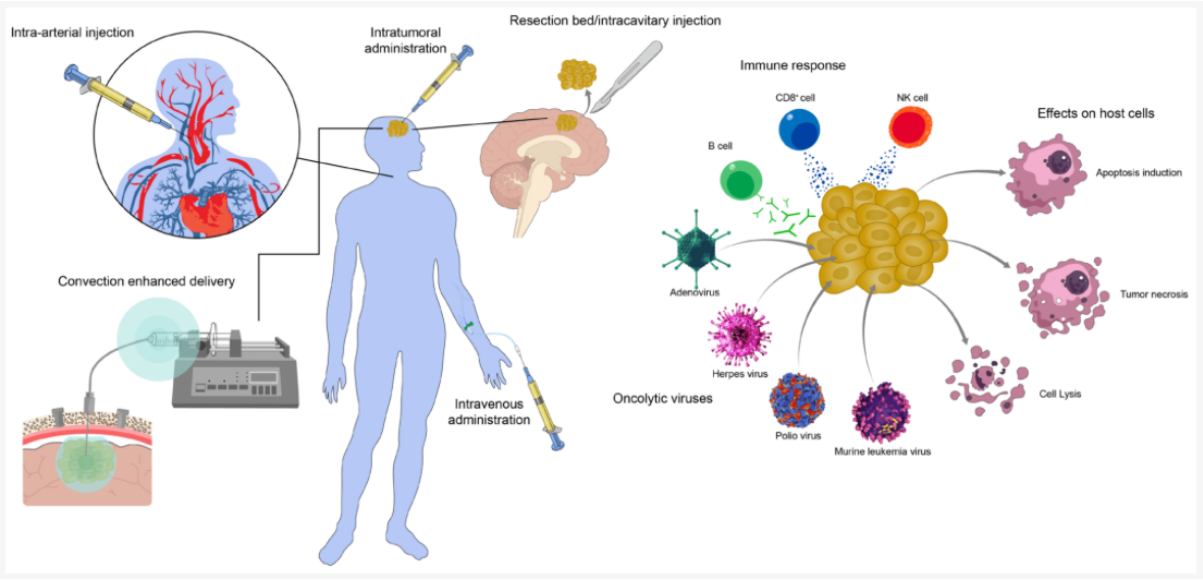


Figure 6: The diagram shows an overview of the delivery method, certain oncolytic viral agents, and antitumor response for OVs in GBM treatment (Webb et al., 2023).

Conclusion:

In conclusion, oncolytic viruses OVs present a promising treatment for patients with glioblastoma mutation GBM, offering future improvement, potentially for personalised OVs that aim to overcome the heterogeneity of brain tumours among adult patients. Despite all the advantages, this treatment faces limitation that reduces its efficacy. However, further research and advances are crucial to enhance the effectiveness of OVs through improved combination therapies and delivery methods.

SACE ID: 178578W

STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

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STAGE 2 BIOLOGY
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STAGE 2 BIOLOGY
INVESTIGATION FOLIO TASKS
SCIENCE AS A HUMAN ENDEAVOUR (SHE) RESEARCH TASK

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