SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Targeting the Tumor Micro-environmental in Glioblastoma: Barriers, Pathways, and Experimental Strategies

By Thomas Figueroa

AUTHOR BIOGRAPHY

Thomas Figueroa is a senior in high school at St. Ignatius College Preparatory in San Francisco, California. He plans on studying biology with an emphasis on pre-med, with a long-term goal of becoming an emergency physician

ABSTRACT

Glioblastoma (GBM) is the most common and aggressive malignant brain tumor in adults, with a median survival of 14-16 months per the Stupp regimen, a treatment which uses surgery followed by radiation and chemotherapy with temozolomide. Its resistance to treatment is largely due to the tumor microenvironment (TME), a complex network of immune cells; stromal components; and signaling pathways that promote tumor growth and suppress immune responses. In addition, the blood-brain barrier (BBB) restricts drug delivery and complicates immunotherapy strategies. This review examines the challenges and emerging directions in targeting the TME in glioblastoma. Sections include strategies for transiently and safely opening the BBB, the role of insulin-like growth factor (IGF) signaling in therapy resistance, immunosuppressive mechanisms within the TME, and the limited effectiveness of immune checkpoint blockade. We also review genetic mutations, innovative therapeutic agents, and survival-linked biomarkers. Across studies, we find that BBB disruption alters key endothelial genes, IGF signaling drives therapy resistance, the TME suppresses antitumor immunity, checkpoint inhibitors show limited benefit except in select immune-activated cases, and specific mutations such as IDH1 strongly predict patient survival. Collectively, this review highlights how understanding and targeting the TME may improve outcomes for patients with GBM and reveals how new technologies like focused ultrasound and single-cell transcriptomics are advancing the field.

Keywords: *glioblastoma, tumor microenvironment, immunotherapy, blood–brain barrier, Tumor Treating Fields, oncolytic viruses, PI3Kγ inhibition, IGF pathway, drug resistance, focused ultrasound, single-cell transcriptomics, immune suppression*

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

INTRODUCTION

Glioblastoma (GBM) is the most common adult malignant primary brain tumor and one of the deadliest cancers, with 14–16 months of median survival (Maris et al., 2015). Despite numerous decades of research and establishment of the standard treatment protocol, surgical resection, radiation, and temozolomide chemotherapy, prognosis remains poor due to the tumor's highly invasive and refractory rate (McFaline-Figueroa et al., 2024). Such challenges are a result of the biological complexity of GBM, since it is characterized by genetic and epigenetic heterogeneity and an active immunosuppressive TME (Weathers et al., 2025).

One of the most important physical barriers to effective treatment is the blood-brain barrier (BBB), a tight junction and endothelial cell system limiting drug entry into the brain (Gould et al., 2025). Even if drugs can cross the BBB, they must also contend with an immunosuppressive TME, allowing cancer cells to evade immune destruction (McFaline-Figueroa et al., 2024). Modifying this environment, instead of attacking the cancer itself, is now a primary area of investigation.

Recent technological advancements in single-cell analysis, transcriptomics, and imaging have enabled researchers to identify patient subgroups that can be treated using personalized approaches (Weathers et al., 2025). Altering the TME, disrupting the BBB for improved drug delivery, and developing immunotherapies efficiently within the brain-specific environment are some of the current research areas. This review evaluates novel approaches and analyzes how researchers are addressing GBM's most uncooperative features.

BBB DISRUPTION AND BYPASS

The BBB is a network of endothelial cells that is tightly connected and protects the brain by strictly controlling what can pass from the blood into the brain tissue. While this mechanism of protection is crucial for preventing infection, it is also a huge obstacle when trying to treat GBM, a highly aggressive brain tumor. The cells that make up the BBB are connected by the tight and adherens junctions, which keep most large and polar molecules, including most cancer drugs, from bypassing the barrier (Godinho-Pereira et al., 2021). When the BBB is disrupted, it alters gene expression at the cellular level. For example, genes relating to the transport of materials, like Major Facilitator Superfamily Domain-Containing Protein 2A (MFSD2A), become more active ($\log_2FC = 0.592$, adjusted $P = 1.31 \times 10^{-6}$), while genes relating to structural maintenance of the barrier, like Caveolin-1 (CAV1), are suppressed ($\log_2FC = -0.77$, adjusted $P = 1.14 \times 10^{-32}$) (Gould et al., 2025). For patients, this means that standard therapies like chemotherapy and immunotherapy are often blocked by the very framework designed to protect the brain. Because of this, researchers have started to view the BBB as not only an obstacle to be overcome, but as a target to be manipulated in the quest for more efficacious GBM

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

therapies.

One current research method that safely and temporarily opens the BBB to introduce treatments to the brain without causing damage is low-intensity pulsed ultrasound with microbubbles (LIPU/MB). LIPU/MB uses sound waves along with tiny gas bubbles to temporarily open the BBB. In current clinical trials on patients with recurring glioblastoma, imaging shows that BBB integrity was restored within approximately one hour after treatment (Gould et al., 2025).

Similarly, GBM cells exploit methods to bypass the BBB by using both paracellular routes, in which they enter between cells; and transcellular blood–tumor barrier (BTB), which can be heterogeneous within GBM (Gould et al., 2025). They can also cross through the endothelial cells themselves, using transcellular transport to invade the brain tissue (Godinho-Pereira et al., 2021). By studying and mimicking these natural approaches, researchers aim to design therapies that can open the BBB in a controlled way that still preserves its ability to protect the brain.

Tumor Microenvironment (TME) and Immunosuppression

The TME is a community of non-cancerous cells, blood vessels, and signaling molecules that surround the location of a tumor. In GBM, the TME becomes immunosuppressive, so instead of helping the body fight cancer, it actually blocks the immune system from recognizing the tumor cells that comprise GBM (McFaline-Figueroa et al., 2024). As a result, these surrounding cells that the TME is composed of, such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), all work against the immune system's response to cancer. Researchers found that the expression of the gene V-set and immunoglobulin domain-containing protein 4, which is found in TAMs, is closely associated with the TME's suppressive nature (Liu et al., 2025). This suppressive environment helps GBM cells survive, grow, and resist therapies meant to help fight it.

Furthermore, recent lab studies have shown just how powerful and dangerous the TME actually is. GBM TAMs often display an M2-like, immunosuppressive phenotype; macrophage polarization is plastic and context dependent (Liu et al., 2025). Another study found that blocking PI3Kγ, a signal pathway, could shift the differences in macrophages and make the TME more responsive to treatment. When researchers inhibited PI3Kγ, they observed noticeable changes in immune cell activity, suggesting that this pathway could be a valuable target for modifying the TME (Xu et al., 2024). These findings are crucial to understanding how the TME functions, and developing innovative strategies to target these pathways is promising. Researchers are focused on ways to reprogram the TME, thereby inhibiting its growth mechanism and inhibiting the fast proliferation of cancer cells.

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

IGF Pathway and Therapy Resistance

The IGF pathway is crucial in keeping GBM undetectable from immune responses. In GBM, both the IGF1 and IGF2 receptors are overexpressed in comparison to normal brain tissue cells, highlighting their role in tumor progression (Maris et al., 2015). In the TME, IGF2 not only enhances IFG1R signaling but also promotes tumor regrowth and immunosuppression, resulting in further treatment resistance (Noh et al., 2024). The overexpression of the IGF1R signaling pathway is known to be associated with poor survival in patients with GBM (Noh et al., 2024). To address this, researchers developed an oncolytic Herpes virus (oHSV-D11) that releases a decoy IGF2 receptor that is aimed to block the signaling feedback loop (Noh et al., 2024). In preclinical and early clinical studies, IGF2 blockade reprogrammed the TME and showed significant antitumor activity (Noh et al., 2024). In the small clinical cohort, 71.4% (10 out of 14) of patients with recurring GBM showed significantly increased IGF2 expression post HSV-1 herpes virus ($p=0.0020$) (Noh et al., 2024). This offers a new targeting therapy to mitigate GBM resistance, suggesting better future treatments for patients with therapy-resistant GBM (Maris et al., 2015).

Immunotherapy Challenges and Checkpoint Inhibitors

Although immunotherapy was once a hopeful method for treating GBM, it has faced significant challenges in clinical use. One of the major challenges is the immunosuppressive nature of the TME, which slows down immune responses, reducing the effectiveness of immune-based treatments (McFaline-Figueroa et al., 2024). Immune checkpoint inhibitors (ICIs) are designed to target proteins that restore T cell activity; however, their success is limited in GBM due to the fact that this disease is highly effective at evading immune detection. Resistance to ICI treatment has been a major barrier in treating GBM. (McFaline-Figueroa et al., 2024).

Despite ICI resistance being a barrier, there's still hope. Studies using a combination of anti-Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and anti-Programmed Death 1 (PD-1) antibodies. Combination anti-CTLA-4 and anti-PD-1 therapy was feasible and immunologically active, but efficacy conclusions remain premature (Sloan et al., 2024). This is achieved by increasing $CD8^+$ T cell infiltration and reducing suppressive immune cells such as regulatory Tregs, as well as removing MDSCs. Both Tregs and MDSCs block immune responses in GBM, resulting in greater success (Sloan et al., 2024). Another new approach involved giving PD-1 inhibitors before surgical removal. This showed pharmacodynamic activity and immune infiltration changes; survival benefit remains unproven in clinical trials (Weathers et al., 2025). These results highlight the success of combining treatments to revitalize immunotherapy treatments despite single-agent checkpoint inhibitors being ineffective.

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Survival Factors: Clinical Outcomes and Prognostic Markers

Survival rates vary among GBM patients based on multiple factors. Studies confirmed that improved survival rates among patients who had received the anti-Programmed Death-Ligand 1 (PD-L1) ICI are linked with trimodal immune, genetic, and microbiome characteristics (Weathers et al., 2025). Steroid use during treatment was one of the most frequent predictors of fatalities due to the weakened immune response caused by steroids. Increased cytotoxic and memory T cells in the TME also correlate with better therapeutic effects (Sloan et al., 2024). This shows that the immune response plays a very significant role in both patient survival and prognosis. Contrarily, tumors containing high cytokines displayed therapy resistance, which was reflected by higher fatalities overall (McFaline-Figueroa et al., 2024). The Isocitrate Dehydrogenase (IDH) mutation is one of the strongest indicators of GBM patient outcomes. Patients with IDH-mutant tumors consistently experience better survival outcomes than patients with IDH-wildtype tumors (Sun et al., 2024).

Glioblastoma Formation & Molecular Markers

GBM is the most common malignant primary brain tumor in adults, and it's notoriously resistant to standard treatments (Maris et al., 2015). GBM is driven by genetic changes that affect the critical pathways that regulate cell growth, survival, and death. One of the most frequently mutated genes in GBM is the Tumor Protein 53 (TP53) gene, which plays a key role in both cell cycle control and apoptosis. TP53 was determined to be the most frequently mutated gene within its signaling pathways (Sun et al. 2024). Another major marker is the IDH1 R132H mutation, which is associated with slowed tumor progression and improved patient predictions (Sun et al., 2024). Along with other biomarkers, EGFR activity is a key factor in tumor growth due to its ability to proliferate and extend survival (McFaline-Figueroa et al., 2024). Genes such as PCDHGA10 have been reported as altered in GBM, but their role in gliomagenesis remains to be validated. These mutations play an unrecognizable role in gliomagenesis, which leads to the possibility for future studies on targeting GBM (Sun et al., 2024). Overall, GBM formation results from disrupted cell cycle regulation, unchecked growth signaling, and impaired apoptotic processes, all of which combine to create a tumor that's highly resistant to current treatments (Zhou et al., 2024).

Surgical Outcomes & Standard Treatments

Surgical resection is currently the primary treatment of GBM, in which surgeons remove as much of the tumor mass as possible, including a buffer zone around it, referred to as margins, to be sure not a single cell is left behind. Tumor Treating Fields (TTFields) during maintenance temozolomide improved overall survival in the EF-14 trial. Patients who underwent macroscopic complete resection of GBM experienced a significant survival increase, from 8.4 months to 13.1 months (Maris et al., 2015). This finding reinforces the benefits found in surgical intervention as the primary method for removing GBM. In addition to surgical treatments, the current

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

standard of care includes radiotherapy combined with temozolomide chemotherapy, which is widely accepted and has shown moderate increases in survival rates of GBM patients (McFaline-Figueroa et al., 2024).

One limitation of the treatments described is the high likelihood of tumor progression, which reduces effectiveness of standard therapies and leaves patients with few options at recurrence (McFaline-Figueroa et al., 2024). Although surgical resection and chemotherapy become less effective as tumors progress, bevacizumab, an anti-angiogenic agent, can be considered for treatment post progression. At recurrence, bevacizumab improves progression-free survival and symptoms but does not extend overall survival in randomized trials; therefore, its benefit is typically palliative rather than curative (Pinto-Fraga et al., 2025). Additionally, attempts at enhancing survival outcomes by combining Protein Kinase Inhibitors (PKIs) with other therapies have not been successful (Pinto-Fraga et al., 2025). With surgery and chemoradiation being the only two current methods for GBM removal, there is a growing need to develop more advanced therapeutic strategies to target tumors that have already progressed.

Novel & Experimental Treatments

With GBM therapies facing limitations, several experimental strategies are promising in both lab and animal models. One developing approach involves combining Focused Ultrasound (FUS) with microbubbles to temporarily and selectively open the BBB, improving drug delivery into the tumor site without creating permanent damage or harm (Gould et al., 2025). In preclinical trials, the FUS-treated side of the brain enhanced contrast imaging as well as a greater uptake of therapeutic compounds, emphasizing FUS's potential for precise drug delivery into the brain (Gould et al., 2025). Another experimental method uses oHSV engineered to express an IGF2 decoy receptor (oHSV-IGF2.11). Single-cell and spatial transcriptomics may enable precision therapy by identifying resistant subclones. Initial studies show that these treatments significantly extended survival in mouse GBM models (Noh et al., 2024).

Besides direct tumor targeting, immune modulation is emerging as another powerful strategy. Immune modulation combines checkpoint inhibitors with oHSV-Interleukin-12 (oHSV-IL12) enhanced $CD8^+$ T-cell infiltration to illustrate the potential of dual immune-based therapies (Noh et al., 2024). Researchers are also exploring PI3Kγ pathway inhibitors, which have been promising in reducing tumor-supportive immune cells within the TME (Xu et al., 2024). Immune modulation may also be promising when combined with targeted therapies for therapy-resistant gliomas. One final experimental treatment to note is single-cell and spatial transcriptomics. This has allowed scientists to identify resistant tumors for more specific and adaptive treatments. Oncolytic HSV constructs (e.g., IL-12 or IGF2-decoy) show preclinical efficacy and clinical testing is ongoing. Single-cell and spatial transcriptomics may also enable precision therapy by identifying resistant subclones (Weathers et al., 2025).

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

CONCLUSION

In conclusion, GBM remains one of the most aggressive and treatment-resistant cancers, with patient outcomes limited by the tumor's infiltrative nature, immunosuppressive TME, and resistance to standard therapies (Maris et al., 2015; McFaline-Figueroa et al., 2024). Decades of research have illuminated the complex interaction between genetic mutations, TME dynamics, and the BBB, all of which obstruct drug delivery (Sun et al., 2024; Gould et al., 2025). Even though the standard surgical resection and chemoradiation offers some survival benefit, it is not curative (McFaline-Figueroa et al., 2024). Some recent innovations, such as FUS for BBB opening, IGF pathway inhibition, immune checkpoint blockage, and genetically modified oncolytic viruses, have shown encouraging results in preclinical and early clinical settings (Noh et al., 2024; Gould et al., 2025; Sloan et al., 2024). However, these approaches face a limitation, revealing the need for combination therapies for different tumor subtypes and variations in the immune landscape (Xu et al., 2024). Alongside surgery and chemoradiation, Tumor Treating Fields now provide a validated survival benefit. Emerging approaches, including focused ultrasound BBB opening, myeloid reprogramming, and viro-immunotherapy, show early promise but require rational combinations and rigorous clinical validation (Gould et al., 2025; Xu et al., 2024; Noh et al., 2024). Despite these enormous challenges in treating GBM, growing research suggests future hope with precision medicine to finally overcome this malignant disease (Weathers et al., 2025).

ACKNOWLEDGEMENTS

I am grateful to Dr. Sanchita Bhatnagar (University of California, Davis) for supervision and to Ph.D. candidate Sultan Mussakhan (Brock University, Canada) for mentorship.

REFERENCES

Godinho-Pereira, J., Garcia, A. R., Figueira, I., Malhó, R., & Brito, M. A. (2021). Behind Brain Metastases Formation: Cellular and Molecular Alterations and Blood-Brain Barrier Disruption. *International journal of molecular sciences*, *22*(13), 7057. https://doi.org/10.3390/ijthowms22137057

Gould, A., Luan, Y., Hou, Y., Korobova, F. V., Chen, L., Arrieta, V. A., Amidei, C., Ward, R., Gomez, C., Castro, B., Habashy, K., Zhang, D., Youngblood, M., Dmello, C., Bebawy, J., Bouchoux, G., Stupp, R., Canney, M., Yue, F., Iruela-Arispe, M. L., ... Sonabend, A. M. (2024). Endothelial response to blood-brain barrier disruption in the human brain. *JCI insight*, *10*(4), e187328. https://doi.org/10.1172/jci.insight.187328

Liu, Z., Yang, Y., Fang, H., Cen, B., Fan, Y., Li, J., Wang, L., & He, S. (2025). Single-cell and spatial analyses reveal the effect of VSIG4+S100A10+TAMs on the immunosuppression of glioblastoma and anti-PD-1 immunotherapy. *International journal of biological macromolecules*, *308*(Pt 3), 142415. https://doi.org/10.1016/j.ijbiomac.2025.142415

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Maris, C., D'Haene, N., Trépant, A. L., Le Mercier, M., Sauvage, S., Allard, J., Rorive, S., Demetter, P., Decaestecker, C., & Salmon, I. (2015). IGF-IR: a new prognostic biomarker for human glioblastoma. *British journal of cancer*, *113*(5), 729–737. https://doi.org/10.1038/bjc.2015.242

McFaline-Figueroa, J. R., Sun, L., Youssef, G. C., Huang, R., Li, G., Kim, J., Lee, E. Q., Nayak, L., Chukwueke, U., Beroukhim, R., Batchelor, T. T., Chiocca, E. A., Everson, R. G., Doherty, L., Stefanik, J., Partridge, K., Spearman, A., Myers, A., Westergaard, C., Russ, A., ... Wen, P. Y. (2024). Neoadjuvant anti-PD1 immunotherapy for surgically accessible recurrent glioblastoma: clinical and molecular outcomes of a stage 2 single-arm expansion cohort. *Nature communications*, *15*(1), 10757. https://doi.org/10.1038/s41467-024-54326-7

Noh, M. H., Kang, J. M., Miller, A. A., Nguyen, G., Huang, M., Shim, J. S., Bueso-Perez, A. J., Murphy, S. A., Rivera-Caraballo, K. A., Otani, Y., Kim, E., Yoo, S. H., Yan, Y., Banasavadi-Siddegowda, Y., Nakashima, H., Chiocca, E. A., Kaur, B., Zhao, Z., Lee, T. J., & Yoo, J. Y. (2024). Targeting IGF2 to reprogram the tumor microenvironment for enhanced viro-immunotherapy. *Neuro-oncology*, *26*(9), 1602–1616. https://doi.org/10.1093/neuonc/noae105

Pinto-Fraga, J., García-Chico, C., Lista, S., Lacal, P. M., Carpenzano, G., Salvati, M., Santos-Lozano, A., Graziani, G., & Ceci, C. (2025). Protein kinase inhibitors as targeted therapy for glioblastoma: a meta-analysis of randomized controlled clinical trials. *Pharmacological research*, *212*, 107528. https://doi.org/10.1016/j.phrs.2024.107528

Sloan, A. E., Winter, K., Gilbert, M. R., Aldape, K., Choi, S., Wen, P. Y., Butowski, N., Iwamoto, F. M., Raval, R. R., Voloschin, A. D., Kamiya-Matsuoka, C., Won, M., & Mehta, M. P. (2024). NRG-BN002: Phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma. *Neuro-oncology*, *26*(9), 1628–1637. https://doi.org/10.1093/neuonc/noae058

Sun, X., Jia, Q., Li, K., Tian, C., Yi, L., Yan, L., Zheng, J., Jia, X., & Gu, M. (2024). Comparative genomic landscape of lower-grade glioma and glioblastoma. *PloS one*, *19*(8), e0309536. https://doi.org/10.1371/journal.pone.0309536

Weathers, S. P., Li, X., Zhu, H., Damania, A. V., Knafl, M., McKinley, B., Lin, H., Harrison, R. A., Majd, N. K., O'Brien, B. J., Penas-Prado, M., Loghin, M., Kamiya-Matsuoka, C., Yung, W. K. A., Solis Soto, L. M., Maru, D. M., Wistuba, I., Parra Cuentas, E. R., Hernandez, S., Futreal, A., ... de Groot, J. F. (2025). Improved overall survival in an anti-PD-L1 treated cohort of newly diagnosed glioblastoma patients is associated with distinct immune, mutation, and gut microbiome features: a single arm prospective phase I/II trial. *Nature communications*, *16*(1), 3950. https://doi.org/10.1038/s41467-025-56930-7

Xu, H., Russell, S. N., Steiner, K., O'Neill, E., & Jones, K. I. (2024). Targeting PI3K-gamma in myeloid driven tumour immune suppression: a systematic review and meta-analysis of the preclinical literature. *Cancer immunology, immunotherapy : CII*, *73*(10), 204. https://doi.org/10.1007/s00262-024-03779-2

Xuan, F., Lv, T., Zheng, L., Yu, S., & Ding, M. (2025). Analysis of the correlation between inflammatory cytokines and glioblastoma: A Mendelian randomization study. *Medicine*, *104*(22), e42137. https://doi.org/10.1097/MD.0000000000042137

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Zhou, R., Zhang, K., Dai, T., Guo, Z., Li, T., & Hong, X. (2024). Construction and validation of cell cycle-related prognostic genetic model for glioblastoma. *Medicine*, *103*(40), e39205. https://doi.org/10.1097/MD.0000000000039205

Zhu, F., Qiu, J., Ye, H., Su, W., Wang, R., & Fu, Y. (2025). The Prognostic Significance of Epidermal Growth Factor Receptor Amplification and Epidermal Growth Factor Receptor Variant III Mutation in Glioblastoma: A Systematic Review and Meta-Analysis with Implications for Targeted Therapy. *International journal of molecular sciences*, *26*(8), 3539. https://doi.org/10.3390/ijms26083539