2026 Volume: 02 Issue: 04 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-09

# MRNA VACCINES IN BRAIN CANCER: CURRENT ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES IN PERSONALIZED THERAPY

**Vimala S[1], Sivaranjani J[2], Keerthika M[3], Udhaya Abisha M[4], Mithra D[5] Eswara Priya B*[6]**

[1,2,3,4,5]B. Tech Biotechnology, St. Michael College of Engineering and Technology, Kalayarkoil-630551, Sivaganga District, TamilNadu, India.

[6]Professor & Head, Department of Biotechnology, St. Michael College of Engineering and Technology, Kalayarkoil-630551, Sivaganga District, TamilNadu, India.

**Article Received: 06 March 2026**
**Article Revised: 26 March 2026**
**Published on: 16 April 2026**

***Corresponding Author: Eswara Priya B**
Professor & Head, Department of Biotechnology, St. Michael College of Engineering and Technology, Kalayarkoil-630551, Sivaganga District, TamilNadu, India.

DOI: https://doi-doi.org/101555/ijrpa.7032

## ABSTRACT

Brain cancer remains one of the most aggressive and difficult-to-treat cancers. Conventional treatments such as surgery, chemotherapy, and radiotherapy often provide limited survival benefits, especially in high-grade tumors like glioblastoma (GBM). Recently, mRNA vaccine technology has emerged as a promising strategy in personalized cancer therapy. This review summarizes current advances in mRNA vaccines for brain cancer, including delivery systems, antigen identification, clinical trials, and combination therapies. It also discusses major challenges such as tumor heterogeneity, the blood–brain barrier (BBB), and the immunosuppressive tumor microenvironment. Finally, future directions for improving vaccine design and therapeutic outcomes are highlighted.

**KEYWORDS:** mRNA vaccines; glioblastoma; brain cancer; neoantigen; lipid nanoparticles; tumor microenvironment; personalized immunotherapy.

## 1. INTRODUCTION

Brain tumors, particularly glioblastoma multiforme (GBM), are among the most lethal malignancies, characterized by rapid growth, diffuse infiltration of brain tissue, and profound resistance to therapy. The median survival for GBM patients remains approximately 14–16

months despite aggressive multimodal treatment [1]. Standard care includes maximal safe surgical resection, followed by concurrent temozolomide (TMZ) chemotherapy and radiotherapy (the Stupp protocol), yet recurrence is nearly universal [2]. The aggressive nature of GBM is driven by intra-tumoral heterogeneity, the immunosuppressive tumor microenvironment (TME), and the restrictive blood–brain barrier (BBB), which collectively limit the efficacy of conventional and emerging therapies [3].

Personalized medicine aims to tailor therapeutic strategies based on the genetic, molecular, and immunological profile of each patient's tumor. In this context, mRNA-based vaccines represent an innovative immunotherapeutic approach. By delivering messenger RNA encoding tumor-specific neoantigens or tumor-associated antigens (TAAs), these vaccines prime the host immune system to mount a targeted and durable cytotoxic T-lymphocyte (CTL) response against cancer cells [4]. Building on the extraordinary success of mRNA vaccine platforms demonstrated during the COVID-19 pandemic, researchers are now applying this technology to oncology, with brain cancer as a critical target [5].

This review comprehensively examines the current state of mRNA vaccines for brain cancer, covering the fundamental mechanisms, delivery innovations, clinical trial progress, major challenges, and future perspectives to guide the development of effective personalized immunotherapy.

## 2. CONCEPT OF mRNA VACCINES IN CANCER

mRNA vaccines operate by introducing synthetic messenger RNA molecules encoding selected tumor antigens into the patient's own cells, typically dendritic cells (DCs) or somatic cells at the injection site. Once internalized, the mRNA is translated by host ribosomes into the corresponding tumor antigen proteins. These proteins are processed and presented via major histocompatibility complex (MHC) class I and II pathways, stimulating CD8+ cytotoxic T lymphocytes and CD4+ helper T cells, respectively, thereby generating a multi-faceted anti-tumor immune response [6].

Compared to traditional peptide-based or whole-cell vaccines, mRNA vaccines offer several clinically significant advantages:

- Rapid and scalable design and production using in vitro transcription (IVT) technology
- High biosafety profile: mRNA is non-integrating, transient, and non-infectious
- Ability to encode multiple tumor antigens simultaneously in a single construct (polyvalent vaccines)

- Strong activation of both innate immunity (via pattern recognition receptor stimulation) and adaptive immunity
- Compatibility with personalized neoantigen-based approaches tailored to individual patients

Critically, mRNA molecules do not enter the nucleus and are degraded by normal cellular pathways after translation, eliminating the risk of insertional mutagenesis. These properties make mRNA vaccines particularly suitable for the individualized treatment landscape required in neuro-oncology [7].

## 3. DELIVERY SYSTEMS FOR mRNA VACCINES

A principal challenge of mRNA-based therapeutics is the inherent instability of mRNA in biological environments. Naked mRNA is highly susceptible to degradation by ubiquitous ribonucleases (RNases) and exhibits poor cellular uptake due to its large molecular weight and negative charge. Accordingly, advanced delivery vehicles have been engineered to protect mRNA integrity, enhance intracellular delivery, and facilitate endosomal escape [8].

### *3.1 Lipid Nanoparticles (LNPs)*

LNPs are the most clinically validated mRNA delivery platform, serving as the delivery vehicle for approved COVID-19 mRNA vaccines. They consist of ionizable cationic lipids, phospholipids, cholesterol, and PEGylated lipids, which together form a protective lipid envelope that encapsulates mRNA. LNPs facilitate endosomal escape and cytosolic release of mRNA, enabling efficient antigen expression. Modifications such as ionizable lipids with optimized pKa values have significantly improved tissue targeting and reduced systemic toxicity [9].

### *3.2 Cationic Liposomes and Polymeric Nanoparticles*

Cationic liposomes interact electrostatically with negatively charged mRNA, forming stable lipoplexes. Polymeric carriers, including polyethylenimine (PEI) and PLGA-based nanoparticles, offer tunable physicochemical properties, sustained release, and co-encapsulation of immunostimulatory adjuvants. However, concerns regarding cytotoxicity and inflammatory potential require further optimization [10].

### *3.3 Dendritic Cell (DC)-Based Platforms*

Ex vivo DC-based platforms involve isolating patient-derived monocytes, differentiating

them into DCs, electroporating or transfecting them with mRNA encoding tumor antigens, and reinfusing these antigen-loaded DCs into the patient. DCs are professional antigen-presenting cells that efficiently prime naïve T cells, making this approach highly effective at generating robust anti-tumor immunity. Early clinical trials in GBM using DC-based mRNA vaccines have demonstrated immunogenicity and feasibility [11].

## 4. IDENTIFICATION OF TUMOR ANTIGENS

The therapeutic success of mRNA vaccines critically depends on the selection of appropriate tumor antigens. In brain tumors, particularly GBM, profound genomic and immunological heterogeneity represents a fundamental ch
allenge in antigen target selection [12].

### *4.1 Tumor-Associated Antigens (TAAs)*

TAAs are proteins that are overexpressed on tumor cells relative to normal tissues. In GBM, established TAAs include EGFRvIII (a constitutively active mutant of epidermal growth factor receptor), survivin, Wilms' tumor 1 (WT1), and IL13Rα2. These antigens have been incorporated into early mRNA vaccine prototypes; however, because TAAs are expressed at low levels in normal tissues, they carry the risk of central immune tolerance and off-target autoimmune toxicity [13].

### *4.2 Neoantigens*

Neoantigens arise from somatic mutations unique to each patient's tumor, rendering them highly tumor-specific and immunogenic. Personalized neoantigen vaccines are designed by performing whole-exome sequencing (WES) and RNA sequencing (RNA-seq) of the patient's tumor biopsy, applying bioinformatic pipelines (e.g., pVACtools, IEDB analysis) to predict MHC-binding peptides, and synthesizing mRNA encoding the predicted neoantigens [14]. The landmark trials by Keskin et al. and Hilf et al. demonstrated that personalized neoantigen-based vaccines can generate robust neoantigen-reactive T cell responses in newly diagnosed GBM patients [15, 16].

## 5. CLINICAL TRIALS AND CURRENT PROGRESS

The clinical translation of mRNA vaccines in brain cancer is actively progressing through multiple early-phase trials [17].

### *5.1 Key Clinical Studies*

A pivotal study by Keskin et al. (2019, Nature) demonstrated that personalized neoantigen vaccines could be manufactured within the clinical timeframe for GBM patients and generated neoantigen-specific CD4+ and CD8+ T cell responses in all evaluated patients. Notably, vaccine-induced T cells displayed an effector memory phenotype and were capable of tumor infiltration [15]. Similarly, the APVAC1/APVAC2 trial (Hilf et al., Nature, 2019) using a poly-ICLC adjuvanted vaccine targeting tumor-specific neoantigens and unmutated TAAs demonstrated immunogenicity with favorable safety profiles [16].

Additionally, the DCVax-L trial, the largest randomized controlled trial of a DC-based mRNA vaccine (mRNA-loaded autologous DCs) in newly diagnosed GBM, reported extended overall survival in the vaccine-treated arm. A subset of long-term survivors was identified, suggesting the potential for durable benefit in select patient populations [18].

### *5.2 Combination Strategies*

Given the immunosuppressive nature of the GBM microenvironment, mRNA vaccine monotherapy may be insufficient. Consequently, combination regimens have been increasingly explored:

- mRNA vaccines + Immune checkpoint inhibitors (ICIs): PD-1/PD-L1 blockade (nivolumab, pembrolizumab, atezolizumab) synergizes with vaccine-induced T cell priming by relieving T cell exhaustion within the TME [19].
- mRNA vaccines + Temozolomide (TMZ): TMZ induces immunogenic cell death (ICD) and lymphodepletion followed by homeostatic proliferation, which may amplify vaccine-mediated immune responses [20].
- mRNA vaccines + Radiotherapy: Radiation can act as an in situ vaccine by exposing tumor antigens; combining with mRNA vaccines may enhance antigen cross-presentation [21].
- mRNA vaccines + CAR-T cell therapy: Emerging strategies combine mRNA-based in vivo CAR-T cell generation with neoantigen vaccines to broaden the anti-tumor immune response [22].

## 6. CHALLENGES IN mRNA VACCINE THERAPY

### *6.1 Blood–Brain Barrier (BBB)*

The BBB is a highly selective neurovascular interface composed of tight junction-forming endothelial cells, pericytes, and astrocytic endfeet that restricts the paracellular and

transcellular passage of macromolecules and immune cells into the CNS parenchyma. While mRNA vaccines are administered systemically, the subsequent trafficking of vaccine-activated effector T cells into brain tumors is critically impeded by the BBB. Strategies to enhance T cell infiltration include BBB disruption techniques (focused ultrasound, mannitol), engineered T cells with enhanced CNS-homing chemokine receptors (CXCR3, CCR2), and intracerebral vaccine delivery [23].

### *6.2 Tumor Heterogeneity*

GBM exhibits extensive inter- and intra-tumoral heterogeneity at genetic, epigenetic, and phenotypic levels, including the presence of glioma stem cells (GSCs) that drive therapy resistance and recurrence. Single antigen-targeted vaccines are vulnerable to antigen loss variants (immune escape), wherein tumor clones lacking the targeted antigen can survive and proliferate. Polyvalent mRNA vaccines targeting multiple neoantigens simultaneously represent a critical strategy to overcome immune escape [12, 24].

### *6.3 Immunosuppressive Tumor Microenvironment (TME)*

The GBM TME is profoundly immunosuppressive, characterized by a high density of M2-polarized tumor-associated macrophages (TAMs) and microglia, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and elevated expression of immunosuppressive cytokines (TGF-β, IL-10) and checkpoint ligands (PD-L1, CD47). These elements collectively suppress the effector functions of vaccine-induced T cells. Overcoming the immunosuppressive TME is a critical prerequisite for the clinical success of mRNA vaccination strategies [25].

### *6.4 mRNA Stability and Manufacturing Scalability*

Despite advances in chemical modifications (N1-methylpseudouridine substitution, optimized 5' cap structures, poly(A) tail engineering) that enhance mRNA stability and translation efficiency, maintaining cold chain requirements and ensuring batch-to-batch consistency in personalized vaccine manufacturing remains technically demanding. The manufacturing turnaround for personalized neoantigen vaccines (typically 4–12 weeks from tumor biopsy to product release) must be further compressed to ensure clinical feasibility, particularly for rapidly progressing tumors [26].

## 7. FUTURE PERSPECTIVES

The future development of mRNA vaccines for brain cancer is expected to leverage advances

across multiple domains:

- AI-driven neoantigen prediction: Machine learning and deep learning algorithms trained on HLA-peptide binding data, mass spectrometry immunopeptidomics, and tumor RNA expression profiles are expected to substantially improve the precision and coverage of personalized neoantigen selection [27].
- Optimized CNS-targeted delivery: Novel LNP formulations functionalized with brain-targeting ligands (transferrin receptor antibodies, ApoE peptides) or intranasal delivery routes may enhance direct CNS delivery and overcome BBB restrictions [28].
- mRNA self-amplifying (saRNA) constructs: Self-amplifying mRNA platforms incorporating alphaviral replicase elements enable prolonged antigen expression from lower mRNA doses, potentially improving immunogenicity while reducing dosing burden [29].
- Integration of multi-omics data: Incorporating genomic, transcriptomic, proteomic, and single-cell immune profiling data through systems immunology approaches will enable holistic personalization of vaccine design and patient stratification [30].
- In situ vaccination strategies: Combining mRNA vaccines with oncolytic viruses, intratumoral immunostimulants (STING agonists, TLR agonists), or tumor-ablating modalities (thermal ablation, photodynamic therapy) that release tumor antigens in situ may create synergistic in vivo vaccination effects [31].
- Randomized controlled trials: The field urgently requires large-scale, adequately powered, randomized clinical trials incorporating robust biomarker programs to definitively establish efficacy and identify predictive biomarkers of response [32].

## 8. CONCLUSION

mRNA vaccines represent a transformative and promising modality in the evolving landscape of personalized medicine for brain cancer. Their inherent flexibility in antigen design, favorable safety profile, and capacity to activate robust multi-arm adaptive immune responses position them as compelling candidates for neuro-oncology immunotherapy. Preclinical and early-phase clinical evidence demonstrates that mRNA vaccines can generate clinically relevant antigen-specific T cell responses in GBM patients and, when combined with complementary immunotherapies, may provide meaningful improvements in survival.

Nevertheless, the realization of mRNA vaccine efficacy in brain cancer requires overcoming formidable biological barriers including the BBB, profound tumor heterogeneity, and the immunosuppressive TME. Continued innovation in delivery systems, neoantigen prediction

algorithms, combination immunotherapy regimens, and the design of rigorous clinical trials will be essential to translate this scientifically compelling approach into a clinical standard of care for patients with brain cancer.

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge the guidance and mentorship of Dr. B. Eswara Priya and the Department of Pharmaceutical Sciences for their support throughout the preparation of this review.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-996.
2. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261-279.
3. Sahin U, Tureci O. Personalized vaccines for cancer immunotherapy. Science. 2018;359(6382):1355-1360.
4. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. Nature. 2019;565(7738):234-239.
5. Hilf N, Kuttruff-Coqui S, Frenzel K, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. Nature. 2019;565(7738):240-245.
6. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078-1094.
7. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. J Transl Med. 2018;16(1):142.
8. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. Cancer Cell. 2017;31(3):326-341.
9. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20(1):26-41.
10. Cloughesy TF, Mochizuki AY, Orpilla JR, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med. 2019;25(3):477-486.

11. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med. 2016;375(26):2561-2569.
12. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol. 2017;18(10):1373-1385.