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Dendritic-Cell Vaccines and Cytokine-Induced Killer Cell Immunotherapy for Glioblastoma: A Translational Review of Biological Rationale, Clinical Evidence, and Combination Strategies

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ABSTRACT

Glioblastoma, IDH-wildtype, CNS WHO grade 4, is an infiltrative and immunologically complex adult-type diffuse glioma with poor prognosis despite maximal safe resection, radiotherapy, temozolomide, and selected use of tumor-treating fields. The current histomolecular definition of glioblastoma, together with its antigenic heterogeneity, myeloid-rich tumor microenvironment, blood-brain/tumor barrier, treatment-induced lymphopenia, and corticosteroid-associated immunosuppression, creates major challenges for immunotherapy. Dendritic-cell vaccines and cytokine-induced killer cell-based therapy provide complementary biological solutions. Dendritic-cell vaccines can process broad tumor-antigen repertoires and prime adaptive antitumor immunity, whereas CIK cells provide ex vivo-expanded cytotoxic effector function with T-cell and natural killer-like properties. This review synthesizes developments over the last decade in glioblastoma-directed DC vaccination, CIK-cell therapy, and DC-CIK strategies, while situating them within the broader landscape of surgery, radiochemotherapy, tumor-treating fields, immune checkpoint blockade, CAR-T cells, oncolytic virotherapy, anti-angiogenic therapy, and recurrent-disease management. Current evidence supports the safety and biological plausibility of DC and CIK-based immunotherapy, with encouraging survival signals from DCVax-L and randomized CIK-cell studies. However, definitive implementation requires molecularly homogeneous cohorts, standardized GMP-compliant manufacturing, validated potency assays, steroid-adjusted immune monitoring, biomarker-guided patient selection, and rational combination designs. DC and DC-CIK platforms should therefore be viewed not as isolated alternatives but as immune-amplifying components of multimodal neuro-oncology.

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ABBREVIATIONS

BBB, blood-brain barrier; CAR-T, chimeric antigen receptor T cell; CIK, cytokine-induced killer; CNS, central nervous system; DC, dendritic cell; DC-CIK, dendritic cell-cytokine-induced killer; EGFR, epidermal growth factor receptor; GBM, glioblastoma; GMP, good manufacturing practice; HLA, human leukocyte antigen; ICI, immune checkpoint inhibitor; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine-DNA methyltransferase; MHC, major histocompatibility complex; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide; TME, tumor microenvironment; TTFields, tumor-treating fields; WHO, World Health Organization.

GRAPHICAL CONCEPTUAL FRAMEWORK

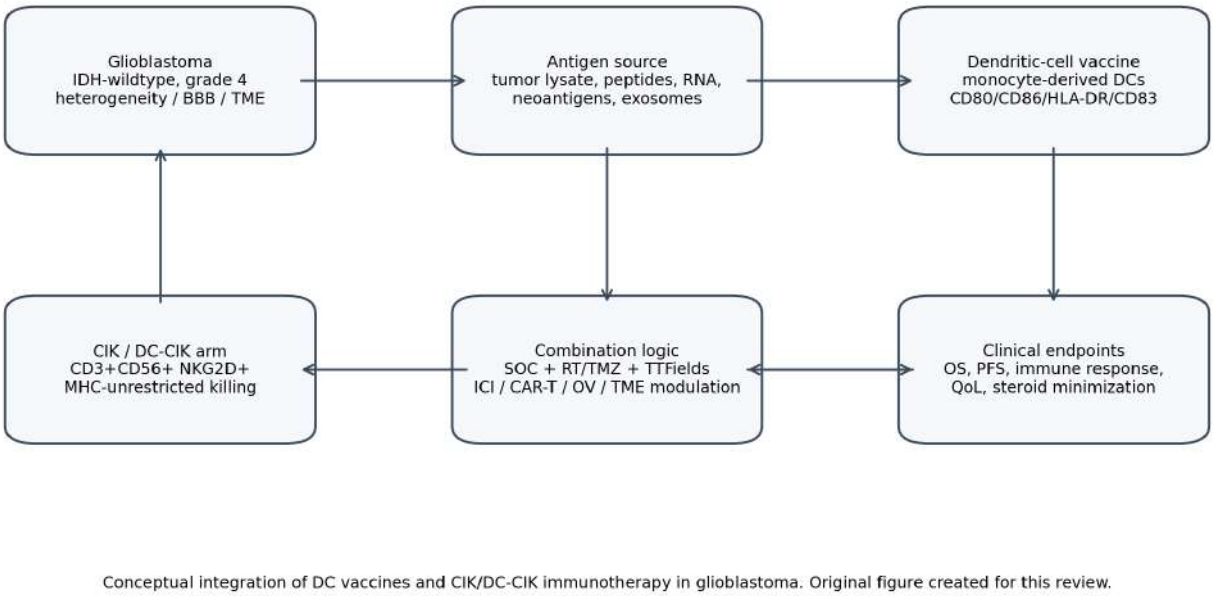

Figure 1. Conceptual integration of dendritic-cell vaccination and CIK/DC-CIK immunotherapy in glioblastoma. The figure is original and summarizes how molecularly defined glioblastoma, tumor-antigen acquisition, dendritic-cell priming, CIK/DC-CIK effector function, and multimodal combination strategies converge on clinically relevant endpoints.

TABLES

Table 1. Glioblastoma categories and implications for immunotherapy.

Category	Core definition	Typical relevance	Immunotherapy implication
Histological glioblastoma	IDH-wildtype diffuse astrocytic tumor with necrosis and/or microvascular proliferation	Classical grade 4 morphology	Usually high tumor burden and hypoxic/myeloid-rich niches; antigen breadth favors lysate or multi-antigen approaches
Molecular glioblastoma	IDH-wildtype diffuse astrocytic tumor with EGFR amplification, TERT promoter mutation, or +7/-10 signature even without classic grade 4 histology	Earlier molecular recognition of grade 4 biology	Trial eligibility should be molecularly defined; lower residual disease may create a better vaccine window
IDH-mutant astrocytoma, grade 4	Diffuse IDH-mutant astrocytoma with grade 4 features or molecular grading criteria	Not termed glioblastoma in WHO CNS5	Should not be pooled with IDH-wildtype GBM in immunotherapy analyses unless prespecified
Recurrent glioblastoma	Progressive disease after standard therapy	No universal standard of care	Higher immune dysfunction and steroid exposure; may require combination or debulking before immune therapy

Table 2. Selected immunotherapeutic strategies in glioblastoma and relationship to DC/CIK platforms.

Strategy	Main mechanism	Representative evidence	Strength	Key limitation
DC vaccine	Ex vivo antigen loading and adaptive T-cell priming	DCVax-L phase III externally controlled cohort; ICT-107 phase II; meta-analyses	Best-developed vaccine platform in GBM	Manufacturing heterogeneity; control-arm controversies; need biomarkers

CIK cells	Ex vivo-expanded CD3+CD56+ cytotoxic cells with NK-like activity	Randomized phase III CIK trial with RT/TMZ; later selected analyses	Broad cytotoxicity and feasible autologous manufacture	Trafficking, persistence, standardization, and immunosuppressive TME
DC-CIK	DC-mediated antigen education plus CIK effector cytotoxicity	Solid-tumor meta-analysis; emerging GBM preclinical evidence	Combines priming and effector arms	GBM clinical evidence still limited
Checkpoint blockade	PD-1/PD-L1 or CTLA-4 axis inhibition	Negative/neutral phase III trials; neoadjuvant signals	Potential partner for vaccine-induced T cells	Low baseline T-cell infiltration and myeloid suppression
CAR-T cells	Engineered antigen-specific T-cell cytotoxicity	Early clinical responses against IL13Ralpha2, EGFR/EGFRvIII, HER2-related targets	Potent target-directed killing	Antigen escape, limited persistence, neurotoxicity
Oncolytic viruses	Tumor lysis, antigen release, innate immune activation	Recombinant poliovirus and other viral platforms	Can convert tumor into in situ vaccine	Delivery, antiviral immunity, variable response

Table 3. Minimum reporting elements recommended for future DC/CIK glioblastoma studies.

Domain	Recommended variables	Rationale
Integrated diagnosis	IDH, MGMT, TERT, EGFR, +7/-10, CDKN2A/B, methylation class if available	Avoids mixing biologically distinct gliomas
Clinical context	Age, KPS/ECOG, residual tumor, steroid dose, lymphocyte count, line of therapy	Controls major immune and survival confounders
DC product	Antigen source, maturation cocktail, route, schedule, phenotype, viability, potency	Enables reproducibility and cross-trial comparison
CIK/DC-CIK product	Activation protocol, culture duration, cytokines, CD3+CD56+ fraction, NKG2D, cytotoxicity assay	Defines effector quality and release criteria
Immune monitoring	TCR clonality, cytokines, antigen-specific T cells, myeloid suppressor markers	Links clinical outcome to mechanism
Endpoints	OS, PFS, steroid-adjusted response, neurocognitive function, QoL, safety	Captures clinically meaningful benefit beyond imaging

1. INTRODUCTION

Glioblastoma is the paradigmatic example of a biologically aggressive, spatially infiltrative, and immunologically refractory solid tumor of the central nervous system. The contemporary diagnostic term glioblastoma, IDH-wildtype, CNS WHO grade 4 is no longer a purely histological label; it is an integrated histomolecular entity defined by IDH-wildtype diffuse astrocytic morphology in combination with either classical grade 4 histological features or molecular signatures such as TERT promoter mutation, EGFR amplification, or combined whole-chromosome 7 gain and chromosome 10 loss [1, 2, 9, 49]. This definitional shift is not semantic. It determines prognosis, trial eligibility, biomarker interpretation, and the rational design of immunotherapy because molecular glioblastoma can be diagnosed before necrosis or microvascular proliferation becomes histologically evident [9-11].

Standard therapy remains anchored in maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide, with tumor-treating fields considered for eligible patients during maintenance therapy [2-6]. Nevertheless, glioblastoma almost invariably recurs. Clinical benefit from cytotoxic therapy is constrained by diffuse invasion, inter- and intra-tumoral heterogeneity, DNA-repair programs such as MGMT promoter status, and the blood-brain/tumor barrier [2, 5, 12, 50]. These constraints justify a sustained effort to develop immune-based approaches that can recognize heterogeneous tumor antigens, generate systemic and intracranial antitumor immunity, and ideally produce durable immune memory.

Among immunotherapeutic strategies, dendritic-cell vaccines and cytokine-induced killer cell therapy occupy a biologically coherent niche. Dendritic cells are professional antigen-presenting cells that license tumor-specific T-cell priming, whereas CIK cells are ex vivo-expanded effector lymphocytes with mixed T-cell and natural killer-like cytotoxicity, typically enriched for CD3+CD56+ cells and NKG2D-mediated, partly MHC-unrestricted killing [19, 25-31]. The DC-CIK concept links antigen education and effector-cell amplification: DCs process tumor antigens and provide costimulation, while CIK cells provide immediate cytotoxic pressure and cytokine support. In glioblastoma, this model is attractive because antigen heterogeneity and local immunosuppression reduce the efficacy of single-antigen or single-axis therapies.

This narrative review synthesizes developments from approximately the last decade, with inclusion of selected foundational studies when necessary for clinical context. The review focuses on glioblastoma as the target indication while situating DC and CIK approaches within the broader therapeutic landscape, including conventional standard of care, tumor-treating fields, immune checkpoint blockade, CAR-T-cell therapy, oncolytic virotherapy, anti-angiogenic therapy, and recurrent-disease strategies.

2. REVIEW SCOPE AND LITERATURE APPROACH

This article is a narrative review rather than a formal systematic review. The scope was defined around four interconnected questions: first, how the current biological definition of glioblastoma affects immunotherapy development; second, how DC vaccines and CIK/DC-CIK therapy have evolved in glioblastoma and solid tumors over the last decade; third, what clinical and translational evidence supports their use; and fourth, which combination strategies may overcome the dominant barriers of glioblastoma immunoresistance. Recent peer-reviewed studies, clinical trials, meta-analyses, and guideline documents were prioritized. Older sources were retained when they established current standard-of-care therapy or remain necessary to interpret modern clinical trials [2-4, 17, 24].

The review follows the general article structure recommended for review articles by Academia Biology: abstract, introduction, topic-based sections, conclusions, and mandatory declarations. Because no new human or animal data are generated, the manuscript does not include original patient-level analyses or unpublished observations. References are formatted in numerical Vancouver style, as required by the journal style guide.

3. CONTEMPORARY GLIOBLASTOMA TAXONOMY AND BIOLOGICAL SUBTYPES

The 2021 WHO CNS classification simplified adult-type diffuse gliomas into three principal entities: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype [1, 9, 10]. In adults, the diagnosis of glioblastoma is reserved for IDH-wildtype diffuse astrocytic tumors with CNS WHO grade 4 behavior. Histological glioblastoma is defined by necrosis and/or microvascular proliferation. Molecular glioblastoma, by contrast, may lack these microscopic features but is upgraded to glioblastoma when EGFR amplification, TERT promoter mutation, or combined chromosome 7 gain and chromosome 10 loss is present [1, 9, 49]. This has practical consequences for immunotherapy trials because a radiologically or histologically lower-grade appearing lesion can carry glioblastoma-like molecular risk.

Classical labels such as primary versus secondary glioblastoma are increasingly replaced by molecularly integrated taxonomy. Historically, primary glioblastoma referred to de novo IDH-wildtype disease in older adults, whereas secondary glioblastoma referred to progression from lower-grade IDH-mutant astrocytoma. Under the current WHO scheme, IDH-mutant grade 4 astrocytoma is not called glioblastoma, even when it has necrosis or microvascular proliferation [1, 9]. Therefore, modern DC/CIK studies must define whether enrolled patients had IDH-wildtype glioblastoma, IDH-mutant astrocytoma grade 4, or mixed high-grade glioma cohorts. Failure to separate these entities can obscure therapeutic signals.

Glioblastoma also contains transcriptional and cellular-state heterogeneity. Tumor cells may occupy proneural-like, classical-like, mesenchymal-like, and neural progenitor-like states, with plastic transitions influenced by genetic alterations and microenvironmental cues [42, 43]. Mesenchymal transition is clinically important because it is associated with inflammatory signaling, myeloid infiltration, tissue injury, and treatment resistance. From an immunotherapy perspective, this plasticity means that a fixed antigen or a single immune intervention may be insufficient. A multi-antigen DC vaccine, autologous tumor lysate, RNA-based antigen loading, or combined DC-CIK platform is therefore biologically more plausible than a narrow monovalent vaccine for many patients.

Biomarkers that are already clinically relevant include MGMT promoter methylation, extent of resection, age, performance status, steroid exposure, IDH status, TERT promoter mutation, EGFR amplification, CDKN2A/B loss, and radiographic burden [2, 5, 11, 12]. For vaccine and cellular therapy, additional biomarkers are needed: antigen expression, neoantigen burden, HLA genotype, T-cell receptor clonality, peripheral lymphocyte count, myeloid-derived suppressor-cell burden, tumor-associated macrophage phenotype, corticosteroid dose, and treatment-induced lymphopenia. Future trials should avoid treating glioblastoma as a single immunological category.

4. STANDARD AND EMERGING THERAPEUTIC STRATEGIES IN GLIOBLASTOMA

The therapeutic backbone for newly diagnosed glioblastoma remains maximal safe resection followed by focal radiotherapy with concomitant and adjuvant temozolomide [2, 3, 5]. Maximal safe resection reduces mass effect and provides tissue for integrated diagnosis, but microscopic infiltration prevents curative surgery. Temozolomide provides survival benefit particularly in patients with MGMT promoter methylation, whereas unmethylated MGMT tumors are less responsive. Postoperative radiotherapy is usually delivered to a focal target volume, and treatment planning increasingly integrates molecular diagnosis and advanced imaging.

Tumor-treating fields are a device-based modality that uses alternating electric fields to disrupt mitosis. In the EF-14 trial, the addition of tumor-treating fields to maintenance temozolomide improved progression-free and overall survival compared with temozolomide alone, although implementation depends on adherence, patient acceptance, access, and quality-of-life considerations [4, 6, 7]. In the context of immunotherapy, tumor-treating fields are relevant because they can be combined with systemic or cellular therapies without overlapping classic myelosuppression.

For recurrent glioblastoma, there is no universally accepted standard of care. Options include reoperation in selected patients, reirradiation, lomustine, regorafenib, bevacizumab, clinical-trial enrollment, and best supportive care [2, 5, 47, 48]. Regorafenib improved survival compared with lomustine in the REGOMA trial, while bevacizumab can improve edema and steroid requirements but has not consistently improved overall survival in newly diagnosed disease [8, 48]. These recurrent-disease realities are central for DC/CIK development: immunotherapy may be more effective when administered earlier, when tumor burden and steroid exposure are lower and immune competence is less compromised.

Other immunotherapy strategies have produced mixed results. Immune checkpoint blockade has transformed melanoma, lung cancer, and renal cancer, but phase III data in glioblastoma have been largely disappointing. Nivolumab did not improve survival compared with bevacizumab in recurrent glioblastoma in CheckMate 143, and adding nivolumab to standard chemoradiation did not improve outcomes in newly diagnosed MGMT-methylated glioblastoma [14, 15]. However, neoadjuvant anti-PD-1 studies suggest that timing may matter: preoperative checkpoint blockade can alter intratumoral and systemic immune responses in selected recurrent patients [16]. Thus, checkpoint inhibitors should not be dismissed entirely, but their use likely requires rational combinations and biomarker selection.

CAR-T-cell therapy is an active area of glioblastoma research, with targets including IL13Ralpha2, EGFRvIII, HER2, EphA2, B7-H3, and multi-antigen constructs [34-36]. Early clinical responses, including dramatic radiographic regression in selected cases, show that engineered T cells can traffic to and act within the CNS. However, antigen heterogeneity, antigen loss, local immunosuppression, limited persistence, and neurotoxicity remain obstacles. Oncolytic viruses and viral-vector approaches may convert immunologically cold tumors into inflamed lesions by inducing immunogenic cell death, antigen release, and type I interferon signaling [37-39]. These approaches can be conceptually paired with DC vaccination or CIK/DC-CIK infusion to enhance antigen presentation and effector function.

5. IMMUNOBIOLOGY OF GLIOBLASTOMA: WHY VACCINES AND CELLULAR THERAPIES ARE DIFFICULT BUT RATIONAL

Glioblastoma is not immunologically inert; rather, it is immunologically distorted. The tumor microenvironment contains resident microglia, recruited macrophages, T cells, regulatory T cells, endothelial cells, astrocytes, and extracellular matrix elements that jointly shape immune function [13, 41, 44, 45]. Myeloid cells often dominate the leukocyte compartment and may acquire immunosuppressive phenotypes through CSF-1, TGF-beta, IL-10, prostaglandins, hypoxia, adenosine, and tumor-derived metabolites. T-cell infiltration is often limited, exhausted, spatially excluded, or functionally suppressed.

The CNS has specialized immune surveillance rather than absolute immune privilege. Antigens can drain through meningeal lymphatic pathways, and activated lymphocytes can access the CNS under inflammatory conditions. Nonetheless, the blood-brain barrier and blood-tumor barrier restrict immune-cell trafficking and drug delivery. Glioblastoma further induces systemic immune dysfunction, including lymphopenia, T-cell sequestration, myeloid skewing, and steroid-associated immunosuppression. These factors explain why checkpoint blockade alone has underperformed and why active vaccination must be paired with careful timing, antigen choice, adjuvant selection, and reduction of immunosuppressive co-medications.

DC vaccines and CIK/DC-CIK therapy address complementary immunological problems. DC vaccines aim to initiate or amplify tumor-specific adaptive immunity by presenting tumor antigens with costimulatory signals and cytokine polarization. CIK cells provide broad cytotoxicity that is less dependent on classical HLA-restricted antigen recognition. Co-culture of DCs and CIK cells can increase effector expansion, cytotoxicity, IFN-gamma secretion, and tumor recognition in some settings [27-31]. For glioblastoma, this dual mechanism is attractive because tumors frequently downregulate antigen-presentation machinery and display intratumoral antigenic mosaics.

6. DENDRITIC-CELL VACCINES IN GLIOBLASTOMA

Dendritic-cell vaccines generally involve ex vivo generation of autologous monocyte-derived DCs, loading with tumor antigens, maturation with cytokines or innate immune agonists, and reinfusion by intradermal, subcutaneous, intranodal, or other routes.

Antigen sources include autologous tumor lysate, defined peptides, tumor-associated antigens, total tumor RNA, mRNA, neoantigen candidates, and exosome-associated antigens. In glioblastoma, autologous tumor lysate has a major theoretical advantage because it captures patient-specific antigenic breadth and reduces dependence on a single target.

The most visible late-phase evidence comes from the autologous tumor lysate-loaded DCVax-L program. In the phase III externally controlled cohort analysis, DCVax-L added to standard care was associated with improved overall survival in newly diagnosed and recurrent glioblastoma compared with matched external controls [19]. Median overall survival for newly diagnosed patients was reported as 19.3 months from randomization versus 16.5 months for external controls, and recurrent glioblastoma patients had a median overall survival of 13.2 months from recurrence versus 7.8 months in controls [19]. The trial also suggested greater benefit in MGMT-methylated tumors. These findings support biological and clinical plausibility but should be interpreted with methodological caution because the final analysis used external controls after crossover and endpoint changes [19, 20].

Other DC vaccine programs have used defined antigen panels. ICT-107, an autologous DC vaccine pulsed with multiple glioblastoma-associated peptides, was evaluated in a randomized phase II trial in newly diagnosed glioblastoma [18]. Although the overall study did not establish a definitive registration-level survival benefit, exploratory analyses suggested that antigen expression, HLA type, and patient selection may influence outcome. Peptide-based vaccines such as rindopepimut targeting EGFRvIII demonstrated immunogenicity but failed to improve survival in a randomized phase III trial, partly illustrating the vulnerability of single-antigen strategies to antigen-negative escape [17].

Updated meta-analyses of DC vaccination in glioblastoma generally report signals of improved survival with acceptable toxicity, but heterogeneity remains substantial [21]. Differences across studies include tumor grade, molecular classification, extent of resection, timing relative to chemoradiation, steroid dose, antigen source, maturation cocktail, route, number of vaccine doses, use of adjuvants, control-arm design, and immune-monitoring assays. Therefore, the conclusion should be balanced: DC vaccines are among the most mature immunotherapy platforms in glioblastoma and have encouraging safety and survival signals, but harmonized manufacturing, biomarker-driven stratification, and rigorously controlled trials remain necessary.

Mechanistically, DC vaccines may be most effective when there is low residual disease after resection, adequate lymphocyte reserve, limited corticosteroid exposure, and sufficient antigenic material. Radiotherapy and temozolomide may enhance antigen release and lymphodepletion-induced homeostatic proliferation, but temozolomide can also impair lymphocyte compartments. The optimal timing is therefore not obvious. Vaccination before profound lymphopenia, during minimal residual disease, or in a neoadjuvant/perioperative window may be more rational than late administration in heavily treated recurrent disease.

7. CIK AND DC-CIK IMMUNOTHERAPY IN GLIOBLASTOMA

CIK cells are generated by ex vivo stimulation of peripheral blood mononuclear cells, commonly using IFN-gamma priming, anti-CD3 antibody, IL-2, and sometimes IL-1 or other cytokine support. The resulting population is heterogeneous but typically contains cytotoxic CD3+CD56+ cells with T-cell and NK-like properties. CIK-mediated killing involves perforin/granzyme release, Fas/FasL interactions, cytokine secretion, and activating receptors such as NKG2D. Because part of their activity is MHC-unrestricted, CIK cells may retain cytotoxicity against tumor cells with impaired antigen presentation [29-32].

The key glioblastoma clinical evidence is the randomized phase III trial by Kong and colleagues, which tested autologous CIK-cell immunotherapy with standard radiotherapy and temozolomide in newly diagnosed glioblastoma [25]. The study reported improved progression-free survival but did not demonstrate a statistically definitive overall survival benefit in the full cohort. Subsequent analyses in pathologically pure glioblastoma suggested that CIK immunotherapy combined with conventional chemoradiotherapy could prolong both progression-free and overall survival in selected patients [26]. These data justify further development, especially under current WHO molecular classification and with improved immune monitoring.

DC-CIK therapy attempts to enhance CIK performance through antigen education and costimulatory interaction with mature DCs. Across solid tumors, systematic review and meta-analysis data suggest that DC-CIK therapy can improve survival and response outcomes with acceptable safety, although most evidence comes from heterogeneous tumor types and variable trial quality [27]. In glioblastoma specifically, clinical data remain more limited than for DC vaccines or CIK cells alone, but preclinical work has recently provided evidence that DC-CIK cells can exert antitumor activity against glioblastoma models, including temozolomide-resistant contexts [28]. These findings are particularly relevant because temozolomide resistance is a major clinical problem and because DC-CIK therapy can be manufactured as an autologous, multi-functional cell product.

The principal limitations of CIK/DC-CIK therapy are biological and logistical. Biological limitations include limited trafficking to infiltrative brain lesions, suppressive myeloid niches, antigenic and metabolic adaptation, short persistence, and potential exhaustion. Logistical limitations include variability in starting leukocyte quality, culture media, serum use, cytokine concentrations, expansion duration, release criteria, potency assays, cryopreservation, and batch-to-batch comparability. Serum-free and closed-system manufacturing protocols, gas-permeable culture devices, standardized release phenotyping, and potency assays are therefore not technical details but core translational requirements [31].

8. COMBINATION STRATEGIES: CONNECTING DC/CIK PLATFORMS TO THE BROADER IMMUNOTHERAPY LANDSCAPE

The most realistic future for DC and CIK/DC-CIK therapy in glioblastoma is combination treatment. The biological objective is not simply to add multiple therapies, but to align mechanisms: increase antigen release, improve antigen presentation, amplify effector cells, reduce suppressive myeloid barriers, support trafficking, and prevent adaptive immune escape. Surgery provides antigenic material and cytoreduction. Radiotherapy can induce immunogenic cell death and increase antigen release, but can also drive lymphopenia. Temozolomide can synergize through lymphodepletion and antigen release in some contexts, but sustained lymphotoxicity may impair vaccine responses. Therefore, dose, sequence, and lymphocyte monitoring matter.

Checkpoint inhibitors may be more rational as partners than as monotherapy. DC vaccination can expand tumor-specific T cells, and checkpoint blockade may prevent exhaustion of these vaccine-induced clones. However, phase III glioblastoma checkpoint trials have been negative or neutral, so future combinations should require biomarker logic, such as inflamed tumor signatures, low steroid requirement, mismatch repair deficiency, hypermutation context, or neoadjuvant immune activation [14-16].

Oncolytic viruses are attractive partners because they can create an in situ vaccine effect. Viral lysis releases tumor antigens, danger-associated molecular patterns, and inflammatory cytokines, potentially improving DC activation. A DC vaccine or DC-CIK infusion after oncolytic priming could theoretically convert antigen release into organized adaptive immunity. CAR-T-cell therapy can provide highly potent antigen-directed killing, but antigen escape remains a major problem. DC vaccination against broader antigen repertoires, or CIK/DC-CIK therapy with MHC-unrestricted cytotoxicity, may complement CAR-T specificity.

Anti-angiogenic and myeloid-modulating therapies may also be relevant. Bevacizumab can reduce edema and steroid dependence, indirectly improving immune competence, although it may also alter immune trafficking. CSF-1R inhibitors, TGF-beta inhibitors, adenosine-pathway inhibitors, IDO inhibitors, and Wnt/beta-catenin pathway modulation have mechanistic appeal, but clinical validation remains incomplete. The recent preclinical observation that DC-CIK treatment may interact with Wnt/beta-catenin-related pathways suggests a possible future axis for rational combinations in glioblastoma [28].

9. MANUFACTURING, QUALITY CONTROL, AND TRANSLATIONAL REQUIREMENTS

For publication and clinical translation, DC and CIK/DC-CIK therapy must be described as advanced biological products rather than generic immunotherapy. Key DC manufacturing variables include leukapheresis or blood draw timing, monocyte isolation, GM-CSF/IL-4 differentiation, maturation cocktail, antigen-loading method, sterility testing, endotoxin testing, viability, phenotype, cytokine secretion, potency, cryopreservation, and transport conditions. Typical phenotypic release markers include HLA-DR, CD80, CD83, CD86, CD11c, and low CD14 for mature monocyte-derived DC products, although exact specifications differ by protocol.

CIK manufacturing variables include starting lymphocyte count, activation reagent, IFN-gamma priming, anti-CD3 stimulation, IL-2 concentration, culture duration, feeding schedule, serum-free versus serum-containing medium, expansion platform, sterility, mycoplasma, endotoxin, viability, phenotype, cytotoxic potency, and residual reagents. Relevant phenotype includes CD3, CD56, CD8, CD4, NKG2D, NKp30/NKp44/NKp46, PD-1, TIM-3, LAG-3, and memory markers. For DC-CIK co-culture, the ratio of DCs to CIK precursors, co-culture duration, antigen loading, maturation state, and cytokine milieu are critical.

Potency assays should match mechanism. For DC vaccines, antigen uptake, maturation phenotype, IL-12p70 secretion, mixed lymphocyte reaction, antigen-specific T-cell activation, and T-cell receptor repertoire expansion may be informative. For CIK/DC-CIK products, cytotoxicity against glioblastoma cell lines, patient-derived glioma stem-like cells, or autologous tumor cells, IFN-gamma release, degranulation marker CD107a, and receptor-blocking assays can be used. A future Academia Biology submission should emphasize these translational details because they distinguish a scientifically credible review from a generic overview.

10. BIOMARKERS AND PATIENT SELECTION

The failure of several glioblastoma immunotherapy trials can be partly attributed to inadequate patient selection. For DC vaccination, candidate biomarkers include tumor antigen profile, HLA type, MGMT promoter methylation, extent of resection, residual tumor volume, steroid exposure, lymphocyte count, T-cell receptor clonality, interferon-gamma signatures, and myeloid inflammation. For CIK/DC-CIK therapy, biomarkers should include baseline lymphocyte quality, expansion potential, CD3+CD56+ yield, NKG2D-ligand expression on tumor cells, HLA class I status, and suppressive ligand expression such as PD-L1.

Radiogenomics and spatial profiling may help identify immunotherapy-responsive subgroups. MRI-derived signatures, perfusion imaging, diffusion metrics, radiomic features, and integrated molecular data may estimate immune infiltration or molecular subtype before treatment [46]. Single-cell analyses show that glioblastoma immune states are not uniform; myeloid compartments, T-cell exhaustion, and tumor-cell plasticity vary by patient and disease stage [43-45]. Therefore, future trials should collect matched tumor tissue, blood, imaging, and manufacturing data. The goal is not merely to show whether DC/CIK therapy works on average, but to determine which patients, at which disease stage, with which product attributes, are most likely to benefit.

11. SAFETY AND CLINICAL IMPLEMENTATION

DC vaccines are generally well tolerated, with common adverse events including injection-site reactions, fever, fatigue, and transient inflammatory symptoms. Severe autoimmune or neurological toxicity appears uncommon, although inflammatory pseudoprogression can complicate radiographic assessment. CIK and DC-CIK infusions are also generally reported as tolerable, but cytokine-related symptoms, fever, fatigue, transient laboratory abnormalities, and theoretical risks of neuroinflammation require monitoring [19, 21, 25-28]. Compared with CAR-T therapy, CIK/DC-CIK products may have a lower risk of severe cytokine release syndrome, but glioblastoma-specific neurotoxicity data remain limited.

Clinical implementation should include standardized neurological assessment, steroid documentation, MRI response assessment using RANO-informed criteria, pseudoprogression management, seizure monitoring, infection surveillance, and quality-of-life endpoints. In glioblastoma, survival alone is insufficient: durable neurological function, reduced steroid dependence, cognitive preservation, and treatment feasibility are clinically meaningful. For a vaccine or cellular product to become practice-changing, it must demonstrate not only statistical survival benefit but also reproducible manufacturing, manageable logistics, and a clear place in the care pathway.

12. PROPOSED TRANSLATIONAL MODEL FOR DC-CIK DEVELOPMENT IN GLIOBLASTOMA

A rational next-generation model would enroll molecularly confirmed glioblastoma, IDH-wildtype, CNS WHO grade 4 patients after maximal safe resection, stratified by MGMT promoter methylation, residual disease, age, performance status, and steroid exposure. Tumor tissue would be used for autologous lysate or multi-omics-informed antigen selection. Peripheral blood or leukapheresis would support parallel generation of mature antigen-loaded DCs and CIK cells. The product could be administered after completion of chemoradiotherapy or in a peri-maintenance window with immune monitoring.

A second model would target recurrent disease after reoperation, where fresh tumor tissue and immune profiling are available. In this setting, the trial should avoid uncontrolled single-arm interpretation where possible. Randomized designs, external-control safeguards, or adaptive platform structures would improve interpretability. Biomarker endpoints should include antigen-specific T-cell responses, peripheral immune reconstitution, TCR clonality, CIK expansion quality, intratumoral immune-cell density at reoperation when available, cytokine profiles, and steroid-adjusted outcomes.

Combination arms could include DC-CIK plus tumor-treating fields, DC-CIK plus checkpoint blockade in biomarker-selected patients, DC vaccine after oncolytic-virus priming, or DC/CIK plus myeloid modulation. However, each combination should be justified by mechanism rather than enthusiasm. Glioblastoma trials are vulnerable to false-positive signals when small, uncontrolled, molecularly mixed, or confounded by crossover and post-progression therapies. The next decade should prioritize fewer but better-designed trials.

13. CONCLUSIONS

Dendritic-cell vaccines and CIK/DC-CIK therapy represent complementary immunotherapy strategies for glioblastoma. DC vaccines address the need for antigen presentation and adaptive immune priming, while CIK/DC-CIK platforms add broadly cytotoxic effector function that may be less constrained by HLA loss and antigen heterogeneity. The strongest glioblastoma-specific clinical evidence for DC vaccination comes from the DCVax-L phase III program, which reported survival extension but also raised methodological debates related to external controls and crossover. CIK-cell therapy has randomized glioblastoma data suggesting progression-free survival benefit and possible survival benefit in selected analyses. DC-CIK therapy has broader solid-tumor evidence and emerging glioblastoma preclinical support, but glioblastoma-specific clinical validation remains insufficient.

The future of DC and CIK/DC-CIK therapy in glioblastoma will depend on integrated molecular diagnosis, biomarker-guided patient selection, standardized GMP-compliant manufacturing, rational combination strategies, and rigorous trial design. Rather than viewing these platforms as isolated alternatives to standard therapy, they should be positioned as immunological amplifiers within multimodal neuro-oncology. For Academia Biology, the topic is well aligned with translational and biomedical biology because it connects tumor taxonomy, cell biology, immune regulation, manufacturing science, and clinical neuro-oncology.

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