


Drug Discovery in Glioblastoma: Current Status and Future Perspectives

Adil Husain¹, Niharika Pandey¹, Dhananjay Singh¹, Firoz Ahmad¹, Rolee Sharma³, Mohammed Haris Siddiqui^{2,*} 

¹ Department of Biosciences, Integral University, Lucknow, Uttar Pradesh, India

² Department of Bioengineering, Integral University, Lucknow, Uttar Pradesh, India

³ Department of Life Sciences, Chatrapati Shahuji Maharaj University, Kanpur, Uttar Pradesh, India

* Correspondence: mohdharis.siddiqui22@gmail.com (M.H.S.);

Scopus Author ID 55194716500

Received: 28.10.2022; Accepted: 11.01.2023; Published: 26.02.2023

Abstract: Glioblastoma (GB) is the prevalent and malignant type of solid brain tumor, having 10,000 novel incidents recorded each year in the United States. Even though rigorous multi-modal treatment, the overall survival after diagnosis is reported to be less than 15 months, the surgical excision of the tumor, observed by radiotherapy and chemotherapy, is a widely utilized treatment strategy for GB. However, contemporary advances exhibit that exosomes, dendrimers, liposomes, and certain metallic nanoparticles in the form of prodrugs advance the infiltration of the drugs into the blood-brain barriers, consequently contributing to novel chances of combating the GB confrontation with chemotherapeutics. The Food and Drug Administration of the United States (FDA) has accepted numerous medications, and significant initiatives have been adopted for advanced novel chemotherapeutic agents for GB. This overview provides new insights into developing a strong platform likely to be used for exploring certain novel drugs as well as means to treat GB clinically.

Keywords: glioblastoma; drug discovery; nanocarrier; blood-brain barrier; drug delivery.

© 2023 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Glioblastoma (GB) is one of the most malignant brain tumors with an abysmal prognosis. GB shows low median survival (approximately 14-16 months) and a 5-year survival rate of less than 5%, classified as a grade IV astrocytoma, which attests to its lethality [1–6]. Even after following the recommended treatment procedure, the recurrence chance increases due to numerous physical and biological barriers in the GB microenvironment [7-9]. Despite numerous efforts to overcome these obstacles to precise diagnosis [10] and successful treatment of GB [11], much more development is needed. To achieve a complete cure [12,13]. Primary resection surgery, chemotherapy, and radiotherapy comprise conventional GB treatment.[9,14]. When compared to surgery alone, this combined therapy showed that the median survival increased by about three times [15]. However, treatment efficacy is restricted by the intrinsic malignant nature of GB [16], the brain's vascular structure [17], and the brain's radiation dose tolerance [18].

For instance, infiltrating tumor cells make it difficult to distinguish between the normal and tumoral parts of the brain; as a result, a number of residual tumor cells persist even after surgical excision [19]. The recurrence of GB is facilitated by these residual tumor cells. Furthermore, the blood-brain barrier (BBB) prevents anticancer medications from passing

through the brain's extracellular matrix, rendering conventional systemic delivery of chemotherapy medicines frequently ineffective. The effectiveness of radiotherapy is also restricted by the brain tissue's radiation tolerance. Alternative therapies, such as gene therapy [20,21], angiogenesis inhibition [22,23], and immunotherapy [24,25], have, to a limited extent, shown promise in the treatment of GB. The BBB reduces the effectiveness of the systemic delivery of the drug to the targeted brain tumor. Increasing medicine dosage would harm normal cells and raise the likelihood of side effects while maintaining therapeutic effectiveness. The same heightened risk of side effects restricts the use of several medications to treat people with GB because of their significant genetic heterogeneity. Considering the drawbacks of both the gold standard and alternative treatments, recent studies have dramatically improved drug delivery efficiency to brain tumors [26,27]. Many different drug delivery methods have been proposed, including systemic drug delivery that penetrates the BBB (such as nanostructure-induced BBB penetration and external-stimulus-induced BBB temporal disruption) and local drug delivery that avoids the BBB (such as intranasal delivery, solid implant-based delivery, intratumoral delivery, and convection-enhanced delivery) (CED). Temozolomide (TMZ) with resection also confers a significant overall survival benefit in patients with resectable and recurrent GB [28]. Many studies suggest that biocompatible and eco-friendly polymeric particles can serve as inert carriers for anti-microbial agents and prospective stimulators of the innate microbicidal responses in macrophages [29]. Drug delivery efficiency by integration additionally, a number of methods have improved drug delivery effectiveness by combining the microscopic strategy of tailoring the drug to be easily absorbed by the tumor with the macroscopic strategy of boosting drug permeability through the BBB [30,31].

In this review, we discuss treatment modalities currently in practice, drug delivery challenges, advancement in drug delivery systems and new modalities of drugs, and delivery strategies. We outline first-line treatments and the clinical difficulties they face as a result of GB's anatomical, cytologic, and genetic characteristics. Following a discussion of the most recent advancements in drug delivery technology for the treatment of GB, clinically available therapeutic techniques are covered, with a focus on relatively fresh approaches and full descriptions of their benefits and drawbacks. Their drug administration mode is classified into two categories: systemic drug delivery versus local drug delivery. Our focus is on macro-micro/nanoscope strategies to overcome obstacles in GB treatment and to overlook the unresolved issues in GB and the outlook of advanced drug delivery technology.

2. Current Treatment Modalities for GB

GB is one of the fatal malignancies with a dismal 5-year survival rate despite sophisticated treatment choices such as chemotherapy, immunotherapy, and radiation [32]. GB's current standard of care is to do the maximum possible surgical resection, concurrent chemoradiotherapy followed by chemotherapy alone. After confirmation via medical imaging, the first step is maximal resection. For decades, radiotherapy has been used to treat residual cancer patients [33]. Radiation therapy induces death in tumor cells via double-strand breaks in the DNA [34]. However, amplification of the epidermal growth factor receptor (EGFR) gene is expressed in over 50% of GBs, and its truncated version III, known as EGFRvIII, is present in around 25% of GBs. EGFRvIII confers radiation resistance on GBs by promoting rapid repair of DNA double-strand breaks [35].

Additionally, radiotherapy for brain cancers may encourage tumor recurrence or develop secondary gliomas [36,37]. Recent research using both *in vivo* and *in vitro* models

suggested that the formation of high-grade gliomas may be triggered by radiation-induced DNA double-strand breaks in combination with preexisting tumor suppressor inactivation. [36]. Combining ionizing radiation and bio-active DNA repair inhibitors can improve GB therapy [38]. While new techniques for radiosurgery have been developed in recent years, stereotactic radiosurgery enables treatment to be focused on the desired tumor spot. Therefore, stereotactic radiosurgery in recurrent GB has been significantly associated with more progression-free as well as overall survival[39].

The combination of radiotherapy and concurrent and adjuvant TMZ was initially described in 2005 [9]. It was found superior to radiotherapy alone in patients who underwent surgical resection [40,41] and those who received only a biopsy [40]. MGMT is a DNA repair protein that has been shown to be a response-predictor to alkylating chemicals [42]. Additionally, TMZ-induced DNA damage in healthy cells is a cause for concern. Given the drawbacks and problems associated with current standard GB care, especially concurrent chemotherapy following complete resection, innovative therapeutic approaches are urgently needed to increase treatment efficacy and specifically target GB tumor cells Table 1.

Table 1. Summary of Characteristics and limitations of currently available treatment strategies for GB.

Treatment		Characteristics	Limitation
Surgery		Mass removal of the tumor	Hard to excise the infiltrative tumor Invasive in nature
Radiation Therapy		Non-invasive Treatment efficiency is high	Issues of Radioresistance Have Side effects
Chemotherapy	TMZ (Gold Standard) Bevacizumab (Anti-angiogenic) Phenytoin/Dexamethasone (Symptomatic Treatment) Carmustine (Gliadel Wafer)	No procedure Patient compliance Symptom mitigation Bypass of BBB Perisurgical administration High drug concentration at the target site	Chemo-resistance Limited drug penetration in tumor Low therapeutic efficacy Mechanical mismatch Short drug delivery period Limited drug penetration
Stimuli-Responsive Therapy		Minimally invasive administration Bypass of BBB Programmable treatment	Limited use Specialized instruments are required Low detectability of tumor progression
Electrotherapy		Non-invasive administration Tumor targetability Minimal side effect	Less clinical verification Expensive Requirement for specialized instrument

3. Drug Discovery Challenges in GB

3.1. Brain barriers.

The primary obstacle comes from the low permeability of the BBB, which makes the delivery of drugs to intracranial tumors very difficult [43]. Tight junction complexes in the BBB line the endothelial cells of brain capillaries, prevent pinocytosis and fenestrations and decrease anticancer drug permeability [44]. Additionally, active efflux transporters (AETs) carry medications back to the bloodstream, and the presence of metabolizing enzymes renders pharmaceuticals inert before their release to the tumor site [44]. To overcome the AETs clearance effects and boost anticancer agent trafficking across the BBB, the receptor-mediated transport pathway must be active by binding the medicines to a cell-surface receptor.

GBs disrupt the BBB's integrity, resulting in a highly heterogeneous vasculature with specific characteristics of non-uniform permeability and active molecular efflux. The blood-

tumor barrier (BTB) is a term that refers to this occurrence [45]. The BBB and the BTB preclude potentially effective chemotherapeutic drugs from reaching metastatic lesions. Numerous strategies have been investigated recently to overcome these barriers, including developing novel smaller molecules with permeability to the BBB, novel formulations of anti-cancer agents, and various disruptive techniques [45,46]. A drug-loaded nanocarrier has been created to cross the BBB and BTB via improved affinity for an endocytic receptor expressed on the surface of endothelial cells, resulting in efficient delivery to tumor locations [47,48] (Figure 1).

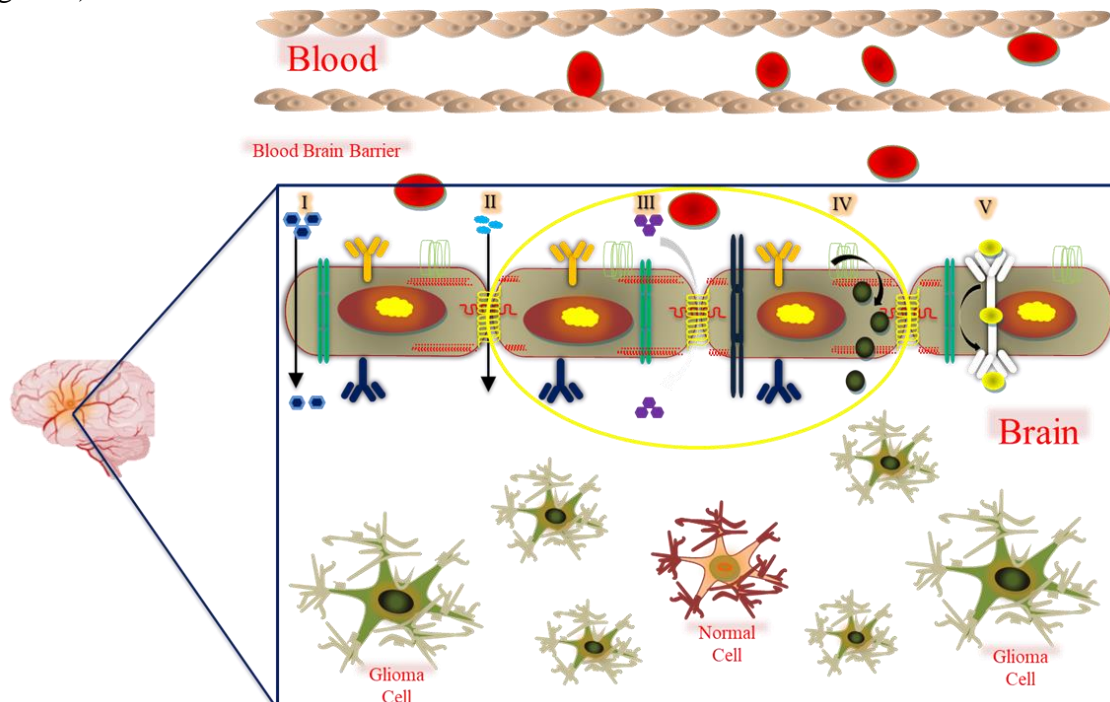


Figure 1. Structure of drug transport route of the blood-brain barrier; (I) penetration of the drug through tight junction; (II) passive diffusion across the endothelial cell; (III) carrier-mediated transport; (IV) adsorption-mediated transcytosis or endocytosis; and (V) receptor-mediated transcytosis.

3.2. GB stem cells.

The most prevalent mechanism of GB resistance is the presence of stem-like glioma stem cells (GSCs) and the low permeability of the blood-brain barrier (BBB) for most chemotherapeutics. GSCs are functionally defined and separated from differentiated GB cells by their capability to initiate tumors following repeated transplantation, self-renewal, and recapitulate tumor heterogeneity [49]. Although the origin of GSCs is still debated, it is assumed that these progenitor cells either originate from neural stem cells or are transformed astrocytes that get access to stem-specific transcriptional programs [49–51]. Most therapeutic modalities targeting GSCs have failed in clinical trials because GSCs exhibit a variety of epigenetic and post-transcriptional regulatory mechanisms that can promote differentiation, invasive growth, and GSC maintenance [49,51,52]. GSCs have a high metabolic capacity, proliferating rapidly and adapting to adverse microenvironments [53].

3.3. Choosing the right target.

Preclinical target validation is essential before undertaking clinical development. It depends on the predictive quality of each cell-based and *in vivo* model to test a given hypothesis. However, these could bear no relation to the *in vivo* architecture of human tissues;

therefore, as Horvath *et al.* suggested, more effort must be put into developing more-predictive preclinical models. These can include models based on pluripotent stem cells, 3D co-culture, and organ-on-a-chip systems, complemented by advances in single-cell imaging and gene editing technologies [54]. One practical example is Miller *et al.*, who used RNA interference screening technology to demonstrate that gene expression in primary explanted GB cells significantly differs from that in xenograft models when human cells are transplanted into mouse brains [55].

3.4. Drug resistance.

The primary reasons for poor prognosis in GB patients treated with the DNA alkylating agent TMZ are the emergence of acquired resistance to this drug and the outgrowth of malignant cells. TMZ methylates DNA at the O6 position in guanine, leading to impaired DNA repair and apoptosis. Resistance to TMZ therapy is mediated by removing the DNA adduct created by this alkylating drug by the O6-methylguanine DNA methyltransferase (MGMT), with DNA methylation on the MGMT promoter being a key predictor. [56]. Loss of function in the MutS homolog 6 (MSH6) mismatch repair gene is another resistance mechanism.[57]. In addition to resistance to TMZ, the drug is mutagenic and can introduce new driver mutations during the initial successful phase of treatment, thereby leading to malignant progression [58]. Therefore, interventions that target TMZ-resistant cells are desirable. Screening a range of GB cell lines with FDA-approved chemotherapeutic drugs identified compounds that overcome resistance to TMZ by interfering with specific resistance pathways [59,60].

3.5. Tumor heterogeneity.

The variety of GBs complicates treatment even more. Recent sequencing techniques have revealed the whole genetic landscape of GBs and the remarkable tumor heterogeneity, even at a single-cell level [61]. For example, the EGFR genes have shown amplifications and mutations in more than half of GBs, frequently resulting in anti-EGFR therapies' ineffectiveness [62]. Researchers have attempted to identify particular biomarkers for GSC populations to differentiate them from non-GSC populations to target GSCs and sensitize tumors to conventional treatment [63,64]. Cell membrane surface antigens are suitable biomarkers because they are quickly recognized by anti-tumor drugs, enhancing therapeutic efficacy [63]. On the other hand, the optimum markers for GSCs have not yet been found. CD133, CD15/SSEA-1, CD44, integrin-, and A2B5 are all possible biomarkers for GSCs. Certain biomarkers can also assess therapy response as a prognosis index for GBs [65].

4. Advances in Drug Delivery

4.1. Nanocarriers.

Drug delivery systems have major advantages, including progressive bioavailability, peculiarly for hydrophobic drugs, the prolonged half-life of the drug, and fewer wastage of drugs; along with these advancements, these drug delivery systems also face challenges like the problem of drug solubility, stability, harmfulness, and selective targeting [66]. Nanocarriers and nanotechnology-based drug delivery are colloidal-based particulate systems that have the potential to penetrate the BBB due to their sustained drug release, biosafety, increased solubility, enhanced drug bioactivity, BBB penetrability, and self-assembly [47,48].

Chemotherapeutic chemicals are entrapped inside the matrix or bonded to the surface of nanoparticles, which can penetrate narrow capillaries due to their small size. The primary advantage of nanoparticles made of biodegradable materials is that they deliver drugs to the intended place in a controlled manner [67,68]. Through appropriately engineered ligands on the surface, drug-loaded nanoparticles can be non-toxic, non-immunogenic, and stable inside the blood circulation [69]. Nanoparticles with ligands on their surfaces can deliver the carrier system to particular receptor sites. [70,71]. Transferrin, apolipoprotein (Apo) E, B, and A, and some antibodies on the surface of nanoparticles are all possible ligands that enable the drug-nanoparticle complex to pass efficiently through the BBB via receptor-mediated endocytosis [70–72]. The size and surface charge of nanoparticles contribute significantly to their ability to escape from the reticuloendothelial system (RES) [73]. Nanoparticles with a 5–500 nm size range and a positive charge are critical for improved cellular uptake. Particles with a diameter of 200 nm are particularly well suited for systemic injection [73,74]. Surface coatings and other modifications are required to make nanoparticles suitable for clinical medicine to increase the nanoparticles’ safety in the body.

For more than a decade, researchers have researched surface modification of nanoparticles using various chemicals to decrease undesirable interactions between nanomaterials and normal tissues [75]. To improve the affinity and specificity of nanoparticles for the targeted tissue, chitosan PEGylated albumin-coated nanoparticles were later created for brain drug delivery via receptor-mediated transporter endocytosis [76,77]. Although numerous drug delivery systems to the central nervous system have been developed [78,79], newly developed nanoparticles made of poly (ethylene glycol)-poly(-pentadecalactone-co-p-dioxanone) have a longer duration of sustained release and do not require repeated infusions, which improves safety and translatability [80] Table 2.

Table 2. Summary of Advantages and disadvantages of drug delivery strategies for GB treatment

Treatment	Advantage	Disadvantage
Systemic delivery		
Nanocarriers	Minimally invasive, simple administration Tunable material design	Low efficiency from BBB Host reactions (e.g., protein corona)
Cellular carriers	Stealth against host reactions Spontaneous homing/surface interaction	Potential side effect No consensus on delivery efficiency
Transient disruption of BBB	Minimally invasive Complementary to first-line therapy	Specialized equipment required Nonspecific diffusion
Local delivery		
Intranasal delivery	Non-invasive, simple administration method Bypass the BBB	Non-targeted Low delivery efficiency due to mucociliary Small administration volume
Solid-based implant delivery	Direct delivery from the brain surface A large amount of implantable drug reservoir	Mechanical mismatch Hard to refill
Intratumoral delivery	The high-loading amount of drug Bypass the BBB	Invasive administration Low penetration
Convection-enhanced delivery	Deep penetration Can deliver various types of drugs	Invasive administration

4.2. Applicable strategies to improve delivery.

The major obstacle to GB treatment is the presence of BBB, the capture and clearance of anticancer agents by the RES, and the lack of a specific targeting mechanism by which the drugs can bind specifically to GSCs. Special designs and administration routes of nano-carrier-based delivery systems are urgently needed to overcome these obstacles. A newly synthesized

nanoparticle from magnetotactic bacteria was injected in mice with intracranial glioma and followed by altering magnetic field or magnetic hyperthermia, which showed enhanced anti-tumor efficacy with almost complete tumor disappearance [81,82]. This concept demonstrates an additional treatment option for invading malignancies such as glioma. It is challenging to acquire complete tumor coverage with nanoparticles.

Another option is to administer anticancer medications by intranasal injection. For example, the potential for direct transport from the nose to the brain, which circumvents the BBB, was examined in GB mice employing miRNAs loaded in theranostic nanoparticles of Au-Fe Oxide [83]. Additionally, this nanoformulation enables the systemic delivery of GB cells to TMZ [83]. The intranasal route of drug administration via the nose to the brain may have various advantages over the standard IV route. However, this delivery strategy is primarily in the preclinical stage of development, and intranasal administration also has disadvantages [84]. Reduced peptide bioavailability, rapid evacuation from the nasal cavity, and other limits imposed by the nasal cavity's structure are challenges that must be addressed [84].

MRI-guided targeted ultrasounds or injecting bradykinin can weaken or open the main barrier, allowing chemotherapeutic drugs to diffuse more efficiently through the BBB [85,86]. Cisplatin-loaded nanoparticles coated with PEG, which inhibit macrophage capture, have been shown to have a brain-penetrating ability following MR image-guided focused ultrasound [85,87]. The combination's efficacy in animal models may pave the way for a new potent strategy to treat resistant GB and recurrence control [87].

Strategies targeting AET and tight junctions are critical for bypassing and modifying the BBB and BTB [88]. Historically, inhibitors of multidrug resistance efflux transporters are ineffective in most investigations. On the other hand, P-gp inhibitors encapsulated in surfactant-based nanoparticles have been designed to reverse multidrug resistance efflux transporters, which can be employed to enhance the therapeutic efficacy of the drug [89].

A magnetic field was used to initiate the diffusion of magnetic anti-GB medicines into GB cells [81,82]. Previously encountered obstacles included a lack of equipment capable of producing a sufficient and precise magnetic field and concerns about unintended effects on normal tissue [90,91]. However, direct intratumoral delivery of magnetic nanoparticles (MNPs) is now feasible for GB treatment due to the high accumulation of MNPs at the tumor site following the development of a magnetic platform driveable by an external magnetic field [92,93]. Another example is a novel design of lipid-based hybrid magnetic nano vectors and functionalized with angiop2 to enhance GB cell death by combining lysosomal membrane permeabilization and chemotherapy [94,95].

4.3. Targeting the GB cells and GB stem cells.

Active targeting for GB currently relies on compounds linked to the surface of nanoparticles that can precisely target the receptors or antigens on GB cells or GSCs [8,96]. GB cells contain a variety of receptors and proteins, including metalloproteinase-2, the IL-13 receptor, Integrin 53, CD33, and CD133; nanoparticles may target them [93].

Since the existence of GSCs is a significant risk factor for GB recurrence, the critical targeting of GSCs has been explored in recent years [97]. GSCs express various receptors and indicators that specifically target nanocarrier-based drug delivery systems. GSCs express cell surface markers (e.g., CD15, CD133), transcription factors (e.g., OCT4), post-transcriptional factors, and cytoskeletal proteins (e.g., nestin) in accordance with their sites [98]. Most GSC-

targeting therapies have failed in clinical trials, even though several theoretically available GSC-targeting treatments exist [99,100].

Recent GSC targeting by nanotechnology includes creating calf thymus DNA mixed with gold nanoparticles, which makes GSCs more susceptible to radiotherapy [101]. NFL-TBS.40-63 and LinTT1 peptides are generated from neurofilaments with increased binding to target GSCs [102,103]. Gold nanorods functionalized with an engineered peptide can also be used to specifically detect nestin-positive GSCs, which has been demonstrated to be a promising approach for developing an efficient nanomedicine for treating recurrent GB [104]. The targeting peptide CBP4-coated gold nanoparticles were designed as a drug carrier for therapeutic methods against the cell surface marker CD133 in GSCs [93,105].

4.4. Current nanocarriers and associated strategies.

Additionally, the new development of nanocarrier-based combination therapy for GBs has several advantages, including improved sequential drug exposure, accurate confirmation of the synergistic drug ratio, and improved localization of anti-cancer agents into the tumor site [106–108]. Depending on their preparation methods, nanocarriers can be classed as nanocapsules, nanoparticles, or nanospheres. Nanoparticles are the most often employed colloidal drug carriers in treating GBs and can be categorized as liposomes, polymeric nanoparticles, solid lipid nanoparticles, polymeric micelles, silica, or dendrimers [106].

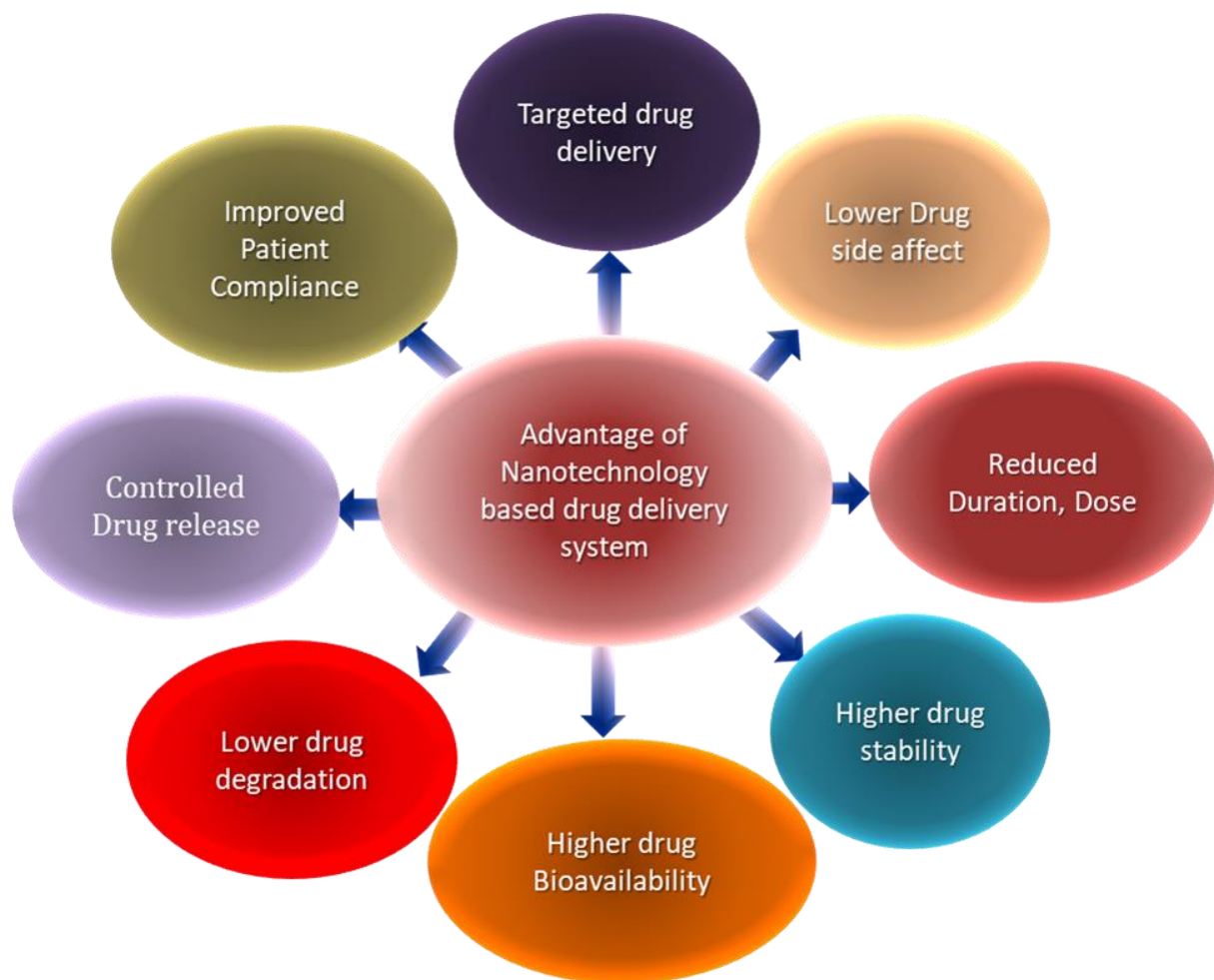


Figure 2. Advantages of nano-based drugs for Glioblastoma.

4.4.1. Liposomes.

Liposomal nanoparticles have several advantages, including ease of preparation, easy encapsulation of a broad range of anticancer drugs, favorable biocompatibility, efficacy, non-immunogenicity, increased solubility of anticancer agents, and commercial availability [109,110]. Liposomes were initially developed to encapsulate radiosensitizers and chemotherapeutic drugs such as doxorubicin to treat refractory tumors over two decades ago [109]. Several liposomal formulations for treating GBs, like new conjugated medicines and receptor-mediated transcytosis, have been studied during the last decade to enable their transport across the BBB [110–112]. Polyethylene glycol (PEG) conjugation is a rapidly evolving strategy to overcome the hurdles of therapeutic delivery. PEG coating is a crucial factor in improving nanoparticle biophysical and chemical properties. It can increase the half-life of liposomes in circulation by helping the nanoparticles evade RES capture [113,114].

Certain unique receptors or antigens overexpressed on GB cells may serve as novel nanotechnology targets. For example, interleukin (IL)-13-conjugated liposomes and doxorubicin liposomal doxorubicin targeting the IL-4 receptor has been studied in mice models, with indications of considerable tumor size reduction when compared to unconjugated liposomes [111,112]. This method does not increase toxicity in animals receiving receptor-conjugated liposomes [111], indicating that it could be used as nanotechnology. Additionally, an antibody can mark liposomes to direct them to tumors. Anti-EGFR immuno-liposomes were developed over a decade ago to target GB cells overexpressing EGFR in an animal model and proved that they dramatically enhanced the efficacy of numerous anticancer treatments [115].

Despite the common use of liposomal nanoparticles in treating GB, several drawbacks exist. Liposomal nanoparticles exhibit non-uniform effects across all brain regions, and their permeability through the BBB varies according to the loaded drug or surface molecules [111,112].

4.4.2. Polymeric micelles.

A hydrophobic polymer core is encased in a hydrophilic shell to form polymeric micelles. The self-assembly of block copolymers generates this architecture, and the design can be used to control the efficiency of chemotherapeutic drug incorporation and release rate [116]. The distinctive core-shell structure and narrow size distribution of 10–100 nm shield the drug-loaded core from contact with the complement system and macrophage absorption, resulting in prolonged circulation and a more than 10-hour half-life [117,118]. Biodegradable polyesters such as poly (D, L-lactide), poly (caprolactone), poly (D, L-lactide-co-glycolide), and long-chain alkyl derivatives are frequently employed as the core-forming polymer [116]. PEG is the optimal shell-forming polymer since it does not interact with serum proteins [116,117].

After overcoming the earlier problem of insufficient drug circulation time, the primary impediment to implementing polymeric micelles-based GB therapy is a paucity of targeting moieties capable of enhancing GB-specific accumulation [116]. As a result, additional studies targeting receptors expressed on GB cells are being conducted to optimize the existing formulation's potency. For example, polymeric mixed micelles composed of Pluronic P-123 and F-127 and containing 17-Allylamino-17-demethoxy geldanamycin (17-AAG) may be an effective drug delivery carrier based on nanomaterials because 17-AAG is a potent inhibitor of heat-shock protein 90 (Hsp90) and can destabilize Hsp90-related client proteins in cancer cells

[118,119]. The design of 17-AAG-loaded Pluronic P-123 and F-127 mixed micelles is attractive, and 17-AAG's targeting ability, regulated release rate, and high drug loading have been demonstrated as a promising delivery system for GB treatment [118]. The transferrin receptor (TfR) is an attractive target location due to its overexpression in BBB and GB cells. Sun *et al.* created TfR-PEG polymeric micelles rapidly absorbed by tumor cells and effectively crossed the BBB [120]. TfR-PEG polymeric micelles loaded with paclitaxel have successfully limited the growth of U87 GB cells *in vitro* and significantly lengthened the median survival of nude mice with GBs [120].

4.4.3. Dendrimers.

Dendrimers are the tiniest molecules, measuring less than 12 nm in diameter, and possess a highly branching and compact scaffold design ideal for transporting and preserving short interfering RNA (siRNA) from degradation in circulation [121,122]. Additionally, dendrimers loaded with methotrexate have a higher pharmacological potency and a high efficiency in bridging the BBB [123]. However, dendrimers have some drawbacks, including quick RES clearance, toxicity to normal tissue due to membrane contact, and relatively poor regulated release behavior [121,124]. As a result, several functionalized procedures have been employed to modify dendrimers, including the attachment of a lipid, amino acid, peptide, or aptamer [122,125].

Recently, two distinct siRNA for oncogene silencing were compacted using poly (amidoamine) (PAMAM) dendrimer-entrapped gold (Au) nanoparticles. The newly developed technique coats the PAMAM-Au dendrimers with beta-cyclodextrin (-CD), a carrier that is an excellent carrier for siRNA delivery to glioma cells [124,125]. Endogenous amino acids improve the biocompatibility and endosomal escape of amino acid-functionalized dendrimers., whereas phosphate dendrimers with a hydrophobic backbone and a hydrophilic surface can penetrate the BBB more effectively [126]. Another example is the arginine-glycine-aspartic-functionalized dendrimer-entrapped gold nanoparticles, which exhibit excellent cytocompatibility and high transfection efficiency and are potentially effective as gene therapy for GBs [126]. Dendrimers composed of polyether-copolyester (PEPE) and d-glucosamine have improved drug delivery across the BBB and tumor targeting [123]. The *in vitro* model demonstrated that glycosylation of the PEPE dendrimers accelerates their accumulation around tumor spheroids and overcomes MTX resistance since methotrexate-loaded glucosylated PEPE dendrimers were able to kill even MTX-resistant cells [123].

4.4.5. Metal particles.

Metal particles can improve GB tumor cells' radiosensitization, and considerable DNA damage to tumor cells has been reported in animal models treated with metal particles before radiation therapy [127,128]. Due to their high X-ray absorption, synthetic adaptability, and unique electrical properties, metal particles are excellent candidates for use as radiosensitizers [129]. One of the ideal nanomedicine materials for GB therapy is gold nanoparticles (AuNPs), which are simple to manipulate, have tunable diameters, and have a high surface-to-volume ratio. [130]. Although AuNPs' regulated size enables them to cross the BBB easily, their clinical utility is hampered by their lack of targeting ability [130,131].

A DNA aptamer targeting EGFRvIII in GBs was recently produced using a huge random single-stranded DNA library [131]. The aptamer's targeting efficiency is further

increased by entrapment in AuNPs via a gold-sulfur covalent link [131]. Aptamer-AuNP complexes have been identified as a novel class of pharmacological candidates for GB therapy due to their efficacy *in vivo* and *in vitro* tumor proliferation inhibition [131]. Appropriately sized AuNPs overcome aptamer's limited transmembrane penetration. Additionally, nanoparticles can facilitate the delivery of therapeutic gene targets. Recently, a new polyfunctional gold-iron oxide nanoparticle was created and demonstrated to improve the sensitization of GMB cells to systemically administered TMZ in mice [83].

Metal particles have previously been associated with cytotoxicity and physical damage to normal tissue following long-term accumulation in the blood [132]. Metal particle toxicity is mediated via the production of oxidative stress, the release of pro-inflammatory cytokines, lysosome degradation, and DNA damage [132,133]. However, the American Food and Drug Administration (FDA) has already cleared several gold and silver nano formulations entrapped with chemotherapeutic drugs for clinical studies. Their biodistribution and clearance method are now well recognized [134].

4.4.6. Silica.

Silica nanoparticles (SiNPs) have many advantages that make them a popular choice for medicinal applications, including their high biocompatibility, large surface area for drug loading, stability, and low cost [135,136]. Concerning their cytotoxicity, DNA damage and the formation of reactive oxygen species have precluded SiNPs from being used clinically as biomarkers, cancer treatments, or drug delivery systems [114,135]. Later SiNPs were examined for their clinical safety and prospective applications in various research areas. Because the toxicity of SiNPs can be regulated by adjusting the particle size, dosage, and cell type [114,137], researchers may experiment with multi-modal adjustments to make SiNPs therapeutically beneficial. Smaller-sized SiNPs have higher toxicity, which can be changed synthetically [138].

Transferrin-modified porous silica nanoparticles are the most often used formulation for GB treatment because they have high biocompatibility, degradability, and drug-loaded capacity [139–141]. Because the transferrin receptor is frequently overexpressed on the BBB and the surface of the GB cell, the transferrin-functionalized pSiNPs can provide a prolonged release of the drug (like doxorubicin) at the targeted region. A multicomponent nanoparticle with an iron oxide core and a mesoporous silica shell that contains fibronectin-targeting ligands has been developed.. When exposed to an external low-power radiofrequency field, this nanoparticle can efficiently be delivered widespread drugs into GBs [142].

4.4.7. Nanoparticle-induced hyperthermia.

The combination of hyperthermia and contemporary radiation and chemotherapy has been used for nearly half a century. The mechanisms through which hyperthermia induces radiosensitization and chemosensitization include enhanced apoptotic pathways, defective DNA repair, heat-induced inhibition of AKT-pathway, and disruption of BBB [143–146]. In a mouse animal model, local temperatures as high as 45°C trigger apoptosis in GMB cells [144]. However, various techniques have been used to induce hyperthermia in tumors, including radiofrequency, ultrasonic waves, water baths or heat blankets, microwaves, laser-induced interstitial thermotherapy, and magnetic nanoparticles (MNPs). MNPs have the advantages of

direct intratumoral administration, high localized accumulation to generate sufficient heat in tumors, and high efficacy [144].

MNPs are excellent candidates for CED treatment of GBs. Researchers have examined real-time MRI-guided MNP delivery into the brain for decades using CED [147,148]. Due to their high heating capacity, iron oxide MNPs are chosen for magnetic hyperthermia and have been engineered therapeutically to target cancer cells [147]. Iron-oxide nanoparticles linked with the EGFR inhibitor cetuximab were recently shown to have a considerable anti-tumor effect in GSCs expressing EGFRvIII [147]. Fan *et al.* demonstrated a novel theranostic complex of super-paramagnetic iron-oxide-loaded microbubbles for brain medication delivery and correctly estimated the distribution of agents and quantified deposition. [149].

While an accurate and reliable treatment plan can validate the safety and effectiveness of MNPs, the diverse response to magnetic hyperthermia within the GB mass limits their clinical utility. For example, in a recent xenograft model, a transitory increase in the growth of the CD133 subtype of gliomas was observed following hyperthermic preconditioning [150]. Additionally, the issue of MNP toxicity warrants further investigation because it depends on the chemical composition, surface coatings, physical properties, and local concentration of MNPs. MNPs containing iron oxide and titanium, for example, are less harmful than those containing gold, silver, cobalt, zinc, and cadmium. Recent research has proven that coating MNPs with dextran and bovine serum albumin reduces toxicity and prevents intravascular coagulation [144,151].

4.4.8. Nanoparticles as carriers of antitumor antibiotics.

Numerous chemotherapeutic agents, including doxorubicin, bleomycin, epirubicin, daunorubicin, and actinomycin D, are classified as anti-tumor anti-biotics because they are produced by bacteria (*Streptomyces*) and induce cell death in GB cells by interfering with DNA replication and damaging DNA[152]. These anti-tumor drugs are highly effective *in vitro* against GB cells but are unsuccessful *in vivo* due to their failure to pass the BBB [43]. The approach encapsulates these chemotherapeutic drugs in PEGylated liposomes and distributes them effectively [79]. For instance, putting doxorubicin into poly (lactide-co-glycolide) nanoparticles coated with poloxamer 188 (Dox-PLGA) enhances doxorubicin delivery to the brain [79,153]. Another example is ultrasound-induced microbubbles which successfully carry medicines into the brain via a transitory opening of BBB in a rat glioma model [154].

4.5. Prodrugs.

Due to the BBB's existence, only a limited amount of medicine delivered reaches the brain. While nanoparticles are a potential option for addressing this issue, another appealing chemical modification-based strategy, the prodrug, has been developed to boost BBB permeability [155].

A prodrug combines a drug and a chemical component that improves the drug's solubility or permeability to cells [156]. Active medicine is released and controlled depending on each organ or tissue's unique biological circumstances, such as pH, enzyme distribution, and transporter expression [157,158]. Prodrugs are intended to overcome various physicochemical and biological barriers, including limited solubility in water or lipid membranes, low target selectivity, chemical instability, and toxicity [159]. Numerous prodrug techniques have facilitated drug delivery into the central nervous system Table 3.

Table 3. Prodrug strategies for the transport of drugs into the CNS.

Strategy	Prodrugs	Mode of Action	Reference (s)
Lipidization	Heroin	Acetylation of the hydroxyl group alters heroin's physicochemical characteristics, favoring brain absorption.	[160]
Chemical delivery system	Estradiol-CDS	After oxidation and hydrolysis, the concentration of estradiol CDS in rat brains was elevated four to five times longer than after estradiol treatment.	[161]
Carrier-drug conjugates	LAT1	The conversion of dopamine into its α -amino acid, L-dopa, enables the brain to uptake dopamine via LAT1.	[162]
	GLUT1 SVCT2	Dopamine linked to the C6 position of glucose had the best affinity for GLUT1. When nipecotic, kynurenic, and diclophenamic acids were conjugated to ascorbic acid, interaction with SVCT2 transporters improved.	[160] [163]
Ligand-drug conjugates	Insulin/transferrin	CNS accumulation of methotrexate is improved by conjugating it to an antibody (OX-26), which is recognized by the transferrin receptor.	[164–166]
Targeting moiety-drug conjugates	<i>N, N</i> -dimethyl amino	Conjugation with <i>N</i> and <i>N</i> -dimethyl amino significantly enhanced the brain-uptake efficiency of dexibuprofen, naproxen, 5-fluorouracil, and dopamine. Chlorambucil-scopine prodrug significantly improved the cellular uptake both <i>in vitro</i> and <i>in vivo</i> .	[167]

GLUT1, glucose transporter; LAT, large neutral amino acid transporter; SVCT2, sodium-dependent vitamin C transporters.

4.6. Ultra sound focused drug delivery.

Focused ultra sound (FUS) is an image-guided, non-invasive technique for transiently opening the blood barrier and thereby increasing the efficacy of medicinal administration to GB. FUS can disrupt the BBB reversibly without causing irreversible tissue damage [168,169]. In combination with circulating microbubbles, FUS disrupts the BBB transiently [170]. Besides the cavitation and thermal ablation effects, FUS may also exert an immunomodulatory effect [171]. The prospect of future use of non-invasive FUS in conjunction with other forms of therapeutic drug administration in GB seems encouraging.

FUS can improve the delivery of various therapeutic medicines to the tumor by enhancing BBB permeability. For example, disruption of the BBB by FUS boosted the local delivery of temozolomide to tumors and increased overall survival in rats harboring artificially generated gliomas [172,173]. In rats, FUS treatment followed by BCNU administration resulted in a decreased rate of tumor growth and increased survival [174].

Low-intensity fluorescence ultrasound (LIFU) was used to deliver a liposomal O6-(4-bromophenyl) guanine (O6BTG) derivative that inhibits MGMT in a mouse model with temozolomide-resistant glioma [175]. Since MGMT promotes DNA repair in tumor cells, suppressing MGMT has been associated with improved outcomes following temozolomide treatment [56].

The combination of imaging methods and FUS accelerates the delivery of drugs to specifically identified tumor tissues [176]. MRI-guided FUS (MRgFUS) was employed in rats to increase tissue delivery of liposome-encapsulated doxorubicin, temozolomide, and cisplatin-conjugated gold nanoparticles [172]. In another study, MRgFUS was utilized to safely deliver the monoclonal antibody trastuzumab to Her2-positive brain metastases in breast cancer patients [177].

This non-invasive method allows therapeutic drugs to be administered at very low systemic concentrations, hence minimizing systemic adverse effects [178]. Transient FUS application results in a transient BBB opening and does not result in long-term BBB problems [179]. FUS can potentially improve the efficacy of therapeutic drugs against GB due to its non-invasive nature and consistent enhancements in drug delivery in early investigative investigations. FUS-based clinical trials in GB are underway [168]. However, FUS is not

without complications, including edema, intracerebral hemorrhage, and uncontrolled thermal harm to the brain [88].

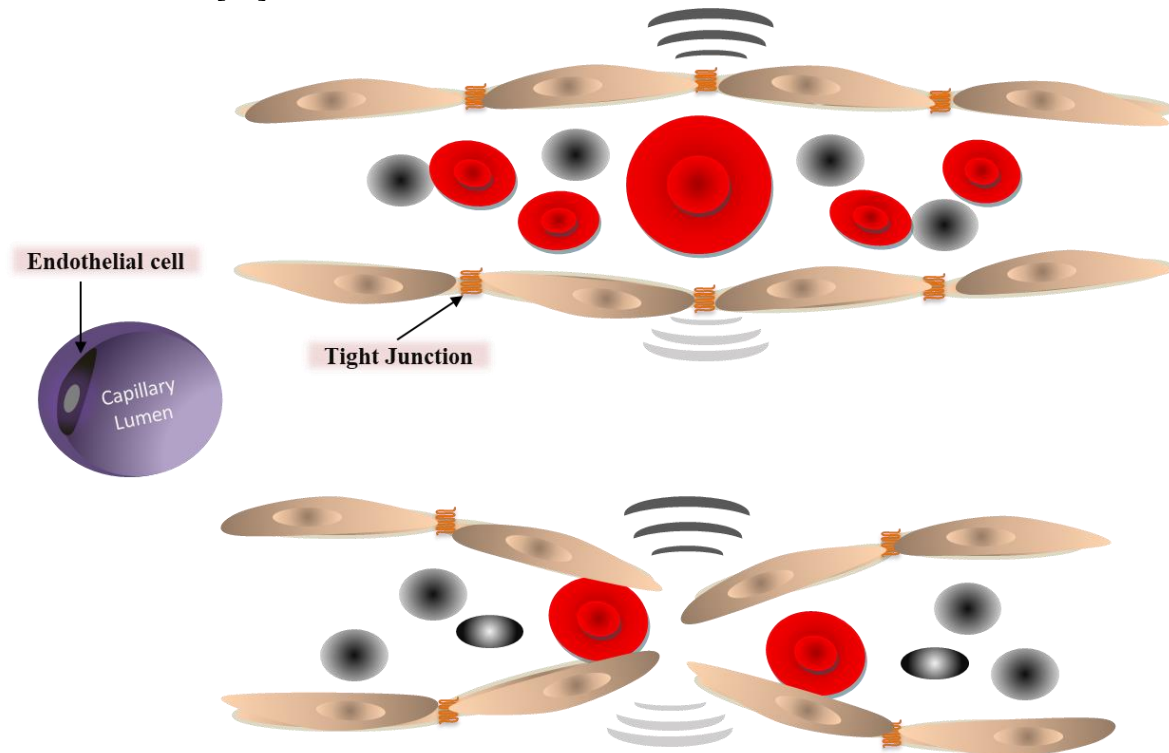


Figure 3. An illustration of BBB modification with focused ultrasound and intravenous microtubule injection.

Microtubules in motion and contracting in the acoustic field strain capillary walls and exert stresses on endothelial cells, causing the BBB to become more permeable. The ultrasonic field's frequency, which with a clinical system is 220,000 times/s, drives the expansion and contraction.

4.7. Exosomes.

Exosomes from various sources can passively or actively target cancer cells to deliver therapeutic agents such as small molecule medicines, nucleic acids, and proteins[180]. These exosomes can encapsulate medications, prolonging their half-life and enhancing the stability of their release. Exosomes are endogenous and biocompatible, so they can be employed as nanocarriers for tissue-specific targeted distribution [181].

4.8. Vaccine therapy.

Novel treatment options are being investigated, and some progress has been made, particularly in tumor immunotherapy, particularly vaccine therapy[182]. Vaccine therapy is predicated on the tumor-specific immune response to foreign antigens injected into the patient. Foreign antigens introduced into antigen-presenting cells induce and improve host immunity [183]. Vaccinations against GB are currently being tested in clinical studies, largely using peptide-based vaccines and cells from *Phytophthora* seedlings.

Because the protein/peptide variations generated by the mutant gene are particular to tumor cells and are not found in normal cells, they can be exploited as specific antigens to trigger immune responses against tumor cells. These antigens are known as tumor-specific antigens (TSAs) and were formerly referred to as “neo-antigens.” Only a few mutations are processed into new epitopes; when these epitopes are given by antigen-presenting cells in the form of the human leukocyte antigen (human leukocyte antigen, HLA), they result in T cell-mediated immunity. Numerous possible tumor antigens are not the result of mutations but an

erroneous or excessive expression of normal proteins found in other organs. In some instances, targeting the antigen may result in autoimmunity, manifesting as non-target consequences such as brain inflammation [184]. The lack of selectivity and high epitope expression in GB impedes the development of peptide vaccine-based methods.

Clinical trials for treating the GB vaccine are presently underway, making it the most clinically available DC vaccination trial. In humans, DCs are the most effective antigen-presenting cells; they promote innate and acquired immunity and the conversion of immunity. Additionally, they affect lymphocyte immunological responses, differentiation, and antigen presentation [185]. Steinman identified DCs in 1973; nevertheless, it was not until the early 1990s that their critical involvement in the immune response was recognized [186]. This DC vaccine production procedure is a reasonable anti-tumor strategy because it is the primary component of silence-T, the first FDA-approved cancer vaccine. Sepulture-T has improved prostate cancer patients' median overall survival time by four months [187]. DCs are extracted from peripheral blood CD-14 positive monocytes to treat GB with the DC vaccination, and immature DCs are differentiated using GM-CSF and IL-4 [188]. The tumor antigens (polypeptides, RNA, DNA, and tumor lysates) are loaded into immature DCs, which are then presented on MHCs and matured by the various cytokines (GM-CSF, IL-4, TNF-, and IL-6) [188,189].

Like antiviral vaccinations, tumor cell vaccines are frequently used to kill or inactivated tumor cells. Due to the poor success rate, gene editing of tumor cells was undertaken in the late 1980s to produce certain immune-stimulating cytokines; granulocyte-macrophage colony-stimulating factor (GM-CSF) was the most often employed. Tumor cells that secrete GM-CSF are being examined for use in the treatment of GB [190]. Clinical trials in phase I are conducted employing the current generation of autologous and allogeneic tumor cell lines secreting GM-CSF (K-562). Vaccination success depends on T cell activation and anti-tumor immunity [191]. Additionally, direct injection of formalin-fixed GB as an antigen is being investigated to treat GB [192,193]. Overall survival was 22.2 months in a clinical trial assessing DC vaccinations in 24 GB patients [193].

5. Conclusions and Future Directions

Even though recent pharmacologic handling options in GBs are meager, the drug expansion channel is gradually rising. In particular, the surge of designated immunotherapies detected in the last years raises the hope that elaborate combination possibilities between classical therapeutic backbones (radiotherapy and chemotherapy) and currently experimental therapeutics may help to provide better prospects for this deadly disease in the future. Clinical cure for glioma is difficult due to the shielding effect of the blood-brain barrier; therapies directed to deliver a drug directly to the brain in a controlled and secure are gaining attention. The complex interaction of drug and target is usually limited by the characteristics of the drug delivery system as well as the pathological structure of the body. To cope with such complex interactions, biomimetic drugs/materials with homologous binding and immune escape functions have been an ideal alternative—autologous human body tissues as carriers help the drug reach the target without destruction. The future direction of nanotechnology and clinical applications may consider monoclonal antibodies, combining GSC-targeting SGT-53 with traditional TMZ, or novel nanoformulations loaded with therapeutic miRNAs to improve immunotherapy and anti-angiogenic processes. Micronanoparticles are hopeful nanoparticles that can treat intratumoral hyperthermic patients suffering from GB. However, due to the

unpredictable heterogeneous nature of tumors, the same could not be replicated in clinical trials.

Funding

This study was supported by a JRF-NET Fellowship by the University Grants Commission, New Delhi (Fellowship No. NOV-2017-343185).

Acknowledgments

The authors would like to acknowledge University Grant Commission, New Delhi, for JRF-NET Fellowship to Adil Husain (NOV-2017-343185) and Integral University, Lucknow, for providing Manuscript Communication Number (MCN).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Beiko, J.; Suki, D.; Hess, K.R.; Fox, B.D.; Cheung, V.; Cabral, M.; Shonka, N.; Gilbert, M.R.; Sawaya, R.; Prabhu, S.S.; *et al.* IDH1 Mutant Malignant Astrocytomas Are More Amenable to Surgical Resection and Have a Survival Benefit Associated with Maximal Surgical Resection. *Neuro Oncol* **2014**, *16*, 81–91, <https://doi.org/10.1093/neuonc/not159>.
2. Das, M. Iniparib for Newly Diagnosed Glioblastoma. *The Lancet Oncology* **2018**, *19*, e514, [https://doi.org/10.1016/S1470-2045\(18\)30665-X](https://doi.org/10.1016/S1470-2045(18)30665-X).
3. Ohgaki, H.; Kleihues, P. Population-Based Studies on Incidence, Survival Rates, and Genetic Alterations in Astrocytic and Oligodendroglial Gliomas. *J Neuropathol Exp Neurol* **2005**, *64*, 479–489, <https://doi.org/10.1093/jnen/64.6.479>.
4. Reynoso-Noverón, N.; Mohar-Betancourt, A.; Ortiz-Rafael, J. Epidemiology of Brain Tumors. In *Principles of Neuro-Oncology: Brain & Skull Base*; Monroy-Sosa, A., Chakravarthi, S.S., de la Garza-Salazar, J.G., Meneses Garcia, A., Kassam, A.B., Eds.; Springer International Publishing: Cham, **2021**; pp. 15–25.
5. Scott, J.G.; Bauchet, L.; Fraum, T.J.; Nayak, L.; Cooper, A.R.; Chao, S.T.; Suh, J.H.; Vogelbaum, M.A.; Peereboom, D.M.; Zouaoui, S.; *et al.* Recursive Partitioning Analysis of Prognostic Factors for Glioblastoma Patients Aged 70 Years or Older. *Cancer* **2012**, *118*, 5595–5600, <https://doi.org/10.1002/cncr.27570>.
6. Tran, B.; Rosenthal, M.A. Survival Comparison between Glioblastoma Multiforme and Other Incurable Cancers. *Journal of Clinical Neuroscience* **2010**, *17*, 417–421, doi:10.1016/j.jocn.2009.09.004.
7. Bastiancich, C.; Danhier, P.; Pr at, V.; Danhier, F. Anticancer Drug-Loaded Hydrogels as Drug Delivery Systems for the Local Treatment of Glioblastoma. *Journal of Controlled Release* **2016**, *243*, 29–42, <https://doi.org/10.1016/j.jconrel.2016.09.034>.
8. Ganipineni, L.P.; Danhier, F.; Pr at, V. Drug Delivery Challenges and Future of Chemotherapeutic Nanomedicine for Glioblastoma Treatment. *Journal of Controlled Release* **2018**, *281*, 42–57, <https://doi.org/10.1016/j.jconrel.2018.05.008>.
9. Stupp, R.; Weller, M.; Belanger, K.; Bogdahn, U.; Ludwin, S.K.; Lacombe, D.; Mirimanoff, R.O. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *The New England Journal of Medicine* **2005**, *10*, <https://doi.org/10.1056/nejmoa043330>.
10. Yi, H.-G.; Jeong, Y.H.; Kim, Y.; Choi, Y.-J.; Moon, H.E.; Park, S.H.; Kang, K.S.; Bae, M.; Jang, J.; Youn, H.; *et al.* A Bioprinted Human-Glioblastoma-on-a-Chip for the Identification of Patient-Specific Responses to Chemoradiotherapy. *Nat Biomed Eng* **2019**, *3*, 509–519, <https://doi.org/10.1038/s41551-019-0363-x>.
11. Seano, G.; Nia, H.T.; Emblem, K.E.; Datta, M.; Ren, J.; Krishnan, S.; Kloepper, J.; Pinho, M.C.; Ho, W.W.; Ghosh, M.; *et al.* Solid Stress in Brain Tumours Causes Neuronal Loss and Neurological Dysfunction and Can Be Reversed by Lithium. *Nat Biomed Eng* **2019**, *3*, 230–245, <https://doi.org/10.1038/s41551-018-0334-7>.
12. Baldi, I.; Loiseau, H. Epidemiology of Primary Brain Tumors. In *Tumors of the Central Nervous System*,

- Volume 4: Brain Tumors (Part 2)*; Hayat, M.A., Ed.; Tumors of the Central Nervous System; Springer Netherlands: Dordrecht, **2012**; pp. 3–13.
13. Rasheed, S.; Rehman, K.; Akash, M.S.H. An Insight into the Risk Factors of Brain Tumors and Their Therapeutic Interventions. *Biomedicine & Pharmacotherapy* **2021**, *143*, 112119, <https://doi.org/10.1016/j.biopha.2021.112119>.
 14. Kim, Y.Z.; Kim, C.-Y.; Lim, J.; Sung, K.S.; Lee, J.; Oh, H.-J.; Kang, S.-G.; Kang, S.-H.; Kong, D.-S.; Kim, S.H.; *et al.* The Korean Society for Neuro-Oncology (KSNO) Guideline for Glioblastomas: Version 2018.01. *Brain Tumor Research and Treatment* **2019**, *7*, 1–9, <https://doi.org/10.14791/btrt.2019.7.e25>.
 15. Brodbelt, A.; Greenberg, D.; Winters, T.; Williams, M.; Vernon, S.; Collins, V.P. Glioblastoma in England: 2007–2011. *European Journal of Cancer* **2015**, *51*, 533–542, <https://doi.org/10.1016/j.ejca.2014.12.014>.
 16. Furnari, F.B.; Fenton, T.; Bachoo, R.M.; Mukasa, A.; Stommel, J.M.; Stegh, A.; Hahn, W.C.; Ligon, K.L.; Louis, D.N.; Brennan, C.; *et al.* Malignant Astrocytic Glioma: Genetics, Biology, and Paths to Treatment. *Genes Dev* **2007**, *21*, 2683–2710, <https://doi.org/10.1101/gad.1596707>.
 17. Abbott, N.J.; Rönnbäck, L.; Hansson, E. Astrocyte–Endothelial Interactions at the Blood–Brain Barrier. *Nat Rev Neurosci* **2006**, *7*, 41–53, <https://doi.org/10.1038/nrn1824>.
 18. Yamahara, T.; Numa, Y.; Oishi, T.; Kawaguchi, T.; Seno, T.; Asai, A.; Kawamoto, K. Morphological and Flow Cytometric Analysis of Cell Infiltration in Glioblastoma: A Comparison of Autopsy Brain and Neuroimaging. *Brain Tumor Pathol* **2010**, *27*, 81–87, <https://doi.org/10.1007/s10014-010-0275-7>.
 19. Brown, T.J.; Brennan, M.C.; Li, M.; Church, E.W.; Brandmeir, N.J.; Rakszawski, K.L.; Patel, A.S.; Rizk, E.B.; Suki, D.; Sawaya, R.; *et al.* Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-Analysis. *JAMA Oncol* **2016**, *2*, 1460–1469, <https://doi.org/10.1001/jamaoncol.2016.1373>.
 20. Banerjee, K.; Núñez, F.J.; Haase, S.; McClellan, B.L.; Faisal, S.M.; Carney, S.V.; Yu, J.; Alghamri, M.S.; Asad, A.S.; Candia, A.J.N.; *et al.* Current Approaches for Glioma Gene Therapy and Virotherapy. *Frontiers in Molecular Neuroscience* **2021**, *14*, <https://doi.org/10.3389/fnmol.2021.621831>.
 21. Pulkkanen, K.J.; Yla-Herttuala, S. Gene Therapy for Malignant Glioma: Current Clinical Status. *Molecular Therapy* **2005**, *12*, 585–598, <https://doi.org/10.1016/j.ymthe.2005.07.357>.
 22. Ishikawa, E.; Miyazaki, T.; Takano, S.; Akutsu, H. Anti-Angiogenic and Macrophage-Based Therapeutic Strategies for Glioma Immunotherapy. *Brain Tumor Pathol* **2021**, *38*, 149–155, <https://doi.org/10.1007/s10014-021-00402-5>.
 23. Sousa, F.; Dhaliwal, H.K.; Gattacceca, F.; Sarmiento, B.; Amiji, M.M. Enhanced Anti-Angiogenic Effects of Bevacizumab in Glioblastoma Treatment upon Intranasal Administration in Polymeric Nanoparticles. *Journal of Controlled Release* **2019**, *309*, 37–47, <https://doi.org/10.1016/j.jconrel.2019.07.033>.
 24. Hwang, E.I.; Sayour, E.J.; Flores, C.T.; Grant, G.; Wechsler-Reya, R.; Hoang-Minh, L.B.; Kieran, M.W.; Salcido, J.; Prins, R.M.; Figg, J.W.; *et al.* The Current Landscape of Immunotherapy for Pediatric Brain Tumors. *Nat Cancer* **2022**, *3*, 11–24, <https://doi.org/10.1038/s43018-021-00319-0>.
 25. McGranahan, T.; Therkelsen, K.E.; Ahmad, S.; Nagpal, S. Current State of Immunotherapy for Treatment of Glioblastoma. *Curr. Treat. Options in Oncol.* **2019**, *20*, 24, <https://doi.org/10.1007/s11864-019-0619-4>.
 26. Achar, A.; Myers, R.; Ghosh, C. Drug Delivery Challenges in Brain Disorders across the Blood–Brain Barrier: Novel Methods and Future Considerations for Improved Therapy. *Biomedicines* **2021**, *9*, 1834, <https://doi.org/10.3390/biomedicines9121834>.
 27. Han, L.; Jiang, C. Evolution of Blood–Brain Barrier in Brain Diseases and Related Systemic Nanoscale Brain-Targeting Drug Delivery Strategies. *Acta Pharmaceutica Sinica B* **2021**, *11*, 2306–2325, <https://doi.org/10.1016/j.apsb.2020.11.023>.
 28. Reddy, S.; Tatiparti, K.; Sau, S.; Iyer, A.K. Recent Advances in Nano Delivery Systems for Blood-Brain Barrier (BBB) Penetration and Targeting of Brain Tumors. *Drug Discovery Today* **2021**, *26*, 1944–1952, <https://doi.org/10.1016/j.drudis.2021.04.008>.
 29. Fatima, N.; Upadhyay, T.; Ahmad, F.; arshad, md; Kamal, M.; Sharma, D.; Sharma, R. Particulate β -Glucan Activates Early and Delayed Phagosomal Maturation and Autophagy within Macrophage in a NOX-2 Dependent Manner. *Life Sciences* **2020**, *266*, <https://doi.org/10.1016/j.lfs.2020.118851>.
 30. Omidi, Y.; Kianinejad, N.; Kwon, Y.; Omidian, H. Drug Delivery and Targeting to Brain Tumors: Considerations for Crossing the Blood-Brain Barrier. *Expert Review of Clinical Pharmacology* **2021**, *14*, 357–381, <https://doi.org/10.1080/17512433.2021.1887729>.
 31. Patel, J.P.; Spiller, S.E.; Barker, E.D. Drug Penetration in Pediatric Brain Tumors: Challenges and Opportunities. *Pediatric Blood & Cancer* **2021**, *68*, e28983, <https://doi.org/10.1002/pbc.28983>.

32. Noch, E.K.; Ramakrishna, R.; Magge, R. Challenges in the Treatment of Glioblastoma: Multisystem Mechanisms of Therapeutic Resistance. *World Neurosurgery* **2018**, *116*, 505–517, <https://doi.org/10.1016/j.wneu.2018.04.022>.
33. Corso, C.D.; Bindra, R.S.; Mehta, M.P. The Role of Radiation in Treating Glioblastoma: Here to Stay. *J Neurooncol* **2017**, *134*, 479–485, <https://doi.org/10.1007/s11060-016-2348-x>.
34. Lopez Perez, R.; Nicolay, N.H.; Wolf, J.-C.; Frister, M.; Schmezer, P.; Weber, K.-J.; Huber, P.E. DNA Damage Response of Clinical Carbon Ion versus Photon Radiation in Human Glioblastoma Cells. *Radiotherapy and Oncology* **2019**, *133*, 77–86, <https://doi.org/10.1016/j.radonc.2018.12.028>.
35. Mukherjee, B.; McEllin, B.; Camacho, C.V.; Tomimatsu, N.; Sirasanagandala, S.; Nannepaga, S.; Hatanpaa, K.J.; Mickey, B.; Madden, C.; Maher, E.; *et al.* EGFRvIII and DNA Double-Strand Break Repair: A Molecular Mechanism for Radioresistance in Glioblastoma. *Cancer Research* **2009**, *69*, 4252–4259, <https://doi.org/10.1158/0008-5472.CAN-08-4853>.
36. Todorova, P.K.; Fletcher-Sananikone, E.; Mukherjee, B.; Kollipara, R.; Vemireddy, V.; Xie, X.-J.; Guida, P.M.; Story, M.D.; Hatanpaa, K.; Habib, A.A.; *et al.* Radiation-Induced DNA Damage Cooperates with Heterozygosity of TP53 and PTEN to Generate High-Grade Gliomas. *Cancer Research* **2019**, *79*, 3749–3761, <https://doi.org/10.1158/0008-5472.CAN-19-0680>.
37. Yamanaka, R.; Hayano, A.; Kanayama, T. Radiation-Induced Gliomas: A Comprehensive Review and Meta-Analysis. *Neurosurg Rev* **2018**, *41*, 719–731, <https://doi.org/10.1007/s10143-016-0786-8>.
38. Gil del Alcazar, C.R.; Hardebeck, M.C.; Mukherjee, B.; Tomimatsu, N.; Gao, X.; Yan, J.; Xie, X.-J.; Bachoo, R.; Li, L.; Habib, A.A.; *et al.* Inhibition of DNA Double-Strand Break Repair by the Dual PI3K/MTOR Inhibitor NVP-BEZ235 as a Strategy for Radiosensitization of Glioblastoma. *Clinical Cancer Research* **2014**, *20*, 1235–1248, <https://doi.org/10.1158/1078-0432.CCR-13-1607>.
39. Sharma, M.; Schroeder, J.L.; Elson, P.; Meola, A.; Barnett, G.H.; Vogelbaum, M.A.; Suh, J.H.; Chao, S.T.; Mohammadi, A.M.; Stevens, G.H.J.; *et al.* Outcomes and Prognostic Stratification of Patients with Recurrent Glioblastoma Treated with Salvage Stereotactic Radiosurgery. *Journal of Neurosurgery* **2018**, *131*, 489–499, <https://doi.org/10.3171/2018.4.JNS172909>.
40. Kole, A.J.; Park, H.S.; Yeboa, D.N.; Rutter, C.E.; Corso, C.D.; Aneja, S.; Lester-Coll, N.H.; Mancini, B.R.; Knisely, J.P.; Yu, J.B. Concurrent Chemoradiotherapy versus Radiotherapy Alone for “Biopsy-Only” Glioblastoma Multiforme. *Cancer* **2016**, *122*, 2364–2370, <https://doi.org/10.1002/cncr.30063>.
41. Yang, L.-J.; Zhou, C.-F.; Lin, Z.-X. Temozolomide and Radiotherapy for Newly Diagnosed Glioblastoma Multiforme: A Systematic Review. *Cancer Investigation* **2014**, *32*, 31–36, <https://doi.org/10.3109/07357907.2013.861474>.
42. Mansouri, A.; Hachem, L.D.; Mansouri, S.; Nassiri, F.; Laperriere, N.J.; Xia, D.; Lindeman, N.I.; Wen, P.Y.; Chakravarti, A.; Mehta, M.P.; *et al.* MGMT Promoter Methylation Status Testing to Guide Therapy for Glioblastoma: Refining the Approach Based on Emerging Evidence and Current Challenges. *Neuro-Oncology* **2019**, *21*, 167–178, <https://doi.org/10.1093/neuonc/noy132>.
43. Dréan, A.; Goldwirt, L.; Verreault, M.; Canney, M.; Schmitt, C.; Guehenec, J.; Delattre, J.-Y.; Carpentier, A.; Idbaih, A. Blood-Brain Barrier, Cytotoxic Chemotherapies and Glioblastoma. *Expert Review of Neurotherapeutics* **2016**, *16*, 1285–1300, <https://doi.org/10.1080/14737175.2016.1202761>.
44. Papademetriou, I.T.; Porter, T. Promising Approaches to Circumvent the Blood–Brain Barrier: Progress, Pitfalls and Clinical Prospects in Brain Cancer. *Therapeutic Delivery* **2015**, *6*, 989–1016, <https://doi.org/10.4155/tde.15.48>.
45. Arvanitis, C.D.; Ferraro, G.B.; Jain, R.K. The Blood–Brain Barrier and Blood–Tumour Barrier in Brain Tumours and Metastases. *Nat Rev Cancer* **2020**, *20*, 26–41, <https://doi.org/10.1038/s41568-019-0205-x>.
46. Sprowls, S.A.; Arsiwala, T.A.; Bumgarner, J.R.; Shah, N.; Lateef, S.S.; Kielkowski, B.N.; Lockman, P.R. Improving CNS Delivery to Brain Metastases by Blood–Tumor Barrier Disruption. *Trends in Cancer* **2019**, *5*, 495–505, <https://doi.org/10.1016/j.trecan.2019.06.003>.
47. Ding, S.; Khan, A.I.; Cai, X.; Song, Y.; Lyu, Z.; Du, D.; Dutta, P.; Lin, Y. Overcoming Blood–Brain Barrier Transport: Advances in Nanoparticle-Based Drug Delivery Strategies. *Materials Today* **2020**, *37*, 112–125, <https://doi.org/10.1016/j.mattod.2020.02.001>.
48. Liao, W.; Du, Y.; Zhang, C.; Pan, F.; Yao, Y.; Zhang, T.; Peng, Q. Exosomes: The next Generation of Endogenous Nanomaterials for Advanced Drug Delivery and Therapy. *Acta Biomaterialia* **2019**, *86*, 1–14, <https://doi.org/10.1016/j.actbio.2018.12.045>.
49. Gimple, R.C.; Bhargava, S.; Dixit, D.; Rich, J.N. Glioblastoma Stem Cells: Lessons from the Tumor Hierarchy in a Lethal Cancer. *Genes Dev.* **2019**, *33*, 591–609, <https://doi.org/10.1101/gad.324301.119>.

50. Akindona, F.A.; Frederico, S.C.; Hancock, J.C.; Gilbert, M.R. Exploring the Origin of the Cancer Stem Cell Niche and Its Role in Anti-Angiogenic Treatment for Glioblastoma. *Frontiers in Oncology* **2022**, *12*, <https://doi.org/10.3389/fonc.2022.947634>.
51. Hu, B.; Wang, Q.; Wang, Y.A.; Hua, S.; Sauv e, C.-E.G.; Ong, D.; Lan, Z.D.; Chang, Q.; Ho, Y.W.; Monasterio, M.M.; *et al.* Epigenetic Activation of WNT5A Drives Glioblastoma Stem Cell Differentiation and Invasive Growth. *Cell* **2016**, *167*, 1281–1295.e18, <https://doi.org/10.1016/j.cell.2016.10.039>.
52. Liao, B.B.; Sievers, C.; Donohue, L.K.; Gillespie, S.M.; Flavahan, W.A.; Miller, T.E.; Venteicher, A.S.; Hebert, C.H.; Carey, C.D.; Rodig, S.J.; *et al.* Adaptive Chromatin Remodeling Drives Glioblastoma Stem Cell Plasticity and Drug Tolerance. *Cell Stem Cell* **2017**, *20*, 233–246.e7, <https://doi.org/10.1016/j.stem.2016.11.003>.
53. Nakod, P.S.; Kim, Y.; Rao, S.S. Biomimetic Models to Examine Microenvironmental Regulation of Glioblastoma Stem Cells. *Cancer Letters* **2018**, *429*, 41–53, <https://doi.org/10.1016/j.canlet.2018.05.007>.
54. Horvath, P.; Aulner, N.; Bickle, M.; Davies, A.M.; Nery, E.D.; Ebner, D.; Montoya, M.C.;  stling, P.; Pieti inen, V.; Price, L.S.; *et al.* Screening out Irrelevant Cell-Based Models of Disease. *Nat Rev Drug Discov* **2016**, *15*, 751–769, <https://doi.org/10.1038/nrd.2016.175>.
55. Miller, T.E.; Liao, B.B.; Wallace, L.C.; Morton, A.R.; Xie, Q.; Dixit, D.; Factor, D.C.; Kim, L.J.Y.; Morrow, J.J.; Wu, Q.; *et al.* Transcription Elongation Factors Represent *in vivo* Cancer Dependencies in Glioblastoma. *Nature* **2017**, *547*, 355–359, <https://doi.org/10.1038/nature23000>.
56. Hegi, M.E.; Diserens, A.-C.; Gorlia, T.; Hamou, M.-F.; de Tribolet, N.; Weller, M.; Kros, J.M.; Hainfellner, J.A.; Mason, W.; Mariani, L.; *et al.* MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. *New England Journal of Medicine* **2005**, *352*, 997–1003, <https://doi.org/10.1056/NEJMoa043331>.
57. Yip, S.; Miao, J.; Cahill, D.P.; Iafrate, A.J.; Aldape, K.; Nutt, C.L.; Louis, D.N. *MSH6* Mutations Arise in Glioblastomas during Temozolomide Therapy and Mediate Temozolomide Resistance. *Clin Cancer Res* **2009**, *15*, 4622–4629, <https://doi.org/10.1158/1078-0432.CCR-08-3012>.
58. Johnson, B.E.; Mazor, T.; Hong, C.; Barnes, M.; Aihara, K.; McLean, C.Y.; Fouse, S.D.; Yamamoto, S.; Ueda, H.; Tatsuno, K.; *et al.* Mutational Analysis Reveals the Origin and Therapy-Driven Evolution of Recurrent Glioma. *Science* **2014**, *343*, 189–193, <https://doi.org/10.1126/science.1239947>.
59. Kang, H.; Lee, H.; Kim, D.; Kim, B.; Kang, J.; Kim, H.Y.; Youn, H.; Youn, B. Targeting Glioblastoma Stem Cells to Overcome Chemoresistance: An Overview of Current Therapeutic Strategies. *Biomedicines* **2022**, *10*, 1308, <https://doi.org/10.3390/biomedicines10061308>.
60. Teng, J.; Hejazi, S.; Hiddingh, L.; Carvalho, L.; de Gooijer, M.C.; Wakimoto, H.; Barazas, M.; Tannous, M.; Chi, A.S.; Noske, D.P.; *et al.* Recycling Drug Screen Repurposes Hydroxyurea as a Sensitizer of Glioblastomas to Temozolomide Targeting de Novo DNA Synthesis, Irrespective of Molecular Subtype. *Neuro-Oncology* **2018**, *20*, 642–654, <https://doi.org/10.1093/neuonc/nox198>.
61. Qazi, M.A.; Vora, P.; Venugopal, C.; Sidhu, S.S.; Moffat, J.; Swanton, C.; Singh, S.K. Intratumoral Heterogeneity: Pathways to Treatment Resistance and Relapse in Human Glioblastoma. *Annals of Oncology* **2017**, *28*, 1448–1456, <https://doi.org/10.1093/annonc/mdx169>.
62. Eskilsson, E.; R sland, G.V.; Solecki, G.; Wang, Q.; Harter, P.N.; Graziani, G.; Verhaak, R.G.W.; Winkler, F.; Bjerkvig, R.; Miletic, H. EGFR Heterogeneity and Implications for Therapeutic Intervention in Glioblastoma. *Neuro-Oncology* **2018**, *20*, 743–752, <https://doi.org/10.1093/neuonc/nox191>.
63. Jin, X.; Kim, L.J.Y.; Wu, Q.; Wallace, L.C.; Prager, B.C.; Sanvoranart, T.; Gimple, R.C.; Wang, X.; Mack, S.C.; Miller, T.E.; *et al.* Targeting Glioma Stem Cells through Combined BMI1 and EZH2 Inhibition. *Nat Med* **2017**, *23*, 1352–1361, <https://doi.org/10.1038/nm.4415>.
64. Tan, S.K.; Pastori, C.; Penas, C.; Komotar, R.J.; Ivan, M.E.; Wahlestedt, C.; Ayad, N.G. Serum Long Noncoding RNA HOTAIR as a Novel Diagnostic and Prognostic Biomarker in Glioblastoma Multiforme. *Mol Cancer* **2018**, *17*, 74, <https://doi.org/10.1186/s12943-018-0822-0>.
65. Pointer, K.B.; Clark, P.A.; Zorniak, M.; Alrfaei, B.M.; Kuo, J.S. Glioblastoma Cancer Stem Cells: Biomarker and Therapeutic Advances. *Neurochemistry International* **2014**, *71*, 1–7, <https://doi.org/10.1016/j.neuint.2014.03.005>.
66. Upadhyay, T.; Fatima, N.; Sharma, D.; Saravanakumar, V.; Sharma, R. Preparation and Characterization of Beta-Glucan Particles Containing a Payload of Nanoembedded Rifabutin for Enhanced Targeted Delivery to Macrophages. *EXCLI Journal* **2017**, *16*, 210–228, <https://doi.org/10.17179/excli2016-804>.
67. Sharma, G.; Kumar, A.; Sharma, S.; Naushad, Mu.; Prakash Dwivedi, R.; ALOthman, Z.A.; Mola, G.T. Novel Development of Nanoparticles to Bimetallic Nanoparticles and Their Composites: A Review. *Journal*

- of King Saud University - Science **2019**, *31*, 257–269, <https://doi.org/10.1016/j.jksus.2017.06.012>.
68. Zhou, Y.; Peng, Z.; Seven, E.S.; Leblanc, R.M. Crossing the Blood-Brain Barrier with Nanoparticles. *Journal of Controlled Release* **2018**, *270*, 290–303, <https://doi.org/10.1016/j.jconrel.2017.12.015>.
69. Khongkow, M.; Yata, T.; Boonrunsiman, S.; Ruktanonchai, U.R.; Graham, D.; Namdee, K. Surface Modification of Gold Nanoparticles with Neuron-Targeted Exosome for Enhanced Blood-Brain Barrier Penetration. *Sci Rep* **2019**, *9*, 8278, <https://doi.org/10.1038/s41598-019-44569-6>.
70. Abdul Razzak, R.; Florence, G.J.; Gunn-Moore, F.J. Approaches to CNS Drug Delivery with a Focus on Transporter-Mediated Transcytosis. *International Journal of Molecular Sciences* **2019**, *20*, 3108, <https://doi.org/10.3390/ijms20123108>.
71. Jain, R.; Jordan, N.; Weiss, S.; Foerstendorf, H.; Heim, K.; Kacker, R.; Hübner, R.; Kramer, H.; van Hullebusch, E.D.; Farges, F.; *et al.* Extracellular Polymeric Substances Govern the Surface Charge of Biogenic Elemental Selenium Nanoparticles. *Environ. Sci. Technol.* **2015**, *49*, 1713–1720, <https://doi.org/10.1021/es5043063>.
72. Gagliardi, M. Biomimetic and Bioinspired Nanoparticles for Targeted Drug Delivery. *Therapeutic Delivery* **2017**, *8*, 289–299, <https://doi.org/10.4155/tde-2017-0013>.
73. Mohammadinejad, R.; Moosavi, M.A.; Tavakol, S.; Vardar, D.Ö.; Hosseini, A.; Rahmati, M.; Dini, L.; Hussain, S.; Mandegary, A.; Klionsky, D.J. Necrotic, Apoptotic and Autophagic Cell Fates Triggered by Nanoparticles. *Autophagy* **2019**, *15*, 4–33, <https://doi.org/10.1080/15548627.2018.1509171>.
74. Jo, D.H.; Kim, J.H.; Lee, T.G.; Kim, J.H. Size, Surface Charge, and Shape Determine Therapeutic Effects of Nanoparticles on Brain and Retinal Diseases. *Nanomedicine: Nanotechnology, Biology and Medicine* **2015**, *11*, 1603–1611, <https://doi.org/10.1016/j.nano.2015.04.015>.
75. Shin, S.W.; Song, I.H.; Um, S.H. Role of Physicochemical Properties in Nanoparticle Toxicity. *Nanomaterials* **2015**, *5*, 1351–1365, <https://doi.org/10.3390/nano5031351>.
76. Cai, Q.; Wang, L.; Deng, G.; Liu, J.; Chen, Q.; Chen, Z. Systemic Delivery to Central Nervous System by Engineered PLGA Nanoparticles. *Am J Transl Res* **2016**, *8*, 749–764, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846924/>
77. Monsalve, Y.; Tosi, G.; Ruozi, B.; Belletti, D.; Vilella, A.; Zoli, M.; Vandelli, M.A.; Forni, F.; López, B.L.; Sierra, L. PEG-g-Chitosan Nanoparticles Functionalized with the Monoclonal Antibody OX26 for Brain Drug Targeting. *Nanomedicine* **2015**, *10*, 1735–1750, <https://doi.org/10.2217/nnm.15.29>.
78. Alli, S.; Figueiredo, C.A.; Golbourn, B.; Sabha, N.; Wu, M.Y.; Bondoc, A.; Luck, A.; Coluccia, D.; Maslink, C.; Smith, C.; *et al.* Brainstem Blood Brain Barrier Disruption Using Focused Ultrasound: A Demonstration of Feasibility and Enhanced Doxorubicin Delivery. *Journal of Controlled Release* **2018**, *281*, 29–41, <https://doi.org/10.1016/j.jconrel.2018.05.005>.
79. Lundy, D.J.; Nguyễn, H.; Hsieh, P.C.H. Emerging Nano-Carrier Strategies for Brain Tumor Drug Delivery and Considerations for Clinical Translation. *Pharmaceutics* **2021**, *13*, 1193, <https://doi.org/10.3390/pharmaceutics13081193>.
80. Chen, E.M.; Quijano, A.R.; Seo, Y.-E.; Jackson, C.; Josowitz, A.D.; Noorbakhsh, S.; Merlettoni, A.; Sundaram, R.K.; Focarete, M.L.; Jiang, Z.; *et al.* Biodegradable PEG-Poly(ω -Pentadecalactone-Co-p-Dioxanone) Nanoparticles for Enhanced and Sustained Drug Delivery to Treat Brain Tumors. *Biomaterials* **2018**, *178*, 193–203, <https://doi.org/10.1016/j.biomaterials.2018.06.024>.
81. Alphandéry, E.; Idbaih, A.; Adam, C.; Delattre, J.-Y.; Schmitt, C.; Guyot, F.; Chebbi, I. Chains of Magnetosomes with Controlled Endotoxin Release and Partial Tumor Occupation Induce Full Destruction of Intracranial U87-Luc Glioma in Mice under the Application of an Alternating Magnetic Field. *Journal of Controlled Release* **2017**, *262*, 259–272, <https://doi.org/10.1016/j.jconrel.2017.07.020>.
82. Alphandéry, E.; Idbaih, A.; Adam, C.; Delattre, J.-Y.; Schmitt, C.; Guyot, F.; Chebbi, I. Development of Non-Pyrogenic Magnetosome Minerals Coated with Poly-L-Lysine Leading to Full Disappearance of Intracranial U87-Luc Glioblastoma in 100% of Treated Mice Using Magnetic Hyperthermia. *Biomaterials* **2017**, *141*, 210–222, <https://doi.org/10.1016/j.biomaterials.2017.06.026>.
83. Sukumar, U.K.; Bose, R.J.C.; Malhotra, M.; Babikir, H.A.; Afjei, R.; Robinson, E.; Zeng, Y.; Chang, E.; Habte, F.; Sinclair, R.; *et al.* Intranasal Delivery of Targeted Polyfunctional Gold-Iron Oxide Nanoparticles Loaded with Therapeutic MicroRNAs for Combined Theranostic Multimodality Imaging and Presensitization of Glioblastoma to Temozolomide. *Biomaterials* **2019**, *218*, 119342, <https://doi.org/10.1016/j.biomaterials.2019.119342>.
84. Bruinsmann, F.A.; Richter Vaz, G.; de Cristo Soares Alves, A.; Aguirre, T.; Raffin Pohlmann, A.; Stanisçuaski Guterres, S.; Sonvico, F. Nasal Drug Delivery of Anticancer Drugs for the Treatment of

- Glioblastoma: Preclinical and Clinical Trials. *Molecules* **2019**, *24*, 4312, <https://doi.org/10.3390/molecules24234312>.
85. Coluccia, D.; Figueiredo, C.A.; Wu, M.Y.; Riemenschneider, A.N.; Diaz, R.; Luck, A.; Smith, C.; Das, S.; Ackerley, C.; O'Reilly, M.; *et al.* Enhancing Glioblastoma Treatment Using Cisplatin-Gold-Nanoparticle Conjugates and Targeted Delivery with Magnetic Resonance-Guided Focused Ultrasound. *Nanomedicine: Nanotechnology, Biology and Medicine* **2018**, *14*, 1137–1148, <https://doi.org/10.1016/j.nano.2018.01.021>.
 86. Parodi, A.; Rudzińska, M.; Deviatkin, A.A.; Soond, S.M.; Baldin, A.V.; Zamyatnin, A.A. Established and Emerging Strategies for Drug Delivery Across the Blood-Brain Barrier in Brain Cancer. *Pharmaceutics* **2019**, *11*, 245, <https://doi.org/10.3390/pharmaceutics11050245>.
 87. Timbie, K.F.; Afzal, U.; Date, A.; Zhang, C.; Song, J.; Wilson Miller, G.; Suk, J.S.; Hanes, J.; Price, R.J. MR Image-Guided Delivery of Cisplatin-Loaded Brain-Penetrating Nanoparticles to Invasive Glioma with Focused Ultrasound. *Journal of Controlled Release* **2017**, *263*, 120–131, <https://doi.org/10.1016/j.jconrel.2017.03.017>.
 88. Wang, D.; Wang, C.; Wang, L.; Chen, Y. A Comprehensive Review in Improving Delivery of Small-Molecule Chemotherapeutic Agents Overcoming the Blood-Brain/Brain Tumor Barriers for Glioblastoma Treatment. *Drug Delivery* **2019**, *26*, 551–565, <https://doi.org/10.1080/10717544.2019.1616235>.
 89. Singh, M.S.; Lamprecht, A. Cargoing P-Gp Inhibitors via Nanoparticle Sensitizes Tumor Cells against Doxorubicin. *International Journal of Pharmaceutics* **2015**, *478*, 745–752, <https://doi.org/10.1016/j.ijpharm.2014.11.064>.
 90. Gupta, R.; Sharma, D. Evolution of Magnetic Hyperthermia for Glioblastoma Multifomre Therapy. *ACS Chem. Neurosci.* **2019**, *10*, 1157–1172, <https://doi.org/10.1021/acschemneuro.8b00652>.
 91. Rego, G.N.A.; Nucci, M.P.; Mamani, J.B.; Oliveira, F.A.; Marti, L.C.; Filgueiras, I.S.; Ferreira, J.M.; Real, C.C.; Faria, D. de P.; Espinha, P.L.; *et al.* Therapeutic Efficiency of Multiple Applications of Magnetic Hyperthermia Technique in Glioblastoma Using Aminosilane Coated Iron Oxide Nanoparticles: *In vitro* and *In vivo* Study. *International Journal of Molecular Sciences* **2020**, *21*, 958, <https://doi.org/10.3390/ijms21030958>.
 92. Grillone, A.; Battaglini, M.; Moscato, S.; Mattii, L.; de Julián Fernández, C.; Scarpellini, A.; Giorgi, M.; Sinibaldi, E.; Ciofani, G. Nutlin-Loaded Magnetic Solid Lipid Nanoparticles for Targeted Glioblastoma Treatment. *Nanomedicine* **2019**, *14*, 727–752, <https://doi.org/10.2217/nnm-2018-0436>.
 93. Hsu, J.-F.; Chu, S.-M.; Liao, C.-C.; Wang, C.-J.; Wang, Y.-S.; Lai, M.-Y.; Wang, H.-C.; Huang, H.-R.; Tsai, M.-H. Nanotechnology and Nanocarrier-Based Drug Delivery as the Potential Therapeutic Strategy for Glioblastoma Multifomre: An Update. *Cancers* **2021**, *13*, 195, <https://doi.org/10.3390/cancers13020195>.
 94. Dhar, D.; Ghosh, S.; Das, S.; Chatterjee, J. A Review of Recent Advances in Magnetic Nanoparticle-Based Theranostics of Glioblastoma. *Nanomedicine* **2022**, *17*, 107–132, <https://doi.org/10.2217/nnm-2021-0348>.
 95. Pucci, C.; De Pasquale, D.; Marino, A.; Martinelli, C.; Lauciello, S.; Ciofani, G. Hybrid Magnetic Nanovectors Promote Selective Glioblastoma Cell Death through a Combined Effect of Lysosomal Membrane Permeabilization and Chemotherapy. *ACS Appl. Mater. Interfaces* **2020**, *12*, 29037–29055, <https://doi.org/10.1021/acsami.0c05556>.
 96. Jiang, Y.; Song, Y.; Wang, R.; Hu, T.; Zhang, D.; Wang, Z.; Tie, X.; Wang, M.; Han, S. NFAT1-Mediated Regulation of NDEL1 Promotes Growth and Invasion of Glioma Stem-like Cells. *Cancer Research* **2019**, *79*, 2593–2603, <https://doi.org/10.1158/0008-5472.CAN-18-3297>.
 97. Mattei, V.; Santilli, F.; Martellucci, S.; Delle Monache, S.; Fabrizi, J.; Colapietro, A.; Angelucci, A.; Festuccia, C. The Importance of Tumor Stem Cells in Glioblastoma Resistance to Therapy. *International Journal of Molecular Sciences* **2021**, *22*, 3863, <https://doi.org/10.3390/ijms22083863>.
 98. Kalkan, R. Glioblastoma Stem Cells as a New Therapeutic Target for Glioblastoma. *Clin Med Insights Oncol* **2015**, *9*, CMO.S30271, <https://doi.org/10.4137/CMO.S30271>.
 99. Sabu, A.; Liu, T.-I.; Ng, S.S.; Doong, R.-A.; Huang, Y.-F.; Chiu, H.-C. Nanomedicines Targeting Glioma Stem Cells. *ACS Appl. Mater. Interfaces* **2022**, <https://doi.org/10.1021/acsami.2c03538>.
 100. Tarasov, V.V.; Svistunov, A.A.; Chubarev, V.N.; Zatsepilova, T.A.; Preferanskaya, N.G.; Stepanova, O.I.; Sokolov, A.V.; Dostdar, S.A.; Minyaeva, N.N.; Neganova, M.E.; *et al.* Feasibility of Targeting Glioblastoma Stem Cells: From Concept to Clinical Trials. *Current Topics in Medicinal Chemistry* **2019**, *19*, 2974–2984, <https://doi.org/10.2174/1568026619666191112140939>.
 101. Kunoh, T.; Shimura, T.; Kasai, T.; Matsumoto, S.; Mahmud, H.; Khayrani, A.C.; Seno, M.; Kunoh, H.; Takada, J. Use of DNA-Generated Gold Nanoparticles to Radiosensitize and Eradicate Radioresistant Glioma Stem Cells. *Nanotechnology* **2018**, *30*, 055101, <https://doi.org/10.1088/1361-6528/aaedd5>.

102. Lépinoux-Chambaud, C.; Eyer, J. The NFL-TBS.40–63 Peptide Targets and Kills Glioblastoma Stem Cells Derived from Human Patients and Also Targets Nanocapsules into These Cells. *International Journal of Pharmaceutics* **2019**, *566*, 218–228, <https://doi.org/10.1016/j.ijpharm.2019.05.060>.
103. Säälük, P.; Lingasamy, P.; Toome, K.; Mastandrea, I.; Rouso-Noori, L.; Tobi, A.; Simón-Gracia, L.; Hunt, H.; Paiste, P.; Kotamraju, V.R.; *et al.* Peptide-Guided Nanoparticles for Glioblastoma Targeting. *Journal of Controlled Release* **2019**, *308*, 109–118, <https://doi.org/10.1016/j.jconrel.2019.06.018>.
104. Gonçalves, D.P.N.; Rodriguez, R.D.; Kurth, T.; Bray, L.J.; Binner, M.; Jungnickel, C.; Gür, F.N.; Poser, S.W.; Schmidt, T.L.; Zahn, D.R.T.; *et al.* Enhanced Targeting of Invasive Glioblastoma Cells by Peptide-Functionalized Gold Nanorods in Hydrogel-Based 3D Cultures. *Acta Biomaterialia* **2017**, *58*, 12–25, <https://doi.org/10.1016/j.actbio.2017.05.054>.
105. Cho, J.-H.; Kim, A.-R.; Kim, S.-H.; Lee, S.-J.; Chung, H.; Yoon, M.-Y. Development of a Novel Imaging Agent Using Peptide-Coated Gold Nanoparticles toward Brain Glioma Stem Cell Marker CD133. *Acta Biomater* **2017**, *47*, 182–192, <https://doi.org/10.1016/j.actbio.2016.10.009>.
106. Smiley, S.B.; Zarrinmayeh, H.; Das, S.K.; Pollok, K.E.; Vannier, M.W.; Veronesi, M.C. Novel Therapeutics and Drug-Delivery Approaches in the Modulation of Glioblastoma Stem Cell Resistance. *Therapeutic Delivery* **2022**, *13*, 249–273, <https://doi.org/10.4155/tde-2021-0086>.
107. Zhao, M.; Wan, S.; Peng, X.; Zhang, B.; Pan, Q.; Li, S.; He, B.; Pu, Y. Leveraging a Polycationic Polymer to Direct Tunable Loading of an Anticancer Agent and Photosensitizer with Opposite Charges for Chemo-Photodynamic Therapy. *J. Mater. Chem. B* **2020**, *8*, 1235–1244, <https://doi.org/10.1039/C9TB02400J>.
108. Zhou, J.; Patel, T.R.; Sirianni, R.W.; Strohhahn, G.; Zheng, M.-Q.; Duong, N.; Schafbauer, T.; Huttner, A.J.; Huang, Y.; Carson, R.E.; *et al.* Highly Penetrative, Drug-Loaded Nanocarriers Improve Treatment of Glioblastoma. *Proceedings of the National Academy of Sciences* **2013**, *110*, 11751–11756, <https://doi.org/10.1073/pnas.1304504110>.
109. Glaser, T.; Han, I.; Wu, L.; Zeng, X. Targeted Nanotechnology in Glioblastoma Multiforme. *Frontiers in Pharmacology* **2017**, *8*, <https://doi.org/10.3389/fphar.2017.00166>.
110. Hosseini, M.; Haji-Fatahaliha, M.; Jadidi-Niaragh, F.; Majidi, J.; Yousefi, M. The Use of Nanoparticles as a Promising Therapeutic Approach in Cancer Immunotherapy. *Artif Cells Nanomed Biotechnol* **2016**, *44*, 1051–1061, <https://doi.org/10.3109/21691401.2014.998830>.
111. Madhankumar, A.B.; Slagle-Webb, B.; Wang, X.; Yang, Q.X.; Antonetti, D.A.; Miller, P.A.; Sheehan, J.M.; Connor, J.R. Efficacy of Interleukin-13 Receptor-Targeted Liposomal Doxorubicin in the Intracranial Brain Tumor Model. *Mol Cancer Ther* **2009**, *8*, 648–654, <https://doi.org/10.1158/1535-7163.MCT-08-0853>.
112. Yang, F.-Y.; Wong, T.-T.; Teng, M.-C.; Liu, R.-S.; Lu, M.; Liang, H.-F.; Wei, M.-C. Focused Ultrasound and Interleukin-4 Receptor-Targeted Liposomal Doxorubicin for Enhanced Targeted Drug Delivery and Antitumor Effect in Glioblastoma Multiforme. *J Control Release* **2012**, *160*, 652–658, <https://doi.org/10.1016/j.jconrel.2012.02.023>.
113. Ghaferi, M.; Raza, A.; Koochi, M.; Zahra, W.; Akbarzadeh, A.; Ebrahimi Shahmabadi, H.; Alavi, S.E. Impact of PEGylated Liposomal Doxorubicin and Carboplatin Combination on Glioblastoma. *Pharmaceutics* **2022**, *14*, 2183, <https://doi.org/10.3390/pharmaceutics14102183>.
114. Kim, J.; Ahn, S.I.; Kim, Y. Nanotherapeutics Engineered to Cross the Blood-Brain Barrier for Advanced Drug Delivery to the Central Nervous System. *Journal of Industrial and Engineering Chemistry* **2019**, *73*, 8–18, <https://doi.org/10.1016/j.jiec.2019.01.021>.
115. Limasale, Y.D.P.; Tezcaner, A.; Özen, C.; Keskin, D.; Banerjee, S. Epidermal Growth Factor Receptor-Targeted Immunoliposomes for Delivery of Celecoxib to Cancer Cells. *International Journal of Pharmaceutics* **2015**, *479*, 364–373, <https://doi.org/10.1016/j.ijpharm.2015.01.016>.
116. Nishiyama, N.; Matsumura, Y.; Kataoka, K. Development of Polymeric Micelles for Targeting Intractable Cancers. *Cancer Science* **2016**, *107*, 867–874, <https://doi.org/10.1111/cas.12960>.
117. Karim, R.; Palazzo, C.; Evrard, B.; Piel, G. Nanocarriers for the Treatment of Glioblastoma Multiforme: Current State-of-the-Art. *Journal of Controlled Release* **2016**, *227*, 23–37, <https://doi.org/10.1016/j.jconrel.2016.02.026>.
118. Saxena, V.; Hussain, M.D. Formulation and *in vitro* Evaluation of 17-Allyl-17-Demethoxygeldanamycin (17-AAG) Loaded Polymeric Mixed Micelles for Glioblastoma Multiforme. *Colloids and Surfaces B: Biointerfaces* **2013**, *112*, 350–355, <https://doi.org/10.1016/j.colsurfb.2013.07.031>.
119. Talaei, S.; Mellatyar, H.; Asadi, A.; Akbarzadeh, A.; Sheervalilou, R.; Zarghami, N. Spotlight on 17-AAG as an Hsp90 Inhibitor for Molecular Targeted Cancer Treatment. *Chemical Biology & Drug Design* **2019**, *93*, 760–786, <https://doi.org/10.1111/cbdd.13486>.

120. Sun, P.; Xiao, Y.; Di, Q.; Ma, W.; Ma, X.; Wang, Q.; Chen, W. Transferrin Receptor-Targeted PEG-PLA Polymeric Micelles for Chemotherapy Against Glioblastoma Multiforme. *Int J Nanomedicine* **2020**, *15*, 6673–6688, <https://doi.org/10.2147/IJN.S257459>.
121. Stenström, P.; Manzanares, D.; Zhang, Y.; Ceña, V.; Malkoch, M. Evaluation of Amino-Functional Polyester Dendrimers Based on Bis-MPA as Nonviral Vectors for SiRNA Delivery. *Molecules* **2018**, *23*, E2028, <https://doi.org/10.3390/molecules23082028>.
122. Tambe, V.; Thakkar, S.; Raval, N.; Sharma, D.; Kalia, K.; Tekade, R.K. Surface Engineered Dendrimers in SiRNA Delivery and Gene Silencing. *Curr Pharm Des* **2017**, *23*, 2952–2975, <https://doi.org/10.2174/1381612823666170314104619>.
123. Dhanikula, R.S.; Argaw, A.; Bouchard, J.-F.; Hildgen, P. Methotrexate Loaded Polyether-Copolyester Dendrimers for the Treatment of Gliomas: Enhanced Efficacy and Intratumoral Transport Capability. *Mol Pharm* **2008**, *5*, 105–116, <https://doi.org/10.1021/mp700086j>.
124. Qiu, J.; Kong, L.; Cao, X.; Li, A.; Wei, P.; Wang, L.; Mignani, S.; Caminade, A.-M.; Majoral, J.-P.; Shi, X. Enhanced Delivery of Therapeutic SiRNA into Glioblastoma Cells Using Dendrimer-Entrapped Gold Nanoparticles Conjugated with β -Cyclodextrin. *Nanomaterials* **2018**, *8*, 131, <https://doi.org/10.3390/nano8030131>.
125. Ghaffari, M.; Dehghan, G.; Abedi-Gaballu, F.; Kashanian, S.; Baradaran, B.; Ezzati Nazhad Dolatabadi, J.; Losic, D. Surface Functionalized Dendrimers as Controlled-Release Delivery Nanosystems for Tumor Targeting. *European Journal of Pharmaceutical Sciences* **2018**, *122*, 311–330, <https://doi.org/10.1016/j.ejps.2018.07.020>.
126. Li, J.; Liang, H.; Liu, J.; Wang, Z. Poly (Amidoamine) (PAMAM) Dendrimer Mediated Delivery of Drug and PDNA/SiRNA for Cancer Therapy. *International Journal of Pharmaceutics* **2018**, *546*, 215–225, <https://doi.org/10.1016/j.ijpharm.2018.05.045>.
127. Bazi Alahri, M.; Arshadizadeh, R.; Raeisi, M.; Khatami, M.; Sadat Sajadi, M.; Kamal Abdelbasset, W.; Akhmadeev, R.; Irvani, S. Theranostic Applications of Metal–Organic Frameworks (MOFs)-Based Materials in Brain Disorders: Recent Advances and Challenges. *Inorganic Chemistry Communications* **2021**, *134*, 108997, <https://doi.org/10.1016/j.inoche.2021.108997>.
128. Bobyk, L.; Edouard, M.; Deman, P.; Vautrin, M.; Pernet-Gallay, K.; Delaroche, J.; Adam, J.-F.; Estève, F.; Ravanat, J.-L.; Elleaume, H. Photoactivation of Gold Nanoparticles for Glioma Treatment. *Nanomedicine: Nanotechnology, Biology and Medicine* **2013**, *9*, 1089–1097, <https://doi.org/10.1016/j.nano.2013.04.007>.
129. Her, S.; Jaffray, D.A.; Allen, C. Gold Nanoparticles for Applications in Cancer Radiotherapy: Mechanisms and Recent Advancements. *Advanced Drug Delivery Reviews* **2017**, *109*, 84–101, <https://doi.org/10.1016/j.addr.2015.12.012>.
130. Liu, J.; Peng, Q. Protein-Gold Nanoparticle Interactions and Their Possible Impact on Biomedical Applications. *Acta Biomater* **2017**, *55*, 13–27, <https://doi.org/10.1016/j.actbio.2017.03.055>.
131. Peng, L.; Liang, Y.; Zhong, X.; Liang, Z.; Tian, Y.; Li, S.; Liang, J.; Wang, R.; Zhong, Y.; Shi, Y.; *et al.* Aptamer-Conjugated Gold Nanoparticles Targeting Epidermal Growth Factor Receptor Variant III for the Treatment of Glioblastoma. *Int J Nanomedicine* **2020**, *15*, 1363–1372, <https://doi.org/10.2147/IJN.S238206>.
132. Ajdary, M.; Moosavi, M.A.; Rahmati, M.; Falahati, M.; Mahboubi, M.; Mandegary, A.; Jangjoo, S.; Mohammadinejad, R.; Varma, R.S. Health Concerns of Various Nanoparticles: A Review of Their *in vitro* and *in vivo* Toxicity. *Nanomaterials* **2018**, *8*, 634, <https://doi.org/10.3390/nano8090634>.
133. Coccini, T.; Grandi, S.; Lonati, D.; Locatelli, C.; De Simone, U. Comparative Cellular Toxicity of Titanium Dioxide Nanoparticles on Human Astrocyte and Neuronal Cells after Acute and Prolonged Exposure. *Neurotoxicology* **2015**, *48*, 77–89, <https://doi.org/10.1016/j.neuro.2015.03.006>.
134. Bourquin, J.; Milosevic, A.; Hauser, D.; Lehner, R.; Blank, F.; Petri-Fink, A.; Rothen-Rutishauser, B. Biodistribution, Clearance, and Long-Term Fate of Clinically Relevant Nanomaterials. *Adv Mater* **2018**, *30*, e1704307, <https://doi.org/10.1002/adma.201704307>.
135. Krętowski, R.; Kusaczuk, M.; Naumowicz, M.; Kotyńska, J.; Szynaka, B.; Cechowska-Pasko, M. The Effects of Silica Nanoparticles on Apoptosis and Autophagy of Glioblastoma Cell Lines. *Nanomaterials (Basel)* **2017**, *7*, E230, <https://doi.org/10.3390/nano7080230>.
136. Mendanha, D.; Vieira de Castro, J.; Ferreira, H.; Neves, N.M. Biomimetic and Cell-Based Nanocarriers – New Strategies for Brain Tumor Targeting. *Journal of Controlled Release* **2021**, *337*, 482–493, <https://doi.org/10.1016/j.jconrel.2021.07.047>.
137. Yazdimamaghani, M.; Moos, P.J.; Dobrovolskaia, M.A.; Ghandehari, H. Genotoxicity of Amorphous Silica Nanoparticles: Status and Prospects. *Nanomedicine: Nanotechnology, Biology and Medicine* **2019**, *16*, 106–

- 125, <https://doi.org/10.1016/j.nano.2018.11.013>.
138. Dong, X.; Wu, Z.; Li, X.; Xiao, L.; Yang, M.; Li, Y.; Duan, J.; Sun, Z. <p>The Size-Dependent Cytotoxicity of Amorphous Silica Nanoparticles: A Systematic Review of *in vitro* Studies</P>. *IJN* **2020**, *15*, 9089–9113, <https://doi.org/10.2147/IJN.S276105>.
139. A. Bielecki, P.; E. Lorkowski, M.; M. Becicka, W.; U. Atukorale, P.; J. Moon, T.; Zhang, Y.; Wiese, M.; Covarrubias, G.; Ravichandran, S.; Karathanasis, E. Immunostimulatory Silica Nanoparticle Boosts Innate Immunity in Brain Tumors. *Nanoscale Horizons* **2021**, *6*, 156–167, <https://doi.org/10.1039/D0NH00446D>.
140. Luo, M.; Lewik, G.; Ratcliffe, J.C.; Choi, C.H.J.; Mäkilä, E.; Tong, W.Y.; Voelcker, N.H. Systematic Evaluation of Transferrin-Modified Porous Silicon Nanoparticles for Targeted Delivery of Doxorubicin to Glioblastoma. *ACS Appl. Mater. Interfaces* **2019**, *11*, 33637–33649, <https://doi.org/10.1021/acsami.9b10787>.
141. Sheykhzadeh, S.; Luo, M.; Peng, B.; White, J.; Abdalla, Y.; Tang, T.; Mäkilä, E.; Voelcker, N.H.; Tong, W.Y. Transferrin-Targeted Porous Silicon Nanoparticles Reduce Glioblastoma Cell Migration across Tight Extracellular Space. *Sci Rep* **2020**, *10*, 2320, <https://doi.org/10.1038/s41598-020-59146-5>.
142. Turan, O.; Bielecki, P.A.; Perera, V.; Lorkowski, M.; Covarrubias, G.; Tong, K.; Yun, A.; Loutrianakis, G.; Raghunathan, S.; Park, Y.; *et al.* Treatment of Glioblastoma Using Multicomponent Silica Nanoparticles. *Adv Ther (Weinh)* **2019**, *2*, 1900118, <https://doi.org/10.1002/adtp.201900118>.
143. Hurwitz, M.; Stauffer, P. Hyperthermia, Radiation and Chemotherapy: The Role of Heat in Multidisciplinary Cancer Care. *Semin Oncol* **2014**, *41*, 714–729, <https://doi.org/10.1053/j.seminoncol.2014.09.014>.
144. Mahmoudi, K.; Bouras, A.; Bozec, D.; Ivkov, R.; Hadjipanayis, C. Magnetic Hyperthermia Therapy for the Treatment of Glioblastoma: A Review of the Therapy’s History, Efficacy and Application in Humans. *Int J Hyperthermia* **2018**, *34*, 1316–1328, <https://doi.org/10.1080/02656736.2018.1430867>.
145. Man, J.; Shoemake, J.D.; Ma, T.; Rizzo, A.E.; Godley, A.R.; Wu, Q.; Mohammadi, A.M.; Bao, S.; Rich, J.N.; Yu, J.S. Hyperthermia Sensitizes Glioma Stem-like Cells to Radiation by Inhibiting AKT Signaling. *Cancer Res* **2015**, *75*, 1760–1769, <https://doi.org/10.1158/0008-5472.CAN-14-3621>.
146. Minaei, S.E.; Khoei, S.; Khoei, S.; Mahdavi, S.R. Sensitization of Glioblastoma Cancer Cells to Radiotherapy and Magnetic Hyperthermia by Targeted Temozolomide-Loaded Magnetite Tri-Block Copolymer Nanoparticles as a Nanotheranostic Agent. *Life Sciences* **2022**, *306*, 120729, <https://doi.org/10.1016/j.lfs.2022.120729>.
147. Kaluzova, M.; Bouras, A.; Machaidze, R.; Hadjipanayis, C.G. Targeted Therapy of Glioblastoma Stem-like Cells and Tumor Non-Stem Cells Using Cetuximab-Conjugated Iron-Oxide Nanoparticles. *Oncotarget* **2015**, *6*, 8788–8806, <https://doi.org/10.18632/oncotarget.3554>.
148. Ung, T.H.; Malone, H.; Canoll, P.; Bruce, J.N. Convection-Enhanced Delivery for Glioblastoma: Targeted Delivery of Antitumor Therapeutics. *CNS Oncology* **2015**, *4*, 225–234, <https://doi.org/10.2217/cns.15.12>.
149. Fan, C.-H.; Cheng, Y.-H.; Ting, C.-Y.; Ho, Y.-J.; Hsu, P.-H.; Liu, H.-L.; Yeh, C.-K. Ultrasound/Magnetic Targeting with SPIO-DOX-Microbubble Complex for Image-Guided Drug Delivery in Brain Tumors. *Theranostics* **2016**, *6*, 1542–1556, <https://doi.org/10.7150/thno.15297>.
150. Zeng, X.; Han, I.; Abd-El-Barr, M.; Aljuboori, Z.; Anderson, J.E.; Chi, J.H.; Zafonte, R.D.; Teng, Y.D. The Effects of Thermal Preconditioning on Oncogenic and Intraspinal Cord Growth Features of Human Glioma Cells. *Cell Transplant* **2016**, *25*, 2099–2109, <https://doi.org/10.3727/096368916X691493>.
151. Abakumov, M.A.; Semkina, A.S.; Skorikov, A.S.; Vishnevskiy, D.A.; Ivanova, A.V.; Mironova, E.; Davydova, G.A.; Majouga, A.G.; Chekhonin, V.P. Toxicity of Iron Oxide Nanoparticles: Size and Coating Effects. *Journal of Biochemical and Molecular Toxicology* **2018**, *32*, e22225, <https://doi.org/10.1002/jbt.22225>.
152. Shao, R.-G. Pharmacology and Therapeutic Applications of Eneidyne Antitumor Antibiotics. *Current Molecular Pharmacology* *1*, 50–60, <https://doi.org/10.2174/1874467210801010050>.
153. Maksimenko, O.; Malinovskaya, J.; Shipulo, E.; Osipova, N.; Razzhivina, V.; Arantseva, D.; Yarovaya, O.; Mostovaya, U.; Khalansky, A.; Fedoseeva, V.; *et al.* Doxorubicin-Loaded PLGA Nanoparticles for the Chemotherapy of Glioblastoma: Towards the Pharmaceutical Development. *Int J Pharm* **2019**, *572*, 118733, <https://doi.org/10.1016/j.ijpharm.2019.118733>.
154. Aryal, M.; Park, J.; Vykhodtseva, N.; Zhang, Y.-Z.; McDannold, N. Enhancement in Blood-Tumor Barrier Permeability and Delivery of Liposomal Doxorubicin Using Focused Ultrasound and Microbubbles: Evaluation during Tumor Progression in a Rat Glioma Model. *Phys Med Biol* **2015**, *60*, 2511–2527, <https://doi.org/10.1088/0031-9155/60/6/2511>.
155. Miao, Y.-B.; Chen, K.-H.; Chen, C.-T.; Mi, F.-L.; Lin, Y.-J.; Chang, Y.; Chiang, C.-S.; Wang, J.-T.; Lin,

- K.-J.; Sung, H.-W. A Noninvasive Gut-to-Brain Oral Drug Delivery System for Treating Brain Tumors. *Advanced Materials* **2021**, *33*, 2100701, <https://doi.org/10.1002/adma.202100701>.
156. Laksitorini, M.; Prasasty, V.D.; Kiptoo, P.K.; Siahaan, T.J. Pathways and Progress in Improving Drug Delivery through the Intestinal Mucosa and Blood–Brain Barriers. *Therapeutic Delivery* **2014**, *5*, 1143–1163, <https://doi.org/10.4155/tde.14.67>.
157. Gupta, D.; Gupta, S.V.; Lee, K.-D.; Amidon, G.L. Chemical and Enzymatic Stability of Amino Acid Prodrugs Containing Methoxy, Ethoxy and Propylene Glycol Linkers. *Mol. Pharmaceutics* **2009**, *6*, 1604–1611, <https://doi.org/10.1021/mp900084v>.
158. Yang, J.; Lv, Q.; Wei, W.; Yang, Z.; Dong, J.; Zhang, R.; Kan, Q.; He, Z.; Xu, Y. Bioresponsive Albumin-Conjugated Paclitaxel Prodrugs for Cancer Therapy. *Drug Delivery* **2018**, *25*, 807–814, <https://doi.org/10.1080/10717544.2018.1451935>.
159. Rautio, J.; Laine, K.; Gynther, M.; Savolainen, J. Prodrug Approaches for CNS Delivery. *AAPS J* **2008**, *10*, 92–102, <https://doi.org/10.1208/s12248-008-9009-8>.
160. Fernández, C.; Nieto, O.; Fontenla, J.A.; Rivas, E.; Ceballos, M.L. de; Fernández-Mayoralas, A. Synthesis of Glycosyl Derivatives as Dopamine Prodrugs: Interaction with Glucose Carrier GLUT-1. *Org. Biomol. Chem.* **2003**, *1*, 767–771, <https://doi.org/10.1039/B212066F>.
161. Mullersman, G.; Derendorf, H.; Brewster, M.E.; Estes, K.S.; Bodor, N. High-Performance Liquid Chromatographic Assay of a Central Nervous System (CNS)-Directed Estradiol Chemical Delivery System and Its Application after Intravenous Administration to Rats. *Pharm Res* **1988**, *5*, 172–177, <https://doi.org/10.1023/a:1015964907110>.
162. Gomes, P.; Soares-da-Silva, P. L-DOPA Transport Properties in an Immortalised Cell Line of Rat Capillary Cerebral Endothelial Cells, RBE 4. *Brain Res* **1999**, *829*, 143–150, [https://doi.org/10.1016/s0006-8993\(99\)01387-6](https://doi.org/10.1016/s0006-8993(99)01387-6).
163. Manfredini, S.; Pavan, B.; Vertuani, S.; Scaglianti, M.; Compagnone, D.; Biondi, C.; Scatturin, A.; Tanganelli, S.; Ferraro, L.; Prasad, P.; *et al.* Design, Synthesis and Activity of Ascorbic Acid Prodrugs of Nipecotic, Kynurenic and Diclophenamic Acids, Liable to Increase Neurotropic Activity. *J Med Chem* **2002**, *45*, 559–562, <https://doi.org/10.1021/jm015556r>.
164. Friden, P.M.; Walus, L.R.; Musso, G.F.; Taylor, M.A.; Malfroy, B.; Starzyk, R.M. Anti-Transferrin Receptor Antibody and Antibody-Drug Conjugates Cross the Blood-Brain Barrier. *Proc Natl Acad Sci U S A* **1991**, *88*, 4771–4775, <https://doi.org/10.1073/pnas.88.11.4771>.
165. Fukuta, M.; Okada, H.; Inuma, S.; Yanai, S.; Toguchi, H. Insulin Fragments as a Carrier for Peptide Delivery across the Blood-Brain Barrier. *Pharm Res* **1994**, *11*, 1681–1688, <https://doi.org/10.1023/a:1018942728317>.
166. Wang, X.; Li, J.; Xu, C.; Li, Y.; Gong, T.; Sun, X.; Fu, Y.; He, Q.; Zhang, Z. Scopine as a Novel Brain-Targeting Moiety Enhances the Brain Uptake of Chlorambucil. *Bioconjug Chem* **2014**, *25*, 2046–2054, <https://doi.org/10.1021/bc5004108>.
167. Li, Y.; Zhou, Y.; Qi, B.; Gong, T.; Sun, X.; Fu, Y.; Zhang, Z. Brain-Specific Delivery of Dopamine Mediated by n,n-Dimethyl Amino Group for the Treatment of Parkinson’s Disease. *Mol Pharm* **2014**, *11*, 3174–3185, <https://doi.org/10.1021/mp500352p>.
168. Bunevicius, A.; McDannold, N.J.; Golby, A.J. Focused Ultrasound Strategies for Brain Tumor Therapy. *Oper Neurosurg (Hagerstown)* **2020**, *19*, 9–18, <https://doi.org/10.1093/ons/opa374>.
169. Bunevicius, A.; Pikiš, S.; Padilla, F.; Prada, F.; Sheehan, J. Sonodynamic Therapy for Gliomas. *J Neurooncol* **2022**, *156*, 1–10, <https://doi.org/10.1007/s11060-021-03807-6>.
170. Wu, S.-K.; Tsai, C.-L.; Huang, Y.; Hynynen, K. Focused Ultrasound and Microbubbles-Mediated Drug Delivery to Brain Tumor. *Pharmaceutics* **2020**, *13*, 15, <https://doi.org/10.3390/pharmaceutics13010015>.
171. Cohen-Inbar, O.; Xu, Z.; Sheehan, J.P. Focused Ultrasound-Aided Immunomodulation in Glioblastoma Multiforme: A Therapeutic Concept. *Journal of Therapeutic Ultrasound* **2016**, *4*, 2, <https://doi.org/10.1186/s40349-016-0046-y>.
172. Wei, K.-C.; Chu, P.-C.; Wang, H.-Y.J.; Huang, C.-Y.; Chen, P.-Y.; Tsai, H.-C.; Lu, Y.-J.; Lee, P.-Y.; Tseng, I.-C.; Feng, L.-Y.; *et al.* Focused Ultrasound-Induced Blood–Brain Barrier Opening to Enhance Temozolomide Delivery for Glioblastoma Treatment: A Preclinical Study. *PLOS ONE* **2013**, *8*, e58995, <https://doi.org/10.1371/journal.pone.0058995>.
173. Hersh, A.M.; Bhimreddy, M.; Weber-Levine, C.; Jiang, K.; Alomari, S.; Theodore, N.; Manbachi, A.; Tyler, B.M. Applications of Focused Ultrasound for the Treatment of Glioblastoma: A New Frontier. *Cancers* **2022**, *14*, 4920, <https://doi.org/10.3390/cancers14194920>.

174. Liu, H.-L.; Hua, M.-Y.; Yang, H.-W.; Huang, C.-Y.; Chu, P.-C.; Wu, J.-S.; Tseng, I.-C.; Wang, J.-J.; Yen, T.-C.; Chen, P.-Y.; *et al.* Magnetic Resonance Monitoring of Focused Ultrasound/Magnetic Nanoparticle Targeting Delivery of Therapeutic Agents to the Brain. *Proceedings of the National Academy of Sciences* **2010**, *107*, 15205–15210, <https://doi.org/10.1073/pnas.1003388107>.
175. Papachristodoulou, A.; Signorell, R.D.; Werner, B.; Brambilla, D.; Luciani, P.; Cavusoglu, M.; Grandjean, J.; Silginer, M.; Rudin, M.; Martin, E.; *et al.* Chemotherapy Sensitization of Glioblastoma by Focused Ultrasound-Mediated Delivery of Therapeutic Liposomes. *Journal of Controlled Release* **2019**, *295*, 130–139, <https://doi.org/10.1016/j.jconrel.2018.12.009>.
176. Anastasiadis, P.; Gandhi, D.; Guo, Y.; Ahmed, A.-K.; Bentzen, S.M.; Arvanitis, C.; Woodworth, G.F. Localized Blood–Brain Barrier Opening in Infiltrating Gliomas with MRI-Guided Acoustic Emissions–Controlled Focused Ultrasound. *Proceedings of the National Academy of Sciences* **2021**, *118*, e2103280118, <https://doi.org/10.1073/pnas.2103280118>.
177. Meng, Y.; Reilly, R.M.; Pezo, R.C.; Trudeau, M.; Sahgal, A.; Singnurkar, A.; Perry, J.; Myrehaug, S.; Pople, C.B.; Davidson, B.; *et al.* MR-Guided Focused Ultrasound Enhances Delivery of Trastuzumab to Her2-Positive Brain Metastases. *Science Translational Medicine* **2021**, *13*, eabj4011, <https://doi.org/10.1126/scitranslmed.abj4011>.
178. Timbie, K.F.; Mead, B.P.; Price, R.J. Drug and Gene Delivery across the Blood–Brain Barrier with Focused Ultrasound. *Journal of Controlled Release* **2015**, *219*, 61–75, doi:10.1016/j.jconrel.2015.08.059.
179. Burgess, A.; Shah, K.; Hough, O.; Hynynen, K. Focused Ultrasound-Mediated Drug Delivery through the Blood–Brain Barrier. *Expert Review of Neurotherapeutics* **2015**, *15*, 477–491, <https://doi.org/10.1586/14737175.2015.1028369>.
180. Song, M.; Cui, M.; Fang, Z.; Liu, K. Advanced Research on Extracellular Vesicles Based Oral Drug Delivery Systems. *Journal of Controlled Release* **2022**, *351*, 560–572, <https://doi.org/10.1016/j.jconrel.2022.09.043>.
181. Liang, S.; Xu, H.; Ye, B.-C. Membrane-Decorated Exosomes for Combination Drug Delivery and Improved Glioma Therapy. *Langmuir* **2022**, *38*, 299–308, <https://doi.org/10.1021/acs.langmuir.1c02500>.
182. Blass, E.; Ott, P.A. Advances in the Development of Personalized Neoantigen-Based Therapeutic Cancer Vaccines. *Nat Rev Clin Oncol* **2021**, *18*, 215–229, <https://doi.org/10.1038/s41571-020-00460-2>.
183. Ebrahimi, N.; Akbari, M.; Ghanaatian, M.; Roozbahani moghaddam, P.; Adelian, S.; Borjian Boroujeni, M.; Yazdani, E.; Ahmadi, A.; Hamblin, M.R. Development of Neoantigens: From Identification in Cancer Cells to Application in Cancer Vaccines. *Expert Review of Vaccines* **2022**, *21*, 941–955, <https://doi.org/10.1080/14760584.2021.1951246>.
184. Bigner, D.D. Biology of Gliomas: Potential Clinical Implications of Glioma Cellular Heterogeneity. *Neurosurgery* **1981**, *9*, 320–326, <https://pubmed.ncbi.nlm.nih.gov/6272152/>.
185. Mildner, A.; Jung, S. Development and Function of Dendritic Cell Subsets. *Immunity* **2014**, *40*, 642–656, <https://doi.org/10.1016/j.immuni.2014.04.016>.
186. Steinman, R.M. The Dendritic Cell System and Its Role in Immunogenicity. *Annu Rev Immunol* **1991**, *9*, 271–296, <https://doi.org/10.1146/annurev.iy.09.040191.001415>.
187. Kantoff, P.W.; Higano, C.S.; Shore, N.D.; Berger, E.R.; Small, E.J.; Penson, D.F.; Redfern, C.H.; Ferrari, A.C.; Dreicer, R.; Sims, R.B.; *et al.* Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *New England Journal of Medicine* **2010**, *363*, 411–422, <https://doi.org/10.1056/NEJMoa1001294>.
188. Nair, S.; Archer, G.E.; Tedder, T.F. Isolation and Generation of Human Dendritic Cells. *Current Protocols in Immunology* **2012**, *99*, 7.32.1-7.32.23, <https://doi.org/10.1002/0471142735.im0732s99>.
189. Schuler, G.; Schuler-Thurner, B.; Steinman, R.M. The Use of Dendritic Cells in Cancer Immunotherapy. *Current Opinion in Immunology* **2003**, *15*, 138–147, [https://doi.org/10.1016/S0952-7915\(03\)00015-3](https://doi.org/10.1016/S0952-7915(03)00015-3).
190. Parney, I.F.; Chang, L.-J.; Farr-Jones, M.A.; Hao, C.; Smylie, M.; Petruk, K.C. Technical Hurdles in a Pilot Clinical Trial of Combined B7-2 and GM-CSF Immunogene Therapy for Glioblastomas and Melanomas. *J Neurooncol* **2006**, *78*, 71–80, <https://doi.org/10.1007/s11060-005-9058-0>.
191. Curry, W.T., Jr; Gorrepati, R.; Piesche, M.; Sasada, T.; Agarwalla, P.; Jones, P.S.; Gerstner, E.R.; Golby, A.J.; Batchelor, T.T.; Wen, P.Y.; *et al.* Vaccination with Irradiated Autologous Tumor Cells Mixed with Irradiated GM-K562 Cells Stimulates Antitumor Immunity and T Lymphocyte Activation in Patients with Recurrent Malignant Glioma. *Clinical Cancer Research* **2016**, *22*, 2885–2896, <https://doi.org/10.1158/1078-0432.CCR-15-2163>.
192. Ishikawa, E.; Tsuboi, K.; Yamamoto, T.; Muroi, A.; Takano, S.; Enomoto, T.; Matsumura, A.; Ohno, T. Clinical Trial of Autologous Formalin-Fixed Tumor Vaccine for Glioblastoma Multiforme Patients. *Cancer Science* **2007**, *98*, 1226–1233, <https://doi.org/10.1111/j.1349-7006.2007.00518.x>.

193. Ishikawa, E.; Muragaki, Y.; Yamamoto, T.; Maruyama, T.; Tsuboi, K.; Ikuta, S.; Hashimoto, K.; Uemae, Y.; Ishihara, T.; Matsuda, M.; *et al.* Phase I/IIa Trial of Fractionated Radiotherapy, Temozolomide, and Autologous Formalin-Fixed Tumor Vaccine for Newly Diagnosed Glioblastoma: Clinical Article. *Journal of Neurosurgery* **2014**, *121*, 543–553, <https://doi.org/10.3171/2014.5.JNS132392>.