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REVIEW

Novel therapeutics for brain tumors: current practice and future prospects

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ABSTRACT

Introduction: Malignant gliomas are the most common and aggressive primary brain tumor with current available therapies increasing median survival to a modest 20 months. Multiple preclinical research efforts aim to further this improvement through advances in therapeutic options for these patients.

Areas covered: The unique obstacles that must be managed in developing and delivering safe and efficacious therapeutics into the central nervous system are reviewed. We describe the successes and challenges in local drug delivery in the field of neuro-oncology and explore convection enhanced delivery and high frequency ultrasound as tools for safe and effective delivery. Drug delivery systems are described in addition to combination therapies that are being tested both preclinically, as well as ones currently in clinical trials. The field of immunotherapy is also discussed along with specific considerations as it relates to the brain's microenvironment.

Expert opinion: While there have been incremental advances in brain cancer therapeutics over the last few years, novel therapeutics are expanding with multiple opportunities in neuro-oncology. Overcoming the brain's unique challenges might allow for breakthroughs and discoveries in the future.

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Blood-brain-barrier; glioma; immunotherapy; nanoparticle; polymer; ultrasound

1. Introduction

The World Health Organization (WHO) updated the classification of brain tumors in 2016 with both genotypic and phenotypic values to facilitate greater accuracy in clinical, experimental, and epidemiological studies [1]. This new classification included the genetic basis of tumorigenesis to add predictive data for more effective targeted treatments. Glioblastoma (GB) tumors, both the isocitrate dehydrogenase (IDH) wild type and the IDH mutant, are classified as Grade IV brain tumors [1] and remain one of the most lethal cancers in humans with a median survival after maximal therapy of less than 2 years [2]. The standard treatment for patients with newly diagnosed GB consists of maximal surgical resection and radiotherapy with concomitant and adjuvant chemotherapy. Several factors inherent to GB tumors are responsible for the limited efficacy of standard chemotherapeutic agents. Such factors include the tumor's high invasiveness, high proliferative index, tendency toward immunologic escape, genetic heterogeneity and instability, and the blood–brain barrier's (BBB's) role in limiting systemically delivered therapy [3]. The therapeutic efficacy of a drug is only possible providing its dose is very high or it is specifically cytotoxic to these invasive cells.

One way in which these challenges have been addressed is through local drug delivery by local polymer implantation encapsulated with chemotherapeutic agents. The polyanhydride delivery of BCNU was shown to be both safe, as well as effective in preclinical models and has translated into significant effects clinically. These efficacious results have led to investigations of other local delivery formulations, including biodegradable polymers, nanoparticles, and liposomes. These have all been tested preclinically in brain tumor models with varying successes and will be discussed in this review (a brief summary of advantages and challenges is shown in Table 1).

Targeted gene therapy is an approach based on the local delivery of genetic material using a vehicle to shuttle genes to tumor cells to determine higher expression of a transgene or silencing of an endogenous gene [9–11]. New insights into specific gene mutations and dysregulated signaling pathways have provided insight into the pathogenesis of brain tumors and have highlighted gene therapy as a potential approach for the treatment of GB tumors [12,13]. Immunotherapy also represents a new paradigm that has drastically improved the prognosis for a wide range of cancers [14,15]. Effective immunotherapy is especially attractive for the treatment of highly invasive tumors as surgical resection often does not remove all malignant cells. A method to enhance immune cells' innate ability to target, track, and specifically eliminate tumor cells could dramatically change the prognosis and treatment of brain tumors. There has been recent debate however regarding the effect of immunotherapy within the brain and the extent to which it is an immune privileged site [16]. Utilizing local delivery strategies may provide an advantage in combining chemo and immunotherapy for optimal efficacy. Targeting pertinent antigens with vaccines and checkpoint inhibitors could lead to a new area of treatment and increase the therapeutic armamentarium for treatment of gliomas. In this review we will describe the unique challenges that are inherent in developing treatments

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Article highlights

- Successes and challenges are discussed regarding optimizing new therapeutics for the treatment of malignant gliomas.
- Drug delivery systems such as biodegradable polymers, nanoparticles, and liposomes delivering standard chemotherapeutic agents as well as novel targeted compounds and combinations of drugs with complimentary mechanisms of action are presented.
- Immunotherapy in the context of local chemotherapy for the treatment of brain tumors is discussed.

for brain tumor therapies. Advances in classification, genetic analysis, drug delivery, and technology have increased therapeutic opportunities. Novel platforms taking advantage of these novel advances are described.

2. Challenges of treatment

2.1. BBB and blood brain tumor barrier

The BBB is a major obstacle to drug delivery in the brain, as the strongly connected tight junctions of epithelial cells form a filter that selectively allows small molecules to pass through (Figure 1). The BBB plays an important role in protecting the central nervous system (CNS) from injury, pathogens, and toxins; however, this restrictive quality also presents a major challenge in the treatment of glioma. Besides the cellular components, such as pericytes, astrocytes, and basement membrane [17], the molecular components of the BBB create an additional challenge. These molecular components, such as efflux transporters and nutrient transporters [18], aid in the interaction between the CNS, and the vascular system, allowing for further regulation of influx and efflux through the BBB.

The epithelial cells of the BBB, known as brain microvascular endothelial cells (BMECs), uniquely have continuous tight junctions, and have the ability to shuttle nutrients to the brain using the efflux transporters mentioned, such as p-glycoprotein [19]. P-glycoprotein, along with multidrug resistance-associated proteins (MRP) and breast cancer resistance protein (BCRP) pose a particularly significant challenge to drug delivery, as they actively pump out potential therapeutics from the CNS [20]. The BMECs are surrounded by pericytes, which are involved in the formation of the BBB through gene expression and induction of the polarization of astrocyte end feet [21]. The astrocyte end feet ensheath the capillaries and contribute to the maintenance of the BBB by secretion of various factors [22]. As a key regulator and protector of the CNS, the BBB plays a dynamic role in maintaining cerebral homeostasis [23].

In addition to the BBB, gliomas themselves create a blood–brain tumor barrier (BBTB) that helps facilitate nutrient and oxygen transfer to the growing tumor cells. The BBTB is formed due to the expression of vascular endothelial growth factor (VEGF), which induces growth of brain tumor capillaries in the hypoxic area. Similarly to the BBB, the BBTB also expresses the efflux transporters, creating yet another barrier for potential therapeutic drug delivery to brain tumors [24].

In terms of permeability of the BBTB, there are two major variables: the type of tumor microvessel population and the

Table 1. Advantages and limitations of several local delivery methods for the treatment of GB.

Local Delivery Method	Advantages	Limitations	Challenges
Carmustine wafer (Gliadel®)	Improved efficacy compared to systemic delivery, useable with multiple drugs, increased median survival without increased morbidity, allows treatment of tumor regardless of vascularization [2,52,58–60,63]	Requires surgical intervention [63]	Limited to BCNU release [58]
OncoGel® copolymer	Well tolerated, prolonged drug release, decreased tumor burden in inoperable esophageal cancer, not limited by resistance to alkylating agents [4,80]	Requires surgical intervention, clinical trial results unavailable to date [5]	Translation from rat tumor models to clinical models [4,5]
Nanoparticle therapy	Improved delivery to tumor cells over normal tissue, customizable delivery by shell formulation, improved BBB crossing [6,84,95,96]	Controversy on tumor microenvironment changes due to NPs affecting tumor growth [6]	Targeting process is complex and specific, excess ROS production by NPs might be deleterious [6,84]
PLGA nanoparticles	Better drug accumulation compared to unloaded nanoparticles and drug in brain tissue, biodegradable, improved drug efficacy in causing apoptosis [81,88]	Degradation can result in acidic species effecting stability, capability effected by surface charge, hydrophobicity and particle size [7]	Direct tumor cavity implantation, preclinical model translation to clinical models [59,88]
Ultrasound-based Delivery	Noninvasive, redirection of established technology, can thermally ablate GB, and can temporarily disrupt BBB to improve chemotherapy penetration [119,124]	Requires MRI assistance, only has FDA approval for Parkinson's disease [119,121]	Continuous monitoring required during use to ensure safety, BBB disruption [125,128]
Combined Drug & Immunotherapy	Counteraction of immunosuppressive environment of GB allows increased drug therapy efficacy, noninvasive [109,111]	Role of certain cytokines uncertain in tumor genesis [117]	Chemo-immunotherapy has been immunosuppressive when presented systemically [109–111]
Convection-Enhanced Delivery	Wide variety of drugs/particles can be delivered, direct infusion of drug across BBB [29]	Catheter placement, unpredictable drug dispersal, increased chance of infection with prolonged or repeated infusions [8]	Backflow and reflux of infused fluid, rate of infusion and infusion regimen needs to be determined for each solute [8,34]
Gene Therapy	Ability to target specific factors to inhibit tumor growth [9–11,47]	Low clinical efficacy; low spatial distribution, poor gene transfer efficiency [47]	Host immunity, GB heterogeneity [47]

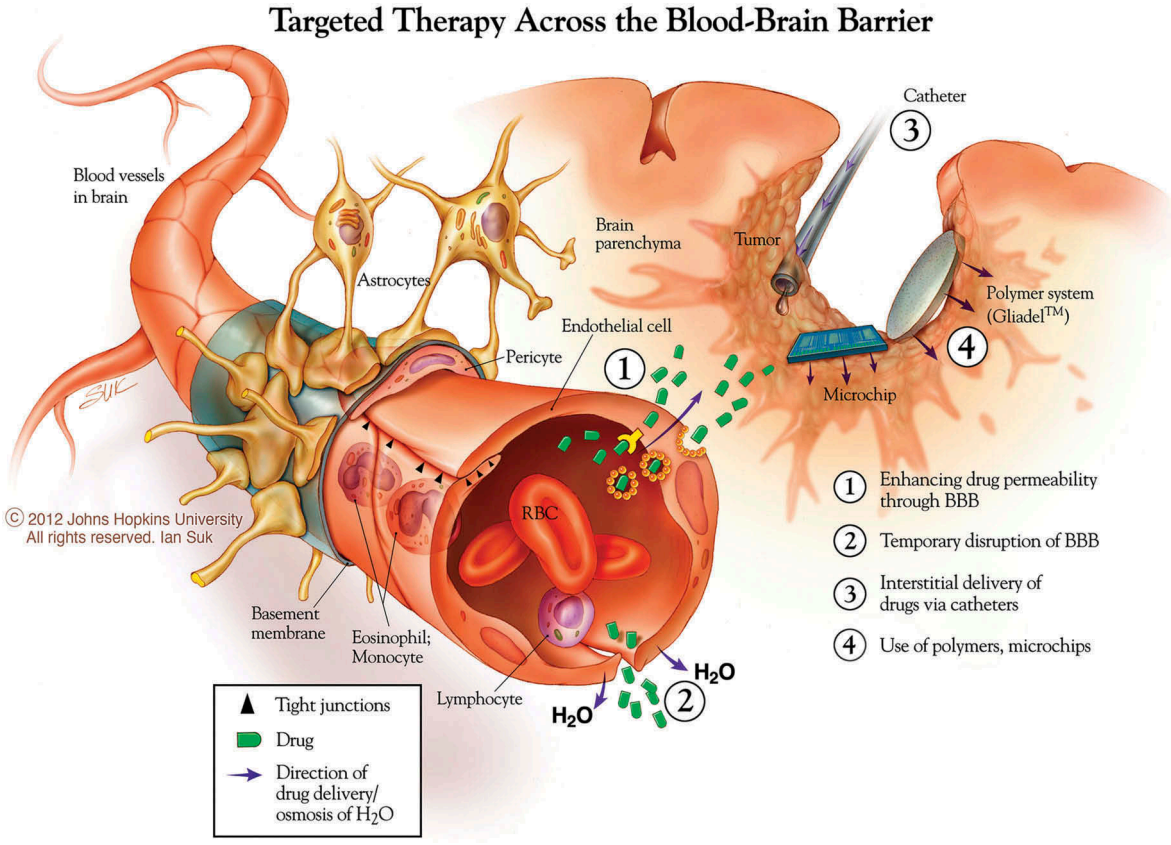

Figure 1. Targeted therapy across the blood–brain barrier. Ian Suk is the copyright holder for his illustration in Figure 1.

spatial distribution of the vessels. There are three microvessel populations, which are continuous fenestrated, continuous non-fenestrated, and interendothelial gaps. Each microvessel population varies in the size of the molecules to which they are permeable [25]. The BBTB also differs from the BBB in many crucial ways. Unlike the BBB, the BBTB is formed by abnormal capillaries that do not express normal proteins and astrocyte end feet. These differences could be potentially explored as a way to target the BBTB without affecting the BBB [26]. Drug delivery and local intracranial drug delivery have been investigated to obtain therapeutically sufficient concentrations of effective agents across the BBB and the BBTB.

3. Overcoming the challenges of the BBB

3.1. Convection enhanced delivery

Convection-enhanced drug delivery (CED) developed as a technique to bypass the BBB has been utilized for locally delivering a continuous injection of a fluid under positive pressure using intracranial catheters. CED was developed by Bobo et al. in 1994 [27] and has been used to deliver a variety of therapeutic compounds for a diversity of diseases such as Alzheimer's disease, Parkinson's disease, and GB and can be a powerful tool for drug delivery [28]. The delivery and distribution of a solute by CED can be affected by many conditions, such as molecular weight of the compound being delivered, the tumor size, rate of infusion, cannula size and shape, and the volume of the infused fluid [29]. CED has shown some complications with drug administration due to backflow or reflux, air bubbles, edema, and abnormal tumor vasculature that has led to leakage of the drug into the subarachnoid space [29]. Animal studies show that CED has the capability to deliver a drug centimeters from the site of injection [27]. By using computer models and algorithms, developing modified catheters, targeting tissue anatomy, and improving the delivery method, drug delivery can be and has been further optimized [30]. Many clinical trials have tested safety and efficacy of CED with varying success rates [28].

The PRECISE trial was a Phase III trial in patients with recurrent GB which compared CED of IL13-PE38QQR, a recombinant Pseudomonas exotoxin that targets the interleukin 13 α-receptor highly expressed in GB, and Gliadel®, the carmustine wafer. The median survival was found to be higher in patients who had received Gliadel® as compared to the patients who received CED of IL13-PE38QQR [28]. Poor drug distribution due to catheter positioning was cited as one of the reasons for the unsatisfactory efficacy results [31,32]. Lidar et al. delivered paclitaxel by CED to patients with recurrent GB and investigated its safety, neuroimaging of the distribution, and clinical response [33]. While CED of paclitaxel showed some antitumor response, there were also numerous treatment-associated complications, including chemical meningitis, infectious complications, and transient neurological deterioration due to increased peritumoral edema.

Similarly, Young et al. describes CED of polymeric magnetite nanoparticles encapsulating temozolomide in canines with spontaneously occurring gliomas [34]. Magnetic resonance imaging (MRI) was used to examine distribution and it was found that even with optimal catheter placement only 70% of the cases

were accurately reached with the infusion. Observable decrease in tumor volume was only detected in 1 of 10 animals. To take advantage of nanoparticle technology and its unique diffusion characteristics Zhang et al. utilized CED to deliver cisplatin-loaded brain penetrating nanoparticles in a rodent model of glioma [35]. The brain penetrating particles were PEGylated for further penetrance and increased diffusion. Delivered via CED, the cisplatin nanoparticles reached effective concentrations intracranially which decreased tumor growth and significantly prolonged median survival as compared to cisplatin alone, cisplatin in non-PEGylated particles, and saline-treated controls. The treatment groups were treated through CED and all groups included cisplatin but only the PEGylated nanoparticle cisplatin delivery showed a statistically significant increase in survival with 80% long-term survivors.

The delivery of carboplatin for the treatment of preclinical models of GB, as well as clinical safety studies has been investigated. Initially carboplatin was delivered via CED in a rodent model of GB and showed promising intracranial distribution both in rodents and pig brains with confirmation of carboplatin remaining in the brain for 24 h [36]. This data led to the Phase I study for the dose escalation of carboplatin administered by CED to patients with recurrent GB [37]. However, the nonspecific cytotoxicity of free carboplatin coupled with its rapid clearance from the brain led to the development of an encapsulated method for this drug's delivery. Arshad et al. formulated injectable poly-lactic acid-glycolic acid copolymer (PLGA) with carboplatin and confirmed cytotoxicity in GB cell cultures as well as confirmed increased distribution, reduced clearance, and decreased neuronal toxicity of the carboplatin nanoparticles after CED in rat and porcine models [38]. Shi et al. used CED to deliver carboplatin encapsulated in liposomes to animal models of GB with contradictory conclusions [39]. Their results showed that their least efficient formulation in vitro was their most effective treatment in vivo, supporting the theory that the choice and use of animal models are important aspects of this translational work.

The use of CED to deliver chemotherapeutic agents, such as cisplatin, temozolomide and doxorubicin, via liposomes has also been investigated in preclinical models of GB but has mostly resulted in safety issues [40–42]. Much remains to be determined with CED including optimizing the drug or encapsulating the drug of choice, determining relevant animal models, ensuring local delivery, establishing pharmacokinetics, and drug clearance, and confirming increased diffusion of active and bioavailable agents in therapeutic concentrations. Studies addressing these issues have included the fabrication of transcutaneous bone-anchored ports for repeated CED infusions [43] and the more recent Cleveland Multiport Catheter that is currently under evaluation [44]. This optimized catheter technology will need to be combined with an infusate ideal for both CED delivery and specificity for tumor cytotoxicity all with reflux-free infusions and an effective infusion regimen [45].

3.2. Gene therapy and virotherapy

Gene therapy has been explored to take advantage of the altered gene expression found in GB tumors. Various strategies for gene therapy include viral delivery of genes, stem cell therapy, and nanotechnology therapy. Each of these therapies has multiple distinctions utilized to deliver one of a multitude of gene therapy solutions comprised of suicide genes, tumor suppressor genes, immunomodulatory genes, anti-angiogenic factors or immunostimulating cytokines, as well as acting as gene therapies themselves if oncolytic. A gene target often employed in viral therapy is a type of Herpes simplex virus (HSV), which can deliver thymidine kinase (HSV-TK) as a suicide gene to target the DNA replication in rapidly dividing cells. Stem cell therapies possess the unique quality to actively migrate toward a tumor site, even crossing the BBB. Neural and mesenchymal stem cell therapy has also been used to deliver immunostimulatory cytokines like Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) which alone or in conjunction with radiotherapy have been shown to reduce tumor burden [9]. One altered pathway is the p53 pathway, which is responsible for tumor suppression, tumorigenesis, and tumor invasion. Other signaling cascades thought to have a role are the PI3K-PTEN-Akt-mTOR pathway, which is involved in cell proliferation, apoptosis, cell invasion, and mobility; the RAS/MAPK signaling pathway; and the STAT3 pathway [12]. Nandhu et al. describes tumor-derived fibulin-3, linked to poor survival, as a pathway to target for novel combination therapies [46]. Gene therapy is a potentially powerful technology; however, it has shown a relative lack of clinical efficacy, probably in part due to the limited spatial distribution, poor gene transfer efficiency, host immunity, and the heterogeneity inherent in GB [47]. The use of local delivery strategies may assist in overcoming these challenges, to aid in gene targeting and delivery to tumor cells [48–50].

Studies have shown support for the use of TG6002, an oncolytic virus, for treatment of GB in vitro. TG6002 replicates in tumor cells primarily, localizing the therapy to those cells with deletion of genes for thymidine kinase and ribonucleotide reductase. When delivered in combination with the antimetabolite 5-flucytosine (5-FC), TG6002 transforms 5-FC into its cytotoxic metabolites 5-FU and 5-FUMP, driving tumor lysis. Studies in mice with orthotopic GB demonstrated prolonged survival in those treated with TG6002 and 5-FC together, indicating support for a Phase 1 clinical trial to proceed [51]. This trial will help to elucidate the safety effectiveness of this oncolytic virus in the clinical setting.

3.3. The carmustine wafer

Intracranial drug delivery was developed to bypass the problems associated with systemic delivery due to the challenges of the BBB and the BBTB. Various polymer formulations have been developed and tested to deliver chemotherapeutic agents at the site of tumor resection. Initially, several polymers were tested to determine the optimal formulation from which to deliver carmustine, an FDA-approved, and historically, systemically utilized drug for patients with GB [52,53]. The biodegradable polyanhydride polymer, poly [bis(p-carboxyphenoxy)]propane-sebacic acid copolymer was determined to be the best formulation for delivery showing no toxicity profile when implanted intracranially. This was determined through multiple safety studies in rodents and non-human primates [54,55]. Autoradiographic biodistribution studies in rabbits

showed that carmustine released from the polymer diffused through the parenchyma in pharmacologically effective concentrations and was detected 3 weeks after implantation as compared to direct injection of a carmustine solution which was detectable only 72 h after injection [56]. Yang et al. showed that the drug concentration in the implanted hemisphere was initially 40 times higher than the drug levels in the contralateral hemisphere and the peripheral circulation in a rat model [53]. Additionally intact bioactive carmustine was detected in the polymer implanted hemisphere up to 9 days, while it was detected in the contralateral hemisphere and the peripheral circulation for only 1 day. Distribution studies in non-human primates showed similar carmustine release *in vivo* with carmustine detected 5 mm from the site of implantation after the first day and 1 mm on days 3 through 14 after implantation [54]. Efficacy studies consistently demonstrated both safety and efficacy of the carmustine-loaded wafer in a rodent model of gliosarcoma [52,55].

The rigor of this preclinical data led to the first Phase I–II trial in 21 patients with recurrent malignant glioma which tested three loading doses of carmustine – 1.93%, 3.85%, and 6.35% [57]. The study demonstrated feasibility and safety of this novel concept with the 3.85% dose chosen for a subsequent placebo controlled randomized study. The prospective, placebo-controlled, double-blind, randomized study included 27 cm and 222 patients with recurrent malignant glioma requiring re-operation [58]. Following tumor removal, up to 8 BCNU wafers were placed into the tumor resection cavity. The median survival of the 110 patients who received the carmustine wafers was 31 weeks compared to 23 weeks for the 112 patients who received placebo wafers. These initial studies in patients with recurrent glioma were then followed by studies in patients with newly diagnosed GB. Valtonen et al. showed an increase in the median survival of 13.4 months for carmustine-treated patients versus 9.2 months for placebo wafer treated patients ($p = 0.012$) [59]. The carmustine-treated group also had significantly improved overall survival at 12 months. Another study of patients newly diagnosed with GB resulted in a median survival of 13.9 months in the treated group as compared to 11.6 months in the placebo treated group [60]. The FDA approved the use of the carmustine wafers in 1996 for implantation in patients with recurrent GB [61]. In 2003, the FDA expanded this approval for the use of the wafers in initial surgery and for all malignant gliomas. Pallud et al. conducted a study including 787 patients with newly diagnosed GB and showed that the wafer implantation was associated with longer progression-free survival [62]. There have been a few meta-analyses on the benefit of the locally implanted wafers [63,64]. Chowdhary et al. included 60 studies totaling 4,898 patients and showed that for newly diagnosed high grade glioma, the 1-year overall survival was 67% with a median survival of 16.4 months with the carmustine wafers, compared to a 48% 1-year survival and median survival of 13.1 months without the wafers [63]. The 2-year overall survival was 26% with the wafer and 15% without the wafers. The biodegradable carmustine wafers have been shown to be safe and effective and have become an accepted form of therapy for newly diagnosed and recurrent GB. Given the significant but modest improvement in patient outcomes with these wafers, further localized treatments should be explored and brought to clinical testing. Potent chemotherapeutics, novel small molecules which typically cannot sustain systemic delivery, and combination therapies can utilize local delivery strategies for translation to the clinical setting.

3.4. Local delivery formulations

3.4.1. Paclitaxel

In addition to the local intracranial delivery of BCNU from Gliadel®, which surpassed results of systemic delivery of the same agent [52], other promising compounds have been investigated for their benefit via local delivery (Table 2). Paclitaxel, an inhibitor of microtubule function and growth, has a long history

Table 2. Preclinical delivery systems investigated for treatment of GB.

Type of Delivery System	Drug Encapsulated	Animal Model Tested	Delivery Mode [Ref]	Safety/ Biodistribution Profile?	Statistical Efficacy?
Polyanhydride P(CPP:SA)	BiCNU or carmustine	9L Gliosarcoma-F344 rat	Intracranial [52,55]	Yes/Yes	Yes
Polyanhydride P(CPP:SA)	Doxorubicin	9L Gliosarcoma-F344 rat	Intracranial [70]	Yes/No	Yes
Polyanhydride P(CPP:SA)	Acriflavine	9L Gliosarcoma-F344 rat	Intracranial [71]	Yes/No	Yes
Polyanhydride P(CPP:SA)	Temozolomide	9L Gliosarcoma-F344 rat	Intracranial [86]	Yes/No	Yes
Polilactofilate microspheres	Paclitaxel	9L Gliosarcoma-F344 rat	Intracranial [68]	Yes/Yes	Yes
Liposomes	Cisplatin	F98 glioma	Intracranial/Intravenous [40]	No/No	No
Liposomes	Cisplatin/Carboplatin	F98 glioma	Intracarotid infusion [72]	Yes/Yes	Yes with XRT
Liposomes	O^6BTG-C18	SMA-497 murine glioma	Intravenous with low intensity focused ultrasound (FUS) + Temozolomide [73]	Yes/Yes	Yes
Liposomes	Temozolomide	No tumor- naïve rat	Intravenous [74]	NA/Yes	NA
Liposomes	Temozolomide	CNS-1 rat glioma	Intracranial CED [41]	Yes/Yes	No better than Oral delivery
Liposomes	Temozolomide	U87MG	Intracranial CED [75]	Yes/Yes	Yes
Liposomes	pEGFP-TRAIL + Paclitaxel	U87MG	Intravenous [76]	Yes/NA	Yes
Liposomes	Doxorubicin	U87MG	Intravenous [77]	Yes/Yes	NA
Liposomes	Doxorubicin	C6 Glioma	Intravenous + FUS [78]	Yes/Yes	Yes with FUS
PLGA Nanoparticles	Etoposide + Temozolomide	9L Gliosarcoma-F344 rat	Intracranial [103]	Yes/No	Yes
PLGA Nanoparticles	Temozolomide	C6 glioma	Intracranial [88]	Yes/Yes	Yes
PLGA Nanoparticles	Doxorubicin	101/8 glioblastoma	Intravenous [79]	Yes/NA	Yes
Superparamagnetic iron oxide (SPIO) PLGA	Paclitaxel	U87MG	Intravenous [83]	Yes/Yes	Yes

of being used as a potent chemotherapeutic but as it remains notoriously difficult to deliver in therapeutic concentrations intracranially [65,66], it has been investigated as a candidate for local delivery. Safe and effective intracranial paclitaxel delivery has been shown from a biodegradable polyanhydride polymer [67], as well as a polyphosphoester polymer [68] in rodent models of glioma. Pradilla et al. demonstrated safety and pharmacokinetic distribution in a canine model using the polilactofilate microspheres implanted intracranially with minimal to undetectable plasma levels of paclitaxel [69].

Additionally paclitaxel was shown to be safe and effective when delivered from a thermosensitive, biodegradable triblock copolymer composed of poly(lactide-co-glycolide) and poly(ethylene glycol), OncoGel®, in two rodent glioma and gliosarcoma models. Clinically OncoGel® was well tolerated, delivered paclitaxel in a prolonged fashion, and seemed to reduce tumor burden in patients with inoperable esophageal cancer [80], however clinical testing in patients with recurrent glioma was terminated prior to full enrollment. More recently, Lei et al. have shown that paclitaxel delivered via poly (d,l-lactic-co-glycolic acid) (PLGA) nanoparticles coated with d-α-tocopherol polyethylene glycol 1000 succinate (TPGS) had amplified accumulation (>800% after 96 h) in brain tissue when compared with unloaded nanoparticles and paclitaxel in a mouse model [81]. Sun et al. has incorporated paclitaxel into dual-modified cationic liposomes loaded with survivin siRNA and paclitaxel to target the survivin expressed in GB tissue and to deliver a potent therapeutic at the tumor site. They showed a strong efficacy response using U251-CD133+ cells in athymic mice with control groups resulting in a median survival of 25 days and the experimental group having a median survival of 81 days, with no histological abnormalities or toxicity observed [82]. Paclitaxel has recently been incorporated into superparamagnetic iron oxide (SPIO)-loaded PEGylated PLGA-based nanoparticles (PTX/SPIO-NPs) [83]. This effective nanocarrier system combined paclitaxel incorporated into NPs with the application of a noninvasive external magnetic field to enhance the permeability and retention (EPR) effect of the nanocarriers and increase therapeutic efficacy. The BBB was imaged and shown to be disrupted at the tumor site with accumulation of the nanoparticles around the site of magnetic targeting. Magnetic targeting treatments with the PTX/SPIO-NPs also showed a significant increase in median survival in tumor bearing animals as compared to passive targeting and control groups. Other groups are exploring the delivery of paclitaxel combined with focused ultrasound which seems to be promising [84]. The local delivery of this potent therapeutic seems to decrease systemic toxicity but has yet to be shown to be efficacious clinically.

3.4.2. Temozolomide

The Stupp protocol, consisting of surgical resection followed by radiation therapy combined with concomitant and adjuvant oral temozolomide, for the treatment of patients with GB has become an accepted therapeutic regimen clinically, increasing median survival to 14.6 months [85]. A retrospective study was conducted over a 10-year period which included patients undergoing primary resection of GB with or without Gliadel® wafer implantation and with or without concomitant oral temozolomide (Stupp protocol). Overall survival and treatment morbidity were assessed. The patients who were treated with radiation, Gliadel® and temozolomide had an increased median survival of 20.7 months without increased morbidity [2]. Similar findings were found by Pallud et al. [62]. These results led to the hypothesis that locally delivered temozolomide might lead to an additional benefit. Brem et al. demonstrated extended release of temozolomide from a biodegradable polymer while intracranial biodistribution of temozolomide increased threefold as compared to the same drug delivered orally in a rodent glioma model [86]. Efficacy studies showed untreated controls had a median survival of 13 days compared to 92 days of animals treated with intracranial temozolomide polymers. When radiation therapy was added to the temozolomide treatment median survival was not reached, resulting in 87.5% long-term survivors. Recinos et al. investigated a triple therapy regimen with the co-implantation of a temozolomide polymer and a carmustine-loaded polymer along with radiation therapy in both a gliosarcoma model as well as in a glioma model with high levels of alkyltransferase, making the glioma resistant to alkylating agents [87]. This triple combination therapy showed a significant increase in median survival in both tumor types when compared to controls and compared to groups that received oral dosing of temozolomide. Locally delivered temozolomide from PLGA microparticles has also shown superiority in effecting apoptosis and proliferating cell nuclear antigen (PCNA)-positive cells as compared to oral delivery of temozolomide [88]. The co-delivery of BCNU and temozolomide from a PLGA polymer showed reliable release of both drugs and was also shown to significantly increase survival in a rat model of glioma [89].

3.4.3. Other chemotherapeutic compounds

Other compounds have been locally tested in preclinical brain tumor models and are in various stages toward clinical development. Mitoxantrone, a synthetic anthracenedione approved for treatment in systemic cancers but with poor CNS penetration and dose-limiting leukopenia has been explored as a candidate for local delivery – both from polymer matrices and through a more direct injection approach. Dimeco et al. incorporated mitoxantrone into biodegradable polyanhydride and showed both safety and efficacy in a 9L rodent gliosarcoma model. Extended *in vivo* release lasted 35 days and animals with the highest loading dose of mitoxantrone showed increased median survival [90]. Preclinical data showing safety of locally delivered mitoxantrone led to a safety and feasibility study of a Surgifoam-mitoxantrone mixture in patients with recurrent GB. No adverse side effects were observed in this small study [91]. Mitoxantrone has also been successfully delivered from PLGA microspheres in a rat model of glioma and showed safety, extended release, biodistribution, and efficacy [92]. In a retrospective study, toxicity and survival was studied of patients with GB who were treated with locally delivered mitoxantrone in addition to standard chemotherapy [93]. Mitoxantrone delivery was from a Rickam/Ommaya reservoir and used as a locoregional delivery device. Their results indicated effectiveness in smaller resection cavities and showed some promise for this delivery option. Recently Lam et al. have incorporated mitoxantrone into a plant virus-based nanoparticle, the cowpea mosaic virus, for delivery to GB. These *in vitro* studies report uptake into glioma cells and additive effects when given with TRAIL [94].

3.4.4. Nanoparticles and liposomes

Local drug delivery has explored nanoparticle and liposome formulations for the treatment of GB in preclinical models (Table 2). Nanoparticle therapy is formulated via a shell of molecules enveloping the designed therapy, which aims to slow progression of the tumor or induce apoptosis. The shell's chemical composition determines the nanoparticle's delivery primarily by targeting specific cells or features of the tumor microenvironment, thereby enhancing efficacy of treatment by localizing the distribution of the therapy [95,96]. Tumor microenvironment characteristics include decreased pH, increased reactive oxygen species (ROS) presence, and decreased oxygen tension (hypoxic conditions). Nanoparticles engineered to target such microenvironmental characteristics can evoke the EPR effect, inducing the tumor tissue to have increased uptake of nanoparticles compared to normal tissue, which can lead to increased effectiveness of gene or drug therapy [84,97]. Delivery of nanoparticles has been shown to prime the tumor microenvironment via hyperthermia therapy, another relatively new approach to tumors, to sensitize the tumor microenvironment to radiation at a higher level than normal tissue [98].

Delivery of drugs such as doxorubicin and paclitaxel have been enhanced via nanoparticle delivery, particularly in lipid polymer capsules [82,99,100]. Liposomes are constructed with a lipid bilayer structure with an aqueous core surrounded by a hydrophobic membrane. Through change in pH, change in charge, or endocytosis the drug incorporated in the core can be released. Doxorubicin has been delivered through liposomes in preclinical models of GB [99]. Chastagner et al. demonstrated doxorubicin as a radiosensitizer when delivered from liposomes in an orthotopic model of glioma [99]. They also point out the need for rigorous optimization of administration schedules. Targeted strategies have been utilized to increase therapeutic potential for glioma treatment. Transferrin receptors, overexpressed in brain endothelial cells and glioma cells, have been targeted with the T7 peptide used a ligand for BBB penetration and glioma therapy [101] Zhang et al. designed a liposome with dual targeting with T7 as well as with A7R, a peptide can target vascular endothelial growth factor receptor 2 (VEGFR2) [102]. This modified liposome was incorporated with doxorubicin and vincristine, two potent anti-glioma compounds, and was tested against an intracranial model of glioma. The only toxicity was observed in the "free" drug groups and efficacy was statistically increased in the dual targeted dual chemotherapy group. Zou et al. have developed a novel carrier combining the advantages of both the liposome and the nanoparticle by designing a nanoparticle with a lipid monolayer shell with a polymer core for the delivery of paclitaxel. The RVG peptide was used at the targeting ligand for BBB transport and tumor associated macrophage internalization. Their studies showed significant BBB permeation and targeted delivery. By examining potent drug delivery options within the context of nanoparticle design, targeted therapies using combinations of liposomes, nanoparticles, and polymersomes should result in a clinically translational therapeutic product.

3.5. Combination therapy with local delivery

As advancements in drug targeting and delivery options expand, several novel combination therapies are being employed to enhance tumor suppression. In order to bypass the BBB, Smith et al. has explored the local combined delivery of etoposide and temozolomide with a blended paste of poly (DLlactic acid-co-glycolic acid) (PLGA) and poly(ethylene glycol) (PEG) [103]. They showed extended stability and release of both bioactive and intact drugs. *In vivo* studies showed an increase in survival in animals who had received the intracavity combined paste and radiation therapy with over half of the treated animals surviving long term.

Another promising combination therapy currently being studied is folic acid with standard temozolomide to affect MGMT, a DNA repair protein. The unmethylated MGMT gene has been associated with poor prognosis in glioblastoma, as the MGMT protein is responsible for establishing treatment resistance to the common chemotherapy of temozolomide [104]. Folic acid-grafted nanoparticles have been found to improve transmission of antitumor drugs across the BBB and therefore improve local therapy for glioma cells [105,106]. Folic acid has also been found to methylate MGMT. An ongoing Phase 1 trial (NCT01700569) seeks to investigate the ability of folinic acid, the active metabolite of folic acid, to methylate MGMT, which will reduce a tumor's likelihood to repair damaged DNA. This therapy will be delivered in tandem with temozolomide and radiotherapy. Success of this trial may lead to the proposition of folic acid being used to both improve targeting of currently existing chemotherapies as well as directly act as a therapy on the glioma itself.

Apatinib is a small-molecule tyrosine kinase inhibitor with anti-VEGF properties that counteracts tumor angiogenesis. It has been previously utilized to treat several tumor types and has been found to be a valuable therapeutic for glioma [107]. In an ongoing randomized controlled trial (NCT03741244), the combination of apatinib is being investigated to enhance the local effects of temozolomide in high-grade gliomas, particularly for those individuals with unmethylated MGMT as denoted for the reasons above. The potential synergistic effects of apatinib and temozolomide in local destruction of tumorigenic cells are a promising avenue for combination therapies.

Another current investigation in combination therapy for glioma includes the use of olaparib, a poly ADP ribose polymerase (PARP)-1 inhibitor; the PARP pathway enhances DNA repair. Olaparib has been found to potentiate radiosensitization in cancer cells as well as increase DNA damage in neuroblastoma cells [108]. Additionally, the combination of these two therapies prevented the restitution of DNA, leading to threefold greater DNA damage after 24 h and greater G2/M arrest than either agent alone. A current Phase 1/2a trial (NCT03212742) is investigating if administration of olaparib in combination with radiation therapy will synergistically act to sensitize unresectable high-grade gliomas so that a simultaneous temozolomide application will have a more direct and strengthened cytotoxic effect on tumor cells. An assessment of 18-month survival will indicate if this combination therapy is a viable path for optimizing treatment.

3.6. Drug delivery in combination with immunotherapy

A primary feature of the destructive nature of GB is its immunosuppression of the local environment that reinforces major histocompatibility complex (MHC) downregulation and increased immunosuppressive cytokines. Thus, modulation of innate and adaptive immunities is important for immunotherapy of gliomas [109]. However, with chemo-immunotherapy acting in an immunosuppressive fashion when systemically delivered, the challenge and promise of local targeting and delivery of therapy becomes even more urgent, particularly considering the already-immunosuppressive and aggressive nature of GB [109–111]. Several factors have been found to be uniquely altered in tumor cells to create the tumor microenvironment, and thus are promising candidates for localized immunotherapy. Among these factors are stimulators of interferon genes (STING) agonists, cytokines (particularly CXCL10), and programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) interaction.

STING is a protein that triggers type 1 IFN signals, which are typically lost in the tumor microenvironment, promoting tumor growth. Therefore, targeting tumors with STING agonists is a potential avenue to arrest tumor growth with increased immune activity. It has been proven that administering a STING agonist intratumorally enhances anti-glioma immunity with increases in CC15 and CXCL10 mRNA levels and amount of immune cell infiltrates [112,113]. Intratumoral administration of a STING agonist improved the survival of glioma-bearing mice [113]. STING agonists also work synergistically with peptide anti-tumor vaccines to enhance their T cell-activating effects, and therefore these can be combined to increase efficacy [113].

Cytokine manipulation presents yet another encouraging target of immunotherapy, though this can be difficult to control locally; cytokine therapy can have widespread systemic effects [114,115]. One method of increasing pro-inflammatory cytokine levels in tumors is through lipopolysaccharide (LPS) stimulation. LPS, when delivered intratumorally, activates toll-like receptor 4 (TLR-4) to instigate release of cytokines, but this effect only holds if the LPS stimulation is given for short times. Lengthened stimulation eliminates the positive effects of the LPS stimulation [109]. These results suggest potential favorable effects of cytokine-mediated chemo-immunotherapy. In particular, CXCL10, a cytokine secreted in response to IFN-γ and a regulator of the Janus kinases/signal transducers and activators of transcription (JAK-STAT) pathway, is a primary player in the immunosuppression characteristic of the tumor microenvironment. GB overexpresses CXCL10, meaning that it may have a role in stimulating tumor progression [116]. However, the role of CXCL10 as a tumor stimulator is uncertain and must be further investigated, as it is also found to be upregulated in cases of spontaneous tumor regression [117].

Programmed cell death protein 1 (PD-1) and its corresponding ligands have been found to be encouraging targets to block via immunotherapies as their interaction tends to promote the immunosuppression that allows unchecked tumor growth. PD-L1 over-expression in particular has been found in GB, leading to the reasoning that this immune checkpoint may be a key target for GB therapy [110,111]. Current chemotherapeutics, when delivered systemically, immunosuppress universally and hinder the overall immune efforts of the patient, rendering immunotherapies potentially less effective. Endeavors to localize these therapies have been undertaken with the possibility that localized cancellation of tumor immunosuppression will lead to the slowing of growth and eventual degradation of the tumor [111]. When chemotherapy was administered locally with PD-1 there was a synergistic improvement in survival and sustained immunological memory. By contrast systemic chemotherapy diminished the immune response, there was no synergy and no immunological memory. An immunostimulant, polyriboinosinic-polyribocytidylic acid (poly(I:C)), has been found by De Waele et al. to increase immune system activation and lymphocyte attraction to the tumor microenvironment, however, it simultaneously causes de novo synthesis and upregulation of PD-L1 in GB cells. These findings suggest that synergism between poly(I:C) and PD-L1 blockage may increase the immune system's activation and limit its suppression, suggesting they may be a candidate for combined immunotherapy to treat GB [110].

Though local chemo-immunotherapy is in its early stages, the potential for localized delivery is heightened further by biodegradable materials. Risks could be decreased with a biodegradable delivery mechanism that can remove itself from the body, eliminating the need for procedural removal of a more permanent local drug delivery platform.

3.7. Ultrasound and brain tumors

Ultrasound, a term given for a sonic wave with frequency above 20 kHz, is primarily associated clinically as a diagnostic means but has increasingly become a therapeutic tool, particularly when combined with MRI guidance technology as magnetic-resonance guided focused ultrasound (MRgFUS). MRgFUS has received FDA approval for the treatment of essential tremors of Parkinson's disease, and is currently being investigated as a therapy for brain tumor ablation, epilepsy, depression, CSF diversion, and many other neurological conditions [118]. The technique of magnetic-resonance guided focused ultrasound (MRgFUS) allows for focused delivery and absorption of ultrasound energy, which induces thermal ablation of tissues and tumors at the focal area [119]. Uniquely, MRgFUS has been shown to have minimal side effects because the technique does not affect tissue surrounding the focal area [120]. Due to the high intensity of the ultrasonic energy, which can exceed 1000 W/cm^2, high-intensity focused ultrasound can be delivered through the skull and is therefore noninvasive [121]. Additionally, MRI guidance technology serves as feedback and monitoring for the focused ultrasound through its real-time thermometric capabilities [122]. The benefits of focused ultrasound are twofold, both direct and indirect. Directly, the thermal ablation of tissue has potential in the treatment of brain tumors, such as GB [123]. Indirectly, and at lower intensities, focused ultrasound can non-thermally disrupt the BBB through mechanical acoustic cavitation, allowing for the improved penetration of chemotherapy, which will be the focus of the following section [124].

The BBB presents a major challenge for drug delivery in the treatment of glioma. As previously described, the BBB, formed by tight junctions of endothelial cells, creates a separation

between the circulation and extracellular fluid of the brain [125]. It passively allows certain materials to pass through, such as glucose and amino acids, but P-glycoprotein actively pumps out potential neurotoxins, making drug delivery for glioma difficult. However, focused ultrasound in combination with microbubbles (MBs) has been shown to improve efficacy of drug delivery by opening the BBB in rodent models of glioma [125]. Microbubbles are small gas-filled microspheres with a high degree of echogenicity, which allows for a cavitation effect when focused ultrasound is applied and creates vibrations [126]. The characteristics of the microbubbles used in treatment allow for different lengths of BBB opening; for instance, diameter and half-life of BBB opening are inversely related, with larger diameters of microbubbles leading to shorter opening windows. On a small-scale level, focused ultrasound creates micro-level shears in the vasculature and the microbubbles collapse, causing epithelial cell detachment and membrane integrity disruption/puncturing, effecting a BBB opening [127]. In order to achieve BBB disruption, the microbubble oscillations should be sustained at stable oscillations without inertial cavitation or transient bubble collapse. To avoid any damage to the normal tissue in the brain as a result of focused ultrasound with microbubbles, passive cavitation detection (PCD) monitoring can be applied [128]. Studies have shown that long-term cellular and behavioral changes are not found, encouraging the use of focused ultrasound in brain tumor treatment, but it has yet to be FDA-approved for this indication. Several Phase I/II clinical trials are currently underway to further investigate the capabilities of focused ultrasound in opening the BBB [127].

In recent mouse models, the use of focused ultrasound has shown efficacy in delivering polysorbate-80 modified paclitaxel-loaded PLGA nanoparticles across the BBB. The study demonstrated that the mechanism by which the BBB was disrupted involved a combination of tight junction disruptions, reduced P-glycoprotein expression, and APOE-dependent polysorbate-80 permeation [96]. Timbie et al. systemically delivered cisplatin-loaded brain penetrating nanoparticles along with MRgFUS in a rat model of glioma and showed reduced tumor growth and invasiveness in addition to a modest increase in survival [125]. Other mouse model studies showed that bevacizumab, an antiangiogenic monoclonal antibody against VEGF, can be effectively delivered across the BBB using this method in a model of malignant glioma [129]. Moreover, in rat glioma models, focused ultrasound with microbubbles, while implementing PCD monitoring, showed effective delivery of Trypan Blue and liposomal doxorubicin across the BBB [128]. Wei et al. demonstrated increased CSF/plasma ratio of temozolomide concentrations when MRI-monitored focused ultrasound with microbubbles were used to transiently disrupt the BBB in combination with temozolomide treatment [130]. The first clinical use of the MRgFUS in chemotherapy delivery was reported recently in five patients with malignant high-grade glioma. The results of the study demonstrated the feasibility and safety of liposomal doxorubicin and temozolomide delivery across the BBB [124]. Due to these advancements in MRI-guided focused ultrasound, there is great potential in using this technology for the local treatment of glioma with further investigation.

4. Conclusion

Research on the application of various therapeutic techniques for the treatment of GB has accelerated during the last two decades, as demonstrated within the existing literature as well as in the number of current clinical trials. The testing of these promising alternatives could add positively to the current therapeutic standards. The complex challenges of the BBB and the BBTB has limited the efficacy of drug therapy. Biodegradable wafers, a major breakthrough in localized treatment, have been FDA-approved for over a decade and have consistently displayed safety and increased efficacy. With advancements in local delivery options, monotherapy as well as combination therapy of drugs effecting complimentary mechanisms of action are being explored. Alternative therapies including targeted nanoparticle therapy, focused ultrasound, and immunotherapy have been translated from preclinical studies and are primed for testing in clinical trials to determine their therapeutic potential. Current and future studies will continue to optimize local delivery of therapies which could lead to the next pivotal treatment breakthrough.

5. Expert opinion

While there have been advances in brain cancer therapeutics over the last several years, research in the field of local drug delivery is rapidly expanding, providing more opportunities for hope within neuro-oncology. There are several unique treatment challenges inherent to brain tumors that must be considered and overcome, including the BBB and the blood brain tumor barrier. In attempting to overcome these obstacles, careful attention must be paid to the safety and toxicity of chemotherapeutic agents. Therapeutics need to be targeted to the tumor cells in order to spare healthy tissue and preserve neurological function. Early polymer-based drug delivery strategies first opened the door for safe, local therapeutic use of compounds that were previously unable to cross the BBB in dosages high enough to inhibit tumor growth without prohibitive systemic toxicities. Innovations in biocompatible and biodegradable polymer design, followed by improvements in microsphere and nanoparticle technologies, have enabled compounds to be delivered intracranially either as implantable wafers, injectable payloads employing convection-enhanced delivery, or systemically delivered solutions. Improvements in bioengineering such as construction of PEG-coated nanoparticles and polymersomes have allowed easier travel into the brain. These brain-penetrating particles can be designed to target tumor cells delivering a sustained and specific therapeutic payload to further increase efficacy.

There are also multiple pioneering studies utilizing novel combinations of chemotherapies delivered locally or using systemic targeted delivery of agents that work through various mechanisms of action, attacking tumor growth, angiogenesis, migration, and invasion in complementary and synergistic ways. Repurposing drugs proven effective in other cancers and for other diseases may also broaden our armamentarium against brain tumors. Immunotherapies, long studied for use against systemic cancers, are being examined for their use against intracranial neoplasms. Their usage has been observed to be more beneficial with locally delivered

chemotherapy rather than systemically delivered chemotherapies in the laboratory but the role of immunotherapy in brain cancer treatment remains to be determined.

Looking beyond chemotherapy and immunotherapy there is also promise in the area of tumor treating fields that pulse alternating electrical fields across the skin which can disrupt cancer cell division and lead to tumor cell death. Focused ultrasound and the use of microbubbles are being tested with the expectation that this modality, especially in conjunction with MRI-guidance, will aid in disrupting the BBB and allow therapeutic concentrations of cytotoxic agents to inhibit tumor growth locally. Personalized or precision medicine offers the promise that genetic testing of one's tumor tissue can identify integrated molecular information in order to determine a personalized treatment plan. An individual patient's tumor's IDH-1 mutation and methylation status, among other markers, can optimize the most effective personalized treatment plan. Overcoming the brain's unique challenges through innovations in the fields of local ultrasound, gene therapy, and immunotherapy could contribute to pivotal breakthroughs in the future. As new techniques and discoveries are made, the approach to brain tumor therapy continues to broaden. The goal in which every patient's tumor can be genetically screened in order to identify and administer the most effective treatment from an expanding list of therapeutic modalities – or a new therapeutic currently being tested in a research laboratory – is a goal that seeks not just to extend a patient's survival but also to improve upon its quality.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Gupta A, Dwivedi T. A simplified overview of world health organization classification update of central nervous system tumors 2016. J Neurosci Rural Pract. 2017;8(4):629–641.
2. McGirt MJ, Than KD, Weingart JD, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg. 2009;110(3):583–588.
3. Woodworth GF, Dunn GP, Nance EA, et al. Emerging insights into barriers to effective brain tumor therapeutics. Front Oncol. 2014;4:126.
4. Vellimana AK, Recinos VR, Hwang L, et al. Combination of paclitaxel thermal gel depot with temozolomide and radiotherapy significantly prolongs survival in an experimental rodent glioma model. J Neurooncol. 2013;111(3):229–236.
5. Tyler B, Fowers KD, Li KW, et al. A thermal gel depot for local delivery of paclitaxel to treat experimental brain tumors in rats. J Neurosurg. 2010;113(2):210–217.
6. Amini MA, Abbasi AZ, Cai P, et al. Combining tumor microenvironment modulating nanoparticles with doxorubicin to enhance chemotherapeutic efficacy and boost antitumor immunity. J Natl Cancer Inst. 2019;111(4):399–408.
7. Bala I, Hariharan S, Kumar MN. PLGA nanoparticles in drug delivery: the state of the art. Crit Rev Ther Drug Carrier Syst. 2004;21(5):387–422.
8. Jahangiri A, Chin AT, Flanigan PM, et al. Convection-enhanced delivery in glioblastoma: a review of preclinical and clinical studies. J Neurosurg. 2017;126(1):191–200.
9. Kwiatkowska A, Nandhu MS, Behera P, et al. Strategies in gene therapy for glioblastoma. Cancers (Basel). 2013;5(4):1271–1305.
10. Thomas CE, Ehrhardt A, Kay MA. Progress and problems with the use of viral vectors for gene therapy. Nat Rev Genet. 2003;4(5):346–358.
11. Pack DW, Hoffman AS, Pun S, et al. Design and development of polymers for gene delivery. Nat Rev Drug Discov. 2005;4(7):581–593.
12. Mao H, Lebrun DG, Yang J, et al. Deregulated signaling pathways in glioblastoma multiforme: molecular mechanisms and therapeutic targets. Cancer Invest. 2012;30(1):48–56.
13. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol. 2007;170(5):1445–1453.
14. Kakimi K, Karasaki T, Matsushita H, et al. Advances in personalized cancer immunotherapy. Breast Cancer. 2017;24(1):16–24.
15. Gubens MA, Davies M. NCCN guidelines updates: new immunotherapy strategies for improving outcomes in non-small cell lung cancer. J Natl Compr Canc Netw. 2019;17(5.5):574–578.
16. Preusser M, Lim M, Hafler DA, et al. Prospects of immune checkpoint modulators in the treatment of glioblastoma. Nat Rev Neurol. 2015;11(9):504–514.
17. Almutairi MM Gong, C, Xu, YG, et al. Factors controlling permeability of the blood-brain barrier. Cell Mol Life Sci. 2016;73(1):57–77.
18. Tamai I, Tsuji A. Transporter-mediated permeation of drugs across the blood-brain barrier. J Pharm Sci. 2000;89(11):1371–1388.
19. Bhowmik A, Khan R, Ghosh MK. Blood brain barrier: a challenge for effectual therapy of brain tumors. Biomed Res Int. 2015;2015:320941.
20. Begley DJ. ABC transporters and the blood-brain barrier. Curr Pharm Des. 2004;10(12):1295–1312.
21. Armulik A, Genové G, Mäe M, et al. Pericytes regulate the blood-brain barrier. Nature. 2010;468(7323):557–561.
22. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006;7(1):41–53.
23. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1):a020412.
24. Groothuis DR. The blood-brain and blood-tumor barriers: a review of strategies for increasing drug delivery. Neuro Oncol. 2000;2(1):45–59.
25. van Tellingen O, Yetkin-Arik B, de Gooijer MC, et al. Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. Drug Resist Updat. 2015;19:1–12.
26. Zhou W, Chen C, Shi Y, et al. Targeting glioma stem cell-derived pericytes disrupts the blood-tumor barrier and improves chemotherapeutic efficacy. Cell Stem Cell. 2017;21(5):591–603.e4.
27. Bobo RH, Laske DW, Akbasak A, et al. Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci USA. 1994;91(6):2076–2080.
28. Mehta AM, Sonabend AM, Bruce JN. Convection-enhanced delivery. Neurotherapeutics. 2017;14(2):358–371.
29. Raghavan R, Brady ML, Rodríguez-Ponce MI, et al. Convection-enhanced delivery of therapeutics for brain disease, and its optimization. Neurosurg Focus. 2006;20(4):E12.

30. Sampson JH, Brady ML, Petry NA, et al. Intracerebral infusate distribution by convection-enhanced delivery in humans with malignant gliomas: descriptive effects of target anatomy and catheter positioning. Neurosurgery. 2007;60(2 Suppl 1):ONS89–98. discussion ONS98–9.
31. Sampson JH, Akabani G, Archer GE, et al. Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. Neuro Oncol. 2008;10(3):320–329.
32. Sampson JH, Archer G, Pedain C, et al. Poor drug distribution as a possible explanation for the results of the PRECISE trial. J Neurosurg. 2010;113(2):301–309.
33. Lidar Z, Mardor Y, Jonas T, et al. Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: a phase I/II clinical study. J Neurosurg. 2004;100(3):472–479.
34. Young JS, Bernal G, Polster SP, et al. Convection-enhanced delivery of polymeric nanoparticles encapsulating chemotherapy in canines with spontaneous supratentorial tumors. World Neurosurg. 2018;117:e698–e704.
35. Zhang C, Nance EA, Mastorakos P, et al. Convection enhanced delivery of cisplatin-loaded brain penetrating nanoparticles cures malignant glioma in rats. J Control Release. 2017;263:112–119.
36. White E, Bienemann A, Pugh J, et al. An evaluation of the safety and feasibility of convection-enhanced delivery of carboplatin into the white matter as a potential treatment for high-grade glioma. J Neurooncol. 2012;108(1):77–88.
37. White E, Bienemann A, Taylor H, et al. A phase I trial of carboplatin administered by convection-enhanced delivery to patients with recurrent/progressive glioblastoma multiforme. Contemp Clin Trials. 2012;33(2):320–331.
38. Arshad A, Yang B, Bienemann AS, et al. Convection-enhanced delivery of carboplatin PLGA nanoparticles for the treatment of glioblastoma. PLoS One. 2015;10(7):e0132266.
39. Shi M, Anantha M, Wehbe M, et al. Liposomal formulations of carboplatin injected by convection-enhanced delivery increases the median survival time of F98 glioma bearing rats. J Nanobiotechnology. 2018;16(1):77.
40. Huo T, Barth RF, Yang W, et al. Preparation, biodistribution and neurotoxicity of liposomal cisplatin following convection enhanced delivery in normal and F98 glioma bearing rats. PLoS One. 2012;7(11):e48752.
41. Nordling-David MM, Yaffe R, Guez D, et al. Liposomal temozolomide drug delivery using convection enhanced delivery. J Control Release. 2017;261:138–146.
42. Sewing ACP, Lagerweij T, van Vuurden DG, et al. Preclinical evaluation of convection-enhanced delivery of liposomal doxorubicin to treat pediatric diffuse intrinsic pontine glioma and thalamic high-grade glioma. J Neurosurg Pediatr. 2017;19(5):518–530.
43. Barua NU, Hopkins K, Woolley M, et al. A novel implantable catheter system with transcutaneous port for intermittent convection-enhanced delivery of carboplatin for recurrent glioblastoma. Drug Deliv. 2016;23(1):167–173.
44. Vogelbaum MA, Brewer C, Barnett GH, et al. First-in-human evaluation of the cleveland multiport catheter for convection-enhanced delivery of topotecan in recurrent high-grade glioma: results of pilot trial 1. J Neurosurg. 2018;1–10.
45. Barua NU, Gill SS, Love S. Convection-enhanced drug delivery to the brain: therapeutic potential and neuropathological considerations. Brain Pathol. 2014;24(2):117–127.
46. Nandhu MS, Kwiatkowska A, Bhaskaran V, et al. Tumor-derived fibulin-3 activates pro-invasive NF-kappaB signaling in glioblastoma cells and their microenvironment. Oncogene. 2017;36(34):4875–4886.
47. Tobias A, Ahmed A, Moon K-S, et al. The art of gene therapy for glioma: a review of the challenging road to the bedside. J Neurol Neurosurg Psychiatry. 2013;84(2):213–222.
48. Guerrero-Cazares H, Tzeng SY, Young NP, et al. Biodegradable polymeric nanoparticles show high efficacy and specificity at DNA delivery to human glioblastoma in vitro and in vivo. ACS Nano. 2014;8(5):5141–5153.
49. Lynn DM, Anderson DG, Putnam D, et al. Accelerated discovery of synthetic transfection vectors: parallel synthesis and screening of a degradable polymer library. J Am Chem Soc. 2001;123(33):8155–8156.
50. Tzeng SY, Higgins LJ, Pomper MG, et al. Student award winner in the Ph.D. category for the 2013 society for biomaterials annual meeting and exposition, april 10–13,2013, Boston, Massachusetts: biomaterial-mediated cancer-specific DNA delivery to liver cell cultures using synthetic poly(beta-amino ester)s. J Biomed Mater Res A. 2013;101(7):1837–1845.
51. Idbaih A, Erbs P, Foloppe J, et al. TG6002: A novel oncolytic and vectorized gene pro-drug therapy approach to treat glioblastoma. J Clin Oncol. 2017;35(15_suppl):e13510–e13510.
52. Tamargo RJ, Myseros JS, Epstein JI, et al. Interstitial chemotherapy of the 9L gliosarcoma: controlled release polymers for drug delivery in the brain. Cancer Res. 1993;53(2):329–333.
53. Yang MB, Tamargo RJ, Brem H. Controlled delivery of 1,3-bis (2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer. Cancer Res. 1989;49(18):5103–5107.
54. Fung LK, Shin M, Tyler B, et al. Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. Pharm Res. 1996;13(5):671–682.
55. Sipos EP, Tyler B, Piantadosi S, et al. Optimizing interstitial delivery of BCNU from controlled release polymers for the treatment of brain tumors. Cancer Chemother Pharmacol. 1997;39(5):383–389.
56. Grossman SA, Reinhard C, Colvin OM, et al. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. J Neurosurg. 1992;76(4):640–647.
57. Brem H, Mahaley MS, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. J Neurosurg. 1991;74(3):441–446.
58. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. Lancet. 1995;345(8956):1008–1012.
59. Valtonen S, Timonen U, Toivanen P, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. Neurosurgery. 1997;41(1):44–48. discussion 48–9.
60. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol. 2003;5(2):79–88.
61. Mangraviti A, Tyler B, Brem H. Interstitial chemotherapy for malignant glioma: future prospects in the era of multimodal therapy. Surg Neurol Int. 2015;6(Suppl 1):S78–84.
62. Pallud J, Audureau E, Noel G, et al. Long-term results of carmustine wafer implantation for newly diagnosed glioblastomas: a controlled propensity-matched analysis of a French multicenter cohort. Neuro Oncol. 2015;17(12):1609–1619.
63. Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. J Neurooncol. 2015;122(2):367–382.
64. Xing WK, Shao C, Qi Z-Y, et al. The role of Gliadel wafers in the treatment of newly diagnosed GBM: a meta-analysis. Drug Des Devel Ther. 2015;9:3341–3348.
65. Fountzilas G, Karavelis A, Capizzello A, et al. Radiation and concomitant weekly administration of paclitaxel in patients with glioblastoma multiforme. A phase II study. J Neurooncol. 1999;45(2):159–165.
66. Prados MD, Schold SC, Spence AM, et al. Phase II study of paclitaxel in patients with recurrent malignant glioma. J Clin Oncol. 1996;14(8):2316–2321.
67. Walter KA, Cahan MA, Gur A, et al. Interstitial taxol delivered from a biodegradable polymer implant against experimental malignant glioma. Cancer Res. 1994;54(8):2207–2212.
68. Li KW, Dang W, Tyler BM, et al. Polilactofate microspheres for Paclitaxel delivery to central nervous system malignancies. Clin Cancer Res. 2003;9(9):3441–3447.

69. Pradilla G, Wang PP, Gabikian P, et al. Local intracerebral administration of Paclitaxel with the paclimer delivery system: toxicity study in a canine model. J Neurooncol. 2006;76(2):131–138.
70. Lesniak MS, Upadhyay U, Goodwin R, et al. Local delivery of doxorubicin for the treatment of malignant brain tumors in rats. Anticancer Res. 2005;25(6b):3825–3831.
71. Mangraviti A, Raghavan T, Volpin F, et al. HIF-1alpha- targeting acriflavine provides long term survival and radiological tumor response in brain cancer therapy. Sci Rep. 2017;7(1):14978.
72. Charest G, Sanche L, Fortin D, et al. Glioblastoma treatment: bypassing the toxicity of platinum compounds by using liposomal formulation and increasing treatment efficiency with concomitant radiotherapy. Int J Radiat Oncol Biol Phys. 2012;84(1):244–249.
73. Papachristodoulou A, Signorell RD, Werner B, et al. Chemotherapy sensitization of glioblastoma by focused ultrasound-mediated delivery of therapeutic liposomes. J Control Release. 2019;295:130–139.
74. Vanza J, Jani P, Pandya N, et al. Formulation and statistical optimization of intravenous temozolomide-loaded PEGylated liposomes to treat glioblastoma multiforme by three-level factorial design. Drug Dev Ind Pharm. 2018;44(6):923–933.
75. Lin C-Y, Li R-J, Huang C-Y, et al. Controlled release of liposome-encapsulated temozolomide for brain tumour treatment by convection-enhanced delivery. J Drug Target. 2018;26(4):325–332.
76. Sun X, Pang Z, Ye H, et al. Co-delivery of pEGFP-hTRAIL and paclitaxel to brain glioma mediated by an angiopep-conjugated liposome. Biomaterials. 2012;33(3):916–924.
77. Yuan BO, Zhao Y, Dong S, et al. Cell-penetrating peptide-coated liposomes for drug delivery across the blood-brain barrier. Anticancer Res. 2019;39(1):237–243.
78. Lin Q, Mao K-L, Tian F-R, et al. Brain tumor-targeted delivery and therapy by focused ultrasound introduced doxorubicin-loaded cationic liposomes. Cancer Chemother Pharmacol. 2016;77(2):269–280.
79. Steiniger SCJ, Kreuter J, Khalansky AS, et al. Chemotherapy of glioblastoma in rats using doxorubicin-loaded nanoparticles. Int J Cancer. 2004;109(5):759–767.
80. DuVall GA, Tarabar D, Seidel RH, et al. Phase 2: a dose-escalation study of OncoGel (ReGel/paclitaxel), a controlled-release formulation of paclitaxel, as adjunctive local therapy to external-beam radiation in patients with inoperable esophageal cancer. Anticancer Drugs. 2009;20(2):89–95.
81. Lei C, Davoodi P, Zhan W, et al. Development of nanoparticles for drug delivery to brain tumor: the effect of surface materials on penetration into brain tissue. J Pharm Sci. 2019;108(5):1736–1745.
82. Sun X, Chen Y, Zhao H, et al. Dual-modified cationic liposomes loaded with paclitaxel and survivin siRNA for targeted imaging and therapy of cancer stem cells in brain glioma. Drug Deliv. 2018;25(1):1718–1727.
83. Ganipineni LP, Ucakar B, Joudiou N, et al. Magnetic targeting of paclitaxel-loaded poly(lactic-co-glycolic acid)-based nanoparticles for the treatment of glioblastoma. Int J Nanomedicine. 2018;13:4509–4521.
84. Li M, Zhang F, Su Y, et al. Nanoparticles designed to regulate tumor microenvironment for cancer therapy. Life Sci. 2018;201(March 22):37–44.
85. Stupp R, Mason WP, van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–996.
86. Brem S, Tyler B, Li K, et al. Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model. Cancer Chemother Pharmacol. 2007;60(5):643–650.
87. Recinos VR, Tyler BM, Bekelis K, et al. Combination of intracranial temozolomide with intracranial carmustine improves survival when compared with either treatment alone in a rodent glioma model. Neurosurgery. 2010;66(3):530–537. discussion 537.
88. Zhang YH, Zhang H, Liu J-M, et al. Temozolomide/PLGA microparticles: a new protocol for treatment of glioma in rats. Med Oncol. 2011;28(3):901–906.
89. Shapira-Furman T, Serra R, Gorelick N, et al. Biodegradable wafers releasing Temozolomide and Carmustine for the treatment of brain cancer. J Control Release. 2019;295:93–101.
- **The co-delivery of chemotherapeutics already FDA approved for the treatment of glioma could prove beneficial if given locally.**
90. DiMeco F, Li KW, Tyler BM, et al. Local delivery of mitoxantrone for the treatment of malignant brain tumors in rats. J Neurosurg. 2002;97(5):1173–1178.
91. Ferroli P, Broggi M, Franzini A, et al. Surgifoam and mitoxantrone in the glioblastoma multiforme postresection cavity: the first step of locoregional chemotherapy through an ad hoc-placed catheter: technical note. Neurosurgery. 2006;59(2):E433–4. discussion E433–4.
92. Yemisci M, Bozdag S, Cetin M, et al. Treatment of malignant gliomas with mitoxantrone-loaded poly (lactide-co-glycolide) microspheres. Neurosurgery. 2006;59(6):1296–1302. discussion 1302–1303.
93. Boiardi A, Silvani A, Eoli M, et al. Treatment of recurrent glioblastoma: can local delivery of mitoxantrone improve survival? J Neurooncol. 2008;88(1):105–113.
94. Lam P, Lin R, Steinmetz NF. Delivery of mitoxantrone using a plant virus-based nanoparticle for the treatment of glioblastomas. J Mater Chem B. 2018;6(37):5888–5895.
95. Chen Q, Liu L, Lu Y, et al. Tumor microenvironment-triggered aggregated magnetic nanoparticles for reinforced image-guided immunogenic chemotherapy. Adv Sci (Weinh). 2019;6(6):1802134.
96. Li Y, Wu M, Zhang N, et al. Mechanisms of enhanced antiglioma efficacy of polysorbate 80-modified paclitaxel-loaded PLGA nanoparticles by focused ultrasound. J Cell Mol Med. 2018;22(9):4171–4182.
97. Wu J, Chen J, Feng Y, et al. Tumor microenvironment as the "regulator" and "target" for gene therapy. J Gene Med. 2019;21:e3088.
98. Benos L, Spyrou LA, Sarris IE. Development of a new theoretical model for blood-CNTs effective thermal conductivity pertaining to hyperthermia therapy of glioblastoma multiform. Comput Methods Programs Biomed. 2019;172:79–85.
99. Chastagner P, Sudour H, Mriouah J, et al. Preclinical studies of pegylated- and non-pegylated liposomal forms of doxorubicin as radiosensitizer on orthotopic high-grade glioma xenografts. Pharm Res. 2015;32(1):158–166.
100. Zou L, Tao Y, Payne G, et al. Targeted delivery of nano-PTX to the brain tumor-associated macrophages. Oncotarget. 2017;8(4):6564–6578.
101. Kang T, Jiang M, Jiang D, et al. Enhancing glioblastoma-specific penetration by functionalization of nanoparticles with an iron-mimic peptide targeting transferrin/transferrin receptor complex. Mol Pharm. 2015;12(8):2947–2961.
102. Zhang Y, Zhai M, Chen Z, et al. Dual-modified liposome codelivery of doxorubicin and vincristine improve targeting and therapeutic efficacy of glioma. Drug Deliv. 2017;24(1):1045–1055.
103. Smith SJ, Tyler BM, Gould T, et al. Overall survival in malignant glioma is significantly prolonged by neurosurgical delivery of etoposide and temozolomide from a thermo-responsive biodegradable paste. Clin Cancer Res. 2019.
- **This publication introduces a biodegradable paste that will be included in Phase 1 testing soon.**
104. Stupp R, Lukas RV, Hegi ME. Improving survival in molecularly selected glioblastoma. Lancet. 2019;393(10172):615–617.
105. Kuo YC, Chang YH, Rajesh R. Targeted delivery of etoposide, carmustine and doxorubicin to human glioblastoma cells using methoxy poly(ethylene glycol)poly(epsiloncaprolactone) nanoparticles conjugated with wheat germ agglutinin and folic acid. Mater Sci Eng C Mater Biol Appl. 2019;96:114–128.
106. Emamgholizadeh Minaei S, Khoei S, Khoee S, et al. Tri-block copolymer nanoparticles modified with folic acid for temozolomide delivery in glioblastoma. Int J Biochem Cell Biol. 2019;108:72–83.
107. Wang C, Jiang M, Hou H, et al. Apatinib suppresses cell growth and metastasis and promotes antitumor activity of temozolomide in glioma. Oncol Lett. 2018;16(5):5607–5614.
108. Nile DL, Rae C, Hyndman IJ, et al. An evaluation in vitro of PARP-1 inhibitors, rucaparib and olaparib, as radiosensitisers for the treatment of neuroblastoma. BMC Cancer. 2016;16:621.

109. Han S, Wang C, Qin X, et al. LPS alters the immuno-phenotype of glioma and glioma stem-like cells and induces in vivo antitumor immunity via TLR4. J Exp Clin Cancer Res. 2017;36(1):83.
110. De Waele J, Routh ED, Pullikuth A, et al. Poly(I:C) primes primary human glioblastoma cells for an immune response invigorated by PD-L1 blockade. Oncoimmunology. 2018;7(3):e1407899.
111. Mathios D, Kim JE, Mangraviti A, et al. Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM. Sci Transl Med. 2016;8(370):370ra180.
    - **Anti-PD1 therapy is shown to be effective with local chemotherapy but not with systemically delivered chemotherapy. This will be crucial to determine clinically.**
112. Ohkuri T, Sevko A, Heide J, et al. Protective role of STING against gliomagenesis: rational use of STING agonist in anti-glioma immunotherapy. Oncoimmunology. 2015;4(4):e999523.
113. Ohkuri T, Ghosh A, Kosaka A, et al. STING contributes to antiglioma immunity via triggering type I IFN signals in the tumor microenvironment. Cancer Immunol Res. 2014;2(12):1199–1208.
114. Liau LM, Prins RM, Kiertscher SM, et al. Dendritic cell vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local central nervous system tumor microenvironment. Clin Cancer Res. 2005;11(15):5515–5525.
115. Prosniak M, Harshyne LA, Andrews DW, et al. Glioma grade is associated with the accumulation and activity of cells bearing M2 monocyte markers. Clin Cancer Res. 2013;19(14):3776–3786.
116. Sharma I, Siraj F, Sharma KC, et al. Immunohistochemical expression of chemokine receptor CXCR3 and its ligand CXCL10 in low-grade astrocytomas and glioblastoma multiforme: A tissue microarray-based comparison. J Cancer Res Ther. 2016;12(2):793–797.
117. Wang P, Peng X, Zhang J, et al. LncRNA-135528 inhibits tumor progression by up-regulating CXCL10 through the JAK/STAT pathway. Apoptosis. 2018;23(11–12):651–666.
118. Hersh DS, Kim AJ, Winkles JA, et al. Emerging applications of therapeutic ultrasound in neuro-oncology: moving beyond tumor ablation. Neurosurgery. 2016;79(5):643–654.
119. Lee EJ, Fomenko A, Lozano AM. Magnetic resonance-guided focused ultrasound: current status and future perspectives in thermal ablation and blood-brain barrier opening. J Korean Neurosurg Soc. 2019;62(1):10–26.
120. Hijnen NM, Heijman E, Köhler MO, et al. Tumour hyperthermia and ablation in rats using a clinical MR-HIFU system equipped with a dedicated small animal set-up. Int J Hyperthermia. 2012;28(2):141–155.
121. Jenne JW, Preusser T, Gunther M. High-intensity focused ultrasound: principles, therapy guidance, simulations and applications. Z Med Phys. 2012;22(4):311–322.
122. Ries M, de Senneville BD, Roujol S, et al. Real-time 3D target tracking in MRI guided focused ultrasound ablations in moving tissues. Magn Reson Med. 2010;64(6):1704–1712.
123. Colen RR, Sahnoune I, Weinberg JS. Neurosurgical applications of high-intensity focused ultrasound with magnetic resonance thermometry. Neurosurg Clin N Am. 2017;28(4):559–567.
124. Mainprize T, Lipsman N, Huang Y, et al. Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: a clinical safety and feasibility study. Sci Rep. 2019;9(1):321.
    - **This new technology is under investigation but has great potential to transiently open the BBB for increased therapeutic delivery.**
125. Timbie KF, Afzal U, Date A, et al. MR image-guided delivery of cisplatin-loaded brain-penetrating nanoparticles to invasive glioma with focused ultrasound. J Control Release. 2017;263:120–131.
126. Dong Q, He L, Chen L, et al. Opening the blood-brain barrier and improving the efficacy of temozolomide treatments of glioblastoma using pulsed, focused ultrasound with a microbubble contrast agent. Biomed Res Int. 2018;2018:6501508.
127. Poon C, McMahon D, Hynynen K. Noninvasive and targeted delivery of therapeutics to the brain using focused ultrasound. Neuropharmacology. 2017;120:20–37.
128. Sun T, Zhang Y, Power C, et al. Closed-loop control of targeted ultrasound drug delivery across the blood-brain/tumor barriers in a rat glioma model. Proc Natl Acad Sci USA. 2017;114(48). E10281-e10290.
129. Liu H-L, Hsu P-H, Lin C-Y, et al. Focused ultrasound enhances central nervous system delivery of bevacizumab for malignant glioma treatment. Radiology. 2016;281(1):99–108.
130. Wei KC, Chu P-C, Wang H-YJ, et al. Focused ultrasound-induced blood-brain barrier opening to enhance temozolomide delivery for glioblastoma treatment: a preclinical study. PLoS One. 2013;8(3):e58995.