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Advances in drug delivery technology for the treatment of glioblastoma multiforme

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ABSTRACT

Glioblastoma multiforme (GBM) is a particularly aggressive and malignant type of brain tumor, notorious for its high recurrence rate and low survival rate. The treatment of GBM is challenging mainly because several issues associated with the GBM microenvironment have not yet been resolved. These obstacles originate from a variety of factors such as genetics, anatomy, and cytology, all of which collectively hinder the treatment of GBM. Recent advances in materials and device engineering have presented new perspectives with regard to unconventional drug administration methods for GBM treatment. Such novel drug delivery approaches, based on the clear understanding of the intrinsic properties of GBM, have shown promise in overcoming some of the obstacles. In this review, we first recapitulate the first-line therapy and clinical challenges in the current treatment of GBM. Afterwards, we introduce the latest technological advances in drug delivery strategies to improve the efficiency for GBM treatment, mainly focusing on materials and devices. We describe such efforts by classifying them into two categories, systemic and local drug delivery. Finally, we discuss unmet challenges and prospects for the clinical translation of these drug delivery technologies.

1. Introduction

Glioblastoma multiforme (GBM) is one of the deadliest brain tumors, whose prognosis is abysmal. The lethality of this brain tumor, classified as a grade IV astrocytoma, is evidenced by its low median survival (< 2 years) and 5-year survival rates (< 5%) [1–5]. There are many physical and biological barriers in the GBM microenvironment [6,7], which hinder the successful treatment of GBM and increase the risk of recurrence even after going through the standard treatment protocol [8]. Despite many efforts that have been devoted to overcoming such hurdles for precise diagnosis [9] and effective treatment of GBM [10], much more progress is still required for complete cure from GBM [11].

The standard GBM treatment consists of primary resection surgery, followed by chemotherapy and radiotherapy [12,13]. This combinational therapy showed that the median survival improved nearly 3 times compared to surgery alone [14]. However, the efficacy of such treatments is limited by the intrinsically malignant nature of GBM [15], the vascular structure of the brain [16], and the radiation dose tolerance of brain tissue [17]. For example, infiltrating tumor cells obscure the boundary between the normal and tumoral regions within the brain; thus, several residual tumor cells survive even after surgical removal. These remaining tumor cells contribute to the recurrence of GBM. Furthermore, conventional systemic delivery of chemotherapeutic agents is often ineffective because the blood-brain-barrier (BBB) blocks the anticancer drugs from permeating into the extracellular matrix of the brain. Furthermore, the radiation tolerance of brain tissue limits the efficacy of radiotherapy.

Alternative therapeutics, including gene therapy [18,19], angiogenesis inhibition [20,21], and immunotherapy [22,23], have shown potential efficacy for the treatment of GBM, but to a limited extent. The BBB lowers the efficiency of systemic drug delivery to the target tumor in the brain. Increasing the dosage of drugs to enhance their therapeutic efficiency would increase toxicity to normal cells and hence, increase the risk of adverse effects. Multi-drug administration to counter the high level of genetic heterogeneity of GBM in patients is also limited by

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the same increased risk of adverse effects.

Considering the limitations in both approaches, *i.e.*, the gold standard and alternative therapies, many recent studies have aimed at a dramatic improvement in the efficiency of drug delivery to brain tumors. Various drug delivery strategies have been suggested—including the systemic drug delivery penetrating through the BBB (*e.g.*, nanostructure-induced BBB penetration and external-stimulus-induced BBB temporal disruption) and local drug delivery bypassing the BBB (*e.g.*, intranasal delivery, solid implant-based delivery, intratumoral delivery, and convection-enhanced delivery (CED)). Moreover, several approaches have enhanced the efficiency of drug delivery by integrating both the macroscopic strategy of increasing drug permeation through the BBB and the microscopic strategy of designing the drug to be readily taken up by the tumor.

Here, we review such advances in drug delivery technology for GBM treatment. First, we introduce first-line treatments and their clinical challenges stemming from anatomic, cytologic, and genetic properties of GBM. Afterwards, we present clinically available treatment methods, focusing on relatively novel approaches, with detailed descriptions of their advantages and disadvantages. Then, we review the most recent innovations in drug delivery technology for GBM treatment. We describe them by classifying their drug administration modes into two categories, *i.e.*, systemic drug delivery versus local drug delivery. Mainly, we focus on both macro- and micro/nanoscopic strategies to overcome obstacles in GBM treatment. Finally, we conclude this review by presenting unresolved issues and the outlook of drug delivery technology.

2. Clinical protocols, challenges, and strategies for GBM treatment

2.1. Clinical protocols for GBM treatment

The first-line treatment of GBM consists of surgical resection to eliminate tumoral tissues as much as possible, and subsequent chemo/radiotherapy to eradicate residual tumor cells and counter recurrence [24]. The standard treatment and care for a newly diagnosed GBM patient are as follows (Fig. 1A):

(i) A suspected diagnosis of GBM is made as the patient suffers from symptoms such as headache, nausea, and vertigo [25]. (ii) After the primary diagnosis of GBM via magnetic resonance imaging (MRI) and computed tomography (CT) and further confirmation with pathological analysis [26], the patient is diagnosed as GBM, and he/she receives the optimized prescription, such as the incision range and dosage, after consideration of their age, tumor progression, and tumor location. (iii) Surgical resection is implemented first to remove most of the bulk tumor at once, with a minimal margin left as determined by diagnostic imaging. (iv) Adjuvant therapies, including chemotherapy and radiotherapy, are applied periodically as a complementary therapy to remove the remaining tumor cells at the surgical margin or as second-line therapy if GBM recurs [12,13]. Many anti-cancer agents have been developed and are being used in the clinic; temozolomide (TMZ) is a standard chemotherapeutic agent for GBM treatment due to its low systemic toxicity [27,28] and effective therapeutic performance [29]. Such post-surgical treatment options are considered, depending on the condition of the patient, and whether the tumor has progressed or recurred.

According to clinical studies, the median survival rate of patients following the standard treatment for GBM is 64 weeks, which is a four-fold increase compared to that of the control group [30]. Despite the proven therapeutic effect of the standard treatment, there is still room for advances in the clinical strategies of GBM treatment to overcome existing challenges and limitations.

2.2. Clinical challenges for GBM treatment

Despite the advancement of clinical practice and technology, the

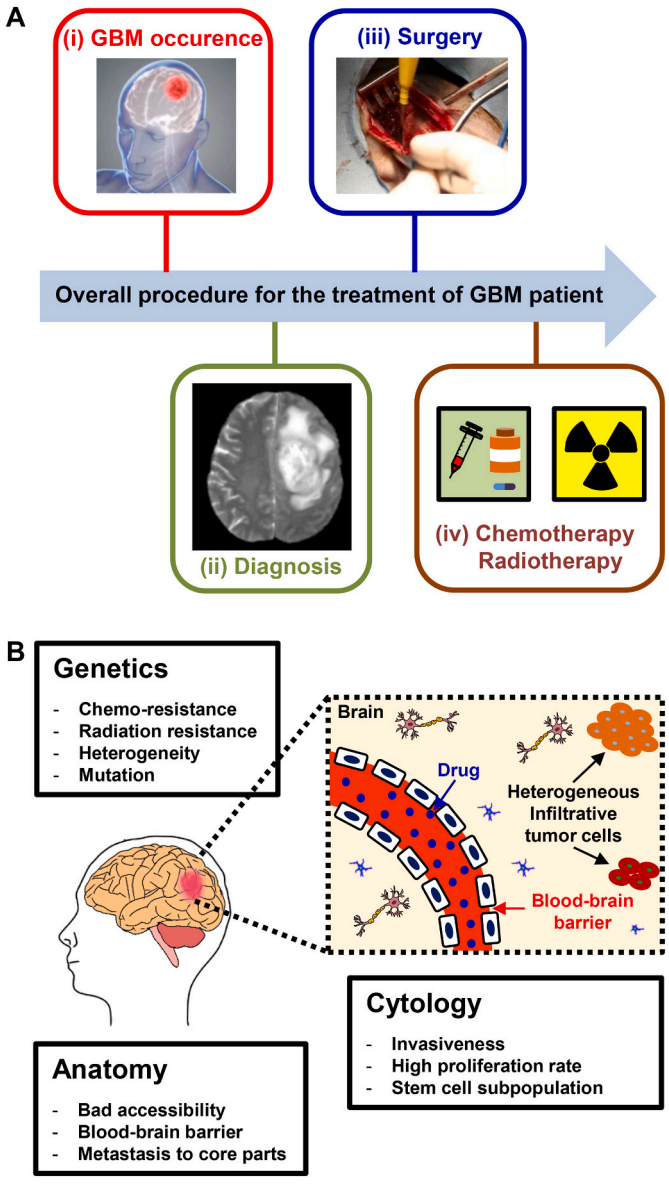

Fig. 1. Schematic illustration of the clinical strategies and challenges for the GBM treatment. A) Schematic illustration of the standard treatment and care for a newly diagnosed GBM patient. B) Schematic illustration of the clinical challenges for GBM treatment. A) GBM occurrence, adapted with permission from [199]. Diagnosis, adapted with permission from [200].

combinations of therapeutic methods for treating GBM available today have yet to overcome the high mortality and recurrence rate. A key hurdle in the treatment of GBM arises from the intrinsic nature of this malignant tumor. Many distinctive characteristics of GBM at the genetic, cytologic, and anatomical levels compromise the efficacy of therapy and therefore need to be overcome for the development of advanced medicines (Fig. 1B).

The fundamental problem that limits the efficacy of conventional therapeutics against GBM stems from the unique anatomy of the brain. As the central processing unit, the brain is the most crucial organ of the body; hence, many layers, including the skull, dura mater, and cerebrospinal fluid (CSF), protect the brain from the external environment [31–33]. These protective layers, however, make it difficult for chemotherapeutic drugs to enter the brain. In particular, the BBB significantly inhibits the permeation of drugs from the bloodstream into the brain, dramatically reducing the efficiency of systemic delivery of chemotherapeutic agents [34,35]. Although the integrity of BBB is

compromised by the infiltrative GBM, the blood-tumor barrier (BTB) is formed following the disrupted site of BBB. The BTB is relatively more permeable than BBB, but its heterogeneous permeability and perfusion still limit the absolute efficiency of the drug delivery [36]. Additionally, metastasis to the core parts of the brain, such as the brainstem and cerebellum, can rapidly exacerbate the prognosis [37].

At the cellular level, the high proliferation rate and the invasiveness of GBM cells contribute to the refractoriness of GBM. The hypoxic environment of GBM attributes largely to this malignancy, by upregulating the proteins that facilitate the invasion and adaptation capabilities of GBM cells [38,39]. In detail, GBM cells upregulate the expression of genes related to angiogenesis and ion channels for rapid proliferation and volume increase, respectively [40,41], which enhances their aggressiveness and invasive properties. In addition, the variants of GBM cells that are resistant or are developing resistance to the drugs continue to proliferate, impeding the chemotherapeutic eradication of GBM cells. Cancer stem-like cells with self-renewal properties are major hurdles with respect to drug resistance [42–44]. Driven by upregulated factors relating to hypoxia, these cells undergo genetic variation that eventually leads to resistance to chemotherapy. As the progenitors differentiate into specific types of cells to adapt to the external environment, cancer stem-like cells induce high rates of heterogeneity and mutation among proliferating GBM cells. Therefore, GBM exhibits multi-drug chemo-tolerance against many clinical treatments, and the difficulty in treating the disease rises dramatically if the therapeutic regimen fails to eradicate the tumor and residual cancer cells at once.

2.3. Novel clinical strategies for GBM treatment

2.3.1. Advanced clinical therapeutic strategies for GBM treatment

To overcome the clinical challenges in GBM treatment, novel therapeutic approaches have been investigated in preclinical studies, and several approaches have reached clinical trials. These approaches can be classified into symptomatic treatment and radical treatment [45]. Symptomatic treatment emphasizes the restoration of the original condition of patients by alleviating their symptoms, whereas radical treatment focuses on removing the underlying cause of the disease for complete cure. However, considering the poor prognosis and high mortality of GBM, most research efforts for GBM treatment have gravitated toward radical treatment.

Surgical resection, by far the most popular first-line therapy for GBM, is a representative example of radical therapy as it removes most of the tumor at once (*i.e.*, average reduction of 99%; Fig. 2A) [46,47]. However, invasive GBM cells infiltrate into the normal brain region contiguous to the tumor, obscure the boundary between the tumor and the normal tissue, and make it difficult to remove the tumor completely. As the complete removal of the tumor by resection is critical for improving the survival rate of patients, fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) was developed to visually distinguish the tumor cells from normal cells and enhance the efficiency of surgical removal (Fig. 2B) [48–50]. When 5-ALA is administered orally, it metabolizes to fluorescent protoporphyrin IX (PpIX), which accumulates preferentially in tumor cells because the tumor cells lack ferrochelatase, the enzyme that metabolizes PpIX to heme. As a result, a strong fluorescent signal of PpIX from the tumor cells guides a surgeon to remove them more efficiently, thus increasing the efficiency of tumor removal by surgical resection.

The progression and recurrence of GBM are monitored continuously after surgery, and patients receive follow-up adjuvant therapy including radiotherapy (Fig. 2C) [51] and oral chemotherapy (Fig. 2D) [52]. In radiotherapy, a radiation dose of 60–65 Gy to the target region is deemed optimal for treatment [53–55]. However, tumor cells in the hypoxic region of the brain tend to resist radiotherapy [56,57]. Besides, collateral damage to the normal brain region is unavoidable as the irradiation of neighboring normal tissues induces nonspecific cytotoxicity [58]. Hence, a moderate level of radiotherapy along with concomitant chemotherapy using TMZ (*i.e.*, an orally administrable anti-cancer agent) is preferred to improve the overall therapeutic efficiency and reduce the risk of side effects from radiotherapy. Studies have shown a nearly 20% increase in the median survival rate of patients who receive both radiotherapy and chemotherapy compared to the patients who receive radiotherapy alone [8,59]. Thus, chemo-radio cocktail therapy is considered as the standard treatment for recurrent GBM [12,13].

2.3.2. Novel clinical therapies for GBM treatment

Despite the advanced clinical therapeutic protocols, the combination of classical chemotherapy and radiotherapy fails to cure GBM completely, due to frequent recurrence and metastasis. Therefore, alternative chemotherapeutic approaches have been investigated to enhance therapeutic efficacy by utilizing biological agents or modifying the mode of administration. One example is the use of antibody for anti-angiogenic therapy. Bevacizumab, a monoclonal antibody that inhibits angiogenesis, has been administered intravenously for the treatment of GBM (Fig. 2E) [52]. Its anti-cancer effect is due to the inhibition of vascular endothelial growth factor A (VEGF-A), which is a key mediator of the hyperangiogenic behavior of GBM [60]. However, the delivery of bevacizumab to the target tumor is inefficient [3,61] as the antibody cannot penetrate the BBB. Therefore, the efficacy of systemic treatment with bevacizumab is reduced significantly because of which there is no improvement in the overall survival of GBM patients treated with bevacizumab [62]. The BBB similarly compromises the efficacy of symptomatic treatment for GBM, in which anticonvulsants (*e.g.*, phenytoin) and corticosteroids (*e.g.*, dexamethasone) used to alleviate the accompanying symptoms, such as brain edema and seizure, only show limited efficacy [63,64].

Therefore, immunotherapy was spotlighted since it promotes the patients' spontaneous antitumor immune system unhindered by the BBB. Diverse approaches, including monoclonal antibodies, cancer vaccines, immune system modulator, adoptive T-cell transfer, and immune checkpoint blockade (ICB), have been developed [65]. Among them, PD-1/PD-L1 ICB is considered as a relevant strategy because PD-L1 is highly expressed on glioblastoma cells. Early studies of combinational checkpoint blockade immunotherapy showed promising efficacy in the preclinical model [66]. However, follow-up clinical results indicated limited efficacy because GBM has a low immunogenic response. Thus, the optimization of therapeutic strategies that stimulate antitumor immune response was required. Additionally, ICB can trigger a nonspecific immune response which may incur lethal side effects. Therefore, it is essential to improve the delivery efficiency of ICB and combine the protocols with other therapeutic strategies for maximizing the therapeutic outcomes.

As another solution to overcome the obstacle of BBB penetration, a patch-type biodegradable polymeric wafer (Gliadel Wafer®, Arbor Pharmaceuticals, USA) for sustained release and local delivery of carmustine has been proposed (Fig. 2F) [67–69]. It is implanted directly into the intracranial cavity after surgical resection, and it releases the drug intracranially to enhance the therapeutic effect and prevent tumor recurrence. Direct diffusion of the drug from the Gliadel Wafer to the residual tumor provides the advantage of bypassing the BBB. In addition, the Gliadel Wafer is biodegradable, which minimizes any potential side effects associated with direct implantation in the brain (*e.g.*, seizure). Immunotherapy, another noteworthy solution to circumvent the BBB, also failed to show any improvement in the treatment efficacy at the clinical level [23].

Another clinically approved strategy for GBM treatment is the injection of stimuli-responsive materials and subsequent actuation by external stimuli. This strategy takes advantage of the stimuli-responsive materials being injected in a minimally invasive manner, and the external stimulus being applied externally, which is easy to counter the frequent recurrence of GBM. In addition, the minimally invasive fashion would allow repeated treatment with a small risk of inflammation.

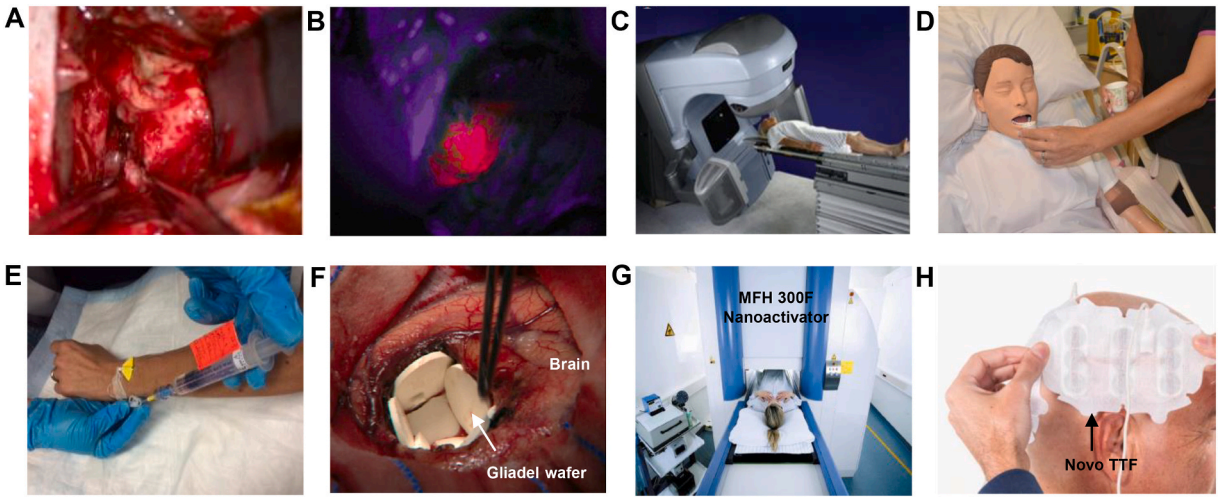

Fig. 2. Clinical therapeutic approaches for GBM treatment. A) Optical image of the surgical resection for the removal of GBM and B) fluorescent image of the GBM obtained after 5-ALA administration. Schematic illustration for the operation of C) radiotherapy, D) orally-administered chemotherapy, and E) intravenously-administered chemotherapy. F) Optical image of the Gliadel wafer at the brain cavity after surgical resection. G) Optical image of the operation of magnetic hyperthermia using an MFH 300F Nanoactivator. H) Optical image of the operation of electrotherapy using a NovoTTF. A) Adpated with permission from [46]. B) Adapted with permission from [48]. C) Adapted with permission from [51]. D), E) Adapted with permission from [52]. F) Adapted with permission from [67]. G) Adapted with permission from [70]. H) Adapted with permission from [83].

Various therapies combined with wirelessly controllable stimuli (*e.g.*, magnetic field, light, ultrasound) have been tested for the GBM treatment at the clinical phase (*e.g.*, magnetic hyperthermia [70–72], photodynamic therapy [73,74]) or at the preclinical phase (*e.g.*, photothermal therapy [75,76], and sonodynamic therapy [77,78]). One example is magnetic hyperthermia that utilizes an external alternating magnetic field (AMF) applicator (MFH 300F NanoActivator, MagForce Nanotechnologies AG, Berlin, Germany) for actuating injected magnetic nanoparticles (MNPs) to generate heat (Fig. 2G). The MNPs are locally injected into the tumor region of the brain, and a high-intensity (~18 kA/m) and low-frequency (100 kHz) magnetic field provided by the AMF applicator to the MNPs increases the local temperature higher than 45°C for thermoablation of the tumor [79]. CT and/or MRI can visualize the distribution of the MNPs in the brain, and the temperature profile at the target site can be estimated.

As an advancement from minimally invasive approaches, wireless electrotherapy has been introduced as a completely non-invasive therapy using only a wearable device to address the aversion of GBM patients towards intracranial invasion during clinical intervention [80]. A tumor-treating field (TTF) device (NOVO TTF-100L^{TM}, St. Helierl, USA) wrapped around the scalp (Fig. 2H) delivers a low-frequency, alternating electric field (100–300 kHz) to the tumor cells [81–83]. The electric energy specifically interferes with proliferating cells by separating tubulin dimers further during mitosis and induces mitotic cell death. As the proliferation rates of tumor cells are much higher than those of normal cells, the associated side effects are less severe than a mild irritation to the skin. The distinctive feature of TTF is its non-invasiveness, which has advantages of countering the metastasis and minimizing the side effects of treatment.

2.3.3. Limitations of currently available treatment strategies

Although these novel approaches have reached the clinical and/or preclinical stage, they still do not achieve a complete cure for GBM. Conventional therapeutic strategies for GBM have their drawbacks of limited therapeutic efficacy and accompanying side effects (Table 1). As briefly explained in the previous Section 2.3.2., many novel clinical strategies have been proposed to overcome the limitations of conventional therapies. However, the clinical outcomes of these novel strategies for GBM are also insufficient.

Polymeric implants are prone to inadvertent burst drug release or limited drug penetration into the brain tissue because the delivery mechanism of such implants—a simple physical mixture—relies solely on the natural diffusion of the drugs [84,85]. Furthermore, the rigid nature of the implants manifests a mechanical mismatch to the contour of the intracranial cavity [86]. The limited drug delivery from implants to the deep region of the brain makes it hard to cope with the metastasis of GBM.

The use of magnetic hyperthermia is prohibited in the case of patients with metallic implants such as pacemakers [87]. Additionally, the progression of the tumor in the brain cannot be detected by MRI due to signal distortion from the high concentration of MNPs [72,88]. Precise control of temperature is required to prevent excessive heating that may lead to damage to healthy tissues and to prevent insufficient heating that may lead to insufficient treatment of the tumor [89]. However, single-point temperature sensing is not accurate for a large tumor because of the heterogeneous temperature distribution in the tumor, and it is not possible to deploy multiple-point sensing with a high spatial resolution at the current technical level [90].

The therapeutic efficacy of electrotherapy is not fully proven in clinical trials, and burdens of high cost and the need for daily access to the medical facility also hinder successful treatment [82]. As the detailed treatment mechanism of TTF devices is not fully known, their feasibility is still questionable [91].

Although many clinical therapeutic approaches have been developed, their therapeutic efficacy remains limited. To overcome these limitations, recent studies have introduced promising solutions, most of them being novel drug delivery technologies. For example, several macroscopic strategies have been described for penetrating the BBB, while other microscopic strategies that modify molecules to improve treatment efficiency have been attempted. More recently, several advanced approaches have achieved nearly full recovery of GBM patients by integrating both macroscopic and microscopic strategies. In the following section, we will describe such drug delivery approaches for the treatment of GBM, classifying them as systemic drug delivery and local drug delivery.

3. Recent advances in drug delivery strategies for GBM treatment

Strategies to treat GBM continue to evolve, and such evolution is directed towards delivering drugs more efficiently and accurately to the

Table 1
Characteristics, advantages, and limitations of currently available treatment strategies for GBM.

Treatment		Characteristic/advantage	Limitation
Surgical resection		Mass removal of tumor	Hard to remove infiltrative tumor
Radiotherapy		Non-invasive administration	Radio-resistance
		High treatment efficiency	Side effects
Chemotherapy	Gold standard (TMZ)	No procedure requirement	Chemo-resistance
	Anti-angiogenic (Bevacizumab)	Patient compliance	Limited drug penetration in tumor tissue
	Symptomatic treatment (Phenytoin/dexamethasone)	Symptom mitigation	Little therapeutic efficacy
	Gliadel wafer (Carmustine)	Bypass of BBB	Mechanical mismatch
		Perisurgical administration	Short drug delivery period
		High drug concentrations at target site	Limited drug penetration
Stimuli-responsive therapy		Minimally-invasive administration	Limited use
		Bypass of BBB	Requirement for specialized instrument
		Programmable treatment	Low detectability of tumor progression
Electrotherapy		Non-invasive administration	Less clinical verification
		Tumor targetability	High cost
		Minimal side effect	Requirement for specialized instrument

target tumor site. Although surgical resection is still a reliable solution against GBM, it has limitations, as described in the previous sections. Furthermore, improving the treatment efficacy of other clinical methods is still a daunting goal.

However, treating GBM via drug delivery has distinct advantages. For instance, the administration of chemical and biological anticancer agents is less invasive than surgical resection. Studies on novel drug delivery systems (DDS) and their pharmacological assessment have helped overcome the shortcomings of chemotherapy. Therefore, many recent studies on GBM have focused on the development of efficient drug delivery strategies.

In designing DDS for GBM treatment, a major pathophysiological hurdle that compromises efficacy is the BBB, which impedes the penetration of anticancer agents into the bloodstream in the tumoral region. Thus, recent investigations have suggested diverse strategies for drug delivery to circumvent the BBB. Meanwhile, although drugs are delivered to the brain through the BBB, their efficacy is still thwarted by certain phenotypic hallmarks of GBM as mentioned in Section 2.2. Therefore, many viable solutions have been developed to overcome the resistance of GBM to the treatment.

Some recent studies on drug delivery against GBM have provided an all-in-one solution to the multiple problems of GBM through the combination of the design of novel materials, devices, and administration protocols. This section introduces recent advances in drug delivery technologies for the treatment of GBM (Table 2). In the first part, the latest studies on optimizing systemic drug administration for effective GBM treatment are introduced, followed by the discussion of local routes for drug administration including novel protocols and devices to facilitate drug delivery into the brain.

3.1. Systemic drug delivery to GBM

Systemic administration of anticancer agents is one of the more popular treatment options for GBM as it is easily accessible and less burdensome to patients. However, the efficacy of systemic drug delivery is limited due to the low efficiency of drug delivery, which largely stems from the aforementioned BBB conundrum. The pathophysiological BBB with malignant GBM is considered leaky and compromised, and early studies argued that systemic administration for GBM treatment would benefit from the EPR effect owing to the compromised integrity of the BBB. However, systemic treatment of GBM with passive targeting only saw limited efficacy, implying that the disruption of BBB caused by GBM is indeed a relative term. Physicochemical drawbacks of conventional chemotherapeutic drugs, such as poor biostability, low circulation, and nonspecificity, also compound the limitations of systemic administration in GBM [92,93].

To overcome such limitations, the latest studies of systemic drug delivery for GBM treatment feature diverse strategies. Nanomaterials offer a promising solution to such limitations as their physicochemical properties can be tuned with the help of surface ligands to facilitate their delivery across the BBB, target cancer cells more specifically, and interact with the tumor microenvironment (TME) for enhanced anticancer efficacy [94–96]. The efficiency of delivery can be enhanced further using nanomaterials because their small size facilitates penetration of the BBB to reach the tumor easily. In addition, a wide variety of targeting moieties can be incorporated into nano-formulated anticancer drugs to accelerate their penetration of the BBB and increase drug uptake by brain tumors. In addition to the targeting capability, advanced nano-formulations may also interact with endogenous or exogenous stimuli to control the delivery of drug payload on-demand [97].

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

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

The multifunctional building blocks of the systemic formulation can release the payload when exposed to the tumor-specific environment, or triggered by external stimuli. In the context of GBM treatment, however, stimuli-responsiveness of the systemic anticancer formulation is only contingent with high efficiency of targeted delivery because the physical barrier of the BBB is still a dominant bottleneck. Therefore, the latest studies of systemic DDS on translational GBM models tend to feature the stimuli-responsive materials accompanied by active targeting agents.

As the systemic DDS for GBM continues to evolve and diversify from PEG-based polymersomes to a comprehensive library of organic and inorganic materials, there is still a set of adverse host reactions which may compromise the efficiency of systemic formulation during circulation. Formation of protein corona is a representative phenomenon which may obstruct the targeting moiety, trigger further opsonization and related humoral immune response, and induce premature degradation and clearance of the injected formulation [98–100]. Coupled with robust physical barriers of the BBB, these pharmacokinetic considerations impose another obstacle to systemic formulations that even the putative stealth polymers such as PEG are not entirely free from this hindrance [101]. To overcome this limitation, a rising trend in using the components of cellular origin for systemic cargo sheds a light in the novel treatment strategy for GBM.

Alternatively, new strategies to penetrate the BBB using external stimuli could also promote the systemic delivery of anticancer agents. Ultrasound is by far the most frequently used modality to disrupt the BBB temporarily; other modalities to transmit energy for the transient opening of the BBB have also been suggested. Biochemical signaling molecules are also administered before the drug so that the BBB opens transiently during the circulation of chemotherapeutics. To date, various pathways to penetrate the BBB have been elucidated (Fig. 3A), which could serve as prospective methods for the systemic delivery of drugs to GBM [36].

3.1.1. Targeted drug delivery using designed nanoscale carriers

Nanomaterials, spotlighted as a promising conduit for drug delivery across the BBB, have been recently investigated for drug delivery in GBM treatment. An early study suggested that nanomaterials can take advantage of the enhanced permeability and retention (EPR) effect for extravasation into the brain [102]. However, the efficiency of EPR has been rendered somewhat dubious as recent studies demonstrate the poor efficiency of BBB penetration and EPR-mediated accumulation of nanomaterials in solid brain tumors [94]. Therefore, researchers have employed diverse targeting agents and designed materials for transcytosis across the BBB to target cancer cells during drug delivery for GBM treatment.

Some of the latest studies for drug delivery to GBM still embrace the EPR effect, but they have introduced follow-up measures to the EPR-mediated drug delivery so that drugs are accumulated at the targeted location. Ruan *et al.* prepared two groups of gold nanoparticles (AuNPs) with different functional ligands, namely, Ala-Ala-Asn-Cys-Lys (AuNPs-AK) and 2-cyano-6-aminobenzothiazole (AuNPs-CABT) [103]. After uptake into the GBM region via the EPR effect, the peptide sequence at the surface of AuNPs-AK is spliced by the enzyme legumain, which is upregulated in the brain tumor. As the 1,2-thioamino group on Cys is exposed due to the proteolysis by legumain, it undergoes a click cycloaddition with the cyano groups on AuNPs-CABT. The resultant AuNPs that aggregate with one another, namely AuNPs-A&C, are less likely to be exocytosed or extravasated out of the BBB (Fig. 3B). The click-reactive aggregation of AuNPs depends on legumain and a mildly acidic pH, which favors tumor-specific accumulation of the AuNPs. Furthermore, doxorubicin (DOX) was conjugated to a separate pH-sensitive linker on the AuNPs for tumor-microenvironment-dependent chemotherapy. Such preferential uptake and retention of the AuNP aggregates to enhance the efficiency of drug delivery to GBM have been confirmed both *in vitro* and *in vivo*.

In a more sophisticated approach than the EPR effect, active targeting elements have been tested, using a wide range of moieties with different motifs including peptides, saccharide derivatives, targets for transporter proteins, and antibodies [104–106]. Since a GBM-specific systemic administration requires targeting both the BBB and the tumor, designating the moieties for dual targeting capability is a key concern for drug delivery in neuro-oncology. Peptides are popular targeting agents in systemic drug delivery for GBM treatment because of their small size, reduced systemic toxicity, and high targetability to tumor cells [107]. Especially, novel peptides with simultaneous dual-targeting of the BBB and the tumor are featured in latest drug delivery for GBM treatment. Thus, recent investigations of targeted drug delivery against GBM adhere to the dual-targeting principle with different directions: targeting the BBB and the tumor by two different moieties; dual-targeting by single motif; and multiple targeting of heterogeneous composition in tumor cells by different ligands [108–111].

The latest report features the combination of brain tumor-targeting peptides and cell-membrane-targeting peptides (CPPs) for a synergistic effect [112,113]. Zhu *et al.* designed tandem nanomicelles functionalized with angiopep-2 (ANG) and TAT peptide (Fig. 3C) [114]; ANG is the tumor-targeting agent as it specifically targets lipoprotein receptor-related protein-1 (LRP1) upregulated in glioma cells, whereas TAT is a putative CPP to facilitate the transcytosis across the BBB. These moieties were dual-functionalized at the copolymer backbone of dithiolane trimethylene carbonate (DTC) and PEGylated for enhanced circulation. The micelles with an optimized conjugation ratio of ANG and TAT demonstrated a markedly increased uptake by glioma cells *in vitro*. Increased permeation through the BBB and subsequent penetration/accumulation at the tumor have also been confirmed in an orthotopic tumor model in mice. The infiltrative property of micelles into the tumor also promoted the anticancer efficacy of docetaxel (DTX), which was incorporated into the micelles (Fig. 3D).

In the study by Wu *et al.,* the formulation demonstrates the synergy between active BBB-targeting ligands and stimuli-responsive capability to distinctive microenvironments within the tumor. Sequential targeting in crosslinking (STICK) nanoparticles have the building blocks which feature both receptor-mediated targeting capability and responsiveness to the endogenous stimulus in TME (Fig. 3E) The PEG backbones of STICK nanoparticles were functionalized with excess maltobionic acid (MA), and the 4-carboxyphenylboronic acid (CBA). MA is the primary brain-targeting moiety for the nanoparticles to cross the BBB via GLUT1-mediated transcytosis, and CBA is the secondary tumor-targeting moiety against the overexpressed sialic acid on glioma cells. The presence of MA and CBA also gives the STICK nanoparticles with responsiveness to endogenously low pH in intratumoral microenvironment. At neutral pH, the CBA terminals formed a covalent boronate-ester bond with the MA, giving the STICK nanoparticles the additional integrity and stability during circulation. After MA-mediated extravasation across the BBB, the covalent bond between MA and CBA is broken due to the low pH of the intratumoral microenvironment. The penetration and the increased tumor penetration of STICK nanoparticles have been experimentally verified and was found to synergistically increase the treatment efficacy of anticancer agents formulated with these STICK nanoparticles (Fig. 3F).

In a recent study by Zheng *et al.*, the putative dual-targeting agent of angiopep-2 for both the BBB and the GBM tumor is employed is incorporated into tumor ROS-responsive polymeric cargo to maximize the efficiency of systemic delivery for their siRNA-based cancer therapy [115]. In this study, the PEG backbones copolymerized with RNA-binding guanidinium - poly(ethylene glycol)-*block*-poly[(*N*-(3-methacrylamidopropyl) guanidinium-*co*-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acrylate)] (PEG-*b*-P(Gu/Hb)); Angiopep-2-poly (ethylene glycol)-*block*-poly(*N*-(3-methacrylamidopropyl) guanidinium) (Ang-PEG-*b*-PGu) – are self-assembled with siRNA to yield 3I-NM@siRNA nanoformulation. In this system, angiopep-2 (Ang), whose cognate low-density lipoprotein receptor-related protein is upregulated

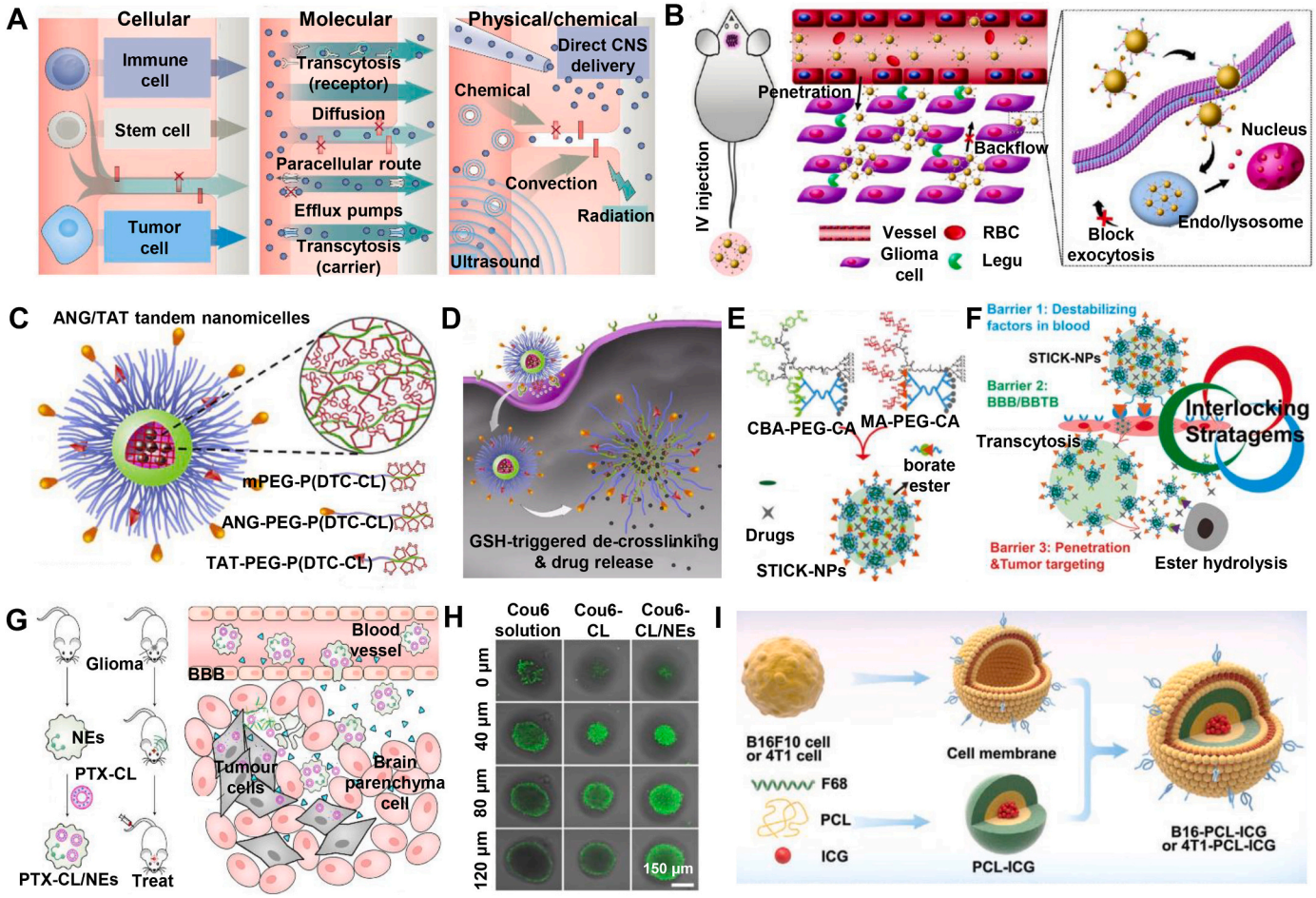

Fig. 3. Systemic drug delivery using nano-/cell-carriers. A) Schematic illustration of the representative cellular, molecular, and physicochemical mechanisms of drug delivery across BBB. B) Schematic illustration of the legumain-mediated aggregation of gold nanoparticles as an ensemble nanoplatform (AuNPs-A&C) and increased accumulation at brain tumor by the inhibition of exocytosis. C) Self-assembly of tandem nanomicelles with tumor-targeting ANG and cell-penetrating TAT. D) Decrosslinking and drug release of tandem nanomicelles triggered by GSH. E) Synthesis of STICK NPs and F) the mechanism of sequential activation, transcytosis across BBB, and tumor targeting. G) Schematic illustration of neutrophils carrying docetaxel-loaded liposomes (PTX-CL/NEs), the postoperative protocol, and the mechanism of cell-mediated delivery of PTX-CL/NEs. H) Penetration profile of Cou6 dye into 3-dimensional G422 tumor spheroids with different carrier formulations. I) Schematic illustration of the fabrication process for cell membrane-coated biomimetic nanocarriers (B16-PCL-ICG or 4T1-PCL-ICG). A) Adpated with permission from [36]. B) Adapted with permission from [103]. C), D) Adapted with permission from [114]. E), F) Adapted with permission from [201]. G), H) Adapted with permission from [124]. I) Adapted with permission from [125].

at both the BBB and the glioma cells, serves as the targeting agent. At physiological environment, the siRNA cargo is stabilized with hydrogen bond and electrostatic force between guanidinium and siRNA, and hydrophobic interactions from phenylboronic esters. However, upon the Ang-mediated delivery across the BBB and to the tumor, the high level of intratumoral ROS triggers the disintegration of ROS-sensitive phenylboronic ester groups within the 3I-NM@siRNA, and the subsequent dissociation of the cargo releases the anticancer siRNA at the target site. The dual-targeting capability of angiopep-2 is validated with enhanced uptake by U87MG glioma cells and higher penetration across the model BBB *in vitro*, and enhanced intratumoral localization and therapeutic efficacy of orthotopic U87MG-Luc glioma models with 3I-NM@siRNA *in vivo*. ROS-mediated dissociation of 3I-NM@siRNA was demonstrated *in vitro*. Although the extent of ROS-responsiveness to therapeutic efficacy *in vivo* was not shown with extensive control groups, this study serves as another representative proof-of-concept study in which specific-targeting strategy may be further enhanced with stimuli-responsiveness.

3.1.2. Targeted delivery using cellular carriers

Cell-mediated delivery of anticancer drugs and nanomaterials represent the latest progress of actively targeted DDS for GBM. Drugs are spontaneously taken up by cells or encapsulated by membranes, and they are extravasated and targeted easily to the brain tumor. While classical tumor targeting involves the integration of specific antibodies or proteins with limited diversity, cell-mediated targeting exploits collective interactions of the BBB or the tumor with various surface proteins on the outer membranes [116,117]. Furthermore, the biomimetic nature of cell-derived cargo gives the novel anticancer formulation with stealth effect, particularly upon its exposure to the systemic circulation [118]. Given that a majority of synthetic formulations for systemic DDS are susceptible to host reactions (*e.g.*, protein corona formation, and premature clearance or degradation), cellular cargos may evade such adverse reactions. With the anticipated advantages, various cell types and components of cellular origin have been employed in the latest studies of novel DDS for cancer therapy: leukocytes [119], erythrocytes [120], platelets [121], stem cells [122], and extracellular vesicles [123]. In the context of GBM treatment, the following studies are representative cases in which cell-mediated delivery of anticancer drugs demonstrates a translational potential in GBM models.

Xue *et al.* designed cell-mediated delivery of anticancer drugs

applicable as a postoperative treatment against recurrent malignant glioma (Fig. 3G) [124]. Inspired by the inherent ability of neutrophils to traverse BBB, they internalized the paclitaxel-loaded cationic liposomes (PTX-CL) within isolated neutrophils. The neutrophils bearing the docetaxel liposomes (PTX-CL/NEs) chemotax to the inflammatory milieu in the postsurgical region of the brain. After extravasation, the PTX-CL/NEs respond to inflammatory factors, release their DTX payload, and form neutrophil extracellular traps. Besides the sustained stability of the PTX-CL within the carrier cells, the significance of this novel drug delivery system lies in the Trojan-horse anticancer drug delivery as a synergistic element to the endogenous response of immune cells to the recurrent tumor. In the same study, neutrophils effectively carried coumarin-6 (Cou6)-loaded liposomes (Cou6-CL/NEs) into the deep tumor tissue, whereas free Cou6 solution or the liposome alone (Cou6-CL) remained at the periphery of the tumor (Fig. 3H). The efficacy of this cell-mediated drug delivery was proved by the slower recurrence of tumor growth and the significant improvement in survival rate *in vivo*.

Wang *et al.* presented an ingenious strategy of applying the properties of metastatic cancer cells to penetration of the BBB [125]. As metastatic cells can penetrate the BBB via concerted interactions between their surface proteins and the receptors of vascular endothelial cells, they hypothesized that nanomaterials masked with metastatic cell membranes would also cross the BBB easily. Membranes extracted from metastatic B16F10 and 4T1 cell lines were used to encapsulate polycaprolactone (PCL) nanoparticles loaded with indocyanine green (ICG) for the fabrication of biomimetic nanocarriers, B16-PCL-ICG and 4T1-PCL-ICG (Fig. 3I). B16-/4T1-PCL-ICG serve as both an imaging probe and a photothermal therapy (PTT) agent, and the BBB penetrability of these membrane-coated nanomaterials was validated *in vitro* and *in vivo*. These membrane-coated nanoparticles administered to orthotopic glioma-bearing mice emit fluorescent signals that are 11-fold higher than those of nanoparticles without a membrane coating.

3.1.3. Transient disruption of the BBB for enhanced drug delivery

An alternative strategy to penetrate the BBB for improving the efficiency of drug delivery to the brain tumor is to disrupt the integrity of the BBB temporarily. An external force can stimulate the vascular endothelial cells of BBB and loosen the junctions between the energetically stimulated cells to allow the infiltration of therapeutic agents into the brain. Biologic anticancer agents such as antibodies are often coupled with stimuli-induced BBB opening due to their inherent size, but nanomaterials can also synergize with the preconditioning of the BBB for their enhanced uptake within the tumoral region [126,127].

Ultrasound, widely applied in clinical settings, has proven its effectiveness to disrupt the BBB transiently. A combination of ultrasound-induced preconditioning of the BBB with drug delivery is a prospective candidate for next-generation drug delivery for GBM treatment. Papachristdoulou *et al.* demonstrated that the application of ultrasound concomitant with the systemic delivery of chemotherapeutic nanoliposomes leads to enhanced chemotherapeutic efficacy [128]. Low-intensity focused ultrasound (LIFU) induces reversible disruption of cellular tight junctions in the BBB. Consequently, intravenously administered liposomes loaded with TMZ could be delivered through the disrupted sites of the BBB and accumulated throughout the brain glioma region (Fig. 4A). LIFU-induced opening of the BBB for efficient drug delivery was confirmed in a dual-modal fashion by the high signal intensities of the MR contrast (Gd-DOTA) and the infrared dye (DiD) in the brain (Fig. 4B). LIFU-mediated delivery of TMZ also successfully reduced tumoral O^6-methylguanine-DNA methyltransferase (MGMT) levels, confirming the efficacy of the ultrasound-assisted systemic drug delivery.

The enhanced uptake of molecules facilitated by ultrasound-induced BBB disruption was further confirmed by Alli *et al* [129]. In their study, MRI was employed to pinpoint the tumoral region in the brain where ultrasound was to be applied. MR-guided focused ultrasound (MRgFUS), along with the concomitant injection of microbubbles (μB), induced a marked increase in the accumulation of Evans Blue dye in the brain (Fig. 4C). A similar enhancement in intracerebral accumulation of DOX has also been demonstrated; however, the increase in cumulative DOX in the brain with the MRgFUS and μB treatment (431.5 ng/g) compared to the control groups (7.6 ng/g) did not have any drastic effect on anticancer efficacy. Nevertheless, the feasibility of ultrasound-mediated BBB opening was demonstrated along with enhanced drug delivery. Similarly, Drean *et al.* investigated the effect of low-intensity pulsed ultrasound (LIPU) on the enhancement of intracerebral delivery of the anticancer drug, carboplatin [130]. Ultrasound-mediated uptake of carboplatin induced a 4.2-fold increase in the accumulation of carboplatin in the ipsilateral region of a brain tumor *in vivo*.

The osmotic opening of the BBB using mannitol, a hyperosmolar agent, increases the penetration efficiency of antibodies across the BBB. Lesniak *et al.* demonstrated that preconditioning of glioma-bearing mice with administration of 25% mannitol opens the BBB transiently and promotes the intraarterial delivery of therapeutic antibodies against GBM [131]. Bevacizumab, a representative anti-GBM antibody, was conjugated with deferoxamine, which contained the PET agent ^{89}Zr for further tracking (Fig. 4D). Compared with the intraarterial delivery without hyperosmolar preconditioning, the proposed drug delivery method resulted in a markedly higher accumulation of PET-tagged antibodies in the ipsilateral hemisphere of the brain. The efficiency of intravenous delivery, which is a more common systemic administration method than intraarterial delivery, was also improved by the hyperosmolar opening of the BBB. However, the differences in the efficiencies of antibody delivery via the intraarterial and intravenous routes warrant further study.

Administering biochemical signaling molecules to stimulate the BBB and open the barrier transiently is another viable method to facilitate drug delivery for GBM treatment. Wen *et al.* utilized SC79, a small-molecule protein kinase B agonist, to stimulate the BBB in a glioma model, open the barrier, and facilitate the delivery of therapeutic nanoparticles to the glioma [132]. The therapeutic nanoparticles, loaded with paclitaxel, were functionalized with ANG for additional LRP1-mediated transcytosis and intrapolymer disulfide bonds for subsequent release of drugs responding to the TME (Fig. 4E). The BBB, disrupted by the preconditioning with SC79, allowed a markedly increased uptake of therapeutic nanoparticles into the brain, and this increased drug delivery via BBB opening could be further visualized with the co-loaded infrared dye DiR (Fig. 4F).

However, the clinical application of this strategy can be limited for some reasons. First, specialized equipment (*e.g.*, focused ultrasound) is required to provide sufficient external stimulation at the GBM site [133]. Second, transient BBB opening strategy using internal stimuli-responsive materials usually requires preemptive invasive administration of chemicals. In addition, side effects related to the non-specific release of the drug in the brain can also occur [134]. Therefore, recent studies have been focused on securing the safety of the technique and improving delivery efficacy.

3.2. Localized drug delivery to GBM

Despite the use of advanced technologies to deliver drugs across the BBB, systemic drug delivery methods need further improvement. Along the long delivery route between the site of administration and the target region, drugs may be cleared out of the body or taken up by other organs and tissues nonspecifically [92,93]. Furthermore, such systemic drug delivery also involves the risk of systemic toxicity, especially in organs with active blood circulation, such as heart, liver, and kidney [135,136].

To address these challenges associated with systemic administration of drugs, advanced materials and device technologies have been adopted to shorten the pathway of drugs and/or directly deliver the

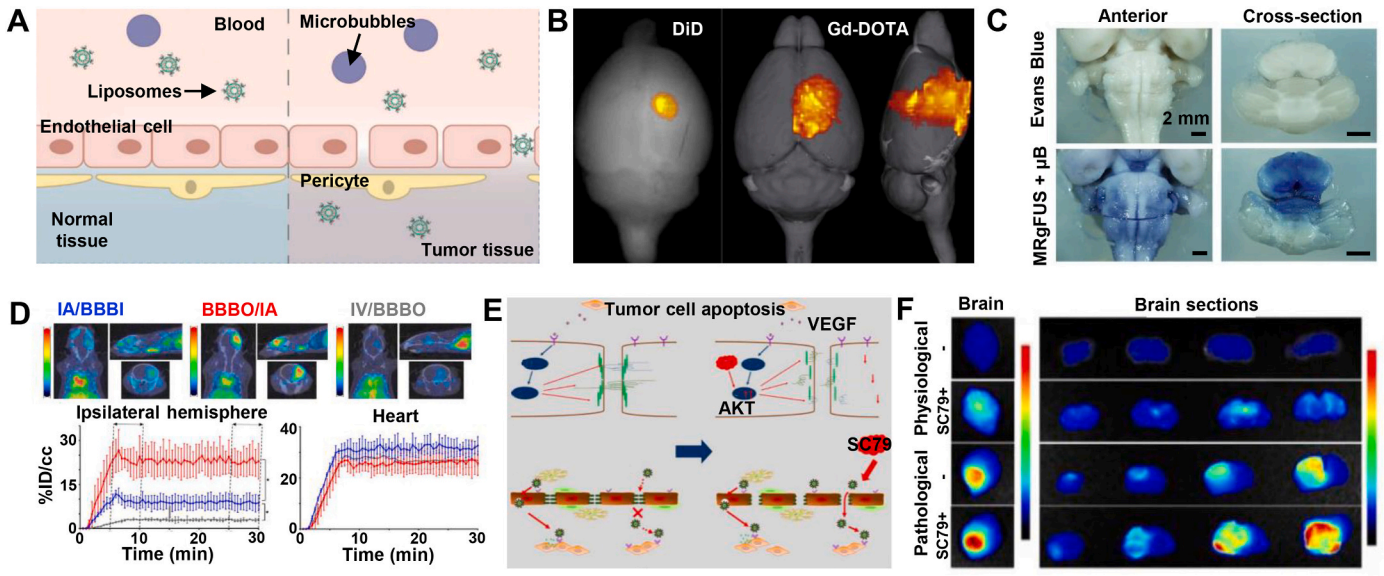

Fig. 4. Systemic drug delivery with transient disruption of BBB. A) Schematic illustration of transient BBB disruption via low-intensity pulsed focused ultrasound (LIFU) and influx of liposomes to tumor region. B) Fluorescence signal from DiD-loaded liposomes, and 3-dimensionally reconstructed T1-weighted MRI by Gd-DOTA-loaded liposomes accumulated at LIFU-treated region. C) Enhanced distribution of Evans Blue at the rodent brainsteming treated with concomitant MR guided focused ultrasound (MRgFUS) and microbubble (μB). D) Time-resolved profile of ^{89}Zr-bevacizumab deferoxamine accumulation dependent on BBB opening. E) Schematic illustration of SC79-mediated opening of pathological BBB and subsequent delivery of therapeutic nanoparticles. F) Enhanced fluorescence signal from DiR dye-loaded nanoparticles facilitated by SC79-mediated BBB opening. A), B) Adpated with permission from [128]. C) Adapted with permission from [129]. D) Adapted with permission from [131]. E), F) Adapted with permission from [132].

drugs to the brain. These include various types of localized drug delivery methods including intranasal drug delivery, solid implant-based drug delivery, intratumoral drug delivery, and convection-enhanced drug delivery. In this section, we focus on such local drug delivery methods for GBM treatment.

3.2.1. Intranasal drug delivery

Intranasal drug administration has been proposed as an effective and non-invasive method to deliver therapeutic molecules to the brain. Therapeutic agents are locally transported across the olfactory mucosa and connected tissues, thereby bypassing the BBB and minimizing systemic side effects (Fig. 5A) [96]. Besides, intranasal delivery possesses advantages such as simplicity of administration with fewer burdens on patients. This method does not require invasive surgical procedures and/or accessories such as syringe needles and catheters; hence, it can avoid the potential side effects of surgeries and procedures such as neurotoxicity, inflammation, and edema [137–139]. Furthermore, repetitive and programmed administration of drugs is easy with the nasal route, which is highly suitable for GBM with its high recurrence rate.

Recently, the intranasal delivery of nanoparticles to the brain has been spotlighted to address the problems associated with conventional intranasal drug administration methods such as limited penetration through the nasal mucosa, high mucociliary clearance, and enzymatic degradation during the transportation of drugs into the brain [140–142]. Various kinds of nanoparticles, including polymeric nanoparticles, inorganic nanoparticles, chitosan nanoparticles, and solid lipid nanoparticles, have been employed. As an example, Sousa *et al.* designed a nano-formulation of bevacizumab encapsulated with PLGA, which was administered intranasally to enhance the anti-angiogenic effects of bevacizumab [20]. These nanoparticles showed higher bioavailability, increased penetration depth, and extended retention while minimizing systemic toxicity compared to free bevacizumab. After 14 days of administration, the residence of bevacizumab in the brain could be confirmed only in the group treated with the bevacizumab-loaded nanoparticles. The increased retention was consistent with the significant decrease in *VEGF* gene expression *in vivo* (Fig. 5B).

Intranasal gene delivery using nanoparticles can be an attractive candidate for GBM treatment. Woensel *et al.* reported the delivery of chitosan nanoparticles loaded with small interfering RNAs (siRNAs) by targeting galectin-1 [143]. Such receptors and proteins are overexpressed in GBM and serve as crucial mediators for GBM progression as well as immune suppressors in the GBM microenvironment. Although the interference with siRNAs has been shown to downregulate *galectin-1* expression, achieving a critical concentration at the GBM site has not been demonstrated due to the lack of delivery technology. Woensel *et al.* synthesized anti-galectin-1 siRNA-loaded, chitosan-based, polymeric nanoparticles by harnessing the electrostatic interactions between the positively charged amine groups on the chitosan and the negatively charged phosphate groups on the siRNAs. The electrostatic attraction stabilizes the siRNA payload, and the encapsulation protects the siRNA cargo from degradation by ribonuclease. Upon intranasal administration, the spread of siRNAs in the tumor microenvironment was observed *in vivo* (Fig. 5C). The significant decrease of *galectin-1* expression in the TME was confirmed in a nanoparticle-treated, tumor-bearing mouse model (Fig. 5C, D).

Recently, Sukumar *et al.* integrated the theranostic multimodality with RNA delivery [144]. They synthesized core-shell type gold-iron oxide nanostars with β-cyclodextrin-chitosan hybrid polymer shells loaded with therapeutic microRNAs (miR-100 and antimiR-21). Then, PEG-T7 peptide was anchored on the surface of the nanostars via cyclodextrin-adamantane host-guest reactions for the active targeting of GBM cells. Overexpression of miR-100 can suppress cell proliferation and induce apoptosis in tumor cells, whereas miR-21 is a primary oncomiR that is overexpressed in the majority of GBM cells. Thus, the combined delivery of miR-100 and antimiR-21 synergized with TMZ therapy (Fig. 5E). The activation of the apoptotic signaling pathway in GBM cells was confirmed by TMZ therapy combined with the antimiR-21 and MiR-100 co-treatment (Fig. 5F). The nanostars could protect their payload from premature degradation in the plasma and improve the efficiency of delivery to the GBM. They also offered multimodal imaging capability to visualize the delivery, trafficking, and treatment effects of the nanostars by using Cy5-labelled miRNAs and by MRI. Upon intranasal administration, the efficient accumulation of Cy5-

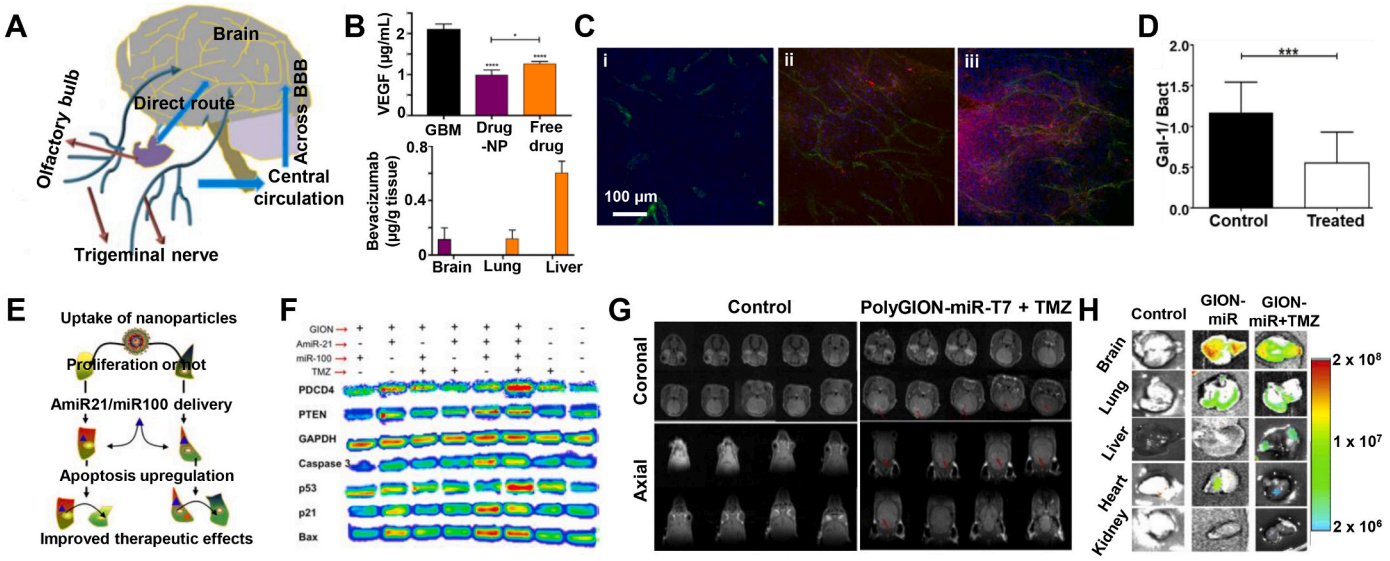

Fig. 5. Intranasal drug delivery. A) Schematic illustration of intranasal delivery. B) Quantitative analysis of the expression levels of VEGF in the brain (top) and bevacizumab in the brain, lung, and liver (bottom), after 2 weeks of treatment. C) Confocal images of the sectioned tumor areas obtained from (i) untreated, and anti-Gal-1 siRNA-loaded chitosan nanoparticle-treated mice after (ii) 4 and (iii) 8 h of intransal delievery (blue: BFP-GL261 tumors, red: vessels, and green: fluorescein-siRNA). D) Quantification of the expression level of Gal-1 in the tumor micro-environment of the treated mice. E) Schematic illustration of the therapeutic effects of gold-iron oxide nanostars with β-cyclodextrin-chitosan hybrid polymer shells co-loading therapeutic microRNAs (polyGION-miRNAs) for GBM treatment. F) Immunoblot of target protein expression for antimiR-21 and miR-100. G) *In vivo* MR images of mice treated with PolyGION-miRNAs and TMZ. H) *Ex vivo* fluorescence images of miRNA distribution in various organs of PolyGION-miRNAs treated mice. A) Adpated with permission from [96]. B) Adapted with permission from [20]. C), D) Adapted with permission from [143]. E)-H) Adapted with permission from [144].

miRNAs was detected in an orthotopic xenograft mouse brain model via fluorescence and MR imaging (Fig. 5G, H). When co-treated with nanostars and systemic TMZ, the mice demonstrated significant suppression of tumor growth and an increased survival rate compared to those treated with TMZ only or non-targeting nanostars only.

3.2.2. Solid implant-based drug delivery

Despite the advantages offered by intranasal administration, this method is still limited by the low volume of drugs that can be sprayed into the nasal cavity and the mucosal damage induced by frequent use of this method. Consequently, direct implantation of the drug delivery reservoir into the brain has been spotlighted, although there are potential side effects regarding this invasive approach to the brain. Solid implant-based delivery was conceived as a complementary follow-up to resection surgery that involves the incision of the skull/dura and leaves a surgical cavity in the brain (Fig. 6A) [145]. Hence, poor accessibility inside the brain does not matter, and the perisurgical implant can be installed in the cavity without additional medical procedures. Therefore, this approach has the advantage of high efficiency of drug delivery, while avoiding excessive surgical burden.

The representative example of a solid implant for intracranial drug delivery to GBM is the Gliadel Wafer. However, drawbacks (*e.g.*, limited penetration, rapid drug release, intracavity migration, drug resistance, and local side effects) of the wafer prevent it from being an effective option to treat GBM [6,84]. In terms of drugs, several groups have suggested switching from alkylating agents (*e.g.*, TMZ and carmustine) to nonspecific cytotoxic agents (*e.g.*, doxorubicin and paclitaxel) because local drug delivery can eliminate the high systemic toxicity of such drugs [146–148]. However, other challenges demand further innovations in the drug delivery platform, leading to the development of various novel implants.

For example, a polyester nanofiber composite, *i.e.*, poly lactic-co-glycolic acid-poly lactic acid-polycaprolactone, was suggested as an implantable polymeric drug reservoir that exhibits an extended drug delivery period (Fig. 6B) [149]. Drugs can be physically encapsulated by the three-dimensional network of nanofibers, leading to a sustained release profile. The extended duration of drug release can be modulated by the molecular weight, fiber diameter, and drug payload ratio (Fig. 6C). The target composition of the nanofiber-based reservoir for a specific duration of drug delivery can be predicted based on drug release profiles and the combinatorial compositions of the nanofibers. Fabricated by co-electrospinning of the nanofibers of a tailored composition, this system can provide a personalized implant with an optimized drug release profile, which is clinically important for accommodating the vast heterogeneity of GBM patients [150].

The mechanical mismatch between the rigid implant and the soft brain tissue can induce neurological side effects and preclude tight contact between them [151–154]. Hydrogels, a quasi-solid polymeric matrix that can carry drugs, have been considered as a promising alternative to solid implants due to their softness and biofriendly properties [155–157]. For example, a scaffold based on a polymer nanofibril hydrogel was proposed to effectively eliminate infiltrating tumor cells (Fig. 6D left) [158]. This scaffold was made of bacterial cellulose, whose structure resembles that of commercial cellulose-based hemostat (Surgicel), so that its gelatinous surface anchors cells on the scaffold to facilitate cell adhesion. Furthermore, the hydrogel scaffold can be combined with chemoattractants to specifically attract tumor cells, thus showing its potential for GBM treatment by targeting and trapping the infiltrating tumor cells (Fig. 6D right).

Although these examples represent progress in solid implant-based drug delivery, most of the challenges related to conventional solid implant-based therapy still exist. The application of electronics can be a promising solution [159–163]. For example, Lee *et al.* developed a novel implantable device that is composed of wireless electronics integrated with a drug-polymer reservoir [164]. The proposed device, a bioresorbable electronic patch (BEP), is highly optimized for solid implant-based drug delivery for the treatment of GBM (Fig. 6E). The flexible, soft, and sticky nature of the proposed device facilitate its seamless integration into the curved brain tissues without any mechanical mismatch. Chemical conjugation of drugs to the polymer reservoir and an additional polymer encapsulation layer on top of the BEP reduces premature drug release into the CSF and enables prolonged

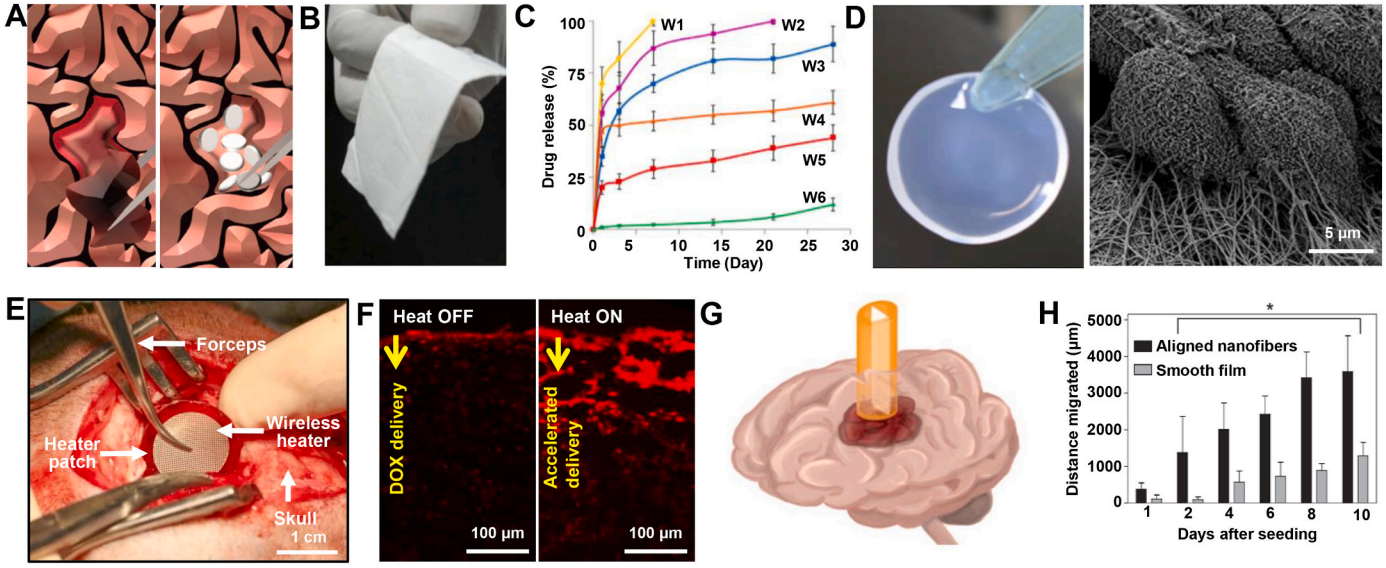

Fig. 6. Solid implant-based local drug delivery. A) Schematic illustration of the surgical resection (left) and implantation of the solid drug reservoir on the cavity (right). B) Optical image of a polyester nanofiber composite and C) its drug release behavior according to the composition. D) Optical (left) and scanning electron microscope (right) images of a polymer nanofibril hydrogel. E) Optical image of a bioresorbable electronic patch and F) the drug diffusion depth from the patch without (left) and with external magnetic actuation (right). G) Schematic illustration of a solid implant composed of a drug-incorporating hydrogel and aligned nanofibers, and H) the distance of tumor cell migration along the aligned nanofibers and on a smooth film. A) Adpated with permission from [145]. B), C) Adapted with permission from [149]. D) Adapted with permission from [158]. E), F) Adapted with permission from [164]. G), H) Adapted with permission from [165].

drug release to the tumor tissues. The wireless electronic device integrated on the patch generates heat in response to an external magnetic field, promoting drug release with an enhanced penetration depth (Fig. 6F). The combined features of BEP synergized to increase therapeutic efficiency, which was confirmed in mouse xenograft and canine tumor models *in vivo*.

Meanwhile, Jain *et al.* proposed a novel strategy against deeply located GBM cells using a solid implant, which was composed of aligned PCL nanofibers and a drug-conjugated hydrogel (Fig. 6G) [165]. The aligned PCL nanofibers in a PCL/polyurethane carrier conduit were directly implanted into the vicinity of GBM cells, and their opposite ends were connected to an extracortical, drug-incorporating hydrogel sink. Compared to the smooth PCL film, the aligned structure of the PCL nanofibers provided a pre-specified escape route for the GBM cells, leading to controlled tumor relocation (Fig. 6H). The GBM cells migrated to the extracortical hydrogel and were induced to undergo apoptosis by cyclopamine, an antagonist to the sonic hedgehog pathway, that is overexpressed in brain tumors.

3.2.3. Direct intratumoral injection of drug-loaded vehicles

Intratumoral drug delivery in GBM treatment refers to the local administration of therapeutic molecules by direct injection into the tumor site (Fig. 7A) [166]. This method has gained scientific and clinical attention because it possesses superior advantages such as high drug concentration at the site of action and minimized toxicity and side effects by reducing the drug exposure of normal cells. However, the clinical results of this method have been limited due to the invasiveness of the administration method which can cause various associated side effects such as infections, bleeding, and neural damage. Additionally, the drug does not diffuse much from the target site in GBM because its penetration depends only on the concentration gradient of the drug. Therefore, increase in penetration depth, decreased damage, and better biocompatibility of materials should be achieved for better results [167–169].

To increase the amounts and prolong the half-life of drugs within the brain, several nanomaterials have been employed as intratumoral formulations for GBM treatment. For example, Nance *et al.* developed brain-penetrating nanoparticles loaded with paclitaxel to treat GBM by intratumoral injection (Fig. 7B) [170]. The 70-nm-sized nanoparticles with dense PEG coating exhibited 100-fold faster diffusion rates within an *ex vivo* glioma tissue compared to similarly sized nanoparticles without PEG coating (Fig. 7C). After intratumoral injection, the PEG-coated, paclitaxel-loaded nanoparticles (PTX-PLGA-PEG) significantly inhibited tumor growth compared to uncoated paclitaxel-loaded nanoparticles (PTX/PLGA) and bare paclitaxel *in vivo*. These results demonstrate that PEG-coated nanoparticles could improve the drug distribution within GBM tissue and thus enhance therapeutic efficacy (Fig. 7D).

An injectable hydrogel is another prospective candidate for intratumoral delivery. Drugs incorporated in injectable hydrogels can be injected into the brain via a needle and gelated for sustained release near the injection site. Recently, several studies have reported the use of injectable lipid nanocapsules, such as the hydrogel loaded with 4-(*N*)-lauroyl-Gemcitabine ($GemC_{12}$) by Bastiancich *et al.* $GemC_{12}$ was synthesized by encapsulating modified gemcitabine in lipid nanocapsules; the hydrogel formed spontaneously depending on the concentration of the $GemC_{12}$-loaded lipid nanocapsules (Fig. 7E) [171]. This hydrogel did not require any gelling agent or external stimuli and demonstrated sustained release of drug for a month *in vitro*. These advantages were verified using various *in vivo* GBM models, including a subcutaneous human GBM model and an orthotopic xenograft mouse model (Fig. 7F) [172]. The results show the promising therapeutic potential of lipid nanocapsules loaded with $GemC_{12}$ for tumor removal and prevention of recurrence [173].

Meanwhile, Chao *et al.* investigated chemoimmunotherapy with reduced systemic toxicity and enhanced therapeutic efficacy by developing a hydrogel composite with the property of *in situ* gelation [174]. The formulation consisted of the chemotherapeutic drug, immune adjuvant (R837), and alginate, each of which was added for immunogenic cancer cell death, immune response boosting, and as a backbone polymer of the hydrogel for *in situ* gelation, respectively. After intratumoral injection, the alginate readily formed a hydrogel in the presence of calcium ions within the tumor tissue. Hence, chemo- and immuno- agents can be physically encapsulated in the hydrogel network, which serves as a reservoir for their sustained release. This reservoir can be further applied in versatile therapeutic approaches by

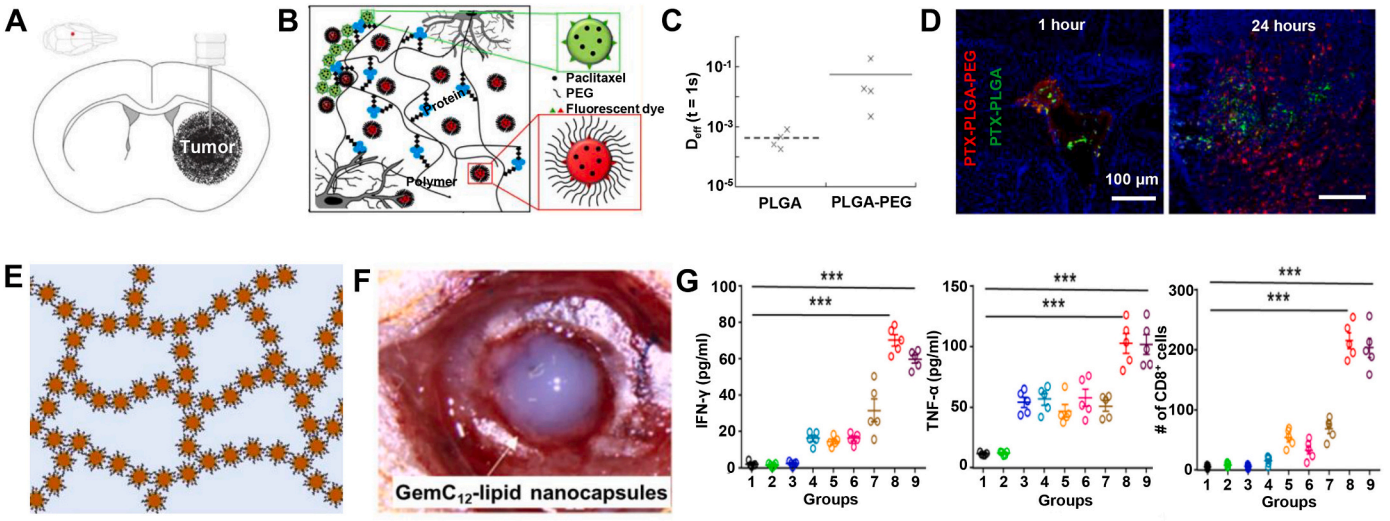

Fig. 7. Direct intratumoral injection for drug delivery. A) Schematic illustration of intratumoral delivery. B) Schematic illustration of brain-penetrating nanoparticles in GBM. C) Effect of PEG coating of nanoparticles on the diffusivity at 1 second. D) Distribution of PTX/PLGA nanoparticles (green) and PTX-PLGA-PEG (red) in intracranial 9L gliosarcomas at 1 and 24 h after intratumoral injection to the tumor core. E) Schematic illustration of $GemC_{12}$- lipid nanocapsule hydrogel. F) Optical image of an injected $GemC_{12}$-lipid nanocapsule hydrogel at the resected tumor site. G) Quantitative analysis of IFN-γ (left) and TNF-α (middle) in mouse sera obtained 5 days after the treatment. Number of $CD8^+$ cells in the tumor slices of the brains (right). (Groups 1: blank, 2: TMZ, 3: R837/αPDL1/alginate (it), 4: Dox/alginate, 5: Dox/R837/αPDL1, 6: Dox/R837/alginate, 7: Dox/αPDL1/alginate, 8: Dox/R837/αPDL1/alginate, 9: Dox/R837/alginate (it) and αPDL1 (iv); it: intratumoral injection, iv: intravenous injection). A) Adapted with permission from [166]. B)-D) Adapted with permission from [170]. E) Adapted with permission from [171]. F), G) Adapted with permission from [172].

including additional elements for immune checkpoint blockade. The local delivery of chemo-drug and immune adjuvant trigger tumor-specific immune responses, which could be augmented by immune checkpoint blockade to enhance the systemic immune responses for removing local tumor and metastases and preventing tumor recurrence. These researchers demonstrated that the proposed cocktail therapy showed an increased survival rate with strong antitumor immune responses in an orthotopic brain tumor model *in vivo*. Furthermore, the potent immune memory effect was verified by the inhibition of the growth of secondarily injected glioma cells *in vivo* (Fig. 7G).

3.2.4. *Convection-enhanced delivery of liquid-state drugs*

Convection-enhanced delivery (CED) is another local therapeutic approach that has been extensively explored to enhance intracerebral drug diffusion (Fig. 8A) [175]. CED utilizes a microcatheter to deliver a drug and a motor-driven pump to generate an external pressure gradient for inducing fluid convection in the brain [175–177]. Therefore, compared to the conventional direct injection, deeper penetration of drugs can be achieved at the target tissue. Additionally, CED is independent of the molecular weight of the therapeutic agent, and the diffusion depends primarily on the pressure gradient. Therefore, various drugs including proteins, antibodies, nucleic acids, and chemical toxins can be easily delivered via CED. The pressure gradient also helps to avoid the backflow of the drug during delivery.

Several clinical trials have reported that CED is safe and feasible, but fails to improve the survival rate significantly. For example, Kunwar *et al.* compared the CED of cintredekin besudotox with Gliadel Wafers for the treatment of recurrent GBM [178]. However, no significant difference was found in the survival rates, which may be due to technical factors such as catheter placement, improper flow rate, and the pathological condition. However, more importantly, the low stability of the drug in the brain and the low efficiency of delivery toward the GBM site should be addressed for better therapeutic efficacy.

Encapsulation of drugs in nano-sized carriers can be a viable solution, which can increase the efficiency of delivery by the programmed release of the payload at the target site while minimizing premature release or side effects during CED [179–181]. Zhang *et al.* developed cisplatin-loaded brain-penetrating nanoparticles for administration by CED [182]. Although cisplatin is a potent antitumor agent, its systemic administration often causes severe nephrotoxicity and neurotoxicity. To reduce its systemic toxicity and enhance the efficiency of delivery, these researchers synthesized cisplatin-loaded nanoparticles with surface functionalization with a dense PEG corona for preventing their adhesion to the extracellular matrix. Owing to their small size and surface functionalization, these nanoparticles could penetrate deeper into the GBM tissue compared to those without the PEG corona (Fig. 8B). Such advantages of the nanoparticles created synergetic effects when combined with the advantages of CED injection; the nanoparticles could be delivered within the striatum with a higher distribution homogeneity and reduced leakage to the white matter tracts (Fig. 8C). These cisplatin-loaded nanoparticles administered via CED injection significantly increased the survival rate in a GBM rat brain tumor model.

Stimuli-responsive theranostic nanoparticles could also be delivered via CED. Zhang *et al.* developed magnetic nanoparticles coated with a redox-responsive and biocompatible chitosan-PEG copolymer to deliver O^6-benzylguanine, an MGMT inhibitor [183]. O^6-benzylguanine is an effective drug for overcoming the resistance of GBM to TMZ, but its effect has been limited because of its short half-life in blood and low BBB permeability. Therefore, these researchers hypothesized that the encapsulation of the drug with a redox-responsive ligand and subsequent administration by CED could offer a more controlled and effective treatment with less systemic toxicity when combined with the oral administration of TMZ. The results showed that ROS-triggered degradation of the nanoparticles enabled an enhanced release of O^6-benzylguanine under intracellular conditions (*e.g.*, acetate buffer pH 5 and 100 mM glutathione) (Fig. 8D). *In vivo* investigation revealed that these nanoparticles, administered by CED, showed excellent distribution within the mouse brain, which was confirmed by T_2-weighted MRI (Fig. 8E). Additionally, a 3-fold increase in median survival rate relative to the untreated group was achieved in the concurrent treatment with TMZ.

Gene therapy via CED has also been studied as a potential therapeutic approach against GBM for its excellent therapeutic effect compared to conventional chemotherapy. The local delivery of a nano-sized carrier loaded with genetic biomaterials can remove tumor cells by inducing overexpression of a specific gene or by replacing a gene

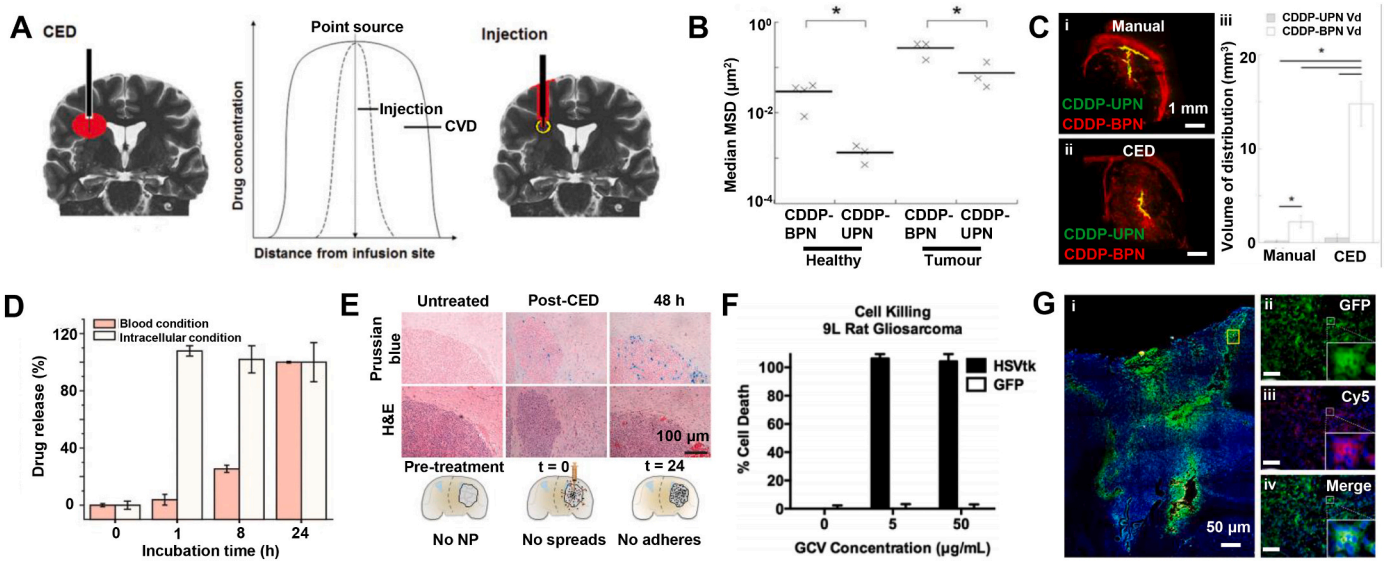

Fig. 8. Convection-enhanced drug delivery. A) Schematic illustration of convection-enhanced delivery compared to the bare injection. B) Mean squared displacement (MSD) of cisplatin-loaded brain penetrating nanoparticles (CDDP-BPN) and cisplatin-loaded un-PEGylated nanoparticles (CDDP-UPN) in healthy or tumor-bearing rat brain tissues *ex vivo*. C) *In vivo* confocal images of CDDP-UPN (green) and CDDP-BPN (red) administered by (i) manual injection or (ii) CED. (iii) Volume of distribution for CDDP-UPN and CDDP-BPN administered by manual injection or CED. D) Drug release profiles of redox-responsive nanoparticles in blood (pH 7.4 and no glutathione) and intracellular condition (pH 5.0 and 100 mM glutathione). E) (i) Prussian blue and (ii) H&E staining of the excised tumor tissues of an untreated or nanoparticle-treated animal performed immediately after CED or 48 h after CED. F) GCV-mediated glioma cell death (9L rat gliosarcoma) with pretreatment of plasmid DNAs encoding either HSVtk or GFP. G) Fluorescence images of (i) GFP + transfected cells in the tumor area and (ii)-(iv) colocalization of GFP and Cy5 which shows the successful penetration into the tumor and transfection of the cells (Cy5: red, GFP: green, DAPI: blue). A) Adapted with permission from [175]. B), C) Adapted with permission from [182]. D), E) Adapted with permission from [183]. F), G) Adapted with permission from [186].

that is missing or underexpressed [184,185]. Gene therapy can be more effective in combination with CED. Mangraviti *et al.* reported biodegradable polymeric nanoparticles for the delivery of herpes simplex virus type I thymidine kinase (HSVtk) DNA combined with the prodrug ganciclovir [186]. They designed a poly(β-aminoester)-based polymer to form DNA-incorporating nanoparticles to increase binding affinity and enhance intracellular toxicity (Fig. 8F) and distribution in the brain. Because of these favorable factors for intrabrain drug diffusion, excellent distribution of the nanoparticles throughout the GBM was demonstrated with a single CED infusion (Fig. 8G). Moreover, tumor-bearing rats treated with the nanoparticles via CED in combination with the systemic administration of ganciclovir showed increased survival rates.

4. Remaining challenges and future outlook

Although the aforementioned methods represent remarkable progress in GBM treatment, many issues still remain. For example, artificial polymersomes and inorganic materials are particularly susceptible to the host reactions regardless of their administration route, and measures to prolong the circulation and evade the protein corona must be taken into account. Although cell-mediated delivery is deemed as a viable solution to many problems, rigorous studies to corroborate whether the stealth carriers made of cellular components do evade the set of host reactions during circulation are required for the final verdict. Compared to live cells, membrane or exosomal extracts may not simulate the collective physicochemical interactions in the physiological environment.

In addition to the material issues related to carriers, there are many unpredictable variables to potentially aggravate the disease such as administration protocol, type of drug, and prognosis of large deviation. The future strategies, no matter how it's organized, must comprehensively consider such issues. Hence, more advanced strategies supported by a deeper understanding of GBM must be developed to increase therapeutic efficacy. Improving the efficiency of drug delivery and exploiting the macroscopic and microscopic hallmarks can generate viable solutions to overcome the formidable obstacles of GBM.

Novel strategies to treat GBM, however, still face many hurdles for their successful clinical translation. First, the development of animal GBM models that reflect the complexity of human GBM is a crucial requirement. In most studies, rodent GBM models are predominantly used and are generated by using diverse methods such as carcinogen exposure, xenograft, and genetic engineering. However, they suffer from either a lack of reproducibility or a phenotypic/genotypic deviation stemming from pathway differences during growth. *In vivo* GBM models in large mammals, which is considered more relevant to clinical applications owing to their similar brain size as that of humans, are rarely reported. Although a canine GBM model has been reported, it exhibits a significant difference in the microenvironment compared to humans. Thus, it is imperative to establish a preclinical animal model that is more relevant to human GBM.

In addition to establishing preclinical models, the combination of various therapies is necessary because no single treatment approach can counter the high rate of mutation and heterogeneity of GBM. There have been many approaches to combining various clinical therapies for GBM treatment, and some of them showed an enhanced therapeutic efficacy (*e.g.*, standard treatment for GBM). However, there is still room for further progress [187]. Therefore, there is an urgent need for the convergence of diverse fields (*e.g.*, soft electronics [188–191], nanocomposites [192–195] and hydrogels [196–198]) for GBM treatment. However, an in-depth understanding of each therapy is required prior to the implementation of the combination therapy to achieve as many potential positive/negative effects originating from such combinations as possible. Breakthroughs in each type of therapy must be incorporated for successful combinatorial therapy. In terms of chemotherapy, for example, progress in pharmacology should be taken into account to increase the therapeutic efficacy and decrease potential side effects [93]. Fundamental research in materials, devices, and their application methods should be also harnessed. Despite the many challenges listed above, these advances could take us a step further towards the complete

recovery of GBM patients and must be investigated further.

Declaration of Competing Interest

The authors declare no conflict of interests.

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