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Review article

Biomedical engineering approaches to enhance therapeutic delivery for malignant glioma

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ABSTRACT

We review the challenges of next-generation therapeutics for both systemic and localised delivery to brain tumours and discuss how recent engineering advances may be used to enhance brain penetration of systemic delivery therapies.

The unmet clinical need which drug delivery seeks to address is discussed with reference to the therapy obstacles that the intra-tumour heterogeneity of glioma present. The unmet chemistry and biomedical engineering challenge to develop controlled release therapeutics is appraised, with commentary on current success/failures in systemic carrier-mediated delivery, including receptor-targeted, cell-based, blood-brain-barrier disrupting and MRI-guided focused ultrasound.

Localised therapeutic delivery is a relatively under-studied research avenue and is discussed with reference to existing technologies in preclinical development. These include convection-enhanced delivery, alternative catheter delivery, and neuro-surgically applied delivery systems such as polymeric hydrogels and interstitial spray.

A myriad of nano-scale therapeutic delivery systems is emerging as potential future medicines for malignant brain tumours. Such biomedically-engineered systems will increasingly feature in next-generation neuro-oncological clinical trials to deliver repurposed and experimental therapeutics, aimed at achieving therapeutic drug concentrations in the brain, with associated mortality and morbidity benefits for patients.

1. Nanoparticles for cancer therapies

Synthetic and biomimetic drug-carriers which are of similar sizes to viruses have been extensively investigated for anti-cancer applications [1,2]. It has been hypothesised that materials in this size range (typically 60–180 nm) may enhance the concentrations of drugs in cancerous cells and tissues when compared to administration of the free drugs. This is because virus-sized particles distribute through the body in a different manner to small molecule drugs, and can be internalised by specific cells *via* pathways which are not accessible to conventional drug molecules [3–5]. In addition, particles in the 'nano-sized' range *i.e.* 10–1000 nm, can accumulate in areas of inflammation, or of poorly-formed vasculature, and their transport away from blood vessels and into tumours can be increased by physical disruption of endothelial barriers [6,7].

Many nanoparticles (NPs) have been reported in the controlled release literature, with increasing numbers of examples in the field of glioblastoma multiforme (GBM), a World Health Organisation-classified grade IV malignant astrocytoma with a dismal worldwide median survival of 14 months from diagnosis, despite multimodal treatment [8–20]. In most cases, these NPs have been designed to overcome non-cellular and cellular based mechanisms of resistance and increase selectivity of drugs towards cancer cells whilst reducing toxicity to healthy tissue [21]. NPs offer the prospect of encapsulating poorly soluble drugs, shielding therapeutic molecules from degradative processes and enhancing blood circulation and tissue distribution, thus increasing bio-distribution and improving the efficacy of drugs of low biological stability [22]. NPs also provide the opportunity to repurpose redundant chemotherapeutics that have previously been deemed too toxic or which have failed clinical development due to stability or solubility issues.

The continued development of biomedical NPs has the potential to

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provide many benefits compared to conventional medicines, including increased personalisation and patient stratification, leading to more effective drug delivery. New controlled release materials are now being designed which, through better control of structure, function, fit to the administration route and mode of delivery, offer real potential to improve patient welfare in comparison with current standard-of-care cancer therapy.

2. Systemic delivery of NPs for brain tumour therapy

Chemotherapeutics are predominantly administered intravenously (IV), often leading to an inefficient treatment modality as only 0.7% of the administered dose accumulates within cancerous cells [23], inducing many side effects as the drugs are distributed throughout the body, resulting in undesirable toxicities and a reduced quality of life for the patient.

2.1. NP penetration of the blood-brain-barrier

A problem when attempting to treat neuro-oncological diseases, such as GBM, is the presence of the blood-brain-barrier (BBB), which acts as a physical protective layer for the brain but thus also as a physical obstacle for systemic therapy to penetrate the brain. The BBB is composed of a layer of tightly packed endothelial cells and supporting cells such as pericytes, which acts as a "barrier" whereby only small (< 500 Da) lipophilic molecules can easily penetrate into the central nervous system (CNS) [24,25]. For chemotherapeutics which do not have these properties to reach a target site in the brain, and to ensure site-selective release of the drugs in their active form, appropriate drug formulations are needed.

Henceforth, through incorporating therapeutics into a NP carrier, the distribution of the drug and its accumulation in tissues can be altered. Lipophilic drugs, which otherwise would not be soluble enough for injection, can be incorporated in, or conjugated to, a hydrophilic carrier. Larger biomolecules such as proteins and nucleic acids can also be formulated with ligand-conjugated carriers in order to use active transporters at the BBB to enable delivery into the brain. Many studies have concluded that particular hydrophilic polymers, for example polyethylene glycol (PEG) [26], can be covalently attached to enhance solubility of small molecule drugs and to extend the circulation time of therapeutics in the body. Polymers such as PEG can, when suitably conjugated to a drug or a particle, also act as a steric and entropic barrier to minimise associative interactions of the drug, or particle surfaces, with plasma proteins or cell membranes. These PEGylation and related NP carrier strategies thus reduce the early clearance of therapeutics and can be combined with ligand-receptor targeting and external physical stimuli, such as focused ultrasound, to further enhance the transport of drugs into the brain.

Another exciting prospect of NPs is that they offer the potential of repurposing chemotherapeutics that have previously been discarded due to their inability to cross the BBB and/or resulting in dose-limiting systemic toxicities to healthy organs and tissues. One example is the NP incorporation of camptothecin, previously deemed ineffective in the treatment of GBM due to the rapid hydrolysation from its active form to a less active, more toxic form which undergoes rapid clearance once bound to plasma proteins [27]. The study showed that poly(lactide-*co*-glycolide) (PLGA) NPs containing camptothecin were able to cross the BBB in an orthotopic murine GBM model, leading to a significant increase in survival compared to controls [28]. In other settings, PLGA NPs stabilised with poloxamer 188 were loaded with doxorubicin and were shown to cross the BBB of rats at therapeutically effective concentrations [29] and paclitaxel loaded into PEGylated poly(trimethylene carbonate) NPs, was effectively used to treat xenograft tumour bearing mice, whereby median survival was significantly increased when compared to taxol [30].

Based on an increasing understanding of GBM intra-tumour heterogeneity, the capability to deliver multiple therapeutic moieties from single formulations is clinically relevant. Vincristine and temozolomide have been combined into solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs) to investigate dual drug delivery methods on the U87 GBM cell line. Significantly greater glioma inhibition was observed when using NLC formulations relative to SLNs [31]. Furthermore, paclitaxel and temozolomide were co-loaded in mPEG-PLGA NPs where the dual drug NPs showed greater inhibition against both U87 and C6 rat glioma cells relative to single drug NPs and significantly inhibited tumour growth in a subcutaneous U87 mouse xenograft model [32].

Despite human brains being relatively similar to those of other mammals and fish [33], there are of course inherent differences between a rodent brain and human brain, which must be considered when modelling BBB permeability using a rodent model. For example, astrocytic end feet are more common in human brains than in mouse brains [33], and rodent brains have neocortical astrocytes of decreased complexity than those of human brains [34], both factors which may result in differences in permeability ratios, for example, between rodent BBB models and human models.

In vitro cell-based models can be used to assess the potential of carriers to cross the BBB. One example of a well-known model utilises a monolayer of hCMEC/D3, a well-characterised brain microvascular endothelial cell line, which mimics the *in vivo* phenotype, as discussed in depth in a review by Weksler *et al* [35]. This model was used by Battaglia *et al*, which demonstrated that bevacizumab loaded SLNs enhanced the permeation of the drug across this BBB mimic, showing greater diffusion through the monolayer and into the collection chamber below, compared to free drug alone (80% *versus* 10%, respectively) [36]. SLNs were also loaded with doxorubicin and observed to increase drug permeation through primary human brain microvascular endothelial cells (HBMEC), which also retain some properties of the BBB *in vitro*. The doxorubicin released from the NPs was found to be efficacious against two primary human GBM cell lines, demonstrating the cytotoxic effects of encapsulated doxorubicin on clinically relevant cells [37]. Another study showed an increased permeability coefficient for propidium iodide and etoposide across the BBB through using HMBEC/U87 co-culture as an *in vitro* model [38]. It is however important to emphasise the limitations of such *in vitro* BBB models utilising cell monolayers, including restricted numbers of relevant cell types and lack of blood circulation and immune components.

2.2. Enhancing systemic NP delivery using engineered technologies

For GBM, there are currently no NP drug delivery methods in clinics due to the inherent pitfalls of their localisation to the target site. Therefore, to enhance delivery of NPs to the brain without relying solely on the intrinsic capability of NPs to cross the BBB and reach the infiltrative cells, engineered systems have been developed to enhance the penetration capability, such as those utilising cell based delivery and disrupting the BBB using focused ultrasound.

2.3. Cell-based drug delivery

Several preclinical studies have reported the use of cells to deliver drugs to brain tumours. Often, these cells are immune cells or stem cells [39–42] which have tumour-homing abilities due to responding to cytokines and chemokines released by tumour cells [43], and can bypass the BBB. One example of such is neutrophils that internalised doxorubicin-loaded magnetic mesoporous silica NPs (ND-MMSNs) which had a dual function: to deliver doxorubicin and to allow magnetic resonance imaging (MRI) tracking of the cells *in vivo*. The functionalised NPs were initially phagocytosed into the neutrophils without affecting their cellular viability or chemoattraction to sites of inflammation (*e.g.* to a resected brain tumour site). U87 and C6 glioma bearing balb/c mice treated with these ND-MMSNs had significant survival benefits over the

control group treated with saline only (47 *versus* 23 days, respectively for U87 bearing mice, with C6 bearing mice showing similar results) and also showed significant reduction in tumour growth when compared to free doxorubicin or non-neutrophil NPs [44]. Xue *et al* similarly utilised neutrophils to deliver paclitaxel-loaded liposomes to malignant gliomas, observing enhanced survival in G422-bearing mice with a 50% survival rate of 61 days compared with 29 days for paclitaxel alone and 38 days for paclitaxel-liposomes without neutrophils. Treatment with blank neutrophils and neutrophils with blank liposomes showed no improvement in survival [45]. Fig. 14e shows a schematic depicting cell-based drug delivery, as described above.

Wang *et al* modified monocytes, relying on the fact that the huge numbers of tumour-associated macrophages (TAM) are recruited to the tumour stroma from circulating monocytes. These monocytes internalised polyglycerol-coated doxorubicin NPs, which were surface modified with a cyclic RGD derivative in order to bind to the integrin receptor $a_v\beta_3$ that is overexpressed on multiple types of cancer cells, including those of GBM [46]. In orthotopic GBM bearing balb/c mice, significant fluorescence was observed in *ex vivo* GBM tissue when counterstaining the doxorubicin-NP monocytes with LysoTracker® Blue DND-22 followed by fluorescence-activated cell sorting, compared to doxorubicin or NPs alone, confirming localisation of monocytes to the tumour site. However, there was also substantial fluorescence observed in the liver and heart, highlighting one of the disadvantages of cell-based therapies, whereby there is potential for undesirable monocyte migration and localisation to systemic tissues [47], an issue also faced by systemically administered NPs.

Despite the enhanced survival of animals bearing gliomas when treated with cell-based drug delivery approaches, there are questions preventing cell therapies from reaching the clinic. These issues can arise dependent on whether the cells would be allogeneic or autologous to the patient, with the latter requiring extraction of the patient's own cells, thus requiring an invasive procedure. Additionally, it may not be possible to generate enough cells for each patient requiring treatment, an issue common in all areas of cell and tissue engineering, with time and cost being a significant barrier [48]. Some issues could be overcome by the generation of induced pluripotent stem cells (iPSCs) from a patient's own dermal fibroblasts [49,50]. These iPSCs can then be differentiated into many cell types such as neutrophils, as demonstrated by Brok-Volchanskaya *et al* [51] or monocytes, demonstrated by Cao *et al* [52], which could then be used to deliver NPs to the tumour site, yet this is still a costly and timely procedure. Currently there are no drug-encapsulating cell-based therapies for brain tumours in clinical trials; however, an Autologous Cytomegalovirus-Specific Cytotoxic T Cell based therapy adjuvant to oral temozolomide is in Phase II trials [ClinicalTrials.gov ID: NCT02661282], showing the potential for other cell-based therapies to reach clinical trials.

2.4. Barrier disrupting techniques

MRI-guided focused ultrasound (MRgFUS) has been developed to further enhance NP penetration into the brain by temporarily opening the tight junctions between endothelial cells in the BBB. Cavitation of the tight junctions occur when systemically injected microbubbles reach the area of a focused ultrasound wave, causing oscillation of the bubbles, forming cavities large enough for systemically injected NPs to penetrate, as shown in Fig. 2. This effect can last up to 6–8 h, resulting in a transient opening of the BBB [53]. Multiple types of NP have been tested using this method [54–57], including cisplatin-conjugated gold NPs, which were tested on NOD-SCID gamma mice bearing a U251 GBM xenograft. Following five injections, control animals injected with saline showed the largest tumour growth, followed by blank NPs and cisplatin alone, whereas mice treated with the cisplatin-conjugated NPs showed minimal to no tumour growth, with an associated increase in caspase-3 levels throughout the tumour tissue, indicative of apoptosis [58]. Another recent study used MRgFUS to open the BBB to deliver liposomal O^6-(4-bromothenyl)guanine (O^6BTG), which increased the sensitivity of GBM cells to temozolomide, the standard-of-care chemotherapy for patients with GBM. Temozolomide is only efficacious against GBM cells when the methylguanine-DNA-methyltransferase (MGMT) promoter is methylated and MGMT gene expression repressed. The unmethylated MGMT promoter induces MGMT gene expression, allowing the translated protein to repair single strand lesions in DNA caused by temozolomide, rendering the temozolomide ineffective. O^6BTG binds to MGMT, as it is analogous to a O^6-methylguanine lesion, thus labelling the MGMT for ubiquitin degradation and sensitising the cell to temozolomide-mediated DNA damage. The study found that using MRgFUS to open the BBB for the delivery of liposomal O^6BTG alongside temozolomide, significantly increased animal survival times and reduced glioma growth, compared to systemic liposomal O^6BTG and temozolomide alone, giving support to the use of MRgFUS to enhance NP delivery to the brain [17]. (See Fig. 1.)

A comprehensive review on the safety and efficacy of MRgFUS by Meng *et al* has recently been published [59], commenting on the data gathered in animal studies and multiple clinical trials. One trial, to assess the safety of BBB disruption in patients with GBM, has been completed [ClinicalTrials.gov ID: NCT03626896], with two more currently recruiting, one of which is trialling the safety of systemic temozolomide with MRgFUS [NCT03712293 and NCT03616860].

Despite the increasing numbers of clinical trials in this arena, several challenges remain to be addressed to achieve successful clinical translation. Dose-limiting toxicities remain a bottleneck for the choice of systemic agent, which may restrict therapeutic concentrations to accumulate in the brain, despite transient BBB disruption. In addition, whilst current FUS trials are assessing systemic delivery of a monotherapy, the molecular heterogeneity underlying malignant gliomas urgently warrants consideration of combination therapeutics predicated on multiple molecular targets. Finally, the likely requirement to administer therapeutics iteratively over several days/weeks, will mean that the high cost of MRI is a realistic obstacle; effective clinical translation may therefore necessitate the development of FUS-induced BBB disruption methodologies which do not depend on MRI.

2.5. Targeting of NPs to GBM following systemic administration

Several small molecule ligands, peptides and antibodies have been conjugated to NPs and drugs to target GBM, as depicted in Fig. 3. For example, monoclonal antibodies have been used to exploit the overexpression of vascular endothelial growth factor (VEGF) and its receptor type II (VEGFR2) in core tumour cells and migrated glioma cells [60–62]. Other studies have targeted the epidermal growth factor receptor (EGFR), which is overexpressed in many types of tumours including GBM [63], through conjugating peptides [64] or antibodies [65,66] to NP surfaces. A study conducted by Nilewski *et al* synthesised PEGylated hydrophilic carbon clusters (PEG-HCCs), whereby the EGFR binding peptide, GE11, was conjugated to surface PEG chains. The resultant "nanosyringes" could be loaded with a wide range of hydrophobic dyes and drugs, including paclitaxel and doxorubicin [64], with efficacy in both U87-EGFR cells and primary human GBM culture. *In vivo* studies investigating flank and intracranial xenograft mouse models found a strong accumulation of the nanosyringes in the subsequent tumour sites, despite differences between rodent and human BBB.

A recent study reported the use of a canine model with late stage *de novo* brain tumours to deliver bacterially derived minicells loaded with doxorubicin, whereby the surface of the minicells were decorated with bispecific antibodies targeting EGFR. The study reported that this delivery method was safe and extremely well tolerated by canines, with no adverse effects observed. In comparison to murine and rodent models, the large size of the canine brain offers a useful model for the assessment of dose volumes and thus effectiveness of brain tumour therapies in a clinically relevant manner. This study, coupled with other preclinical data, formed the design basis of a Phase 1 clinical trial of EGFR-minicell-

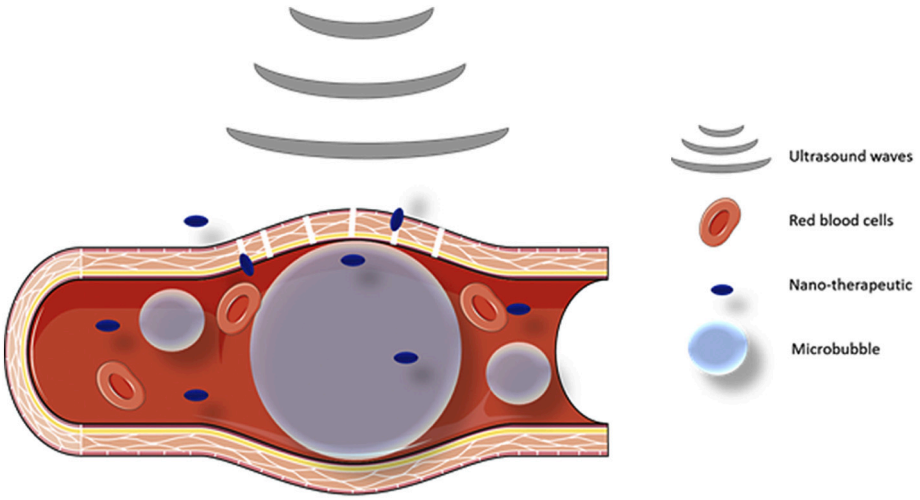


Fig. 2. MRI-guided focused ultrasound (MRgFUS) to enhance BBB penetration of NPs. The arteries lining the BBB stretch as a result of microbubble swelling from focused ultrasound waves, allowing NPs to pass through the temporary gaps between the endothelial cells. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

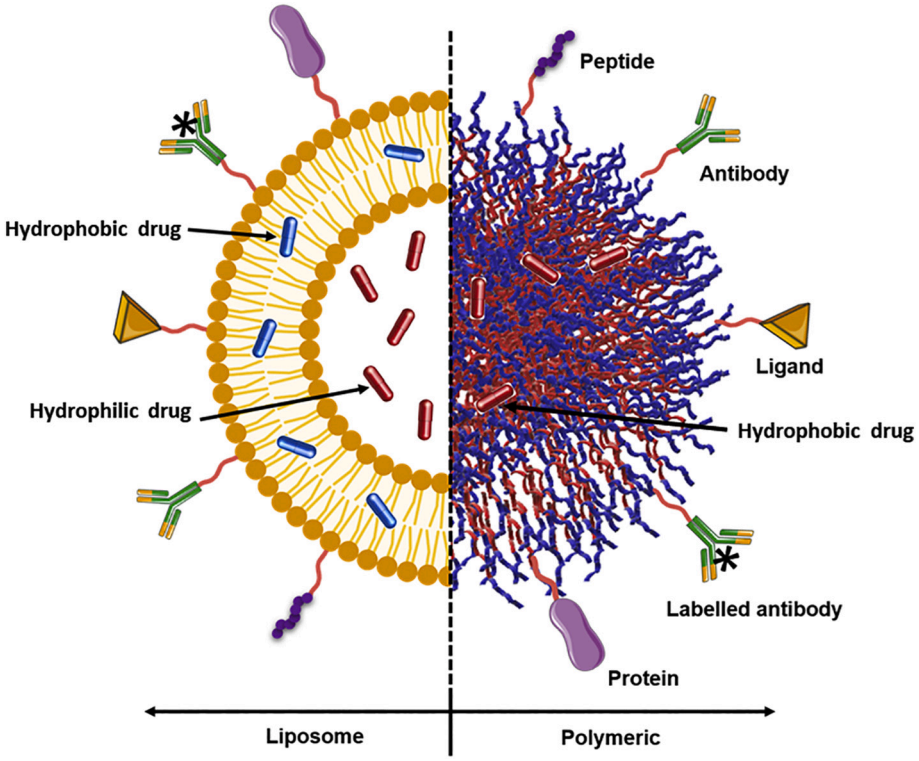


Fig. 3. Representation of functionalised liposome and polymer NP systems. Targeting moieties include proteins, antibodies, labelled antibodies, ligands and peptides. The hydrophobic core of the polymeric NP (right) can contain hydrophobic drugs; whilst for liposomes (left) the aqueous core contains hydrophilic, water soluble drugs, whilst the lipophilic outer bilayer contains hydrophobic drugs. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

doxorubicin in human recurrent GBM [67].

Antibodies have also been used to target the transferrin receptor [68], overexpressed in many cancerous cells, particularly GBM. One study used PLGA NPs to deliver temozolomide and decorated the surface with the monoclonal antibody OX26. Two different glioma cell lines were investigated and the prepared nanocarriers enhanced the anti-cancer activity of temozolomide. In particular, the functionalisation of the nanocarrier was advantageous in enhancing the cellular internalisation in GBM cells [68].

Another study similarly utilised MMP overexpression by formulating PEG-PCL NPs encapsulating paclitaxel, conjugated with an activatable low molecular weight protamine (ALMWP), which is selectively cleaved in an MMP rich tumour environment. Improved anti-glioma efficacy was observed *in vivo* in nude mice bearing intracranial C6 glioma, where mice which received ALMWP-NPs survived significantly longer than mice treated with non-targeted NPs and Taxol. Increased accumulation of the ALMWP-NPs was observed in the tumour in biodistribution studies, whereas LMWP-NPs, which did not exploit the selective cleaving by MMPs, were found to have increased uptake in other organs, such as the heart, liver, lungs and spleen. This further indicates the importance of specifically targeting the tumour site to lessen adverse side effects and increase the efficacy of the drug delivery system.

A considerable challenge for all targeted therapy efforts to date, is the sub-clonal nature of GBM, where only a minority sub-population of cells within a tumour may express molecular targets such as EGFR or VEGF. This warrants the need for targeting strategies which can deliver

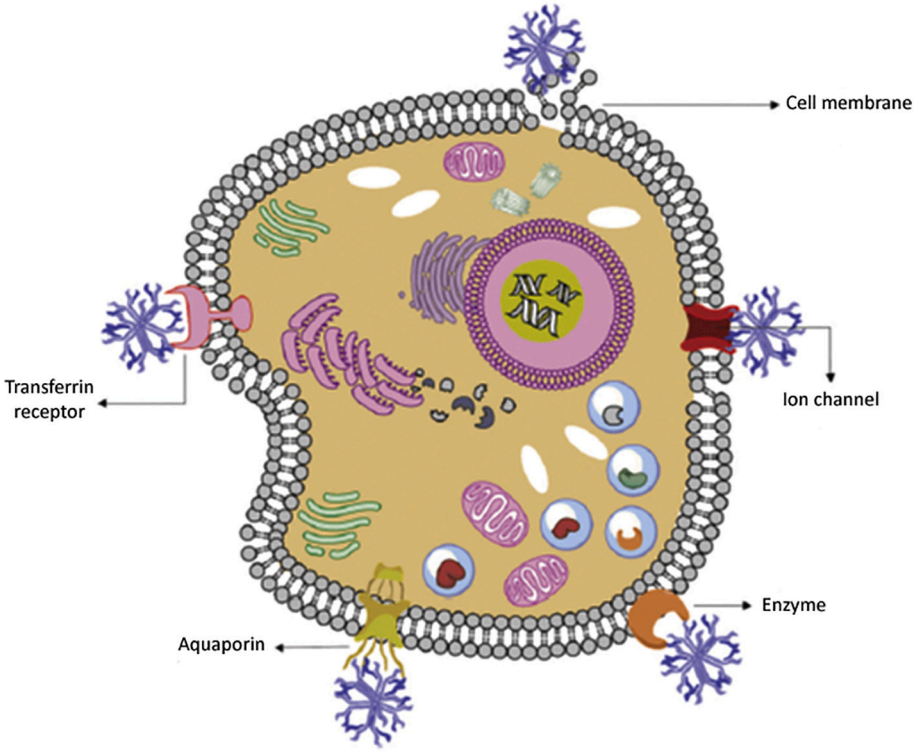
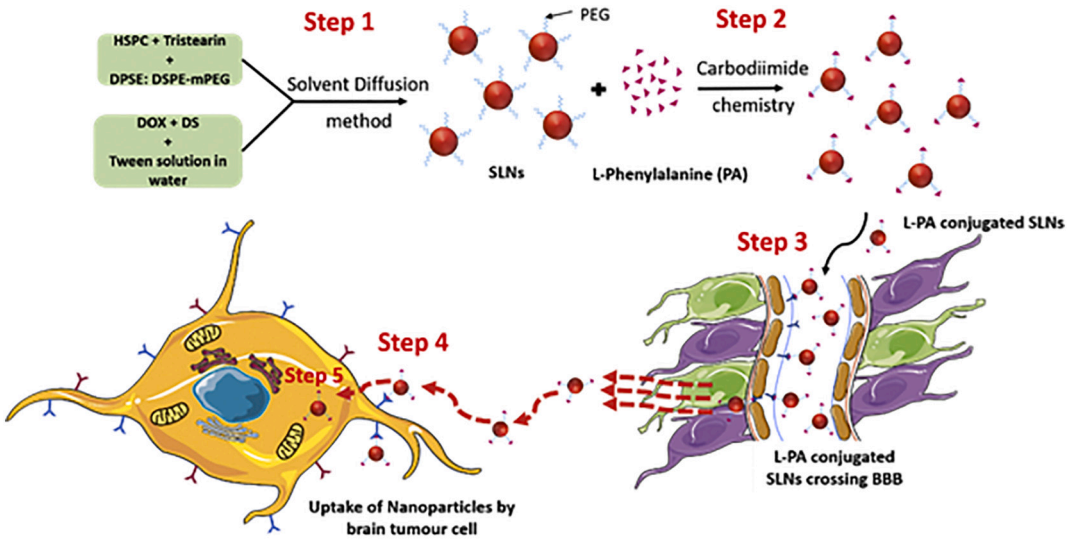


Fig. 4. Possible interactions of dendrimers with various biological assemblies available at the cellular level. Reprinted with permission from [73].



Step 1: Preparation of SLNs using solvent diffusion method.

Step 2: Conjugation of ligand with SLNs using carbodiimide chemistry.

Step 3: Intravenously administered PA-SLNs reach brain blood capillaries and cross the BBB with help of carrier mediated transport system (L-type amino acid transport system (LAT1)) of BBB.

Step 4: Ligand receptor interaction between PA present on surface of SLN and PA receptor on brain tumour cell.

Step 5: Internalisation of PA-SLNs by brain tumour cell.

Fig. 5. Schematic representation of preparation, conjugation and transportation of *L*-phenylalanine (PA)-SLNs. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. Adapted from [76].

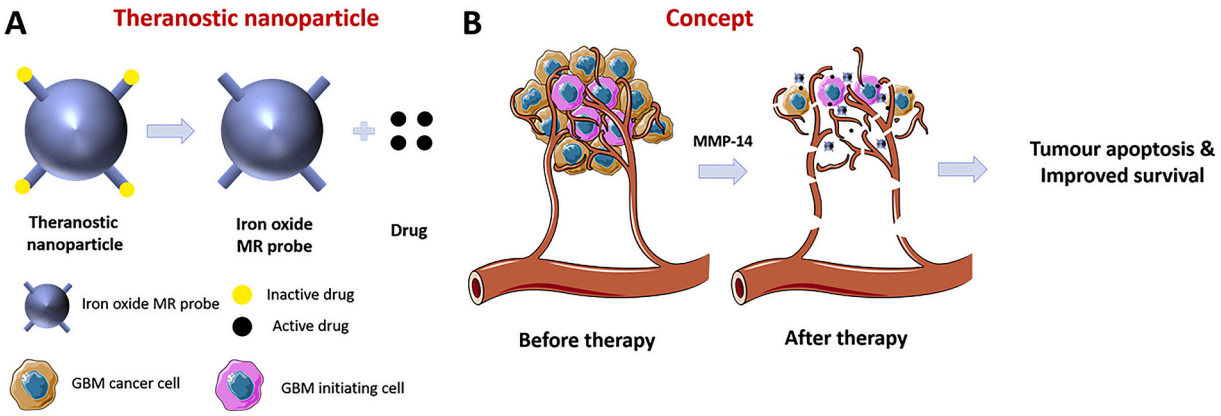


Fig. 6. CLIO-ICT inhibit GBM survival *in vitro* and retard GBM growth *in vivo*. (A) Schematic demonstration of CLIO-ICT activation in the presence MMP-14 tumour enzyme, releases active CLIO-ICT, triggering apoptosis by targeting tubulin. (B) Schematic demonstration of CLIO-ICT-mediated disruption of tumour vasculature and apoptotic induction in the presence of MMP-14, leading to improved survival in orthotopic GBM xenografts. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. Adapted from [78].

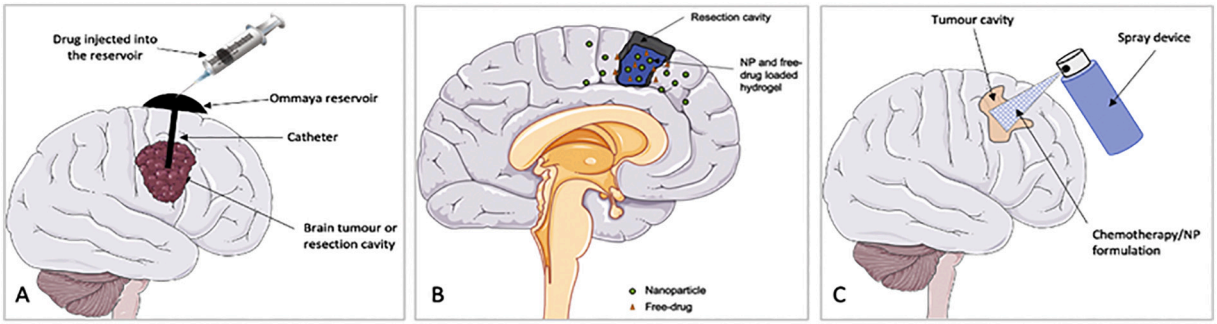


Fig. 7. Schematic illustrating diverse methods of localised drug delivery. (A) Catheter delivery using an Ommaya reservoir. An Ommaya reservoir with the catheter placed in the tumour, allows regular injections of chemotherapeutics. The reservoir can also be placed into the lesion site post-surgery. (B) A free-drug and nanoparticle loaded hydrogel placed within a resection cavity. Free-drug (orange) diffuses locally from the hydrogel and nanoparticles (green) traverse further into the brain parenchyma. (C) The concept of a spray device for drug delivery into a resection cavity. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

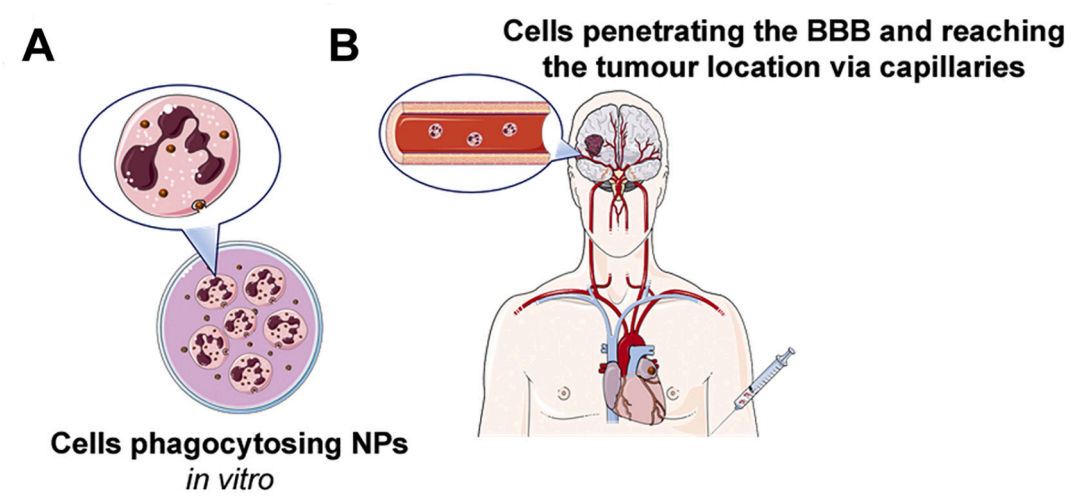


Fig. 1. Cell-based drug delivery for brain tumours. (A) Neutrophils incubated with drug-loaded NPs (brown) *in vitro*, allowing phagocytosis or endocytosis into the cell. (B) Engineered neutrophils are then administered systemically *via* the bloodstream, passing the BBB, allowing NPs to deposit the drugs at the tumour site. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Nanoparticles with dual targeting capabilities for both the BBB and GBM.

NP material used	Target for BBB / Target for GBM / Both	Targeting moiety used	Drug incorporated	*In vitro* model	*In vivo* model	Conclusion of Study	Reference
Poly (caprolactone)	Low-density lipoprotein receptor	Angiopep-2	Paclitaxel	3D spheroids, Brain capillary endothelial cells (BCEC)	Nude mice bearing intracranial tumours	- Post IV treatment, penetration, distribution and accumulation higher than PEG-PCL control - No acute toxicity observed	Xin *et al,* 2012 [78].
PLGA	Transferrin receptor	CRT peptide	Paclitaxel	3D spheroids; BCEC cells	Nude mice bearing intracranial tumours	- CRT-NP significantly prolonged median survival compared to Taxol	Kang *et al, 2015* [79].
Liposome	Transferrin receptor	Anti-transferrin single chain antibody fragments	Temozolomide	U87 (Temozolomide resistant and non-resistant lines) and U251	Nude mice bearing intracranial tumours	- Significantly increased survival compared with free temozolomide	Kim *et al,* 2015 [80].
Liposome	Large amino acid transporter 1 (LAT1)	l-3,4-dihydroxyphenylalanine (l-DOPA)	WP1066 (JAK2 inhibitor)	GL261 cells (mouse GBM cells)	C57BL/ 6 J mice bearing intracranial tumours	- Significantly increased survival compared with free WP1066	Bhunia *et al,* 2017 [81].
Solid lipid NPs	α-subunit of insulin receptor / Anti-epithelial growth factor (AEGFR)	83–14Mab	Etoposide	U87 GBM cells and HBMECs	–	- Dual targeted NPs showed increased antiproliferation efficiency over single targeted and etoposide loaded NPs. - 83-14Mab effectively increased BBB permeability	Kuo *et al,* 2016 [82].
PLGA	Lactoferrin receptor / Folate receptor	Lactoferrin and folate	Etoposide	U87 GBM cells and HBMECs	–	- Dual targeted NPs showed increased antiproliferation efficiency over single targeted and etoposide loaded NPs.	Kuo *et al,* 2015 [83].
Solid lipid NPs	Lactoferrin receptor / Multi-drug resistance proteins (MRPs)	Tamoxifen and lactoferrin	Carmustine	U87 GBM cells and HMBECs	–	- Dual targeting system increased the permeability of the BBB and resulted in greater inhibition of U87 cell growth.	Kuo *et al,* 2016 [84].
Super paramagnetic iron oxide NPs	Transferrin receptor / Nestin (stem cell marker specific to GBM)	Transferrin/polysorbate-80 and antibody against nestin	Temozolomide	–	Nude mice bearing intracranial tumours	- Transferrin coated NPs demonstrated greater tumour regression than polysorbate-80 coated NPs.	Prabhu *et al*, 2017 [85].
Immunoliposomes	Low-density lipoprotein receptor / CD133 glycoprotein	Angiopep-2 and CD133 Mab	Temozolomide	U87 GBM cells and glioma stem cells (GSCs)	Nude mice bearing intracranial tumours	- Significant increase in survival observed relative to free temozolomide	Kim *et al,* 2018 [86].
Liposomes	Transferrin receptor / Folate receptor	Transferrin and folate	Doxorubicin	C6 glioma cells and bEND3 BBB model	Rats bearing intracranial tumours	- Dual targeting effect was observed - NP was less toxic than doxorubicin solution	Gao *et al,* 2013 [87].

combination therapeutic moieties.

2.6. Dual targeting of the BBB and GBM

Researchers are attempting to target the biological properties of both GBM and the BBB by increasing the sophistication and targeting ability of the nanocarriers, and a number of these studies are outlined in Table 1. Several targets are simultaneously overexpressed on both the BBB and GBM cells, potentially allowing NPs bearing a single targeting moiety to cross the BBB more effectively and to enhance internalisation into GBM cells. These targets include the low-density lipoprotein receptor related protein (LRP) [69–71], transferrin receptor [72,73] (Fig. 4) and large amino acid transporter 1 (LAT1) [74–76] (Fig. 5). Conjugating a single targeting moiety to the NP surface has the additional advantage in that it reduces the complexity of the formulation process, a major issue facing the clinical adoption of NPs [77].

Receptor-mediated transcytosis (RMT) *via* the transferrin receptor pathway has been investigated, with one study showing that transferrin-

conjugated self-assembled NPs incorporating zoledronic acid increased the anti-tumour efficacy of zoledrinic acid in mice bearing intracranial xenografts, due to their increased ability to cross the BBB. This was shown by tumour weight inhibition (TWI) from transferrin conjugated NPs of 41% compared to non-targeted NPs at 31% TWI and an increased life span (ILS) of 23% compared to 10%, respectively; in contrast, free drug alone showed only a 20% TWI and an ILS of 10% [88].

Once the BBB has been crossed, NPs encounter the problem of traversing the parenchyma to reach the target site of infiltrative cells, which is required to inhibit the otherwise inevitable tumour reoccurrence. Recent seminal work has investigated the effect of NP size on the ability to penetrate through brain tissue [89,90]. Predominant opinion suggested that materials with diameter ranges of up to 64 nm could traverse at substantial rates across the brain extracellular space (ECS), confirmed by a study utilising 35 nm quantum dots and dextran in rat ECS and modelling the diffusion in ECS and fluid filled pores [91]. The effectiveness of many therapies is therefore limited, as most particulate drug delivery systems carrying therapeutic genes, or viruses, as discussed in the introduction, are too large for efficient penetration at this quoted size range. However, the study estimated that human tissue extracellular space contains some pores larger than 200 nm, and that more than one quarter of the pores are ≥100 nm. These findings were confirmed *in vivo* using mice, where 40 and 100 nm polystyrene (PS) NPs spread rapidly within the brain tissue, if densely coated with PEG. In contrast, 200 nm PEG coated PS NPs did not penetrate the brain tissue. Further work showed that model PS-PEG-coated NPs of 114 nm in diameter were able to rapidly diffuse into normal brain tissue [90] and that paclitaxel-loaded, PLGA-co-PEG block copolymer NPs, with an average diameter of 70 nm, were able to diffuse 100-fold faster than similarly sized paclitaxel-loaded PLGA particles without a PEG coating [89]. The hydrophilic PEG coating acts as a flexible hydrated cloud, creating a barrier which minimises adhesive interactions with cell surfaces, allowing the NPs to pass further into the brain. In short, despite PEGylation being utilised originally for improved circulation time during systemic delivery, it has been shown that PEGylation also improves the penetration of biological barriers, leading to enhanced overall delivery, even locally [92].

2.7. Stimuli responsive NPs in the treatment of GBM

Due to the degree of GBM inter- and intra-tumour heterogeneity and overlap with normal astrocytic markers, no one mechanism for tumour progression applies to all forms of GBM, hence there are currently no specific intrinsic biological markers to target, which is a major impediment in designing therapeutic formulations. Therefore, the ability to extrinsically target the tumour-specific microenvironment is highly desirable. Studies have been conducted in which the acidic environment of GBM [93] has been exploited by adopting pH responsive peptide, $H_7K(R_2)_2$, as a ligand, whereby the $(R_2)_2$ sequence is a cell penetrating peptide, increasing the permeation of a doxorubicin carrying liposome formulation. A specific homing-capacity to GBM triggered by an acidic pH was confirmed *in vivo*, with a significant increase in survival observed in both C6 and U87 mouse xenografts treated with pH-responsive liposomes containing doxorubicin, compared to sterically stabilised non-responsive liposomes containing doxorubicin and saline controls respectively (both $p < 0.01$) [94]. A further study exploiting the acidic tumour microenvironment was carried out whereby lipid micelles containing a pH-responsive N-palmitoyl homocysteine [ammonium salt] (PHC) and temozolomide, were found to have specific and increased uptake in orthotopic *in vivo* models over non-pH responsive micelles. However, increased efficacy was not assessed in this study, and henceforth the advantages observed with the pH responsive micelles cannot be correlated to an overall survival benefit [95].

Aldoxorubicin is a (6-maleimidocaproyl)hydrazone conjugate of doxorubicin which can rapidly and selectively bind to the cysteine-34 position of circulating serum albumin following IV administration. It is a stimuli responsive polymer pro-drug delivery system as it releases doxorubicin selectively *via* hydrazone cleavage at tumour sites due to the low pH of the tumour microenvironment [96]. A study comparing aldoxorubicin-treated mice bearing intracranial tumours with doxorubicin-treated mice, observed that the former mice displayed decreased tumorigenesis and significantly increased survival when compared to untreated and doxorubicin-treated groups [97], suggesting that a stimuli responsive moiety within a NP formulation can lead to increased potency in the treatment of GBM.

An alternative tumour environmental factor exploited in drug delivery systems aimed at the treatment of GBM is the altered redox potential and increased expression of reducing species compared to normal tissue. In particular, the peptidic compound glutathione, which is an important regulator of cellular homeostasis, is overexpressed in many tumours. Disulfide bonds can be broken down by glutathione under certain conditions, which has led to many formulations incorporating disulfide linkages to enable a triggered release upon exposure to increased levels of glutathione; *i.e.* within a tumour microenvironment. One study incorporated the highly potent natural protein toxin, saporin, into a triblock copolymer containing disulfide linkers. Angiopep-2 was used as a peptide targeting low-density lipoprotein receptor-related protein-1 (LRP-1) to increase permeability across the BBB. Once formulated as NPs, *in vitro* experiments showed increased release of saporin (80% within 24 h) in the presence of physiological quantities of glutathione compared to very low concentrations released (15% within 24 h) in the absence of glutathione. Further *in vivo* studies concluded that both the angiopep-2 and disulfide bridges led to an increased survival in orthotopic tumour bearing mice when compared to the presence of the saporin alone [98]. This indicates the importance of delivering the therapeutic in a site-specific manner but also the necessity to traverse the BBB. Based on a similar rationale, SP peptide, a ligand which binds to neurokinin-1 receptor (overexpressed in glioma), was anchored to paclitaxel-loaded human serum albumin NPs *via* incorporation of a redox responsive disulfide bridge [99]. *In vitro* studies showed an increased release of paclitaxel in the presence of glutathione (compared to absence); however *in vivo* studies were ambiguous to the overall survival benefit, leading to concerns regarding the extra complexities introduced to the drug delivery system.

As mentioned previously, matrix metalloproteinases (MMPs) have been identified to be highly overexpressed in GBM [100,101] and additionally, can selectively cleave specific peptide sequences. Therefore, carriers can be encoded with MMP-cleavable linkers, which release drug *in situ* in areas where MMPs are overexpressed, ideal for prodrug activation in the treatment of GBM. One study coupled azademethylcolchicine (ICT) to cross-linked iron oxide (CLIO) NPs to generate theranostic NPs (CLIO-ICT). ICT is a modified peptide conjugate which, when broken down by MMP-14, releases an active vascular-disruptive agent (VDA), [101]. VDAs target endothelial cells at the intraluminal surface of blood vessels leading to vascular collapse and starvation of tumour cells supplied by these vessels [102,103]. *In vivo* studies evaluated the CLIO-ICT NPs alone and in combination with temozolomide on two sets of mice bearing intracranial primary GBM neurospheres, derived from two different patients. One tumour type treated with CLIO-ICT NPs resulted in significantly prolonged survival whilst the other tumour type led to complete tumour remission. Further increased survival was observed when temozolomide was used in combination, leading to a potential synergistic drug delivery system. As MMP-14 expression is positively correlated with tumour grade and disease progression, this approach appears specifically suited for the treatment of high-grade gliomas (Fig. 6).

Despite the exciting promise of the formulations discussed, there remains a significant lack of translation between *in vitro* and *in vivo* studies, and fundamentally pre-clinical trials. Some of these pitfalls are directly related to the models the treatments are tested on. Based on an increasing understanding of brain intra-tumour heterogeneity, the capability to evaluate prospective treatment on primary derived cell

lines from the invasive region of the tumour, is clinically-relevant for the treatment of GBM. Most commercial GBM cell lines have been historically derived from the MRI contrast-enhanced core region of tumours, thus not allowing a realistic, phenotypically accurate representation of the infiltrative cells which remain post-surgery and ultimately result in the inevitable recurrence of GBM [104]. Furthermore, through general cell culture techniques, genetic drift is encouraged leading to cell lines being aberrantly different to the original disease state [105]. This aspect inevitably results in unrealistic translation of treatment efficacy when moving to an aggressive, infiltrative *in vivo* model. An ideal *in vivo* model would have the capability to recapitulate the tumour microenvironment, providing a better understanding of disease biology, including cell-cell and cell-environment interaction and crosstalk.

Despite the use of human GBM cell lines *in vivo* being more clinically relevant than rodent GBM cell lines, murine stroma inevitably takes over implanted cells resulting in a genetic drift. It has also been observed that developing human xenografts for rodent *in vivo* studies leads to problems concerning the lack of infiltrative disease, and does not truly recapitulate the tumour microenvironment with regards to cancer cell-host cell interactions and signalling [106]. It has therefore been suggested that for long term *in vivo* culture, direct patient xenografts may not perform any better than GSC cultures expanded *in vitro* prior to transplantation [107]. Alongside enhancing the complexities of NP formulations to increase targeting specificity, efficacy and drug loading whilst minimising side effects, further consideration needs to be undertaken with regards to the models that these formulations are tested on, enabling a more successful translation between *in vitro/in vivo* models and clinical trials, resulting in successful next-generation treatments for GBM.

3. Localised drug delivery systems for brain tumour therapy

Although there are now many sophisticated NP systems in development for treating GBM, systemic delivery *in vivo* with these systems has not yet been clinically demonstrated [108]. Local, intracranial drug delivery has been developed over the last two decades, in order to circumvent the BBB. As maximal safe resective surgery is usually the first stage in treatment of GBM, the rationale for intracranial drug delivery is based upon a unique treatment window immediately adjuvant to neurosurgery, delivering drugs directly to the site of the tumour. Ideal formulations used to deliver drugs *via* this route should be biodegradable so as not to necessitate a second surgery for device removal and to lessen the prospect of a foreign body immune response.

Currently, there is only one formulation approved by the U.S Food and Drug Administration (FDA) and The National Institute for Health and Care Excellence (NICE) for GBM: Gliadel™ wafers, which were approved in 1996. The wafer is a biodegradable *co*-polymer composed of 1,3-bis-(p-carboxyphenoxy)propane and sebacic acid in a 20:80 ratio, which is impregnated with carmustine, a cytotoxic drug [109]. The wafers are inserted into the cavity after surgical resection of the tumour and carmustine is released over a three-week time frame. Despite this novel treatment method, the overall median survival is only improved by two months, and GBM continues to reoccur [110–112]. This is due to several reasons including: i) the rigid structure of the Gliadel™ wafers, rendering them unable to conform to the irregular-shaped cavity lining and are thus incapable of delivering drug to the entire cavity area; ii) the wafers can dislodge from the cavity wall and fall to the bottom of the cavity, minimising contact with the brain parenchyma, causing a reduction in the effective diffusion distance of carmustine; iii) the therapeutic agent is unable to penetrate far enough into brain parenchyma to eradicate remaining residual cells; iv) the delivery system was designed as a mono-therapeutic approach, purely for the single drug carmustine. The heterogeneous nature of GBM cells makes treatment with a single therapeutic agent poorly effective, since drug resistant tumour sub-clones can rapidly overcome pharmacological interference with a single molecular pathway. Furthermore, the half-life of carmustine is only 15 min [113], which is too short a time for the active drug to diffuse across large distances before drug degradation/metabolism occurs. Nevertheless, the development and approval of Gliadel™ wafers has provided a proof-of-concept that intra-cavity drug delivery, reliant on diffusion, can lead to significant survival benefits for patients with primary and recurrent GBM. This has opened the field to developing more treatment methods of this nature, some of which are discussed further below.

3.1. Polymeric hydrogel systems

Hydrogels are three-dimensional networks, which retain a physically viscoelastic structure while containing large amounts of water. Hydrogels can be synthesised to respond to several physiological stimuli including temperature, pH and ionic strength, making them appealing matrices for controlled drug delivery.

The ReGel™ system consists of a triblock thermosensitive copolymer (PLGA-PEG-PLGA) which is water soluble at 2–15 °C but converts to a viscous, biodegradable, water insoluble, controlled-release gel at body temperature [114]. Oncogel™ is a non Cremaphor EL based formulation of paclitaxel in ReGel™, designed for the local delivery of paclitaxel to solid tumours, thus avoiding the systemic toxicities associated with conventional systemic paclitaxel delivery [115]. Oncogel™ provides a depot for the continuous release of paclitaxel directly to the tumour and surrounding tissue for six weeks. A study assessing the safety and efficacy of intracranial injected Oncogel™ into rats with 9 L gliosarcomas, concluded that when combined with radiotherapy, this treatment method was more effective than either ReGel™ or radiotherapy alone [116]. Ultimately however, a subsequent human clinical trial was discontinued, highlighting the increased lack of translation between successful *in vivo* studies and clinical trials.

More recently, a hydrogel composed of lipid nanocapsules loaded with lauroyl-gemcitabine (GemC12-LNC), an amphiphilic derivative of gemcitabine, has been developed for the localised treatment of GBM, showing a significant survival benefit in pre-clinical studies [117,118]. The same laboratory has further enhanced this hydrogel system through loading a second chemotherapeutic, paclitaxel, into the hydrogel and *in vitro* studies in GBM models showed a promising efficacious and synergistic effect of the dual drug delivery system [119]. A schematic to depict this drug and NP-loaded hydrogel is shown in Fig. 7.

This group has also developed an *in vivo* surgical resection GBM model in mice, whereby the tumour is resected 13 days after inoculation [120]. This is more clinically relevant than non-resective models; in approximately 65–75% of cases, patients undergo surgical resection [121], therefore pre-clinical models must recapitulate this to show a more realistic response to therapy. However, the use of a xenograft GBM model (U87) in mice, carries the same limitations described previously, whereby the tumour is not as infiltrative as the human equivalent, therefore efficacy seen in these models is much higher than reality. Further work from this group recognised the limitations to using a xenograft U87 model in mice, therefore they adapted the resection model for non-immunocompromised rats bearing C6, 9 L and 9 L-LacZ tumours. The conclusions of the paper recognised the need for further development of *in vivo* models, whereby the location, cell type and animal strain are optimised to generate more similar tumour characteristics to those seen in the clinical setting [122].

3.2. Convection enhanced delivery (CED)

CED was introduced in 1994 by Bobo *et al* [123] and consists of a direct, continuous infusion of a therapeutic in the brain parenchyma using a micro-catheter connected to a pumping device. Using hydraulic pressure, a gradient is created to allow the infusion of drug into the brain and surrounding interstitium, treating a spherical or elliptical region of tissue [124]. A major confounding issue facing CED is the short half-life of many chemotherapeutic drugs within the brain and the subsequent fast clearance post-infusion. Studies have been carried out which

enhance CED through the incorporation of drug loaded NPs [125]. It is envisaged that through encapsulation, controlled release of the drug will be achieved, prolonging the half-life of the chemotherapeutic, and hence increasing tumour cytotoxicity. Drug encapsulation is also anticipated to contribute towards a reduction in neurotoxicity and an increase in tissue retention, potentially improving the prognosis for patients with GBM. Studies utilising PLGA NPs encapsulating carboplatin [126], paclitaxel [127] and camptothecin [128], showed improved sustained drug release relative to free drug alone. Some groups have also generated NPs bearing dual functionality for delivery *via* CED, whereby NPs containing a magnetic core can additionally carry drug cargo, allowing the NPs to be detected *via* MRI, permitting tracking *in vivo* [129,130]. A recent study using positron emission tomography (PET) in real-time revealed that nanofiber-bound drugs were retained *in situ* for longer than free-drug alone [131].

Coupling CED with NPs therefore has the realistic potential to improve the outlook for patients with malignant glioma, as it capitalizes on strong elements of two powerful drug delivery strategies. As a result, there is currently an active phase 1 clinical trial using CED to deliver a gold NP-based formulation containing panobinostat (MTX110) to diffuse intrinsic pontine glioma (DIPG), a childhood brain tumour located in the brain stem and which is inoperable [ClinicalTrials.gov ID: NCT03566199]. A second phase 1/2 study is delivering a rhenium nanoliposome formulation by CED to patients with recurrent glioma to determine if the radiation from rhenium is efficacious *in vivo*. The rhenium beta radiation is said to penetrate 2 mm into the parenchyma, which can help overcome the heterogeneity of NP dispersion in the brain [ClinicalTrials.gov ID: NCT01906385].

Nevertheless, infection, catheter obstruction, and inadequate drug distribution have limited the success of this delivery method thus far. Furthermore, CED is only capable of delivering a therapeutic over a fixed period of time, that being when a temporary catheter is in place [132]. It is anticipated that more sustained and effective treatment may require continuous treatment with a chronically infused agent, a concept which has been explored in primate models [133]. This concept has also been well reviewed by Lewis *et al*, addressing the requirement for increased volumes and infusions of rapidly cleared chemotherapies to brain tumours [134]. Later work has shown a significant reduction in tumour volume when chronically infusing carboplatin using robot-guided implantation of catheters [135,136]. Applying NP technology to this promising device could be well received in the field, utilising NPs to increase the potency, specificity and diffusion of the chemotherapies.

3.3. Catheter delivery

Alternative catheter-based therapies to CED have been engineered, one of which is a repurposed reservoir-based system, the Ommaya reservoir (Fig. 7A), originally made in 1963 for ventricular drainage [137]. This system relies on diffusion of drugs from the reservoir into the tumour cavity as a result of a concentration gradient [138]. The therapeutic can be directly injected into the reservoir multiple times (*e.g.* daily) and then released into the parenchyma, allowing for multiple and sustained injections into the lesion. One human study revealed that doxorubicin injected daily into an Ommaya reservoir was safe and effective, with six out of ten patients showing clinical improvements [139]. A wireless monitor to follow fluorescent-drug penetration *in vivo* in real time is currently being developed [140], which could potentially aid drug selection by identifying which drugs penetrate the furthest and reside in the cavity longest, hence potentially leading to greater efficacy. However, despite the benefits of quick access and consistent drug delivery, there are similar complications to the CED device by way of infections and cyst formation [141].

A metronomic feedback pump is another example of a catheter-based system which utilises a pump to deliver microliter doses of drugs. It contains a second catheter to draw from the target site, thus allowing real-time determination of the drug reaching this site *via* the use of a spectrophotometer to measure drug absorbance. The wirelessly controlled pump has a battery life of up to 5 years, minimising necessary invasive procedures [142,143]. However, limitations to this device, like those others utilising a catheter, primarily include a risk of catheter occlusion and infection.

All of the above catheter-based systems can be coupled with further engineered devices to detect the presence of drug at the target site (*e.g.* fluorescent drug monitoring and metronomic feedback pump/spectrophotometer).These allow a means to measure efficacy of the system, which shows an additional benefit to using such devices. As such, these devices could be used to enhance efficacy of drug delivery systems by studying which drugs and systems penetrate the furthest into the parenchyma.

3.4. Spray-based delivery

Another delivery system, which could enhance the penetration of chemotherapeutics to remaining GBM cells is one which utilises air pressure to force the drug and/or NP through the parenchyma before it can naturally diffuse, as demonstrated in Fig. 7C (McCrorie et al. manuscript submitted). Studies, which employed a spray device for drug delivery in glioma have included a single-nozzle, sterile filtered air pressure device that delivered free-drug (taurolidine) *in vitro* [144], and a second study, which sprayed bio-adhesive PLGA and poly-lactic acid NPs held within a poly(N-isopropylacrylamide) hydrogel from a generic spray bottle onto *ex vivo* rat brain, delivering a model drug to mimic release and diffusion [145]. Although neither of these studies reported *in vivo* assessment, other prominent oncological studies have demonstrated efficacious spray devices, such as the delivery of doxorubicin to breast cancers within the flank of balb/c mice. This study reported significant inhibition of growth from the spraying of doxorubicin-NPs compared to free doxorubicin, due to the latter spray system losing drug to bodily fluids [146]. Another study utilised a dual cartridge spray device to deliver fibrinogen and thrombin to a melanoma surgical resection site which generated a fibrin gel *in situ*, holding in place calcium carbonate NPs containing anti-CD47 antibody. These NPs/antibodies trigger an immune response by scavenging H^+ from the wound and increasing phagocytosis by tumour-associated macrophages. This study also found that local delivery of the gel led to efficacy against distant tumours (placed within the opposite flank to the original tumour). However, this effect is not reported to be due to NP penetration, but as a result of local cross presentation of tumour antigens by macrophages [147], an aspect potentially applicable to GBM.

Table 2 summarises studies utilising diverse spray devices in cancer therapy (excluding pulmonary or nasal systems). Despite this, there is a lack of viable approaches designed to measure the increase in penetration of NP/drug in tumours or healthy tissue as a result of spraying. Nevertheless, spraying could be clinically attractive for NP delivery of chemotherapeutics, which may realistically reach the cells within the GBM invasive margin and parenchyma beyond, without relying solely on diffusion of NPs.

3.5. Unmet engineering needs

Several challenging issues persist with all brain tumour drug delivery methods to date, either relating to NP behaviour (*e.g.* rapid or no drug release), off-target localisation and lack of cell targeting, or limitations of the engineering methodologies. Most engineering methods, which are being trialled for GBM drug delivery are being repurposed from other applications, hence carry the risk of non-specific actions. Systemic methods such as barrier disruption or cell-based targeting are not without inherent risks and have low targeting efficiencies. Yet current localised delivery methods are invasive, have associated side effects (*e.g.* foreign body response; oedema) and the therapeutic agents do not diffuse sufficiently far from the implant site, hence do not reach deeply invasive cells which ultimately lead to GBM reoccurrence.

Table 2
Spray devices used in cancer therapy, excluding pulmonary delivery.

Application	Delivery device	Nanoparticles	Hydrogel material	*In vitro* materials characterisation	*In vitro* cytotoxicity	*In vivo* toxicity and safety	*In vivo* model	Reference
Immunotherapy for skin cancer	Dual cartridge sprayer	Yes: $CaCO_3$-PEG	Fibrin	-Cryo-SEM -Confocal microscopy -aCD47 release (ELISA) -Rheology -Degradation (IVIS)	N/A	-IVIS -Phagocytosis of cancer cells *via* confocal microscopy and CytoFLEX flow cytometry -Immunofluorescence -Western blotting	Resected B16F10 melanoma tumour in mouse flank	Chen *et al*, 2018 [147]
Drug delivery (Taurolidine) in glioma	Single nozzle device with filter-sterilized compressed air (1.5 bar)	No	Fibrin sealant	-Coagulation time -Drug release kinetics (colorimetric analysis)	Cell viability with LN18, LN229, U87MG and *ex vivo* GBM cell lines	N/A	N/A	Stendel *et al*, 2004 [144]
Drug delivery (doxorubicin) in breast cancer	Commercial air-pressured atomiser	Yes: mussel protein based NPs	N/A	-Zetasizer -Morphology (FES-EM and AFM) -Localisation (Fluorescence microscopy) -Adhesion efficiency -Cellular uptake	-Release profiles -Cell viability with MCF-7, MDA-MB-231, MC3T3-E1 and HUVEC	-Retention assay (IVIS) -Anticancer efficacy	MCF-7 tumour-bearing mice	Jeong *et al*, 2018 [146]
Drug delivery in glioma	Spray bottle (not-specific)	Microsphere – PLGA and PLA	Poly(N-isopropylacrylamide)	-Zetasizer -Mock-drug encapsulation efficiency -Thermoresponsive hydrogel synthesis -Drug release -*Ex vivo* spray onto rat brains	N/A (mock drug)	N/A	N/A	Floyd *et al*, 2015 [145]
Drug delivery for peritoneal metastases	Pressurised intraperitoneal aerosol chemotherapy (MIP1 Micropump/ Capnopen (Reger Medizintechnik)	No	N/A	N/A	N/A commercial drugs (cisplatin and doxorubicin)	-Human trials underway, efficacy seen in 11 out of 12 patients	N/A	Horvath *et al*, 2018 [148]

Nevertheless, it is vital that engineering systems can be combined with biological and chemical routes to enhance drug delivery to the brain, as no one method is sufficiently effective. Future research needs to focus directly on the application to GBM and seek to increase penetration of drugs/NPs further into the brain parenchyma without catheter blockages or local side effects, with an accompanying means to monitor and assess drug diffusion. Without knowledge of diffusion of a NP/drug, there is little ability to estimate the short and long-term efficacy of the system, therefore hampering the rapid determination of the capability of systems to penetrate far enough to reach remaining GBM cells. Knowing this information could allow for better optimisation of systems and avoid the development of systems, which will never penetrate far enough to be efficacious in the long-term.

To reiterate a persistent theme within this review, it is vital that a more realistic GBM model is generated, which resembles human GBM characteristics. In this light, these engineered systems and targeted nanotherapeutics can be truly assessed for efficacy so that clinical translation is more likely.

3.6. *De novo* GBM in large animal models and companion animals

Despite increasing sophistication of rodent GBM models, including induced transgenic models whereby GBM arises *de novo*, infiltrative disease typically manifests to a much lesser extent than the GBM clinical scenario. Consequently, these models hamper assessment of drug delivery systems designed to target infiltrative GBM in the human brain.

In contrast, the brains of large mammals such as pigs, are physiologically similar to humans and have comparable BBB composition and immune defences [149]. Therefore, the pig offers a model whereby polymeric/drug systems delivered locally within a pseudo-resection cavity and then measured analytically by mass spectrometry modalities post-sacrifice, may in principle permit a more clinically-relevant assessment of effective drug penetration in the brain. Indeed, porcine models have been used recently to assess safety and drug distribution of intracerebral topotecan using CED [150].

Canines are the best example of *de novo* GBM arising in a companion animal, which has led to the establishment of a comparative biology/anatomy brain tumour consortium [151]. Indeed, spontaneously occurring canine glial neoplasms have been exploited in preclinical neuro-oncology research, including the assessment of targeted minicells loaded with doxorubicin [152], addition of procaspase-3 activator to temozolomide [153], and the NanoKnife® system for irreversible electroporation [154]

4. Conclusions

Despite recent preclinical advances within nanomedicine development, greater multidisciplinary efforts are required to develop clinically-viable products. Current engineering methods have typically been repurposed, rather than developed specifically for GBM. In this regard, specificity to GBM biology will potentially enhance efficacy and safety of therapeutic delivery, with consequent patient mortality and morbidity benefits. Whilst coupling physical and biomedical engineering with NP chemistry has the potential to enhance NP delivery to the brain, the suite

of available NPs requires further refinement such as controlling drug loading amount and consistency, drug stability, tumour targeting ability and controlled release.

Despite the poor prognosis for GBM patients worldwide, the homogeneity in front line treatment whereby tumours are neurosurgically-resected, presents a unique opportunity for the consideration of localised, intracranial therapy for most patients. Biomedically-engineered localised and targeted NP drug delivery systems (*e.g.* interstitial and convection enhanced) are attractive candidate technologies which may realistically improve outcomes for patients as these approaches commence oncological treatment immediately post-surgery, thereby targeting minimal volume residual disease and bridging the 3-4-week treatment gap prior to standard-of-care chemo/radiotherapy. As a direct corollary, localised delivery circumvents the problems associated with crossing the BBB, ensuring higher therapeutic drug concentrations in the brain and limiting off-target adverse toxicity associated with systemic drug delivery.

The paucity of brain tumour drug delivery technologies which have reached clinical trials, despite a plethora of innovative and efficacious pre-clinical experimental evidence, is likely to be redressed over the next decade. In this era of integrated omics and systems biology, more clinically-relevant drug targets and associated targeted therapeutics are rapidly emerging, for which nano-scale technologies stand best placed to deliver therapeutic drug(s) concentrations to cancerous brain regions.

Author contributions

PMC, CEV and RR conceived of the review topic and drafted the manuscript. PMC, CEV, SJS, MM, CA and RR critically reviewed and refined the manuscript.

Declarations of Competing Interest

None.

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