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Targeted drug delivery for treatment and imaging of glioblastoma multiforme

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Glioblastoma multiforme is a grade IV astrocytic tumor with a very high mortality rate. Although current treatment often includes surgical resection, this rarely removes all primary tumor cells, so is usually followed by radiation and/or chemotherapy. Remaining migratory tumor cells invade surrounding healthy tissue and contribute to secondary and tertiary tumor recurrence; therefore, despite significant research into glioma removal and treatment, prognosis remains poor. A variety of treatment modalities have been investigated to deliver drug to these cells, including systemic, diffusive and convection-enhanced delivery (CED). As systemic delivery is limited by molecules larger than ~ 500 Da being unable to cross the blood–brain barrier (BBB), therapeutic concentrations are difficult to attain; thus, localized delivery options relying on diffusion and CED have been used to circumvent the BBB. Although CED enables delivery to a greater volume of tissue than diffusive delivery alone, limitations still exist, requiring that these delivery strategies be improved. This review enumerates the strengths and weaknesses of these currently used strategies and details how predictive mathematical modeling can be used to aid investigators in optimizing these delivery modalities for clinical application.

Keywords: convection enhanced delivery, drug delivery, glioblastoma, molecular targeting

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1. Overview

Glioblastoma multiforme (GBM) is the most malignant astrocytic tumor; and although it is not the most common brain cancer, it is responsible for a large percentage of brain cancer-related deaths owing to its grim mortality rate – the overall 5-year survival rate is < 10% [1-4]. Despite current resection strategies, invasive cells are able to migrate a long distance from the primary tumor, and these cells are often the source of glioblastoma recurrence [4-6]. Further, it is often difficult to remove the primary tumor completely or at all owing to proximity to critical areas of the brain. As invasive phenotype correlates strongly with glioblastoma prognosis [7,8], some early treatment strategies consisted of surgical excisions removing the entire hemisphere [9]; yet, successive work by Gardner showed that, even after performing a hemispherectomy, glioma patients were not necessarily cured [10]. In fact, despite hemispherectomies, recurrence was detected as early as 3 months after surgery [11], leading to the discontinuation of this radical approach. Outcome in these cases and further work by Matsukado *et al.* indicated that, if left untreated, up to 50% of brain tumors had already reached the contralateral hemisphere [12]. Particularly if glioblastomas are left untreated, even when these extensive treatments are conducted, patient benefit remains minimal. In cases where the tumor is identified and treatment is provided early in disease progression, a practical delivery goal is to deliver drug to the hemisphere in which the original

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tumor originates in order to prevent invasion of these cells into the distant regions of the brain or even to the contralateral hemisphere. These characteristics and considerations of GBM make the disease a challenging cancer to treat; and, despite significant research in the treatment and targeting of malignant gliomas, prognosis remains poor.

Advances in drug delivery to these difficult-to-resect tumors and invasive cells may substantially improve prognosis of GBM patients. Several different strategies have been used to deliver drugs to the areas of the brain containing primary tumor and/or invasive cells. Most drug delivery is performed systemically by intravenous injection. This has the advantage of carrying drugs to within a few hundred micrometers of all cells in the brain; however, the blood–brain barrier (BBB) severely limits the size of molecule that can cross this barrier and limits further the concentration of drug achieved, even for small molecule drugs. Controlled-release polymers, such as Gliadel® (Eisai Corp.), circumvent the limitation of the BBB by direct implantation in the primary tumor resection site. This technology, relying on passive diffusion of drug from the implant, achieves a very high concentration in the primary tumor site, but the concentration drops off precipitously as distance from the primary tumor increases so that the delivery dose is ineffective at distances of < 1 cm from the implant. Convection-enhanced delivery (CED) has been used to overcome this inherent limitation of passive diffusion. In this approach, a solution containing the drug is delivered by means of a sustained injection (via catheter) in the tissue, thus using convection of bulk fluid to drive drug distribution. Although CED achieves distribution of drug to a much larger volume of tissue than does passive diffusion, single catheter CED can still only deliver drug to ~ 10 – 50 cm^3 of tissue.

This review examines these strategies, assesses their respective strengths and limitations (see **Table 1**), and examines mathematical modeling approaches that can help investigators evaluate these methods before experimentation as an aid to rational development of targeting constructs and delivery techniques.

2. Systemic delivery

Systemic delivery of drugs or imaging agents, typically through intravenous injection, is capable of getting these drugs into the capillary bed of brain tissue. These capillaries traverse through tissue within a few hundred microns of every cell in the brain, including tumor cells; however, transport of the drug through that last few hundred micrometers presents a major obstacle to effective treatment and imaging. The BBB, a combination of a proteinaceous layer (basement membrane) and an endothelial monolayer, allows only lipid-soluble molecules smaller than ~ 500 Da to pass [13-16]. Even though these small, lipid-soluble drugs are present in the brain tissue, typically they are present in concentrations that are often too low to be effective owing to the necessity of limiting systemic dose to avoid debilitating side effects. It has been shown that intravenous perfusion of 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), a typical chemotherapeutic agent that inhibits DNA, RNA and protein synthesis, resulted in a low penetration into brain tissue, thereby leading to low drug efficacy for brain tumors [17,18]. Systemic delivery through intravenous perfusion caused cytotoxic effects to multiple organs, low drug circulation time and low tumor exposure time to the drug, thereby resulting in minimal treatment efficacy [17]. There are several good reviews of existing systemic chemotherapy options for treatment of GBM, so this review focuses on the emerging strategies to enhance delivery of drugs through this approach [19-27].

For drug to penetrate the BBB, the drug must be lipophilic, targeted towards a membrane transporter, and/or the BBB needs to be osmotically disrupted or have its vasculature permeabilized. Although lipophilic drugs will traverse the BBB, there is a limited number of them that kill tumor cells without killing normal cells and it is not possible to conjugate targeting moieties to them while maintaining size < 500 Da. Osmotic treatment can be used to increase the permeability of the BBB and blood–brain–tumor barrier (BBTB) by osmotic shrinkage of the brain capillary endothelial cells [27,28], resulting in the widening of tight junctions. Although osmotic disruption attains delivery through the BBB, there is only a 25% increase in delivery to the tumor compared with a 400% increase to normal brain, resulting in increased neurotoxicity, and the procedure also requires anesthesia [28,29]. Also, although endothelial cell tight junctions may be temporarily opened using hyperosmolar solutions, issues such as change in microvasculature permeability, the duration of transient opening and passage of toxic proteins pose difficulties to this approach [27]. Similarly, vasoactive compounds may be used to disrupt the capillary network comprising the BBTB, resulting in more selective delivery to the tumor, less neurotoxicity and delivery to metastases throughout the CNS, and does not require drug modification; however, this method requires neovascularization of the tumor [16,19,20,27,30,31]. Some common vasomodulators include bradykinin, nitric oxide donors, soluble guanylate cyclase activator, and potassium, calcium or ATP channel agonists [27] to increase BBTB permeability to enhance drug delivery to brain tumors. Although these are potential options, the duration of BBTB opening must be closely controlled so the neural protective effects provided by the BBTB are still exerted. Further, well-established tumors show such neovascularization; but invasive cells and nascent tumors, which are the primary cause of GBM recurrence, have not yet vascularized their tissues with leaky vasculature. Therefore, although systemic delivery is an option, new approaches need to be developed to deliver drugs more successfully and easily to the brain, with minimal toxicity to healthy tissue. Further inherent limitations in terms of molecular size exist that may significantly inhibit therapeutic and imaging agent selection.

Table 1. Comparison of drug delivery mechanisms.

Delivery mechanism	Strengths	Weaknesses
Systemic	Quickest and easiest delivery mechanism Distributes to entire brain	Only small, hydrophobic molecules can cross blood–brain barrier Only primary tumor has leaky vasculature Dose limited by side effects
Diffusion	Relatively quick and easy Can deliver high concentration at implant site Sustained delivery owing to controlled release formulations	Distribution limited to within a few millimeters of implant site Invasive surgery required to prepare implant site (usually at resection site)
Convection-enhanced	Distributes drug in ~ 1 – 2 cm radius spherical volume High concentration of drug within most of delivery volume Spatial limits of delivery can be controlled tightly by infusion duration	Requires catheter(s) placed at delivery site(s) Requires lengthy infusion

Further strategies to traverse the BBB may rely on methods such as active efflux, endogenous, carrier, or receptor-mediated transport. One such modality using peptides with high affinity for transporter (transcytosis) pathways in the brain may be a viable option, in that drugs previously impenetrable to the brain may be delivered using this method. Work done by Demeule *et al.* [32,33] has identified and investigated a family of Kunitz domain-derived peptides called Angiopeps that can be used for drug delivery in the brain. They found that Angiopep-2, a 19 amino acid peptide, has a higher transcytosis ability and parenchymal accumulation than proteins known typically to penetrate the BBB, such as transferrin, lactoferrin and avidin. Further, it was discovered that transport of Angiopep-2 across the BBB is partly receptor-mediated by the low-density lipoprotein receptor-related protein-1 (LRP1), often detected in glioblastomas. Applying this to a drug delivery system, work by Regina *et al.* [34] showed that although the traditionally used chemotherapeutic agent paclitaxel shows a lack of uptake in the brain, when conjugated to Angiopep-2 (ANG1005), paclitaxel crosses the BBB and distributes into the brain at a level four to five times higher than paclitaxel alone. In intracerebral tumor mice models, administration of ANG1005 prolonged the survival of mice with U87-MG glioblastoma and NCI-H460 lung carcinoma tumors, and ANG1005 has entered clinical trials in patients with primary or secondary metastatic brain tumors [34].

So far, we have discussed non-targeted strategies that rely on a fundamental property of cancer cells, such as rapid proliferation, to kill the cancer cells. Recent approaches, such as targeted quantum dots or nanoparticles, have attempted to enhance this strategy by accumulating a greater concentration of drug near the tumor cells. This strategy, recently reviewed by several investigators [35-37], involves decorating a nanoparticle with ligands for cell-surface receptors or antibodies for cell-surface antigens. These particles have been shown to accumulate in tumors despite the endothelial barriers present between the blood and tissue because tumors often have vasculature with enhanced permeability or leakiness. This is thought to be caused by an excess of growth factors important in angiogenesis, such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), resulting in poorly formed tight junctions [38]. Nanoparticles are able to traverse this leaky vasculature in the tumors and then become trapped in the surrounding tissue whose extracellular matrix acts as a filter for the nanoparticles. This is known as the enhanced permeability and retention (EPR) effect, and it is likely that most of the accumulation of nanoparticles in tumors is due to this effect rather than specific targeting [39,40]. Systemic administration of quantum dots also results in accumulation in the liver and spleen, thereby raising health concerns [41,42]. Regardless of the cause of accumulation in the tumor, nanoparticles have been shown to accumulate in tumor tissue; thus, systemic injection of nanoparticles presents a promising new strategy for treatment of primary tumors [43].

In the case of GBM, accumulation of drug in the primary tumor will not suffice to prevent recurrence due to the presence of invasive cells in the tissue surrounding the primary tumor. Also, most drugs injected systemically predominantly kill cells that are rapidly dividing; thus, invasive cells are less likely to be killed by these drugs because they are not dividing while in the process of migrating [44-46]. Even if these factors were not impediments to effective treatment, the vasculature in the tissue where these invasive cells reside has not been permeabilized as it has in the primary tumor, so the intact BBB inhibits transport of drug into the tissue and drastically decreases the dose delivered to these invasive cells. This is thought to be the root

cause of the dismal prognosis of GBM – even if the primary tumor is resected and treated with chemotherapy, invasive cells remain and are ineffectively treated by chemotherapy, allowing recurrence in most patients.

3. Delivery at tumor resection site

Early work in which localized delivery was evaluated as a treatment for drug delivery to the brain involved polymeric drugs, which provide controlled release systems from both degradable and non-degradable polymers. Typically, these were administered in the tumor resection site where there was already a convenient site to place these delivery agents and an invasive delivery route that had already been used for the resection, thereby causing no further damage from drug delivery. These systems allow sustained release for long time periods, from weeks to months. Although both non-degradable (polymer still existing post-delivery) and degradable polymers have been investigated, degradable polymers are preferred owing to the fact that they erode, thereby avoiding risks of chronic problems at the implant site. The main implant of choice for treating GBM with this strategy is Gliadel, which consists of a polymer (poly(carboxyphenoxy-propane/sebacic acid) [PCPP-SA]) combined with the chemotherapeutic agent BCNU. Although Gliadel is tolerated well in terms of toxicity, it produced only a modest improvement in the prognosis of malignant gliomas [17,47]. This is primarily because of the steep decrease in concentration as distance from the implant site increases. The flux of drug from the implant to the surrounding tissue is predominantly a function of the concentration at the implant site (flux is actually proportional to the concentration gradient). As the concentration at the implant site is limited by the need to avoid toxicity to normal brain tissue, there is also an upper bound on the driving force for drug transport from the implant into surrounding tissue. For this reason, the gradient of concentration must be large to drive drug transport and the concentration at the implant site is limited; therefore, the concentration decreases rapidly as distance from the implant site increases. Fung *et al.* [48] and Krewson and Saltzman [49] measured drug distribution, showing that diffusion delivers detectable concentrations < 0.5 mm from the implant site. **Figure 1** shows data from Krewson and Saltzman in which neural growth factor (NGF) concentration released from a polymer implant is plotted with respect to distance for coronal rat brain tissue sections intersecting the NGF-polymer implant. The unbroken line depicts the steady-state solution of mathematical model predictions, and these values are compared with experimental autoradiography measurements collected in different directions from the polymer implant (symbols). The mathematical modeling results accurately predicted distribution observed from the rat autoradiograph data.

These limitations led to mathematical modeling efforts intended to determine whether there was a solution to this problem of steep decrease in concentration with respect to distance from the polymer source. Work by Saltzman and co-workers evaluated the extent and rate of drug distribution and elimination from a polymer implant in a one-dimensional model [50]. Initially, only diffusion and elimination were considered, whereas more complex features inherent to tumors, such as interstitial pressure resulting in a convective flux near tumor edge, were neglected. Later, Mak *et al.* [51] reviewed drug release kinetics from intracranial controlled release polymer implants and molecular transport following release into the interstitium. They used a mathematical model to predict the distance the drug traversed, duration of controlled release, and the corresponding amount of drug released with respect to time. For the purposes of controlled release, slowly eliminated drugs are desired; therefore, high-molecular-mass drugs such as dextran were retained longer in the brain and were more widely distributed than low-molecular-mass drugs from an intracranial implant. It was suggested that using polymer conjugated to an active drug would reduce the elimination rate of drug, as for conjugated drugs the penetration depends on the stability of the linker (spacers, hydrolytic sensitivity, pH) and elimination (route of delivery and dose attached to polymer). Further, methotrexate (MTX)-dextran conjugates and those with longer half-life due to more stable chemical bonds were studied in three-dimensional tumor cell cultures. These studies show that drug modification to attain better stability will probably aid in penetration and spatiotemporal distribution via diffusion.

More recent work expands these models into three dimensions. Wang *et al.* used a three-dimensional mathematical model to investigate delivery of the low-molecular-mass drug BCNU to the brain [17]. Wang *et al.* evaluated the efficacy of traditional systemic bolus injection compared with controlled release from a polymer. In comparison with systemic bolus delivery, controlled release provides greater local concentration for a longer duration with reduced systemic toxicity. It was found that penetration depth varies with intracellular kinetics, transvascular permeability and molecular size. Molecular size plays a role when convection due to Starling flow is of a similar order of magnitude as diffusion, and this is the case for high-molecular-mass drugs but not for low-molecular-mass drugs such as BCNU.

In parallel to these modeling efforts, other investigators have performed *in vivo* studies of drug distribution. Haar *et al.* estimated the diffusion coefficient of a radiolabeled oligonucleotide (^{35}S-PS-ODN) after intraparenchymal infusion in rats by assuming that the distribution followed Fick's second law taking into account interstitial pore fraction and tortuosity [52]. In this analysis the brain was modeled as a homogeneous medium, with loss of drug occurring by means of vascular and cerebral spinal fluid (CSF) uptake, internalization and degradation. Through the comparison of radiogram data with mathematical model results, a spatiotemporal distribution relative to the cannula tip was found. It was observed that diffusion was slower than predicted, perhaps owing to cellular uptake and binding to cell-surface molecules or extracellular matrix.

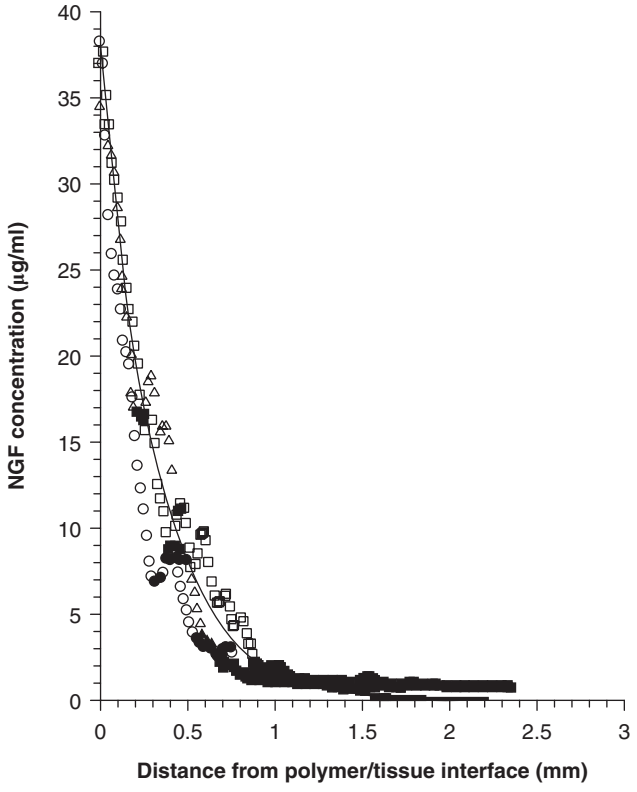

Figure 1. Concentration profiles of [^{125}I]NGF diffusion from a polymer implant comparing mathematical modeling (unbroken line) with experimental results (symbols) after diffusion for 48 h. Different shaped symbols (triangle, circle, square) represent measurements taken in three different directions (angles from the polymer surface). Diffusion extends ~ 0.5 mm after 48 h.
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NGF: Neural growth factor.

Similar work has accounted for the general transport mechanisms and characteristics through porous medium with tortuosity and pore fractions [53-56]. Nicholson and Tao evaluated the diffusion of 3 – 70 kDa dextran molecules experimentally in an agarose gel and rat tissue, and they compared these data with a relevant mathematical model of brain extracellular space (ECS) [57]. Whereas diffusion of 3 – 40 kDa molecules was not restricted, molecules > 70 kDa were unable to access some sites within the porous matrix. These investigators also studied diffusion of various sizes of negatively charged albumins (14, 45 and 66 kDa) in rat cortical slices [58]. They established that negative charge had little effect on their mobility and that size was the primary factor governing movement. Also, when the possibility of uptake or degradation exists, molecules that are large and diffuse slowly are more likely to be removed through these means.

A further consideration for drug delivery to brain tumors is increased tumor vascularity and its effects on transport. Tumors recruit more vasculature than do normal tissues, and this leads to increased interstitial pressure in the tumor and fluid flow from the tumor to surrounding tissue. Jain reviewed the transvascular transport of molecules in tumors and fluid movement governed by hydrostatic and oncotic gradients across vessel walls, determining that a fraction of the fluid filtered into the interstitial space is reabsorbed into the microvascular network and the rest by lymphatics or from the tumor periphery into normal tissue [59]. Although the brain does not include a lymphatic system, the concentration and pressure gradients necessary for diffusion and convection, respectively, are important considerations in the transvascular exchange of fluids in tumors. Of similar concern for more complex considerations is the altered environment surrounding tumor tissue. Jain also reviewed the differences in solute and fluid transport in tumor versus normal tissue interstitial [59]. Tumor interstitium has larger interstitial space, higher collagen content, lower proteoglycan concentration, and typically higher interstitial fluid pressure/bulk fluid flow. Although high interstitial diffusion coefficients may aid movement of molecules in tumor interstitium, high interstitial pressure and low microvascular pressure may slow extravasation of targeted drugs.

Summarizing all of these issues, it is clear that there are many reasons why drugs implanted at the tumor resection site have not resulted in substantial improvements in patient prognosis. Owing to limitations in concentration at the implant site, the gradient of concentration cannot drive a large flux of molecules into the surrounding tissue. As the drug diffuses, it is degraded, taken up into the vasculature, internalized by cells, and binds to extracellular matrix so transport is further hindered. Small molecules are able to avoid some of these mechanisms by moving more rapidly through the tissue, but large molecules are greatly affected and have even more limited distribution than would be predicted. The brain extracellular space is tortuous and the volume fraction available for diffusion and fluid transport is low, further hindering diffusion. Finally, tumors tend to have an increased interstitial pressure that drives fluid flow away from their center. Thus, even if the drug is distributed to the edge of a nascent tumor, this effect will decrease further the dose of drug delivered.

4. Convection-enhanced delivery

Convection-enhanced delivery (CED) is achieved by infusing a liquid carrying the drug as a solute into the tumor tissue, and continuing the infusion process to drive the drug further into the tissue as it is carried by bulk fluid flow. In the presence of fluid flow, solutes move at the speed of the fluid velocity (barring filtration hindering solute flux). When fluid velocity is high, this speed is much greater than the flux achieved by diffusion alone, and the solute travels farther through CED than it would in the same period of time with diffusion alone. This can be defined by a dimensionless number called the Peclet (Pe) number, which is in essence

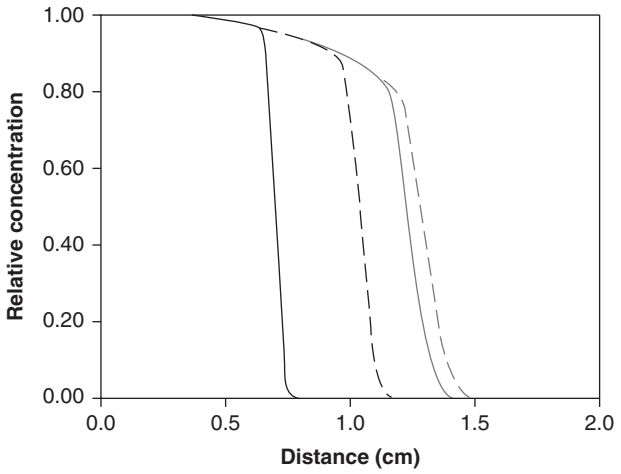

Figure 2. Relative concentration profiles are shown for convection-enhanced delivery of a macromolecule in brain tissue at various times during high-flow microinfusion (3 µl/min). Concentration profiles for 2, 6, 10 and 12 h are denoted by the unbroken black, dashed black, unbroken gray and dashed gray lines, respectively.
Figure adapted from [63].

the ratio of solute velocity due to convection versus solute velocity due to diffusion.

Initial attempts at CED characterized infusion of a dye into brain phantom gels (0.6% agarose). Chen *et al.* observed infusion of a low-molecular-mass dye into a phantom gel and a low-molecular-mass magnetic resonance imaging (MRI) contrast agent, gadodiamide, into porcine brains [60]. They showed that infusion into the agarose gel closely resembled infusion of gadodiamide into the porcine brain, validating the use of agarose gels as a model *in vitro* system, and subsequently evaluated pressure, distribution and catheter performance in injections of 24 h and longer. They developed a mathematical model of drug transport through a poroelastic solid and compared this with data from their *in vitro* gel experiments [61]. By varying the infusion rate from 0.5 – 10 µl/min and port hole diameters, they identified issues inherent to an infusion technique rather than those attributed solely to gel characteristics or drug design to validate protocols and devices that could be used clinically. Although CED drives drugs through the extracellular space more readily than diffusion, they observed that flow rates greater than a few microliters per minute resulted in gel dilation and pore disruptions surrounding the injection site. From these results, practical issues are elucidated, including surface friction and drag force of inserted catheters, reflux along the catheter track (involving considerations such as catheter diameter, insertion process, flow rate to minimize the size and time of backflow) and straight/smooth positioning of the catheter with mechanical guidance that would help seal the insertion path to prevent backflow.

Gillies *et al.* infused small nanoparticles (8 – 12 nm) and viral particles in 0.6% agarose gels to establish a particle size threshold for optimal infusion [62]. They concluded that there is a size threshold of 10 – 100 nm for optimal infusion. This observation also enabled better design of fluorescent tags to achieve a penetration depth so different excitable wavelength particles could be used, therefore expanding the depth at which imaging experiments could be conducted.

Morrison *et al.* extended CED to allow delivery of high-molecular-mass compounds through high-flow microinfusion [63]. They compared experimental data with a mathematical model of transferrin, 81 kDa, infused into the white matter of a feline brain. These investigators increased the convective flow rate to high-flow conditions (0.5 – 6 µl/min), and they estimated time-dependent penetration depth and corresponding concentration profiles by evaluating bulk flow during and post-infusion. Their model builds on the rigid pore transport model of Baxter and Jain [13] but specializes it to the brain and a small catheter source. They compared convective (high flow) and diffusive (low or no flow) microinfusion (in the latter case Pe << 1). High-flow microinfusion provided a 10-fold increase in volume distribution in comparison with low-flow microinfusion. If a slower degradation rate were assumed, larger treatment volumes could be achieved; but, even with more rapid degradation, CED still achieved greater distribution volume than did low-flow microinfusion. **Figure 2**, adapted from Morrison *et al.* [63], shows the relative concentration as a function of distance away from the catheter source at 2, 6, 10 and 12 h. From these results it is evident that, even for a short 2 h infusion, the corresponding distance of drug perfusion exceeds that attained by diffusive delivery.

Morrison *et al.* conducted a subsequent study determining the effect of flow rate, catheter diameter and tissue mechanics on infusate backflow around the catheter shaft [64]. They used a mathematical model to evaluate the relationship among the above parameters, hydraulic flow and tissue deformation. Owing to hydrostatic pressure imposed by the infused agent from the catheter, the infusate may move tissue back, creating an annulus/reservoir, potentially becoming a second source. They developed a mathematical model of backflow along a catheter to evaluate the potential trade-off between catheter diameter and inflow rate to prevent infusate loss from the targeted tissue into adjacent regions or the subarachnoid space. Modeling results indicated that using the smallest catheter radius minimized backflow, while simultaneously increasing the flow rate from the catheter tip.

As mentioned above, Baxter and Jain [13] had previously described mathematical models of fluid transport and macromolecules near tumors. They developed a macroscopic fluid transport model to describe the pressure and velocity distribution, and a macroscopic solute transport model to describe the concentration profile of macromolecules in the tumor interstitium both for a tumor surrounded by normal tissue, and for an isolated tumor. The findings revealed that

the highest pressure originated in the tumor center and increased with tumor growth, and further increases were seen correspondingly in interstitial resistance as the tumor edge was approached. The differences in pressure between the tumor center and tumor edge promote non-uniformity in fluid filtration. This causes very little solute to reach the tumor center.

Other researchers have added more detail regarding the specific architecture of the brain as it relates to drug delivery. Much of this work has focused on more accurately describing the anatomical and physiological characteristics of the brain – specifically the difference in macromolecular transport within gray and white matter. This has led to the emergence of finite element models (FEM), in which detailed anatomical maps of the human brain are used to estimate more precisely transport parameters and spatiotemporal distribution based on the above-mentioned transport concepts. Kalyanasundaram *et al*. predicted intracranial drug distribution and clearance in a two-dimensional model [65]. They validated this model with MRI by quantifying the concentration of a marker perfused by CED. These results were used to predict the delivery of interleukin-2 (IL-2) during and post-CED. Sarntinoranont and co-workers [66] performed FEM of CED into the rat spinal cord. Their work defined hydraulic conductivity and directional anisotropy ratios better in white and gray matter. This group developed their FEM model further to incorporate leaky vasculature, no lymphatics, cell proliferation/invasion, and a more complex mechanical model of growth increments in a vascularized spherical solid tumor [67]. More recent work demonstrates a generalizable methodology to process MRI and diffusion tensor image (DTI) scans, segment gray and white matter, assign transport properties, and model the transport of macromolecules in the interstitium. In comparison with their previous FEM model, imaging data were used to build a full three-dimensional spinal cord versus a single cloned slice extruded into three dimensions. This line of research was applied recently by Linninger *et al*. to human MRI and DTI data to provide patient-specific images for optimization of CED based on patient anatomical features [68,69]. Their model uses first principles of mass transport and chemical kinetics to model intraparenchymal administration of drugs by means of CED. Linninger *et al*. used this reconstruction to determine infusion and catheter design parameters to optimize penetration depth and volume of distribution [69]. One particularly interesting discussion is about the use of multiport catheters (5 holes) to increase distribution by 26% while simultaneously reducing tissue stress.

Although there is still much continuing debate and research regarding the distribution of drugs when delivered by means of CED (and how to best optimize this), there is already some clinical history and continuing use of CED with human patients. Effort has been expended not only to find a feasible way to deliver and achieve a viable distribution of therapeutics by means of CED, but also to include tumor targeting in conjunction with CED [4,70-84]. Clinical trials have been conducted utilizing CED for drug delivery of various agents, including the use of targeted growth factors and immunotoxins for EGFR, TfR, IL-13R and IL-4R [4,76,77]. So far, clinical trials relying on CED and targeted treatment have achieved only limited success for a variety of reasons, including mechanical, anatomical and targeting issues [76,77,85]. Delivery issues including mechanical means comprise backflow due to tissue damage from the catheter, catheter design, edema, elevated interstitial tumor pressure or void creation, which result in dose reduction, leakage outside the area of interest, and increased delivery to non-targeted areas thereby resulting in increased toxicity to healthy tissue and inadequate distribution [81]. Physiological issues, such as immunogenicity, severe inflammation, tissue specificity and heterogeneity of tumor target expression, result in delivery variability to the target site and associated toxicity [78,84]. Similarly, maximum tolerated doses in clinical trials need to be established, but these measurements are confounded by poorly predicted delivery distributions [74]. Therefore, there needs to be a link between optimizing the mechanics of the delivery system and the targeting agent of choice [74,75].

Continued work by Sampson *et al*. has tried to bridge this gap by comparing the ability of a DTI software algorithm to predict patient-specific drug distribution [86]. These results were compared with actual distribution of cintredekin besudotox (IL13-PE38QQR) coinfused with ^{123}I-labeled human serum albumin. Mechanistic issues such as catheter trajectory that failed to deliver drug were identified with this approach. Similar work compared high-molecular-mass drug distribution relative to target anatomy and catheter position in patients using SPECT images coinciding with MRI scans, validating that CED has the potential to deliver these agents in clinically relevant distribution volumes; however, this work acknowledges that target tissue anatomy and catheter position are key parameters that remain in need of optimization [87]. Although research is focused on correlating the practical aspects of delivery with the intricacies of transport governed by mass transport and fluid dynamics, the non-trivial magnitude of considerations make accurate and successful delivery a challenging endeavor. Therefore, although many new therapeutic targets have been investigated, the distribution limitations of current drug delivery systems seem to be the barrier to attaining delivery to distant sites while avoiding adverse side effects.

With respect to CED location, therapeutics are often delivered either intratumorally or peritumorally. Recent work delivering Cotara®, a radiolabeled monoclonal antibody specific for a DNA/histone (H1) complex prevalent in necrotic tumor tissue, is in clinical trials [80,83]. These studies typically deliver Cotara intratumorally. Although delivering a drug into the tumor resection site (or inoperable tumor) seems likely to treat the cancer, unfortunately this focuses the delivery primarily to the inner necrotic or non-migratory

tumor core. As mentioned above, it is the highly migratory/invasive cells that exist on the outer edge of the tumor that are most likely to cause recurrence. Therefore, a drug that targets or distributes only to the tumor core (by means of specific targeting or simply because of lack of distribution) will not be distributed to the migratory cells along the tumor rim, allowing these cells to contribute to recurrence. By contrast, if only peritumoral delivery is administered, the interstitial tumor fluid pressure mentioned above may inhibit drug from penetrating the primary tumor. These delivery strategies focus on existent vascularized tumors, they do not account for the nascent secondary tumors established by migratory cells. One interesting aspect of this study is that, during the safety and efficacy testing, the effects of single or dual catheter delivery were observed, suggesting that a combined therapy with multiple catheters may be the most promising delivery option. Through this approach drug can be delivered effectively to cells at the core and rim, and in transitional migration. In addition to using CED for drug, nanoparticle, or biomacromolecule distribution, CED has also been considered for delivery of virus-mediated, gene, and vector distribution in both solid tumors and central nervous system pathologies in efforts to provide better distribution to pathological cells [70,71,88].

In addition to these human applications of CED, there is a rich history of animal studies of CED [4,89-98]. One caveat to animal studies of CED is the size scale. The velocity of fluid, thus the velocity of solute distribution, decreases with the inverse of radius squared. Therefore, if one is perfusing an animal brain that is only a few centimeters in radius, it is likely that CED can distribute drug to the entire brain. However, this result is not scalable to the human brain, which is much larger. Another way to think of this issue is in terms of the Peclet number. The Peclet number is > 10 (convection dominant) within 1 mm of the catheter; however, the Peclet number is < 0.1 (diffusion dominant) at distances > 60 mm from the catheter [99]. Thus, for most animal studies, the entire brain will be in the convection-dominant or convection-influenced regions, whereas for human brains, a significant portion of tissue will probably be either in the region in which both mechanisms are important or in the diffusion-dominant domain. One study that begins to address this issue is by Thomale *et al.*, who characterize the feasibility of multiple catheter placements in rat brainstem [97]. Their studies found drug distribution to be best when three cannulae were used instead of a single cannula. No neurological deficit was observed, and it appears that unilateral placement of 1 – 3 cannulae in the brainstem combined with intraparenchymal infusion at 1 µl/h is feasible.

Despite this caveat, some issues of note have been raised in animal studies. Prabhu *et al.* observed an alteration in the brain parenchymal microstructure that decreased tissue resistance even at low infusion volumes, raising the concern that high flow infusion may lead to tissue damage [96]; however, studies by Bobo *et al.* [89] and Lieberman *et al.* [94] indicate that this effect may be a short-lived, reversible process. Bobo *et al.* also demonstrated that the concentration in the local extracellular fluid (CNS) following CED was 100 times greater than the concentration in the same tissue following systemic delivery. Lieberman *et al.*'s study, performed in Macaque monkeys, demonstrates delivery of dextran (10 kDa) to a diameter of 4 cm with a 5 h infusion. Owing to the large size of Macaque brains relative to most animal models, this study shows the potential scalability of CED to human use. Kawakami *et al.* confirmed the supposition that the maximum tolerated concentration is greater with CED than with systemic injection [92]. The overall dose is less for CED because a much smaller volume needs to be delivered. This study also shows that drug is completely cleared from the blood within 24 h of systemic injection; however, drug still remains in the tissue at detectable concentration 24 h after CED. Groothuis *et al.* achieved local concentrations several thousand-fold greater than systemic toxicity levels through CED in a dog model [91].

5. Delivery of molecular targeting constructs

In parallel to research investigating delivery options, recent research in cancer drug targeting has focused on exploiting receptor overexpression by tumor cells (relative to healthy cells) to enhance the local concentration of therapeutic and/or imaging molecules. Cellular targeting is advantageous in that adverse side effects may be avoided by targeting only cells of interest (especially in the delicately functional area of the brain), and treatment efficacy may be improved owing to increased local concentration near the tumor cells. Drug targeting may be used for imaging as well, and it is possible that nascent secondary tumors, previously undetectable by commonly used techniques such as MRI and positron emission tomography (PET), may become detectable.

Microarray and immunohistochemical data have supplied knowledge of several cell-surface receptors that are overexpressed by cancer cells [88,100]. Specifically, the $\alpha_6\beta_1$-integrin is overexpressed in invasive glioma cells, allowing these cells to migrate, thus contributing to the invasive phenotype shown by GBM cells [44-46,101-104].

Several strategies have been used to target drugs or imaging agents by means of these overexpressed receptors. Drugs have been conjugated to antibodies for the epidermal growth factor receptor Her-2 to make the targeted drug Herceptin® (Genentech, Inc.), and Avastin® (Genentech, Inc.) is a drug-conjugated antibody to the vascular endothelial growth factor receptor (VEGFR). Limitations include the relatively large size of the antibody compared with the pore size of typical brain extracellular matrix, which can lead to inhibited flow. As mentioned above, modeling efforts have incorporated filtration coefficients to account for hindered flow in CED or diffusive delivery, and antibodies show minor filtration effects of this sort. More importantly, antibodies are far too large to cross intact BBB; thus, antibodies, like all molecular targeting

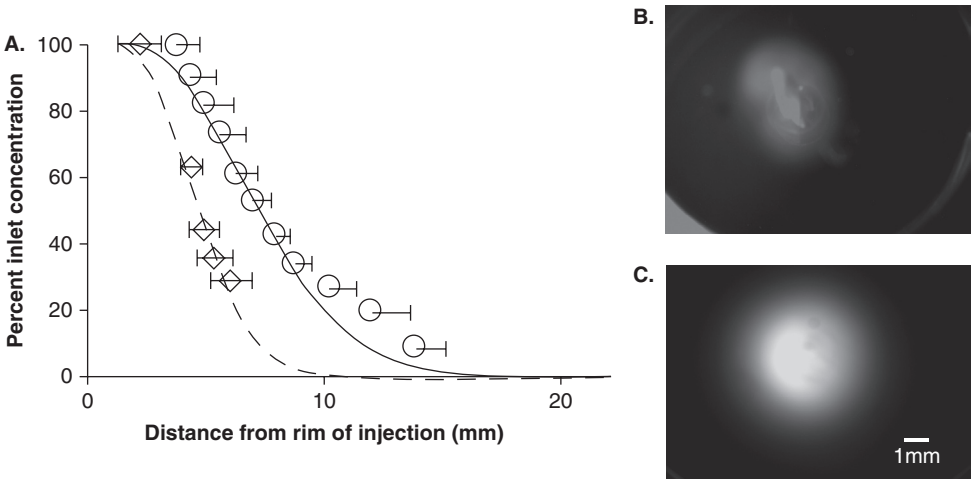

Figure 3. A. Perfusion profiles of quantum dots (diamond, n = 2) and trivalent construct (circle, n = 3). Lines depict model results fit for the diffusion and retardation coefficients, dashed (quantum dot) and unbroken (trivalent). Perfusion patterns of quantum dots **(B)** and trivalent construct **(C)** after 2 h of infusion. Scale = 1 mm.
Figure reproduced from [115]. Copyright © 2007 American Chemical Society.

constructs, must be delivered directly into tissue through one of the other two mechanisms discussed above. From a targeting standpoint antibodies are limited further by their inherently limited ratio of binding to cancer cells. Caplan and Rosca have provided a theoretical proof that antibody targeting can, at best, achieve a ratio of binding equal to the ratio of receptor expression between cancer and normal cells [105]. Current delivery strategies for antibody-conjugated therapies include systemic delivery and CED. One particular antibody-conjugated drug, Cotara, is delivered by CED, and targets the DNA/histone (H1) complex present in the necrotic region of the tumor core. As described above, a few issues exist with this treatment. One is that, as Cotara targets the necrotic region of tumor tissue, it will not target the living invasive cells that are responsible for most GBM recurrences. Further, delivery of Cotara is administered intratumorally, making it difficult for delivery to extend outside the tumor region itself to reach these invasive cells in the first place.

More recent targeting constructs involve conjugating multiple antibodies or receptor ligands to decorate the surface of nanoparticles, such as quantum dots, nanoshells, and so on [106-114]. These particles gain the advantage of multivalency, which, despite individual ligands often having micromolar affinities, show cooperative avidities in the subnanomolar range similar to antibodies. Additionally, Caplan and Rosca have argued that multivalency can potentially overcome the limitation of receptor ratio, allowing an even greater ratio of binding between cancer and non-cancer cells. Nanoparticles are still in the development stage, but most animal studies involve systemic (intravenous) delivery of the particles, which are then able to extravasate in leaky vasculature. Although there continues to be debate, it is likely that much of the targeting observed is actually due to the EPR effect. The most likely effect of targeting ligands in this case is to increase retention at the tumor site relative to retention at other sites of leaky vasculature (such as liver and spleen). Nanoparticles extravasating at the tumor site would be able to bind more receptors, and the relatively slow dissociation rate of these multivalent particles from tumor cells would tend to keep the particles from being taken back up into the blood. CED of nanoparticles is possible; however, Rosca *et al.* have shown that a quantum dot is significantly hindered by pore sizes typical to brain tissue [115]. **Figure 3** shows that after 2 h of delivery, the quantum dots (diamonds) perfused a distance of ~ 5.2 mm, in comparison with the distribution of a trivalent biomacromolecular construct (circles) 8.2 mm from the injection site. When fitted to transport equations, Rosca *et al.* found that quantum dot convection was hindered 75% relative to unhindered solute, resulting in significantly smaller distribution volume and heterogeneous distribution even though delivery was to homogeneous mock tissue (0.6% agar gel).

An *in vivo* study by MacKay and co-workers describes delivery of liposomes by means of CED [95]. These investigators studied the effect of diameter, charge and steric shielding on distribution of liposomes in the brain. Liposomes 40 nm and 80 nm in diameter penetrated less than did 10 kDa dextran, confirming *in vitro* work concluding that particles 10 – 100 nm in diameter will be significantly hindered by the matrix. Neutral particles and those conjugated with poly(ethylene glycol) penetrated farther than unshielded liposomes.

A third type of molecular targeting construct, polymer-conjugated drugs, combines small size with multivalency in an attempt to achieve the increased specificity of nanoparticles with greater mobility of antibody (or even smaller) constructs. In comparison with nanoparticles, a polymeric

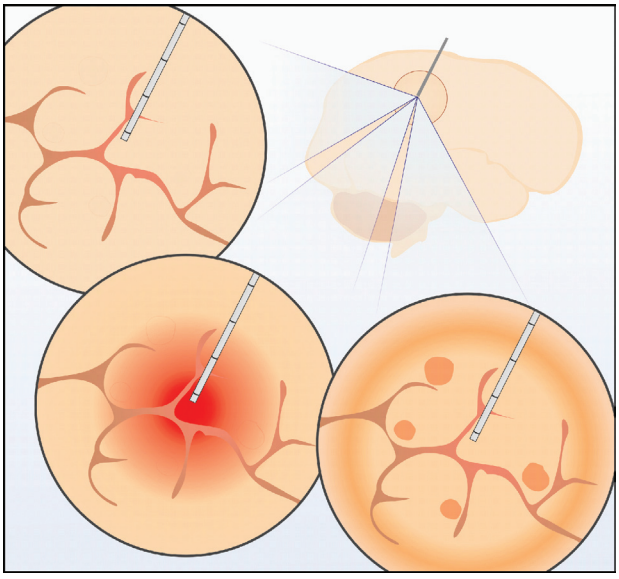

Figure 4. Schematic depiction of proposed delivery strategy for multivalent targeting constructs. (Left) Initially, the position of secondary tumors is not known and a catheter is placed in a region believed to contain secondary tumors or invasive cells. (Middle) Labeled constructs are injected through the catheter by means of convection-enhanced delivery; however, little contrast is observed between tumor sites and normal tissue. (Right) Artificial cerebral spinal fluid is injected, unbound labeled construct is pushed away from the injection site by convection, and remaining bound constructs yield obvious contrast between tumor and non-target tissues.
With kind permission from Springer Science + Business Media (Copyright © 1995). Eur J Cancer, Influence of molecular weight on passive tumour accumulation of a soluble macromolecular drug carrier, 1995 ; 31A (5): 766 -70, Seymour LW *et al.*

construct, three peptides linked by poly(ethylene glycol), was shown not to be inhibited by mock tissue and to display homogenous distribution (**Figure 3 A** circles and bottom right). Constructs of this size are still too large to cross intact BBB, and systemic delivery would most probably not be a useful option for the further reason of short residence time in the blood owing to rapid clearance in the kidneys (these constructs are < 40 kDa) [116,117]. Thus, Stukel *et al.* proposed CED as the most advantageous delivery option for polymeric targeting constructs [118]. As mentioned above for nanoparticles, the principal difference between constructs bound to tumor versus normal cells is the effective dissociation rate. Stukel *et al.* continue to point out that merely delivering constructs to the tumor tissue does not take advantage of this effect. These investigators modeled delivery followed by a convective wash with artificial cerebrospinal fluid, and they demonstrated that contrast between tumor and normal tissue is an order of magnitude greater following this convective wash. It is possible that normal physiological effects such as degradation of constructs (enzymatic or hydrolytic), uptake into vasculature, or other mechanisms will result in the removal of construct to achieve the same effect without the convective wash as shown schematically in **Figure 4**. It is likely that polymeric constructs would be affected by these mechanisms more rapidly than would nanoparticles, which, although it may seem counter-intuitive, may be advantageous for achieving specific targeting of cancer cells through multivalency.

6. Expert opinion

As shown in **Table 1**, each of these delivery methods has strengths and weaknesses depending on the drug or construct to be delivered. Systemic delivery achieves the widest distribution in the brain tissue; however, only very small (< 500 Da) lipid-soluble drugs can cross the BBB, and even then tissue concentrations are at least an order of magnitude less than blood concentrations. Owing to limitations of dose to avoid side effects, this tends to prevent efficacious concentrations of drug from being delivered to the brain and tumor tissue. Implantation in the tumor resection site achieves very high concentrations within a few millimeters of the implant site, and these concentrations can be maintained for weeks or months owing to controlled release polymers. However, concentrations less than a few millimeters away from the implant are far too low to treat glioma cells effectively. CED achieves better distribution than does local delivery, but not as widespread as systemic delivery. Conversely, CED achieves much greater concentration and duration than systemic delivery, but duration of treatment is typically less than that for controlled release polymers implanted in the tumor resection site. Also, it is becoming clear that, to achieve distribution to the tissue in which invasive glioma cells are likely to reside, multiple catheters and multiple day infusions are likely to be necessary, making CED a rather invasive treatment option. As the field moves towards using molecular targeting constructs, it is likely that CED will become a more widely used delivery method because of the incompatibility of multivalent constructs and systemic delivery owing to the inherent size limitation imposed by the BBB (~ 500 Da). Both CED and molecular targeting have great potential to revolutionize the treatment of GBM; however, these strategies must be developed hand-in-hand if their potential is to be realized.

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