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Delivery

Local delivery of antineoplastic agents by controlled-release polymers for the treatment of malignant brain tumours

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Recent advances in the treatment of malignant brain tumours have focused on the development of targeted local delivery of therapeutic agents, which combine various antineoplastic strategies that include cytotoxic, antiangiogenic and immunomodulatory mechanisms, among others. The introduction of local delivery devices for sustained administration of antineoplastic agents represents a new opportunity to effectively treat these malignancies by facilitating the intracranial administration of safe and clinically efficacious doses for prolonged periods of time in a controlled fashion. This technology circumvents the need for high systemic doses with potentially harmful toxicities, bypasses the blood–brain barrier and can be tailored to deliver new agents with complex pharmacological properties. Based on local delivery strategies, new delivery systems, including convection-enhanced delivery and microchips, have been developed. As a result, recent advances in tumour biology have been adopted as potentially translatable treatments and are undergoing preclinical and clinical evaluation at present. These novel approaches could improve the prognosis of patients with these tumours.

Keywords: angiogenesis, brain tumour, controlled-release polymers, convection-enhanced delivery, glioblastoma multiforme, immunotherapy, local delivery, microchip

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1. Introduction

Malignant brain tumours are the most commonly diagnosed adult primary tumours of the central nervous system (CNS). According to the Central Brain Tumour Registry of the United States, the incidence rate of all primary benign and malignant brain tumours is 14 cases per 100,000 person-years (5.7 per 100,000 person-years for benign tumours and 7.7 per 100,000 person-years for malignant tumours) [201]. These tumours account for ~ 1.3% of all cancers diagnosed, and as reported by the American Cancer Society, ~ 13,100 Americans die from such lesions each year [1].

Conventional treatment of malignant gliomas consists of surgical resection of accessible neoplastic tissue [2], followed by radiation therapy [3,4] and chemotherapy [3-5]. Despite significant advances in neuroimaging, neurosurgical techniques, radiation therapy and in the molecular understanding of tumourigenesis, the prognosis for patients with malignant gliomas remains dismal [6]. The median survival after surgical resection alone is 6 months, with only 7.5% of patients surviving 2 years post-operatively. Additional radiation therapy prolongs median survival to 9 months, while systemic chemotherapy provides minimal survival benefits [7,8]. Improvement of existing treatment modalities has been hampered

by several factors, such as morbidity with neurological deficits from elevated radiation doses or extended radiation fields [9], among others. Therefore, an improved understanding of oncogenesis is required to select molecular targets in order to improve available therapeutic options.

Local and controlled delivery of antineoplastic agents represents a new avenue in brain tumour treatments [10]. This review discusses the obstacles encountered in drug delivery to the brain and describes the characteristics of delivery systems developed for local brain tumour therapy.

2. Characteristics of drug delivery to the CNS

The protective environment of the CNS poses significant obstacles in the treatment of malignant brain tumours. Systemic administration of antineoplastic agents by oral or intravenous routes fails to achieve effective drug concentrations into the tumour site even at toxic doses [11]. The presence of biological barriers, including the blood–brain barrier (BBB), blood–cerebrospinal fluid barrier (BCSFB) and the blood–tumour barrier [10], as well as the presence of drug-metabolising enzymes in cerebral microvessels [12] and the activity of efflux transport proteins, such as P-glycoprotein (P-gp) and multi-drug resistance-associated proteins, further prevent accumulation of adequate drug levels [13,14].

The BBB is the regulatory and protective interface that restricts the movement of substances between the bloodstream and the cerebral parenchyma. The surface area of the BBB is estimated to be 5000-fold greater than the surface area of the BCSFB, granting the BBB a more predominant role in drug penetration [14]. This barrier structurally resides in tight junctions between endothelial cells of the capillaries that interface with the cerebral parenchyma. The characteristic low permeability of the BBB permits only the entry of small hydrophobic molecules, a limited set of actively transported molecules such as glucose and particular amino acids, and some macromolecules. Ideal drug candidates tend to be smaller molecules with simple structures, and increased plasma availability and lipid solubility as determined by the octanol:water partition coefficient [15]. This coefficient is a measure of the ratio of agent that equilibrates between oil and water components of a suspension. Accordingly, common chemotherapeutic agents – which are most commonly large, charged or hydrophilic – face significant impedance in vascular delivery to the CNS [16,17].

Efflux transport systems also play a significant role in drug penetration to the CNS, these systems function normally to regulate the transit of hydrophilic nutrients to the brain, but their activity decreases the penetration of several substances. Among the many transport systems described, P-gp, MDR-1 and MDR-2 appear to be specifically related to poor penetration of chemotherapeutical agents [11,13,14].

The obstacles presented by these barriers have led to the development of three different approaches to improve drug delivery to the brain. The first option entails the enhancement of drug permeability through the BBB; this effect can be obtained by tailoring lipophilic variants of chemotherapeutic agents to the natural permeability of the BBB. Within this category, > 20 lipophilic analogues of carmustine (BCNU) have been studied, for instance, lomustine (CCNU) and semustine (methyl-CCNU) have been clinically investigated in patients with malignant gliomas; unfortunately, systemic administration of these analogues did not improve survival of patients when compared with BCNU, which has been shown to modestly improve survival both in preclinical and clinical studies [18-20]. A variation of this approach is to couple antineoplastic agents with lipophilic carriers capable of traversing the BBB [21]. A lipophilic dihydropyridine carrier has been shown to improve intracranial delivery of a myriad of drugs, including antineoplastic agents, antibiotics and neurotransmitters [22]. Further studies with these carriers are anxiously awaited.

The second option to enhance drug delivery involves fenestration of the BBB to deliver antineoplastic agents. Intra-arterial infusion of hyper-osmolar mannitol can cause acute dehydration of endothelial cells, leading to cell shrinkage and consequent expansion of the tight junctions. Williams *et al.* [23] investigated the efficacy of co-administration of carboplatin and etoposide after intra-arterial infusion of mannitol in 34 patients with intracranial tumours. Despite a modest improvement in 4 of 4 patients with primitive neuroectodermal tumours and 2 of 4 patients with CNS lymphomas, no significant benefit was seen in patients with glioblastomata, oligodendrogliomas or metastatic carcinomas.

The third option to overcome delivery limitations is the development of local delivery systems capable of sustained release through surgical implantation within the tumour site. This methodology provides the advantage of sustained local drug exposure while avoiding systemic toxicity. In addition, local delivery proves advantageous in the management of malignant gliomas, as ~ 80 – 90% of postoperative recurrences occur within 2 cm of the original site of the resection. Three variations of this approach can be utilised:

- catheter administration
- convection-enhanced drug delivery
- administration via controlled-release polymers (**Figure 1**)

Catheter systems have been in clinical use for many years. One such system, the Ommaya reservoir, can deliver intermittent bolus injections of desired antineoplastic agents. The recent development of implantable pumps has further permitted the constant infusion of drugs over extended time periods versus bolus delivery. The Infusaid pump (Infusaid Corp., Norwood, MA, USA), the prototype model, utilises compressed vapor pressure to drive solution delivery at a constant rate. Analogous systems include the MiniMed PIMS system (MiniMed, Sylmar, CA, USA) and the Medtronic SynchroMed system (Medtronic, Minneapolis, MN, USA), which employ a solenoid pump and a peristaltic mechanism, respectively, to deliver the infused agents. These delivery mechanisms are restricted by potential mechanical failure, tissue debris or clot obstruction. Further complications

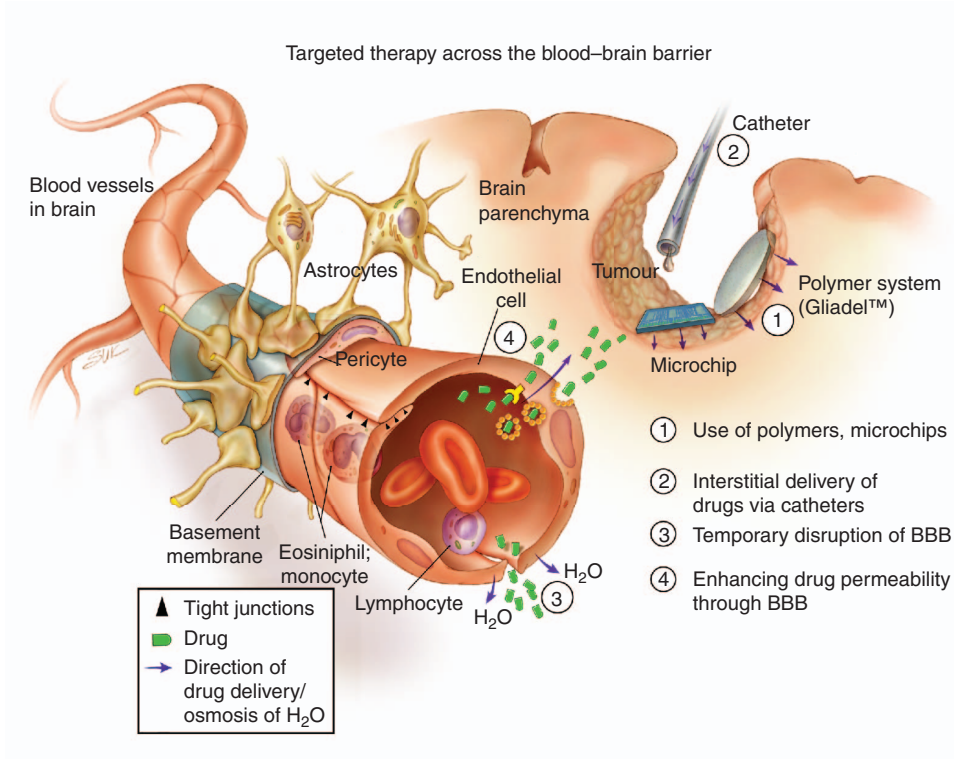

Figure 1. Artist's illustration showing the main approaches for drug delivery to the CNS. Local delivery via controlled-release polymers and microchips is shown in (1), catheter administration is shown in (2), temporary disruption of the BBB is illustrated in (3) and enhancement of drug permeability is depicted in (4). Illustration by I Suk.
BBB: Blood–brain barrier; RBC: Red blood cells.

include infection requiring extra operative interventions for instrumentation removal. In addition, when delivered via such pumps, drugs can often change properties in solution before they reach the site of action. Furthermore, no specific device has been shown to be superior over the others in the treatment of malignant gliomas.

The development of convection-enhanced drug delivery (CEDD) constitutes a promising alternative for brain tumour therapy [24-28]. CEDD is a process employed to increase drug diffusion through the cerebral parenchyma and it relies on a created pressure gradient that is independent of the molecular weight of the delivered agent. When a drug is infused into the cerebral white matter, the pressure gradient is used to introduce high concentrations of drug without any noted structural or functional side effects [29]. Under normal conditions, the compounds delivered travel through the brain parenchyma based primarily on diffusion – a process that is solely dependent on free concentration gradients and the diffusability of the delivered compound. For instance, CEDD has been shown to be safe and effective for delivering gemcitabine and carboplatin to animals implanted intracranially with experimental gliomas [25]. Recently, clinical studies have been performed using CEDD for brain tumour therapy [30-34]. Agents delivered have included paclitaxel [30,35], immunotoxins [32,34,36] and viral vectors for gene therapy [31,33]. These studies have confirmed the safety of CEDD for brain tumour therapy and more conclusive efficacy studies with these agents are expected.

Sustained-release polymeric implants have been developed to directly release therapeutic agents into the brain. Extensive preclinical and clinical studies using controlled-release polymers led to the development of Gliadel® (3.8% BCNU; Guilford Pharmaceuticals, Baltimore, MD, USA), the first Food and Drug Administration (FDA)-approved treatment for newly diagnosed and recurrent malignant gliomas in 23 years. Controlled-release polymers are discussed in detail below.

3. Development of controlled-release polymers for brain tumour therapy

Controlled-release polymers exist in non-biodegradable and biodegradable formulations and differ especially in their diffusion properties, as biodegradable polymers release the agents loaded through diffusion and degradation, whereas non-biodegradable polymers release therapeutic agents only by diffusion, without any polymer decomposition [37]. Among the existent polymeric matrices, only a few meet the criteria required for clinical use. These criteria include absence of toxicity and sustained release of high and low molecular weight agents among others.

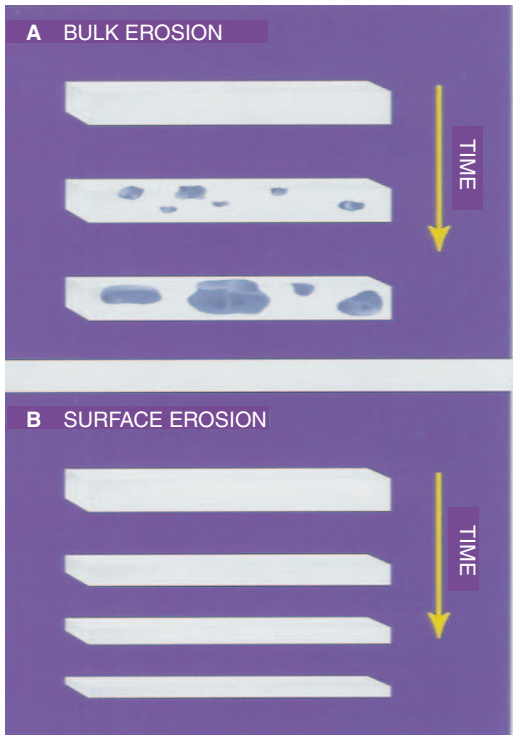

Figure 2. Biodegradable controlled-release polymer implants are intended to release content at nearly constant rate (zero-order kinetics) as they dissolve in body water. Therefore, desired properties include (**A**) surface erosion instead of (**B**) bulk erosion. Reprinted with permission [55].

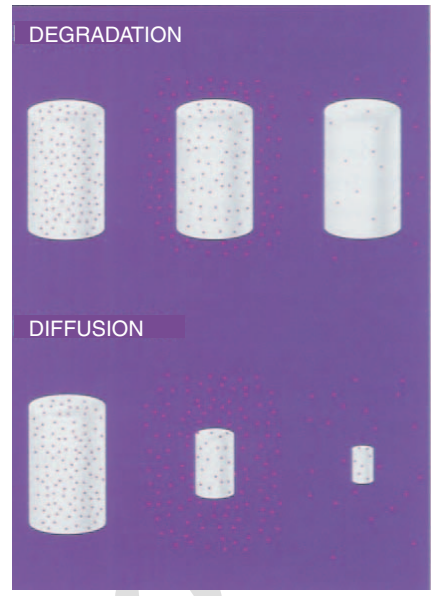

Figure 3. Desired properties of polymer implants include drug release by degradation instead of diffusion. Reprinted with permission [55].

In 1976, Langer and Folkman reported the development of a diffusion-regulated polymer delivery system capable of sustained release of incorporated macromolecules [38]. This non-biodegradable ethylene-vinyl-copolymer (EVAc) permits diffusion of macromolecules through micropores with a rate of diffusion that is dependent on the properties of the bound agent; important factors that influence diffusion from the polymer include the molecular weight, electrostatic charge and liposolubility of the agent released. Non-biodegradable systems are currently used clinically in the treatment of various conditions, including glaucoma [39], dental disease prevention [40], contraception [41] and delivery of chemotherapy [10]. The main limitation for the use of non-biodegradable polymers in the treatment of CNS pathologies is the inertness of the polymer matrix, which requires a subsequent surgical removal [42].

The development of biodegradable polymers permits drug delivery through a combination of polymer degradation and drug diffusion (**Figures 2** and **3**). Among the first polymeric matrices investigated, the poly-lactide-co-glycolide (PLGA), consisting of lactic acid and glycolic acid monomers polymerised with ester bonds, was rapidly introduced for clinical use in the development of absorbable surgical sutures [43,44], and the biocompatibility of this biodegradable polymers in the CNS was confirmed in the rat brain [45,46]. The rate of degradation of PLGA polymers can be adjusted by varying the ratio of lactic acid to glycolic acid [47], and the polymers can be shaped into injectable microspheres that allow direct intratumoural administration [48]. This modality has been employed to deliver a plethora of drugs, including steroids, anti-inflammatory agents, narcotic antagonists, antibiotics, anaesthetics and antineoplastic agents [49-53]. Microsphere-shaped polymers are specially suited for CNS applications, as they can be stereotactically injected into the brain [54]. Unfortunately, although PLGA polymers provide a versatile alternative, their drug release through bulk erosion (analogous to a sugar cube) (**Figure 2B**) can consequently result in sporadic drug release that results in inconsistent and suboptimal tissue exposure profiles with potential unexpected toxicity [55].

The development of biodegradable polymers that have time-dependent surface erosion in addition to drug diffusion was a determinant event in the clinical implementation of controlled-release polymers for brain tumour therapy. The benefits of concomitant polymeric degradation with drug delivery eliminate the need for surgical removal after treatment. In 1985, Leong and colleagues [56] reported the development of the polyanhydride poly[1,3-bis(carboxyphenoxy)propane-co-sebacic-acid] (PCPP:SA) matrix. This polyanhydride copolymer releases incorporated drugs in a sustained fashion through the formation of dicarboxylic acids via a spontaneous reaction with water. Several properties prove advantageous in clinical applications. First, its extremely hydrophobic properties shield embedded chemotherapeutic agents from hydrolysis and enzymatic degradation. Second, zero-order kinetic degradation of the polymer matrix is conducive to the release of a biologically active drug for

prolonged periods at steady concentrations; incorporated drugs would otherwise experience half-lifes of a few minutes when systemically administered. The degradation rate of PCPP:SA can be regulated by varying the ratio of the monomers carboxyphenoxypropane (CPP) and sebacic acid (SA). For example, a 1 mm disk of pure PCPP degrades in ~ 3 years, whereas a PCPP:SA matrix composed of 20% CPP and 80% SA of equal volume has a 3-week biological life [57]. Lastly, the low temperatures (-37°C) and high pressures needed for polymer synthesis allow polymer moulding into a variety of physical shapes – wafers, rods, sheets and microspheres – permitting clinical versatility [57-61]. The biocompatibility of PCPP:SA has been shown in numerous animal studies [62-64], in which no signs of mutagenesis, cytotoxicity or teratogenicity were observed. Histological evaluation of the sites of polymer implantation showed minimal and transient inflammatory reactions, which are similar to the inflammation observed with common surgical haemostatic implants, such as oxidised cellulose (Surgicel®; Ethicon, Inc., USA) and gelatin sponges (Gelfoam®; Pharmacia & Upjohn Co., MI, USA). Further studies where performed with implantation of PCPP:SA polymers into the frontal lobes of cynomolgus monkeys (*Macaca fascicularis*); these studies did not show postimplantation signs of behavioural, neurological or haematological changes [65].

Based on these findings, PCPP:SA was chosen for preclinical testing of nitrosoureas in animal models and was subsequently evaluated for clinical use, receiving regulatory approval in 1996.

A second generation of polyanhydride biodegradable polymers has been developed to enhance the spectrum of deliverable pharmacological agents. The fatty acid dimer:sebacic acid (FAD:SA) copolymer system can deliver hydrophilic compounds that could not be released by the PCPP:SA system [66]. Analogous to PCPP:SA, FAD:SA provides drug shielding, zero-order release kinetics, and biodegradability. Similarly, it can be moulded into any desired configuration and release kinetics can be manipulated by varying the monomer ratio [67,68]. Its ability to locally deliver proteins and antineoplastic agents with biocompatibility has been found to be comparable to PCPP:SA in the rat brain [69,71]. Due to their specificity for the types of agents delivered, the FAD:SA and PCPP:SA technologies complement each other.

In addition to the described polymeric delivery systems, numerous other local delivery modalities have been investigated. Gelatin–chondroitin sulfate-coated microspheres have reproducibly released cytokines *in vivo* [72], while polyethylene glycol-coated liposomes have been fabricated to incorporate anthracyclines [73]. Furthermore, many commonly used surgical materials, such as fibrin glue [74], gelatin sponges [75], Surgicel (oxidised regenerated cellulose) [75], polymethyl methacrylate [76] and silastic tubing [77], have been used to locally deliver drugs to brain tumours with various results. Alternatively, new cotransport agents, including either receptor-specific monoclonal antibodies or modified proteins, have been utilised for successful CNS drug delivery [78]. In summary, due to the extensive investigation into the field of local drug delivery, a wide spectrum of candidate local delivery systems compatible with CNS applications have been developed, and better systems are under investigation.

4. Clinical applications of polyanhydride polymers: BCNU (Gliadel®), development and clinical use

Based on the activity of nitrosoureas against malignant gliomas and its application as a systemic agent in treating brain tumours, carmustine (BCNU) was chosen as the initial drug in the development of polymer-based intracranial therapy. The mechanism of action of carmustine involves the alkylation of nitrogen bases of DNA. Its low molecular weight and lipid solubility permit passage across the BBB at potentially tumouricidal concentrations [22,79,80]. However, dose-limiting side effects (i.e., bone marrow suppression and pulmonary fibrosis), along with its relative short half-life (< 15 min), limit its effectiveness as a systemic agent. Furthermore, clinical investigations into the systemic administration of BCNU in the treatment of brain tumours have shown only modest increases in survival [79,80]. Therefore, in an effort to enhance efficacy and reduce dose-related side effects, BCNU was incorporated into polymers and tested for efficacy against intracranial malignant gliomas.

4.1 Preclinical studies

Preclinical studies were performed to determine the biodistribution of BCNU when delivered via PCPP:SA polymers [81]. The results of these studies indicated that locally delivered BCNU has adequate distribution in the cerebral parenchyma that lasts for prolonged periods of time, and that BCNU tissue concentrations reach therapeutic levels in the brain. Further studies in cynomolgus monkeys documented tumouricidal concentrations of intracranially released BCNU delivered by 20% PCPP:SA polymers at 4 cm from the implantation site at 24 h, 2 cm on day 7, and 1.3 cm on day 30 postadministration [82].

A second set of experiments further investigated the efficacy of BCNU-loaded polymers. Tamargo *et al.* [83] demonstrated that Fischer 344 rats implanted with subcutaneous and intracranial 9L gliosarcoma tumours experienced a statistically significant improvement in survival after local delivery of BCNU in comparison with control animals treated with empty polymers or intraperitoneal injections of BCNU. Polymeric delivery of BCNU resulted in 17% long-term survivors, whereas no long-term survivors were observed among the systemically treated animals.

A final set of preclinical studies evaluated the efficacy of local delivery of a myriad of antineoplastic agents, including BCNU, in the treatment of brain metastases in several metastatic models in mice [84]. Tested tumours lines included B16 melanoma, RENCA renal cell carcinoma, CT 26 colon

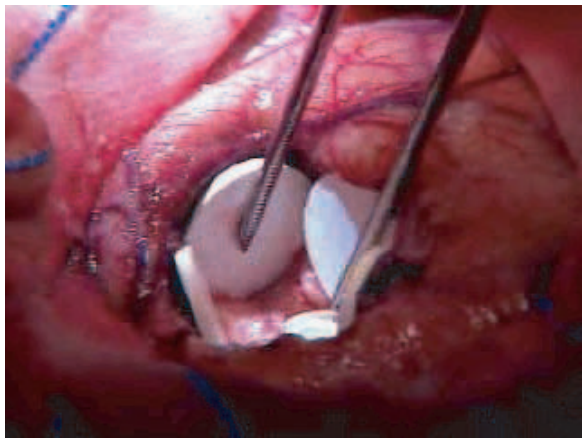

Figure 4. Up to 8 polymer implants line the tumour resection cavity, where the loaded drug is gradually released as they dissolve. This is an original slide.

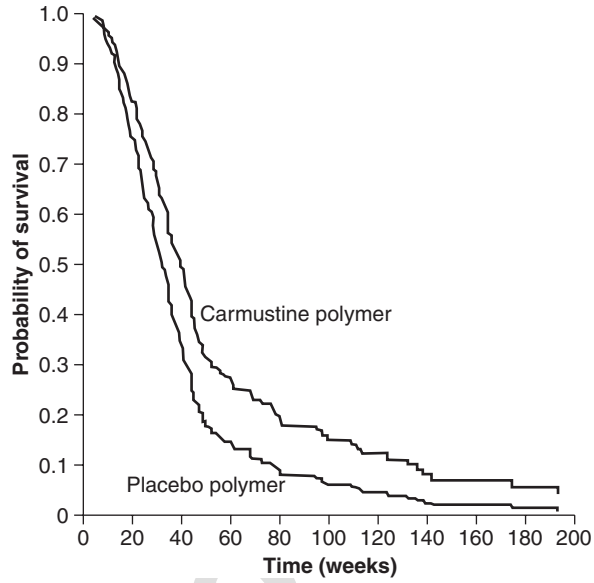

Figure 5. Overall survival for patients receiving BCNU-loaded polymers versus controls at the time of the operation for recurrent malignant gliomas after adjustment for prognostic factors. Reprinted with permission from Elsevier Science [86].

cancer and Lewis lung carcinoma – all of which were effectively treated by local delivery. These findings encouraged subsequent testing of BCNU-loaded PCPP:SA polymers for treating metastatic brain tumours.

4.2 Clinical trials

Earlier preclinical studies established that the BCNU-PCPP:SA polymer delivery system is biocompatible, non-toxic, capable of sustained release of tumouricidal concentrations with a broad distribution zone and improved survival in animals with intracranial tumours. Such results constituted the basis for the subsequent translation of this work into clinical scenarios.

4.2.1 Treatment of recurrent malignant brain tumours

In 1987, a multi-centre Phase I/II clinical trial was initiated to assess the safety of 20:80 PCPP:SA BCNU-loaded polymers into the human brain [85]. Enrolment criteria limited patients to those presenting with recurrent malignant gliomas that had previously undergone surgical debulking and in whom standard therapy had failed. Other requirements included an indication for reoperation, a unilateral single-tumour focus with ≥ 1 cm^3 of enhancing volume on magnetic resonance imaging (MRI) or computed tomography (CT), completion of external beam radiotherapy, a Karnofsky Performance Scale (KPS) score of ≥ 60, and no exposure to nitrosoureas during the 6 weeks prior to polymer implantation. Twenty-one patients were enrolled and three different polymer/BCNU formulations were tested: 1.93, 3.85 and 6.35% (w/w). A maximum of eight wafers, each weighing 200 mg, were implanted into the tumour cavity following resection (**Figure 4**). There was no evidence of systemic toxicity or signs of neurological deterioration following polymer implantation. Further blood chemistry and urinalysis tests did not reveal any signs of bone marrow, hepatic or renal injury. Postoperative T1-weighted MRI scans showed the implanted polymers as areas of decreased signal intensity; CT scans were also able to detect a thin layer of contrast-enhancing signal surrounding the implanted wafers in 13 of 21 patients. These imaging changes were detectable only up to 7 weeks postoperatively, with no correlation between these imaging artifacts and neurological decline. Treated patients experienced a median survival of 46 weeks after polymer implantation and 87 weeks after initial diagnosis. Of 21 patients, 8 (38%) survived > 1 year.

The positive results on safety and efficacy were the foundation for a multi-centre, prospective, randomised, double-blinded placebo-controlled Phase III clinical trial [86]. The study investigated the efficacy of 3.8% BCNU-PCPP:SA polymers for the treatment of recurring gliomas in 222 patients at 27 medical centres throughout North America. The selection criteria were equivalent to those used for the Phase I/II study with the additional provision that no chemotherapy was permitted 4 weeks preoperatively, and no nitrosoureas were allowed for 6 weeks prior to polymer implantation. Six months after initiation of the study, 110 patients had received BCNU wafers, while 112 patients received the placebo. Overall postoperative median survival was 31 weeks for the BCNU-treated group and 23 weeks for the placebo group (hazard ratio = 0.67, p = 0.006) (**Figure 5**). The 6-month survival rate was 60% in the treatment group and 47% in the placebo group. The most remarkable observation was the 50% increase in survival in glioblastoma patients treated with BCNU-loaded polymer in comparison with the placebo treatment (p = 0.02). As before, the BCNU-polymer

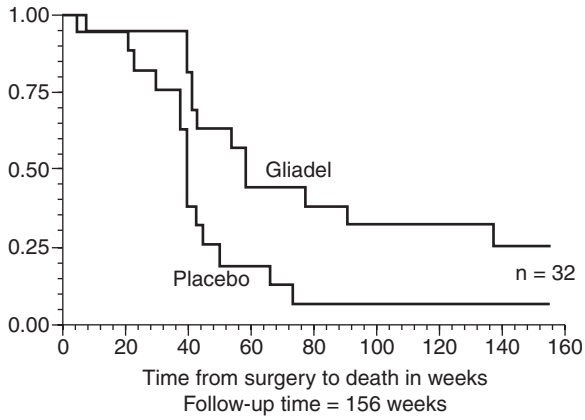

Figure 6. Kaplan-Meier survival curve for patients with initial therapy for Grade III and IV gliomas treated with BCNU-loaded polymer implants versus placebo. Reprinted with permission [88].

treatment was confirmed as being safe and effective with no evidence of systemic toxicity. Together with previous findings, this study led to the FDA's 1996 approval of 3.85% BCNU-loaded PCPP:SA wafer (Gliadel®) for the treatment of recurrent glioblastoma.

4.2.2 Treatment of newly diagnosed malignant gliomas

In general, antineoplastic treatments that demonstrate efficacy for treating recurrent disease are subsequently shown to be effective as initial therapies. In order to determine the efficacy and safety of 3.85% BCNU-loaded PCPP:SA polymers as an initial treatment of malignant brain tumours, a Phase I/II study was carried out with 22 patients who underwent surgical debulking and implantation of up to eight wafers [87]. Enrolment criteria consisted of: unilateral tumour focus ≥ 1 cm^3, age > 18 years, KPS ≥ 60, and intraoperative diagnosis of malignant glioma. All patients received standardised external beam radiation therapy postoperatively. The study indicated a median survival of 42 weeks for the treatment group, with 4 patients surviving > 18 months. This clinical study established that Gliadel was safe and well-tolerated when combined with radiation therapy for patients with newly diagnosed malignant gliomas.

These results prompted a Phase III clinical trial [88]. The study, originally planned for 100 patients, was interrupted due to temporary drug unavailability; therefore, 32 patients were entered in the study. The applied admission criteria were similar to the Phase I/II study except that a histopathological diagnosis of grade III astrocytoma or glioblastoma multiforme was required by intraoperative frozen sections. Five anaplastic astrocytoma and twenty-seven glioblastoma patients were randomised to receive either placebo or BCNU wafers (61.6 mg of BCNU) after maximal surgical resection; patients also underwent radiation therapy. The median survival was 58.1 weeks for the active arm of the study, whereas it was 39.3 weeks for the placebo arm (p = 0.012) (**Figure 6**). The subpopulation of glioblastoma patients had a median survival of 53.3 weeks when treated with BCNU polymers versus a median survival of 39.9 weeks if treated with the placebo (p = 0.008). The results further indicated the 1-, 2- and 3-year survival rates to be 63, 31 and 25%, respectively, for the BCNU group in comparison to 19, 6 and 6% for the placebo group. As with prior studies, no signs of systemic or local toxicity attributable to the polymer were noted.

A third randomised, prospective, placebo-controlled clinical study was then carried out to further define the role of Gliadel as an initial therapeutic modality [89]. A total of 240 adult patients who underwent initial surgical resection for a high-grade malignant glioma were entered into the study. BCNU wafers (Gliadel) or placebo wafers were surgically implanted at the site of initial resection and followed by radiation therapy 2 – 3 weeks later. The primary end point for this study was survival. The median survival was 13.9 months for the intent-to-treat group compared with 11.6 months for the placebo group (p = 0.03). The study indicated that the overall risk of death during the 3 – 4 years post-treatment was reduced in the Gliadel wafer treatment group, as presented by a hazard ratio of 0.73 (95% confidence interval: 0.56 – 0.95; p < 0.05). Based on the conclusions, on February 26th 2003, the FDA approved Gliadel for use in newly diagnosed patients with high-grade malignant gliomas as an adjunct to surgery and radiation therapy. A long-term follow-up study was conducted to determine the survival benefit of Gliadel therapy at 2 and 3 years, based on the study previously published by Westphal and colleagues [89]. The study included 240 patients, 120 of them treated with Gliadel and 120 treated with placebo. As of August 16th 200?, 59 patients were available for long-term follow-up, 1 remained lost to follow-up, 47 had died, and 11 were still alive, resulting in follow-up for 239/240. Of the 11 patients still alive, 9 received Gliadel and 2 received placebo. Median survival for patients treated with Gliadel was 13.9 months compared with 11.6 months in the placebo group (p = 0.018). Treatment with Gliadel resulted in a 27% reduction in the risk of death over the course of the study. In the Gliadel group, 16% of patients were alive at 2 years and 9% were alive at 3 years, compared with 8 and 2%, respectively, in the placebo group.

A subsequent preclinical study was performed to improve the therapeutic efficacy of Gliadel wafers [90]. This study showed that efficacy can be enhanced by increasing the BCNU loading dose to 20% without generating local or systemic toxicity. A National Institute of Health-funded dose-escalation trial at 11 medical centres in the US was designed to evaluate the safety of Gliadel wafers between 6.5 and 20% BCNU in patients with recurrent malignant brain tumours. This Phase I/II escalation study established that the maximal non-toxic loading dose is 20% [91]. At present, a Phase III clinical trial is in the planning phases to evaluate the efficacy of the highest-tolerated BCNU loading dose.

5. Other antitumour agents for local drug delivery

Advances in local drug delivery have increased the interest in the use of antineoplastic agents that were previously not suited for brain tumour therapy due to poor BBB penetration or systemic toxicity, but that are safe and efficacious for the treatment of other tumours. The following agents have been successfully incorporated into local delivery systems and used to treat experimental brain tumours.

5.1 O^6-Benzylguanine

One of the obstacles encountered after local or systemic administration of alkylating agents to brain tumours is the development of resistance, caused by adaptative responses in the tumour cell over time. O^6-alkylguanine-DNA alkyltransferase (AGT) is a DNA-repair enzyme responsible for the resistance seen in malignant brain tumour cells, particularly against BCNU [92]. As BCNU exerts its tumouricidal effects through chloroethylation of DNA at the O^6-position of guanine, AGT is able to protect tumour cells from this damage by removing DNA adducts at this position before cytotoxic interstrand crosslinking can occur. O^6-Benzylguanine (O^6-BG) is an agent that irreversibly inactivates AGT [93], thus resensitising the tumour cells to DNA alkylation after BCNU administration. O^6-BG is also effective when administered concomitantly with combinations of BCNU/cyclophosphamide and temozolomide/irinotecan in animal models [94]. O^6-BG has been administered systemically to patients with anaplastic gliomas in a dose-escalation protocol [95]. In this study, AGT activity was decreased to less than detectable levels after a dose of 120 mg/m^2 when O^6-BG was given 6 h prior to administration of an alkylating agent. Based on these findings, a Phase II trial that combined systemic administration of O^6-BG with systemic BCNU was carried out. In this study, the combination failed to produce tumour regression at the doses administered. A possible explanation for the lack of efficacy seen in this study is the poor penetrance of BCNU into the CNS. To circumvent this problem, Rhines *et al.* combined systemic administration of O^6-BG with intracranial local delivery of BCNU polymers in the F98 rat glioma model [96]. Results reflected an improvement in median survival to 34 days in animals receiving combination therapy as compared with animals receiving BCNU alone (25 days, $p = 0.0001$) or O^6-BG alone (22 days, $p = 0.0002$). These results suggested that the concomitant application of O^6-BG as a supplement to BCNU polymers may play a definitive role in the treatment of malignant brain tumours resistant to existing conventional chemotherapeutic modalities.

5.2 Taxol

A naturally occurring microtubule stabiliser, Taxol® (paclitaxel, Bristol-Myers Squibb, NY, USA) has demonstrated *in vitro* activity against glioblastoma cell cultures and several human tumours [97]. Taxol exhibits poor penetrance through the BBB at maximum tolerated doses, and has marked myelotoxicity and other complications at higher doses [98], making it an ideal candidate for local delivery. Walter *et al.* incorporated Taxol into 20 and 40% loaded PCPP:SA polymers and showed a sustained release of Taxol up to 1000 h [99]. Distribution studies performed *in vivo* demonstrated efficacious concentrations of Taxol 5 cm from the implantation site for up to 30 days post-implantation. Studies in the 9L gliosarcoma rat model indicated that locally delivered Taxol promoted survival two- to threefold (38 days median survival with 40% Taxol and 61.5 days with 20% Taxol versus 19.5 days with placebo). Taxol/PCPP:SA polymers, however, showed a biphasic release profile that caused unexpected toxicity. For this reason, paclitaxel was incorporated into biodegradable polilactofate microspheres (Paclimer® delivery system, Guilford pharmaceutics), and the toxicity and efficacy of this formulation were evaluated in rats intracranially implanted with 9L gliosarcomas [100]. In this study, 10% Paclimer was safe for intracranial implantation and significantly prolonged animal survival. A subsequent study was conducted to determine the toxicity of intracranial Paclimer in the dog brain with a starting dose of 2 mg/kg and a maximum dose of 20 mg/kg (unpublished data). Paclimer was safe at the doses tested, with no signs of local or systemic toxicity observed. Paclitaxel has also been delivered locally to brain tumours using CEDD. Using this system, a high antitumour response rate was obtained, although significant treatment-associated complications were observed [30].

5.3 4-Hydroxyperoxycyclophosphamide

Cyclophosphamide (Cytoxan®; Bristol-Myers Squibb) is an alkylating agent widely used in the treatment of several neoplasms, including multiple myeloma [101], myeloid leukaemia [102] and breast cancer, among others. Its use in brain tumour therapy has been limited by poor BBB penetration of its active metabolite, hydroxycyclophosphamide. Unfortunately, local delivery of cyclophosphamide is further limited, as it requires enzymatic activation by the hepatic cythochrome P450 oxidase system [103]. The active metabolite of cyclophosphamide, 4-hydroxyperoxycyclophosphamide (4-HC) [104], has been locally delivered to the brain using the FAD:SA polymer system [69] with favourable pharmacokinetic profiles and adequate biodistribution *in vitro* and *in vivo* [105]. Toxicity studies in the rat brain have shown that 20% 4-HC/FAD:SA polymers constitute the maximum tolerated dose, and efficacy studies in rats bearing intracranial 9L showed that treatment with 20% 4-HC/FAD:SA polymers prolonged the survival of animals to 77 days with a 40% survival rate beyond 80 days ($p = 0.004$), whereas control animals had a median survival of 14 days. Further studies in tissue samples obtained from human gliomas have shown that 4-HC has increased antitumour activity when compared with other antineoplastic agents [106].

5.4 5-Fluorouracil

5-Fluorouracil (5-FU) is a thymidine analogue that is metabolised to 5-fluoro-2'-deoxyuridine monophosphate and

5-fluorouridine triphosphate by normal and neoplastic cells. These metabolites trigger cell injury by either depriving the cell of necessary precursors for DNA synthesis or through incorporation into RNA sequences where they replace uridine triphosphate and, therefore, interfere with RNA processing and protein synthesis. These properties make 5-FU a powerful cytotoxic and radiosensitising agent. The poor BBB penetration of systemically administered 5-FU at safe doses and the serious systemic toxicities at high doses, such as myelosuppression and gastrointestinal mucosal injury [107], have limited its use in neuro-oncology.

5-FU has been successfully incorporated into PLGA microspheres with reproducible pharmacokinetic profiles [108]. When tested in the intracranial C6 rat glioma model, treatment with 5-FU/PLGA microspheres showed no signs of toxicity and significantly prolonged animal survival [109]. Further investigations have revealed similar efficacy in rats bearing F98 gliomas when treated with 5-FU microspheres [110-113]. Subsequently, in 1999, Menei *et al.* conducted a pilot clinical study [114] with 8 patients with newly diagnosed malignant gliomas who received 5-FU/PLGA microspheres after surgical debulking and external beam therapy. This study demonstrated clinically efficacious 5-FU concentrations in the cerebrospinal fluid up to 1 month postsurgical implantation and an associated significant median survival (98 weeks). A Phase I clinical trial was conducted using 5-FU/PLGA microspheres in 10 patients with newly diagnosed inoperable malignant gliomas [113]. In this study, 5-FU microspheres were effectively implanted into the tumour sites stereotactically, followed by external beam radiotherapy. No signs of local or systemic toxicity were observed, and median overall survival was 40 weeks. Further clinical studies with 5-FU microspheres are awaited to determine the benefit of this approach.

5.5 Doxorubicin

Doxorubicin (Adriamycin®; Pharmacia Corp., MI, USA) is a cytotoxic anthracycline antibiotic that acts via nucleotide base intercalation and cell membrane–lipid interactions. Intercalation inhibits nucleotide replication and the activity of DNA and RNA polymerases. The tumouricidal activity of doxorubicin has been documented in lymphomas, leukaemias, breast cancer and other malignancies [107]. Doxorubicin-loaded EVAc polymers showed significant antiglioma activity in nude mice [115] and improved median survival (33 days versus 13 days in control; $p = 0.0006$) when delivered from PCPP:SA polymers implanted intracranially in rats with 9L gliosarcoma [116].

5.6 Platinum drugs

Platinum drugs, which exert tumouricidal effects by producing DNA interstrand crosslinks, are promising therapeutic alternatives for tumours such as malignant gliomas, medulloblastomata, optic pathway gliomas, brainstem gliomas and ependymomas [117]. Marked systemic toxicity with haematological predominance and poor BBB penetration have limited CNS applications [118], but make them ideal candidates for local delivery. Of all platinum derivatives, carboplatin is the most suitable for local delivery because of its demonstrated *in vitro* efficacy against CNS tumours [119] and its reduced neurotoxicity when delivered to the CNS in comparison to other platinum-based compounds [120]. The authors have therefore optimised the delivery of carboplatin with both the FAD:SA and PCPP:SA polymer systems, obtaining sustained release [70]; FAD:SA was selected given its superior properties to release water-soluble compounds such as carboplatin. The authors have also encapsulated carboplatin into ethylcellulose microcapsules [121] that allow administration via stereotactic injections when surgical resection is not indicated. The authors' studies have found that locally delivered carboplatin through both polymers and microcapsules is safe and highly effective for treating intracranial F98 gliomas in rats [70]. Furthermore, the safety of locally delivered carboplatin has been demonstrated in studies with primates using infusion pumps connected to catheters placed into the pontine region [122].

5.7 Camptothecin

The camptothecin family of agents inhibit topoisomerase I, which relieves DNA torsional strain by inducing reversible single-stranded breaks [123]. Previous clinical investigations have demonstrated significant toxicity after systemic administration of camptothecin [124]. Due to encouraging *in vitro* antiglioma activity, camptothecin was chosen for local delivery to the brain. Weingart *et al.* [125] tested the efficacy of 50% EVAc polymers loaded with sodium camptothecin in the 9L gliosarcoma model, and found a significant extension in animal survival. Rats treated with camptothecin polymers survived for > 120 days in comparison to a median survival of 19 days for controls ($p < 0.001$), and camptothecin polymers were superior to direct intratumoural injection and systemic camptothecin.

Camptothecin has also been incorporated into 50% PCPP:SA polymers and tested against established intracranial 9L gliosarcoma in rats [126]. In this study, no local or systemic toxicity was noted in any of the treated animals, and the median survival was 69 days for rats treated with camptothecin compared with 17 days for the controls. Other analogues of camptothecin have been tested *in vitro* for antiglioma activity by the authors' group; within this group, 10,11-methylenedioxy camptothecins showed the greatest activity when compared with camptothecin, sodium camptothecin, BCNU and other camptothecin analogues [127].

5.8 Mitoxantrone

Mitoxantrone is a DNA-reactive agent that intercalates into DNA through hydrogen binding and causes crosslinks and strand breaks. This agent also interferes with RNA and is a potent inhibitor of topoisomerase II, which is responsible for uncoiling and repairing damaged DNA. Mitoxantrone has been utilised in the treatment of advanced breast cancer,

non-Hodgkin's lymphoma, acute non-lymphoblastic leukaemia and chronic myelogenous leukaemia, and has been approved for clinical applications in hepatic and ovarian cancers. This drug has also been demonstrated as one of the most potent agents against malignant gliomas *in vitro* [128]; however, poor CNS penetration, bone marrow suppression and myocardial toxicity limit systemic delivery. Therefore, the authors have incorporated mitoxantrone into PCPP:SA polymers and determined its release kinetics, toxicity, biodistribution and efficacy for the treatment of experimental brain tumours in rats with intracranial 9L gliosarcomas [129]. Tumouricidal concentrations within the brain were shown for > 35 days and were shown to significantly improve survival. The combined median survival for each group was: controls, 19 days; 1% wafers, 30 days ($p < 0.0001$); 5% wafers, 34 days ($p < 0.0001$); 10% wafers, 50 days ($p < 0.0001$). Further clinical studies have demonstrated increased survival with mitoxantrone when delivered locally through Ommaya reservoirs in the treatment of recurrent malignant gliomas [130]. These findings confirm the role of locally delivered mitoxantrone in the treatment of malignant gliomas and warrant further clinical testing.

6. Biological agents

6.1 Angiogenesis inhibitors

Angiogenesis constitutes a vital mechanism for the expansion of solid tumours. Vascular proliferation facilitates the delivery of nutrients to central cells within the tumour mass that would otherwise be avascular, and angiogenesis further promotes exponential growth. This process requires the combination of endothelial cell proliferation and migration, with the remodelling of the extracellular matrix [131]. Amongst all tumours, glioblastomata display one of the highest degrees of angiogenesis; therefore, the clinical application of antiangiogenic factors has generated wide interest.

The first reported use of a polymer for local delivery of an antiangiogenic agent was based on the observation that cartilage produces a potent diffusible inhibitor of tumour angiogenesis [132]. Once isolated and purified, the cartilage extract was incorporated into EVAc polymers and tested in the rabbit cornea angiogenesis assay [133]. Subsequently, the purified cartilage-derived inhibitor was found to be a protein with potent anticollagenase properties and a high sequence homology to a collagenase inhibitor isolated from cultured human skin fibroblasts [134,135].

Following this principle, other antiangiogenic agents have been incorporated into controlled-release polymers and tested in animal models of brain tumours. Coadministration of heparin and cortisone was evaluated using EVAc polymers, given the fact that cortisone has antiangiogenic properties when administered in combination with heparin, causing tumour regression and inhibiting tumour metastases [136]. This polymer formulation decreased neovascularisation induced by the VX2 carcinoma in the rabbit cornea assay [137]. In the same study, cortisone and heparin were also incorporated into PCPP:SA polymers, which showed significant inhibition of growth in 9L tumours implanted in the flank of rats.

Continuing efforts followed using the tetracycline derivative minocycline, which is a broad-spectrum antibiotic with anticollagenase activity that showed to be an effective antiangiogenic agent in the VX2 carcinoma cornea assay [138]. Minocycline also has the capacity to extend the survival of rats challenged with 9L gliosarcoma cells [139]. Local delivery of minocycline has displayed synergism with systemic administration of BCNU for treating intracranial 9L gliosarcomas [139,140]. Minocycline in all the studies was efficacious when administered simultaneously with the tumour implantation or following tumour resection, but not when administered to established tumours. The combination of minocycline with BCNU significantly extended survival and suggests that coadministration of antiangiogenic agents and chemotherapy is a highly efficacious alternative for treating experimental gliomas in animal models.

6.2 Immunotherapy

Another strategy used in brain tumour therapy involves the activation of the host's immune response towards targeted tumour cells. To initiate this process, cytokines, such as interleukins (ILs), interferons (IFNs) and colony-stimulating factors, are secreted by white blood cells or exogenously administered in order to generate a local inflammatory reaction with further recruitment of active effector cells as well as a long-term immune memory. Several cytokines have demonstrated *in vivo* antineoplastic activity. For example, IL-2 is approved for the systemic treatment of metastatic renal cancer. Given the rationale of local delivery and the notion that the immunomodulatory activity of cytokines occurs in a paracrine fashion, the authors hypothesised that local cytokine-mediated immunotherapy could be clinically effective.

Local delivery of immunotherapy can be achieved using different strategies. The first strategy involves *ex vivo* gene transfer – transfecting tumour cells that secrete desired cytokines in a paracrine fashion. The authors' laboratory proved this strategy to be effective in combating established brain tumours [141,142]. Although experimentally efficacious in animal models, the application of genetically modified cells could face obstacles in the treatment of human brain tumours. Consequently, the authors have used controlled-release technology to accomplish paracrine cytokine production at the tumour site; IL-2 has been tested in its ability to trigger and sustain an immune response against metastatic and primary brain tumour models. Microspheres produced have been optimised for size reproducibility (15 μm mass-average diameter), encapsulation efficiency (85 – 90%) and cytokine release (over 2 weeks *in vitro*). Tested in rodent models, IL-2 microspheres were highly effective in the treatment of B16-melanoma metastases to the brain in mice and 9L gliosarcoma in rats [143]. Histological analysis post-treatment revealed massive tumour necrosis with associated lymphocytic infiltration surrounding IL-2 polymer spheres at the implantation site.

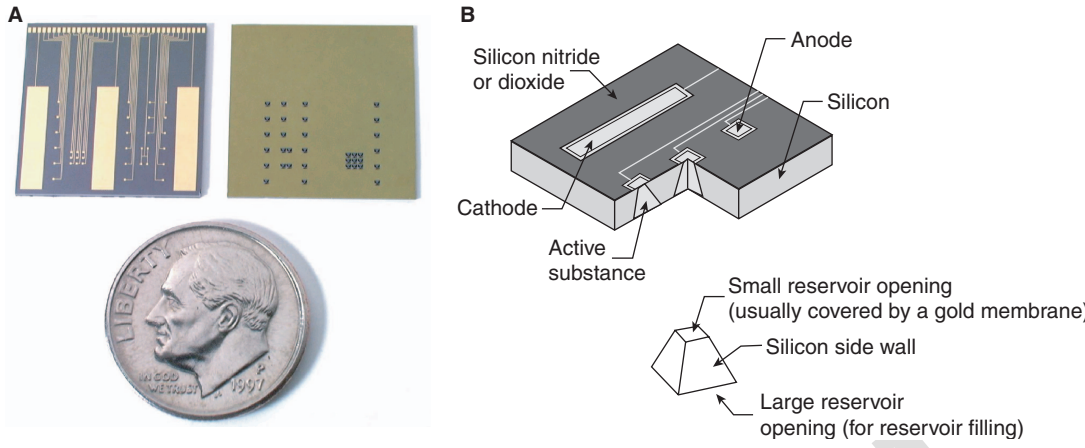

Figure 7. (A) Microchip with dime caption. Front (left) and back views of a new microchip for controlled local release of chemicals. The dots between the three large bars (cathodes) on the front are the caps (anodes) covering the reservoirs holding the chemicals. Electrical voltage applied between the cap and cathode causes a reaction that dissolves the cap, thus releasing the reservoir's contents. The back view shows the larger openings through which the contents of the reservoirs are deposited (these openings are sealed after filling). Photo by P Horowitz, Atlantic Photo Service, Inc. **(B) Schematic of the passive microchip.** Initial models will use PLGA and other existing polymer matrices for the substrate. The entire chip will be biodegradable.
PLGA: Poly-lactide-co-glycolide.

Further immunohistochemistry indicated that the infiltrate was primarily comprised of $CD4^+$ and $CD8^+$ T cells, natural killer cells and polymorphonuclear cells. On the contrary, placebo microspheres were inert in the brain.

Further experimental studies identified potent antiangiogenic and immunomodulatory properties of IL-12 – making it suitable for local paracrine delivery. The authors implanted IL-12-transfected rat 9L gliosarcoma cells intracranially [144]. Reverse polymerase chain reaction confirmed *in vivo* IL-12 expression. Local paracrine delivery of IL-12, in addition to prolonging median survival, also stimulated immunological memory within the animal hosts. The authors further showed that a second injection of wild-type 9L gliosarcoma tumour cells elicited an immune response.

In an effort to eradicate residual tumour cells not reached by intracranial delivery, the authors hypothesised that the combination of paracrine immunotherapy and locally delivered chemotherapy may provide a synergistic tumouricidal response. Sampath *et al.* [145] demonstrated the efficacy of tumour cells engineered to produce IL-2 and local delivery of 10% BCNU-PCPP:SA polymer in producing a synergistic increase in survival of mice intracranially challenged with lethal aliquots of B16-F10 tumour cells. Examination of animals treated with combination therapy at day 14 revealed rare degenerating tumour cells with marked chronic inflammation; examination at day 72 indicated the inflammatory resolution with no remaining tumour cells.

Finally, the authors' group showed the synergistic effect of local delivery of BCNU wafers in combination with IL-2 microspheres in treating 9L gliosarcoma in rats [146]. This study indicated a median survival of 28.5 days in the group receiving IL-2 microspheres and 3.8% BCNU polymer, and 45.5 days with IL-2 microspheres combined with 10% BCNU polymer. The observed median survival of animals receiving monotherapy was 24 days with IL-2 microspheres, 24 days with 3.8% BCNU polymer, and 32.5 days with 10% BCNU polymer. Furthermore, the combination of 3.8 or 10% BCNU polymer with IL-2 microspheres resulted in 7 versus 25% long-term survivors, respectively. Based on the obtained results, continued research in this field is underway.

7. Future directions in local drug delivery

The development of polymer-based delivery systems provides the 'proof of principle' that controlled local drug delivery improves the treatment of brain tumours. Accordingly, this development has heralded new investigations into other modalities of sustained local drug delivery in the brain.

7.1 Microchip drug delivery

The latest avenue in drug delivery showing great clinical potential, microchips provide the capability for single or multiple agent delivery. The microchip's mechanism of action is derived from the solid-state silicon microchip that provides controlled release of multiple microreservoirs [147-149] (**Figure** 7). The release mechanism relies on the dissolution of a thin anode membrane enveloping each microreservoir, which can be filled with solids, liquids or gels. The time of release for each reservoir to deliver its contents can be programmed independently, therefore providing an endless array of release profiles and therapy combinations to be employed [147]. The device is an integrated circuit consisting of its own microbattery, memory and multiplexing circuitry. Alternative biodegradable 'passive chips' are also being developed, where the release mechanism is based on slow degradation of a thn polymeric membrane covering each reservoir of

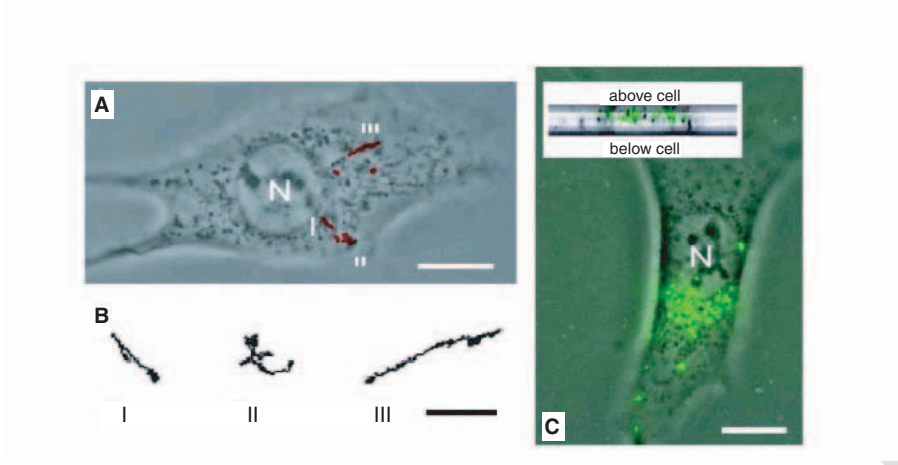

Figure 8. Transport and locations of intracellular PEI/DNA nanocomplexes. (**A**) 20-second trajectories of PEI/DNA complexes in a COS-7 cell 4 h post-transfection. A phase-contrast image of the cell was overlaid with the trajectories of complexes. Three of six complexes shown displayed active transport with linear or curvilinear trajectories. Their detailed trajectories are shown in (**B**). (**C**) COS-7 cell with PEI/DNA complexes accumulated in the perinuclear region. (Inset) Cross-section of the COS-7 cell to demonstrate that PEI/DNA complexes were inside the cell. A phase-contrast image of the cell was overlaid with a fluorescent image of PEI/DNA complexes taken with the charge-coupled device camera. Some complexes appear to be intranuclear, but may be within cytoplasmic invaginations that extend into the nucleus. (Bars: **A** and **C**,10 mm; B,2 mm.) Reprinted with permission [152].
N: Nucleus; PEI: Polyethylenimine.

drug. Its clinical application can be performed either by surgical implantation, mounted on a tip of a small probe, or even by swallowing. Still in the development phases, this 'pharmacy-on-a-chip' could be used to deliver up to 1000 different drugs on demand based on the specific brain tumour pathology of the patient.

7.2 Nanocarriers

The application of therapeutic gene delivery has traditionally been hampered by low success rates with delivery to the target cell nucleus. Nanocarriers – part of the latest evolution in synthetic gene carriers – may provide the ability to carry larger DNA molecules (in comparison to classically utilised viral vectors), reduced immunogenicity and improved safety not afforded by previous gene delivery methodologies. One such example is polyethylenimine (PEI)/DNA nanocomplexes, which are taken up via endocytosis by target cells. As one of the most efficient synthetic vectors, PEI has been shown to be capable of delivering DNA sequences to perinuclear regions via microtubule-mediated mechanisms when administered *in vitro* to target cells [150-153] (**Figure 8**). Sakhalkar *et al.* [154] further demonstrated the tremendous capacity of nanocarriers when they generated biodegradable particles with high selectivity for inflamed respiratory endothelium *in vitro* and *in vivo* based on adhesion molecules used by migrating leukocytes, such as E-selectin, P-selectin, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1. Hence, nanocarriers could be designed with specific targeting based on cell surface receptor expression specific to neoplastic tissue. Although still in the developmental stages at present, the application of nanocarriers could provide the capacity to deliver genomic sequences in an effort to genomically and, hence, biologically modify tumour cells.

8. Expert opinion and conclusions

Neoplasms of the CNS represent a formidable challenge and, despite extensive preclinical and clinical research efforts, the prognosis of patients remains dismal. Physiological barriers pose an obstacle for efficacious delivery of therapeutic concentrations of antineoplastic agents to the CNS without causing undue systemic toxicity. The development of biodegradable polymers provides a means of overcoming these obstacles. Gliadel, the BCNU-loaded PCPP:SA polymer, represents not only the prototype of this approach, but also the first therapy approved by the FDA for malignant gliomas in 23 years. Its safety and efficacy have been demonstrated in numerous clinical trials. The development of biodegradable polymers further provides the 'proof-of-principle', indicating that local drug delivery provides increased survival benefits in the treatment of brain tumours. The development of this field of research has heralded new investigations into different drug–polymer combinations, such as the delivery of immunomodulatory cytokines, different chemotherapeutic and antiangiogenesis agents. Concurrently, there has also been further progression in the development of new drug delivery systems – primarily, convection CEDD and microchips.

In order to provide added therapeutic modalities to patients, further identification of new targets and development of new drug delivery systems are necessary. The elucidation of new molecular targets will primarily occur as a result of improved understanding of tumourigenesis.

Improvements in molecular biology techniques, such as the development of gene microarrays, proteomics and techniques for RNA interference, among others, will provide the capacity to understand the molecular signalling pathways crucial to the development of neoplasms. Subsequent research aimed to determine molecules critical to this process will provide the basis for genomics-based rational therapy. When combined with miniaturised local drug delivery systems, this will provide for an endless array of therapies that target the molecular biology of tumours.

Local drug delivery demonstrates significant potential to change future neurosurgical treatment of malignant gliomas. In the near future, perhaps when a patient diagnosed with a brain tumour undergoes surgical resection, a microchip will be programmed and loaded with a combination of therapeutic agents tailored to the intraoperative frozen pathology diagnosis. Beyond this, with the development of molecular pathology, the administered treatment could be tailored to the specific molecular traits of the patient's tumour. The more promising options include the delivery of drug-loaded polymer microspheres that can be stereotactically injected to enhance treatment. Such an approach could serve useful for patients with tumours considered inoperable. Should there be a recurrence, stereotactic biopsy for diagnosis could be followed by the implantation of angiogenesis inhibitors and further chemotherapy agents delivered via microspheres.

Based on recent developments in the field of local drug delivery, it is evident that future investigations will arm the neurosurgeon with an arsenal consisting of surgery complemented by rational therapies delivered by miniaturised delivery systems that can be administered either intraoperatively or stereotactically in order to target molecular pathways crucial to tumour evolution. Such exciting possibilities for both the physician and patient have been made possible by the development of local and controlled drug delivery to the CNS.

Disclosure

Under a licensing agreement between Guilford Pharmaceuticals and the Johns Hopkins University, Dr Brem is entitled to a share of royalty received by the University on sales of products described in this work. Dr Brem and the University own Guilford Pharmaceuticals stock, which is subject to certain restrictions under University policy. Dr Brem is also a paid consultant to Guilford Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

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Website

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