Drug Delivery to Tumors of the Central Nervous System

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Contemporary treatment of malignant brain tumors has been hampered by problems with drug delivery to the tumor bed. Inherent boundaries of the central nervous system, such as the blood-brain barrier or the blood-cerebrospinal fluid barrier, and a general lack of response to many chemotherapeutic agents have led to alternative treatment modalities. In general, all these modalities have sought to either disrupt or bypass the physiologic brain barriers and deliver the drug directly to the tumor. This article reviews past, as well as current, methods of drug delivery to tumors of the central nervous system. Special emphasis is placed on biodegradable polymers that can release chemotherapeutic agents against malignant gliomas. A variety of other nonchemotherapeutic drugs, including antiangiogenesis and immunotherapeutic agents, are presented in the context of new polymer technology. Finally, future directions in drug delivery are discussed with an overview on new advances in emerging biotechnology.

Introduction

Tumors of the central nervous system (CNS) represent to most individuals and physicians one of the most devastating forms of human illness. In the United States, about 16,800 people are diagnosed with primary brain tumors each year [1]. Approximately half of all primary brain tumors are glial cell neoplasms, and more than three quarters of all gliomas are astrocytomas. The astrocytomas are a heterogeneous group of tumors that can vary from low-grade to the most aggressive (glioblastoma multiforme) based on histopathologic classification. Conventional therapy for glioblastomas consists primarily of surgical debulking followed by radiation therapy. Unfortunately, the median survival after surgical intervention alone is 6 months, with only 7.5% of patients surviving for 2 years. Although systemic chemotherapy has been minimally effective, the addition of radiation therapy has extended the median survival to 9 months [2,3]. In spite of these efforts, little progress has been made in extending overall patient survival. New therapies and novel approaches are urgently need to treat this disease.

Rationale for Local Delivery

In order to understand the difficulties encountered in treating patients with malignant brain tumors, it is important to appreciate the unique environment of the CNS. The first distinguishing physiologic characteristic of the CNS is the blood-brain barrier (BBB). Tight junctions between endothelial cells of the capillaries form a physiologic and pharmacologic barrier that prevents the influx of molecules from the bloodstream into the brain. In general, only small, electrically neutral, lipid-soluble molecules can penetrate this capillary endothelium, and many chemotherapeutic agents do not fall in this category. The second important feature of the CNS environment is the presence of the blood-cerebrospinal fluid barrier (BCB). This barrier is formed by the tightly bound choroid epithelial cells, which are responsible for the production of cerebrospinal fluid (CSF). Because the BCB closely regulates the exchange of molecules between the blood and CSF, it can control the penetration of molecules within the interstitial fluid of the brain parenchyma. Furthermore, because the BCB is fortified by an active organic acid transport system, it can actively remove from the CSF a number of agents, such as methotrexate, and, therefore, actively prevent the diffusion of chemotherapeutic agents directly into the brain parenchyma.

Several approaches have been utilized in recent years in an attempt to increase the delivery of chemotherapeutic agents to the tumor and overcome the natural boundaries presented by the CNS. The first of these builds upon the physical properties of the BBB and seeks, through pharmacologic manipulation, to create a more lipophilic, and thus a more BBB-traversable, agent. Both lomustine (CCNU) and semustine (methyl-CCNU) represent two lipophilic variants of a known chemotherapeutic agent, carmustine (BCNU), which has been shown to modestly improve the survival of patients with malignant brain tumors. However, clinical trials utilizing systemic administration of lomustine or semustine have not shown efficacy of these drugs over BCNU in treating glial tumors [4]. A different approach involves increasing the permeability of a hydrophilic agent by linking the drug to a carrier capable of

traversing the BBB. For example, the lipophilic dihydropyridine carrier readily crosses the BBB and has been shown to increase intracranial concentrations of a variety of drugs, including neurotransmitters, antibiotics, and antineoplastic agents [5]. Likewise, new transport vectors, such as a modified protein or receptor-specific monoclonal antibody, have also led to a successful delivery of a number of drugs across the BBB [6•].

Another strategy involves disrupting the BBB by means of either an intra-arterial infusion of hyperosmolar mannitol or a novel bradykinin agonist, RMP-7. The rationale for the use of a hyperosmolar solution is that it can cause an acute dehydration of endothelial cells resulting in cell shrinkage, which in turn widens the tight junctions connecting adjacent membranes. In a recent clinical study, William *et al*. [7] examined the efficacy of the coadministration of the antineoplastic agents carboplatin and etoposide in conjunction with mannitol in 34 patients with intracranial tumors. Whereas four out of four patients with primitive neuroectodermal tumors (PNETs) and two out of four patients with CNS lymphomas had some degree of response, no benefit was seen in patients with oligodendrogliomas, glioblastomas multiforme, or metastatic carcinomas. These results were further supported by another study in which the survival of patients treated with intra-arterial BCNU was unchanged or worse than those for patients treated with conventional intravenous therapy [8]. In contrast to mannitol, the bradykinin agonist RMP-7 directly disrupts the BBB [9]. Furthermore, intravenous administration of RMP-7 has been shown to selectively increase the uptake of carboplatin in experimental brain tumors, suggesting a potential use for this agent as adjunctive therapy for selective delivery of chemotherapeutic drugs to the brain [10].

An attractive approach that does not depend on the penetration or disruption of any physiologic barrier involves the direct delivery of an antineoplastic agent to the tumor. This may be accomplished by implanting one end of a catheter within the tumor bed and leaving the opposite end easily accessible for injection. One such system, the Ommaya reservoir, has been in clinical use for a number of years, and is used to deliver intermittent bolus injections of chemotherapy to the tumor. Most recently, the advent of implantable pumps has permitted a constant infusion of drugs over an extended period of time. The prototype for this model is the Infusaid pump (Infusaid Corp., Norwood, MA), which depends on compressed vapor pressure to deliver a solution at a constant rate [11]. Other systems include the MiniMed PIMS system (MiniMed, Sylmar, CA), which delivers drugs by a solenoid pumping mechanism [12], and the Medtronic SynchroMed system (Medtronic, Minneapolis, MN), which uses a peristaltic mechanism to deliver the infused agent [13]. All of these devices are limited by mechanical failure, obstruction by tissue debris, and varying rates of infection. None has proven superior over another in the treatment of patients with malignant gliomas.

Polymer-Mediated Drug Delivery

Implantable polymers that release chemotherapeutic agents directly into the CNS provide a novel approach to brain tumor therapy. These polymers were first described in 1976 by Langer and Folkman [14], who reported the sustained and predictable release of macromolecules from a nonbiodegradable ethylene vinyl acetate (EVAc) copolymer. A drug incorporated into this type of polymer is released by means of diffusion through the micropores of its matrix. The rate of diffusion depends on the chemical properties of the drug itself, including molecular weight, charge, and water solubility. In general, the smaller the molecule, the faster it is released from the polymer. Once released, the drug retains its biologic activity. The EVAc polymer has found application in various clinical settings, including glaucoma, asthma, and contraceptive therapy. It has also been experimentally used to deliver drugs intratumorally for glioma therapy [15]. The primary limitation of these nonbiodegradable, controlled-release polymers is that once the drug has been released, it is inert. Consequently, they remain in place permanently as foreign bodies.

In contrast to EVAc, a new generation of biodegradable polymer systems release drugs by a combination of polymer degradation and drug diffusion The polyanhydride poly[bis(p-carboxyphenoxy)propane-sebacic acid] (PCPP-SA) matrix is an example of a biodegradable polymer that breaks down to dicarboxylic acids by spontaneous reaction with water [16]. There are several advantages of these polymers over EVAc. First, the polyanhydrides can be made to release the active drug at a nearly constant rate. Thus, any drug can be theoretically incorporated into the polymer as long as it does not react with the matrix. Second, by modifying the ratio of carboxyphenoxypropane (CPP) to sebacic acid (SA), one can adjust the polymer breakdown rate from 1 day to several years. For example, a 1-mm thick polymer composed of pure CPP would require 3 years to completely degrade, compared with 3 weeks when SA is added to reach 80% [17]. Third, the PCPP-SA polymer can be manufactured in an endless variety of shapes, such as sheets, rods, or wafers, thereby facilitating its clinical application and method of surgical delivery. Finally, because the matrix itself is completely degraded, there is no foreign body that needs to be surgically removed after the drug is released. The degradation products are noncytotoxic, nonmutagenic, and nonteratogenic [18].

Recently, the spectrum of drugs that can be optimally released from the polyanhydride matrix has been broadened with the introduction of second generation of biodegradable polymers. One such matrix is the fatty acid dimer-sebacic acid (FAD-SA) copolymer. This polymer was developed in light of the finding that PCPP-SA does not release a high percentage of many hydrophilic agents or hydrolytically unstable compounds such as methotrexate or carboplatin [19]. In another development, Menei *et al*. [20] introduced a poly(lactide-co-glycolide) polymer that can be formed into microspheres and stereotactically

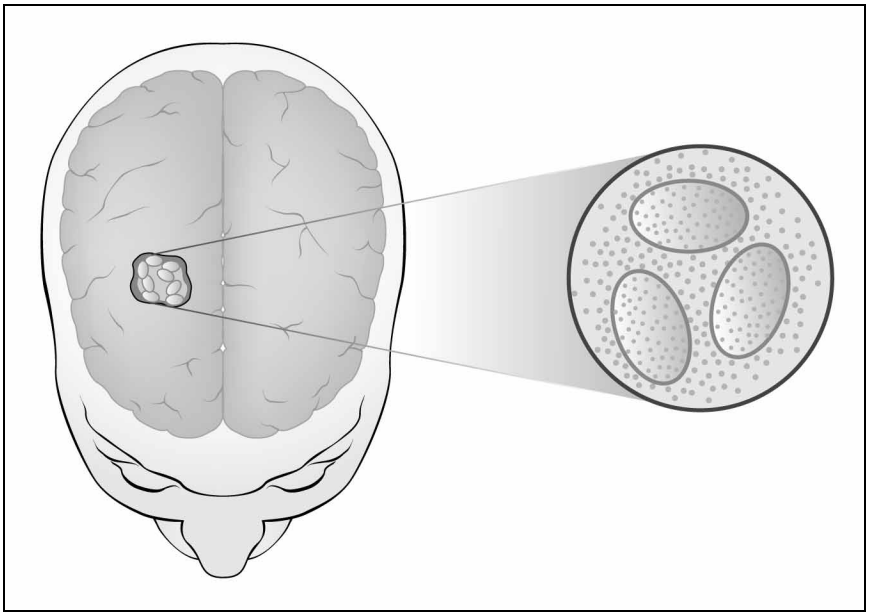

Figure 1. Up to eight polymer implants line the tumor resection cavity, where the loaded drug is gradually released as they dissolve. The inset shows how drug molecules diffuse away from these implants. (*Reprinted from* Brem and Langer [51]; with permission.)

injected into the brain. When covalently linked to polyethylene glycol coating, this polymer matrix has also been shown to reduce opsonization and elimination by the immune system [21]. Other new discoveries include polyethyleneglycol-coated liposomes that encapsulate anthracyclines [22], and gelatin-chondroitin sulfate-coated microspheres, which have been shown to reproducibly release cytokines in vivo [23].

Development of Gliadel

The choice of carmustine, or BCNU, as the prodrug in the development of polymer-based chemotherapy stems from the well-known activity of nitrosoureas against malignant brain tumors. In general, nitrosoureas are low-molecular weight alkylating agents that are relatively lipid soluble and, therefore, capable of crossing the BBB and achieving potentially tumoricidal concentrations [24]. These pharmacologic considerations have been exploited in a number of clinical trials where systemic administration of BCNU has been shown to modestly prolong the survival of patients with brain tumors [25,26]. On the other hand, the relatively short half-life (about 15 minutes) when given intravenously, combined with severe toxicity such as with myelosuppression and pulmonary fibrosis, have precluded the widespread use of systemic BCNU. In an effort to improve its effectiveness and limit the dose-related side effects, BCNU was incorporated into polymers and tested for efficacy against intracranial tumors.

The preclinical studies of BCNU-polymer preparations were performed in several stages. First, it was important to establish the distribution and pharmacokinetics of active drug release in vitro and in vivo. This was done through several experiments, all of which demonstrated that a prolonged, controlled, and sustained release of intact BCNU can be achieved with the polymer system [27,28,29]. Next, the efficacy of BCNU polymers was tested against a rat intracranial glioma. The results clearly showed that local delivery of BCNU by polymer was superior to systemic administration, and led to significant prolongation of survival in animals with malignant glioma [15]. Finally, toxicity studies performed in primates showed that BCNU polymers were well tolerated and that concomitant external beam radiotherapy did not increase toxicity [30]. Cumulatively, these studies proved the safety and efficacy of the polymer technology and set the stage for clinical trials.

In a phase I-II clinical trial, 21 patients were treated with three different doses of BCNU loaded in PCPP-SA polymers (1.93%, 3.85%, and 6.35% BCNU by polymer weight) [31]. Enrollment criteria included patients with a diagnosis of recurrent malignant glioma who had previously undergone a craniotomy for debulking and in whom standard therapy had failed. All of the patients required an indication for reoperation, such as a unilateral single focus of tumor in the cerebral cortex with an enhancing volume of at least 1 cm^3 on computed tomography (CT) or magnetic resonance imaging (MRI) scans, a Karnofsky performance scale score of at least 60 (indicating that the patient is able to function independently), completion of external-beam radiotherapy, and no nitrosoureas for up to 6 weeks prior to enrollment. At the time of reoperation, up to eight BCNU-loaded polymer wafers were implanted within the tumor cavity (Fig. 1). The treatment was well tolerated and no patient experienced any signs of local or systemic toxicity. The overall median survival times were 46 weeks after implant and 87 weeks after initial diagnosis, with 86% of the patients alive more than 1 year after diagnosis. On the basis of this work, the 3.85% BCNU-loaded polymers were chosen for further clinical study.

A phase III prospective, randomized, double-blind, placebo-controlled clinical trial of PCPP-SA polymer

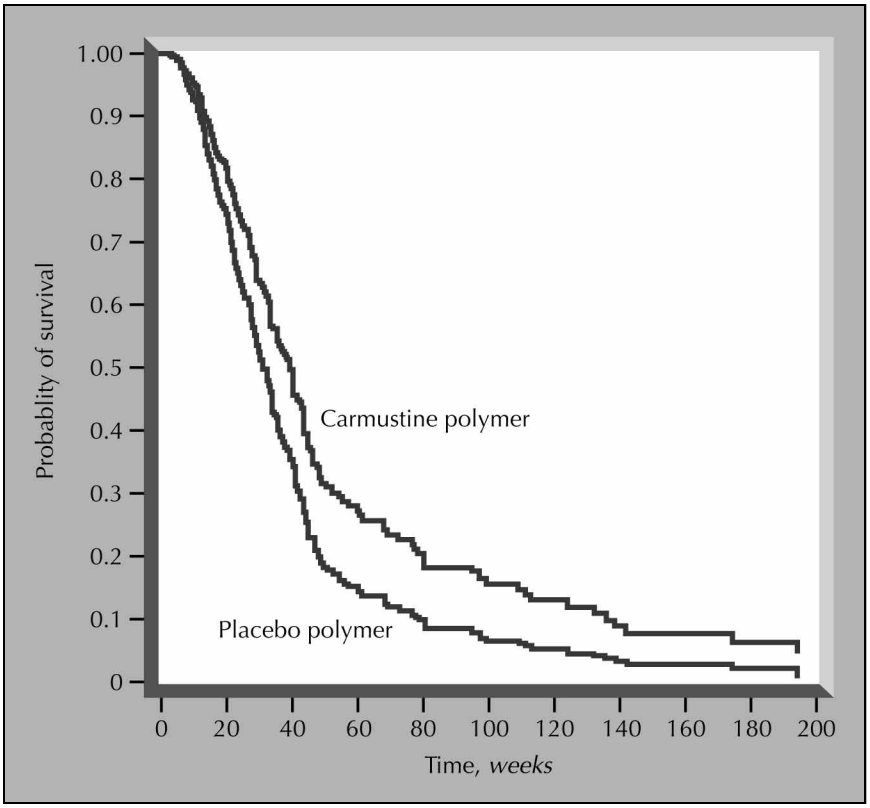

Figure 2. Overall survival for patients receiving implantation of carmustine (BCNU)-loaded polymers or placebo controls at the time of operation for a recurrent brain tumor after adjustment for prognostic factors. (*Reprinted from* Brem *et al*. [32]; with permission.)

containing 3.8% BCNU by weight was conducted in 222 patients with recurrent malignant gliomas at 27 medical centers in the United States and Canada [32]. Patients with recurrent malignant gliomas were randomized to receive either the BCNU polymer or a placebo implanted within the tumor cavity. Selection criteria were the same as for phase I-II study, namely the diagnosis of a recurrent malignant glioma, failure of standard therapy, and the need for reoperation. All of the patients previously underwent external beam radiotherapy, and 52.7% of the BCNU-polymer group and 48.2% of the control group had undergone previous chemotherapy. Whereas the BCNU polymer-treatment group had a median survival of 31 weeks, the median survival of the control group was 23 weeks (hazard ratio=0.69, P=0.005) (Fig. 2). The results were even more striking in the glioblastoma multiforme group, with 50% greater survival at 6 months in patients treated with BCNU polymers than with placebo alone (P=0.02). There were no significant toxicities observed in the BCNU-polymer group. Consequently, this study established that BCNU polymers are safe and effective in the treatment of recurrent malignant gliomas. In 1996, the Food and Drug Administration approved Gliadel (Aventis Pharmaceuticals, Parsippany, NJ) as the first new treatment against malignant brain tumors in 23 years. To date, Gliadel has received regulatory approval in 21 countries.

In general, any treatment for cancers that has been found effective at recurrence has been subsequently shown to be even more effective as initial therapy. Having established Gliadel as a useful agent in recurrent brain tumors, we naturally turned our attention to further elucidating its role in initial therapy. First, a phase I study involving 22 patients with newly diagnosed malignant gliomas was conducted to evaluate the overall safety of the BCNU-polymer combination [33]. None of the 22 patients experienced any local or systemic side effects attributable to Gliadel. Next, Valtonen *et al*. [34] conducted a prospective, randomized, double-blind clinical trial in Europe involving 32 patients with newly diagnosed malignant gliomas. Half the patients received 3.85%-BCNU wafers with the other half receiving placebo wafers at the time of the initial resection. The median survival was 58 weeks for the BCNU-treatment group and 40 weeks for the placebo group (P=0.001) (Fig. 3). At 1 year, 63% of the patients treated with BCNU polymers were alive compared with 19% for the control group; at 2 years, the differences remained highly significant, with 31% of the Gliadel group surviving compared with 6% of the control group. Moreover, even after 3 years, 25% of patients treated with Gliadel were alive compared with 6% of the control group. Based on these highly promising results, a phase IV study involving 250 patients was carried out to fully assess the role of Gliadel in initial therapy. This study has just been completed and the final results have not yet been released.

Potential Drug-Polymer Combinations

A variety of other drugs have been incorporated into the polymer matrix. Taxol, for instance, is a microtubule binding agent with proven efficacy against several human

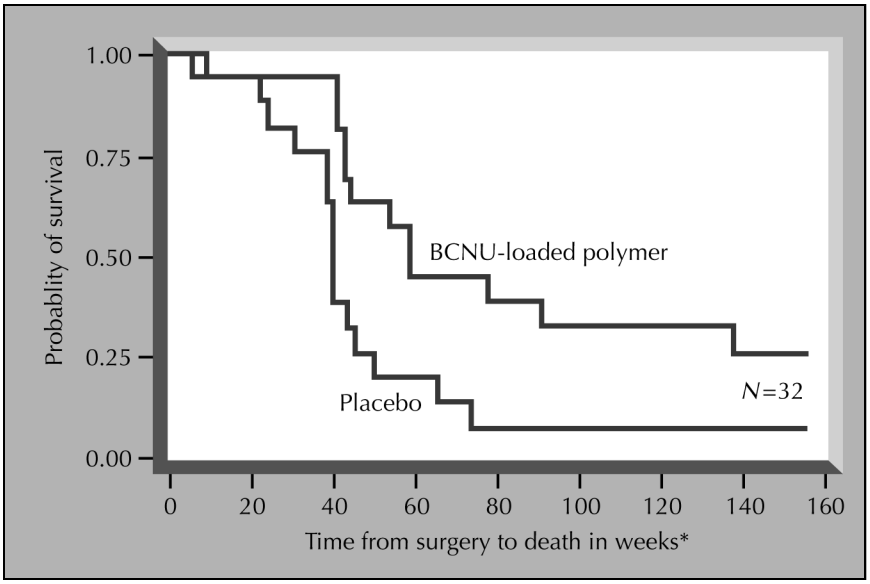

Figure 3. Kaplan-Meier survival curve for patients with initial therapy for grade III and grade IV gliomas treated with BCNU-loaded polymer implants or placebo polymer. *Asterisk* indicates n=156 weeks. (*Reprinted from* Valtonen *et al*. [34]; with permission.)

tumors, including breast, ovarian, and non-small cell lung cancer. Recently, it has also been shown to exhibit cytotoxic activity against rat and human glioma cells in vitro [35]. This finding led to the development of taxol-loaded polymers, which have been reported to triple the survival time of rats challenged with intracranial 9L glioma [36]. Clinical trials are currently underway utilizing taxol polymers for ovarian cancers, and trials involving brain tumor patients are being planned. Camptothecin, an inhibitor of DNA-replicating enzyme topoisomerase I, is another agent with potential antitumor activity. When incorporated into the polymer matrix, camptothecin significantly prolonged the survival of rats challenged with 9L glioma. Moreover, 59% of treated animals remained long-term survivors [37]. Finally, several other chemotherapeutic agents, including carboplatin, 4-HC, methotrexate, 5-FU, and adriamycin, have demonstrated potent local activity against intracranial tumors [38–42].

The spectrum of drugs that can be delivered by means of a biodegradable polymer extends beyond the chemotherapeutic agents. Some of the current drug-polymer combinations include inhibitors of tumor angiogenesis, cytokines, steroids, and even anticonvulsants. Minocycline, for example, a broad-spectrum antibiotic with known antiangiogenic properties, has been found to improve the survival of animals challenged with the rat 9L glioma [43]. Cytokines, such as interleukin-2, when delivered locally via microspheres, have been shown to be highly effective in protecting animals challenged with fatal tumor doses [23,44]. Other drugs, such as dexamethasone, a steroid widely used to control vasogenic edema associated with brain tumors, has been found as effective when delivered via a polymer as systemic drug administration [45]. Based on these experiments, it becomes clear that the principles of local delivery of drugs to the brain have been developed in a variety of problems encountered in the management of patients with gliomas. Ultimately, this approach may broaden the range of currently available drugs, and in time provide the means for further extending the lives of patients with malignant brain tumors.

Future Directions

New methods of drug delivery to the CNS are under active investigation. One area of interest involves convection-enhanced delivery systems. Convection, unlike diffusion, results from a simple pressure gradient and is independent of molecular weight. Taking advantage of this principle, several studies have shown that interstitial infusion of a drug into the cerebral white matter creates a pressure gradient that increases convection and can be used to deliver high concentrations of drugs to large regions of the brain without functional or structural damage [46–48]. Indeed, Lonser *et al*. [49•] have recently used convection-enhanced delivery of excitotoxic agents in the treatment of Parkinsonian symptoms in nonhuman primates. Convection-enhanced delivery may, therefore, offer another important way of delivering chemotherapeutic agents to surgically inaccessible brain tumors.

A novel and potentially powerful method of drug delivery involves the use of newly developed microchips [50••]. This technology depends on a solid-state silicon microchip that can provide controlled release of a single or multiple chemical substances on demand. The release mechanism is based on the electrochemical dissolution of a thin anode membrane covering multiple microreservoirs. The reservoirs can be filled with solids, liquids, or gels, and the release profile can be tailored either sequentially or simultaneously from a single device. A microbattery, multiplexing circuitry, and memory can be integrated onto the device, allowing it be mounted on a tip of small probe, implanted, or swallowed. With proper selection of a biocompatible device material, this "pharmacy-on-a-chip" may be used to deliver up to 1000 different drugs on demand.

Conclusions

The delivery of drugs to tumors of the central nervous system has been a challenging area of research for many years. The two major obstacles, overcoming the physiologic barriers of the brain and achieving high-drug concentrations within the tumor bed, have prompted an intensive search for alternative routes of drug delivery. Within the confines of these limitations, biodegradable polymers have allowed a new approach for delivering pharmaceutical agents to the brain. Gliadel, a BCNU-impregnated polymer, represents the first successful drug developed as a result of this technology. In clinical trials, it has been shown to be safe and effective against malignant brain tumors. As a result of Gliadel, numerous clinical trials involving other new drug-polymer combinations are currently under way. Moreover, recent advances in biotechnology are leading the way in the development of new products. The application of local and controlled drug delivery to the central nervous system represents a major discovery in the field of neurooncology, and it holds great promise for both the patient and the physician in the fight against malignant brain tumors.

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