

TUMOR DELIVERY VEHICLES

BACKGROUND OF THE INVENTION

The present invention is generally in the area of delivery vehicles, for therapeutic agents for the treatment of tumors, especially brain tumors.

One-third of all individuals in the United States alone will develop cancer. Although the five-year survival rate has risen dramatically to nearly fifty percent as a result of progress in early diagnosis and the therapy, cancer still remains second only to cardiac disease as a cause of death in the United States. Twenty percent of Americans die from cancer, half due to lung, breast, and colon-rectal cancer.

Designing effective treatments for patients with cancer has represented a major challenge. The current regimen of surgical resection, external beam radiation therapy, and/or systemic chemotherapy has been partially successful in some kinds of malignancies, but has not produced satisfactory results in others. In some malignancies, such as brain malignancies, this regimen produces a median survival of less than one year. For example, 90% of resected malignant gliomas recur within two centimeters of the original tumor site within one year.

Though effective in some kinds of cancers, the use of systemic chemotherapy has had minor success in the treatment of cancer of the colon-rectum, esophagus, liver, pancreas, and kidney and melanoma. A major problem with systemic chemotherapy for the treatment of these types of cancer is that the systemic doses required to achieve control of tumor growth frequently result in unacceptable systemic toxicity. Efforts to improve delivery of chemotherapeutic agents to the tumor site have resulted in advances in organ-directed chemotherapy, as by continuous systemic infusion, for example. However, continuous infusions of anticancer drugs generally have not shown a clear benefit over pulse or short-term infusions. Implantable elastomer access ports with self-sealing silicone diaphragms have also been tried for continuous infusion, but extravasation remains a problem. Portable infusion pumps are now available as delivery devices and are being evaluated for efficacy. (See *Harrison's Principles of Internal Medicine* 431-446, E. Braunwald et al., ed., McGraw-Hill Book Co. (1987) for a general review).

In the brain, the design and development of effective anti-tumor agents for treatment of patients with malignant neoplasms of the central nervous system have been influenced by two major factors: 1) the blood-brain barrier provides an anatomic obstruction in the normal brain, potentially limiting access of drugs to some regions of the tumors; and 2) the drugs given at high systemic levels are generally cytotoxic. Efforts to improve drug delivery to the tumor bed in the brain have included transient osmotic disruption of the blood brain barrier, cerebrospinal fluid perfusion, local delivery from implanted polymeric controlled release devices and direct infusion into a brain tumor using catheters. Each technique has had significant limitations. Disruption of the blood brain barrier increased the uptake of hydrophilic substances into normal brain, but did not significantly increase substance transfer into the tumor. Only small fractions of agents administered into the cerebrospinal fluid actually penetrated into the brain parenchyma. Controlled release biocompatible polymers for local drug delivery have been utilized for contraception, insulin therapy, glaucoma treatment, asthma therapy, prevention of dental caries, and certain types of cancer chemotherapy. (Langer, R., and D. Wise, eds, *Medical Applications of Controlled*

Release, Vol. I and II, Boca Raton, CRC Press (1986)) Brain tumors have been particularly refractory to chemotherapy. One of the chief reasons is the restriction imposed by the blood-brain barrier. Agents that appear active against certain brain tumors, such as gliomas, in vitro may fail clinical trials because insufficient drug penetrates the tumor. Although the blood-brain barrier is disrupted at the core of a tumor, it is largely intact at the periphery where cells actively engaged in invasion are located. Experimental intratumoral regimens include infusing or implanting therapeutic agents within the tumor bed following surgical resection, as described by Tomita, T, *J. Neuro-Oncol.* 10: 57-74 (1991). Drugs that have been used to treat tumors by infusion have been inadequate, did not diffuse an adequate distance from the site of infusion, or could not be maintained at sufficient concentration to allow a sustained diffusion gradient. The use of catheters has been complicated by high rates of infection, obstruction, and malfunction due to clogging. See T. Tomita, "Interstitial chemotherapy for brain tumors: review" *J. Neuro-Oncology* 10: 57-74 (1991).

Delivery of a low molecular weight, lipid soluble chemotherapeutic, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), in a polymer matrix implanted directly adjacent to brain tumors has some efficacy, as reported by Brem, et al., *J. Neurosurg.* 74: 441-446 (1991); Brem, et al., *Eur. J. Pharm. Biopharm.* 39(1): 2-7 (1993); and Brem, et al., "Intraoperative Chemotherapy using biodegradable polymers: Safety and Effectiveness for Recurrent Glioma Evaluated by a Prospective, Multi-Institutional Placebo-Controlled Clinical Trial" *Proc. Amer. Soc. Clin. Oncology* May 17, 1994. Polymer-mediated delivery of BCNU was superior to systemic delivery in extending survival of animals with intracranial 9L gliosarcoma and has shown some efficacious results in clinical trials. However, BCNU is a low molecular weight drug, crosses the blood-barrier and had previously been demonstrated to have some efficacy when administered systemically.

For example, one promising chemotherapeutic, camptothecin, a naturally occurring alkaloid isolate from *Camptotheca acuminata*, a tree indigenous to China, which exerts its pharmacological effects by irreversibly inhibiting topoisomerase I, an enzyme intimately involved in DNA replication, has been shown to have strong cytotoxic anti-tumor activity against a variety of experimental tumors in vitro, such as the L1210 and rat Walker 256 carcinosarcoma (Venditti, J. M., and B. J. Abbott, *Lloydia* 30: 332-348 (1967); Moertel, C. G., et al., *Cancer Chemother. Rep.* 56(1): 95-101 (1972)). Phase I and II clinical trials of camptothecin in human patients with melanoma and advanced gastrointestinal carcinoma, however, have shown unexpectedly severe systemic toxicity with poor tumoral responses, and clinical investigation therefore halted. (Gottlieb, J. A., and J. K. Luce, *Cancer Chemother. Rep.* 56(1): 103-105 (1972); Moertel, C. G., et al., *Cancer Chemother. Rep.* 56(1): 95-101 (1972); Muggia, F. M., et al., *Cancer Chemother. Rep.* 56(4): 515-521 (1972)). Many other chemotherapeutics which are efficacious when administered systemically must be delivered at very high dosages in order to avoid toxicity due to poor bioavailability. For example, paclitaxel (taxol) has been used systemically with efficacy in treating several human tumors, including ovarian, breast, and non-small cell lung cancer. However, maintenance of sufficient systemic levels of the drug for treatment of tumors has been associated with severe, in some cases "life-threatening" toxicity, as reported by Sarosy and Reed, *J. Nat. Med. Assoc.* 85(6): 427-431 (1993). Paclitaxel is a high molecular weight (854), highly lipophilic diterpenoid