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New Therapeutic Strategies for the Treatment of Brain Tumor

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1. Introduction

Despite significant advances in tumor imaging, neurosurgery, and radiotherapy, the prognosis for patients with malignant gliomas is extremely poor. The five-year survival rate for patients with glioblastoma (GBM), the most aggressive form of malignant glioma, is less than 5% after initial diagnosis (CBTRUS statistical report, 2010). Factors that contribute to the dismal prognosis associated with GBM include its infiltrative nature throughout the brain, which precludes total surgical resection and impair radiotherapy targeting, and resistance to most types of conventional cancer therapeutics. Many clinical studies using potent chemotherapeutic drugs conducted in the past decade have not demonstrated significant improvement in survival. A fundamental limitation in the treatment of brain tumors is that many systemically administered therapeutic agents do not cross the blood-brain barrier (BBB) (Abbott et al., 2010; Brightman, 1977; Huynh et al., 2006; Schlosshauer, 1993). While some small and lipophilic molecules, peptides, and protein-based agents delivered by systemic routes can reach the brain parenchyma by crossing the BBB, high doses are usually needed to achieve therapeutic levels, which can lead to substantial toxicity.

In this chapter, the application of intranasal delivery (IND), in comparison with systemic (intravascular) and/or direct invasive (intraparechymal) drug delivery, for the treatment of brain tumors is discussed.

2. The BBB: An obstacle for drug delivery to brain tumor

The brain parenchyma has both physiological and biological safeguards to prevent the entry of toxins from the bloodstream, which are collectively known as the BBB. The endothelial cells that comprise the cerebral micro-vessels are linked by tight junctions and surrounded by astrocytic processes and adjacent pericytes and a characteristic composition of the extracellular matrix. This structural arrangement prohibits most drugs from entering the brain through pericellular diffusion. Drugs that are able to diffuse through the barrier must be small (<400 Da) and lipophilic. In addition to this physiological barrier, drugs are rapidly cleared by efflux pumps such as P-glycoprotein, and a rapid turnover rate of extracellular fluid in the brain. In combination, these factors have limited the number of successful pharmacologic treatments for diseases of the brain and necessitate a closer examination of

both traditional and novel methods of drug delivery (Choi et al., 2008; Eyal et al., 2009; Saunders et al., 2008).

In brain tumors such as GBM, the BBB is progressively disrupted with tumor growth by inducing large gaps between endothelial cells (Coomber et al., 1985). However, the extent of BBB disruption among individual patients, and/or among various regions within a single tumor, appears to be highly variable. BBB is most likely disrupted in the necrotic center, not at the infiltrative edge of the tumor (Gerstner & Fine, 2007). Recently, the artificially disruption of the BBB using hyper osmotic solutions has demonstrated by intra-arterial infusion of the VEGF specific antibody bevacizumab in patients with recurrent malignant glioma (Boockvar et al., 2010). However, disruption of the BBB could potentially lead to other serious complications, such as brain edema. Therefore, development of strategies to deliver targeted agents across the BBB is a critical priority.

3. Strategies for drug delivery to the brain

In the past decade a number of drug delivery strategies have been developed to overcome challenges presented by BBB. These strategies can be divided into two categories: (a) attempt to increase drug delivery of intravascularly administered drugs by manipulating either the drugs or capillary permeability, and (b) attempt to increase drug delivery by local administration.

3.1 Intravascular delivery

Several strategies have recently developed to increase the fraction of intravascular drug reaching the tumor. These include i) intra-arterial administration, ii) packaging drugs such as microcapsules and liposomes, iii) use of biologically active agents (such as bradykinin and histamine) (Greenwood, 1992), iv) use of replication-competent retroviruses to deliver oncolytic therapies (Tai & Kasahara, 2008), v) use of mesenchymal (Yong et al., 2009) or neural stem cells to deliver small molecules, antibodies, or toxic payloads (Aboody et al., 2000; Frank et al., 2009). There are also several specific transport mechanisms that have been exploited, involving the activity of several independent transporters that mediate the flux of substances important for brain function, such as carrier-mediated transporters, including the glucose and amino acid transporters (Rapoport, 1996; Tamai & Tsuji, 1996; Deeken & Loscher, 2007; Saunders et al., 2008), active efflux transporters, including P-glycoprotein and the other ATP-binding cassette (ABC) gene family members, and receptor-mediated transporters, of which transferrin receptor (TfR), insulin receptor, and low-density lipoprotein receptor (Pardridge, 2007). A further strategy has been to conjugate the therapeutic drug with a protein or a monoclonal antibody that gains access to the brain by receptor-mediated transcytosis (Pardridge, 1999). Small peptide vectors have been used to enhance brain uptake of several therapeutic drugs (Rousselle et al., 2000). These peptide-vectors cross cellular membranes safely and efficiently and have been used successfully to enhance penetration of several drugs.

The strategy of a packaging drugs and/or interfering RNAs into liposomes that more readily cross the BBB and show tumor reduction and increase in survival in mice. Liposomes are a drug carrier system consisting of a phospholipid membrane shell surrounding a hollow core used to stably encapsulate therapeutic molecules allowing increased solubility and half-life resulting in increased bioavailability. Gradual release of the drug from the liposome increases therapeutic efficacy while reducing toxicity (Gabizon,

2003). Liposomal anticancer agents have been widely used in humans and are currently approved for ovarian cancer (Tanguay, 2009) and multiple myeloma (Moreau, 2009), but remain investigational in their use for brain tumors. To increase the specificity of liposomal drugs, targeting antibodies can be attached to the surface of the liposome (Elbayoumi & Torchilin, 2009; Mamot et al., 2005). Antibody-conjugated liposomes increase the rate of liposome internalization, which increase intracellular drug concentration, thereby achieving heightened anti-tumor activity (Mamot et al., 2005). EGFR, a tyrosine kinase receptor that is over-expressed in 30-40% of high grade gliomas (Ekstrand et al., 1991). Attempts to target GBM by delivering EGFR-targeted immunoliposomes encapsulated anti-cancer agents or EGFR-specific shRNA in PEGylated liposomes bearing insulin receptor– and TfR-specific antibodies in an in vivo model has shown some promise (Mamot et al., 2005; Zhang et al., 2004). However, these antibody-based approaches have yet to translate into the clinic. Developing the right targeting antibodies to facilitate crossing of the BBB in humans, and uncovering the molecular mechanism by which the process works, remain significant impediments to clinical application.

3.2 Convection-enhanced delivery

Technology to improve direct drug delivery into the central nervous system (CNS) are currently part of intensive research, and include intraventricular or intraparenchymal injections [e.g. convection-enhanced delivery (CED)]. In particular, CED has shown promising results in both animal models and clinical trials (Huynh et al., 2006; Kawakami et al., 2004; MacKay et al., 2005; Mamot et al., 2004; Ozawa et al., 2002; Saito et al., 2006). CED is a continuous infusion that uses a convective (versus diffusive) flow to drive the therapeutic agent throughout a larger region of tissue. CED uses a slow drug infusion rate by micro infusion pump coupled with a specially designed catheter which is a 1-mm stepped design with a fused silica tubing into 24 gage needle. These optimal CED devices increase drug distribution and reduce reflux (Serwer et al., 2010) (Figure 1,2).
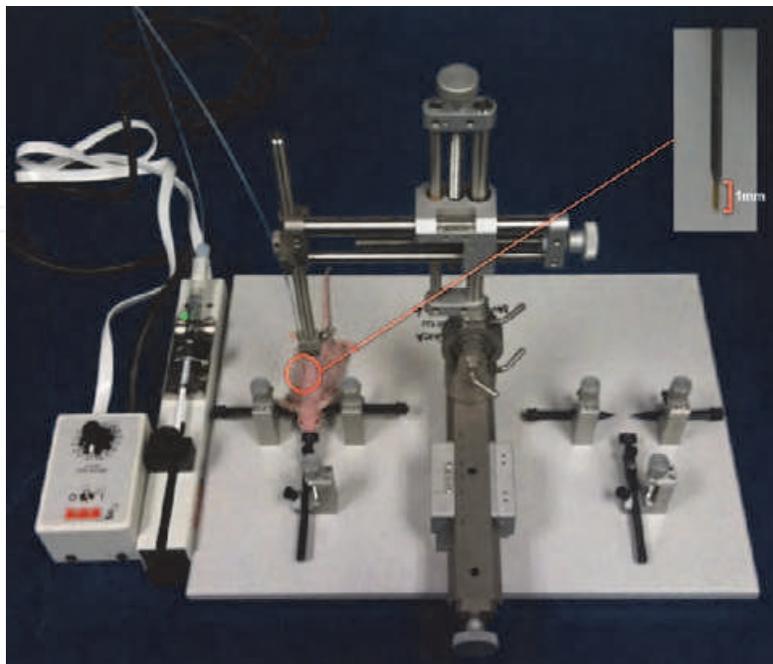

Fig. 1. CED cannula and surgical set-up.

CED is well suited for the delivery of liposomes and particulate drug carriers which have the potential to provide a sustained level of drug and to reach cellular targets with improved specificity (Murad et al., 2006; Saito et al., 2004). CED of liposomal anti-cancer agents have shown greater brain and tumor retention, and effective anti-tumor activity in GBM xenografted animals, as compared to free drugs delivery (Bidros & Vogelbaum, 2009; Noble et al., 2006; Yamashita et al., 2007). Importantly, prolonged exposure to liposomal anti-cancer agents resulted in no measurable CNS toxicity, whereas free drugs induced severe CNS toxicity.
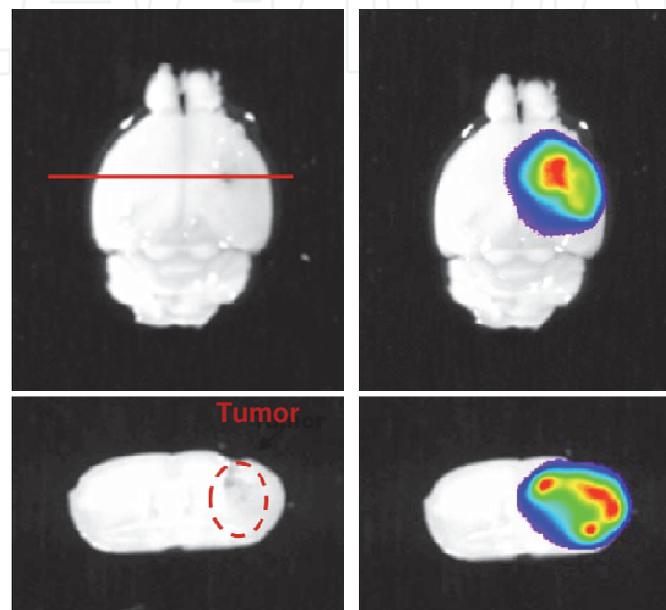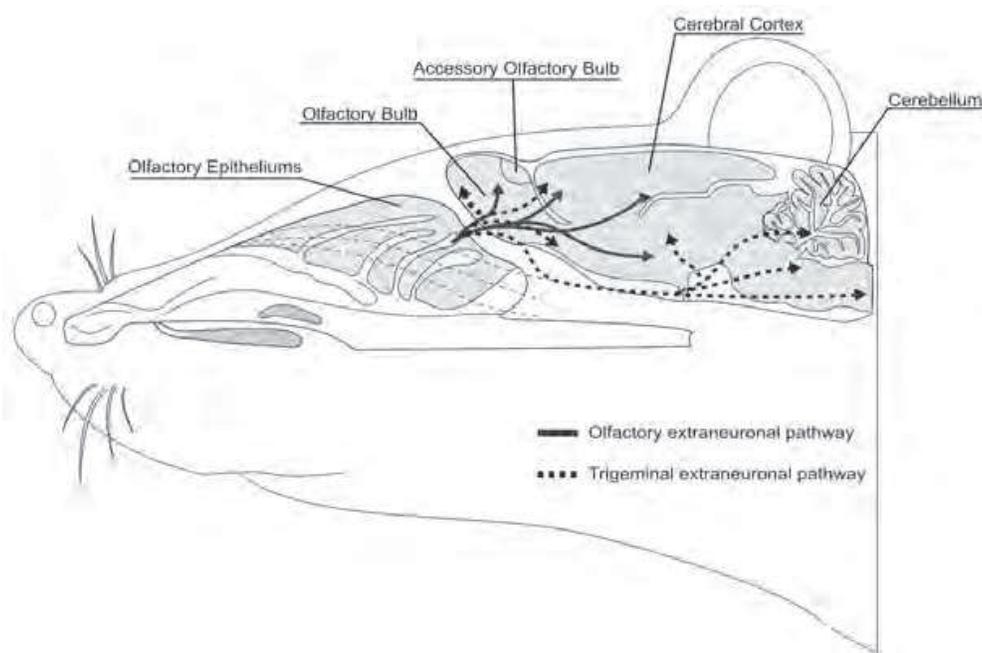

Fig. 2. Representative image of successful CED into the mice brain tumor.

CED has also been used to deliver larger particles, including purified virus and proteins. Currently, CED is being evaluated in 17 clinical trials for the delivery of small molecules, antisense oligonucleotides, and proteins (United States National Institutes of Health, 2011). However, this technique requires the use of potentially risky surgical procedures to position the catheter into the patient's brain parenchyma, and is expensive techniques. Additional limitations of these methods are inadequate CNS distribution due to reflux and leakage along with the needle tracts from the injection site and rapid turnover of the cerebrospinal fluid (CSF). The reflux and leakage through the implanted catheter leads to a measurable and significant inflammation and local edema, because drug solution infuse continuously beyond the tumor boundary into adjacent normal brain tissues (Kawakami et al., 2004; Marmot et al., 2004; Ozawa et al., 2004; Sandberg et al., 2002). Finally, CED infusions can be variable by investigators, in one study the rate of successful infusion was reported as 19% (Sampson et al., 2008).
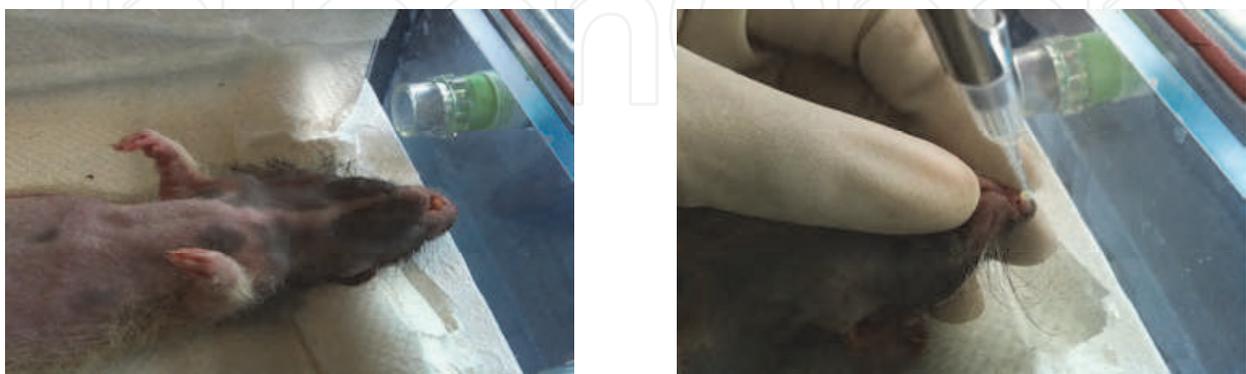
3.3 Intranasal delivery
One technique under current investigations is to integrate a recent innovation in drug delivery to the brain, intranasal delivery (IND). IND is a practical and noninvasive method of bypassing the BBB and eliminating the surgical risk associated with direct drug administration into the brain parenchyma. It is an alternative to systemic (intravascular) and/or direct invasive (intraparechymal) drug delivery. IND relies upon the unique anatomic connections of

the olfactory and trigeminal nerves from the nasal mucosa to the CNS (Dhuria et al., 2010; Thorne et al., 2004). These nerves arise in the brainstem and innervate the nasal mucosa, allowing detection of odors and other sensory stimuli (Dhanda et al., 2006; Thorne et al., 2004). Intranasally administered drugs reach the CNS and/or CSF within minutes of administration by using an extracellular route through perineural and perivascular channels, without binding to any receptor or relying upon axonal transport (Dhuria et al., 2010; Thorne et al., 2004) (Figure 3a). To administer the drugs through the nasal cavity, animals were anesthetized with 2–2.5% isoflurane and placed in an anesthesia chamber. Six µl drops of soluble form of therapeutic agents were administered with a small pipette every 2 min into alternate sides of the nasal cavity for a total of 22 min (a total volume of 66 µl). This method of administration results in consistent deposition in the olfactory epithelium without respiratory distress. Following IND, the animals remained in a supine position for 15 min in order for absorption to occur through the nasal mucosa (Figure 3b).

(a) Anatomical pathways of IND

(b) IND in athymic rats

Fig. 3. (a) Anatomic and extraneuronal pathways of the olfactory and trigeminal nerves following IND (b) Demonstration of IND in an anesthetized athymic rat.

In addition to bypassing the BBB, advantages of IND are the avoidance of hepatic first-pass elimination, thereby reducing systemic side effects, and convenient self-administration for patients, a feature that would clearly aid in clinical applications, particularly in the treatment of brain tumors where repeated dosing is necessary (Dhuria et al., 2010).

Many therapeutic agents, including small molecules, growth factors, proteins, peptides, viral vectors, liposomes, nanoparticles and vaccines, have been delivered into the CNS in both animals and humans using IND for a variety of CNS disorders. Thorne *et al* reported that IGF-1 can be rapidly transported into the rat brain and upper spinal cord via the olfactory and trigeminal pathways (Thorne et al., 2004) and, IFNβ-1b can be delivered into the CNS in monkeys (Thorne et al., 2008). Furthermore, rat mesenchymal stem cells and human glioma cells have been delivered to the brain through the nasal pathway (Danielyan et al, 2009). In humans, IND with insulin improves memory in healthy adults (Banks et al., 2004; Benedict et al., 2004) and in patients with early-stage Alzheimer's disease (Reger et al., 2008) without changing the blood levels of glucose or insulin. Also, IND with the neuropeptide oxytocin has been reported to improve trust (Baumgartner et al., 2008; Kosfeld et al, 2005), social behavior (Domes et al., 2007a, 2007b; Guastella et al., 2009), and social memory (Rimmele et al., 2009), and decreased fear and anxiety (Kirsch et al., 2005; Parker et al., 2005).

In brain tumor model, many anti-cancer agents such as methotrexate (Shingaki et al., 1999; Shingaki et al., 2010), 5-fluorouracil (Sakane et al., 1999) and raltitrexed (Wang et al., 2005) have been delivered successfully to the brain using IND. Shingaki *et al* reported that intranasally delivered methotrexate reached the CSF and reduced tumor weight in rodent glioma allografts (Shingaki et al., 1999). Drug targeting of the chemotherapeutic agent raltitrexed to the brain was significantly higher following IND compared with that of intravenous administration (Wang et al., 2005). However, these chemotherapeutic agents do not discriminate between tumor and normal tissues. Thus, the application of drugs at concentrations required to kill tumor cells can also lead to toxicity in normal neural tissues. To achieve therapeutic efficacy without toxicity, the drugs need to preferentially target brain tumors while sparing normal tissue from damage.

3.3.1 Intranasal delivery of a telomerase inhibitor

Given that telomerase is expressed in essentially all cancer cells, but not in normal somatic cells (Kim et al., 1994; Phatak & Burger, 2007), the inhibition of this enzyme is an attractive therapeutic strategy for selectively targeting brain tumors while sparing normal brain tissue. The human telomerase enzyme is a specialized ribonucleoprotein reverse transcriptase containing essential RNA (hTR) and protein (hTERT) subunits. Telomerase elongates telomeres by adding the (TTAGGG)n telomeric repeats to the ends of chromosomes, protecting the chromosome ends from fusion and DNA damage recognition (Feng et al., 1995; Greider & Blackburn, 1985). During cell division in cancer cells, DNA is continuously extended or maintained by telomerase to compensate for the lost telomeric repeats resulting from the 'end-replication' problem of DNA polymerase (Levy et al., 1992; Röth et al., 2003). In the absence of telomerase activity, chromosome ends shorten with each cell division, eventually resulting in growth arrest or cell death, termed replicative senescence or crisis (Allsopp et al., 1992; Shay & Wright, 2006). Although cancer cells express telomerase, these cells typically have relatively short but stable telomere length, whereas normal cells do not express telomerase and have long, slowly shortening telomeres. These differences between cancer and normal cells make cancer cells more sensitive to telomerase inhibitors, and may

allow for a substantial therapeutic window for telomerase inhibition-based treatments (Asai et al., 2003).

GRN-163, a telomerase enzyme antagonist, is a 13-mer oligonucleotide N3'→P5' thiophosphoramidate, that exhibits high RNA binding affinity for the targeted template region of hTR in a sequence-specific manner (Gryaznov et al., 2001; Herbert et al., 2002). GRN-163 has demonstrated potent inhibitory activity against human telomerase in several biochemical assays, with IC_{50} values of < 1 nM (Gryaznov et al., 2001; Herbert et al., 2002). *In vitro*, telomerase inhibition by GRN-163 induced cellular senescence and apoptosis in various human cancer cell lines (Ozawa et al., 2004; Asai et al., 2003; Herbert, 2002; Akiyama et al., 2003; Gryaznov et al., 2003; Wang et al., 2004). Although a potential limitation of oligonucleotide therapies is the bioavailability in tumor tissues (Corey, 2002), GRN-163 inhibited tumor growth in prostate cancer, multiple myeloma, lymphoma, hepatoma and glioblastoma xenografts in rodents (Ozawa et al., 2004; Asai et al., 2003; Wang et al., 2004; Hashizume et al., 2008; Djojosubroto et al., 2005). GRN-163 has been delivered successfully into the brain using IND and shown impressive oncolytic activity without harming normal brain tissue (Hashizume et al., 2008). Intranasally delivered GRN-163 exhibited favorable tumor uptake, inhibited tumor growth in human glioblastoma xenografts in rats and increased the survival of tumor-bearing animals. Following the IND of the highest possible dose of GRN-163 (0.65 µmol/µl, based on the solubility of the compound in saline solution), the compound could be detected in the cerebral hemispheres, brainstem and intracranial sections of the trigeminal nerve in naïve rats within 10 min of administration. In tumor-bearing rats, GRN-163 was detected at the edge of the tumor after 30 min, and throughout the tumor between 4 and 24 h after administration (Figure 4).
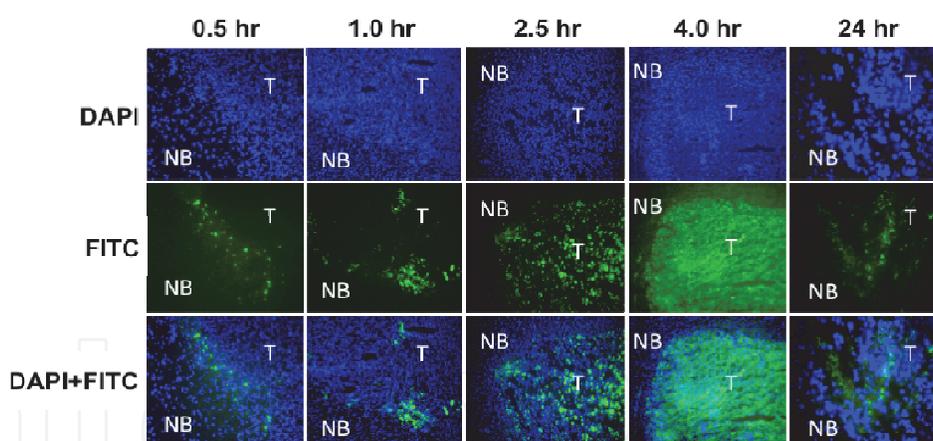

Fig. 4. Distribution of fluorescein-labeled GRN163 by IND into intracerebral tumors in athymic rats. Abbreviations: T, tumor; NB, normal brain.

Importantly, very little or no GRN-163 was found in healthy brain cells adjacent to the tumor or in any other part of the brain. This apparent selectivity may be a result of the specific binding affinity that GRN-163 exhibits for tumor cell telomerase (Herbert et al., 2002). The specificity achieved with IND appears to be superior to the results obtained using CED, which reportedly delivers drugs beyond the tumor boundary into adjacent healthy brain tissue, leading to damage to healthy sections of the brain (Kawakami et al., 2004; Mamot et al., 2004, Ozawa et al., 2004). In addition, intranasally delivered GRN-163 inhibited telomerase activity in intracranial glioblastoma xenografts in rats in a dose-dependent manner (Figure 5).
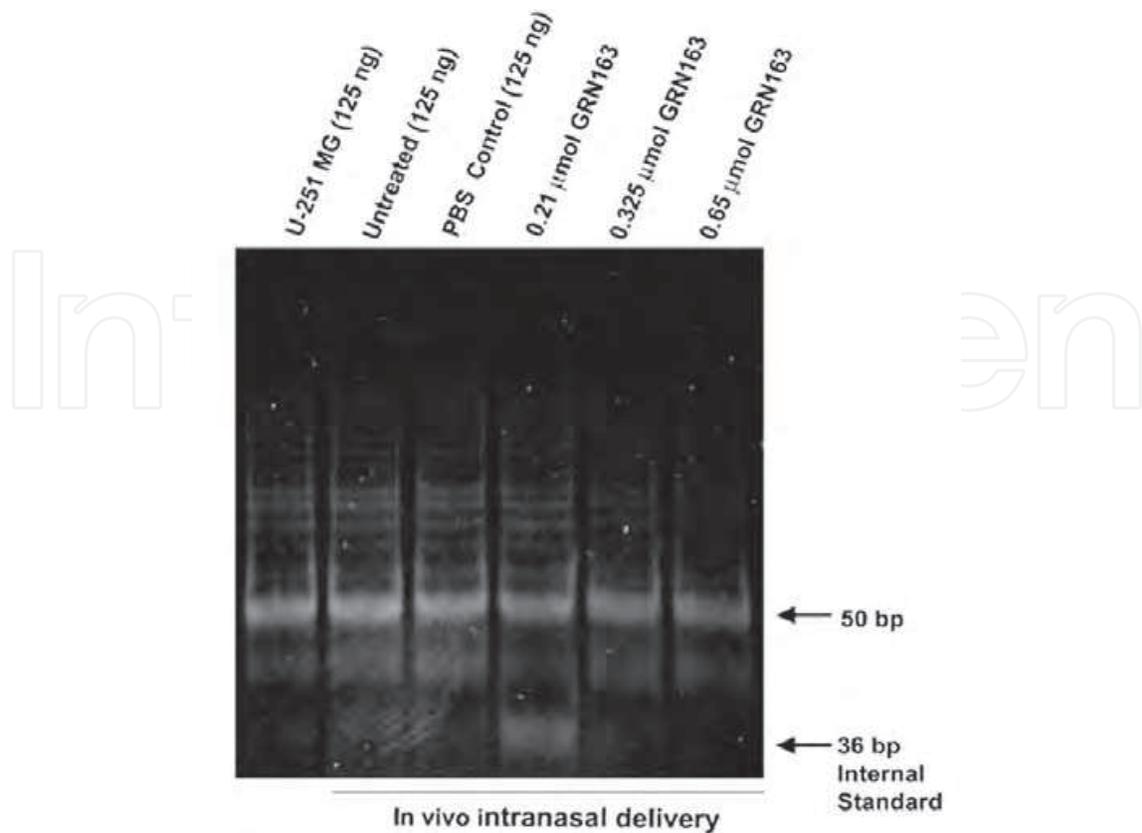
Fig. 5. Inhibition of telomerase activity by GRN163 in intracerebral GBM xenografts.

Moreover, GRN-163 (qd for 12 days) delivered intranasally at the highest solubility dose significantly prolonged the median survival from 35 days in the control group to 75.5 days in the GRN163-treated group. None of the rats that were treated with GRN-163 exhibited signs of toxicity or behavioral abnormalities during the 12-day treatment period (Figure 6).
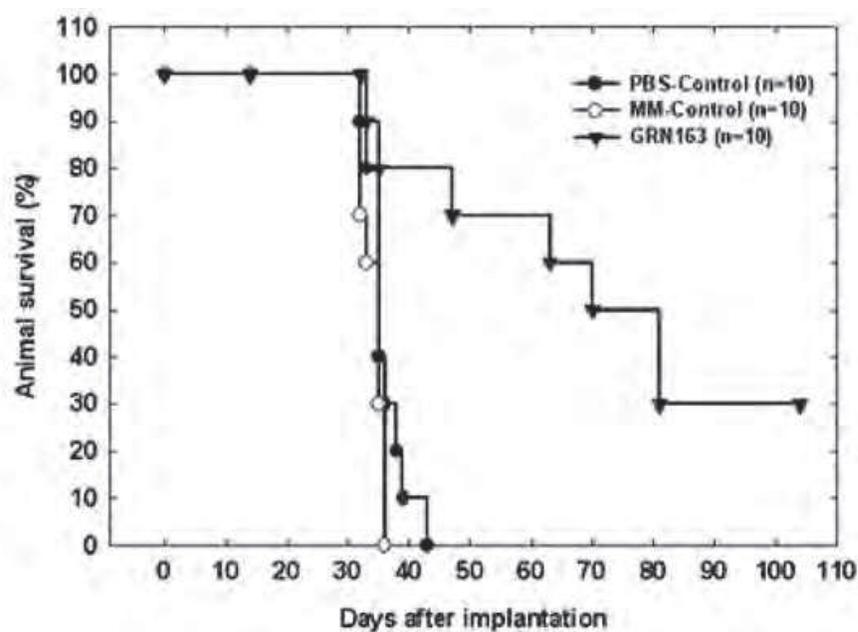

Fig. 6. Survival of rats treated with intranasal GRN163.

Because the mechanism of action of oligonucleotide-based telomerase antagonists such as GRN-163 is through the competitive inhibition of the telomerase enzyme (Gryaznov et al., 2001; Herbert et al., 2002), treated tumor cells can regain baseline telomerase activity following termination of treatment with the telomerase inhibitor. Thus, it is possible that telomerase inhibitor agents will need to be administered for an extended period of time to achieve efficacy. Hypothetically, repeated intranasal treatment is possible, and may be practical as a convenient self-administered treatment.

The lipid-modified N3'→P5' thiophosphoramidate oligonucleotide imetelstat represents the most advanced anti-telomerase therapeutic, and is a more potent derivative of GRN-163 (Herbert et al., 2005). Because of increased lipophilicity, imetelstat exhibits increased bioavailability and cellular uptake in tumors compared with nonlipidated compounds, and it is more acid-resistant than other telomerase-targeted phosphoramidate oligonucleotides (Herbert et al., 2005). Imetelstat also inhibits telomerase activity in various tumor cell lines with IC_{50} values between 3 and 300 nM in the absence of any cellular uptake enhancers (Graznov et al., 2007). In cell-based studies with GRN-163, there was generally a phenotypic lag of at least a few weeks between the onset of exposure and growth inhibition (Akiyama et al., 2003); however, with imetelstat, the addition of a 5' lipid (palmitate) moiety increased potency and resulted in a more rapid loss of telomeres (population doubling [population doubling (PD) ~ 8 for GRN-163L-treated cells and PD ~ 13 for GRN-163-treated cells] and inhibition of cell growth (Herbert et al., 2005). *In vivo* inhibition of tumor growth by imetelstat has been reported in multiple animal models (Djojosubroto et al., 2005; Dikmen et al., 2005; Hochreiter et al., 2006; Marian et al., 2009) and Phase I/II clinical trials with imetelstat have been initiated in patients with chronic lymphocytic leukemia, refractory or relapsed solid tumors, NSCLC, multiple myeloma and breast cancer (Geron Corp., 2009).

3.3.2 Limitations and future prospects of telomerase inhibition by IND as a therapy for GBM

Although the inhibition of telomerase offers exciting therapeutic possibilities for the treatment of GBM patients, there are some potential limitations of this approach, such as the engagement of an alternative telomere-lengthening mechanism that can lead to anti-telomerase treatment (Bollmann et al., 2007). In addition, anti-telomerase therapy may be associated with a delay in efficacy because of the lag period between the initiation of anti-telomerase therapy (telomerase shortening) and the onset of therapeutically beneficial effects (cell death) (Bechter et al., 2004). The combination of IND of telomerase inhibitors with chemotherapy or radiotherapy may produce more rapid effects, and may provide an approach for minimizing the lag phase, potentially preventing or delaying tumor recurrences (Shay & Wright, 2006). The combination of imetelstat with existing chemotherapeutic agents has been demonstrated to enhance chemosensitivity in various human cancer cells (Djojosubroto et al., 2005; Godblatt et al., 2009a, 2009b). More specifically, imetelstat increased doxorubicin sensitivity of Hep3B human hepatoma cells (Djojosubroto et al., 2005), sensitized human breast cancer cells to paclitaxel and trastuzumab (Godblatt et al., 2009a, 2009b), and also enhanced hyperthermia-mediated radiosensitization in human 293 cell lines (Gomez-Millan et al., 2007). Recently, imetelstat in combination with radiation and temozolomide had a statistically significant effect on cell survival and activated the DNA damage response pathway in GBM tumor-initiating cells (Marian et al., 2010).

Further potential limitations of oligonucleotide-based therapies using IND are the low bioavailability and absorption in the nasal mucosa and tumor tissues because of low permeability and solubility (Kausch & Böhle, 2003; Dias & Stein, 2002). The poor absorption of drugs across the nasal membrane is due to low permeability of the nasal membrane, mucociliary clearance, enzymatic degradation, and efflux mechanisms, such as P-glycoprotein and ABC transporters (Dhuria et al., 2010).

3.3.3 Intranasal delivery of liposomal therapeutic agents
Liposomes can be used as biocompatible carriers to improve delivery properties across the nasal mucosa perhaps by increasing residence time of the formulation in the nasal cavity, resulting in higher concentration of encapsulated drugs in the brain. A study of IND with rivastigmine, an acetyl cholinesterase inhibitor, showed that the liposome drug formulation had a longer half-life compared to the free drug due to sustained release of rivastigmine from the liposomes (Arumugam et al., 2008). Migliore *et al* also reported that IND of the liposomal preparation resulted in a higher net delivery and longer retention of ovalbumin in the brain than the nonliposomal preparation (Migliore et al., 2010). Increased tissue retention may be a consequence of the protein's association with cationic lipids, rendering it more likely to undergo cellular binding and adsorptive endocytosis and impeding its diffusion and clearance from the brain (Kumagai et al., 1987). IND with liposomal therapeutic agents is conceptually attractive, and its appeal as a minimally invasive therapeutic strategy would facilitate its translation into clinical trials for the treatment of brain tumor patients.

4. Conclusion

IND of therapeutic agents is an innovative therapeutic strategy capable of targeting drug delivery to the brain for the treatment of brain tumors and could provide an alternative to systemic (intravascular) and/or direct (intraparechymal) drug administrations. IND is a practical and noninvasive method of bypassing the BBB, and is amenable to self-administration by patients. This technique has demonstrated promising results in the treatment of human CNS neurological disorders and rodent brain tumor without obvious toxicity. IND with GRN-163, an oligonucleotide-based telomerase inhibitor, has exhibited impressive oncolytic activity without inducing toxicity to healthy tissue (Hashizume et al., 2008). Data support further development of intranasal GRN-163 as a potential therapy for patients with brain tumors and perhaps as a means for treating multifocal brain tumors, such as metastatic brain tumors and/or pediatric brainstem tumors, which are less amenable to surgical procedures. A telomerase inhibitor, imetelstat, has reached clinical trials, and may therefore become a part of the available cancer therapeutic armamentarium in the future. IND can be further optimized by the use of liposomal drug carriers which provide stable encapsulation for various anticancer agents.

Given the promising results from current animal studies, intranasal therapeutic agents would seem to be prime candidates for clinical trials in patients with brain tumors. Initial trials of intranasal perillyl alcohol have begun in patients with recurrent malignant gliomas, and a reduction in the size of the brain tumors has been reported (Da Fonseca et al., 2006a, 2006b, 2008).

5. References

Abbott, N.J.; Patabendige, A.A.; Dolman, D.E.; Yusof, S.R. & Begley, D.J. (2009). Structure and function of the blood-brain barrier. *Neurobiology of disease*. Vol. 37, No. 1, pp. (13-25).

Aboody, K.S.; Brown, A.; Rainov, N.G.; Bower, K.A.; Liu, S.; Yang, W.; Small, J.E.; Herrlinger, U.; Ourednik, V.; Black, P.M.; Breakefield, X.O. & Snyder, E.Y. (2000). Neural stem cells display extensive tropism for pathology in adult brain: Evidence from intracranial gliomas. *Proceedings of the National Academy of Sciences of the United States of America*. Vol. 97, No. 23, pp. (12846–12851).

Akiyama, M.; Hideshima, T.; Shammas, M.A.; Hayashi, T.; Hamasaki, M.; Tai, Y.T.; Richardson, P.; Gryaznov, S.; Munshi, N.C. & Anderson, K.C. (2003). Effects of oligonucleotide N3'gP5' thio phosphoramidate (GRN163) targeting telomerase RNA in human multiple myeloma cells. *Cancer Research*. Vol. 63, No. 9, pp. (6187-6194).

Allsopp, R.C.; Vaziri, H.; Patterson, C.; Goldstein, S.; Younglai, E.V.; Futcher, A.B.; Greider, C.W. & Harley, C.B. (1992). Telomere length predicts replicative capacity of human fibroblasts. *Proceedings of the National Academy of Sciences of the United States of America.* Vol. 89, No. 21, pp. (10114-10118).

Arumugam, K.; Subramanian, G.S.; Mallayasamy, S.R.; Averineni, R.K.; Reddy, M.S. & Udupa, N. (2008). A study of rivastigmine liposomes for delivery into the brain through intranasal route. *Acta Pharmaceutica*. Vol. 58, No. 3, pp. (287-297).

Asai, A.; Oshima, Y.; Yamamoto, Y.; Uochi, T.A.; Kusaka, H.; Akinaga, S.;Yamashita, Y.; Pongracz, K.; Pruzan, R.; Wunder, E.; Piatyszek, M.; Li, S.; Chin, A.C.; Harley, C.B. & Gryaznov, S.M. (2003). A novel telomerase template antagonist (GRN163) as a potential anticancer agent. *Cancer Research*. Vol. 63, No. 14, pp. (3931-3939).

Banks, W.A.; During, M.J. & Niehoff, M.L. (2004). Brain uptake of the glucagon like peptide-1 antagonist exendin(9-39) after intranasal administration. *The Journal of pharmacology and experimental therapeutics.* Vol. 309, No. 2, pp. (469-475).

Baumgartner, T.; Heinrichs, M.; Vonlanthen, A.; Fischbacher, U. & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*. Vol. 58, No. 4, pp. (639–650).

Bechter, O.E.; Zou, Y.; Walker, W.; Wright, W.E. & Shay, J.W. (2004). Telomeric recombination in mismatch repair deficient human colon cancer cells after telomerase inhibition. *Cancer Research*. Vol. 64, No. 10, pp. (3444-3451).

Benedict, C.; Hallschmid, M.; Hatke, A.; Schultes, B.; Fehm, H.L.; Born, J. & Kern, W. (2004). Intranasal insulin improves memory in humans. *Psychoneuroendocrinology*. Vol. 29, No. 10, pp. (1326-1334).

Bidros, D.S. & Vogelbaum, M.A. (2009). Novel drug delivery strategies in neuro-oncology. *Neurotherapeutics*. Vol. 6, No. 3, pp. (539–546).

Bollmann, F.M. (2007). Targeting ALT: The role of alternative lengthening of telomeres in pathogenesis and prevention of cancer. *Cancer Treatment Reviews*. Vol. 33, No. 8, pp. (704-709).

Boockvar, J.A.; Tsiouris, A.J.; Hofstetter, C.P.; Kovanlikaya, I.; Fralin, S.; Kesavabhotla, K.; Seedial, S.M.; Pannullo, S.C.; Schwartz, T.H.; Stieg, P.; Zimmerman, R.D.; Knopman, J.; Scheff, R.J.; Christos, P.; Vallabhajosula, S. & Riina, H.A. (2010). Safety and maximum tolerated dose of superselective intraarterial cerebral infusion

of bevacizumab after osmotic blood-brain barrier disruption for recurrent malignant glioma. *Journal of Neurosurgery*. Vol. 114, No. 3, pp. (624-632).

Brightman, M.W. (1977). Morphology of blood–brain interfaces. *Experimental eye research*. Vol. 25, pp. (1–25).

CBTRUS statistical report tables: Brain Tumor Registry of The United States, Hinsdale, IL, USA, In: *CBTRUS*, (accessed April 12th 2011). *http://www.cbtrus.org/2010-NPCR-SEER/Table23.pdf*

Choi, Y.K. & Kim, K.W. (2008). Blood-neural barrier: its diversity and coordinated cell-to-cell communication. *BMB Reports*. Vol. 41, No. 5, pp. (345-352).

Coomber, B.L.; Stewart, P.A.; Hayakawa, K.; Farrell, C.L. & Del Maestro, R.F. (1985). Quantitative morphology of human glioblastoma multiforme microvessels: structural basis of blood-brain barrier defect. *Journal of Neuro-oncology*. Vol. 5, No. 4, pp. (299–307).

Corey, D.R. (2002). Telomerase inhibition, oligonucleotides, and clinical trials. *Oncogene*. Vol. 21, No. 4, pp. (631-637).

Da Fonseca, C.O.; Landeiro, J.A.; Clark, S.S.; Quirico-Santos, T.; da Costa Carvalho Mda, G. & Gattass, C.R. (2006). Recent advances in the molecular genetics of malignant gliomas disclose targets for antitumor agent perillyl alcohol. *Surgical Neurology*. Vol. 65, pp. (S1:2-S1:9).

Da Fonseca, C.O.; Masini, M.; Futuro, D.; Caetano, R.; Gattass, C.R. & Quirico-Santos, T. (2006). Anaplastic oligodendroglioma responding favorably to intranasal delivery of perillyl alcohol: a case report and literature review. *Surgical Neurology*. Vol. 66, No. 6, pp. (611-615).

Da Fonseca CO, Schwartsmann G, Fischer J, Nagel J, Futuro D, Quirico-Santos T, Gattass CR. (2008). Preliminary results from a phase I/II study of perillyl alcohol intranasal administration in adults with recurrent malignant gliomas. *Surgical Neurology*. Vol. 70, No. 3, pp. (259-267).

Danielyan, L.; Schäfer, R.; von Ameln-Mayerhofer, A.; Buadze, M.; Geisler, J.; Klopfer, T.; Burkhardt, U.; Proksch, B.; Verleysdonk, S.; Ayturan, M.; Buniatian, G.H.; Gleiter, C.H.; Frey, W.H. 2nd. (2009). Intranasal delivery of cells to the brain. *European Journal of Cell Biology*. Vol. 88, No. 6, pp. (315-324).

Dias, N. & Stein, C.A. (2002). Potential roles of antisense oligonucleotides in cancer therapy. The example of Bcl-2 antisense oligonucleotides. *European journal of pharmaceutics and biopharmaceutics*. Vol. 54, No. 3, pp. (263-269).

Deeken, J.F. & Loscher, W. (2007). The blood-brain barrier and cancer: transporters, treatment and Trojan horses. *Clinical Cancer Research*, Vol. 13, No. 6, pp. (1663-1674).

Dhuria, S.V.; Hanson, L.R. & Frey, W.H. 2nd. (2010). Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *Journal of Pharmaceutical Sciences*. Vol. 99, No. 4, pp. (1654-1673).

Dhanda, D.; Frey, W.H. 2nd.; Leopold, D. & Kompella, U.B. (2006). Approaches for drug deposition in the human olfactory epithelium. *Drug Delivery Technology*. Vol. 5, No. 4, pp. (64-72).

Dikmen, Z.G.; Gellert, G.C.; Jackson, S.; Gryaznov, S.; Tressler, R.; Dogan, P.; Wright, W.E. & Shay, J.W. (2005). *In vivo* inhibition of lung cancer by GRN163L: A novel human telomerase inhibitor. *Cancer Research*. Vol. 65, No. 17, pp. (7866-7873).

Djojosubroto, M.W.; Chin, A.C.; Go, N.; Schaetzlein, S.; Manns, M.P.; Gryaznov, S.; Harley, C.B. & Rudolph, K.L. (2005). Telomerase antagonists GRN163 and GRN163L inhibit tumor growth and increase chemosensitivity of human hepatoma. *Hepatology*. Vol. 42, No. 5, pp. (1127-1136).

Domes, G.; Heinrichs, M.; Glascher, J.; Buchel, C.; Braus, D.F. & Herpertz, S.C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry*. Vol. 62 No. 10, pp. (1187–1190).

Domes, G.; Heinrichs, M.; Michel, A.; Berger, C. & Herpertz, S.C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry* Vol. 61, No. 6, pp. (731–733).

Ekstrand, A.J.; James, C.D.; Cavenee, W.K.; Seliger, B.; Pettersson, R.F. & Collins, V.P. (1991). *Cancer Research*. Vol. 51, No. 8, pp. (2164-2172).

ElBayoumi, T.A. & Torchilin, V.P. (2009). Tumor-targeted nanomedicines: enhanced antitumor efficacy in vivo of doxorubicin-loaded, long-circulating liposomes modified with cancer-specific monoclonal antibody. *Clinical Cancer Research*. Vol. 15, No. 6, pp. (1973-1980).

Eyal, S, Hsiao, P. & Unadkat, J.D. (2009). Drug interactions at the blood- brain barrier: fact or fantasy? *Pharmacology & Therapeutics*. Vol. 123, No. 1, pp. (80-104).

Frank, R.T.; Edmiston, M.; Kendall, S.E.; Najbauer, J.; Cheung, C.W.; Kassa, T.; Metz, M.Z.; Kim, S.U.; Glackin, C.A.; Wu, A.M.; Yazaki, P.J. & Aboody, K.S. (2009). Neural stem cells as a novel platform for tumor-specific delivery of therapeutic antibodies. *Public Library of Science one*. Vol. 4, No. 12, pp. e8314.

Feng, J.; Funk, W.D.; Wang, S.S.; Weinrich, S.L.; Avilion, A.A.; Chiu, C.P.; Adams, R.R.; Chang, E.; Allsopp, R.C. & Yu, J. (1995). The RNA component of human telomerase. *Science*. Vol. 269, No. 5228, pp. (1236-1241).

Gabizon, A.; Shmeeda, H. & Barenholz, Y. (2003). Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. *Clinical pharmacokinetics*. Vol. 42, No. 5, pp. (419-436).

Geron Corp, Menlo Park, CA, USA, (2009). Telomerase inhibitor drug – Imetelstat (GRN163L): *www.geron.com/patients/clinicaltrials/ GRN163L.aspx*

Gerstner, E.R. & Fine, R.L. (2007). Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. *Journal of Clinical Oncology*. Vol. 25, No. 16, pp. (2306-2312).

Godblatt, E.M.; Erickson, P.A.; Gentry, E.R.; Gryaznov, S.M. & Herbert, B.S. (2009). Lipid-conjugated telomerase template antagonists sensitize resistant HER2-positive breast cancer cells to trastuzumab. *Breast Cancer Research and Treatment*. Vol. 118, No. 1, pp. (21-32).

Goldblatt, E.M.; Gentry, E.R.; Fox, M.J.; Gryaznov, S.M.; Shen, C. & Herbert, B.S. (2009). The telomerase template antagonist GRN163L alters MDA-MB-231 breast cancer cell morphology, inhibits growth, and augments the effects of paclitaxel. *Molecular Cancer Therpeutics*. Vol. 8, No. 7, pp. (2027-2035).

Gomez-Millan, J.; Goldblatt, E.M.; Gryaznov, S.M.; Mendonca, M.S. & Herbert, B.S. (2007). Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells.*International journal of radiation oncology, biology, physics*. Vol. 67, No. 3, pp. (897-905).

Guastella, A.J.; Mitchell, P.B. & Dadds, M.R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*. Vol. 63, No. 1, pp. (3–5).

Graznov, S.M.; Jackson, S.; Dikmen, G.; Harley, C.; Herbert, B.S.; Wright, W.E.; Shay, J.W. (2007). Oligonucleotide conjugate GRN163L targeting human telomerase as potential anticancer and antimetastatic agent. *Nucleosides Nucleotides and Nucleic Acids*. Vol. 26, No. 10-12, pp. (1577-1579).

Greenwood, J. (1992). Experimental manipulation of the blood–brain and blood–retinal barriers. In *Physiology and Pharmacology of the Blood–Brain Barrier. Handbook of Experimental Pharmacology*, Bradbury, M.W.B. and Abbott, N.J., pp. 459–486, Springer-Verlag, Berlin, Germany

Gryaznov, S.M.; Pongracz, K.; Matray, T.; Schultz, R.; Pruzan, R.; Aimi, J.; Chin, A.; Harley, C.; Shea-Herbert, B.; Shay, J.; Oshima, Y.; Asai, A. & Yamashita, Y. (2001). Telomerase inhibitors – Oligonucleotide phosphoramidates as potential therapeutic agents. *Nucleosides Nucleotides and Nucleic Acids*. Vol. 20, No. 4-7, pp. (401-410).

Greider, C.W. & Blackburn, E.H. (1985). Identification of a specific telomere terminal transferase activity in *Tetrahymena* extracts. *Cell*. Vol. 43, No. 2, Pt 1, pp. (405-413).

Hashizume, R.; Ozawa, T.; Gryaznov, S.M.; Bollen, A.W.; Lamborn. K.R.; Frey, W.H. 2nd & Deen, D.F. (2008). New therapeutic approach for brain tumors: Intranasal delivery of telomerase inhibitor GRN163. *Neuro-Oncology*. Vol. 10, No. 2, pp. (112-1120).

Herbert, B.S.; Gellert, G.C.; Hochreiter, A.; Pongracz, K.; Wright, W.E.; Zielinska, D.; Chin, A.C.; Harley, C.B.; Shay, J.W. & Gryaznov, S.M. (2005). Lipid modification of GRN163, an N3'gP5' thio- phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene*. Vol. 24, No. 33, pp. (5262-5268).

Herbert, B.S.; Pongracz, K.; Shay, J.W. & Gryaznov, S.M. (2002). Oligonucleotide N3'gP5' phosphoramidates as efficient telomerase inhibitors. *Oncogene*. Vol. 21, No. 4, pp. (638-642).

Hochreiter, A.E.; Xiao, H.; Goldblatt, E.M.; Gryaznov, S.M.; Miller, K.D.; Badve, S.; Sledge, G.W. & Herbert, B.S. (2006). Telomerase template antagonist GRN163L disrupts telomere maintenance, tumor growth, and metastasis of breast cancer. *Clinical Cancer Research*. Vol. 12, No. 10, pp. (3184-3192).

Huynh, G.H.; Deen, D.F. & Szoka, F.C. Jr. (2006). Barriers to carrier mediated drug and gene delivery to brain tumors. *Journal of Control Release*. Vol. 110, No. 2, pp. (236-259).

Kausch, I. & Böhle, A. (2003). Antisense oligonucleotide therapy for urologic tumors. *Current Urology Reports*. Vol. 4, No. 1, pp. (60-69).

Kawakami, K.; Kawakami, M.; Kioi, M.; Husain, S.R. & Puri, R.K. (2004). Distribution kinetics of targeted cytotoxin in glioma by bolus or convection-enhanced delivery in a murine model.*Journal of Neurosurgery*. Vol. 101, No. 6, pp. (1004-1011).

Kim, N.W.; Piatyszek, M.A.; Prowse, K.R.; Harley, C.B.; West, M.D.; Ho, P.L.; Coviello, G.M.; Wright, W.E.; Weinrich, S.L. & Shay,J.W. (1994). Specific association of human telomerase activity with immortal cells and cancer. *Science*. Vol. 266, No. 5193, pp. (2011-2015).

Kirsch, P.; Esslinger, C.; Chen, Q.; Mier, D.; Lis, S.; Siddhanti, S.; Gruppe, H.; Mattay, V.S.; Gallhofer, B. & Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*. Vol. 25, No. 49, pp. (11489–11493).

Kosfeld, M.; Heinrichs, M.; Zak, P.J.; Fischbacher, U. & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*. Vol. 435, No. 7042, pp. (673-676).
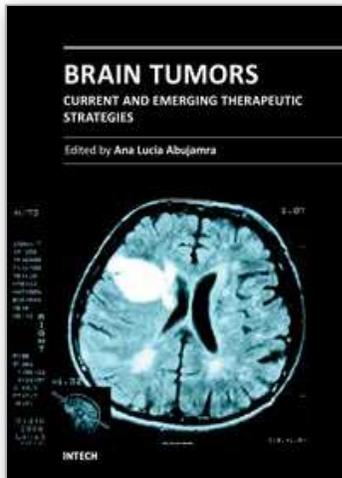
Kumagai, A.K.; Eisenberg, J.B. & Pardridge, W.M. (1987). Absorptive-mediated endocytosis of cationized albumin and a b- endorphin-cationized albumin chimeric peptide by isolated brain capillaries. Model system of blood-brain barrier transport. *The Journal of Biological Chemistry*. Vol. 262, No. 31, pp. (15214–15219).

Levy, M.Z.; Allsopp, R.C.; Futcher, A.B.; Greider, C.W. & Harley, C.B. (1992). Telomere end-replication problem and cell aging. *Journal of Molecular Biology*. Vol. 225, No. 4, pp. (951-960).

MacKay, J.A.; Deen, D.F. & Szoka, F.C. Jr. (2005). Distribution in brain of liposomes after convection enhanced delivery; modulation by particle charge, particle diameter, and presence of steric coating. *Brain Research*. Vol. 1035, No. 2, pp. (139-153).

Mamot, C.; Drummond, D.C.; Noble, C.O.; Kallab, V.; Guo, Z.; Hong, K., Kirpotin, D.B. & Park, J.W. (2005). Epidermal growth factor receptor-targeted immunoliposomes significantly enhance the efficacy of multiple anticancer drugs in vivo. *Cancer Research*. Vol. 65, No. 24, pp. (11631-11638).

Mamot, C.; Nguyen, J.B.; Pourdehnad, M.; Hadaczek, P.; Saito, R.; Bringas, J.R.; Drummond, D.C.; Hong, K.; Kirpotin, D.B.; McKnight, T.; Berger, M.S.; Park, J.W. & Bankiewicz, K.S. (2004). Extensive distribution of liposomes in rodent brains and brain tumors following convection-enhanced delivery. *Journal of Neuro- Oncology*. Vol. 68, No. 1, pp. (1-9).

Marian, C.O.& Shay, J.W. (2009). Prostate tumor-initiating cells: A new target for telomerase inhibition therapy? *Biochimica et biophysica acta*. Vol. 1792, No. 4, pp. (289-296).

Marian, C.O.; Cho, S.K.; McEllin, B.M.; Maher, E.A.; Hatanpaa, K.J.; Madden, C.J.; Mickey, B.E.; Wright, W.E.; Shay, J.W.; Bachoo, R.M. (2010). The telomerase antagonist, imetelstat, efficiently targets glioblastoma tumor-initiating cells leading to decreased proliferation and tumor growth. *Clinical Cancer Research*. Vol. 16, No. 1, pp. (154-163).

Migliore, M.M.; Vyas, T.K.; Campbell, R.B.; Amiji, M.M. & Waszczak, B.L. (2010). Brain delivery of proteins by the intranasal route of administration: a comparison of cationic liposomes versus aqueous solution formulations. *Journal of Pharmaceutical Sciences*. Vol. 99, No. 4, pp. (1745-1761).

Moreau P. (2009). Combination regimens using doxorubicin and pegylated liposomal doxorubicin prior to autologous transplantation in multiple myeloma. *Expert review of anticancer therapy*. Vol. 9, No. 7, pp. (885-890).

Murad GJ, Walbridge S, Morrison PF, Garmestani K, Degen JW, Brechbiel MW, Oldfield EH, Lonser RR. (2006). Real-time, image-guided, convection-enhanced delivery of interleukin 13 bound to pseudomonas exotoxin. *Clinical Cancer Research*. Vol. 12, No. 10, pp. (3145-3151).

Murramatsu, K.; Maitani, Y.; Takayama, K. & Nagai, T. (1999). The relationship between the rigidity of the liposomal membrane and

the absorption of insulin after nasal administration of liposomes modified with an enhancer containing insulin in rabbits. *Drug development and industrial pharmacy.* Vol. 25, No. 10, pp. (1099-1105).

Noble, C.O.; Krauze, M.T.; Drummond, D.C.; Yamashita, Y.; Saito, R.; Berger, M.S.; Kirpotin, D.B.; Bankiewicz, K.S. & Park, J.W. (2006). Novel Nanoliposomal CPT-11 Infused by Convection-Enhanced Delivery in Intracranial Tumors: Pharmacology and Efficacy. *Cancer Research*. Vol. 66, No. 5, pp. (2801-2806).

Ozawa, T.; Wang, J.; Hu, L.J.; Bollen, A.W.; Lamborn, K.R. & Deen, D.F. (2002). Growth of human glioblastomas as xenografts in the brains of athymic rats. *In Vivo*. Vol. 16, No. 1, pp. (55-60).

Ozawa, T.; Gryaznov, S.M.; Hu, L.J.; Pongracz, K.; Santos, R.A.; Bollen, A.W.; Lamborn, K.R. & Deen, D.F. (2004). Antitumor effects of specific telomerase inhibitor GRN163 in human glioblastoma xenografts. *Neuro-Oncology*. Vol. 6, No 3, pp. (218-226).

Parker, K.J.; Buckmaster, C.L.; Schatzberg, A.F. & Lyons, D.M. (2005). Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinology*. Vol. 30, No. 9, pp. (924-929).

Pardridge, W.M. (1999). Non-invasive drug delivery to the human brain using endogenous blood–brain barrier transport systems. *Pharmaceutical science & technology today.* Vol. 2, No. 2, pp. (49–59).

Pardridge, W.M. (2007). Blood-brain barrier delivery. *Drug Discovery Today*. Vol. 12, No 1–2, pp. (54–61).

Phatak, P. & Burger, A.M. (2007). Telomerase and its potential for therapeutic intervention. *British Journal of Pharmacology*. Vol. 152, No. 7, pp. (1003-1011).

Rapoport, S.I. (1996). Modulation of blood–brain barrier permeability.*Journal of Drug Targeting*. Vol. 3, No. 6, pp. (417–425).

Reger, M.A.; Watson, G.S.; Green, P.S.; Wilkinson, C.W.; Baker, L.D.; Cholerton, B.; Fishel, M.A.; Plymate, S.R.; Breitner, J.C.; DeGroodt, W.; Mehta, P. & Craft, S. (2008). Intranasal insulin improves cognition and modulates beta-amyloid in early AD. *Neurology*. Vol. 70, No. 6, pp. (440-448).

Rimmele U, Hediger K, Heinrichs M, Klaver P: Oxytocin makes a face in memory familiar. *Jouranl of Neuroscience* (2009). 29 (1): 38–42.

Röth, A.; Vercauteren, S.; Sutherland, H.J. & Lansdorp, P.M. (2003). Telomerase is limiting the growth of acute myeloid leukemia cells. *Leukemia*. Vol. 17, No. 12, pp. (2410-2417).

Rousselle, C.; Clair, P.; Lefauconnier, J.M.; Kaczorek, M.; Scherrmann, J.M. & Temsamani, J. (2000). New advances in the transport of doxorubicin through the blood–brain barrier by a peptide vector- mediated strategy. *Molecular Pharmacology*. Vol. 57, No. 4, pp. (679–686).

Sakane, T.; Yamashita, S.; Yata, N. & Sezaki, H. (1999). Transnasal delivery of 5-fluorouracil to the brain in the rat. *Journal of Drug Targeting*. Vol. 7, No. 3, pp. (233-240).

Saito, R.; Bringas, J.R.; Panner, A.; Tamas, M.; Pieper, R.O.; Berger, M.S. & Bankiewicz, K.S. (2004). Convection-enhanced delivery of tumor necrosis factor-related apoptosis-inducing ligand with systemic administration of temozolomide prolongs survival in an intracranial glioblastoma xenograft model. *Cancer Research*. Vol. 64, No. 19, pp. (6858-6862).

Saito, R.; Krauze, M.T.; Noble, C.O.; Tamas, M.; Drummond, D.C.; Kirpotin, D.B.; Berger, M.S.; Park, J.W. & Bankiewicz, K.S. (2006). Tissue affinity of the infusate affects the distribution volume during convection-enhanced delivery into rodent brains: Implications for local drug delivery. *Journal of neuroscience methods*. Vol. 154, No. 1-2, pp. (225-232).

Sampson, J.H.; Akabani, G.; Archer, G.E.; Berger, M.S.; Coleman, R.E.; Friedman, A.H.; Friedman, H.S.; Greer, K.; Herndon, J.E. 2nd; Kunwar, S.; McLendon, R.E.; Paolino, A.; Petry, N.A.; Provenzale, J.M.; Reardon, D.A.; Wong, T.Z.; Zalutsky, M.R.;

Pastan, I. & Bigner, D.D. (2008). Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. *Neuro-Oncology*. Vol. 10, No. 3, pp. (320-329).

Sandberg, D.I.; Edgar, M.A. & Souweidane, M.M. (2002). Convection-enhanced delivery into the rat brainstem. *Journal of Neurosurgery*. Vol. 96, No. 5, pp. (885-891).

Saunders, N.R.; Ek, C.J.; Habgood, M.D. & Dziegielewska, K.M. (2008). Barriers in the brain: a renaissance? *Trends in Neurosciences*. Vol. 31, No. 6, pp. (279-286).

Schlosshauer, B. (1993). The blood–brain barrier: morphology, molecules, and neurothelin. *Bioassays*. Vol. 1, pp. (341–346).

Serwer, L.; Hashizume, R.; Ozawa, T. and James, C.D. (2010). Systemic and local drug delivery for treating diseases of the central nervous system in rodent models. *Journal of visualized experiments*. Vol. 42, pii: 1992. doi: 10.3791/1992.

Shay, J.W. & Wright, W.E. (2006). Telomerase therapeutics for cancer: Challenges and new directions. *Nature Reviews Drug Discovery*. Vol. 5, No. 7, pp. (577-584).

Shingaki, T.; Sakane, T.; Yamashita, S.; Sezaki, H.; Yoshiharu, T.; Shoubu, S. (1999). Transnasal delivery of anticancer drugs to the brain tumor: A new strategy for brain tumor chemotherapy. *Drug Delivery System*. Vol. 14, No. 5, pp. (365-371).

Shingaki, T.; Inoue, D.; Furubayashi, T.; Sakane, T.; Katsumi, H.; Yamamoto, A. & Yamashita, S. (2010). Transnasal Delivery of Methotrexate to Brain Tumors in Rats: A New Strategy for Brain Tumor Chemotherapy. *Molecular Pharmaceutics*. Vol. 7, No. 5, pp. (1561–1568).

Tamai, I. & Tsuji, A. (1996). Drug delivery through the blood–brain barrier. *Advanced drug delivery reviews*. Vol. 19, pp. (401–424).

Tai, C. & Kasahara, N. (2008). Replication-competent retrovirus vectors for cancer gene therapy. *Frontiers in Bioscience*. Vol. 13, pp. (3083-3095).

Tanguay, J.S.; Ansari, J.; Buckley, L. & Fernando, I. (2009). Epithelial ovarian cancer: role of pegylated liposomal Doxorubicin in prolonging the platinum-free interval and cancer antigen 125 trends during treatment. *International journal of gynecological cancer*, Vol. 19, No. 3, pp. (361-366).

Thorne, R.G.; Pronk, G.J.; Padmanabhan, V. & Frey, W.H. 2nd. (2004). Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience*. Vol. 127, No. 2, pp. (481-496).

Thorne, R.G., Hanson, L.R.; Ross, T.M.; Tung, D. & Frey, W.H. 2nd. (2008). Delivery of interferon-beta to the monkey nervous system following intranasal administration. *Neuroscience*. Vol. 152, No. 3, pp. (785-797).

United States National Institutes of Health, In: *Clnicaltrial.gov*, (accessed April 12th 2011), http://clinicaltrials.gov/ct2/results?term=Convection-enhanced+delivery

Wang, D.; Gao, Y. & Yun, L. (2005). Study on brain targeting of raltitrexed following intranasal administration in rats. *Cancer Chemotherpy and Pharmacology*. Vol. 57, No. 1, pp. (1-8).

Wang, E.S.; Wu, K.; Chin, A.C.; Chen-Kiang, S.; Pongracz, K.; Gryaznov, S.; & Moore, M.A. (2004). Telomerase inhibition with an oligonucleotide telomerase template antagonist: *In vitro* and *in vivo* studies in multiple myeloma and lymphoma. *Blood*. Vol. 103, No. 1. pp. (258-266).

Yamashita, Y.; Krauze, M.T.; Kawaguchi, T.; Noble, C.O.; Drummond, D.C.; Park, J.W. & Bankiewicz, K.S. (2007). Convection-enhanced delivery of a topoisomerase I

inhibitor (nanoliposomal topotecan) and a topoisomerase II inhibitor (pegylated liposomal doxorubicin) in intracranial brain tumor xenografts. *Neuro-Oncology*. Vol. 9, No. 1, pp. (20–28).

Yong, R.L.; Shinojima, N.; Fueyo, J.; Gumin, J.; Vecil, G.G.; Marini, F.C.; Bogler, O.; Andreeff, M. & Lang, F.F. (2009). Human bone marrow-derived mesenchymal stem cells for intravascular delivery of oncolytic adenovirus Delta24-RGD to human gliomas. *Cancer Research*. Vol. 69, No. 23, pp. (8932–8940).

Zhang, Y.; Zhang, Y.F.; Bryant, J.; Charles, A.; Boado, R.J. & Pardridge, W.M. (2004). Intravenous RNA interference gene therapy targeting the human epidermal growth factor receptor prolongs survival in intracranial brain cancer. *Clinical Cancer Research*. Vol. 10, No. 11, pp. (3667–3677).

Brain Tumors - Current and Emerging Therapeutic Strategies

Edited by Dr. Ana Lucia Abujamra

Brain Tumors: Current and Emerging Therapeutic Strategies focuses on tumor models, the molecular mechanisms involved in the pathogenesis of this disease, and on the new diagnostic and treatment strategies utilized to stage and treat this malignancy. A special section on immunotherapy and gene therapy provides the most up-to-date information on the pre-clinical and clinical advances of this therapeutic venue. Each chapter in Brain Tumors: Current and Emerging Therapeutic Strategies is authored by international experts with extensive experience in the areas covered.

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