Nano to micro delivery systems: targeting angiogenesis in brain tumors

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Abstract

Treating brain tumors using inhibitors of angiogenesis is extensively researched and tested in clinical trials. Although anti-angiogenic treatment holds a great potential for treating primary and secondary brain tumors, no clinical treatment is currently approved for brain tumor patients. One of the main hurdles in treating brain tumors is the blood brain barrier - a protective barrier of the brain, which prevents drugs from entering the brain parenchyma. As most therapeutics are excluded from the brain there is an urgent need to develop delivery platforms which will bypass such hurdles and enable the delivery of anti-angiogenic drugs into the tumor bed. Such delivery systems should be able to control release the drug or a combination of drugs at a therapeutic level for the desired time. In this mini-review we will discuss the latest improvements in nano and micro drug delivery platforms that were designed to deliver inhibitors of angiogenesis to the brain.

Introduction

It is now evident that solid tumors beyond a given volume are dependent on the supply of oxygen and nutrients from the vascular system, which has to grow concomitantly with the tumor, similar to embryonic development. This process, of newly developed blood capillaries and blood vessels from pre-existing ones, has been termed angiogenesis and enables the tumor not only to increase its size but also its aggressiveness and its ability to metastasize [1–4]. The process of angiogenesis is implicated not only in the pathology of tumors but also in many other diseases including psoriasis [5, 6], age-related macular degeneration[7, 8] and rheumatoid arthritis [9].

Some of the most deadly malignancies that depend on the angiogenic process for their growth are primary brain tumors[10], among which glioblastoma multiforme (GBM) represents 40% of all cases. GBM has been targeted with many inhibitors of angiogenesis including tissue inhibitors of matrix metalloproteinases[11–13], chemokines [14–16], tyrosine kinase inhibitors [17–20], interleukins [21, 22], and naturally occurring proteolytic fragments of large precursor molecules such as endostatin, vasostatin, canstatin, angiostatin and others [23–29]. These molecules exert their inhibitory functions on endothelial cells by multiple mechanisms including proliferation, migration, protease activity, as well as the induction of apoptosis [30]. Although such angiogenesis inhibitors hold great promise, the ones that reached clinical trials for brain tumor

patients have failed to achieve significant therapeutic outcome. One possible explanation for this outcome that is supported by many researchers is the lack of combinatory treatment with standard chemo and radiotherapy [31]. Another obstacle which may hamper the therapeutic outcome of anti-angiogenic therapy is the blood brain barrier (BBB, although destabilized in high grade GBM patients) which therapeutics need to bypass to exert a significant brain tumor inhibitory effect. The brain vasculature is predominantly different that of other tissues as its principal role is to prevent un-desirable and pathological substances from entering the brain parenchyma (Figure 1) [32]. The physical properties of the BBB, which include continuous tight junctions and low pinocytotic activity as well as high electrical resistance (attributed to occludin expression), form a tight barrier against materials with high molecular weight and ionic substances that can enter the brain parenchyma only through active transport [33, 34]. As such, the BBB hampers and complicates the systemic delivery of therapeutics to the brain [35, 36]. Small lipophilic drugs, which are expected to diffuse across the BBB, are removed from the central nerve system (CNS) by efflux transporters, such as P-glycoprotein (P-gp) [32, 37]. Other drug-based transporters that enable multi-drug resistance include the multi-drug resistance-associated protein (MRP) family (MRP1-MRP9) expressed in brain endothelial cells, breast cancer-resistant protein (ABCG2) [38, 39] and organic anion and cation transporters (OAT and OCT respectively) [40, 41]. Figure 1

Comparison between cerebral and noncerebral blood vessels. Cerebral blood vessel has tight junctions, which do not allow the passage of un-desirable and pathological substances to the brain parenchyma while non cerebral blood vessel allows better diffusion of drugs. Targeting the brain can be achieved using the drug itself or by using drug delivery platforms that release the drug at a specified location.

Nonetheless, it is also possible that the method of administration, which may destabilize the drugs, the therapeutic level needed to reach the tumor or a combination of all the above hurdles contribute to the disappointing outcome of such therapy approach.

These obstacles have resulted in a more urgent focus on developing alternative delivery modalities, which may bypass the BBB and efficiently target tumorangiogenesis while protecting and stabilizing the drug until reaching the tumor bed. These delivery modalities, may not only solve the problem of the BBB permeability and the need for a combinatorial treatment, but also reduce the therapeutic amount of drug needed to be delivered to the tumor, thus lowering toxicity and side effects of the drugs. Nevertheless such delivery modalities, whether local or systemic, have to deliver the therapeutics to the tumor mass, where the diffusion and distribution of the drug is governed by abnormal high tumor cell density, high interstitial fluid pressure within the tumors and leakiness of tumor microvasculature, resulting in fast clearance of the diffusing drug [42, 43].

In this review, we will discuss the progress made in designing and developing different nano and micro drug delivery platforms that aim to bypass the BBB and deliver systematically or locally therapeutics that target brain tumor angiogenesis. Table 1summarizes the current clinical status of therapeutics, which are also utilized in studies aimed to develop drug delivery platforms for brain tumor therapy as will be discussed later on.

Table 1

FDA approved or under clinical trails drugs for brain tumors therapy

Drug	FDA approved for brain tumors/Brain clinical trails	Approved routes of administration (Brain tumors & other disorders)	Drug delivery platforms in research for approved drugs
Temozolomide	Approved	Oral	Intracerebral Biodegradable gel matrices/Polymer nanoparticles

Drug	FDA approved for brain tumors/Brain clinical trails	Approved routes of administration (Brain tumors & other disorders)	Drug delivery platforms in research for approved drugs
Procarbazine	Approved	Oral	-
lomustine	Approved	Oral	Liposomes/Microcapsules
Vincristine	Approved	IV	Intra-arterially
Carmustine	Approved	IV/Oral/Wafer	CED/Polymer microchips and microspheres
Carboplatin	Approved	IV	CED/Intracerebral/Intraarterial/Liposomes
Bevacizumab	Approved	IV	Intra-arterial
Doxorubicin	Phase I/II/III	injection;liposomal *	-
Imatinib mesylate	Phase I/II/III	Oral; Intravenous *	-
Cisplatin	Phase I/II/III	Injection *	-
Topotecan	Phase I/II/III	Injection; Oral *	-
Interferon-alpha	Phase I/II	Injection; Subcutaneous; Oral *	-
Paclitaxel	Phase I/II	Intravenous; Injection *	-
Arsenic trioxide	Phase I/II	Injection *	-

* These routes are approved for other disorders

Local drug delivery platforms

Local delivery to the brain utilizes BBB disruption, as well as local implantation of the delivery system directly in the tumor bed. These delivery systems which include cerebral infusion methods, polymeric nano-particles, wafers and more, are comprehensively studied and represent promising approaches for the delivery of drugs to the brain.

Intra-arterial cerebral infusion

Intra-arterial cerebral infusion involves the insertion of micro-catheters into the small arteries of the brain via the carotid artery [44]. This unique approach was used to infuse mannitol into the area of interest for transient disruption of the BBB, followed by the infusion of a therapeutic such as bevacizumab. As bevacizumab is selectively delivered to brain tumors, larger amount of the drug may be used when compared to the amount of drug used by intravenous administration of bevacizumab resulting with reduced side effects [44]. This delivery system may also enable the direct delivery of other drugs, which target the angiogenic processes in brain tumors.

Polymeric particles

Another popular approach, which is still in preclinical studies, is based on polymeric nano and micro-particles using polymers such as poly(butyl cyanoacrylate), Poly(ethylene-glycol), Poly(lactic-co-glycolic) acid, Poly-glycerol and others [45– 48]. These particles can be loaded with or attached to different therapeutics and can then be delivered directly to the tumor site. The use of particle platforms significantly reduces (in some cases more than 50 folds) the amounts of

drugs needed to reduce tumor volume and weight when compared to systemic administration. Such platforms need to be carefully designed, taking into account the properties of the drug carrier in term of immunogenicity, stability, preparation method, manufacturing costs, biodegradability and its pharmaceutical qualities (stability of the therapeutic, dosage capability, distribution and site specific targeting). These delivery vehicles must also retain the biological activity of the drug and allow its sustained release over extended periods of time when needed [49]. This is particularly important when attempting to deliver endogenous inhibitors of angiogenesis as opposed to chemotherapeutic drugs.

PLGA particles

One of the widely used polymers for the design of different delivery platforms is the poly-lactic-co-glycolic based polymer (PLGA). The huge advantages of delivery formulations based on PLGA, are their non immunogenicity and the ability to control the release profile of the drugs by manipulating the ratio of lactic to glycolic acids. An interesting publication by Shahani *et al* . showed that curcumin encapsulated in PLGA microspheres down regulates markers of angiogenesis such as CD31 and vascular endothelial growth factor (VEGF) in nude mice bearing MDA-MB-231 xenografts. Furthermore, curcumin levels in the brain were 10 to 30 folds higher than in blood indicating the possibility to use this formulation to treat brain tumors [50]. Arai *et al* . showed the feasibility of using thermoreversible gelation polymer combined with doxorubicin loaded PLGA microspheres or liposomes for local treatment of malignant glioma [51]. PLGA microspheres have also been used to carry glioma cell lysates for the induction of protective immunity in rat glioma model. Although this system was less efficient than irradiated cell lysate it does exhibit adjuvant properties [52].
In our lab, PLGA has been used to produce particles loaded with PEX, a fragment of matrix metalloproteinase (MMP)-2, or platelet factor 4 fragments (PF-4/CTF) for the delivery of these angiogenesis inhibitors to glioma bearing nude mice (Figure 2). PEX was detected and isolated from the culture medium of several cell lines and acts as inhibitor of angiogenesis, cell proliferation and migration, demonstrating a 99% suppression of glioma tumor growth in human glioma xenografts [13]. PF-4 is a strong anti-angiogenic factor that inhibits angiogenesis by blocking FGF-2 binding to endothelial cells [16, 53]. PEX and PF-4/CTF administered in this mode showed 88% and 95% reduction in tumor volume 30 days post treatment, respectively, demonstrating the advantage of PLGA microspheres for angiogenesis inhibitor delivery to glioma tumors [49].

Figure 2
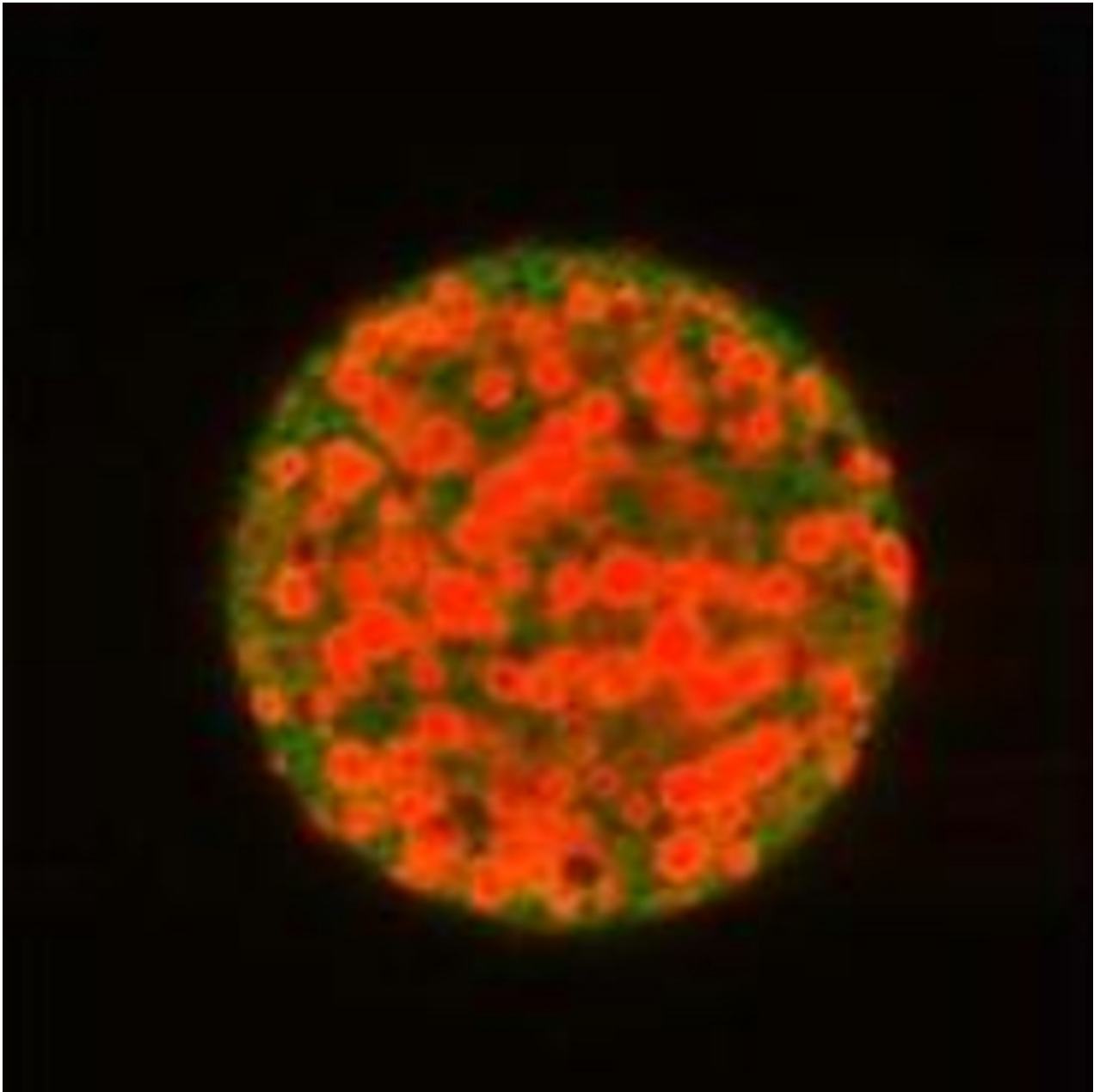
PLGA particles loaded with therapeutic. PLGA particles (50:50 lactic to glycolic), labeled with 6-coumarin and loaded with rhodamine labeled PF-4/CTF.

Other drugs and proteins encapsulated in PLGA microspheres for the treatment of glioma include temozolomide [54], paclitaxel [55], imatinib mesylate for treating intracranial glioma xenografts [56], BCNU as an alternative for Gliadel [57], cisplatin [58], mitoxantrone [59] interleukin-18 [60] and 5-Fluorouracil [61, 62].

Wafers

Wafers are composed of biodegradable polymers that deliver the drugs into brain tumors via local administration, thus, bypassing the BBB. Such device may also be used for the delivery of angiogenesis inhibitors alone or in combination with other chemotherapeutic drugs.
The first device approved by the FDA was Gliadel[®] , a polymeric wafer designed for the delivery of carmustine [63]. Gliadel[®] is placed directly in the brain cavity created by the resection of the tumor. Clinical studies with Gliadel have shown increased survival rates in newly diagnosed malignant gliomas patient particularly when combined with a chemo-treatment [64, 65]. Due to the fact that not all of GBM patients are responsive to carmustine there is a need to evaluate other drugs for the treatment of GBM patients [66].

Cell delivery platform

Different studies have attempted to use cells, particularly stem cells, that are engineered to secret inhibitors of angiogenesis for brain tumor therapy [67, 68]. Another approach, which is based on cell delivery, is polymeric cell encapsulation. The encapsulation system consists of viable cells surrounded by a non-degradable, selectively permeable barrier that physically isolates the transplanted cells from host tissue and the immune system. This platform relies on host homeostatic mechanisms for the control of pH, metabolic waste removal, electrolytes and nutrients. One of the most studied cell micro-encapsulation methods has been based upon alginates, which are polysaccharides extracted from various species of brown algae (seaweed) and purified to a white powder. The alginates have different characteristics of viscosity and reactivity based on the specific algal source and the ions in the solution. Alginate has also hydrophilic properties, which minimize protein adsorption and cell adhesion, thus exhibit a high degree of biocompatibility. For cell encapsulation, the alginate gel is further complexed with polycations such as Poly-L-Lysine (PLL) to form a semi-permeable membrane, which allows the delivery of different bioactive substances to the surrounding while preventing the diffusion of antibodies and other components of the immune system. Cell encapsulation has been used for broad therapeutic applications such as delivery of neuroactive agents for the treatment of age-related degeneration [69, 70], Alzheimer's disease[71– 74], amyotrophic lateral sclerosis [75, 76], neuroprotection [77], Huntington's disease [78, 79] and Parkinson's disease[80– 82]. This approach has also been used to deliver inhibitors of angiogensis to glioma tumors. Read *et al* . showed that human fetal kidney 293 cells expressing endostatin, an anti-angiogenic 20 kDa fragment of collagen XVIII, encapsulated in sodium alginate, and intracerebral injected near BT4C glioma bearing rats prolonged the survival of the animals by 84% due to induction of apoptosis, hypoxia and large necrotic avascular areas [24, 83]. Endostatin released from such delivery system, reduced the functionality and the diameter of blood vessels as well as tumor cell invasion as shown by intravital microscopy [84]. Bjerkvig *et al* . also used the same methodology to deliver endostatin into rat brains [85].
Joki *et al* . demonstrated the encapsulation of baby hamster kidney cells (BHK-21) engineered to secrete human endostatin, for the inhibition of glioblastoma xenograft in nude mice [24, 86]. In our lab, Goren *et al* . showed that encapsulation of human mesenchymal stem cells (hMSCs), known to be hypo-immunogenic, within alginate-PLL micro-capsules (Figure 3), led to a 3-fold decrease in cytokine expression making them the cell of choice for micro encapsulation cell based-therapy. In this system, the hMSC were genetically modified to express PEX and their injection adjacent to glioblastoma bearing nude mice had led to 87% and 83% reduction in tumor volume and weight, respectively [87]. Feasibility of encapsulated cells to produce single-chain TRAIL has been shown by Kuijlen *et al*. using intracerebral implantation of these capsules in mice brains [88]. Cell encapsulation for CNS malignancies is reviewed in more detailed by Visted *et al* [89].

Figure 3
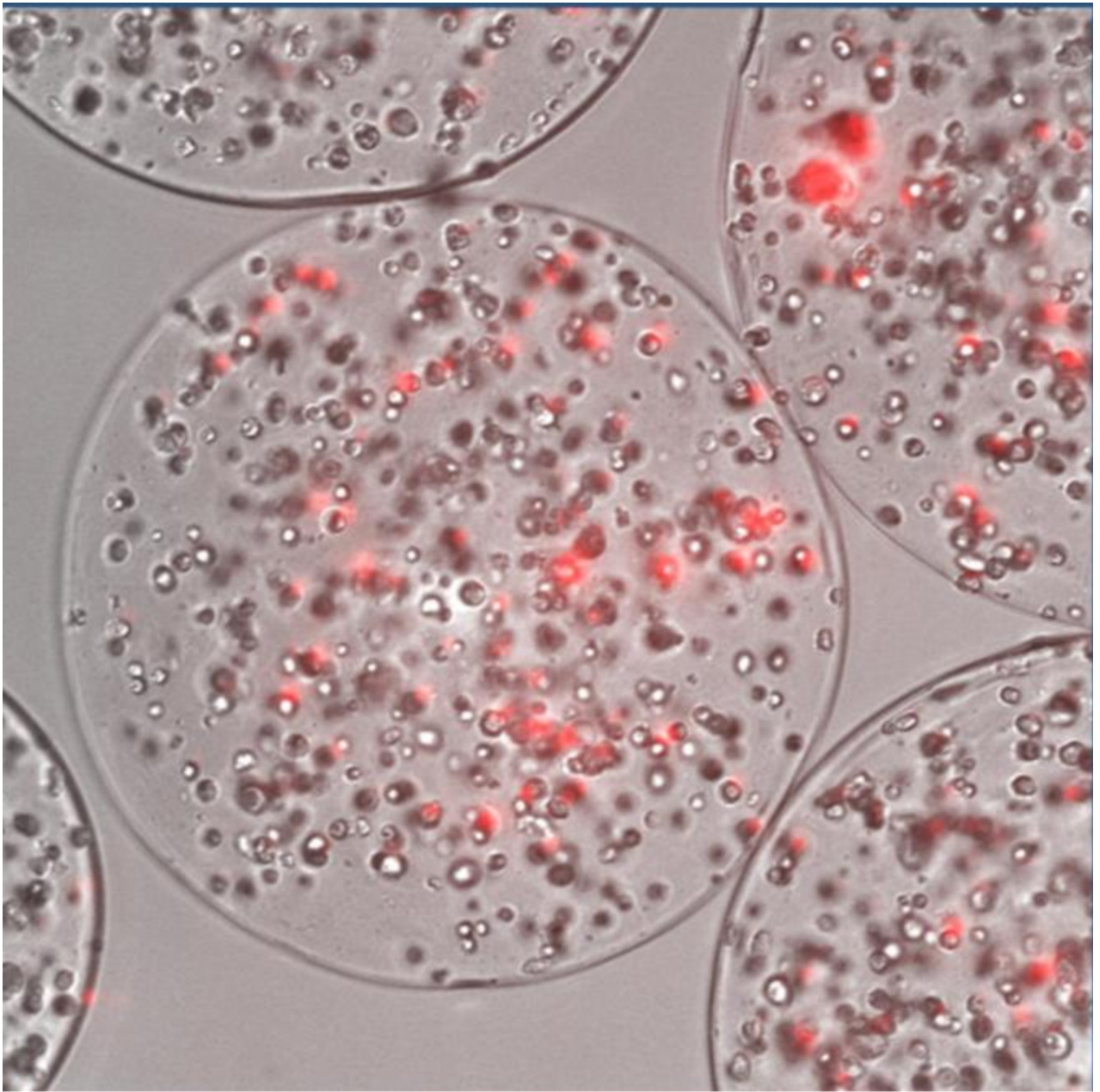
Cell encapsulation platform. Human mesenchymal stem cells (hMSCs) labeled with the mCherry fluorescence marker engineered to express PEX and encapsulated in alginate capsules.

Convection-enhanced delivery

Convection-enhanced delivery (CED) was developed to overcome poor brain drug distribution. CED uses hydrostatic pressure to deliver drugs via a catheter located within or around a tumor. As poor drug diffusion through the brain interstitium restricts intratumoral drug administration, fluid convection within the brain (under pressure gradient), can greatly enhance the distribution of molecules in the tumor area. Distribution of drugs via CED is not restricted to white matter and penetration into gray matter can be observed 24 hours after infusion [90]. Nonetheless, Real-time monitoring of CED variability in efficacies as well as limited distribution of the drug still need to be addressed [91].

Saito *et al* . used CED to deliver topotecan entrapped in nano-liposomes (liposomes as drug delivery system will be further discussed in this review in a separate section). CED of liposomal topotecan exerted strong anti-angiogenic activity and disruption of tumor vessels. This delivery platform enabled inhibition of angiogenesis at low concentrations of the therapeutic and demonstrated the ability to deliver anti-angiogenic drugs via CED systems [92]. In another study, Ohlfest *et al* . used CED to co-deliver soluble vascular endothelial growth factor receptor

(sFlt-1) and angiostatin-endostatin fusion gene transposons into intracranial glioma model achieving anti-angiogenic effect [93].

Systemic drug delivery platforms

Systemic drug delivery to the brain requires the consideration of the BBB as previously discussed. More over, systemic delivery systems need to overcome other obstacles such as protein adsorption, enzymatic digestion and engulfment of the delivery particles by phagocytic cells when using 300 nm-10 micrometer particle sizes. Nonetheless, systemic administration can have the benefit of non-invasiveness when compared to local administration using intracranial surgery. Different delivery systems have been developed to achieve systemic therapeutic targeting to the brain including pegylation of drugs, liposomes, polymeric nano-particles, dendrimers and bionanocapsules. We will discuss some of these designed nano-sized delivery systems, which may enable the delivery of drugs to the brain via systemic administration.

Drug Pegylation

One simplified approach designed to bypass the BBB is the modification of a drug by a polymeric composite, which some term as nano vehicles and other as drug conjugates. One example is the pegylation of interferon-alpha, which is known for its anti-angiogenic effects on tumors and other angiogenic diseases such as AIDS-related Kaposi sarcoma [46]. The motivation behind the pegylation of interferon-alpha was to both reduce its neurologic and immune system toxicities and to improve its circulation time [46, 48, 94, 95]. Pegylation of interferon alpha resulted in a long-lasting form of interferon that may target angiogenesis in glioma [94]. Pegylation has also been used on camptothecin and doxorubicin, improving their solubility, circulation time and lowering their toxicity [96, 97].

Liposomes

Liposomes are one of the most popular nano-system designs for systemic drug delivery. Liposomes are defined as delivery vehicles composed of phospholipidsbilayers (one or more) ranging from tens to hundreds of nanometers in diameter (Figure 4). Liposomes' structure enables the entrapment of water soluble drugs at the aqueous core of the system, while hydrophobic drugs can be entrapped in the lipid bilayer composed of synthetic or natural lipids [98]. Liposomes have been widely researched for their ability to deliver proteins [99], chemotherapeutics [100, 101], RNA [102, 103], DNA [104] and other therapeutics. Their advantages include biocompatibility, low toxicity, enhanced efficacy of the encapsulated drugs and reduced side effects [105]. Fundamental disadvantage of conventional liposomes is their rapid removal from blood circulation by the mononuclear phagocyte system (MPS). Although this characteristic can be exploited to deliver drugs into phagocytic cells, it hampers the liposomal abilities to target the therapeutic to other cells and organs[106]. Liposomal clearance from the blood circulation is due to recognition of surface bounded opsonins by the MPS [107, 108] and membrane lysis of charged liposomes by complement components [109]. One approach to extend liposome circulation time and bypass such fast blood clearance, is to anchor Poly(ethylene glycol) (PEG), to the liposomal membrane- rendering them as stealth liposomes [110]. Adding PEG to the liposome preparations also decreases aggregation and reduces interactions with plasma proteins thus increases their circulation time [111, 112]. In gliomas, the BBB is disrupted at the site of the malignant lesion and the leaky endothelium enables passive convective transport of liposomes into the brain. Studies show that stealth liposomes extravasate into the extracellular space forming clusters and acting as a reservoir within the tumor area [113, 114]. Caelyx® is a novel formulation of stealth® liposomal doxorubicin. A study with 10 patients with metastatic brain tumors and five patients with brain glioblastoma undergoing radiotherapy confirmed intense accumulation of radio-labeled Caelyx® in the brain tumor as compared to the normal brain tissue[115]. In another study, doxorubicin encapsulated in liposomes exhibited

break down of tumor vasculature [116]. Other drugs encapsulated in liposomes for treating brain tumors include taxol [117] and arsenic trioxide which down-regulated the expression of VEGF [118].

Figure 4
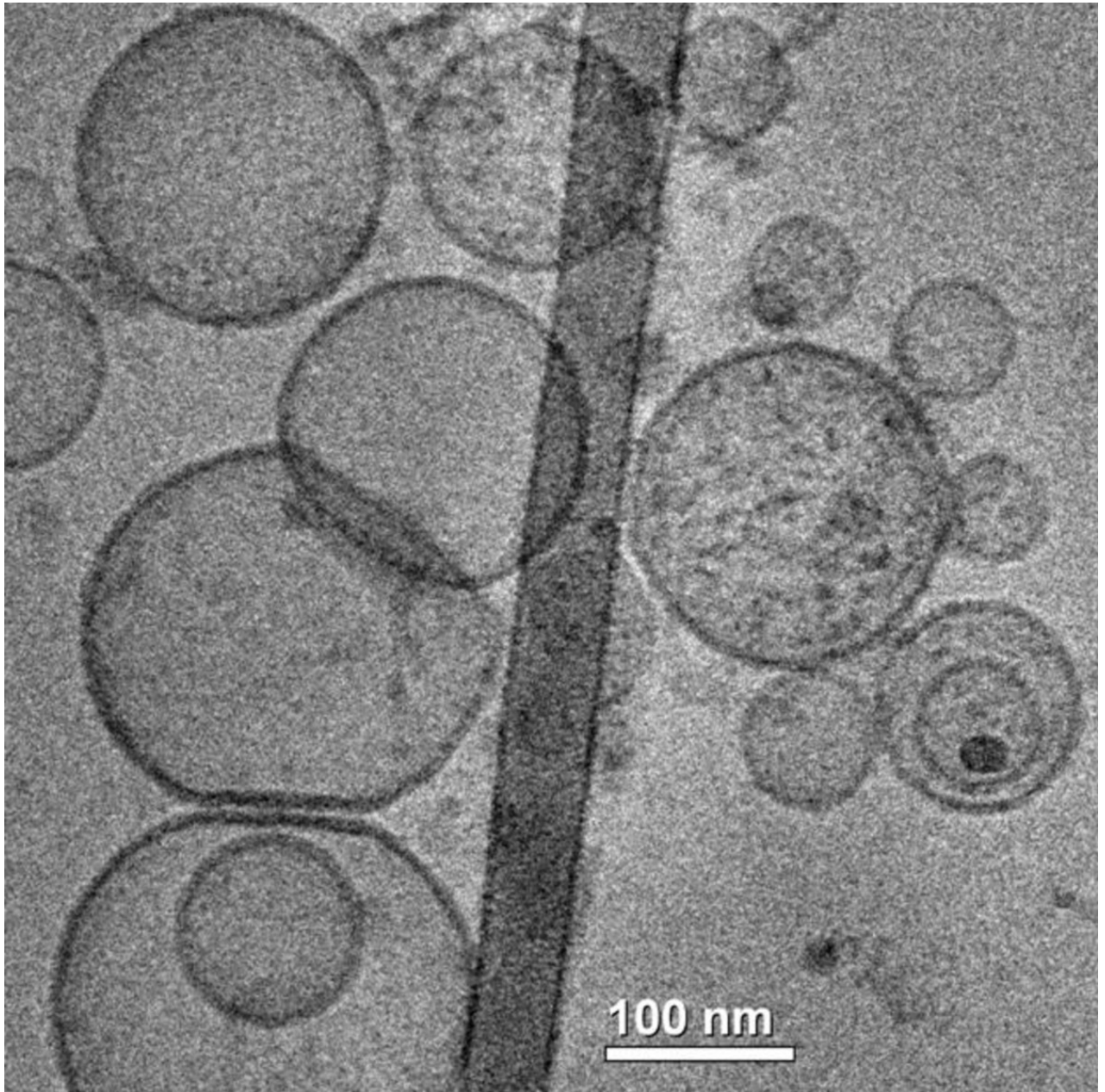
Liposomes. TEM image of liposomes made of DOPE -1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, DMPA -1,2-dimyristoyl-sn-glycero-3-phosphate, POPE - 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine and POPC - 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

Polymeric nano-particles

Polymeric nano-particles (1-999 nano-meters) have attracted much attention as vehicles for systemic drug delivery due to their biocompatibility and stability properties. The diversity of materials, mostly synthetic, used to formulate nano-particles include poly(butyl cyanoacrylate), Poly(ethylene-glycol), Poly(lactic-co-glycolic) acid, Poly-glycerol and others [45– 48]. Hekmatara *et al* . showed that doxorubicin bound to polysorbate-coated nano-particles made of Poly(butyl cyanoacrylate) and injected intravenously into tumor bearing Wistar rats, had a drastic effect on vessel density with neither neuronor systemic toxicity [45]. Another approach that

might be feasible for brain tumor targeting is a novel delivery system termed 'nanocell'. This delivery system is composed of nuclear nano-particle enveloped with pegylated-phospholipid block-copolymer [95]. The idea behind this system is to deliver inhibitors of angiogenesis followed by the delivery of cytotoxic drugs into the tumors. In this system, the angiogenic inhibitor is located within the lipid layer and the chemotherapeutic drug is incorporated to the nano-particle. Sengupta *et al* . showed that doxorubicin conjugated to the copolymer poly-(lactic-co-glycolic) acid (PLGA) enveloped within PEG distearoylphosphatidyl-ethanolamine (PEG-DSPE), phosphatidylcholine and cholesterol in an optimal ratio with combretastatin (which causes rapid vascular shutdown) had significant effect on tumor vasculature [95]. Another interesting approach for targeting angiogenesis is the use of RNA-based inhibitors [31]. Glioma angiogenesis has being targeted by RNA-based inhibitors, which include short hairpin RNAs (shRNAs) and short interfering RNAs (siRNAs) against urokinase-type plasminogen activator and MMP-2 respectively [119– 121]. These studies showed significant anti-angiogenic effect and impaired glioma invasion in mouse models. Recently, microRNAs (miRNAs), a new group of RNA inhibitors, have attracted much attention as unlike siRNAs and shRNAs they can interact with many mRNAs due to incomplete nucleotide complementarities [122]. One such group of miRNAs was related to angiogenesis [123]. Ofek *et al* . developed a novel polymerized polyglycerol-based cationic dendrimer core shell structures, which can deliver siRNAs to cells and inhibit angiogenesis [47]. These siRNA-dendrimers improved the stability, uptake and intracellular trafficking of siRNAs demonstrating *in-vivo* targeting of luciferase in luciferase-expressing tumors in mice [47]. In another study, Schneider *et al* . showed that poly-(butyl cyanoacrylate) nano-particles coated with Polysorbate-80 were capable of delivering antisense oligonucleotide, specifically against TGF-β2, into intracerebral tumors via the BBB [48, 124]. A different concept of nano-delivery system has been recently introduced and termed 'bionanocapsules' [125]. Bionanocapsulses are hollow nano-particles with an average diameter of 80 nm, displaying specific affinity to human hepatocytes via the pre-S1 peptide displayed on their surface and have successfully delivered peptides, genes and siRNA to the liver [125]. Tsutsui *et al* . demonstrated that the deletion of the pre-S1 peptide and conjugation of the anti-human EGFR, recognizing EGFRvIII, abolished hepatocytes targeting, making them capable of targeting brain tumor *in-vitro* and *in-vivo* [126]. These studies suggest a new drug delivery system for brain tumor and possible use of such delivery systems for the delivery of anti-angiogenic drugs should be considered.

Optimizing therapeutic delivery using bio-mathematical models

Mathematical models are based on the optimization of natural algorithms within the growing biomathematical tool kit and can provide a deeper understanding of the dynamic biological process involved with tumor angiogenesis, tumor growth or other tumor properties. Using mathematical modeling, tumor behavior upon drug treatment (free or released), from a delivery platform can be predicted. This is a powerful tool that can minimize invasive protocols, reduce drug quantities, force combinational drug treatments and reduce the number of animals required for *in-vivo* experiments.

These methodologies have already been applied in the fields of cancer chemotherapy and cancer immunotherapy with minimization of tumor burden as their primary objective [127– 130] and may be of great importance when considering GBM treatments. Gevertz *et al* . described for the first time, a biomathemathical model for the follow up of GBM growth, which is based on the evolution of the tumor microvasculature and mass. In this model they assume that the key players in glioma angiogenesis are VEGF, Ang-1 and Ang-2 (Angiopoietins) and were able to show that an "angiogenic switch" is valid, just as Folkman predicted [131, 132]. Kronik *et al* . successfully created a mathematical model which describes the growth rate of high grade gliomas post stimulation of alloreactive CTLs. The mathematical analysis shows that differences in the

growth rate parameter alone suffice for explaining the difference in the success of cellular immunotherapy treatment for grade III and grade VI glioma patients [133].

In our lab, Benny *et al* . presented a pre-clinical study that used PLGA microspheres loaded with imatinib mesylate in GBM model in mice [56]. Together with Kronic *et al* ., we were able to extract, using mathematical modeling, the pharmaco kinetics of imatinib mesylate, which correlated significantly with the kinetics obtained experimentally (unpublished data). The models allow us to predict the release of drug in the intracranial environment, its clearance and the therapeutic window needed for additional administration of the loaded PLGA particles.

Conclusions

Targeting brain tumor angiogenesis is a promising approach to arrest tumor growth. Nonetheless, clinical studies with inhibitors of angiogenesis have produced disappointing results. This may be due to the fact that these inhibitors were administered alone, without standard chemo and radiotherapy. It is also strongly possible that the way of administration (mostly intravenously), drug stability and quantities needed to achieve therapeutic outcome, hamper the therapeutic potential of such group of drugs. More over as the brain is a unique organ, protected via the BBB and efflux transporters (although disrupted in high grade glioma patients), the drugs need to bypass such barriers and reach the tumor in a therapeutic dosage. Therefore developing drug delivery platforms that bypass such barriers and target the therapeutics to the tumor site and on the other hand stabilize and protect the drug until it is released near or in the tumor bed can result in surprising therapeutic effects for such group of inhibitors.The progress made in the field of biomaterials together with the pharmaceutical field, contribute vastly to the development of such local and systemic delivery platforms.Yet, regardless of the enormous advantageous that these technologies can offer, the road to clinical studies using these platforms is still facing problems, which need to be studied and solved as they target the most protected and closed organ, the brain. Selection of polymers, preparation methods, drug loading and release profile, clearance of the drugs and immune aspects need to be taken in account and studied carefully to pave the way for new and promising delivery platform to reach the clinical setting.

Declarations

Authors' original submitted files for images

Below are the links to the authors' original submitted files for images.

Authors' original file for figure 1

Authors' original file for figure 2

Authors' original file for figure 3

Authors' original file for figure 4

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

References

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285:1182-1186.
   View Article   Google Scholar

2. Seaman S Stevens J Yang MY Logsdon D Graff-Cherry C St Croix B Genes that distinguish physiological and pathological angiogenesis Cancer Cell 2007 11 539 5542039723

3. Jouanneau E. Angiogenesis and gliomas: current issues and development of surrogate markers. Neurosurgery. 2008;62:31-50.
   View Article   Google Scholar

4. Folkman J. Angiogenesis: an organizing principle for drug discovery?. Nat Rev Drug Discov. 2007;6:273-286.
   View Article   Google Scholar

5. Chua RA, Arbiser JL. The role of angiogenesis in the pathogenesis of psoriasis. Autoimmunity. 2009;42:574-579.
   View Article   Google Scholar

6. Heidenreich R Rocken M Ghoreschi K Angiogenesis drives psoriasis pathogenesis Int J Exp Pathol 2009 90 232 2482697548

7. Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004;351:2805-2816.
   View Article   Google Scholar

8. Carneiro A, Falcao M, Azevedo I, Falcao Reis F, Soares R. Multiple effects of bevacizumab in angiogenesis: implications for its use in age-related macular degeneration. Acta Ophthalmol. 2009;87:517-523.
   View Article   Google Scholar

9. Szekanecz Z, Besenyei T, Szentpetery A, Koch AE: Angiogenesis and vasculogenesis in rheumatoid arthritis. Curr Opin Rheumatol. 22: 299-306. 10.1097/BOR.0b013e328337c95a.

10. Kim WY Lee HY Brain angiogenesis in developmental and pathological processes: mechanism and therapeutic intervention in brain tumors Febs J 2009 276 4653 46642847309

11. Murray GI, Duncan ME, O'Neil P, Melvin WT, Fothergill JE. Matrix metalloproteinase-1 is associated with poor prognosis in colorectal cancer. Nat Med. 1996;2:461-462.
    View Article   Google Scholar

12. Brooks PC, Silletti S, von Schalscha TL, Friedlander M, Cheresh DA. Disruption of angiogenesis by PEX, a noncatalytic metalloproteinase fragment with integrin

binding activity. Cell. 1998;92:391-400.
View Article   Google Scholar

13. Bello L, Lucini V, Carrabba G, Giussani C, Machluf M, Pluderi M, Nikas D, Zhang J, Tomei G, Villani RM, et al. Simultaneous inhibition of glioma angiogenesis, cell proliferation, and invasion by a naturally occurring fragment of human metalloproteinase-2. Cancer Res. 2001;61:8730-8736.
View Article   Google Scholar

14. Arenberg DA, Polverini PJ, Kunkel SL, Shanafelt A, Strieter RM. In vitro and in vivo systems to assess role of C-X-C chemokines in regulation of angiogenesis. Methods Enzymol. 1997;288:190-220.
View Article   Google Scholar

15. Maione TE, Gray GS, Petro J, Hunt AJ, Donner AL, Bauer SI, Carson HF, Sharpe RJ. Inhibition of angiogenesis by recombinant human platelet factor-4 and related peptides. Science. 1990;247:77-79.
View Article   Google Scholar

16. Jouan V, Canron X, Alemany M, Caen JP, Quentin G, Plouet J, Bikfalvi A. Inhibition of in vitro angiogenesis by platelet factor-4-derived peptides and mechanism of action. Blood. 1999;94:984-993.
View Article   Google Scholar

17. Lu D, Jimenez X, Zhang H, Wu Y, Bohlen P, Witte L, Zhu Z. Complete inhibition of vascular endothelial growth factor (VEGF) activities with a bifunctional diabody directed against both VEGF kinase receptors, fms-like tyrosine kinase receptor and kinase insert domain-containing receptor. Cancer Res. 2001;61:7002-7008.
View Article   Google Scholar

18. Dias S Hattori K Heissig B Zhu Z Wu Y Witte L Hicklin DJ Tateno M Bohlen P Moore MA Rafii S Inhibition of both paracrine and autocrine VEGF/VEGFR-2 signaling pathways is essential to induce long-term remission of xenotransplanted human leukemias Proc Natl Acad Sci USA 2001 98 10857 1086258564

19. Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, Ferrara N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993;362:841-844.
View Article   Google Scholar

20. Strawn LM, McMahon G, App H, Schreck R, Kuchler WR, Longhi MP, Hui TH, Tang C, Levitzki A, Gazit A, et al. Flk-1 as a target for tumor growth inhibition. Cancer Res. 1996;56:3540-3545.
View Article   Google Scholar

21. Stearns ME, Rhim J, Wang M. Interleukin 10 (IL-10) inhibition of primary human prostate cell-induced angiogenesis: IL-10 stimulation of tissue inhibitor of metalloproteinase-1 and inhibition of matrix metalloproteinase (MMP)-2/MMP-9 secretion. Clin Cancer Res. 1999;5:189-196.
View Article   Google Scholar

22. Luca M Huang S Gershenwald JE Singh RK Reich R Bar-Eli M Expression of interleukin-8 by human melanoma cells up-regulates MMP-2 activity and increases tumor growth and metastasis Am J Pathol 1997 151 1105 11131858026

23. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell. 1994;79:315-328.
View Article   Google Scholar

24. O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, Flynn E, Birkhead JR, Olsen BR, Folkman J. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell. 1997;88:277-285.
View Article   Google Scholar

25. Yamaguchi N Anand-Apte B Lee M Sasaki T Fukai N Shapiro R Que I Lowik C Timpl R Olsen BR Endostatin inhibits VEGF-induced endothelial cell migration and tumor growth independently of zinc binding Embo J 1999 18 4414 44231171516

26. Xiao F, Wei Y, Yang L, Zhao X, Tian L, Ding Z, Yuan S, Lou Y, Liu F, Wen Y, et al. A gene therapy for cancer based on the angiogenesis inhibitor, vasostatin. Gene Ther. 2002;9:1207-1213.
View Article   Google Scholar

27. Lange-Asschenfeldt B, Velasco P, Streit M, Hawighorst T, Pike SE, Tosato G, Detmar M. The angiogenesis inhibitor vasostatin does not impair wound healing at tumor-inhibiting doses. J Invest Dermatol. 2001;117:1036-1041.
View Article   Google Scholar

28. Kamphaus GD, Colorado PC, Panka DJ, Hopfer H, Ramchandran R, Torre A, Maeshima Y, Mier JW, Sukhatme VP, Kalluri R. Canstatin, a novel matrix-derived inhibitor of angiogenesis and tumor growth. J Biol Chem. 2000;275:1209-1215.
View Article   Google Scholar

29. Sim BK, MacDonald NJ, Gubish ER. Angiostatin and endostatin: endogenous inhibitors of tumor growth. Cancer Metastasis Rev. 2000;19:181-190.
View Article   Google Scholar

30. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature. 2005;438:967-974.
View Article   Google Scholar

31. Wurdinger T Tannous BA Glioma angiogenesis: Towards novel RNA therapeutics Cell Adh Migr 2009 3 230 2352679892

32. Deeken JF, Loscher W. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. Clin Cancer Res. 2007;13:1663-1674.
View Article   Google Scholar

33. Wolburg H, Lippoldt A. Tight junctions of the blood-brain barrier: development, composition and regulation. Vascul Pharmacol. 2002;38:323-337.
View Article   Google Scholar

34. Butt AM Jones HC Abbott NJ Electrical resistance across the blood-brain barrier in anaesthetized rats: a developmental study J Physiol 1990 429 47 621181686

35. de Boer AG, Gaillard PJ. Drug targeting to the brain. Annu Rev Pharmacol Toxicol. 2007;47:323-355.
View Article   Google Scholar

36. Miller G. Drug targeting. Breaking down barriers. Science. 2002;297:1116-1118.
View Article   Google Scholar

37. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta. 1976;455:152-162.
View Article   Google Scholar

38. Zhang Y, Schuetz JD, Elmquist WF, Miller DW. Plasma membrane localization of multidrug resistance-associated protein homologs in brain capillary endothelial cells. J Pharmacol Exp Ther. 2004;311:449-455.
View Article   Google Scholar

39. Eisenblatter T, Huwel S, Galla HJ. Characterisation of the brain multidrug resistance protein (BMDP/ABCG2/BCRP) expressed at the blood-brain barrier. Brain Res. 2003;971:221-231.
View Article   Google Scholar

40. Deguchi T, Isozaki K, Yousuke K, Terasaki T, Otagiri M. Involvement of organic anion transporters in the efflux of uremic toxins across the blood-brain barrier. J Neurochem. 2006;96:1051-1059.
View Article   Google Scholar

41. Ueno M Mechanisms of the penetration of blood-borne substances into the brain Curr Neuropharmacol 2009 7 142 1492730006

42. Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer. 2006;6:583-592.
View Article   Google Scholar

43. Weinberg BD, Blanco E, Gao J. Polymer implants for intratumoral drug delivery and cancer therapy. J Pharm Sci. 2008;97:1681-1702.
View Article   Google Scholar

44. Riina HA, Fraser JF, Fralin S, Knopman J, Scheff RJ, Boockvar JA. Superselective intraarterial cerebral infusion of bevacizumab: a revival of interventional neuro-oncology for malignant glioma. J Exp Ther Oncol. 2009;8:145-150.
View Article   Google Scholar

45. Hekmatara T, Bernreuther C, Khalansky AS, Theisen A, Weissenberger J, Matschke J, Gelperina S, Kreuter J, Glatzel M. Efficient systemic therapy of rat glioblastoma by nanoparticle-bound doxorubicin is due to antiangiogenic effects. Clin Neuropathol. 2009;28:153-164.
View Article   Google Scholar

46. Gutterman JU Cytokine therapeutics: lessons from interferon alpha Proc Natl Acad Sci USA 1994 91 1198 120543124

47. Ofek P, Fischer W, Calderon M, Haag R, Satchi-Fainaro R. In vivo delivery of small interfering RNA to tumors and their vasculature by novel dendritic nanocarriers. Faseb J. 2010;9:3122-3134.
View Article Google Scholar

48. Schneider T, Becker A, Ringe K, Reinhold A, Firsching R, Sabel BA. Brain tumor therapy by combined vaccination and antisense oligonucleotide delivery with nanoparticles. J Neuroimmunol. 2008;195:21-27.
View Article Google Scholar

49. Benny O, Duvshani-Eshet M, Cargioli T, Bello L, Bikfalvi A, Carroll RS, Machluf M. Continuous delivery of endogenous inhibitors from poly(lactic-co-glycolic acid) polymeric microspheres inhibits glioma tumor growth. Clin Cancer Res. 2005;11:768-776.
View Article Google Scholar

50. Shahani K, Swaminathan SK, Freeman D, Blum A, Ma L, Panyam J: Injectable sustained release microparticles of curcumin: a new concept for cancer chemoprevention. Cancer Res. 70: 4443-4452. 10.1158/0008-5472.CAN-09-4362.

51. Arai T, Benny O, Joki T, Menon LG, Machluf M, Abe T, Carroll RS, Black PM: Novel local drug delivery system using thermoreversible gel in combination with polymeric microspheres or liposomes. Anticancer Res. 30: 1057-1064.

52. Sapin A, Garcion E, Clavreul A, Lagarce F, Benoit JP, Menei P. Development of new polymer-based particulate systems for anti-glioma vaccination. Int J Pharm. 2006;309:1-5.
View Article Google Scholar

53. Hagedorn M, Zilberberg L, Lozano RM, Cuevas P, Canron X, Redondo-Horcajo M, Gimenez-Gallego G, Bikfalvi A. A short peptide domain of platelet factor 4 blocks angiogenic key events induced by FGF-2. Faseb J. 2001;15:550-552.
View Article Google Scholar

54. Zhang YH, Zhang H, Liu JM, Yue ZJ. Temozolomide/PLGA microparticles: a new protocol for treatment of glioma in rats. >Med Oncol. 2010;:-.
View Article Google Scholar

55. Ranganath SH, Kee I, Krantz WB, Chow PK, Wang CH. Hydrogel matrix entrapping PLGA-paclitaxel microspheres: drug delivery with near zero-order release and implantability advantages for malignant brain tumour chemotherapy. Pharm Res. 2009;26:2101-2114.
View Article Google Scholar

56. Benny O, Menon LG, Ariel G, Goren E, Kim SK, Stewman C, Black PM, Carroll RS, Machluf M. Local delivery of poly lactic-co-glycolic acid microspheres containing imatinib mesylate inhibits intracranial xenograft glioma growth. Clin Cancer Res. 2009;15:1222-1231.
View Article Google Scholar

57. Esther Gil-Alegre M, Gonzalez-Alvarez I, Gutierrez-Pauls L, Torres-Suarez AI. Three weeks release BCNU loaded hydrophilic-PLGA microspheres for interstitial chemotherapy: Development and activity against human glioblastoma cells. J Microencapsul. 2008;25:561-568.
View Article   Google Scholar

58. Xie J, Tan RS, Wang CH. Biodegradable microparticles and fiber fabrics for sustained delivery of cisplatin to treat C6 glioma in vitro. J Biomed Mater Res A. 2008;85:897-908.
View Article   Google Scholar

59. Yemisci M, Bozdag S, Cetin M, Soylemezoglu F, Capan Y, Dalkara T, Vural I. Treatment of malignant gliomas with mitoxantrone-loaded poly (lactide-coglycolide) microspheres. Neurosurgery. 2006;59:1296-1302.
View Article   Google Scholar

60. Lagarce F, Garcion E, Faisant N, Thomas O, Kanaujia P, Menei P, Benoit JP. Development and characterization of interleukin-18-loaded biodegradable microspheres. Int J Pharm. 2006;314:179-188.
View Article   Google Scholar

61. Menei P, Boisdron-Celle M, Croue A, Guy G, Benoit JP. Effect of stereotactic implantation of biodegradable 5-fluorouracil-loaded microspheres in healthy and C6 glioma-bearing rats. Neurosurgery. 1996;39:117-123.
View Article   Google Scholar

62. Menei P, Capelle L, Guyotat J, Fuentes S, Assaker R, Bataille B, Francois P, Dorwling-Carter D, Paquis P, Bauchet L, et al. Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of malignant glioma: a randomized phase II trial. Neurosurgery. 2005;56:242-248.
View Article   Google Scholar

63. Guerin C, Olivi A, Weingart JD, Lawson HC, Brem H. Recent advances in brain tumor therapy: local intracerebral drug delivery by polymers. Invest New Drugs. 2004;22:27-37.
View Article   Google Scholar

64. Balossier A, Dorner L, Emery E, Heese O, Mehdorn HM, Menei P, Singh J: Incorporating BCNU wafers into malignant glioma treatment: European case studies. Clin Drug Investig. 30: 195-204.

65. Menei P, Metellus P, Parot-Schinkel E, Loiseau H, Capelle L, Jacquet G, Guyotat J: Biodegradable carmustine wafers (Gliadel) alone or in combination with chemoradiotherapy: the French experience. Ann Surg Oncol. 17: 1740-1746. 10.1245/s10434-010-1081-5.

66. Brem H, Gabikian P. Biodegradable polymer implants to treat brain tumors. J Control Release. 2001;74:63-67.
View Article   Google Scholar

67. De Bouard S, Guillamo JS, Christov C, Lefevre N, Brugieres P, Gola E, Devanz P, Indraccolo S, Peschanski M. Antiangiogenic therapy against experimental glioblastoma using genetically engineered cells producing interferon-alpha, angiostatin, or endostatin. Hum Gene Ther. 2003;14:883-895.
View Article   Google Scholar

68. Ehtesham M, Kabos P, Kabosova A, Neuman T, Black KL, Yu JS. The use of interleukin 12-secreting neural stem cells for the treatment of intracranial glioma. Cancer Res. 2002;62:5657-5663.
View Article   Google Scholar

69. Emerich DF, McDermott PE, Krueger PM, Winn SR. Intrastriatal implants of polymer-encapsulated PC12 cells: effects on motor function in aged rats. Prog Neuropsychopharmacol Biol Psychiatry. 1994;18:935-946.
View Article   Google Scholar

70. Emerich DF, Plone M, Francis J, Frydel BR, Winn SR, Lindner MD. Alleviation of behavioral deficits in aged rodents following implantation of encapsulated GDNF-producing fibroblasts. Brain Res. 1996;736:99-110.
View Article   Google Scholar

71. Hoffman D, Breakefield XO, Short MP, Aebischer P. Transplantation of a polymer-encapsulated cell line genetically engineered to release NGF. Exp Neurol. 1993;122:100-106.
View Article   Google Scholar

72. Winn SR Hammang JP Emerich DF Lee A Palmiter RD Baetge EE Polymer-encapsulated cells genetically modified to secrete human nerve growth factor promote the survival of axotomized septal cholinergic neurons Proc Natl Acad Sci USA 1994 91 2324 232843363

73. Emerich DF, Winn SR, Hantraye PM, Peschanski M, Chen EY, Chu Y, McDermott P, Baetge EE, Kordower JH. Protective effect of encapsulated cells producing neurotrophic factor CNTF in a monkey model of Huntington's disease. Nature. 1997;386:395-399.
View Article   Google Scholar

74. Garcia P, Youssef I, Utvik JK, Florent-Bechard S, Barthelemy V, Malaplate-Armand C, Kriem B, Stenger C, Koziel V, Olivier JL, et al: Ciliary neurotrophic factor cell-based delivery prevents synaptic impairment and improves memory in mouse models of Alzheimer's disease. J Neurosci. 30: 7516-7527. 10.1523/JNEUROSCI.4182-09.2010.

75. Aebischer P, Schluep M, Deglon N, Joseph JM, Hirt L, Heyd B, Goddard M, Hammang JP, Zurn AD, Kato AC, et al. Intrathecal delivery of CNTF using encapsulated genetically modified xenogeneic cells in amyotrophic lateral sclerosis patients. Nat Med. 1996;2:696-699.
View Article   Google Scholar

76. Zurn AD, Henry H, Schluep M, Aubert V, Winkel L, Eilers B, Bachmann C, Aebischer P. Evaluation of an intrathecal immune response in amyotrophic lateral sclerosis

patients implanted with encapsulated genetically engineered xenogeneic cells. Cell Transplant. 2000;9:471-484.

View Article   Google Scholar

77. Deglon N, Heyd B, Tan SA, Joseph JM, Zurn AD, Aebischer P. Central nervous system delivery of recombinant ciliary neurotrophic factor by polymer encapsulated differentiated C2C12 myoblasts. Hum Gene Ther. 1996;7:2135-2146.

View Article   Google Scholar

78. Hammang JP, Emerich DF, Winn SR, Lee A, Lindner MD, Gentile FT, Doherty EJ, Kordower JH, Baetge EE. Delivery of neurotrophic factors to the CNS using encapsulated cells: developing treatments for neurodegenerative diseases. Cell Transplant. 1995;4:S27-28.

View Article   Google Scholar

79. Borlongan CV, Thanos CG, Skinner SJ, Geaney M, Emerich DF. Transplants of encapsulated rat choroid plexus cells exert neuroprotection in a rodent model of Huntington's disease. Cell Transplant. 2008;16:987-992.

View Article   Google Scholar

80. Emerich DF, Cain CK, Greco C, Saydoff JA, Hu ZY, Liu H, Lindner MD. Cellular delivery of human CNTF prevents motor and cognitive dysfunction in a rodent model of Huntington's disease. Cell Transplant. 1997;6:249-266.

View Article   Google Scholar

81. Lindner MD, Plone MA, Mullins TD, Winn SR, Chandonait SE, Stott JA, Blaney TJ, Sherman SS, Emerich DF. Somatic delivery of catecholamines in the striatum attenuate parkinsonian symptoms and widen the therapeutic window of oral sinemet in rats. Exp Neurol. 1997;145:130-140.

View Article   Google Scholar

82. Lindvall O, Wahlberg LU. Encapsulated cell biodelivery of GDNF: a novel clinical strategy for neuroprotection and neuroregeneration in Parkinson's disease?. Exp Neurol. 2008;209:82-88.

View Article   Google Scholar

83. Read TA, Sorensen DR, Mahesparan R, Enger PO, Timpl R, Olsen BR, Hjelstuen MH, Haraldseth O, Bjerkvig R. Local endostatin treatment of gliomas administered by microencapsulated producer cells. Nat Biotechnol. 2001;19:29-34.

View Article   Google Scholar

84. Read TA, Farhadi M, Bjerkvig R, Olsen BR, Rokstad AM, Huszthy PC, Vajkoczy P. Intravital microscopy reveals novel antivascular and antitumor effects of endostatin delivered locally by alginate-encapsulated cells. Cancer Res. 2001;61:6830-6837.

View Article   Google Scholar

85. Bjerkvig R, Read TA, Vajkoczy P, Aebischer P, Pralong W, Platt S, Melvik JE, Hagen A, Dornish M. Cell therapy using encapsulated cells producing endostatin. Acta Neurochir Suppl. 2003;88:137-141.

View Article   Google Scholar

86. Joki T, Machluf M, Atala A, Zhu J, Seyfried NT, Dunn IF, Abe T, Carroll RS, Black PM. Continuous release of endostatin from microencapsulated engineered cells for tumor therapy. Nat Biotechnol. 2001;19:35-39.
View Article   Google Scholar

87. Goren A, Dahan N, Goren E, Baruch L, Machluf M: Encapsulated human mesenchymal stem cells: a unique hypoimmunogenic platform for long-term cellular therapy. Faseb J. 24: 22-31. 10.1096/fj.09-131888.

88. Kuijlen JM, de Haan BJ, Helfrich W, de Boer JF, Samplonius D, Mooij JJ, de Vos P. The efficacy of alginate encapsulated CHO-K1 single chain-TRAIL producer cells in the treatment of brain tumors. J Neurooncol. 2006;78:31-39.
View Article   Google Scholar

89. Visted T Bjerkvig R Enger PO Cell encapsulation technology as a therapeutic strategy for CNS malignancies Neuro Oncol 2001 3 201 2101920619

90. Bobo RH Laske DW Akbasak A Morrison PF Dedrick RL Oldfield EH Convection-enhanced delivery of macromolecules in the brain Proc Natl Acad Sci USA 1994 91 2076 208043312

91. Laquintana V Trapani A Denora N Wang F Gallo JM Trapani G New strategies to deliver anticancer drugs to brain tumors Expert Opin Drug Deliv 2009 6 1017 10322752842

92. Saito R Krauze MT Noble CO Drummond DC Kirpotin DB Berger MS Park JW Bankiewicz KS Convection-enhanced delivery of Ls-TPT enables an effective, continuous, low-dose chemotherapy against malignant glioma xenograft model Neuro Oncol 2006 8 205 2141871954

93. Ohlfest JR, Demorest ZL, Motooka Y, Vengco I, Oh S, Chen E, Scappaticci FA, Saplis RJ, Ekker SC, Low WC, et al. Combinatorial antiangiogenic gene therapy by nonviral gene transfer using the sleeping beauty transposon causes tumor regression and improves survival in mice bearing intracranial human glioblastoma. Mol Ther. 2005;12:778-788.
View Article   Google Scholar

94. Dickinson MD, Barr CD, Hiscock M, Meyers CA. Cognitive effects of pegylated interferon in individuals with primary brain tumors. J Neurooncol. 2009;95:231-237.
View Article   Google Scholar

95. Sengupta S, Eavarone D, Capila I, Zhao G, Watson N, Kiziltepe T, Sasisekharan R. Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system. Nature. 2005;436:568-572.
View Article   Google Scholar

96. Conover CD, Pendri A, Lee C, Gilbert CW, Shum KL, Greenwald RB. Camptothecin delivery systems: the antitumor activity of a camptothecin-20-0-polyethylene glycol ester transport form. Anticancer Res. 1997;17:3361-3368.
View Article   Google Scholar

97. Zhu S, Hong M, Zhang L, Tang G, Jiang Y, Pei Y: PEGylated PAMAM dendrimer-doxorubicin conjugates: in vitro evaluation and in vivo tumor accumulation. Pharm Res. 27: 161-174. 10.1007/s11095-009-9992-1.

98. Immordino ML Dosio F Cattel L Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential Int J Nanomedicine 2006 1 297 3152426795

99. Abrishami M, Ganavati SZ, Soroush D, Rouhbakhsh M, Jaafari MR, Malaekeh-Nikouei B. Preparation, characterization, and in vivo evaluation of nanoliposomes-encapsulated bevacizumab (avastin) for intravitreal administration. Retina. 2009;29:699-703.
View Article   Google Scholar

100. Park JW Liposome-based drug delivery in breast cancer treatment Breast Cancer Res 2002 4 95 99138729

101. Xiao W, Chen X, Yang L, Mao Y, Wei Y, Chen L. Co-delivery of doxorubicin and plasmid by a novel FGFR-mediated cationic liposome. Int J Pharm. 2010;393:119-26.
View Article   Google Scholar

102. Barichello JM, Ishida T, Kiwada H: Complexation of siRNA and pDNA with cationic liposomes: the important aspects in lipoplex preparation. Methods Mol Biol. 605: 461-472. full_text.

103. Herringson TP, Altin JG. Convenient targeting of stealth siRNA-lipoplexes to cells with chelator lipid-anchored molecules. J Control Release. 2009;139:229-238.
View Article   Google Scholar

104. Pardridge WM Blood-brain barrier delivery of protein and non-viral gene therapeutics with molecular Trojan horses J Control Release 2007 122 345 3482701689

105. Oku N, Namba Y. Long-circulating liposomes. Crit Rev Ther Drug Carrier Syst. 1994;11:231-270.
View Article   Google Scholar

106. Basu MK, Lala S. Macrophage specific drug delivery in experimental leishmaniasis. Curr Mol Med. 2004;4:681-689.
View Article   Google Scholar

107. Patel HM. Serum opsonins and liposomes: their interaction and opsonophagocytosis. Crit Rev Ther Drug Carrier Syst. 1992;9:39-90.
View Article   Google Scholar

108. Chonn A, Semple SC, Cullis PR. Beta 2 glycoprotein I is a major protein associated with very rapidly cleared liposomes in vivo, suggesting a significant role in the immune clearance of "non-self" particles. J Biol Chem. 1995;270:25845-25849.
View Article   Google Scholar

109. Devine DV, Wong K, Serrano K, Chonn A, Cullis PR. Liposome-complement interactions in rat serum: implications for liposome survival studies. Biochim

Biophys Acta. 1994;1191:43-51.
View Article   Google Scholar

110. Allen C, Dos Santos N, Gallagher R, Chiu GN, Shu Y, Li WM, Johnstone SA, Janoff AS, Mayer LD, Webb MS, Bally MB. Controlling the physical behavior and biological performance of liposome formulations through use of surface grafted poly(ethylene glycol). Biosci Rep. 2002;22:225-250.
View Article   Google Scholar

111. Needham D, McIntosh TJ, Lasic DD. Repulsive interactions and mechanical stability of polymer-grafted lipid membranes. Biochim Biophys Acta. 1992;1108:40-48.
View Article   Google Scholar

112. Blume G, Cevc G. Molecular mechanism of the lipid vesicle longevity in vivo. Biochim Biophys Acta. 1993;1146:157-168.
View Article   Google Scholar

113. Yuan F, Leunig M, Huang SK, Berk DA, Papahadjopoulos D, Jain RK. Microvascular permeability and interstitial penetration of sterically stabilized (stealth) liposomes in a human tumor xenograft. Cancer Res. 1994;54:3352-3356.
View Article   Google Scholar

114. Siegal T, Horowitz A, Gabizon A. Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: biodistribution and therapeutic efficacy. J Neurosurg. 1995;83:1029-1037.
View Article   Google Scholar

115. Koukourakis MI Koukouraki S Fezoulidis I Kelekis N Kyrias G Archimandritis S Karkavitsas N High intratumoural accumulation of stealth liposomal doxorubicin (Caelyx) in glioblastomas and in metastatic brain tumours Br J Cancer 2000 83 1281 12862408790

116. Zhou R, Mazurchuk R, Straubinger RM. Antivasculature effects of doxorubicin-containing liposomes in an intracranial rat brain tumor model. Cancer Res. 2002;62:2561-2566.
View Article   Google Scholar

117. Riondel J, Jacrot M, Fessi H, Puisieux F, Potier . Effects of free and liposome-encapsulated taxol on two brain tumors xenografted into nude mice. In Vivo. 1992;6:23-27.
View Article   Google Scholar

118. Zhao S, Zhang X, Zhang J, Zou H, Liu Y, Dong X, Sun X. Intravenous administration of arsenic trioxide encapsulated in liposomes inhibits the growth of C6 gliomas in rat brains. J Chemother. 2008;20:253-262.
View Article   Google Scholar

119. Gondi CS Lakka SS Dinh DH Olivero WC Gujrati M Rao JS Downregulation of uPA, uPAR and MMP-9 using small, interfering, hairpin RNA (siRNA) inhibits glioma cell invasion, angiogenesis and tumor growth Neuron Glia Biol 2004 1 165 1761483066

120. Gondi CS Lakka SS Dinh DH Olivero WC Gujrati M Rao JS Intraperitoneal injection of a hairpin RNA-expressing plasmid targeting urokinase-type plasminogen activator (uPA) receptor and uPA retards angiogenesis and inhibits intracranial tumor growth in nude mice Clin Cancer Res 2007 13 4051 40602139987

121. Kargiotis O Chetty C Gondi CS Tsung AJ Dinh DH Gujrati M Lakka SS Kyritsis AP Rao JS Adenovirus-mediated transfer of siRNA against MMP-2 mRNA results in impaired invasion and tumor-induced angiogenesis, induces apoptosis in vitro and inhibits tumor growth in vivo in glioblastoma Oncogene 2008 27 4830 48402574662

122. Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, Bartel DP, Linsley PS, Johnson JM. Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature. 2005;433:769-773.
View Article   Google Scholar

123. Wurdinger T Tannous BA Saydam O Skog J Grau S Soutschek J Weissleder R Breakefield XO Krichevsky AM miR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells Cancer Cell 2008 14 382 3932597164

124. Kreuter J, Ramge P, Petrov V, Hamm S, Gelperina SE, Engelhardt B, Alyautdin R, von Briesen H, Begley DJ. Direct evidence that polysorbate-80-coated poly(butylcyanoacrylate) nanoparticles deliver drugs to the CNS via specific mechanisms requiring prior binding of drug to the nanoparticles. Pharm Res. 2003;20:409-416.
View Article   Google Scholar

125. Yamada T, Iwasaki Y, Tada H, Iwabuki H, Chuah MK, VandenDriessche T, Fukuda H, Kondo A, Ueda M, Seno M, et al. Nanoparticles for the delivery of genes and drugs to human hepatocytes. Nat Biotechnol. 2003;21:885-890.
View Article   Google Scholar

126. Tsutsui Y, Tomizawa K, Nagita M, Michiue H, Nishiki T, Ohmori I, Seno M, Matsui H. Development of bionanocapsules targeting brain tumors. J Control Release. 2007;122:159-164.
View Article   Google Scholar

127. Acharya RS, Sundareshan MK. Development of optimal drug administration strategies for cancer-chemotherapy in the framework of systems theory. Int J Biomed Comput. 1984;15:139-150.
View Article   Google Scholar

128. Boldrini JL, Costa MI. Therapy burden, drug resistance, and optimal treatment regimen for cancer chemotherapy. IMA J Math Appl Med Biol. 2000;17:33-51.
View Article   Google Scholar

129. Cappuccio A, Elishmereni M, Agur Z. Cancer immunotherapy by interleukin-21: potential treatment strategies evaluated in a mathematical model. Cancer Res. 2006;66:7293-7300.
View Article   Google Scholar

130. Cappuccio A, Elishmereni M, Agur Z. Optimization of interleukin-21 immunotherapeutic strategies. J Theor Biol. 2007;248:259-266.
View Article   Google Scholar

131. Gevertz JL, Torquato S. Modeling the effects of vasculature evolution on early brain tumor growth. J Theor Biol. 2006;243:517-531.
View Article   Google Scholar

132. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med. 1995;1:27-31.
View Article   Google Scholar

133. Kronik N, Kogan Y, Vainstein V, Agur Z. Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics. Cancer Immunol Immunother. 2008;57:425-439.
View Article   Google Scholar