Glioblastoma multiforme (GBM), the most malignant and most frequent primary brain tumor, is currently incurable, with a median survival of less than 2 years after diagnosis and treatment. Worldwide, approximately 175,000 cases occur annually, of which 17,000 are diagnosed in the USA. Several innovative treatments are being developed, but the mainstays of conventional treatment are chemotherapy and radiation. Chemotherapy gives inconsistent results in terms of prolongation of survival. GBM is a complex, heterogeneous disease, which makes it unlikely that a uniform approach would be suitable for all patients. Treatment of GBM is one of the most challenging problems in neurooncology, with several controversies as to the best way of dealing with this problem. There is a need for the use of refined tools of nanobiotechnology for targeted delivery of therapeutics to brain tumors [1].

“The fluorescent nanoparticles improved the contrast between the tumor tissue and the normal tissue in both MRI and optical imaging, which are used during surgery to see the tumor boundary more precisely.”

Along with the introduction of innovative methods, there is a need to choose the best treatment suitable for an individual (i.e., personalized medicine) [2]. Personalized treatment is usually based on pharmacogenetics, pharmacogenomics and pharmacoproteomics, but other individual variations in patients are also taken into consideration. Integration of diagnosis and therapy is an important feature of personalized therapy. At present, cancer is the most important area for application of targeted and personalized approaches to treatment. In the case of GBM, the variation in behavior of the tumor of the same histological type from one patient to another is also taken into consideration, and development of a personalized approach to treatment will address the heterogeneity of this complex tumor phenotype. A number of tests for gene-expression patterns are being used in an effort to predict the response of GBM to a particular chemotherapy. Nanobiotechnology is providing methods for diagnosis, as well as personalization of the treatment of GBM.

**Nanoparticles for refinement of imaging of GBM**

Current diagnosis of GBM is by brain imaging, such as CT and MRI. Nanoimaging could also help with early detection of brain tumors. Current imaging techniques have a maximum resolution of 1 mm. Nanoparticles could improve the resolution by a factor of ten or more, allowing detection of smaller tumors and earlier treatment. Several nanoparticle-based contrast materials have been used to enhance MRI of the brain.

In *vivo* application of nanoparticle-based platforms in brain tumors is limited by insufficient accumulation and retention within tumors owing to limited specificity for the target, and an inability to traverse the blood–brain barrier (BBB). A nanoprobe has been designed that can cross the BBB and specifically target brain tumors in a genetically engineered mouse model, by using *in vivo* magnetic resonance and biophotonic imaging, as well as histological and biodistribution analyses [3]. The nanoprobe is composed of an iron oxide nanoparticle-coated with biocompatible poly(ethylene glycol) (PEG)-grafted chitosan copolymer, to which a tumor-targeting agent, chlorotoxin (a small...
peptide isolated from scorpion venom), and a near-infrared fluorophore are conjugated. The particle is approximately 33 nm in diameter when wet (i.e., approximately a third of the size of similar particles used in other parts of the body). The nanoprobe shows an innocuous toxicity profile and sustained retention in tumors. The nanoparticles remained in mouse tumors for up to 5 days and did not show any evidence of damaging the BBB. With the versatile affinity of the targeting ligand and the flexible conjugation chemistry for alternative diagnostic and therapeutic agents, this nanoparticle platform can potentially be used for the diagnosis and treatment of a variety of brain tumors. The fluorescent nanoparticles improved the contrast between the tumor tissue and the normal tissue in both MRI and optical imaging, which are used during surgery to see the tumor boundary more precisely. Precise imaging of brain tumor margins is important because patient survival for brain tumors is directly related to the amount of tumor that can be excised.

Nanoparticles for detection of biomarkers of GBM
Several molecular biomarkers have been identified in GBM that carry diagnostic and prognostic information. In addition, some of these and other biomarkers predict the response of these tumors to particular chemotherapeutic approaches [4]. Nanobiotechnology has refined the detection of biomarkers. A study has evaluated the feasibility and specificity of using quantum dot (QD)-labeled antibodies for rapid visualization of EGF receptor (EGFR) expression in human brain tumor cells and in surgical frozen section slides of glioma tissue [5]. Streptavidin-coated QDs were conjugated to anti-EGFR antibodies and incubated with target cultured tumor cells and tissues. The bioconjugated QDs used in the study were found to bind selectively to brain tumor cells expressing EGFR. QD complexed quickly to the cell membrane, and binding was highly specific according to the expression level of EGFR on the cell membrane. These findings demonstrate that QD-labeled antibodies can provide a quick and accurate method for characterizing the presence or absence of a specific predictive biomarker of GBM.

Nanotechnology for combination of diagnostics & therapeutics
A polymeric nanobioconjugate drug based on biodegradable, nontoxic and nonimmunogenic polymeric acid as a universal delivery nanoplatform is used for design of a nanomedicine for intravenous treatment of brain tumors [6]. The polymeric drug passes through the blood–tumor barrier (BTB) and tumor cell membrane using tandem monoclonal antibodies targeting the BTB and tumor cells. The next step for polymeric drug action is inhibition of tumor angiogenesis by specifically blocking the synthesis of a tumor neovascular trimer protein, laminin-411, by attached antisense oligonucleotides, which are released into the target cell cytoplasm via pH-activated trileucine, an endosomal escape moiety. Introduction of a trileucine endosome escape unit results in significantly increased antisense oligonucleotide delivery to tumor cells, inhibition of laminin-411 synthesis, specific accumulation in brain tumors, and suppression of intracranial glioma growth compared with pH-independent leucine ester. The availability of a systemically active polymeric drug-delivery system that crosses BTB, targets tumor cells and inhibits its tumor growth is a promising strategy of glioma treatment.

Role of nanotechnology in thermotherapy of GBM
Hyperthermia, the heating of cancerous tissues to between 41 and 45°C, has been shown to improve the efficacy of cancer therapy when used in conjunction with irradiation and/or chemotherapy. Hydrogel nanocomposites based on PEG methyl ether methacrylate and dimethacrylate with iron oxide can be used as implantable biomaterials for thermal cancer therapy applications [7]. These can be remotely heated upon exposure to an external alternating magnetic field. Thermotherapy using magnetic nanoparticles in conjunction with a reduced radiation dose is safe and effective and leads to longer overall survival compared with conventional therapies in the treatment of recurrent GBM [8].

Nanotechnology-based drug delivery to brain tumors
Surgery remains the basic treatment in which the bulk of the tumor is removed and the peripheral infiltrating part is the target of supplementary treatments. BBB is a significant hurdle to the delivery of anticancer therapies to the brain. GBM is not easily targeted but advances in nanobiotechnology have improved the prospects of delivery of therapeutics to GBM [9]. Nanoparticulate vectors may be designed to interact with BBB-forming cells at a molecular level, as a result of which the transport of
Role of nanobiotechnology in the personalized management of glioblastoma multiforme

Role of nanobiotechnology for gene therapy of brain tumors

Brain tumors may be amenable to gene therapy with cytotoxic genes, but vectors carrying these are usually administered intravenously, thus excluding viral vectors as they cannot cross the BBB. Among nonviral vectors, intravenous administration of transferrin-bearing polypropyleneimine complexed to a therapeutic DNA has been shown to result in gene expression mainly in brain tumors in experimental animals with sustained tumor regression and long-term survival of 100% of the animals [12,13]. The treatment was well tolerated by the animals and this approach may be a promising gene delivery system for therapy of GBM.

Studies of molecular pathways that are involved in the pathogenesis of GBM are providing new targets for RNA interference (RNAi)-based therapies. However, the in vivo delivery of siRNA is a challenge because of poor penetration into the target tissue. A polymerized polyglycerol-based dendrimer core has been shown to improve the stability of the siRNA, its intracellular trafficking, its silencing efficacy, and its accumulation in the tumor environment of an animal model of brain tumor [14]. This is a promising therapy for GBM.

Conclusion & future perspective

Personalized management of GBM is based on a better understanding of the cancer at the molecular level, early diagnosis, combination of diagnosis with treatment and improved delivery of therapeutics with possibility to monitor the effects. Nanotechnology will play an important role in all of these areas. Nonviral nanoparticles represent a good alternative to viral vectors in gene therapy of GBM, but transfection efficiency has to be increased to reach levels that would be relevant for therapeutic purposes.

Glioblastoma multiforme still remains a challenge in treatment because complete eradication is required for cure, which is rendered more difficult because of its location in the brain. Considerable data are being generated from experimental studies and clinical trials for GBM. Advances in bioinformatics provide computational tools to analyze the massive data generated from numerous studies using new technologies in this area and help in choosing the most effective and safest treatment for an individual patient. Nanobiotechnology will provide more efficient tools for diagnosis and targeted personalized therapy, and increase the chances for cure.
Bibliography


