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# Radiolabelled Nanoparticles for Brain Targeting

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## **Abstract**

Tumors like glioblastoma are inaccessible due to blood brain barrier. The permeability of radioisotopes can be improved by conjugating them with nanoparticles. The most common malignant adult brain tumor is glioblastoma, which has very poor patient prognosis. The mean survival for highly proliferative glioblastoma is only 10–14 months despite an aggressive radiotherapy and chemotherapy following debulking surgery.  $\beta^-$  particle emitters like  $^{131}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{186/188}\text{Re}$ , and  $^{177}\text{Lu}$  have been coupled with nanoparticles and used for treatment of glioblastoma. These radiopharmaceutical compounds have resulted in a stabilization and improvement of the neurological status with minimal side effects. Similarly,  $\alpha$  particle emitters like  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ , and  $^{225}\text{Ac}$  are an innovative and interesting alternative. Alpha particles deliver a high proportion of their energy inside the targeted cells within a few micrometers from the emission point versus several millimeters for  $\beta^-$  particles. Thus,  $\alpha$  particles are highly efficient in killing tumor cells with minimal irradiation of healthy tissues and permits targeting of isolated tumor cells. This has been confirmed by subsequent clinical trials which showed better therapeutic efficacy and minimal side effects, thus opening a new and promising era for glioblastoma medical care using  $\alpha$  therapy.

**Keywords:** radioisotopes, nanoparticles, brain targeting, glioblastoma, blood brain barrier, theranostics

## **1. Introduction**

Nuclear medicine involves use of radioactive atoms for diagnosis and/or therapy. For therapeutic purposes, to obtain specific irradiation of tumor cells, radioactivity is attached to a pharmaceutical molecule that binds to specific molecules expressed on the target tumor cells. This specific radioactive molecule is known as radiopharmaceutical. The pharmacological specific component of a therapeutic radiopharmaceutical can be based on the target protein structure which may include peptides or monoclonal antibodies, or molecular structures like nanoparticles [1]. The radioactive part may consist of massive particle emitters capable of delivering ionizing energy locally as Auger electrons, or  $\beta^-$  or  $\alpha$  particles. Auger electrons are low-energy electrons that emit localized irradiation, few nanometers around the emission point with high biological effects. Beta-negative particles have a comparatively low linear energy transfer (LET) and emit their energy over a few millimeters in comparison to alpha particles. The choice of the radionuclide is based upon the size of the tumor. For example, yttrium-90 emits a long-range beta emission and could be useful for proliferating tumors of large size, while lutetium-177 having a

short range emission could be used for treatment retreating tumors of small size. Alpha particles deliver a high fraction of their energy inside the targeted cells, leading to highly efficient killing. This makes them suitable for targeting cells of isolated tumor and minimal residual disease [2, 3].

Radioimmunotherapy, radiopeptide therapy and radionanoparticles are three important strategies of nuclear medicine for glioblastoma therapy. The four main prerequisites for successful radionuclide therapy for glioblastoma are selection of an appropriate target (integrin, tenascin, cadherin, EGFR, chemokine receptors or neurokinin receptors), physicochemical properties of the radionuclide, physicochemical properties of the targeting vector and its size [4]. For therapeutic purposes, nuclear medicine practitioners typically use  $\beta^-$  particle emitters like  $^{131}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{186/188}\text{Re}$ , and  $^{177}\text{Lu}$ . These radioisotopes have been coupled with nanoparticles, monoclonal antibodies, or peptides for treatment of glioblastoma. These radiopharmaceuticals have resulted in maintenance and/or improvement of the neurological status with only short-term side effects. The evidence for glioblastoma targeted radiotherapy has not only proven for  $\beta^-$  particle emitters but also for  $\alpha$  particle emitters.  $^{213}\text{Bi}$ ,  $^{211}\text{At}$ , and  $^{225}\text{Ac}$  are some of the particle emitters which are recently attracting the interest of the scientific community. They are capable of delivering high amount of their energy within few micrometers close to their emission point in comparison to some few millimeters for  $\beta^-$  particles. The  $\alpha$  particles have been found highly efficient in killing tumor cells with minimal irradiation of healthy tissues and permits targeting of isolated tumor cells [1, 5].

## 2. Understanding WHO Classification of CNS tumors

Gliomas are the most frequent, very diverse group of intrinsic tumors of the central nervous system and are conventionally classified in harmony to their microscopic likeness with recognized cells of origin according to glial precursor cell families. Major groups consist of diffuse gliomas, categorized by widespread growth into the adjoining CNS parenchyma, and more confined “nondiffuse” gliomas, with pilocytic astrocytoma and ependymomas [6]. The fourth edition of the WHO Classification of CNS tumors published in 2016 has essentially changed the classification of diffuse gliomas. These tumors are presently defined based on presence/absence of IDH mutation and 1p/19q codeletion. It can be attributed to massive expansion of knowledge on molecular alterations in tumors of the central nervous system (CNS) [2]. Until now, tumors were defined based on their histology. Any molecular information was mainly provided as supplementary information within histologically defined categories. Current advances in the molecular conceptualization of gliomas recommend some probable reasons for the failure of targeted therapies in gliomas. Specially, the histologic-based glioma categorization comprises of multiple molecular subtypes with discrete biology, usual history, and diagnosis. These observations have resulted in improvement in diagnosis and classification by the World Health Organization [7]. These perceptions regarding glioma biomarkers and subtypes highlight several clinical challenges. Firstly, the field is witnessing the struggle of reconsidering the results of previous studies and retrospective data using the new classifications to explain prognostic assessments and treatment recommendations for patients. Secondly, the new classification requires changes in the design and stratification of future clinical trials. Hence, these observations offer the required framework for the growth and evaluation of novel targeted therapies for specific glioma subtypes [2, 8].

Drug delivery to tumor can be monitored using nuclear medicine imaging techniques like single-photon emission computed tomography (SPECT),

positron-emission-tomography (PET). In single-photon emission computed tomography (SPECT), a gamma-emitting tracer allows for three dimensional visualization of the drug [9]. The radioisotope is either administered with the drug or directly bound to the biologically active molecule such as siRNA, so that their volume of distribution can be determined easily. Accurate anatomic estimates can be obtained by combining SPECT with CT or MRI. This approach is less expensive in comparison to other nuclear medicine imaging modalities [10]. Conventional SPECT suffer from poor limitation. However, recent advances involving pinhole-SPECT has improved the resolution to millimeter level [11].

Another promising modality for imaging drug delivery to tumor is positron-emission-tomography (PET). PET tracers are administered with the drug or are bound to the carrier like nanoparticles [12]. The PET scan can be correlated with CT scan in order to determine path of diffusion of tracer.

Similar to gadolinium and SPECT contrast agents, PET tracers can be infused concurrently with drug or bound to the delivery system, such as nanoparticles [12]. When PET is coupled with CT, molecular movement can be correlated with anatomy, with measurement of area of diffusion of tracer or tracer-incorporated carrier. PET imaging can estimate the borders of a tumor through the use of tracers that are derivatives of amino acid such as O-(2-[<sup>18</sup>F]fluoroethyl)-L-tyrosine (FET) thus allowing precise assessment of drug distribution relative to tumor volume than MRI [13]. Limitations of PET and SPECT imaging include radiation exposure, the high cost, and short-lived nature of PET tracers. Another important limitation similar to gadolinium agents in MRI is the tracer has to directly couple to the delivery agent; otherwise the measurement of the area of diffusion is indirect. These limitations can be overcome by direct radiolabeling of nanoparticles [14].

### **3. Nanocarrier-mediated CNS delivery of diagnostic and therapeutic agents**

Drug delivery across the BBB requires knowledge of both “barrier” and permeability properties of the brain endothelial cells. Transport across BBB may involve simple diffusion, facilitated diffusion, diffusion through aqueous pores, and active transport through protein carriers. In case of simple diffusion solute molecules travels along concentration gradient. Facilitated diffusion involves binding with specific membrane-traversing protein, coupled with movement along the concentration gradient. Charged ions and solutes cross the BBB by diffusion through aqueous pores. Active transport of solutes through protein carrier against concentration gradient involves expenditure of ATP. The presence of large number of mitochondria in the endothelial cells is thought to provide the required energy in form of ATP [15]. This mechanism involves an alteration in the affinity of a carrier for the solute molecules as it travels across the BBB. While designing nanocarrier mediated CNS delivery, transporter systems involved in ferrying essential molecules such as glucose are of utmost importance. These systems can be employed for delivery of potential nanotheranostics across the BBB. There are five types of sodium-independent glucose transporters (GLUT) which transport 2-deoxyglucose, 3-O-methylglucose, mannose, galactose and glucose across the BBB. The most important being 45–55 kDa glycosylated protein GLUT-1. It is mostly present in endothelial cells of arterioles, venules and capillaries, wherein it facilitates movement of D-glucose from the peripheral circulation into the brain. Other worth mentioning glucose transporters are GLUT-3 in brain neurons and GLUT-5 in microglial cells in the brain. They transport 2-deoxyglucose, 3-O-methylglucose, mannose, galactose and glucose across the BBB [16].



Another significant transport system that works in an analogous manner is P-glycoprotein multiple drug resistant protein (P-gp, MDR1). It has been comprehensively investigated as a possible carrier for drug delivery. This efflux transporter is usually expressed on luminal surface of endothelial cells, astrocytes and microglial cells. It prevents toxins from gaining entry into the brain parenchyma [17, 18]. Anticancer agents like Vinca alkaloids, anthracyclines, and taxanes are substrates for MDR1 are transported by Pgp. It limits their accumulation in the brain. Recently, it has been found that MDR1 regulation is altered by various disease conditions, and, in turn, diseases of the brain influence MDR1 expression [19, 20]. The presence of large number of receptors at the surface of BBB can be utilized by potential nanocarriers for enhanced brain by coupling with receptor-specific molecules or analogues. A large number of molecules such as insulin, insulin-like growth factors (IGF-1 and IGF-2), leptins, and transferrin can be transported into the brain following receptor-mediated endocytosis [13]. The nanoparticles should be designed to bypass efflux transport systems present at the luminal side (such as MDR1). Instead, nanoparticles could be substrates of transport mechanisms enhancing the passage of specific molecules like GLUT-1, IGF-1, and IGF-2 across the BBB [21].

#### 4. Paradigm shift in glioma diagnosis and treatment strategies

The WHO 2016 Classification of gliomas represents a paradigm shift as; for the first time, the definition of many of these neoplasms is partly based on genetic characteristics based on molecular markers. This was a major step forward toward a more precise diagnosis of gliomas and will in the course of time certainly facilitate improved therapeutic management of the patients suffering from these tumors. Diffuse gliomas are the most common intrinsic CNS neoplasms, found in adults. On the basis of histopathological analysis, these gliomas were conventionally diagnosed as diffuse astrocytomas (with glioblastoma as it is most common and malignant representative), oligodendrogliomas, or as tumors with a mixed astrocytic and oligodendroglial phenotype (oligoastrocytomas) [6]. Within these subgroups, a malignancy grade (WHO grade II, III or IV) was assigned based on the presence/absence of marked mitotic activity, necrosis and florid microvascular proliferation. The major change can be attributed to use of isocitrate dehydrogenase (IDH mutation) as a marker in diffuse glioma classification. The categorization of diffuse gliomas on the basis of genotype involves high incidence of point mutations in isocitrate dehydrogenase 1 and 2 (*IDH1/IDH2*) in WHO grade II and III astrocytomas, oligodendrogliomas, oligoastrocytomas and secondary glioblastomas. Lower grade neoplasms usually develop into secondary glioblastomas [8]. Hence, it became clear that tumors with identical histology can lead to different clinical outcome such as IDH-wildtype and IDH-mutant diffuse gliomas. Many histologically similar WHO grade II and WHO grade III IDH-wild type diffuse gliomas exhibit molecular characteristics like glioblastoma. These facts ultimately led to inclusion of IDH mutation as a crucial marker for glioma classification and the introduction of, genetically defined entities: diffuse astrocytoma, IDH-mutant; anaplastic astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant; anaplastic oligodendroglioma, IDH-mutant; and glioblastoma, IDH-mutant [7]. The molecular features of IDH-mutant glioma outweigh the histological diagnosis. A tumor having histology of an astrocytoma, detection of complete 1p/19q codeletion leads to diagnosis of oligodendroglioma. Likewise, for diffuse, IDH-mutant gliomas with oligodendroglial phenotype with complete absence of 1p/19q codeletion, the collective diagnosis may be astrocytoma, IDH-mutant and 1p/19q-non-codeleted [8]. Based on IDH mutation status, glioblastomas were reclassified as glioblastoma, IDH-wildtype and glioblastoma,

IDH-mutant. This latter category largely overlaps with what previously described secondary glioblastoma based on clinical, radiological and/or pathological evidence of a lower grade precursor lesion. Patients with a secondary glioblastoma or IDH-mutant glioblastoma are normally younger and have improved diagnosis than those with glioblastoma, IDH-wildtype. Analogous to grade II and grade III oligoastrocytic tumors, most glioblastomas with oligodendroglioma as explained in the WHO 2016 Classification are part of one of the genetic subgroups of diffuse glioma [7, 8]. One of the treatment strategies which are catching the attention of oncologist is nanotechnology. Nanoparticles (NP) are entities possessing diameter of 10–200 nm that hold great possibilities for design and biological applications. There has been an upsurge in development of nanodevices for diagnosis and treatment of brain tumors. Nanoparticles are carriers that can be designed to ferry one or more types of molecules to brain including MRI contrast agents, fluorescent and visible dyes, chemotherapeutic agents and photosensitizers. The targeted delivery of nanoparticles to brain tumors can be augmented by altering their particle size and surface characteristics [22, 23].

## 5. Multimodal tumor imaging and therapy

There has been moderate impact of targeted therapies in glioma. The therapies that have demonstrated a significant survival benefit for gliomas in Phase III clinical trials, including radiation, chemotherapy (temozolomide and PCV [procarbazine, lomustine, vincristine]), and tumor-treating fields, are based on nonspecific targeting of proliferating cells. An emerging field in glioblastoma nuclear medicine is use of radionanoparticles. These radioactive nanocarriers can be used passively as a simple tumor brachytherapy or can be actively used with a specific targeting to vectorize a large amount of radioactivity. The targeting is usually directed against a glioblastoma-specific antigen or receptor. Antigen targets, like epidermal growth factor receptor (EGFR), tenascin, or DNA histone H1 complex. Radiolabeled antibodies and peptides hold promise for molecular radiotherapy but are often limited by a low payload resulting in inadequate delivery of radioactivity to tumor tissue and, therefore, inadequate therapeutic effect and adverse effects due irradiation of normal tissues [24]. Song et al. developed a synthetic method of radiolabeling indium-111 ( $^{111}\text{In}$ ) to epidermal growth factor (EGF)-gold nanoparticles ( $^{111}\text{In}$ -EGF-Au NP) with a high payload [25]. By using radiolabeled nanoparticles, comparatively higher payloads are obtained due to large surface area to volume ratio. This results in multivalent effect of nanoparticles, thus accommodating a large number of targeting ligands, such as antibodies, peptides or aptamers on a single nanoparticle. This facilitates maximal binding to the molecular target in vivo, thus enhancing delivery of radioactivity to target tissue with improved imaging and therapeutic efficacy. PEGylation of nanoparticles and alteration of their surface properties improves their stability and mean residence time in vivo [26]. It also permits loading a combination of imaging, radiotherapeutic and/or chemotherapeutic moieties for multimodal tumor imaging and therapy [27]. Antibodies, radiolabeled antibodies, antibody fragments or peptides because of their small size easily penetrate surrounding normal tissues. Loading onto nanoparticles limits their penetration through normal vasculature and capillaries, thus minimizing their side-effects [28].

Different nanocarriers such as metallofullerenes, liposomes, or lipid nanocapsules have been used to deliver radionanoparticle passively. A typical metallofullerene ( $^{177}\text{Lu}$ -DOTA-f-Gd<sub>3</sub>N@C<sub>80</sub>) radionanoparticles when administered by convection-enhanced delivery (CED) in brain tumor model showed an improved

survival time of more than 2.5 times that of the control group [29]. Similarly liposomes loaded with beta-negative emitters such rhenium-186 and demonstrated promising results when administered by CED in an orthotopic glioblastoma rat model [30]. Lipid nanocapsules loaded with rhenium-188 in a rat orthotopic model showed a significant survival benefit after intratumoral stereotactic injection at day 6 and CED injection at day 12 [31].

A recent approach using radionanoparticles consists of an active targeting approach where the nanoparticles are functionalized and directed against a tumor target. The aim of this active targeting is to optimize the spatial localization of the radioactivity close to the tumor cells. As an example, lipid nanocapsules can be loaded with rhenium-188 and coupled to a monoclonal antibody directed against the CXCR4 antigen. These CXCR4-recognizing immune-nanoparticles irradiate the tumor cells and have been shown to increase efficacy in an orthotopic mouse model. Recurrence for the passive protocol was observed at 65 versus 100 days for the active targeting approach, and this appears to be the most effective therapy with the longest measured time to progression [32].

## **6. Neural stem cells functionalized with radiolabeled nanoparticles**

Neural stem cells (NSCs) are increasingly being used as carriers for targeted delivery of therapeutics to glioblastoma. This requires multimodal dynamic in vivo imaging of NSC in the brain. Such type of technology is in development phase. Cheng et al. reported an innovative strategy for neural stem cell tracking in brain using silica nanoparticles via SPECT [33].  $^{111}\text{In}$  radioisotopes were conjugated to porous silica nanoparticles having large surface area. A series of nanomaterial characterization assays were performed to evaluate the modified mesoporous silica nanoparticles. Loading efficiency and viability of NSCs with  $^{111}\text{In}$ -MSN complex was validated. Radiolabeled NSCs were administered to glioma-bearing mice via intracranial or systemic injection. SPECT and bioluminescence imaging were performed periodically after NSC injection. Histology and immunocytochemistry were performed to endorse the findings.  $^{111}\text{In}$ -MSN complexes showed minimal toxicity to NSCs and adequate in vitro and in vivo stability. Phantom studies establish possibility of mesoporous silica nanoparticles for NSC imaging. It was found that decayed  $^{111}\text{In}$ -MSN complexes exhibited significant fluorescent profiles in preloaded NSCs, thus validating ex vivo data. In vivo, SPECT images reveal actively migrating NSCs toward glioma xenografts in real time after both intracranial and systemic injection. This is in consonance with findings of histology, confocal microscopy and bioluminescence live imaging [33].

## **7. Conclusion**

An urgent requirement for rapid detection and diagnosis of diseases has led to development of contrast agents and imaging techniques. The present challenge is for fast and complete imaging of tissues and lesion categorization that could be obtained by development of nontoxic contrast agents with longer blood circulation time. Nanotechnology provides apt solution to this problem. Nanoparticle based contrast agents have been employed in most biomedical imaging techniques like MRI, fluorescence imaging, CT, ultrasound, PET and SPECT. However, these imaging techniques have certain limitations. These can be overcome by use of multifunctional nanoplatforms to enhance safety, efficacy and theranostic attributes. The WHO 2016 Classification is a major step forward toward a more precise


diagnosis of gliomas and will in the course of time certainly facilitate improved therapeutic management of the patients suffering from these tumors. The paradigm shift is IDH mutation as a marker in diffuse glioma classification and reclassification of glioblastoma. Novel drug delivery approaches have substantially influenced the glioblastoma treatment. There is urgent requirement of smart delivery systems for future therapies targeted to specific cells, dependent on intracellular delivery of agents impermeable to BBB. Polymer implants, convection enhanced delivery and degradable nanoparticles are some of the platform technologies for design of novel methods for treatment of glioblastoma. One strategy to optimize the efficacy of molecularly targeted radionuclide agents is to develop nanoparticle-based targeted delivery systems. An abundance of receptors at the surface of the BBB can be utilized by nanoparticles for enhanced brain uptake by coupling with receptor-specific molecules or analogues. The nanoparticles should be designed to bypass efflux transport systems present at the luminal side (such as MDR1). Instead, nanoparticles could be substrates of transport mechanisms enhancing the passage of specific molecules like GLUT-1, IGF-1, and IGF-2 across the BBB. Radiolabelled nanoparticles seem to be novel promising arsenal for potential neurotheranostics.

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