

Invited Review

Stem cell transplantation in brain tumors:

A new field for molecular imaging?

Nora Sandu, MD,¹⁾ and Bernhard Schaller MD, DSC,²⁾

¹⁾ Department of Neurosurgery, University of Lausanne, Switzerland

²⁾ Departments of Neurosurgery, University of Paris, France

Address of Correspondence

Bernhard Schaller, MD, DSC

University of Oradea

Romania

key-words: neural stem cell - brain tumors - molecular imaging - transplantation - therapy - animal models

UNCORRECTED PROOF

Abstract

Neural stem cells have been proposed as a new and promising treatment modality in different pathologies of the central nervous system, including (malignant) brain tumors. The underlying mechanism remains elusive.

Monitoring these cells is currently done by different modes of molecular imaging, like optical imaging, magnet resonance imaging and positron emission tomography, representing a novel technology for visualizing metabolism and signal transduction to gene expression. In this new context, the microenvironment of (malignant) brain tumors and the blood brain barrier gains increased interest. The authors give a unique overview about the current molecular imaging techniques used in different therapeutic experimental brain tumor models in relation to neural stem cells. Such molecular imaging of gene-engineered neural stem/progenitor cells are currently used to trace the location and temporal level of expression of therapeutic and endogenous genes in malignant brain tumors closing the gap between in vitro and in vivo integrative biology of disease in neural stem cell transplantation.

UNCORRECTED PROOF

Neural stem cells (NSCs) are capable of tremendous migratory potential to areas of pathology in the central nervous system (CNS) [1-2]. When implanted into diseased or injured CNS, NSCs can travel through great distances to and engraft within areas of discrete as well as diffuse neuronal abnormalities [1-2]. Engraftment is often followed by integration into the local neural milieu, accompanied by stable gene expression from the NSCs [1-2]. In addition, the pluripotency of NSCs endows them with the capability to replace diseased CNS tissues in an appropriate manner [1-2]. Recent evidence has also suggested that engrafted exogenous NSCs may have effects on the surrounding microenvironment, such as promoting neuroprotection and/or regeneration of host neural pathways [1-4]. These characteristics of NSCs make them an ideal agent for the treatment of various CNS pathologies, especially brain tumors [1-2].

The use of biology of neural stem cells for brain tumor therapy

Brain tumors are generally difficult to treat because of the unique neuroanatomical location of the lesions next to critical neurovascular structures [1,5,6]. In addition, the extensive infiltrative nature of the tumor cells presents very often a challenge for their effective and total eradication, hence reflecting the high rate of treatment failure and disease recurrence [1]. In addition, normal brain structures are distorted and often destroyed by the growing neoplasm [1]. Even with effective therapy to surgically resect and destroy the neoplastic tissues, the brain is still injured, which often leaves the patient in a debilitated state [1,3,4].

The inherent tumor-tropism of NSCs to primary and invasive tumor foci can be exploited to deliver therapeutics to invasive brain tumor cells in humans [1,2]. NSCs have a tremendous migratory potential to the pathological brain areas. When implanted into a diseased or injured nervous system, NSCs can travel through great distances to and engraft within target areas [1]. Engraftment is often followed by integration into the local neural milieu, accompanied by stable gene expression from the NSCs [1,7]. Use of such strategy of converting prodrug to drug via therapeutic transgenes delivered by immortalized therapeutic NSC lines have shown efficacy in animal models [1,2]. In addition, the pluripotency of NSCs endows them with the capability to replace diseased (neural) tissues in an appropriate manner. Recent evidence has also suggested that engrafted exogenous NSCs

may have effects on the surrounding microenvironment, such as promoting protection and/or regeneration of host neural pathways [1,7]. These characteristics of NSCs would seem to make them as an ideal agents for the treatment of brain tumors [1,2].

The microenvironment of brain tumors

The pathological characteristics of malignant brain tumors are exemplified by an active invasiveness, necrosis and a specialized form of angiogenesis, known as microvascular hyperplasia. Such pathological features are thought to be due to tissue hypoxia. Hypoxia represents therefore a critical aspect of the surrounding microenvironment of brain tumors and generally signifies unfavorable clinical outcome [3,4,8-12]. Cells that are under hypoxic stress can either develop an adaptive response that includes increased rate of glycolysis and angiogenesis or undergo cell death by promoting apoptosis and/or necrosis [3,8,13]. The ability of tumor cells to maintain a balance between an adaptation to hypoxia and cell death is regulated by a family of transcription factors called hypoxia-inducing factors (HIF), which are essential for the regulation of the expression of a large number of hypoxia-responsive genes [13,14]. The hypothesis is that tumor hypoxia would facilitate the likelihood of metastases, tumor recurrence, resistance to chemotherapy and radiotherapy and the invasive potential; all of which culminate in a decrease in patient survival. For this reason, effective targeting of hypoxic areas in brain tumors remains a significant therapeutic challenge [3,4,8-10]. Even so new therapeutic options NSC for tumor-targeted drug delivery show promise in treatment of brain tumors that are refractory to traditional therapies [1,3,4,9], the molecular mechanisms of NSC targeting to hypoxic tumor areas are not well understood [3,4,9]. The unique ability of NSCs to "home in" on tumor cells followed by the delivery of a desired gene product makes the NSC a very promising agent in brain tumor therapy [1]. Cytolytic viruses and genes coding for anti-tumor cytokines, pro-drug converting enzymes, and various neurotrophic factors have all been engineered into engraftable NSCs for delivery to tumors [1]. The current development of such novel treatment strategies for brain tumors based on the transplantation or infusion of cells that can seek out invading tumor cells demand a thorough in vivo monitoring [3-8,15,16]. Especially, NSCs attract great interest as they show a tropism to tumor cells and will even migrate long distances to track down single tumor cells [17,18]. It is thought that the migration of NSCs to neoplastic cells is

mediated by the secretion of chemical factors, such as vascular endothelial growth factor (VEGF) [19], that are involved in the proliferation, growth, and maintenance of tumors. Transplantation of unaltered NSCs has resulted in a prolonged survival of animals with experimental tumors [20], but the insertion of anti-tumor cytokine genes (e.g., IL-12) or proapoptotic genes (e.g., TRAIL) further improves the efficiency of this approach [21]. Little is known about how these cells exert their beneficial effects in vivo. Despite contrary evidence from preclinical studies, there is some concern that transplantation of stem cells could further exacerbate tumor formation as there is mounting evidence that brain tumors are potentially caused by a single NSCs that did not differentiate [22]. The ability to monitor cell therapy in vivo is therefore desirable to potentially provide more control over the activity of NSCs [23]. One possibility is that stem cells will be engineered with a suicide gene [24] that could be activated if transplanted cells would not behave in a therapeutic manner.

The problem of the blood-brain barrier

One hallmark of malignant brain tumors is seen in the disruptions of the normal homeostasis between angiogenic and antiangiogenic factors. The resulting vasculature is characterized by tortuous vessels that feature disruptions in their structural integrity, increased leakiness, uneven focal thickness, and arteriovenous shunts not seen in normal brain vasculature; also changing also the physiology of the blood-brain barrier (BBB). However, brain delivery of therapeutic cells is physiologically limited by the BBB which remains one of the recognized rate-limiting steps [25,26]. As the BBB limitation is more and more acknowledged, many innovative surgical and pharmacological strategies have been developed to circumvent it. Since its inception by Rapoport in 1972, pre-clinical studies have provided important information on the extent of BBB permeation [27]. Although the BBB is frequently leaky in the centre of malignant brain tumors, the well-vascularized actively proliferating edge of the tumor, has been shown to have variable and complex barrier integrity [27]. Current experimental data show that brain penetration of peripherally circulating cells - like stem cells or immune cells targeting the CNS - requires BBB disruption and it is limited to the immediate perivascular space. In addition, it has demonstrated that oncolytic virus treatment of rat gliomas is associated with a significant increase in the

permeability of the tumor vasculature and consequently with significant increases in tumor inflammation and leukocyte infiltration [28].

Different imaging modalities

Molecular imaging has given investigators a high-throughput, inexpensive, and sensitive means for tracking *in vivo* cell proliferation over days, weeks, and even months [29,30] (see *Table 1*). This advancement has significantly increased the understanding of the spatio-temporal kinetics of NSCs engraftment, localization, viability and proliferation in living subjects [29-31]. A major advance in molecular imaging has been the extension of noninvasive reporter gene assays from molecular and cellular biology into *in vivo* multi-modality imaging platforms [15,29,30]. The ability to control the activity of transplanted cells presupposes that it is possible to visualize the presence, location, and activity of stem cells *in vivo*. An innovative approach to harness the respective strengths of various imaging platforms is the creation and use of a fusion reporter construct composed [31]. These reporter genes, under control of engineered promoters and enhancers that take advantage of the host cells transcriptional machinery, are introduced into cells using a variety of vector and non-vector methods [5]. Once in the cell, reporter genes can be transcribed either constitutively or only under specific biological or cellular conditions, depending on the type of promoter used [32,29,30]. Transcription and translation of reporter genes into bioactive proteins is then detected with sensitive, noninvasive instrumentation (e.g., CCD cameras) using signal-generating probes such as D-luciferin for optical imaging [30]. To avoid the need for excitatory light to track stem cells *in vivo* as is required for fluorescence imaging, bioluminescence reporter gene imaging systems require only an exogenously administered probe to induce light emission that can be monitored by optical imaging [30]. Stably transduced cells that carry the reporter construct within their chromosomal DNA will pass the reporter construct DNA to daughter cells, allowing for longitudinal monitoring NSCs survival and proliferation *in vivo*. However, the clinical utility of these imaging modalities is limited by poor tissue penetration and low spatial resolution, making them impractical for use in patient trials. In the context of NSCs-based therapies, magnetic resonance imaging (MRI) can be used both to non-invasively follow dynamic spatio-temporal patterns of NSC tumor targeting allowing for the optimization of treatment strategies and to assess efficacy

of the therapy [33]. Clinical MRI at 3 Tesla, however, has high spatial resolution with excellent soft tissue contrast for non-invasive, dynamic *in vivo* assessment of cellular trafficking at multiple time points [33]. Research on MRI cellular tracking is rapidly expanding, and many studies have been published during the last decade. Relevant studies include mouse or rat-derived stem or progenitor cells transplanted into the brain, spinal cord or vasculature of laboratory animals using strongly T1-weighted paramagnetic contrast labels such as gadolinium [34,35], and using T2 and T2*-weighted super-paramagnetic iron oxide nanoparticles [36]. Although magnetic resonance imaging (MRI) has been extensively used to track cells repeatedly *in vivo* [37], it is the higher specificity of positron emission tomography (PET) ligands and its ability to detect reporter genes that are attractive features to develop long-term *in vivo* monitoring of transplanted cells. Such molecular imaging has expanded its role from the research domain into clinical application for neurosciences [6,32,38]. More recently, PET is being used as a clinical molecular imaging tool in neurosurgery. For cellular imaging by MRI, the contrast agents used to detect transplanted cells from the background of the brain are incorporated into the cell *in vitro* before transplantation. The presence of the contrast agent inside the cell therefore allows the prolonged visualization of grafted cells on MRI scans. However, the continued presence of the contrast agent inside the cell can also affect cellular functions [37]. Although this approach has been demonstrated with PET/single photon emission computed tomography (SPECT) ligands and allowed monitoring for up to 14 days [39], it is the short half-life of PET ligands that compromises the long-term visualization of cells. A more promising method is to engineer reporter genes inside the cells before grafting and to systemically inject the PET ligand to detect transplanted cells [40]. The use of reporter genes avoids most issues pertaining to the long-term effects the contrast agent might exert onto cellular functions. The repeated application of a contrast agent complements a flexible imaging approach that can target various relevant targets, such as 2-deoxy-2 [(18)F] fluoro-D-glucose (FDG)-PET to investigate tumor metabolism. An important mechanism to transport FDG into the transformed cell is based upon the action of glucose transporter proteins; furthermore, highly active hexokinase bound to tumor mitochondria helps to trap FDG into the cell. In addition, enhanced FDG uptake may be due to relative hypoxia in brain tumor masses, which activates the anaerobic glycolytic pathway [41]. Especially for the continued assessment of tumor evaluation in response to treatment, it is important to be able to assess the

UNCORRECTED PROOF

malignancy of the tumor noninvasively at various time points and for these reasons it seems that quantitative instead of semiquantitative assessment of tumor metabolism using FDG-PET may be preferable [42,43]. The main concerns with this approach regard the potential immunogenic properties of reporter genes that might lead to graft rejection or the down-regulation of the reporter gene abolishing graft detection. Unfortunately, at present little research is dedicated to the development of PET techniques that would allow the continued assessment of cell therapy. The use of radioligands to a reporter gene will provide maximum flexibility and further integration into a wider molecular imaging strategy of brain tumors. Apart from in vivo monitoring, PET will also be instrumental to gain a greater mechanistic understanding of how cell therapy exerts its therapeutic effects. As stem cells can be engineered to express particular genes and serve as Bsmart delivery vehicles [44], their effects on tumor cells could be through inhibition of angiogenesis, induction of apoptosis in tumor cells, or induction of differentiation of tumor cells. Being able to study how stem cells will alter the molecular composition of the tumor will allow an in vivo monitoring of the therapeutic efficacy of cell therapy. Additionally, PET imaging allows the serial in vivo assessment of the inflammatory and immunological response by visualizing, for instance, a T-cell response [45]. Modulation of the immune response could provide additional benefit to combat tumor cells. PET imaging is at present the only in vivo technology that can assess these various molecular aspects of stem cell efficacy and lead to a mechanistic understanding of how stem cells attack tumor cells. PET is already used clinically to evaluate stem cell therapy for lymphoma. Simple FDG-PET leads to a 92% positive and 88% negative prediction of treatment outcome and correlates stronger with disease-free survival than computer tomography [46]. FDG-PET can therefore already serve an exquisite role in patient selection and help to determine which conditions are most suitable for stem cell therapy [47,48]. Serial quantitative PET will provide a means to monitor treatment progression [49] and afford a refinement of dosage and integration with other therapies. Imaging of brain tumors already commonly uses FDG-PET. Translation of cell therapy for brain tumors will be best suited in conditions where imaging technology can already provide a robust baseline assessment that would allow patient selection. As the clinical translation of stem cell therapy for brain tumors progresses [49], preclinical validation studies will need to rely more on molecular imaging to ensure the safety and efficacy of this promising therapy. A growing sophistication of molecular imaging will allow increasingly sophisticated therapeutic

approaches being envisaged and monitored in vivo [50-53]. The multitude of therapeutic effects that can be exerted by unaltered and genetically engineered stem cells will need to be determined in terms of their efficacy in relation to the molecular composition of the tumor. Being able to select patients at an early stage based on a molecular signature of the entire tumor will allow the clinicians to determine what strategy might be best suited to remove the neoplastic cells. Although PET is commonly used in pre-clinical and clinical studies for visualization of various tumors and drug interactions and for understanding tumor metabolism with high specificity, its relatively low spatial, its radiation dose, and relatively short-term signal production make it a non-ideal technique for clinical tracking of cells to tumors, which requires extended periods of observation. Further developments in molecular imaging will therefore provide the diagnostic framework of a molecular medicine of brain tumors [6].

From bench-to-bedside

The current research under monitoring by molecular imaging is helping to understand stem cells and stem cell regulation and in turn this will help to develop novel therapies to eliminate (malignant) brain tumors. From the present status of therapeutic developments in neuro-oncology it can be expected that a sufficient number of drug targets emerge which can be exploited by means of interstitial or intracavitary delivery, which are not neurotoxic and which may even be imaged in their action with the new molecular imaging modalities [59]. Convection enhanced delivery, conditionally replicating oncolytic viruses and motile, genetically engineered neural stem cells all seem to fulfill the distribution requirements which an effective therapeutic for (malignant) brain tumors will need to overcome the very limited efficacy which surgery, conventional chemotherapy and radiation have to offer. Whereas the genomics based discovery approaches are not specific for neuro-oncology, the development of delivery strategies is highly specific for the CNS, thus creating a unique set of organ and disease specific therapies.

UNCORRECTED PROOF

References

1. **Yip S, Aboody KS, Burns M, et al.** Neural stem cell biology may be well suited for improving brain-tumor therapies. *Cancer J* 2003; 9:189-204.
2. **Thu MS, Najbauer J, Kendall SE, et al.** Iron labelling and pre-clinical MRI visualization of therapeutic human neural stem cell in a murine glioma model. *PLoSOne* 2009; 4:e7218.
3. **Schaller B.** Neuroprotection in brain tumors. Good sense or nonsense from the pathophysiological viewpoint? *Nervenarzt* 2003; 74:134-6.
4. **Schaller BJ, Buchfelder M.** Neuroprotection in primary brain tumors: Sense or nonsense? *Expert Rev Neurother* 2006; 6:723-30.
5. **Schaller BJ, Cornelius JF, Sandu N, et al.** Molecular imaging of brain tumors: Personal experience and review of the literature. *Curr Mol Med* 2008; 8:711-26.
6. **Schaller B, Cornelius JF, Sandu N.** Molecular medicine successes in neuroscience. *Mol Med* 2008;14:361-4.
7. **Kosztowski T, Zaidi HA, Quinones-Hinojosa A.** Application of neural and mesenchymal stem cells in the treatment of gliomas. *Expert Rev Anticancer Ther* 2009; 9:597-612.
8. **Schaller B.** Influences of brain tumor-associated pH changes and hypoxia on epileptogenesis. *Acta Neurol Scand* 2005; 111:75-83.
9. **Zhao P, Najbauer J, Garcia E, et al.** Neural stem cell tropism to glioma: critical role of tumor hypoxia. *Mol Cancer Res* 2008; 6:1819-29.
10. **Matuski E, Wajgt A, Janowska J, et al.** Cell adhesion markers in ischaemic stroke patients: Correlation with clinical outcome and comparison with primary autoimmune disease. *Arch Med Sci* 2009; 5:182-189.
11. **Schaller BJ.** The role of endothelin in stroke: Experimental data and underlying pathophysiology. *Arch Med Sci* 2006; 2:146-158.
12. **Schaller B.** Ischemic preconditioning as induction of ischemic tolerance after transient ischemic attacks in human brain: its clinical relevance. *Neurosci Let* 2005; 377:206-11.
13. **Oliver L, Olivier C, Marhuenda FB, et al.** Hypoxia and the malignant glioma microenvironment: Regulation and implications for therapy. *Curr Mol Pharmacol* 2009; 2:263-84.
14. **Schaller B, Graf R.** Cerebral ischemia and reperfusion: The pathophysiologic concept as a basis for clinical therapy. *J Cereb Blood Flow Metab* 2004; 24:351-71.
15. **Schaller BJ, Modo M, Buchfelder M.** Molecular imaging of brain tumors: A bridge between clinical and molecular medicine? *Mol Imaging Biol* 2007; 9:60-71.
16. **Schaller B, Cornelius JF, Sandu N, et al.** Oxygen-conserving reflexes of the brain: the current molecular knowledge. *J Cell Mol Med* 2009; 13:644-7.
17. **Aboody K, Brown A, Rainov NG, et al.** Neural stem cells display extensive tropism for pathology in adult brain: Evidence from intracranial gliomas. *Proc Natl Acad Sci U S A* 2000; 97:12846-12851.
18. **Benedetti S, Pirola B, Pilo B, et al.** Gene therapy of experimental brain tumors using neural progenitor cells. *Nat Med* 2000; 6:447-450.
19. **Schmidt NO, Przylecki W, Yang W, et al.** Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. *Neoplasia* 2005; 7:623-629.
20. **Staflin K, Honeth G, Kalliomaki S, et al.** Neural progenitor cell lines rat inhibit tumor growth in vivo. *Cancer Res* 2004; 64:5347-5354.
21. **Ethesham M, Kabos P, Kabosova A, et al.** The use of interleukin 12-secreting neural stem cells for the treatment of intracranial glioma. *Cancer Res* 2002; 62:5657-5663.

22. **Fomchenko EI, Holland EC.** Stem cells and brain cancer. *Exp Cell Res* 2005; 306:323-329.
23. **Modo M, Roberts TJ, Sandhu JK, Williams SCR.** In vivo monitoring of cellular transplants by magnetic resonance imaging and positron emission tomography. *Expert Opin Bio Ther* 2004; 4:145-155.
24. **Zlokovic BV, Apuzzo ML.** Cellular and molecular neurosurgery: Pathways from concept to reality VPart 1: Target disorders and concept approaches to gene therapy of the central nervous system. *Neurosurgery* 1997; 40:789-803.
25. **Marchi N, Teng Q, Nguyen MT, et al.** Multimodal investigations of trans-endothelial cell trafficking under condition of disrupted blood-brain barrier integrity. *BMC Neurosci* 2010; 9:11-34.
26. **Gera A, Steinberg GK, Guzman R.** In vivo neural stem cell imaging: Current modalities and future directions. *Regen Med* 2010; 5:73-86.
27. **Rapoport SI, Hori M, Klatzo I.** Testing of a hypothesis for osmotic opening of the blood-brain barrier. *Am J Physiol* 1972; 223:323-31.
28. **Kurozumi K, Hardcastle J, Thakur R, et al.** Effect of tumor microenvironment modulation on the efficacy of oncolytic virus therapy. *J Natl Cancer Inst* 2007; 99:1768-81.
29. **Bradbury MS, Panagiotakos G, Chan BK, et al.** Optical bioluminescence imaging of human ES cell progeny in the rodent CNS. *J Neurochem* 2007; 102:2029-39.
30. **Wilson K, Yu J, Lee A, et al.** In vitro and in vivo bioluminescence reporter gene imaging of human embryonic stem cells. *J Vis Exp* 2008; (14) pii: 740.
31. **Narsinh KH, Cao F, Wu JC.** Molecular imaging of human embryonic stem cells. *Methods Mol Biol* 2009; 515:13-32.
32. **Jacobs AH, Li H, Winkeler A, et al.** PET-based molecular imaging in neuroscience. *Eur J Nucl Med Mol Imaging* 2003; 30:1051-65.
33. **Thu MS, Najbauer J, Kendall SE, et al.** Iron labeling and pre-clinical MRI visualization of therapeutic human neural stem cells in a murine glioma model. *PLoS* 2009; 4(9):e7218.
34. **Modo M, Cash D, Mellodew K, et al.** Tracking transplanted stem cell migration using bifunctional, contrast agent-enhanced, magnetic resonance imaging. *Neuroimage* 2002; 17:803-811.
35. **Modo M, Mellodew K, Cash D, et al.** Mapping transplanted stem cell migration after a stroke: A serial, in vivo magnetic resonance imaging study. *Neuroimage* 2004; 21:311-317.
36. **Corot C, Robert P, Idee JM, et al.** Recent advances in iron oxide nanocrystal technology for medical imaging. *Adv Drug Deliv Rev* 2006; 58:1471-1504.
37. **Modo M, Hoehn M, Bulte J.** Cellular MR imaging. *Mol Imaging* 2005; 4:1Y21.
38. **Schaller BJ.** Strategies for molecular imaging dementia and neurodegenerative diseases. *Neuropsychiatr Dis Treat* 2008; 4:585-612.
39. **Chin BB, Nakamoto Y, Bulte JW, et al.** ¹¹¹In oxine labeled mesenchymal stem cell SPET after intravenous administration in myocardial infarction. *Nucl Med Commun* 2003; 24:1149-1154.
40. **Jacobs A, Braulich I, Graf R, et al.** Quantitative kinetics of (¹²⁴I)FIAU in cat and man. *J Nucl Med* 2001; 42:467-475.
41. **Pauwels EK, Ribeiro MJ, Stoot JH, et al.** FDG accumulation and tumor biology. *Nucl Med Biol* 1998; 25:317-22.
42. **Weber WA, Schwaiger M, Avril N.** Quantitative assessment of tumor metabolism using FDG-PET imaging. *Nucl Med Biol* 2000; 27:683-7.
43. **Schaller B.** Usefulness of positron emission tomography in diagnosis and treatment follow-up of brain tumors. *Neurobiol Dis* 2004; 15:437-48.

44. **Shah K, Hsich G, Breakefield XO.** Neural precursor cells and their role in neuro-oncology. *Dev Neurosci* 2004; 26:118-130.
45. **Koehne G, Doubrovin M, Doubrovina E, et al.** Serial in vivo imaging of targeted migration of human HSV-TK-transduced antigen-specific lymphocytes. *Nat Biotechnol* 2003; 21:405-413.
46. **Filmont JE, Czernin J, Yap C, et al.** Value of F-18 fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation. *Chest* 2003; 124:608-613.
47. **Becherer A, Mitterbauer M, Jaeger U, et al.** Positron emission tomography with [18F]2-fluoro-D-2-deoxyglucose (FDG-PET) predicts relapse of malignant lymphoma after high-dose therapy with stem cell transplantation. *Leukemia* 2002; 16:260-267.
48. **Spaepen K, Stroobants S, Dupont P, et al.** Prognostic value of pretransplantation positron emission tomography using fluorine 18- fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. *Blood* 2003; 102:53-59.
49. **Cremerius U, Fabry U, Wildberger JE, et al.** Pre-transplant positron emission tomography (PET) using fluorine-18-fluoro-deoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkins lymphoma. *Bone Marrow Transplant* 2002; 30:103-111.
50. **Su H, Forbes A, Gambhir SS, et al.** Quantization of cell number by a positron emission tomography reporter gene strategy. *Mol Imaging Biol* 2004; 6:139-148.
51. **Brower V.** Search and destroy: Recent research exploits adult stem cells_ attraction to cancer. *J Natl Cancer Inst* 2005; 97:414-416.
52. **De Witte O, Lefranc F, Levivier M, et al.** FDG-PET as a prognostic factor in high-grade astrocytoma. *J Neuro-oncol* 2000; 49:157-163.
53. **Padma MV, Said S, Jacobs M, et al.** Prediction of pathology and survival by FDG PET in gliomas. *J Neuro-oncol* 2003; 64:227-237.
54. **Shah K, Hingtgen S, Kasmieh R, et al.** Biomodal viral vectors and in vivo imaging reveal the fate of human neural stem cells in experimental glioma model. *J Neurosci* 2008; 28:4406-13.
55. **Brekke C, Williams SC, Price J, et al.** Cellular multiparametric MRI of neural stem cell therapy in a rat glioma model. *Neuroimage* 2007; 37:769-82.
56. **Anderson SA, Glod J, Arbab AS, et al.** Noninvasive MR imaging of magnetically labelled stem cells to directly identify neovasculature in a glioma model. *Blood* 2005; 105:420-5.
57. **Hata N, Shinojima N, Gumin J, et al.** Platelet-derived growth factor BB mediates the tropism of human mesenchymal stem cells for malignant gliomas. *Neurosurgery* 2010; 66:144-56.
58. **Miletic H, Fischer Y, Litwak S, et al.** Bystander killing of malignant glioma by bone marrow-derived tumor-infiltrating progenitor cells expressing a suicide gene. *Mol Ther* 2007; 15:1373-81.
59. **Shah K, Weissleder R.** Molecular optical imaging: Applications leading to the development of present day therapeutics. *NeuroRx* 2005; 2:215-25.

Table 1: Representative examples of different molecular imaging modalities in experimental brain tumor models related to neural stem cells.

Autor	Imaging	Modell	Stem Cell	Monitoring
Hata N, et al. [57], 2010 Shah K et al. [54], 2008	optical optical	clone mouse	mesenchymal neural	incorporation migration, survival
Brekke et al. [55], 2007 Anderson et al. [56], 2005	MRI MRI	rat mouse	neural bone-marrow	migration, therapeutic efficacy incorporation
Miletec H, et al. [58], 2007	PET/MRI	rat	mesenchymal	therapeutic efficacy

Legend: MRI - magnetic resonance imaging; PET - positron emission tomography

UNCORRECTED PROOF