MATHEWS Open Access Journals

ISSN: 2474-6797

Research Article | Mathews Journal of Cancer Science

Using Immune Cells for Transport of Therapeutics to Brain Tumors

Elena V. Batrakova[1]

[1]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill.

Corresponding Author: Elena V. Batrakova, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, **Tel:** +919-537-3712; **Email:** batrakov@email.unc.edu

Received Date: 08 Dec 2016

Accepted Date: 04 Jan 2016

Published Date:

Citation: Batrakova EV. (2016). Using Immune Cells for Transport of Therapeutics to Brain Tumors. M J Canc. 2(1): 008.

ABSTRACT

Glioblastoma (GBM) is the most common and aggressive form of primary brain tumor. Currently, no curative therapies are available for GMB. Merely palliative treatments only prolong survival 12-14 months after diagnosis. One of the greatest obstacles to GBM therapy is the blood-brain barrier (BBB) that severely limits the brain penetration of more than 95% of all promising therapeutics. However, classes of immune cells (monocytes and macrophages), as well as stem cells have an extraordinary ability to cross the BBB due to enhanced margination and extravasation. These immune cells can be genetically modified to express diagnostic markers or secreted therapeutic molecules directed against death receptors on GBM cells. Furthermore, exosomes released from immune cells can be loaded with cytotoxic agents and utilized for the drug transport across the BBB. Capitalizing on the powerful tumor-focused homing of immune cells, this approach directly addresses the critical deficiencies in traversing the BBB and tumor-specific accumulation plaguing current anti-GBM therapies. Noteworthy, beside the treatment of primary brain tumor, eradication of brain metastasis may also be addressed by means of cells-mediated drug delivery. In this review, we discuss new drug delivery systems that utilize living cells for drug carriage to the brain tumors.

INTRODUCTION

The use of living cells for active targeted drug delivery to brain tumors is a new concept that has a potential to open different therapeutic avenues within the central nervous system (CNS) [1]. The current standard of care for glioblastoma multiforme (GBM) is surgery and chemo-radiation therapy, yet this approach is grossly inadequate and patient mortality remains high universally. Cell-based therapy is an innovative approach that is not only a departure from traditional systemic or forced-infusion drug delivery, but also alters kinetics to provide prolonged and focused drug delivery to tumors. Using inflammatory response cells enables targeted drug transport and prolonged circulation times, along with reductions in cell and tissue toxicities. In addition, these cells are capable of cell-to-cell transmission of their cargo that improves therapeutic outcomes. Noteworthy, a proper differentiation of drug carriers into particular subtypes may further boost the therapeutic efficiency of cell-based drug formulations.

To achieve anti-tumor efficacy, immune cells should be loaded with therapeutics. However, drug loading in cell-carriers is often low, drugs must be efficiently unloaded at the tumor, and drugs must not affect the survival or migration of the carrier [2]. This has created a bottleneck for cell-based cancer therapy. To this end, protein-based therapies that are the ideal drug for cell-mediate delivery to GBM have been recently developed [3-7]. Thus cell-based carriers "armed" with the targeted anti-cancer proteins could represent a novel and highly effective therapy for GBM.

Another approach is based on using exosomes, released from immune cells. These nano-sized naturally occurred extracellular vesicles can be loaded with cytotoxic drugs and then used for drug transport to the brain tumors. Reflective of their origin, these nanocarriers can cross the blood-brain barrier (BBB) and target cancer cells in the brain. Such systems for drug carriage and targeted release represent a novel strategy that can be applied to a spectrum of human disorders.

Brain Inflammation Targeted by Immune Cells

The drug targeting to sites of tissue injury, tumor or infection is one of the main goals for successful pharmaceutics. Using inflammatory-response cells enables targeted drug transport

and prolonged circulation times, along with reductions in toxicities in non-inflammatory cells and tissue. Immune cells are highly mobile, capable of travel toward inflammation signals with the ability to cross the endothelial wall due to their increased margination and extravasation [8]. Importantly, the numbers of cell-carriers that can penetrate the BBB and reach the disease site is crucial for the therapeutic efficacy of cell-mediated formulations. Therefore, identification suitable of cellular sources and optimization of cell transport are essential, when developing a cell-based delivery system.

It is well recognized that both endogenous and exogenous macrophages robustly migrate from the systemic circulation, rapidly traverse the BBB and accumulate in large numbers in the GBM through their natural role as part of the body's anti-tumor defense [9, 10]. Macrophages are the predominant immune cells infiltrating gliomas [11]. Hypoxia is widespread in malignant human tumors due to their poorly organized vasculature. The cytokines released by tumor cells in response to hypoxia and other physiological stresses usually attract immune cells [9, 12]. This may allow them to target micro-metastatic GBM sites regardless of their distance from the primary tumor. This migratory activity allows utilizing them for the drug carriage and decrease severe side effects of antineoplastic agents. It was reported that the cells migrate via the processes known as diapedesis and chemotaxis, and cross the BBB causing the barrier breakdown [13-17]. Interestingly, blood-circulating monocytes are capable of crossing the BBB, and then differentiating into microglia at the sites of neurodegeneration [18, 19]. Reactive oxygen species produced in the disease site further increase BBB permeability [20]. Although an intraparenchymal injection of stem cells has traditionally been used for cell-based GBM therapy, these intrinsic properties of macrophages offer distinct advantages in the attractive signal, carrier accumulation, and route of administration [21].

A robust migration of immune cells, monocytes and macrophages to the inflamed brain areas was shown in several studies [6, 22-28]. Thus, studies using hematopoetic stem cells transplanted into lethally irradiated animals demonstrated that blood circulating monocytes can be recruted to inflammatory sites, and differentiated into resident macrophages and macroglia cells in the brain [29, 30]. This uniquely supports macrophages for exploitation as effective drug carriers to GBM.

Typically, bone marrow-derived progenitor cells can be isolated from donor animals, differentiated in culture to produce specific type of carrier cells, loaded or genetically modified to produce a therapeutic agent, and adoptively transferred to the animal with a model disease [31]. A significant brain transport of systemically-administered macrophages was demonstrated in several studies using nice with brain inflammation [24, 32-34]. In contrast, in healthy mice without brain inflammation, a majority of systemically administered macrophages became trapped in peripheral organs such as lungs, liver, and spleen and then cleared out [35]. The localized intracranial intoxications provided a rear opportunity to analyze the specific targeting of the cell-mediated drug delivery into affected brain sub-regions using the un-injected contralateral brain hemisphere as an internal control. Thus, bone marrow-derived macrophages (BMM) increased drug transport only to the ipsilateral hemisphere, but not in the contralateral healthy hemisphere [24]. Images obtained by epifluorescence in vivo microscopy in mice with thin-skull cranial windows revealed three stages of macrophage translocation across the BBB to the inflamed brain [24]. Loaded BMM were first seen to move along the microvessels (immediately following injection), then adhered to the endothelial wall (4 hours post-injection), and finally translocated across the BBB into the parenchyma (24 hours post-injection).

Neural stem cells (NSCs) can also be used as drug delivery vehicles for gene therapy in the CNS [6, 22, 26-28, 36]. NSCs possess a set of several unique properties, which make them ideally suited for the gene and drug delivery to treat both neurodegenerative disorders, and cancer. These properties include: 1) a relative ease of isolation; 2) ability to differentiate into a wide variety of functional cell types; 3) ability to be extensively expanded in culture without loss of differentiative capacity; 4) hypo immunogenicity; 5) pronounced anti-inflammatory properties; and 6) ability to home to damaged tissues, tumors, and metastases. Indeed, these cells are highly migratory and transfer to areas of brain pathology including ischemic and neoplastic brain lesions that are commonly present in brain cancer. How the mobility of stem cells are directed, is not well understood, although NSCs express a wide variety of receptors that should enable them to respond to many chemotactic signals present in brain pathologies [22]. Noteworthy, capability of stem cells to penetrate far from vasculature into diseased tissues is of importance, especially in case of irregular, damaged, or obliterated tumor micro vessels.

A migration and characterization of therapeutic stem cells was evaluated, when they were labelled with diagnostically active compounds, such as iron oxides for magnetic resonance imaging, indium-111 for single-photon emission computed tomography, or quantum dots for fluorescence imaging techniques [37-39]. In some cases, the cell-carriers were genetically modified to express fluorescent or luminescent markers. For example, a macroscopic migration of NSCs to intracranial GBM expressing firefly luciferase (Fluc) was reported by sev-

eral investigators [6, 40-42]. Various routes of cell administration were studied [40]. Indeed, the intraventricular and intracranial implantation of the cell-carriers provided the highest percentage (3.3%) of NSCs homing into the tumor. Nevertheless, a significant amount of the NSCs (1.4%) also reached the GBM following intravenous injections [40]. Noteworthy, no NSCs were found in the brain tumors following an intraperitoneal administration. Furthermore, intranasal (i.n.) route of administration of genetically-modified NSCs was evaluated as an alternative, non-invasive, and direct passage for the GBM treatment [43]. Considerable numbers of NSCs were accumulated specifically at the intracerebral glioma site after i.n. delivery. In addition, systemic distribution of the cells via the microvasculature of the nasal mucosa was reported [43]. A high-resolution intravital microscopy in mice with intracranial windows revealed that NSCs selectively migrate towards GBM deposits by day 5 and accumulated in the tumor by day 10 6. Remarkable, about 75% of engrafted NSCs survive longer than 10 days in the presence of tumors [44]. However, the interpretation of cell tracking images has been hampered by the fact that when the transplanted cells die, macrophages or other neighbouring cells often take up the labelling material and the signal remains in the tissue, yielding a false-positive result that the transplanted cells are still resident in the tissue [44]. In total, 14.4 ± 2% of the intranasally administered NSCs were able to enter the intracerebral compartment and displayed a targeted tumor tropism [44]. These studies demonstrated the potential of NSCs as therapeutically effective delivery vehicles for the treatment of gliomas.

Finally, exosomes released from macrophages were also shown to cross the BBB and reach brain inflammed areas [45]. Thus, a wide distribution of exosomes throughout the brain, in particular, cerebral frontal cortex, central sulcus, and cerebellum was achieved upon the i.n. administration of fluorescently-labeled exosomes released from macrophages ex vitro. Confocal images showed diffuse fluorescent staining throughout the brain tissues along with the stained vesicular compartments localized predominantly in perinuclear regions [46]. For the purpose of brain tumor therapy, exosomes possess an extraordinary ability to interact with and accumulate in target cancer cells. Furthermore, the ability of exosomes released from macrophages to target cancer cells in vivo was demonstrated in murine Lewis Lung Carcinoma pulmonary metastases model [47]. Intriguely, a nearly complete co-localization of airway-delivered exosomes with tumor metastases was reported. It was hypothesized that macrophage-released exosomes are likely to have specific proteins on their surface, which might allow for their preferential accumulation in cancer cells. Thus, extracellular vesicles were shown to express lymphocyte function associated antigen-1 (LFA-1) that can bind endothelial cell adhesion molecules (CAMs), overexpressed on activated endothelial cells, such as found in tumors [48]. Furthermore, it is known that exosome-mediated cell-to-cell communication is key in the battle between cancer and the immune system [49]. Thus, Parolini et al. [49] showed that exosome fusion with target cells occurs more efficiently under acidic conditions, implying that exosomes may be taken up preferentially by tumors (which have an acidic microenvironment) rather than the surrounding healthy tissue.

Antitumor efficacy of cell-based therapies

Although significant amount of immune-response cells (macrophages, myeloid dendritic cells (DCs), plasmacytoid DCs, and T cells) infiltrate gliomas, they show lack of effective immune activation against malignant human gliomas [11]. Therefore, these cells should be modified/loaded to release antitumor agents for anticancer therapy.

The first reports suggesting that living cells may have a therapeutic potential for targeted drug delivery across biological barriers were published in 1980s [50, 51]. In particular, transport of peripheral blood neutrophils (PMNs), loaded with fluorescently of radioactively-labeled liposomes, was studied across confluent Madin Darby canine kidney (MDCK) epithelial cell monolayers in vitro [51]. Transmission electron micrographs demonstrated that, in response to the chemotactic signal, PMNs adhered to the apical surface of MDCK cells, emigrated across the MDCK cell layer, passed through the 3-micron pores in the polycarbonate membrane, and finally, appeared in the bottom well. Noteworthy, most, if not all, of the migrated PMNs were positive for a fluorescent dye, Lucifer yellow that was used to stain liposomes, suggesting these cells carry liposomes across the MDCK cell layer, and therefore can be used for the transport of loaded Nano formulated therapeutics across biological barriers. Since then, different studies have demonstrated the successful cell-mediated delivery of therapeutics to the inflamed brain tissues [6, 22-28].

The inherent tumor-tropism of NSCs to primary and invasive tumor foci was exploited to deliver cytotoxic therapies to primary brain tumours, specifically GMB [4-6, 40, 41, 44, 52-57]. To provide antitumor activity, NSCs are engineered to express tumor-specific cytotoxic biomolecules, such as tumor necrosis factor apoptosis inducing ligand (TRAIL) and secreteable TRAIL (S-TRAIL); or prodrug-converting enzymes, such as carboxyl esterase. These cell-carriers have been already shown to home to and eradicate GBMs in preclinical mouse models [57, 58]. Furthermore, a successful targeting of breast to brain metastatic tumors with genetically-modified NSCs was reported [59, 60]. Metastatic brain tumors are the most commonly

observed intracranial tumors frequently occurring in patients with metastatic cancers, particularly from those of the lung, breast, and skin [61]. Similar to primary brain tumors, one of the major causes of therapeutic failure in metastatic brain cancer is the insufficient delivery of drugs across the BBB. In this regard, systemically administered or implanted in the tumor resection cavity engineered S-TRAIL-NSCs efficiently suppressed metastatic tumour growth and prolonged the survival of mice bearing metastatic breast tumours. Moreover, the incorporation of pro-drug converting enzyme, herpes simplex virus thymidine kinase, into therapeutic S-TRAIL secreting stem cells allowed their eradication post-tumour treatment [60].

Using monocytes/macrophages for drug delivery to the brain was also reported [62]. In this work, an additional driving force toward the disease site can be provided by the application of local magnetic fields, when cell-carriers are loaded with drug-incorporated magnetic nanoparticles. Specifically, magnetic liposomes were vectorized with RGD peptide (i.e. small peptide domain Arg-Gly-Asp) utilized for selective binding by monocytes and neutrophils expressing integrin receptors on their surface. Then, albino rats with brain inflammation (induced by intrastratial microinjection of human recombinant interleukin-1β, IL-1β) received intravenous injections of RGD-coated magnetic liposomes, or uncoated magnetic liposomes, or non-magnetic liposomes as a control. The local magnetic field was applied near the brain of the injected rats. Magnetic liposomes demonstrated a 6.6 - fold increase in brain levels compared with non-magnetic carriers, when local magnetic field was applied. This suggests that drug-loaded magnetic liposomes were taken by blood monocytes/neutrophils and then guided to target tissue brain sites. Other innovative features of macrophage-mediated drug delivery include: (i) facilitated transfer of therapeutic proteins from cell-carriers to target cells through macrophage bridging conduits, filopodia and lamellipodia; and (ii) secretion by macrophages therapeutic proteins incorporated in exosomes, specialized membranous vesicles, which allow the efficient accumulation in target cells [63, 64]. This process was shown to be accomplished by facilitated membrane interactions and fusion due to expression of adhesive proteins and specific vector ligands (tetraspanins and integrins) on the surface of exosomes. Regarding the cell-carriers, using classically-activated M1 macrophages is a novel strategy that may further enhance therapeutic effect of anti-neoplastic agent [3].

Another approach for tumor therapy is using T lymphocytes, which can recognize and destroy malignant cells [63]. In this study, T cells were genetically modified to stably express antibody binding domains on their surface that confer novel antigen specificities that are major histocompatibility complex (MHC)–independent. The engineered T cells expanded more than a thousand-fold in vivo, continued to express functional chimeric antigen receptors (CARs) at high levels for at least six months. The treatment was performed in patients with advanced chronic lymphocytic leukemia (CLL), and resulted in a complete remission, in two of three patients. On average, each infused CAR-expressing T cell was calculated to eradicate at least 1000 CLL cells. This approach can be also applied for the treatment of brain tumors, as it is known that T cells can cross the BBB in response to brain inflammation [64].

Using the inflammation as a driving force for targeted cell-mediated drug delivery is a very attractive approach. Nevertheless, one should take into consideration that any other inflammatory processes in addition to the CNS inflammation may divert cell-carriers from the brain and decrease the therapeutic efficacy of cell-incorporated drug formulations. In clinic, if this is the case, a short pre-treatment of a patient with antibiotics should be carried out before the cell-based therapy is initiated.

Overall, development of the cell-based therapy with potent anti-cancer proteins for systematic administration would represent a major therapeutic advance in multiple fields of cancer-related research.

REFERENCES

1. Mason C, Brindley DA, Culme-Seymour EJ and Davie NL. (2011). Cell therapy industry: billion dollar global business with unlimited potential. Regen Med. 6(3), 265-272.
2. Batrakova EV, Gendelman HE and Kabanov AV. (2011). Cell-mediated drug delivery. Expert Opin Drug Deliv. 8(4), 415-433.
3. Batrakova EV and Kabanov AV. (2013). Cell-mediated drug delivery to the brain. Journal of Drug Delivery Science and Technology, 23(5). 419-433.
4. Hingtgen S, Kasmieh R, Elbayly E, Nesterenko I, et al. (2012). A first-generation multi-functional cytokine for simultaneous optical tracking and tumor therapy. PLoS One. 7(7), e40234.
5. Hingtgen S, Ren X, Terwilliger E, Classon M, et al. (2008). Targeting multiple pathways in gliomas with stem cell and viral delivered S-TRAIL and Temozolomide. Mol Cancer Ther. 7(11), 3575-3585.
6. Hingtgen SD, Kasmieh R, van de Water J, Weissleder R, et al. (2010). A novel molecule integrating therapeutic and diagnostic activities reveals multiple aspects of stem cell-based therapy. Stem Cells. 28(4), 832-841.
7. Fischbach MA, Bluestone JA and Lim WA. (2013). Cell-based therapeutics: the next pillar of medicine. Sci Transl Med. 5, 179ps7.
8. Daneman R. (2012). The blood-brain barrier in health and disease. Ann Neurol. 72(5), 648-672.

9. Mantovani A, Allavena P, Sica A and Balkwill F. (2008). Cancer-related inflammation. Nature. 454(7203), 436-444.
10. Hickey WF. (1999). Leukocyte traffic in the central nervous system: the participants and their roles. Semin Immunol. 11(2), 125-137.
11. Hussain SF, Yang D, Suki D, Aldape K, et al. (2006). The role of human glioma-infiltrating microglia/macrophages in mediating antitumor immune responses. Neuro Oncol. 8(3), 261-279.
12. Vaupel P, Kallinowski F and Okunieff P. (1989). Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. Cancer Res. 49(23), 6449-6465.
13. Kuby J. (1994). Immunology. New York: Freeman, WH. and Co.
14. Anthony DC, Blond D, Dempster R and Perry VH. (2001). Chemokine targets in acute brain injury and disease. Prog Brain Res. 132, 507-524.
15. Blamire AM, Anthony DC, Rajagopalan B, Sibson NR, et al. (2000). Interleukin-1beta -induced changes in blood-brain barrier permeability, apparent diffusion coefficient, and cerebral blood volume in the rat brain: a magnetic resonance study. J Neurosci. 20, 8153-8159.
16. Zlokovic BV. (2008). The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 57(2), 178-201.
17. Liu Y, Uberti MG, Dou H, Banerjee R, et al. (2008). Ingress of blood-borne macrophages across the blood-brain barrier in murine HIV-1 encephalitis. J Neuroimmunol. 200(1-2), 41-52.
18. Ling EA and Wong WC. (1993). The origin and nature of ramified and amoeboid microglia: a historical review and current concepts. Glia. 7(1), 9-18.
19. Rodriguez M, Alvarez-Erviti L, Blesa FJ, Rodriguez-Oroz MC, et al. (2007). Bone-marrow-derived cell differentiation into microglia: a study in a progressive mouse model of Parkinson's disease. Neurobiol Dis. 28(3), 316-325.
20. Pun PB, Lu J and Moochhala S. (2009). Involvement of ROS in BBB dysfunction. Free Radic Res. 43(4), 348-364.
21. Ahmed AU, Alexiades NG and Lesniak MS. (2010). The use of neural stem cells in cancer gene therapy: predicting the path to the clinic. Curr Opin Mol Ther. 12(5), 546-552.
22. Muller FJ, Snyder EY and Loring JF. (2006). Gene therapy: can neural stem cells deliver? Nat Rev Neurosci. 7(1), 75-84.
23. Batrakova EV, Li S, Reynolds AD, Mosley RL, et al. (2007). A macrophage-nanozyme delivery system for Parkinson's disease. Bioconjug Chem. 18(5), 1498-1506.
24. Zhao Y, Haney MJ, Mahajan V, Reiner BC, et al. (2011). Active Targeted Macrophage-mediated Delivery of Catalase to Affected Brain Regions in Models of Parkinson's Disease. J Nanomed Nanotechnol. S4.
25. Dou H, Grotepas CB, McMillan JM, Destache CJ, et al. (2009). Macrophage delivery of nanoformulated antiretroviral drug to the brain in a murine model of neuroAIDS. J Immunol. 183(1), 661-669.
26. Martinez-Serrano A, Hantzopoulos PA and Bjork Lund A. (1996). Ex vivo gene transfer of brain-derived neurotrophic factor to the intact rat forebrain: neurotrophic effects on cholinergic neurons. Eur J Neurosci. 8(4), 727-735.
27. Martinez-Serrano A and Bjorklund A. (1998). Ex vivo nerve growth factor gene transfer to the basal forebrain in presymptomatic middle-aged rats prevents the development of cholinergic neuron atrophy and cognitive impairment during aging. Proc Natl Acad Sci U S A. 95(4), 1858-1863.
28. Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, et al. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci U S A. 106(32), 13594-13599.
29. Bechmann I, Goldmann J, Kovac AD, Kwidzinski E, et al. (2005). Circulating monocytic cells infiltrate layers of anterograde axonal degeneration where they transform into microglia. Faseb J. 19(6), 647-649.
30. Simard AR and Rivest S. (2004). Bone marrow stem cells have the ability to populate the entire central nervous system into fully differentiated parenchymal microglia. Faseb J. 18(9), 998-1000.
31. Klyachko NL, Haney MJ, Zhao Y, Manickam DS, et al. (2014). Macrophages offer a paradigm switch for CNS delivery of therapeutic proteins. Nanomedicine. 9(9), 1403-1422.
32. Brynskikh AM, Zhao Y, Mosley RL, Li S, et al. (2010). Macrophage delivery of therapeutic nanozymes in a murine model of Parkinson's disease. Nanomedicine (Lond). 5(3), 379-396.
33. Haney MJ, Zhao Y, Harrison EB, Mahajan V, et al. (2013). Specific Transfection of Inflamed Brain by Macrophages: A New Therapeutic Strategy for Neurodegenerative Diseases. Plos One. 8(4), e61852.
34. Zhao Y, Haney MJ, Klyachko NL, Li S, et al. (2011). Polyelectrolyte complex optimization for macrophage delivery of redox enzyme nanoparticles. Nanomedicine (Lond). 6(1), 25-42.
35. Kennedy DW and Abkowitz JL. (1998). Mature monocytic cells enter tissues and engraft. Proc Natl Acad Sci U S A. 95(25), 14944-14949.
36. Thu MS, Najbauer J, Kendall SE, Harutyunyan I, et al. (2009). Iron labeling and pre-clinical MRI visualization of therapeutic human neural stem cells in a murine glioma model. PLoS One. 4(9), e7218.
37. Carney BJ and Shah K. (2011). Migration and fate of therapeutic stem cells in different brain disease models. Neuroscience. 197, 37-47.

38. Hajjar RJ and Cormode DP. (2012). Tracking cell therapy: bioluminescence lighting the way. JACC Cardiovasc Imaging. 5(1), 56-58.
39. Rombouts WJ and Ploemacher RE. (2003). "Primary murine MSC show highly efficient homing to the bone marrow but lose homing ability following culture," Leukemia. 17(1), 160–170.
40. Tang Y, Shah K, Messerli SM, Snyder E, et al. (2003). In vivo tracking of neural progenitor cell migration to glioblastomas. Hum Gene Ther. 14(13), 1247-1254.
41. Shah K, Bureau E, Kim DE, Yang K, et al. (2005). Glioma therapy and real-time imaging of neural precursor cell migration and tumor regression. Ann Neurol. 57(1), 34-41.
42. Sasportas LS, Kasmieh R, Wakimoto H, Hingtgen S, et al. (2009). Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. Proc Natl Acad Sci U S A. 106(12), 4822-4827.
43. Reitz M, Demestre M, Sedlacik J, Meissner H, et al. (2012). Intranasal delivery of neural stem/progenitor cells: a noninvasive passage to target intracerebral glioma. Stem Cells Transl Med. 1(12), 866-873.
44. Shah K, Hingtgen S, Kasmieh R, Figueiredo JL, et al. (2008). Bimodal viral vectors and in vivo imaging reveal the fate of human neural stem cells in experimental glioma model. J Neurosci. 28(17), 4406-4413.
45. Terrovitis J, Stuber M, Youssef A, Preece S, et al. (2008). Magnetic resonance imaging overestimates ferumoxide-labeled stem cell survival after transplantation in the heart. Circulation. 117(12), 1555-1562.
46. Haney MJ, Klyachko NL, Zhao Y, Gupta R, et al. (2015). Exosomes as drug delivery vehicles for Parkinson's disease therapy. J Control Release. 207, 18-30.
47. Kim MS, Haney MJ, Zhao Y, Mahajan V, et al. (2015). Development of Exosome-encapsulated Paclitaxel to Overcome MDR in Cancer cells. Nanomedicine. 12(3), 655-664.
48. Finn OJ. (2012). Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Ann Oncol. 23(Suppl 8), 6-9.
49. Parolini I, Federici C, Raggi C, Lugini L, et al. (2009). Microenvironmental pH is a key factor for exosome traffic in tumor cells. J Biol Chem. 284(49), 34211-34222.
50. Poste G, Bucana C, Raz A, Bugelski P, et al. (1982). Analysis of the fate of systemically administered liposomes and implications for their use in drug delivery. Cancer Res. 42(4), 1412-1422.
51. Cho MJ, Scieszka JF, Cramer CT, Thompson DP, et al. (1989). Neutrophil-mediated transport of liposomes across the Madin Darby canine kidney epithelial cell monolayer. Pharm Res. 6(1), 78-84.
52. Park KI, Ourednik J, Ourednik V, Taylor RM, et al. (2002). Global gene and cell replacement strategies via stem cells. Gene Ther. 9(10), 613-624.
53. Schmidt NO, Przylecki W, Yang W, Ziu M, et al. (2005). Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. Neoplasia. 7(6), 623-629.
54. Corsten MF and Shah K. (2008). Therapeutic stem-cells for cancer treatment: hopes and hurdles in tactical warfare. Lancet Oncol. 9(4), 376-384.
55. Aboody KS, Najbauer J and Danks MK. (2008). Stem and progenitor cell-mediated tumor selective gene therapy. Gene Ther. 15(10), 739-752.
56. Zhao D, Najbauer J, Garcia E, Metz MZ, et al. (2008). Neural stem cell tropism to glioma: critical role of tumor hypoxia. Mol Cancer Res. 6(12), 1819-1829.
57. Stuckey DW and Shah K. (2014). Stem cell-based therapies for cancer treatment: separating hope from hype. Nat Rev Cancer. 14, 683-691.
58. Yip S and Shah K. (2008). Stem-cell based therapies for brain tumors. Curr Opin Mol Ther. 10(4), 334-342.
59. Kauer TM, Figueiredo JL, Hingtgen S and Shah K. (2012). Encapsulated therapeutic stem cells implanted in the tumor resection cavity induce cell death in gliomas. Nat Neurosci. 15(2), 197-204.
60. Bagci-Onder T, Du W, Figueiredo JL, Martinez-Quintanilla J, et al. (2015). Targeting breast to brain metastatic tumours with death receptor ligand expressing therapeutic stem cells. Brain. 138(6), 1710-1721.
61. Eichler AF, Chung E, Kodack DP, Loeffler JS, et al. (2011). The biology of brain metastases-translation to new therapies. Nat Rev Clin Oncol. 8(6), 344-356.
62. Jain S, Mishra V, Singh P, Dubey PK, et al. (2003). RGD-anchored magnetic liposomes for monocytes/neutrophils-mediated brain targeting. Int J Pharm. 261(1-2), 43-55.
63. Kalos M, Levine BL, Porter DL, Katz S, et al. (2011). T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med. 3(95), 95ra73.
64. Ruck T, Bittner S, Meuth SG and Herty M. (2015). Insights from mathematical modelling for T cell migration into the central nervous system. Math Med Biol.