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Review

An overview of Albumin - Based Nanoparticles: Targeted Precision in Cancer Chemotherapy

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Abstract

Cancer is the leading cause of death worldwide. According to WHO estimates, cancer ranks as the first or second leading cause of death in 183 countries. Chemotherapy is the most widely used promising treatment for cancer. However, patients undergoing chemotherapy often suffer from serious side effects due to the impact of chemo-drugs on normal cells. Targeted delivery of cytotoxic drugs in chemotherapy presents a major challenge, which can be addressed by using nanoparticles. Nanoparticles serve as an excellent carrier for cytotoxic drugs to target tumor cells, resulting in a reduction of side effects. These nanoparticles are biodegradable and biocompatible. Recent research has demonstrated that nutrient transporters can improve targeting in tumor cells. Cancer cells often over express nutrient transporters to fulfill their nutritional requirements for rapid growth. Albumin binding proteins (ABPs) are more numerous in tumor cells, making them a good target for tumor-specific drug delivery. Albumin is a plasma protein characterized by high biocompatibility, biodegradability, and non-immunogenicity. When drugs are infused with albumin, it helps protect the drugs from elimination and immune responses. For example: Abraxane is a solvent-free nano version of Taxol, which is already marketed albumin-based nanoparticles used in the treatment of breast cancer, pancreatic cancer, and non-small lung cancer. It contains paclitaxel as an anti-cancer agent. Albumin-based nanoparticles also have the ability to cross the blood-brain barrier, offering new possibilities for the treatment of brain cancer and CNS diseases. Therefore, this review focuses on the significance of albumin nanoparticles in cancer chemotherapy, their advantages, and recent updates in albumin-based nanoparticles.

Keywords: Chemotherapy, Nanoparticles, Albumin Nanoparticles, Target delivery, Brain tumor targeting.

INTRODUCTION

The disease known as cancer is typified by the body's cells growing out of control and spreading to other parts of the body. Healthy cells and tissues are destroyed when a tumor, which is a clump of malignant cells, continues to grow [1]. So far, over 100 distinct forms of cancer have been found [2]. More over 1.5 million new instances of cancer were reported in India in 2022, and the country' cancer mortality rate also rose during same year [3].

Therapies of Cancer

Patients with cancer are treated using a variety of clinical techniques, including radiotherapy, chemotherapy, and surgery. Tumor size, location, and the patient's medical history all have a role in the treatment plan selection [4]. Patients undergoing radiotherapy are exposed to high levels of radiation, which may harm neighboring healthy cells and tissues. [5].

Chemotherapy

Chemotherapy is a widely used cancer treatment that involves employing one or more cytotoxic or anticancer drugs to kill rapidly proliferating faulty cancer cells in the body. Most chemotherapy treatments target cells that are actively reproducing, however other drugs target specific stages of the cell cycle [2].Chemotherapeutic treatments often have a limited ability to reach the active site [6]; the majority of the chemicals diffuse throughout the body, with only a small portion reaching the malignant location. Because of this, patients need large dosage levels, and the toxicity of the medicine increases with dosage [7]. Chemotherapy's primary drawback is that its cytotoxic chemicals damage both cancerous and healthy cells since they are unable to discriminate between the two. Damage to healthy organs and tissues may arise from this [10].
Eg: 5-Fluorouracil - Toxic side effects on bone marrow, liver, cardiac tissue and gastrointestinal tract [8,9].

Advantages of Nanoparticles in Cancer Therapy

The primary disadvantages of radiation and chemotherapy have been their lack of specificity, which results in insufficient drug delivery to the intended site, as well as their high toxicity to neighboring healthy cells, tissues, and organs, which promotes the emergence of drug resistance while the patient is receiving treatment [11]. Utilizing nanotechnology as a tactic has a lot of promise to address these issues [12], particularly by improving drug distribution to target areas, raising efficacy, and lowering side effects [13]. Recently, nanoparticles have drawn a lot of attention, and the field of using them to treat cancer is expanding. [14]. The majority of the time, resistance arises from the expression of p-glycoprotein, a protein that allows anticancer medications to be pumped out of a cell as soon as they pass through the outer membrane. According to recent studies, anticancer medications may be delivered to cells via nanoparticles without activating the p-glycoprotein pump [15]

Nanoparticles Drug Delivery

The delivery of the drug to the target tissue can be achieved primarily in two ways [16]:

Passive Target

A leaking and defective architecture is made possible by the rapid vascularization needed to support the rapidly growing cancerous tissue. As such, harmful chemotherapy medicines may have easy access to it [10]. The Enhanced Permeability and Retention (EPR) effect, which takes use of the features of the delivery method and the tumor environment, allows for the passive targeting of nanoparticles [17,18].

Active Target

Using ligands on the surface of nanoparticles, active targeting enables cancer cells to be identified from healthy cells by preferentially binding to overexpressed molecules on the cancer cells. This targeted approach enhances drug delivery precision, increases therapeutic concentration at the tumor site, and minimizes side effects by sparing normal tissues [19, 20].

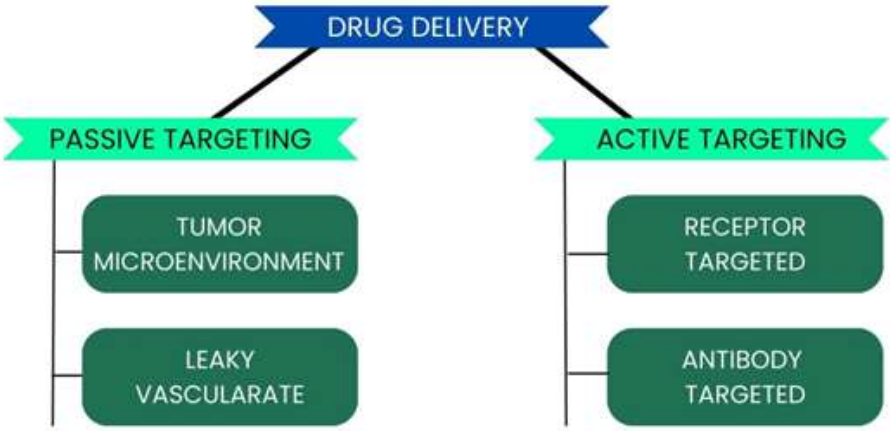

Fig 1: Mechanism of nanoparticle drug delivery via two main mechanisms—passive and active targeting.

Albumin Nanoparticels in Cancer Treatment

Because the albumin molecule has multiple drug binding sites, one of the main benefits of albumin nanoparticles is their high binding capacity for a variety of medicines, both soluble and insoluble in water [21]. Commercial sources of albumin protein include egg white, human serum (HSA), and bovine serum (BSA) [22]. The most common types of albumin employed in the manufacturing of micro or nanoparticles are human or bovine. It is a protein that is both biocompatible and biodegradable [23]. Desolvation, emulsification, thermal gelation, nanospray drying, nab (nanoparticle albumin bound) - technology, and self-assembly are the methods used to create albumin nanoparticles [23]. Albumin nanoparticles have garnered significant interest as drug delivery vehicles due to their numerous benefits, including high drug binding capacity; high charge amino acid content enabling electrostatic adsorption of molecules; anticancer drug targeting; and enhanced uptake in solid tumors [24].The majority of anti-cancer medications have low water solubility and are hydrophobic by nature. However, injecting a hydrophobic substance intravenously (IV) results in major safety problems such as embolizing blood capillaries, which have major side effects. Numerous intriguing pharmacological candidates never go past the stage of solubility issues [25]. Albumin nanoparticles can help with this problem by increasing the solubility of medications. Both hydrophilic and hydrophobic medicines can be loaded into albumin NPs.

Albumin NP's target the cancer cells by both active and passive targeting mechanism:

- Passive by the nano size range due EPR effect
- Active by the ABP receptors present in the cancer cells [26].

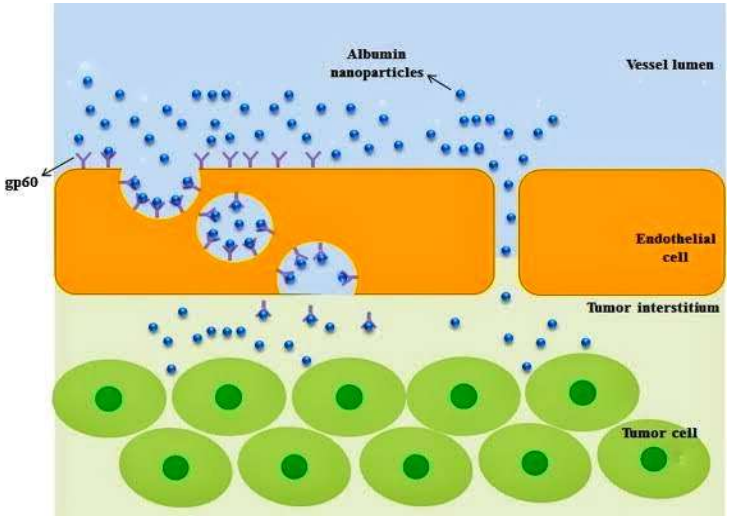

Fig 2: Uptake of the albumin nanoparticles mediated by EPR effect and also by the glycoprotein gp60 [2].

Abraxane Success Story

The anti-cancer medication paclitaxel is sold as an injection under the Taxol brand. In 1992, the US FDA approved it to treat ovarian cancer, and in 1994, it was approved to treat breast cancer. Its nonspecific and indiscriminate biodistribution in the body following intravenous treatment has resulted in the documented occurrence of significant adverse effects, such as nephrotoxicity, neurotoxicity, hypersensitivity responses, and cardiotoxicity. The drug's hydrophobic properties cause problems with solubility, necessitating the use of more organic solvents [27].

Abraxane, the first albumin-bound drug delivery system licensed for cancer treatment, is a solvent-free nano form of Taxol [28]. It was created utilizing NAB technology, and American Bioscience began selling it in 2005 to treat breast cancer in the US. In addition, it is undergoing clinical studies in numerous more countries and has been approved in 41 nations [29]. The FDA authorized the use of Abraxane as a first-line treatment for pancreatic cancer and non-small cell lung cancer in 2012 and 2013 [30]. The way that Abraxane works is one of its most intriguing features. Abraxane quickly dissolves upon intravenous administration, creating soluble albumin-bound PTX complexes. These complexes accumulate in the tumor through the well-known Enhanced Permeability and Retention (EPR) effect because of their range of sizes. Moreover, albumin-binding proteins (ABPs) including gp60 and SPARC, which are found in the endothelial cells at the cancer site, help them get to the cancer site [31 32,33].

Table 1: Comparison between Abraxane and Taxol[34].

Drug	Contents	Tolerated dose	Infusion time	Premedication
Taxol	Paclitaxel 6 mg, Cremophor 537 mg/ml, Ethanol 396 mg/m	175 mg/m^2	3 - 24hrs	Required to prevent hypersensitivity
Abraxane	100 mg paclitaxel, 900 mg albumin, No Surfactants/Solvents	300 mg/m^2	30 min	Not Required

Crossing of Blood Brain Barrier (BBB)

Worldwide, brain tumors are the main cause of disability [35 - 39], and relatively few medications have been found to be effective in treating brain tumors. A number of issues also restrict their therapeutic efficacy [40], the primary one being the inefficient passage of medications over the blood-brain barrier [41, 42]. The blood-brain barrier (BBB) is a major obstacle to the successful delivery of drugs for brain cancer [43]. The BBB, however, is not a static barrier—instead, it promotes the vast movement of nutrients [44]. Serving as the brain's security gate, it permits the entry of necessary nutrients including sugar, proteins, amino acids, and more while blocking the entry of undesirable items. These transporters act as a conduit for the transportation of drugs to the brain [45]. The human body needs albumin as a source of protein. Tumors consume more albumin when cancer cells grow quickly because they have a higher need for nutrition [46, 47]. ABPs, such as gp60 and SPARC, are overexpressed in tumor cells [48] and play a critical role in the uptake of albumin by malignancies. The concept of employing albumin nanoparticles for the effective treatment of brain tumors has been the subject of numerous investigations. The outcomes show promise: albumin nanoparticles have shown strong intracellular delivery, intratumoral infiltration, and BBB penetration. Research is currently being conducted to investigate the possibility of treating brain tumors more successfully by putting two distinct anti-cancer medications into albumin nanoparticles [49]. If the research is successful, it could represent a significant advancement in the treatment of brain cancer. Additionally, albumin nanoparticles have been utilized to treat a variety of CNS disorders.

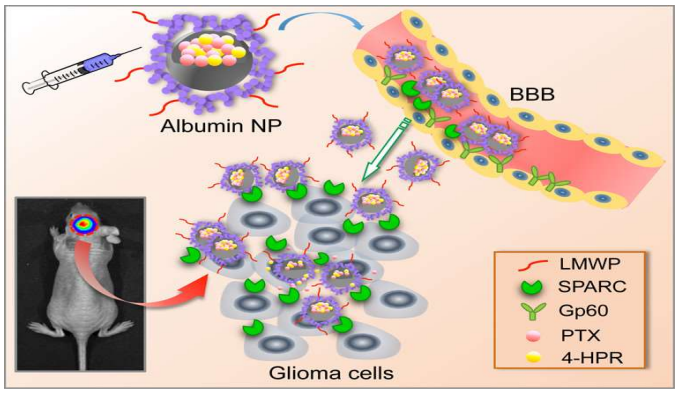

Fig 3: The BBB penetrating NPs are delivered into brain tumor cells via the mechanisms by targeting the ABP's like gp60 and SPARC [50].

CONCLUSION

Albumin nanoparticles are transforming cancer treatment, overcoming the drawbacks of traditional chemotherapy. They elevate target precision, minimize side effects, and display remarkable efficiency. The success of Abraxane stands as a testament to the impact of albumin-bound drug delivery systems in diverse cancer treatments. Ongoing research developing into dual drug loading sparks hope for breakthroughs in brain cancer treatment. The prospect of albumin nanoparticles ushering in a more targeted and effective era in cancer therapy.

REFERENCES

1. Brown JS, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the definition of cancer. Mol Cancer Res. 2023 Nov 1; 21(11):1142-7. doi: 10.1158/1541-7786.MCR-23-0411, PMID 37409952.
2. Estanqueiro M, Amaral MH, Conceição J, Sousa Lobo JM. Nanotechnological carriers for cancer: the state of the art. Colloids Surf B Biointerfaces. 2015; 126:631-48. doi: 10.1016/j.colsurfb.2014.12.041, PMID 25591851.
3. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: result from National Cancer Registry Programme, India. Indian J Med Res. 2022 Oct-Nov; 156(4&5):598-607. doi: 10.4103/ijmr.ijmr_1821_22, PMID 36510887.
4. Reijneveld EAE, Bor P, Dronkers JJ, Argudo N, Ruurda JP, Veenhof C. Impact of Curative Treatment on the physical fitness of Patients with Esophageal Cancer: A Systematic Review and Meta-Analysis. Eur J Surg Oncol. 2022; 48(2):391-402. doi: 10.1016/j.ejso.2021.08.015, PMID 34426032.
5. Chen YH, Molenaar D, Uyl-de Groot CA, van Vulpen M, Blommestein HM. Medical Resource Use and Medical costs for Radiotherapy-Related Adverse Effects: A Systematic Review. Cancers. 2022; 14(10):2444. doi: 10.3390/cancers14102444, PMID 35626049.
6. Chaplin DJ, Hill SA, Bell KM, Tozer GM. Modification of tumor blood flow: current status and future directions. Semin Radiat Oncol. 1998; 8(3):151-63. doi: 10.1016/s1053-4296(98)80041-6, PMID 9634492.
7. Needham D, Dewhirst MW. The development and testing of a new temperature-sensitive drug delivery system for the treatment of solid tumors. Adv Drug Deliv Rev. 2001; 53(3):285-305. doi: 10.1016/s0169-409x(01)00233-2, PMID 11744173.
8. Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, Maillart PJ, Goudier MJ, Burtin PC et al. Relationship between 5- fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. Cancer. 1996; 77(3):441-51. doi: 10.1002/(SICI)1097-0142(19960201)77:3<441::AID-CNCR4>3.0.CO;2-N, PMID 8630950.
9. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiol J. 2012; 19(5):453-8. doi: 10.5603/cj.2012.0084, PMID 23042307.
10. Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Mol Cancer Ther. 2006 Aug 1; 5(8):1909-17. doi: 10.1158/1535-7163.MCT-06-0141, PMID 16928810.
11. Narayana A. Applications of nanotechnology in cancer: A literature review of imaging and treatment. J Nucl Med Radiat Ther. 2014; 05(4):1-9. doi: 10.4172/2155-9619.1000195.
12. Chatterjee P, Kumar S. Current developments in nanotechnology for cancer treatment. Mater Today Proc. 2022; 48:1754-8. doi: 10.1016/j.matpr.2021.10.048.
13. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov. 2004; 3(8):711-5. doi: 10.1038/nrd1470, PMID 15286737.
14. Rasool M, Malik A, Waquar S, Arooj M, Zahid S, Asif M et al. New challenges in the Use of nanomedicine in Cancer Therapy. Bioengineered. 2022; 13(1):759-73. doi: 10.1080/21655979.2021.2012907, PMID 34856849.
15. Niazi M, Zakeri-Milani P, Najafi Hajivar S, Soleymani Goloujeh M, Ghobakhlou N, Shahbazi Mojarrad J, et al. Nano- based strategies to overcome p-glycoprotein-mediated drug resistance. Expert Opin Drug Metab Toxicol. 2016 Jun 13; 12(9):1021-33. doi: 10.1080/17425255.2016.1196186, PMID 27267126.
16. Kreuter J. Nanoparticles - a historical perspective. Int J Pharm. 2007; 331(1):1-10. doi: 10.1016/j.ijpharm.2006.10.021, PMID 17110063.
17. Maeda H, Matsumura Y. Tumoritropic and lymphotropic principles of macromolecular drugs. Crit Rev Ther Drug Carrier Syst. 1989; 6(3):193-210. PMID 2692843.
18. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986; 46(12 Pt 1):6387-92. PMID 2946403.

19. Shi J, Xiao Z, Kamaly N, Farokhzad OC. Self-assembled targeted nanoparticles: evolution of technologies and bench to bedside translation. Acc Chem Res. 2011; 44(10):1123-34. doi: 10.1021/ar200054n, PMID 21692448.
20. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chem Soc Rev. 2012; 41(7):2971-3010. doi: 10.1039/c2cs15344k, PMID 22388185.
21. Patil GV. Biopolymer albumin for diagnosis and in drug delivery. Drug Dev Res. 2003; 58(3):219-47. doi: 10.1002/ddr.10157.
22. Elzoghby AO, Samy WM, Elgindy NA. Albumin-based nanoparticles as potential controlled release drug delivery systems. J Control Release. 2012; 157(2):168-82. doi: 10.1016/j.jconrel.2011.07.031, PMID 21839127.
23. Sharma RI, Pereira M, Schwarzbauer JE, Moghe PV. Albumin-derived nanocarriers: substrates for enhanced cell adhesive ligand display and cell motility. Biomaterials. 2006; 27(19):3589-98. doi: 10.1016/j.biomaterials.2006.02.007, PMID 16527347.
24. Kratz F. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. J Control Release. 2008; 132(3):171-83. doi: 10.1016/j.jconrel.2008.05.010, PMID 18582981.
25. Narvekar M, Xue HY, Eoh JY, Wong HL. Nanocarrier for poorly water-soluble anticancer drugs—barriers of translation and solutions. AAPS PharmSciTech. 2014 Apr 2; 15(4):822-33. doi: 10.1208/s12249-014-0107-x, PMID 24687241.
26. Elsadek B, Kratz F. Impact of albumin on drug delivery--new applications on the horizon. J Control Release. 2012; 157(1):4-28. doi: 10.1016/j.jconrel.2011.09.069, PMID 21959118.
27. Van Zuylen L, Verweij J, Sparreboom A. Role of formulation vehicles in taxane pharmacology. Investig New Drugs. 2001; 19(2):125-41. doi: 10.1023/a:1010618632738, PMID 11392447.
28. Ma P, Mumper RJ. Paclitaxel nano-delivery systems: A comprehensive review. J Nanomed Nanotechnol. 2013; 4(2):1000164. doi: 10.4172/2157-7439.1000164, PMID 24163786.
29. Elsadek B, Kratz F. Impact of albumin on drug delivery--new applications on the horizon. J Control Release. 2012; 157(1):4-28. doi: 10.1016/j.jconrel.2011.09.069, PMID 21959118.
30. Green MR, Manikhas GM, Orlov S, Afanasyev B, Makhson AM, Bhar P, et al. Abraxane, a novel cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol. 2006; 17(8):1263-8. doi: 10.1093/annonc/mdl104, PMID 16740598.
31. Schnitzer JE. gp60 is an albumin-binding glycoprotein expressed by continuous endothelium involved in albumin transcytosis. Am J Physiol. 1992; 262(1 Pt 2):H246-54. doi: 10.1152/ajpheart.1992.262.1.H246, PMID 1733316.
32. Tiruppathi C, Song W, Bergenfeldt M, Sass P, Malik AB. Gp60 activation mediates albumin transcytosis in endothelial cells by tyrosine kinase-dependent pathway. J Biol Chem. 1997; 272(41):25968-75. doi: 10.1074/jbc.272.41.25968, PMID 9325331.
33. Wang Z, Tiruppathi C, Minshall RD, Malik AB. Size and dynamics of caveolae studied using nanoparticles in living endothelial cells. ACS Nano. 2009; 3(12):4110-6. doi: 10.1021/nn9012274, PMID 19919048.
34. Kouchakzadeh H, Safavi MS, Shojaosadati SA. Efficient delivery of therapeutic agents by using targeted albumin nanoparticles. Adv Protein Chem Struct Biol. 2015; 98:121-43. doi: 10.1016/bs.apcsb.2014.11.002, PMID 25819278.
35. Nazem A, Mansoori GA. Nanotechnology solutions for Alzheimer's disease: advances in research tools, diagnostic methods and therapeutic agents. J Alzheimers Dis. 2008; 13(2):199-223. doi: 10.3233/JAD-2008-13210.
36. Srikanth M, Kessler JA. Nanotechnology-novel therapeutics for CNS disorders. Nat Rev Neurol. 2012; 8(6):307-18. doi: 10.1038/nrneurol.2012.76, PMID 22526003.
37. Sweeney MD, Sagare AP, Zlokovic BV. Cerebrospinal fluid biomarkers of neurovascular dysfunction in mild dementia and Alzheimer's disease. J Cereb Blood Flow Metab. 2015; 35(7):1055-68. doi: 10.1038/jcbfm.2015.76, PMID 25899298.
38. Vijayan M, Reddy PH. Stroke, Vascular dementia, and Alzheimer's disease: molecular links. J Alzheimers Dis. 2016; 54(2):427-43. doi: 10.3233/JAD-160527, PMID 27567871.
39. Reddy PH, Tonk S, Kumar S, Vijayan M, Kandimalla R, Kuruva CS et al. A critical evaluation of neuroprotective and neurodegenerative microRNAs in Alzheimer's disease. Biochem Biophys Res Commun. 2017; 483(4):1156-65. doi: 10.1016/j.bbrc.2016.08.067, PMID 27524239.
40. Vilella A, Ruozi B, Belletti D, Pederzoli F, Galliani M, Semeghini V et al. Endocytosis of nanomedicines: the Case of Glycopeptide engineered PLGA nanoparticles. Pharmaceutics. 2015; 7(2):74-89. doi: 10.3390/pharmaceutics7020074, PMID 26102358.
41. Gao H, Pang Z, Jiang X. Targeted delivery of nano-therapeutics for major J. Xie, et al. Biomaterials. 2019: 11949115 disorders of the central nervous system, Pharm. Res. 30; (2013); 224:2485-98.

42. Dong X. Current strategies for brain drug delivery. Theranostics. 2018; 8(6):1481-93. doi: 10.7150/thno.21254, PMID 29556336.
43. Brown RC, Morris AP, O'Neil RG. Tight junction protein expression and barrier properties of immortalized mouse brain microvessel endothelial cells. Brain Res. 2007; 1130(1):17-30. doi: 10.1016/j.brainres.2006.10.083, PMID 17169347.
44. Geldenhuys WJ, Mohammad AS, Adkins CE, Lockman PR. Molecular determinants of blood-brain barrier permeation. Ther Deliv. 2015; 6(8):961-71. doi: 10.4155/tde.15.32, PMID 26305616.
45. Mittapalli RK, Manda VK, Adkins CE, Geldenhuys WJ, Lockman PR. Exploiting nutrient transporters at the blood-brain barrier to improve brain distribution of small molecules. Ther Deliv. 2010; 1(6):775-84. doi: 10.4155/tde.10.76, PMID 22834013.
46. Stehle G, Sinn H, Wunder A, Schrenk HH, Stewart J. C, Hartung. G, Maier-Borst. W, Heene. D. L, Plasma Protein (Albumin) Catabolism by the Tumor Itself Implications for Tumor Metabolism and the Genesis of Cachexia. Crit. Rev. Oncol. Hematol. 1997; 26: 77 - 100.
47. Wunder A, Stehle G, Sinn H, Schrenk H, Hoffbiederbeck D, Bader F et al. Enhanced albumin uptake by rat tumors. Int J Oncol. 1997; 11(3):497-507. doi: 10.3892/ijo.11.3.497, PMID 21528238.
48. Merlot AM, Kalinowski DS, Richardson DR. Unraveling the mysteries of serum albumin-more than just a serum protein□More Than Just a Serum Protein. Front Physiol. 2014; 5: 299. doi: 10.3389/fphys.2014.00299, PMID 25161624.
49. Rempel SA, Golembieski WA, Fisher JL, Maile M, Nakeff A. SPARC modulates cell growth, attachment and migration of U87 glioma cells on brain extracellular matrix proteins. J Neurooncol. 2001; 53(2):149-60. doi: 10.1023/a:1012201300188, PMID 11716067.
50. Lin T, Zhao P, Jiang Y, Tang Y, Jin H, Pan Z, et al. Blood-brain-barrier-penetrating albumin nanoparticles biomimetic drug delivery via albumin – binding protein pathways for antiglioma therapy. ACS Nano. 2016 Nov 8; 10(11):9999-10012. doi: 10.1021/acsnano.6b04268, PMID 27934069.