

selective association with cancer cells for the treatment and diagnosis of brain tumors.^[129]

Yang and David formulated magnetic iron oxide nanoparticles (MIONs) coated with a molecule that is noncovalently associated with a brain-targeting molecule. The coated MIONs comprise an anti-tumor agent linked to a cell-penetrating peptide.^[130] MIONs are oriented at the site of the brain tumor with an external magnetic field.^[130] In a patent by Dixit *et al.*^[131] gold nanoparticles conjugated with peptides against both EGFR and TfR and loaded with the photosensitizer phthalocyanine 4 have been designed and characterized. Laser was then applied to activate the photosensitizer, causing subsequent cell death.^[131]

On the other hand, nonthermal techniques to reversibly open BBB have been studied. One of these techniques is using ultrasound in the presence of microbubbles (MB).^[132,133] MB work by resonating in an ultrasound beam, rapidly contracting and expanding in response to the pressure changes of the sound wave.^[134] Inertial cavitation and destruction of microbubbles are capable of producing strong mechanical stress to enhance the permeability of the surrounding tissues and further increase the extravasation of drugs into the cytoplasm or interstitial cells.^[135] Chen *et al.*^[136] studied MB-carrying TGF β 1 inhibitor combined with ultrasound sonication to induce BBB/BBB disruption and enhance drug delivery. Pulsed-mode ultrasound exposure therapy was recently shown to enhance the antitumor effect of an EGFR-targeting chemotherapeutic drug facilitating glioma treatment.^[137]

NUCLEIC ACID TECHNOLOGIES

MicroRNA

MicroRNAs (miRNAs) are endogenous RNAs composed of about 22 nucleotides. The miRNAs can play important regulatory roles in animals and plants by targeting mRNAs for cleavage or translational repression.^[138,139] Currently, about 2% of known human genes encode microRNAs.^[140] A growing body of evidence shows that miRNAs are one of the key players in cell differentiation and growth, mobility, and apoptosis.^[141-143] Most microRNAs in animals are thought to function by inhibition of effective mRNA translation of target genes through imperfect base pairing with the 3-untranslated region of target mRNAs.^[138,140]

MiRNAs are appealing therapeutic targets and potential biomarkers of GBMs.^[141-143] Chan *et al.*^[144] were the first to investigate the functional properties of a single miRNA in GBM cell lines. They discovered that high expression of miR-21 is a common feature of GBM.^[144] In GBM, 15 types of miRNAs are the most studied (miR-7, miR-10b, miR-15b, miR-17, miR-21, miR-23a, miR-25, miR-124, miR-128a, miR-128b, miR-132, miR-137, miR-195, miR-221 and miR-222).^[145] In a patent by Park *et al.*^[146] hypoxia-induced angiogenesis-associated diseases including cancers was suggested to be treated by miRNA-125.

Aptamers

Aptamers are nonbiological oligonucleotides that can bind

to protein targets.^[147] Aptamers can be used for therapeutic purposes in the same way as monoclonal antibodies.^[147] However, unlike traditional methods for producing monoclonal antibodies, no organisms are required for the *in vitro* selection of oligonucleotides.^[147] For this reason, aptamers avoid the immunogenicity of antibodies while maintaining all their properties.^[147] However, there still remain largely unknown pharmacokinetic properties which make them harder to develop than any given therapeutic antibody.^[147]

Aptamers, consisting of a single-stranded nucleic acid having 100 nucleotides or less that specifically bind to tumor-initiating cancer cells, were developed and described by Rich *et al.*^[148] The aptamer specifically binds to tumor-initiating cells of GBM.^[148] Aptamers were the targeting agent of choice for a patent by Bloembergen *et al.*^[149] where they used an aptamer-biopolymer-active agent conjugate system for the treatment of cancer.

CONCLUSIONS AND FUTURE DIRECTIONS

The development cycle of new therapeutic drug entities for brain and CNS costs from \$500 million to \$1.5 billion to get to market. Such huge expense could be directly attributed to drugs failing late in clinical trials or during the post-market follow-up (Phase IV).^[150] In spite of the advances in drug discovery technologies and high-throughput screening techniques, the development cycle of new therapeutic entities is still costly and lengthy. It is challenging to ensure efficacy and safety throughout the four phases of clinical trials.^[151,152]

To overcome these problems and alleviate some of the costs associated with new drug entity letdown, pharmaceutical formulators spend effort modifying and reinventing therapeutic and diagnostic agents, giving them new characteristics with enhanced safety and efficacy profiles. The use of novel nano-sized drug delivery systems (nanoDDS) is a major approach in such reinvention process. The nanoDDS can provide methods for targeting and releasing large quantities of therapeutic agents in exact, well-defined organs or tissues. Furthermore, they can easily be tailored, decorated, and modified via various agents such as stimuli-sensitive moieties, targeting agents, pharmacokinetics-modifying mediators, diagnostic agents, cell-penetrating peptides, protective PEGylation layer, or antibodies. Such modifying moieties can provide novel functions and better efficacy or safety profiles to current therapeutic agents. Furthermore, most nanoDDSs provide both hydrophobic and hydrophilic environments, facilitating better drug solubility and enhanced physicochemical characteristics.^[153]

Despite their advantages, nanoDDS suffer from many problems such as stability issues, formulation scale-up difficulties, and short shelf life. Developing novel complexes and sophisticated systems that could never reach the market due to high cost, inability of scaling-up the system, or instability of the final formulation is a major problem. Major process and formulation development concerns exist with respect to the scale-up process of complex nanoparticulate carriers. To overcome

these problems, pharmaceutical formulators started to divert their effort from nanoDDS to simple bioconjugate techniques to directly attach old problematic active pharmaceutical agents such as stimuli-sensitive moieties, targeting agents, pharmacokinetics-modifying mediators, diagnostic agents, cell-penetrating peptides, protective PEGylation layer, or antibodies. Active pharmaceutical ingredients can be directly conjugated to antibodies against specific cell-type markers to create a hybrid smart molecule that is able to direct the active molecule to the disease tissue specifically. Consequently, many patents currently focus on simple bioconjugate structures that are easily synthesized with high yield, reduced cost, and high stability of the final formulation. This could provide a practical direction for the development of novel management tools and therapeutics for brain cancer for researchers worldwide, paving the road to affordable, scalable, stable, efficient, and safe management strategies.

All such techniques and technologies were illustrated in the recent patents analyses discussing brain drug delivery during 2010 to 2015. Despite such efforts, the development of brain drug delivery carrier system is still costly and troublesome in its transformation from bench to bedside. Such systems require huge effort in their *in vivo*, *in vitro* testing and clinical trials. Most of the research funding in academia for brain delivery research comes from investing companies. Most of the companies investing in this field are small startups such as to-BBB and BiOasis Therapeutics. If such industrial startups fail to develop a promising moiety or carrier for brain drug delivery, their existence is usually jeopardized.^[154,155] An integrated "bench-to-clinic" approach, realized through a structural collaboration between industry and academia, would strongly promote the development of brain tumor-targeted nanomedicines towards effective and safe clinical application.^[156]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCE

- Jex HS. The Edwin Smith Surgical Papyrus: first milestone in the march of medicine. *Merck Rep* 1951;60:20-2.
- Sanchez GM, Meltzer ES. The Edwin Smith Papyrus: Updated translation of the trauma treatise and modern medical commentaries: Lockwood Press;2012.
- Brayn CP, Smith GE. The Papyrus Ebers, translated from the german version. Letchworth, Herts. The Guardian City Press LTD;1930.
- Papavramidou N, Papavramidis T, Demetriou T. Ancient Greek and Greco-Roman methods in modern surgical treatment of cancer. *Ann Surg Oncol* 2010;17:665-7.
- Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Globocan 2012, Cancer Incidence and Mortality Worldwide: IARC. In: internet N, editor. Cancer Fact Sheets. Lyon, France: International Agency for Research on Cancer; 2013.
- Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol* 2012;14 Suppl 5:v1-49.
- Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol* 2013;15 Suppl 2:ii1-56.
- Molnár Pt. Classification of primary brain tumors: molecular aspects, management of CNS tumors. InTech;2011.
- Chandana SR, Movva S, Arora M, Singh T. Primary brain tumors in adults. *Am Fam Physician* 2008;77:1423-30.
- Parrish KE, Sarkaria JN, Elmquist WF. Improving drug delivery to primary and metastatic brain tumors: Strategies to overcome the blood-brain barrier. *Clin Pharmacol Ther* 2015;97:336-46.
- Aliferis C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. *Pharmacol Ther* 2015;152:63-82.
- Armstrong TS. Head's up on the treatment of malignant glioma patients. *Oncol Nurs Forum* 2009;36:E232-40.
- Wen PY, Kesari S. Malignant Gliomas in Adults. *N Engl J Med* 2008;359:492-507.
- Kleihues P, Ohgaki H. Primary and secondary glioblastomas: from concept to clinical diagnosis. *Neuro Oncol* 1999;1:44-51.
- Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis* 2004;16:1-13.
- Cook LJ, Freedman J. Brain Tumors. New York: The Rosen Publishing Group; 2012.
- Dauchy S, Miller F, Couraud PO, Weaver RJ, Weksler B, Romero IA, Scherrmann JM, De Waziers I, Declèves X. Expression and transcriptional regulation of ABC transporters and cytochromes P450 in hCMEC/D3 human cerebral microvascular endothelial cells. *Biochem Pharmacol* 2009;77:897-909.
- Abbott NJ, Friedman A. Overview and introduction: the blood-brain barrier in health and disease. *Epilepsia* 2012;53:1-6.
- van Tellingen O, Yetkin-Arik B, de Gooijer MC, Wesseling P, Wurdinger T, de Vries HE. Overcoming the blood-brain tumor barrier for effective glioblastoma treatment. *Drug Resist Updat* 2015;19:1-12.
- Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev* 2005;57:173-85.
- Deeken JF, Loscher W. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. *Clin Cancer Res* 2007;13:1663-74.
- Barthoumeuf C, Chollet P, Bayet-Robert M. Curcuminoids in Combination Docetaxel for the Treatment of Cancer and Tumour Metastasis. In: Institut National De La Sante Et De La Recherche Medicale (Inserm); 2014. (ISBN No. US20140128337 A1)
- Loscher W, Potschka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. *NeuroRx* 2005;2:86-98.
- Ghosh C, Gonzalez-Martinez J, Hossain M, Cucullo L, Fazio V, Janigro D, Marchi N. Pattern of P450 expression at the human blood-brain barrier: Roles of epileptic condition and laminar flow. *Epilepsia* 2010;51:1408-17.
- Minn A, Ghersi-Egea JF, Perrin R, Leininger B, Siest G. Drug metabolizing enzymes in the brain and cerebral microvessels. *Brain Res Brain Res Rev* 1991;16:65-82.
- Dhermain FG, Hau P, Lanfermann H, Jacobs AH, van den Bent MJ. Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas. *Lancet Neurol* 2010;9:906-20.
- Tzeng SY, Green JJ. Therapeutic nanomedicine for brain cancer. *Ther Deliv* 2013;4:10.4155/tde.13.38.
- Madsen SJ, Hirschberg H. Site-specific opening of the blood-brain barrier. *J Biophotonics* 2010;3:356-67.
- Kazantsev AG, Outeiro TF. Drug discovery for CNS disorders: from bench to bedside. *CNS Neurol Disord Drug Targets* 2010;9:668.
- Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. *Neurobiol Dis* 2010;37:48-57.
- Pardridge WM. Drug delivery to the brain. *J Cereb Blood Flow Metab* 1997;17:713-31.
- Drappatz J, Brenner A, Wong ET, Eichler A, Schiff D, Groves MD, Mikkelsen T, Rosenfeld S, Sarantopoulos J, Meyers CA, Fielding RM, Elian K, Wang X, Lawrence B, Shing M, Kelsey S, Castaigne JP, Wen PY.

- Phase I Study of GRN1005 in Recurrent Malignant Glioma. *Clin Cancer Res* 2013;19:1567-76.
33. Jones AR, Shusta EV. Blood-brain barrier transport of therapeutics via receptor-mediation. *Pharm Res* 2007;24:1759-71.
 34. Rip J, Schenk GJ, de Boer AG. Differential receptor-mediated drug targeting to the diseased brain. *Expert Opin Drug Deliv* 2009;6:227-37.
 35. Wang YY, Lui PC, Li JY. Receptor-mediated therapeutic transport across the blood-brain barrier. *Immunotherapy* 2009;1:983-93.
 36. Papademetriou LT, Porter T. Promising approaches to circumvent the blood-brain barrier: progress, pitfalls and clinical prospects in brain cancer. *Ther Deliv* 2015;6:989-1016.
 37. Demeule M, Regina A, Che C, Poirier J, Nguyen T, Gabathuler R, Castaigne JP, Beliveau R. Identification and design of peptides as a new drug delivery system for the brain. *J Pharmacol Exp Ther* 2008;324:1064-72.
 38. Jefferies W. CNS-targeted conjugates having modified fc regions and methods of use thereof. In: Bioasis Technologies Inc.; 2015. (ISBN No. US20150093399 A1)
 39. Demeule M, Currie JC, Bertrand Y, Che C, Nguyen T, Regina A, Gabathuler R, Castaigne JP, Beliveau R. Involvement of the low-density lipoprotein receptor-related protein in the transcytosis of the brain delivery vector angioprep-2. *J Neurochem* 2008;106:1534-44.
 40. Kurzrock R, Gabrail N, Chandhasin C, Moulder S, Smith C, Brenner A, Sankhala K, Mita A, Elian K, Bouchard D, Sarantopoulos J. Safety, pharmacokinetics, and activity of GRN1005, a novel conjugate of angioprep-2, a peptide facilitating brain penetration, and paclitaxel, in patients with advanced solid tumors. *Mol Cancer Ther* 2012;11:308-16.
 41. Menlo Park C. Geron Discontinues GRN1005 and Restructures to Focus on Imetelstat Development in Hematologic Malignancies and Solid Tumors with Short Telomeres. In: 2012.
 42. Che C, Yang G, Thiot C, Lacoste MC, Currie JC, Demeule M, Regina A, Beliveau R, Castaigne JP. New Angioprep-modified doxorubicin (ANG1007) and etoposide (ANG1009) chemotherapeutics with increased brain penetration. *J Med Chem* 2010;53:2814-24.
 43. Bertrand Y, Currie JC, Demeule M, Regina A, Che C, Abulrob A, Fatehi D, Sartelet H, Gabathuler R, Castaigne JP, Stanimirovic D, Beliveau R. Transport characteristics of a novel peptide platform for CNS therapeutics. *J Cell Mol Med* 2010;14:2827-39.
 44. Thomas FC, Taskar K, Rudraraju V, Goda S, Thorsheim HR, Gaasch JA, Mittapalli RK, Palmieri D, Steeg PS, Lockman PR, Smith QR. Uptake of ANG1005, a novel paclitaxel derivative, through the blood-brain barrier into brain and experimental brain metastases of breast cancer. *Pharm Res* 2009;26:2486-94.
 45. Xin H, Jiang X, Gu J, Sha X, Chen L, Law K, Chen Y, Wang X, Jiang Y, Fang X. Angioprep-conjugated poly(ethylene glycol)-co-poly(epsilon-caprolactone) nanoparticles as dual-targeting drug delivery system for brain glioma. *Biomaterials* 2011;32:4293-305.
 46. Shen J, Zhan C, Xie C, Meng Q, Gu B, Li C, Zhang Y, Lu W. Poly(ethylene glycol)-block-poly(D, L-lactide acid) micelles anchored with angioprep-2 for brain-targeting delivery. *J Drug Target* 2011;19:197-203.
 47. Sun X, Pang Z, Ye H, Qiu B, Guo L, Li J, Ren J, Qian Y, Zhang Q, Chen J, Jiang X. Co-delivery of pEGFP-hTRAIL and paclitaxel to brain glioma mediated by an angioprep-conjugated liposome. *Biomaterials* 2012;33:916-24.
 48. Gaillard PJ. Conjugates for targeted drug delivery across the blood-brain barrier. In: to-BBB Holding B.V.; 2013. (ISBN No. EP2308514 B1)
 49. Gaillard PJ, De Boer AG, Brink A. Differentially Expressed Nucleic Acids in the Blood-Brain Barrier Under Inflammatory Conditions. In: Gaillard, P.J.De Boer, A.G. Brink, A.; 2008. (ISBN No. US20080213179 A1)
 50. Gaillard PJ. Glutathione-based drug delivery system. In: To-Bbb Holding B.V.; 2010. (ISBN No. WO2010095940 A2)
 51. Dickerson IM, Brown EB. Methods of treating cancer using an agent that modulates activity of the calcitonin-gene related peptide ("CGRP") receptor. In: University Of Rochester; 2011. (ISBN No. US 20110189205 A1)
 52. Furness S, Johns T, Wookey PJ. Diagnosis and treatment of brain tumors. In: Welcome Receptor Antibodies Pty Ltd; 2012. (ISBN No. WO2012000062 A1)
 53. Tortorella S, Karagiannis TC. Transferrin receptor-mediated endocytosis: a useful target for cancer therapy. *J Membr Biol* 2014;247:291-307.
 54. Ding H, Ljubimova JY, Holler E, Black KL. Poly(beta malic acid) with pendant Leu-Leu-Leu tripeptide for effective cytoplasmic drug delivery. In: Cedars-Sinai Medical Center; 2014. (ISBN No. US 8795648 B2)
 55. Patil R, Holler E, Black KL, Ljubimova JY. Drug delivery of temozolomide for systemic based treatment of cancer. In: Cedars-Sinai Medical Center; 2014. (ISBN No. US20140161762 A1)
 56. Weiss N, Miller F, Cazaubon S, Couraud PO. [Blood-brain barrier part III: therapeutic approaches to cross the blood-brain barrier and target the brain]. *Rev Neurol* 2010;166:284-8.
 57. Estella-Hermoso de Mendoza A, Preat V, Mollinedo F, Blanco-Prieto MJ. *In vitro* and *in vivo* efficacy of edelfosine-loaded lipid nanoparticles against glioma. *J Control Release* 2011;156:421-6.
 58. Coley HM. Overcoming multidrug resistance in cancer: clinical studies of p-glycoprotein inhibitors. *Methods Mol Biol* 2010;596:341-58.
 59. Das M, Sahoo SK. Folate decorated dual drug loaded nanoparticle: role of curcumin in enhancing therapeutic potential of nultin-3a by reversing multidrug resistance. *PLoS One* 2012;7:e32920.
 60. Kim MK, Choo H, Chong Y. Water-soluble and cleavable quercetin-amino acid conjugates as safe modulators for P-glycoprotein-based multidrug resistance. *J Med Chem* 2014;57:7216-33.
 61. Kim MK, Park KS, Choo H, Chong Y. Quercetin-POM (pivaloxymethyl) conjugates: Modulatory activity for P-glycoprotein-based multidrug resistance. *Phytomedicine* 2015;22:778-85.
 62. Romiti N, Tramonti G, Donati A, Chieli E. Effects of grapefruit juice on the multidrug transporter P-glycoprotein in the human proximal tubular cell line HK-2. *Life Sci* 2004;76:293-302.
 63. Banks WA, Kumar VB, Darling T, Clayton R. Modulation of blood-brain barrier protein expression. In: St. Louis University; 2010. (ISBN No. US20100196393 A1)
 64. McChesney JD, Tapolsky G, Emerson DL, Marshall J, Ahmed T, Cohn A, Kurman M, Modiano M. Taxane analogs for the treatment of brain cancer. In: Tapestry Pharmaceuticals, Inc.; 2011. (ISBN No. US 20110318334 A1)
 65. Tosi G, Vergoni AV, Ruozi B, Bondioli L, Badiali L, Rivasi F, Costantino L, Forni F, Vandelli MA. Sialic acid and glycopeptides conjugated PLGA nanoparticles for central nervous system targeting: *In vivo* pharmacological evidence and biodistribution. *J Control Release* 2010;145:49-57.
 66. Bazile D, Prud'homme C, Bassoullet MT, Marlard M, Spenlehauer G, Veillard M. Stealth Me. PEG-PLA nanoparticles avoid uptake by the mononuclear phagocytes system. *J Pharm Sci* 1995;84:493-8.
 67. Niidome T, Yamagata M, Okamoto Y, Akiyama Y, Takahashi H, Kawano T, Katayama Y, Niidome Y. PEG-modified gold nanorods with a stealth character for *in vivo* applications. *J Control Release* 2006;114:343-7.
 68. Weissenbock A, Wirth M, Gabor F. WGA-grafted PLGA-nanospheres: preparation and association with Caco-2 single cells. *J Control Release* 2004;99:383-92.
 69. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. *Adv Drug Deliv Rev* 2002;54:631-51.
 70. Zhang P, Ling G, Sun J, Zhang T, Yuan Y, Sun Y, Wang Z, He Z. Multifunctional nanoassemblies for vincristine sulfate delivery to overcome multidrug resistance by escaping P-glycoprotein mediated efflux. *Biomaterials* 2011;32:5524-33.
 71. Petkar KC, Chavhan SS, Agatonovik-Kustrin S, Sawant KK. Nanostructured materials in drug and gene delivery: a review of the state of the art. *Crit Rev Ther Drug Carrier Syst* 2011;28:101-64.
 72. Meyers JD, Doane T, Burda C, Basilion JP. Nanoparticles for imaging and treating brain cancer. *Nanomedicine* 2013;8:123-43.
 73. Chen Y, Liu L. Modern methods for delivery of drugs across the blood-brain barrier. *Adv Drug Deliv Rev* 2012;64:640-65.
 74. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine* 2008;3:133.
 75. Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. Colloidal carriers and blood-brain barrier (BBB) translocation: a way to deliver drugs to the

- brain? *Int J Pharm* 2005;298:274-92.
76. Wesselinova D. Current major cancer targets for nanoparticle systems. *Curr Cancer Drug Targets* 2011;11:164-83.
 77. Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. *J Pharm Sci* 2003;92:1343-55.
 78. Li AJ, Zheng YH, Liu GD, Liu WS, Cao PC, Bu ZF. Efficient delivery of docetaxel for the treatment of brain tumors by cyclic RGD-tagged polymeric micelles. *Mol Med Rep* 2015;11:3078-86.
 79. Krebs MD. Biodegradable polymers for delivery of therapeutic agents. In: Colorado School Of Mines; 2014. (ISBN No. US20140377366 A1)
 80. Bae YH, Na K, Lee ES. PH-sensitive polymeric micelles for drug delivery. In: University Of Utah Research Foundation; 2010. (ISBN No. US 7659314 B2)
 81. Zhou Z, Patel TR, Piepmeier JM, Saltzman WM. Highly penetrative nanocarriers for treatment of CNS disease. In: Yale University; 2015. (ISBN No. US20150118311 A1)
 82. Wu XY, Shalviri A. Polymeric nanoparticles useful in theranostics. In: The Governing Council Of The University Of Toronto; 2013. (ISBN No. WO2013127004 A1)
 83. Yerushalmi N, Kredon-Russo S, Lithwick YG, Satchi-Fainaro R, Ofek P. Nanocarrier system for micromas and uses thereof. In: Rosetta Genomics Ltd. and Ramot At Tel-Aviv University Ltd; 2014. (ISBN No. WO2014203189 A1)
 84. Tour JM, Berlin J, Marcano D, Baskin DS, Sharpe MA. Targeted nanovectors and their use for treatment of brain tumors. In: The Methodist Hospital Research Institute & William Marsh Rice University; 2014. (ISBN No. US 20140154269 A1)
 85. Muller LK, Landfester K. Natural liposomes and synthetic polymeric structures for biomedical applications. *Biochem Biophys Res Commun* 2015;468:411-8.
 86. Lai F, Fadda AM, Sinico C. Liposomes for brain delivery. *Expert Opinion on Drug Delivery* 2013;10:1003-22.
 87. Xiang Y, Liang L, Wang X, Wang J, Zhang X, Zhang Q. Chloride channel-mediated brain glioma targeting of chlorotoxin-modified doxorubicin-loaded liposomes. *J Control Release* 2011;152:402-10.
 88. Li XY, Zhao Y, Sun MG, Shi JF, Ju RJ, Zhang CX, Li XT, Zhao WY, Mu LM, Zeng F, Lou JN, Lu WL. Multifunctional liposomes loaded with paclitaxel and artemether for treatment of invasive brain glioma. *Biomaterials* 2014;35:5591-604.
 89. Chen H, Qin Y, Zhang Q, Jiang W, Tang L, Liu J, He Q. Lactoferrin modified doxorubicin-loaded procationic liposomes for the treatment of gliomas. *Eur J Pharm Sci* 2011;44:164-73.
 90. Migliore MM, Vyas TK, Campbell RB, Amiji MM, Waszczak BL. Brain delivery of proteins by the intranasal route of administration: a comparison of cationic liposomes versus aqueous solution formulations. *J Pharm Sci* 2010;99:1745-61.
 91. Munson JM, Bellamkonda RV, Arbiser JL. Nanocarrier therapy for treating invasive tumors. In: Emory University & Georgia Institute Of Technology; 2010. (ISBN No. WO2010124004 A2)
 92. Redelmeier T, Luz M. Liposomal Composition for Convection-Enhanced Delivery to the Central Nervous system. In: MedGenesis Therapeutix Inc.; 2011. (ISBN No. US20110274625 A1)
 93. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. *Adv Drug Deliv Rev* 2001;47:165-96.
 94. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. *J Control Release* 2008;127:97-109.
 95. Panyam J, Chavanpatil MD. Lipid-derived nanoparticles for brain-targeted drug delivery. In: Panyam, J. and Chavanpatil, M. D.; 2010. (ISBN No. US 20100076092 A1)
 96. Jin J, Bae KH, Yang H, Lee SJ, Kim H, Kim Y, Joo KM, Seo SW, Park TG, Nam DH. *In vivo* specific delivery of c-Met siRNA to glioblastoma using cationic solid lipid nanoparticles. *Bioconjug Chem* 2011;22:2568-72.
 97. Singh I, Swami R, Pooja D, Jeengar MK, Khan W, Sistla R. Lactoferrin bioconjugated solid lipid nanoparticles: a new drug delivery system for potential brain targeting. *J Drug Target* 2016 24:212-23
 98. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev* 2004;56:185-229.
 99. Gaillard PJ, Appeldoorn CCM, Dorland R, van Kregten J, Manca F, Vugts DJ, Windhorst B, van Dongen GAMS, de Vries HE, Maussang D, van Tellingen O. Pharmacokinetics, Brain Delivery, and Efficacy in Brain Tumor-Bearing Mice of Glutathione Pegylated Liposomal Doxorubicin (2B3-101). *PLoS One* 2014;9:e82331.
 100. Gaillard PJ, Kerklan BM, Aftimos P, Altintas S, Jager A, Gladdines W, Lonnqvist F, Soetekouw P, Verheul H, Awada A, Schellens J, Brandsma D. Abstract CT216: Phase I dose escalating study of 2B3-101, glutathione PEGylated liposomal doxorubicin, in patients with solid tumors and brain metastases or recurrent malignant glioma. *Cancer Res* 2014;74:CT216.
 101. Nektar Therapeutics. Etirinotecan Pegol (NKTR-102): A Next-Generation Topoisomerase I Inhibitor Being Developed in Breast, Ovarian and Colorectal Cancers. In: Etirinotecan Pegol (NKTR-102). USA: "Nektar Therapeutics"; 2013.
 102. Nagpal S, Recht CK, Bertrand S, Thomas RP, Ajlan A, Pena J, Gershon M, Coffey G, Kunz PL, Li G, Recht LD. Phase II pilot study of single-agent etirinotecan pegol (NKTR-102) in bevacizumab-resistant high grade glioma. *Neuro Oncol* 2015;123:277-82.
 103. Hermanson GT. Chapter 1 - Introduction to Bioconjugation. In: editor~editors, editor. *Bioconjugate Techniques*. Boston:Academic Press;2013.p.1-125.
 104. Duncan R. Polymer conjugates as anticancer nanomedicines. *Nat Rev Cancer* 2006;6:688-701.
 105. Bacha JA, Brown D, Dunn S, Steinø A. Use of dianhydrogalactitol and analogs and derivatives thereof to treat glioblastoma multiforme. In: Del Mar Pharmaceuticals; 2014. (ISBN No. US20140221442 A1)
 106. Tschoepe M, Kaleta K, Kumar V. Anti-egfr antibody drug conjugate formulations. In: Abbvie Deutschland GmbH & Co.Kg, Abbvie Inc.; 2014. (ISBN No. WO2014143765 A1)
 107. Adair JH, Kester M, Smith JP, Altinoglu EI, Barth BM, Kaiser JM, Matters GL, Mcgovern C, Morgan TT, Sharma R. Bioconjugation of calcium phosphosilicate nanoparticles for selective targeting of cells *in vivo*. In: The Pennsylvania State Research Foundation; 2011. (ISBN No. WO 2011057216 A1)
 108. Hutchison R, Vitalis TZ, Gabathuler R. P97-antibody conjugates and methods of use. In: Bioasis Technologies, Inc.; 2013. (ISBN No. US 20130183368 A1)
 109. Kang T, Jiang M, Jiang D, Feng X, Yao J, Song Q, Chen H, Gao X, Chen J. Enhancing Glioblastoma-Specific Penetration by Functionalization of Nanoparticles with an Iron-Mimic Peptide Targeting Transferrin/Transferrin Receptor Complex. *Mol Pharm* 2015;12:2947-61.
 110. Dardevet L, Rani D, Aziz TA, Bazin I, Sabatier JM, Fadl M, Brambilla E, De Waard M. Chlorotoxin: a helpful natural scorpion peptide to diagnose glioma and fight tumor invasion. *Toxins (Basel)* 2015;7:1079-101.
 111. Pyrko P, Wang W, Markland FS, Swenson SD, Schmitmeier S, Schonthal AH, Chen TC. The role of contortrostatin, a snake venom disintegrin, in the inhibition of tumor progression and prolongation of survival in a rodent glioma model. *J Neurosurg* 2005;103:526-37.
 112. Kasai T, Nakamura K, Vaidyanath A, Chen L, Sekhar S, El-Ghban S, Okada M, Mizutani A, Kudoh T, Murakami H, Seno M. Chlorotoxin Fused to IgG-Fc Inhibits Glioblastoma Cell Motility via Receptor-Mediated Endocytosis. *J Drug Deliv* 2012;2012:975763.
 113. Yoo B, Ifediba MA, Ghosh S, Medarova Z, Moore A. Combination treatment with theranostic nanoparticles for glioblastoma sensitization to TMZ. *Mol Imaging Biol* 2014;16:680-9.
 114. Locatelli E, Naddaka M, Uboldi C, Loudos G, Fragogeorgi E, Molinari V, Pucci A, Tsotakos T, Psimadas D, Ponti J, Franchini MC. Targeted delivery of silver nanoparticles and alisertib: *in vitro* and *in vivo* synergistic effect against glioblastoma. *Nanomedicine (Lond)* 2014;9:839-49.
 115. Zhao L, Zhu J, Cheng Y, Xiong Z, Tang Y, Guo L, Shi X, Zhao J. Chlorotoxin-Conjugated Multifunctional Dendrimers Labeled with Radionuclide ¹³¹I for Single Photon Emission Computed Tomography

- Imaging and Radiotherapy of Gliomas. *ACS Appl Mater Interfaces* 2015;7:19798-808.
116. Zhao L, Shi X, Zhao J. Chlorotoxin-conjugated nanoparticles for targeted imaging and therapy of glioma. *Curr Top Med Chem* 2015;15:1196-208.
 117. Wang X, Guo Z. Chlorotoxin-conjugated onconase as a potential anti-glioma drug. *Oncol Lett* 2015;9:1337-42.
 118. Wang H, Gu W, Xiao N, Ye L, Xu Q. Chlorotoxin-conjugated graphene oxide for targeted delivery of an anticancer drug. *Int J Nanomedicine* 2014;9:1433-42.
 119. Cheng Y, Zhao J, Qiao W, Chen K. Recent advances in diagnosis and treatment of gliomas using chlorotoxin-based bioconjugates. *Am J Nucl Med Mol Imaging* 2014;4:385-405.
 120. Zhang M, Ellenbogen RG, Kievit F, Silber JR, Stephen Z, Veiseh O. Nanoparticle for targeting brain tumors and delivery of o6-benzylguanine. In: University of Washington through its Center for Commercialization; 2014. (ISBN No. US20140286872 A1)
 121. Veiseh O, Kievit FM, Fang C, Mu N, Jana S, Leung MC, Mok H, Ellenbogen RG, Park JO, Zhang M. Chlorotoxin bound magnetic nanovector tailored for cancer cell targeting, imaging, and siRNA delivery. *Biomaterials* 2010;31:8032-42.
 122. Kievit FM, Veiseh O, Fang C, Bhattarai N, Lee D, Ellenbogen RG, Zhang M. Chlorotoxin labeled magnetic nanovectors for targeted gene delivery to glioma. *ACS Nano* 2010;4:4587-94.
 123. Butte PV, Mamelak A, Parrish-Novak J, Drazin D, Shweikeh F, Gangalum PR, Chesnokova A, Ljubimova JY, Black K. Near-infrared imaging of brain tumors using the Tumor Paint BLZ-100 to achieve near-complete resection of brain tumors. *Neurosurg Focus* 2014;36:E1.
 124. Fidel J, Kennedy KC, Dermell WS, Hansen S, Wiss V, Stroud MR, Molho JI, Knoblauch SE, Meganck J, Olson JM, Rice B, Parrish-Novak J. Preclinical Validation of the Utility of BLZ-100 in Providing Fluorescence Contrast for Imaging Spontaneous Solid Tumors. *Cancer Res* 2015;75:4283-91.
 125. Rodriguez-Devora JI, Ambure S, Shi Z-D, Yuan Y, Sun W, Xu T. Physically facilitating drug-delivery systems. *Ther Deliv* 2012;3:125-39.
 126. Davalos RV, Rossmelst JH, Garcia PA. Acute blood-brain barrier disruption using electrical energy based therapy. In: Virginia Tech Intellectual Properties, Inc.; 2014. (ISBN No. US20140039489A1)
 127. Qiu LB, Ding GR, Li KC, Wang XW, Zhou Y, Zhou YC, Li YR, Guo GZ. The role of protein kinase C in the opening of blood-brain barrier induced by electromagnetic pulse. *Toxicology* 2010;273:29-34.
 128. Braun S, Oppermann H, Mueller A, Renner C, Hovhannisyana A, Baran-Schmidt R, Gebhardt R, Hipkiss A, Thierry J, Meixensberger J, Gaunitz F. Hedgehog signaling in glioblastoma multiforme. *Cancer Biol Ther* 2012;13:487-95.
 129. Akhtari M, Engel J. Use of functionalized magnetic nanoparticles in cancer detection and treatment. In: The Regents Of The University Of California; 2015. (ISBN No. US 9011913 B2)
 130. Yang VC, David AE. Compositions and methods for targeting tumors. In: The Regents Of The University Of Michigan; 2011. (ISBN No. US20110054236 A1)
 131. Dixit S, Miller K, Zhu Y, McKinnon E, Novak T, Kenney ME, Broome AM. Dual Receptor-Targeted Theranostic Nanoparticles for Localized Delivery and Activation of Photodynamic Therapy Drug in Glioblastomas. *Mol Pharm* 2015;12:3250-60.
 132. Liu H-L, Fan C-H, Ting C-Y, Yeh C-K. Combining Microbubbles and Ultrasound for Drug Delivery to Brain Tumors: Current Progress and Overview. *Theranostics* 2014;4:432-44.
 133. Hynynen K, McDannold N, Sheikov NA, Jolesz FA, Vykhodtseva N. Local and reversible blood-brain barrier disruption by noninvasive focused ultrasound at frequencies suitable for trans-skull sonications. *Neuroimage* 2005;24:12-20.
 134. Blomley MJK, Cooke JC, Unger EC, Monaghan MJ, Cosgrove DO. Microbubble contrast agents: a new era in ultrasound. *BMJ : British Medical Journal* 2001;322:1222-5.
 135. Kang ST, Yeh CK. Ultrasound microbubble contrast agents for diagnostic and therapeutic applications: current status and future design. *Chang Gung Med J* 2012;35:125-39.
 136. Chen YC, Chiang CF, Wu SK, Chen LF, Hsieh WY, Lin WL. Targeting microbubbles-carrying TGFbeta1 inhibitor combined with ultrasound sonication induce BBB/BBB disruption to enhance nanomedicine treatment for brain tumors. *J Control Release* 2015;211:53-62.
 137. Liao AH, Chou HY, Hsieh YL, Hsu SC, Wei KC, Liu HL. Enhanced Therapeutic Epidermal Growth Factor Receptor (EGFR) Antibody Delivery via Pulsed Ultrasound with Targeting Microbubbles for Glioma Treatment. *Journal of Medical and Biological Engineering* 2015;35:156-64.
 138. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281-97.
 139. Iwakawa HO, Tomari Y. The Functions of MicroRNAs: mRNA Decay and Translational Repression. *Trends Cell Biol* 2015;10.1016/j.tcb.2015.07.011.
 140. Alvarez-Garcia I, Miska EA. MicroRNA functions in animal development and human disease. *Development* 2005;132:4653-62.
 141. LeBlanc VC, Morin P. Exploring miRNA-Associated Signatures with Diagnostic Relevance in Glioblastoma Multiforme and Breast Cancer Patients. *J Clin Med* 2015;4:1612-30.
 142. Hummel R, Maurer J, Haier J. MicroRNAs in brain tumors : a new diagnostic and therapeutic perspective? *Mol Neurobiol* 2011;44:223-34.
 143. Novakova J, Slaby O, Vyzula R, Michalek J. MicroRNA involvement in glioblastoma pathogenesis. *Biochem Biophys Res Commun* 2009;386:1-5.
 144. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res* 2005;65:6029-33.
 145. Møller HG, Rasmussen AP, Andersen HH, Johnsen KB, Henriksen M, Duroux M. A Systematic Review of MicroRNA in Glioblastoma Multiforme: Micro-modulators in the Mesenchymal Mode of Migration and Invasion. *Molecular Neurobiology* 2013;47:131-44.
 146. Park JB, Lee SH, Park EK, Lee D, Yang HS, Yoo H, Kim HJ, Kim TH, Kwak HJ. Anti-cancer composition comprising micromolecules. In: National Cancer Center; 2011. (ISBN No. US20110124712 A1)
 147. Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. *Nat Rev Drug Discov* 2010;9:537-50.
 148. Rich JN, Kim Y, Hjelmeland A. Aptamers for tumor initiating cells. In: The Cleveland Clinic Foundation; 2014. (ISBN No. WO2014121256 A1)
 149. Bloembergen S, McLennan IJ, Jones N, Wagner R, Shermion AKG, Elsayed AR, Liu J. Aptamer bioconjugate drug delivery device. In: Ecosynthetix Ltd.; 2013. (ISBN No. US 20130090467 A1)
 150. Jataru A, Peptu C, Popa M, Indrei A. Micro- and nanoparticles--medical applications. *Rev Med Chir Soc Med Nat Iasi* 2009;113:1160-9.
 151. Burgess R. Medical applications of nanoparticles and nanomaterials. *Stud Health Technol Inform* 2009;149:257-83.
 152. Irache JM. [Nanomedicine: nanoparticles with medical applications]. *An Sist Sanit Navar* 2008;31:7-10.
 153. Dusinska M, Dusinska M, Fjellsbo L, Magdolenova Z, Rinna A, Runden Pran E, Bartonova A, Heimstad E, Harju M, Tran L, Ross B, Juillerat L, Halamoda Kenzaui B, Marano F, Boland S, Guadagnini R, Saunders M, Cartwright L, Carreira S, Whelan M, Kelin C, Worth A, Palosaari T, Burello E, Housiadas C, Pilou M, Volkovova K, Tulinska J, Kazimirova A, Barancokova M, Sebekova K, Hurbankova M, Kovacicova Z, Knudsen L, Poulsen M, Mose T, Vila M, Gombau L, Fernandez B, Castell J, Marcomini A, Pojana G, Bilanicova D, Vallotto D. Testing strategies for the safety of nanoparticles used in medical applications. *Nanomedicine* 2009;4:605-7.
 154. to-BBB technologies BV. Company restarting as 2-BBB Medicines BV. In: The Netherlands; 2015.
 155. TEDxMaastricht. Brain Train. Effective Brain Cancer Treatment: Pieter Gaillard at TEDxMaastricht. In: TEDxMaastricht, editor: Gaillard, P.; 2013.
 156. Lammers T, Hennink WE, Storm G. Tumour-targeted nanomedicines: principles and practice. *Br J Cancer* 2008;99:392-7.