Supplementary Table 2. Recent research publications using active targeting technology(s) in targeting brain metastases of breast cancer

Title of paper	API	Delivery system	Targeting moiety	Mechanism of targeting	Year	Ref.
Improved treatment of MT-3 breast cancer and brain metastases in a mouse xenograft by LRP-targeted oxaliplatin liposomes	Oxaliplatin, a platinum chemotherapeutic agent	Angiopep targeted fluid membrane liposomes containing Oxaliplatin.	Angiopep ligand that specifically targets the LRP protein	When Angiopep binds to LRP, this mediates transcytosis of the Liposomal formulation across BBB	2016	[1]
Uptake of ANG1005, A novel paclitaxel derivative, through the blood-brain barrier into brain and experimental brain metastases of breast cancer	Paclitaxel	Angiopep-2 paclitaxel conjugate	Angiopep-2	Angiopep-2 peptide-paclitaxel conjugate designed to improve delivery of paclitaxel across the BBB through LRP receptor-mediated transcytosis	2009	[2]
Treatment of experimental brain metastasis with MTO-liposomes: impact of fluidity and LRP-targeting on the therapeutic result	Mitoxantrone (MTO)	Ligand-targeted fluid membrane liposomes containing MTO	Angiopep-2 that binds specifically to a member of the low-density lipoprotein receptor-related protein family (LRP)	Angiopep-2 equipped liposomes were developed to target LRP that is expressed on the surface of barrier-forming cells, which enhances endocytosis of liposomes containing mitoxantrone across BBB	2012	[3]
Focused ultrasound delivers targeted immune cells to metastatic brain tumors	Natural killer cells, the cytotoxic lymphocytes	Transfected HER2-specific NK-92 cells with superparamagnetic iron oxide nanoparticles	Chimeric HER2 antigen receptor	FUS caused BBBD resulting in an increased HER2-targeted NK-92 cell accumulation in the sonicated tumor volume	2013	[4]
Paclitaxel-hyaluronic nanoconjugates prolong overall survival in a preclinical brain metastases of breast cancer model	Paclitaxel (PTX)	An ultra-small hyaluronic acid (HA) paclitaxel nanoconjugate	Hyaluronic acid	The ultra-small nanoconjugate crosses BTB and actively targets the metastatic cancer cell by CD44 receptor-mediated endocytosis Hyaluronic acid bind specifically to CD44 receptors that are overexpressed in brain metastases of breast cancer	2013	[5]
A multifunctional polymeric nanotheranostic system delivers doxorubicin and imaging agents across the blood brain barrier targeting brain metastases of breast cancer	Doxorubicin is the therapeutic agent while gadolinium (Gd) MR contrast agent and Hoechst 33342 (NIR fluorescence dye) are used as diagnostic agents	A nanocarrier system based on poly (methacrylic acid) polysorbate 80-grafted-starch	Polysorbate 80	Polysorbate 80 leads to the enhanced adsorption of apolipoprotein-E (Apo-E) to the particle surface The presence of Apo-E promotes nanoparticle internalization in the brain capillary endothelial cells via LDL receptor-mediated endocytosis	2014	[6]
ANG4043, a novel brain-penetrant peptide-mAb conjugate, is efficacious against HER2-positive intracranial tumors in mice	anti-HER 2 monoclonal antibody (trastuzumab)	Angiopep-2 -anti-HER2 mAb conjugate	Angiopep-2 is a 19-amino acid peptide that specifically binds LRP 1 a member of the LDL receptor family)	Angiopep-2-trastuzumab conjugate efficiently penetrates the BBB through LRP1 receptor-mediated transcytosis, which is highly expressed on BBB capillary endothelial cells	2015	[7]
Enhanced antitumor effects of the BRBP1 compound peptide BRBP1-TAT-KLA on human brain metastatic breast cancer	KLA, a proapoptotic peptide, that disrupts mitochondrial membrane	A targeting peptide composite system (BRBP1-TAT-KLA) comprised of KLA peptide as the drug, TAT as a cell penetrating peptide, and BRBP1 as a targeting element	BRBP1, a linear dodecapeptide peptide binds specifically to the brain metastatic breast cancer	BRBP1 is the peptide that targets the composite system specifically to the cancer cells TAT facilitates the penetration of the system to deliver proapoptotic KLA within cells KLA induces mitochondrial damage and triggers apoptosis	2015	[8]
Targeting breast to brain metastatic tumors with death receptor ligand expressing therapeutic stem cells	TNF receptor superfamily member 10A/10B apoptosis-inducing ligand (TRAIL) that is capable of inducing apoptosis through receptor-mediated mechanism	TRAIL-secreting engineered neural stem cells	Tumor tropic Neural stem cells, which can penetrate brain endothelium and migrate towards metastatic foci in the brain	TRAILs are capable of inducing apoptosis in a number of cancer cells via the binding to their cognate receptors and the initiation of death receptor-mediated signaling TRAIL is a promising candidate for cancer therapies due to its capability of specifically	2015	[9]

Title of paper	API	Delivery system	Targeting moiety	Mechanism of targeting	Year	Ref.
				targeting tumor cells while sparing normal cells		
Nanoparticles coated with the tumor-penetrating peptide iRGD reduce experimental breast cancer metastasis in the brain	iRGD peptide (Arginine-glycine-aspartic acid	Nanoparticles coated with a tumor-penetrating peptide (iRGD)	iRGD peptide	iRGD peptide targets tumor by binding to αv integrins, useful molecular targets that are overexpressed on many cancer cells Proteolytically processed iRGD also exerts anti-metastatic activity by binding to neuropilin-1 and activating an endocytic bulk transport pathway through tumor tissue	2015	[10]
Anti-cancer antibody trastuzumab-melanotransferrin conjugate (BT2111) for the Treatment of Metastatic HER2+ breast cancer tumors in the brain: an *in-vivo* study	Trastuzumab	Trastuzumab melanotransferrin conjugate	Melanotransferrin which is a unique blood-brain barrier transporter	Human melanotransferrin-trastuzumab conjugate is actively transported across BBB through a receptor-mediated transcytosis involving a member of the low-density lipoprotein receptor-related protein family (LRP)	2016	[11]
Blood-brain barrier-penetrating amphiphilic polymer nanoparticles deliver docetaxel for the treatment of brain metastases of triple negative breast cancer	Docetaxel	A PS 80-based amphiphilic polymer nanocarrier system	Polysorbate 80	Polysorbate 80 leads to the enhanced adsorption of apolipoprotein-E (Apo-E) to the particle surface The presence of Apo-E promotes nanoparticle internalization in the brain capillary endothelial cells via LDL receptor-mediated endocytosis	2017	[12]
Regional delivery of chimeric antigen receptor-engineered T cells effectively targets HER2+ breast cancer metastasis to the brain	The HER2-targeted scFv sequence was derived from the humanized monoclonal antibody trastuzumab and cloned into the antigen-binding domain of the HER2-CAR	Chimeric antigen receptor (CAR)-based T cell immunotherapy	The HER2-targeted scFv sequence derived from trastuzumab will target HER2 receptors	Following intracranial or intracerebroventricular injection (i.c.v), HER2-CAR T-cells effectively targeted breast cancer brain metastasis	2018	[13]
Two-step targeted hybrid nanoconstructs increase brain penetration and efficacy of the therapeutic antibody trastuzumab against brain metastasis of HER2-positive breast cancer	Trastuzumab	A nano-construct system made by self-assembly of a polysorbate 80 (PS 80)-containing terpolymer, a lipid, and polymer-bound trastuzumab	Polysorbate 80	Polysorbate 80 leads to the enhanced adsorption of apolipoprotein-E (Apo-E) to the system surface allowing its penetration across BBB by receptor-mediated transcytosis The gradual dissociation of the particle allows trastuzumab to efficiently target HER2+ cancer cells to exert its therapeutic effect	2018	[14]
Synergistic tumor microenvironment targeting and blood-brain barrier penetration via a pH-responsive dual-ligand strategy for enhanced breast cancer and brain metastasis therapy	PTX	An acid-cleavable FA and dNP2 dual modified liposome (cFd-Lip) was formulated as the delivery system of PTX	Acid cleavable **Folic acid** was used as targeting ligand in addition to a BBB-permeable peptide **dNP2 peptide**	Folic acids bind with high affinity to folate receptors that are overexpressed on multiple tumor cells and BBB which enhances delivery of PTX loaded liposomes to cancer cells Low pH of tumor microenvironment cleaves folic acid moiety allowing deeper penetration of liposomal formulation within cancer cells via dNP2 peptide	2018	[15]
Cell-penetrating peptide-modified gold nanoparticles for	Doxorubicin	PEGylated gold nanoparticle conjugated	TAT, cell-penetrating peptide derived from HIV.	TAT peptide facilitated penetration of NPs across BBB	2016	[16]

Title of paper	API	Delivery system	Targeting moiety	Mechanism of targeting	Year	Ref.
the delivery of doxorubicin to brain metastatic breast cancer		to HIV-derived TAT peptide as well as doxorubicin		by the help of its transmembrane domain TAT peptide was shown to destabilize a brain capillary monolayer increasing its permeability		
MRI virtual biopsy and treatment of brain metastatic tumors with targeted nanobioconjugates: nanoclinic in the brain	Specific mRNA suppressors (AONs)	poly(β-L-malic acid) delivery platform	MsTfR-mAb Trastuzumab to bind to HER2 receptors Cetuximab to bind to EGFR	Receptor-mediated transcytosis	2015	[17]
Delivery of nanoparticles to brain metastases of breast cancer using a cellular Trojan horse	Gold Nanoshells	Monocytes/macrophages	The authors had claimed that monocytes/macrophages were able to cross BBB and actively transport loaded nanoparticles, but the exact mechanism was unknown	Nanoparticles grafted with monocytes/macrophages were recruited to metastatic lesions by the effect of some chemo-attractants The activated macrophages were able to cross BBB and envelop the metastatic cells delivering loaded nanoparticles	2012	[18]

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