Supplementary Table 1. Recent research publications using passive targeting technology(s) in targeting brain metastases of breast cancer

Paper	API	Delivery system (if present)	Means of targeting	Year	Ref.
Liposomal irinotecan accumulates in metastatic lesions, crosses the blood-tumor barrier (BTB), and prolongs survival in an experimental model of brain metastases of triple negative breast cancer	Irinotecan that is converted to its active metabolite SN-38 upon administration, a potent topoisomerase I inhibitor	Liposomal preparation composed of distearoylphosphatidylcholine, cholesterol and polyethylene glycol-distearoylphosphatidyl-ethanolamine	Irinotecan liposomal preparation penetrates BTB and preferentially accumulates within brain metastases via EPR Optimal size of liposomes and impaired lymphatic drainage within tumor have led to reduced clearance and prolonged drug exposure	2018	[1]
NKTR-102 efficacy versus irinotecan in a mouse model of brain metastases of breast cancer	Irinotecan is subsequently metabolized to the active metabolite SN38	NKTR-102 is an Irinotecan-3D PEG conjugate linked with a hydrolysable ester bond	The 3D PEG moiety in NKTR-102 led to prolonged circulation time which facilitates its penetration into brain tumors via EPR NKTR-102 was able to avoid P-glycoprotein mediated efflux which increases concentration of irinotecan and its metabolite within tumor	2015	[2]
Combined targeting of HER2 and VEGFR2 for effective treatment of HER2-amplified breast cancer brain metastases	1. Trastuzumab (anti-HER2 monoclonal antibody) 2. Lapatinib, a small-molecular-weight HER2 kinase inhibitor 3. DC101, an antimurine VEGFR2 antibody	Combined therapy of 3 monoclonal antibodies	Lapatinib can penetrate the BTB due to its small molecular weight Combination therapy of two anti-HER2 agents was able to reduce resistance accompanied by trastuzumab monotherapy In addition to the antiangiogenic benefit of DC101 which synergizes the direct tumor cytotoxicity induced by two anti-HER2 agents	2012	[3]
MicroRNA-1258 suppresses breast cancer brain metastasis by targeting heparanase	microRNA (miR-1258)	N/A	miR-1258 in BMBC cells inhibited heparanase which regulates many molecules involved in angiogenesis and metastasis of the tumor	2011	[4]
Ultrasound-mediated blood-brain/blood-tumor barrier disruption improves outcomes with trastuzumab in a breast cancer brain metastasis model	Trastuzumab	N/A	The use of focused ultrasound combined with circulating microbubbles is a non-invasive method that increases permeability of BTB and improves outcomes of trastuzumab	2012	[5]
Tumor-targeting salmonella typhimurium A1-R arrests growth of breast-cancer brain metastasis	Genetically-modified Salmonella typhimurium A1-R (S. typhimurium A1-R) strain	N/A	S. typhimurium A1-R is auxotrophic for Leu and Arg, which precludes it from growing continuously in normal tissues but allows high tumor virulence The system ability to destruct tumor blood vessel enhances its antitumor efficacy	2015	[6]
Activation of the c-Met pathway mobilizes an inflammatory network in the brain microenvironment to promote brain metastasis of breast cancer	Pterostilbene is a resveratrol analogue natural compound	N/A	Pterostilbene (PTER) is permeable to BBB where it can reach its target within brain tumor cells PTER treatment had reduced metastatic growth in brain by blocking c-Met pathway mediated angiogenesis and perivascular growth	2016	[7]
Silica-based nanoparticles are efficient delivery systems for temoporfin	A photosensitizer called temoporfin	Silica-based nanoparticles	Silica nanoparticles with the immobilized photosensitizer temoporfin was able to cross the blood-brain barrier which led to highly obtained concentration of photosensitizer in tumor cells and higher therapeutic efficacy	2018	[8]
Targeting brain-adaptive cancer stem cells prohibits brain metastatic colonization of triple-negative breast cancer	Edelfosine is a synthetic alkyl-lysophospholipid and a selective PLC inhibitor	N/A	Edelfosine targets brain adaptive cancer stem cells by suppressing astrocyte-involved PCDH7-PLCb-Ca2þ CaMKII/S100A4 pathway The drug incorporates into the cell	2018	[9]

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			membrane and does not target the DNA, thus it causes selective apoptosis in tumor cells, sparing healthy cells		
Preclinical efficacy of ado-trastuzumab emtansine in the brain microenvironment	Trastuzumab was the selected antibody and cytotoxic Emtansine (DM1) was the drug molecule conjugated to it (T-DM1)	Antibody-drug conjugate	The later stages of tumor development are contributed with increased BBB impairment This heterogeneous leakiness of the tumor vasculature increased the delivery of TDM1 through BTB despite its relatively high molecular weight	2016	[10]
Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood-tumor barrier disruption	1. Doxorubicin 2. Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate	Antibody-drug conjugate	Focused ultrasound (FUS) in combination with microbubbles enhances blood brain barrier permeability resulting in increased tumor tissue penetration	2018	[11]
Growth inhibition in a brain metastasis model by antibody delivery using focused ultrasound-mediated blood-brain barrier disruption	Trastuzumab and Pertuzumab combination	N/A	FUS in combination with microbubbles was able to temporarily disrupt the BBB enhancing the anti-tumor efficacy of the two anti-HER2 agents combination therapy	2016	[12]
Therapy targeted to the metastatic niche is effective in a model of stage IV breast cancer	Anti-miR10b within Nanodrug system combined with low dose of doxorubicin	Iron oxide nanoparticles conjugated to LNA-based antagomirs targeting miRNA-10b(MN-anti-miR10b) termed Nanodrug	Immunofluorescence confirmed accumulation of the nanodrug within brain metastases Combination treatment of MN-anti-miR10b and low-dose doxorubicin resulted in regression of distant metastases in 65% of the animals with minimal mortality	2017	[13]
Challenging metastatic breast cancer with the natural defensin PvD1	A natural antimicrobial plant defensin purified peptide, PvD1	N/A	PvD1 internalizes in cancer cells where it accumulates in endothelial cell membranes Detached circulating cancer cells intending to metastasize to the brain becomes more susceptible to PvD1. These circulating damaged cells become unable to efficiently attach to the brain endothelial cell wall. Therefore, PvD1 suppresses cancer cell adhesion	2017	[14]
Trastuzumab uptake and its relation to efficacy in an animal model of HER2-positive breast cancer brain metastasis	1. Trastuzumab alone 2. muMAb 4D5 (murine parent of trastuzumab) alone 3. Combination of muMAb 4D5 and PI3K/mTOR inhibitor GNE-317 4. TDM1	TDM1 is an antibody (trastuzumab)-drug (Emtansine) conjugate	Co-administration of anti-HER2 agent and a brain penetrant agent as GNE-317 showed better efficacy and longer survival in mice with brain lesions than monotherapy Trastuzumab-Emtansine conjugate (TDM1) was demonstrated to have superior anti-tumor activity compared with Trastuzumab alone	2017	[15]
Trastuzumab distribution in an *in-vivo* and *in-vitro* model of brain metastases of breast cancer	Trastuzumab	N/A	This study demonstrates that, trastuzumab does cross the blood-brain and blood-tumor barriers though probably below efficacious concentrations	2017	[16]
Short-time focused ultrasound hyperthermia enhances liposomal doxorubicin delivery and antitumor efficacy for brain metastasis of breast cancer	Doxorubicin	Pegylated liposomes loaded with doxorubicin	The short-time FUS hyperthermia treatment can increase BTB permeability and blood perfusion of the tumors which enhances penetration of liposomal formulation into brain metastases	2014	[17]
Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced	Herceptin	N/A	MRI-guided focused ultrasound disrupts BBB resulting in transient increased permeability of antibody-based therapy within brain metastases	2006	[18]

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blood-brain barrier disruption					
Pharmacokinetics and efficacy of PEGylated liposomal doxorubicin in an intracranial model of breast cancer	1. Doxorubicin 2. Blood brain barrier permaeble ABT-888, an inhibitor of a poly (ADP-ribose) polymerase and subsequent DNA repair	Pegylated liposomal loaded with doxorubicin (PLD)	Prolonged systemic exposure of pegylated liposomes allows its passive transport across compromised BBB due to presence of tumor resulting in a better therapeutic efficacy compared to non-liposomal doxorubicn Co-administration PLD and BBB permeable ABT-888 had exerted synergistic effect with higher survival rate	2013	[19]
Human neural stem cells can target and deliver therapeutic genes to breast cancer brain metastases	prodrug 5-fluorocytosine (5-FC) that can penetrate BBB	Human neural stem cells (NSCs) encoding cytosine deaminase (CD) enzyme	Tumor tropic NSCs selectively migrate to brain metastases delivering CD enzyme, which activates permeable 5-FC into cytotoxic 5-FU to exert its antitumor effect selectively within tumor cells	2009	[20]
Neural stem cells secreting anti-HER2 antibody improve survival in a preclinical model of HER2 overexpressing breast cancer brain metastases	Anti-HER2 antibody	Genetically modified neural stem cells secreting high amount of anti-HER2 antibody	The genetically modified stem cells can cross BBB, secreting large amounts of anti-HER2 antibodies that bind specifically to their target exerting the required anti-tumor effect	2015	[21]
Src family kinases as novel therapeutic targets to treat breast cancer brain metastases	Lapatinib (EGFR/HER2 inhibitor) Saracatinib (BBB permeable Src inhibitor)	N/A	Src pathway plays a critical role in promoting brain metastasis and a key downstream transducer of tyrosine kinase receptors Co-administration of Lapatinib and Saracatinib inhibited the outgrowth of established experimental brain metastases, prolonging the survival of metastases-bearing mice	2013	[22]
Targeting aV-integrins decreased metastasis and increased survival in a nude rat breast cancer brain metastasis model	Anti-aV integrin monoclonal antibody intetumumab	Drug does not cross BBB	Intetumumab binds to and inhibits integrins that promote the proliferation of tumor cells and are involved in multiple aspects of metastasis Intetumumab was shown to have potential prophylactic effect in preventing breast cancer metastasis	2012	[23]
Caveolin-1 upregulation mediates suppression of primary breast tumor growth and brain metastases by Stat3 inhibition	SOCS-1, a negative regulator of Stat3	N/A	Activation of Stat3 downregulates Caveolin-1 expression which acts as a tumor suppressor protein in human breast cancer Administration of SOCS-1, a negative regulator of Stat3, had increased expression of Caveolin resulting in reduced tumor metastasis Stat3 can be a potential therapeutic target for brain metastases of breast cancer	2011	[24]
Combination inhibition of PI3K and mTORC1 yields durable remissions in mice bearing orthotopic patient-derived xenografts of HER2-positive breast cancer brain metastases	Lapatinib (a HER2 kinase inibitor) BKM120, a pan-PI3K inhibitor RAD001, an mTORC1 inhibitor	N/A	Co-administration of the two BBB permeable agents BKM120 and RAD001, had resulted in marked tumor regression that was resistant to other combinatory therapies This emphasized that some HER2-positive BCBMs depend on the AKT-mTOR pathway	2016	[25]
Stat3 orchestrates interaction between endothelial and tumor cells and inhibition of Stat3 suppresses brain metastasis of breast cancer	A Stat3 inhibitor, WP1066	N/A	WP1066, which can be highly distributed into brain tissue, had suppressed Stat3 and as a result decreased VEGFR-induced signaling and angiogenesis The resulting anti-angiogenic effect	2015	[26]

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cells			decreased tumor growth and metastasis VEGF-R2 can be overexpressed within brain metastases, which appears to be a critical target for the suppression of brain metastasis		
Inhibition of Polo-like kinase 1 prevents the growth of metastatic breast cancer cells in the brain	Selective Plk1 inhibitor, GSK461364A. It is an imidazotriazine, competitive ATP kinase inhibitor highly specific for Plk1	N/A	BBB permeable GSK461364A significantly inhibited micro-metastasis formation, consistent with its brain permeability characteristics	2011	[27]

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