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REVIEW

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Nanoparticle drug delivery to target breast cancer brain metastasis: Current and future trends

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Abstract

Breast cancer brain metastasis (BCBM) is rapidly becoming an impediment to continuing survival gains seen in breast cancer patients. Drug delivery across the blood-brain barrier is the main issue hindering systemic therapy against BCBM. This review details recent advances in nanoparticle (NP) drug delivery systems to target BCBM. Their primary benefits are: enhanced circulating and intra-BCBM drug biodistribution, BCBM targeting through NP functionalization, opportunities for gene manipulation and their theragnostic applications. Multiple NPs have been synthesized to deliver therapeutic HER2 blockade, which is particularly important given HER2-positive breast cancer's tendency to form BCBM. Finally, we review the clinical context in which NP-based therapeutics have been investigated in BCBM patients. While a breakthrough in improving patient outcomes remain awaited, these clinical trials represent positive steps in the changing attitude towards BCBM as a treatable illness. Although multiple challenges remain in the clinical translation of BCBM-directed NP therapies, ongoing research in the field offers promising avenues for novel targeting of this devastating disease.

KEYWORDS
biodistribution, brain metastasis, breast cancer, drug delivery, nanoparticle

1 | INTRODUCTION

Breast cancer is the second leading cause of cancer deaths worldwide, contributing to 11.6% of total cancer deaths in 2018.[1] It is also the second most common cause of metastatic brain tumors after lung cancer.[2] The incidence of breast cancer brain metastasis (BCBM) varies according to the molecular subtype of cancer, with studies reporting triple-negative (up to 22% of cases) and human epidermal

Abbreviations: aAPC, artificial antigen-presenting cell; ANG, angiopep-2; AP30NPs, AMD100-conjugated to PEG30 nanoparticles; ApoE, apolipoprotein E; ATP, adenosine triphosphate; BBB, blood-brain barrier; BCBM, breast cancer brain metastasis; BMEC, brain microvascular endothelial cell; BTB, blood-tumor barrier; CNS, central nervous system; CSF, cerebrospinal fluid; DART, "decreased non-specific adhesivity, receptor targeted"; EC-K1, *Escherichia coli* K1; EGFR, epidermal growth factor receptor; EP, etirinotecan pegol; EPR, enhanced permeability and retention; FDA, U.S. Food and Drug Administration; Fn14, fibroblast growth factor-inducible 14; gp60, 60 kDa glycoprotein; HA, hyaluronic acid; HER2, human epidermal growth factor receptor 2; HMG-CoA reductase, (3-hydroxy-3-methyl-glutaryl)-coenzyme A reductase; iRGD, cyclic 9-amino acid internalizing peptide; K_{ATP}, ATP-sensitive potassium channel; LHNP, lapatinib loaded in human serum albumin nanoparticles; LPS, lipopolysaccharide; LRP1, lipoprotein receptor-related protein-1; Mfsd2a, major facilitator superfamily domain-containing protein 2a; miRNA10b, microRNA10b; MMP1, matrix metalloproteinase-1; MRI, magnetic resonance imaging; NP, nanoparticle; OmpA, outer membrane protein A; OMV, outer membrane vesicle; OS, overall survival; PEG, polyethylene glycol; PET, positron emission tomography; PFS, progression free survival; P-gp, P-glycoprotein; PLD, PEGylated liposomal doxorubicin; PLGA, poly(lactic-*co*-glycolic acid); PLL, poly(ε-carbobenzoxy-L-lysine); PMMA-PS80-*g*-St, poly(methacrylic acid) and polysorbate 80 engrafted onto starch; PS 80, polysorbate 80; PSMA, prostate-specific membrane antigen; SRS, stereotactic radiosurgery; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; TRA-TPN, terpolymer-conjugated trastuzumab; TTP, trancytosis-targeting peptide; WBRT, whole brain radiotherapy.

growth factor receptor 2 (HER2) overexpressing (up to 28.7% of cases) subtypes as having a particular propensity to spread to the brain.[3,4] The incidence of BCBM is rising, largely due to increased use of neuroimaging associated with clinical trials and improved survival of patients with metastatic breast cancer. Therefore, developing effective treatment strategies against BCBM is imperative for maintaining survival and quality of life for these patients.[5]

Brain localized therapies, in the form of whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and surgical resection remain the most effective treatments available for BCBM. Surgery is the most common form of treatment for solitary BCBM and is usually followed by a form of radiotherapy.[6] While both SRS and WBRT have a similar efficacy on overall survival, numerous studies have shown that WBRT is associated with more adverse effects such as cognitive deterioration compared to SRS.[7]

Cytotoxic chemotherapy and molecularly targeted systemic agents are frequently used in conjunction with the brain localized therapies. However, the therapeutic efficacy of most drugs in the brain is limited by poor penetration through the blood-brain barrier (BBB), when administered through the systemic circulation. Moreover, the therapeutic benefit of many systemic agents against BCBM is generally less clear due to the historic practice of systematically excluding these patients from clinical trials.

In the context of HER2-amplified BCBM, trastuzumab is a highly effective treatment for patients with metastatic HER2-positive breast cancer, although patients receiving trastuzumab have been shown to have a higher incidence of BCBM.[7] Due to its nature as an anti-HER2 antibody with a high molecular weight (148 kDa), trastuzumab has low BBB penetration.[8] Lapatinib is a small molecule drug that is a dual tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) and HER2. Preclinical evidence of lapatinib biodistribution in experimental BCBM indicates that lapatinib poorly passes the BBB, with average concentrations in BCBM at most reaching 20% of concentrations in extracranial metastases.[9] In a clinical pharmacokinetic study, using drug concentration in cerebrospinal fluid (CSF) as a surrogate for BBB penetration, Gori et al found that orally administered lapatinib resulted in low CSF levels; although intracranial activity against BCBM and higher uptake of radiolabeled lapatinib were observed suggesting improved penetrance at the tumor-disrupted BBB.[10]

2 | CHALLENGES IN THERAPEUTIC DRUG DESIGN FOR BCBM

The BBB is a highly selective, semipermeable boundary that physically and functionally separates the systemic and cerebral circulations. By restricting and preventing the free entry of water-soluble substances and large molecules from entering the brain, the BBB imposes unique challenges in effective delivery of drugs to the brain. A prime example of limited drug efficacy against BCBM is illustrated by trastuzumab, a monoclonal antibody that specifically binds to the HER2 protein expressed on the surface of breast cancer cells and inhibits cell proliferation.[6] Like most monoclonal antibodies, trastuzumab does not cross the BBB.[11] However, various studies have shown that when the BBB has been disrupted by either radiotherapy or surgery, the penetration of trastuzumab increases.[12-14] Several mechanisms, such as the presence of the tight junctions between endothelial cells and various transport channels that regulate the movement of substance across the BBB,[15] prevent the entry of many small molecule drugs as they have shown to become substrates of efflux transporters, resulting in limited penetration.[7] Due to the lack of transcellular or paracellular channels, the BBB permits three routes for molecules to gain access to the brain interstitial fluid, through (a) receptor-mediated transport through the BBB, (b) lipid-mediated free diffusion through the BBB or (c) via carrier-mediated transport systems.[16,17]

P-glycoprotein (P-gp), expressed on the endothelial cell surface, is responsible for expelling toxins from the intracellular to the extracellular space via an adenosine triphosphate (ATP) activated process, further limiting the intratumoral drug concentration.[18] High expression of P-gp on tumor cells is also proposed to be one of the main causes of multiple drug resistance in cancer.[19]

In primary and secondary brain tumors, the BBB is modified to form the blood-tumor barrier (BTB).[20] The BTB is characterized by a mixture of disorganized network of defective tumor-associated capillaries and original brain capillaries co-opted by tumor cells, with anatomical and physiological differences that are distinct from the BBB.[21-23] The BTB has been termed "leaky" in comparison to the BBB, as it allows the movement of large molecules such as antibodies; however, it is also characterized by significant intratumoral and intertumoral heterogeneity.[24]

Hence, developing alternative approaches to treat BCBM, specifically to overcome the challenges of drug delivery, is a major source of research activity. One emerging treatment option is to use nanoparticles (NPs) to overcome some of the challenges posed by the BBB/BTB in delivering drugs directly to the site of the secondary brain tumor.

3 | ROLE OF NANOPARTICLES IN BREAST CANCER AND CNS DRUG THERAPY

Nanoparticles belong to a class of ultrafine materials, measuring between 1 and 100 nm in two or more dimensions. Due to their extremely small size, NPs exhibit unique physicochemical properties that markedly differ from equivalent larger scale materials. When used for drug delivery, the therapeutic payload can be dissolved, encapsulated, entrapped or conjugated to the nanoparticle.[25] Currently, NPs have been used to overcome a variety of pharmacokinetic shortcomings associated with systemic anticancer treatment, such as drug instability, side effects and nonspecific cell-targeting.[26] NPs have been shown to improve the pharmacokinetic profile of systemic therapies; for example, they are able to maintain an effective dose ratio of combined drugs and are capable of accumulating at the tumor site due to the enhanced permeability and retention (EPR) effect.[27] More recently, the use of functionalized nanoparticles to deliver drugs has become widely appreciated due to its ability to precisely home to target tissues and allow a controlled release of the therapeutic payload.[28]

There are various materials from which nanoparticles can be created, such as lipids, polymer and viral particles.[29] Table 1 provides a brief overview about the various types of NPs that can be used as drug carrier systems; outlining the relative advantages and disadvantages of each NP system. NPs may be coated by a polymer which releases the drug from the core across the polymeric membrane via controlled diffusion or erosion.[27] The polymeric membrane can be made of a variety of material such as liposomes, that contain the drug within the membrane or drugs can be conjugated to gold particles via ionic or covalent bonding.[28] Viral particle-based NPs will not be discussed further in this review, as they have not yet been shown to be applicable in the management of BCBM.

The rising incidence of BCBM places greater urgency in the need to find new treatment strategies against this disease. With the wealth of therapeutic drugs that are known to be effective in metastatic breast cancer, overcoming the challenges of CNS delivery via the systemic circulation is an attractive means to rapidly widen our armamentarium against BCBM. In light of the opportunities provided by NPs in improving CNS drug delivery, in this review we will examine the studies investigating NPs as a drug delivery system in BCBM and discuss the ongoing challenges in the application of NPs in BCBM. Our aim was to describe the current landscape and to provide fresh impetus to ongoing research efforts in this area.

4 | METHODS

Using the following search terms "breast cancer," "brain metastasis" and "nanoparticles" a review was conducted of published literature across four electronic databases: Scopus, Google Scholar, PubMed and Clinicaltrials.gov.

Articles that focused on the current treatment strategies and NPs as drug delivery systems for the treatment of BCBM were included. Articles that focused on the use of NPs for treatment of other cancer types or applications other than drug delivery were excluded.

5 | NANOPARTICLES IN THE TREATMENT OF BCBM

5.1 | Nanoparticles to enhance drug biodistribution in BCBM

One of the more widely exploited properties of NPs for drug delivery is their enhanced pharmacokinetic profile, specifically by increasing the bioavailability of the drug in the systemic circulation and, subsequently, in the tumor. He et al, developed an amphiphilic nanocarrier, comprising a lipid domain stabilized with a copolymer, to deliver docetaxel.[30] These docetaxel-loaded nanoparticles showed rapid uptake by breast cancer cells, more prolonged drug circulation time and elevated brain bioavailability which significantly inhibited brain metastasis development and prolonged animal survival. Furthermore, the amphiphilic nanoparticles were shown to cross the BBB via a process of endogenous lipidation along with apolipoprotein E (ApoE). In another example with liposomal irinotecan, mice bearing BCBM showed prolonged plasma drug exposure and increased survival compared to mice treated with either liposomal vehicle alone or free irinotecan.[31] Figure 1 shows several mechanisms through which NPs can enhance drug biodistribution again BCBM.

The drug oxaliplatin is an anticancer drug that is rarely used to treat BCBM due to its lack of BBB penetrability. However, a preclinical study has shown that oxaliplatin encased by a liposomal NP resulted in increased plasma accumulation in mice bearing a subcutaneously engrafted human breast (MT-3) tumor compared to free drug. Mice-bearing intracranial MT-3 tumors also had better tumor control when treated with liposomal oxaliplatin compared to either free drug or vehicle alone.[32] Similar findings, in intracranial MT-3 tumors, were found with mitoxantrone chemotherapy entrapped within fluid membrane liposomes that were functionalized to target the low-density lipoprotein receptor-related protein-1 (LRP1).[33] A study comparing polyethylene glycol (PEG) surface modified- or "PEGylated"-liposomal doxorubicin (PLD) with free doxorubicin, found that PLD had a 20-fold higher concentration in the intracranial tumor and 1500-fold higher plasma levels compared to the free form of the drug. PLD was still detectable in the circulation 96 hours later, but the free form was

TABLE 1 The three main nanoparticle systems used for drug delivery, with reported comparative advantages and disadvantages.

System	Structure	Advantages	Disadvantages	References
Lipids (liposomes)	Tend to be self-assembling bilayers in the form of a planar or closed bilayer	Highly compatible with cells. Reduced toxicity Modifiable structure	Moderate loading capacity Difficulty in storage	[29] [28]
Polymer	Drugs are bonded to the side chain of the polymer	High loading capacity Modifiable structure Biodegradable	Potential toxicity Lack of polymer chemical stability Possibility of forming an embolus	[30] [31]
Viruses	They are dynamic and self-assembling that form highly symmetrical and monodisperse structures	Biocompatible Biodegradable Potential for different derivatization routes	Large-scale manufacturing process. Possibility of eliciting an immune response	[32] [33]

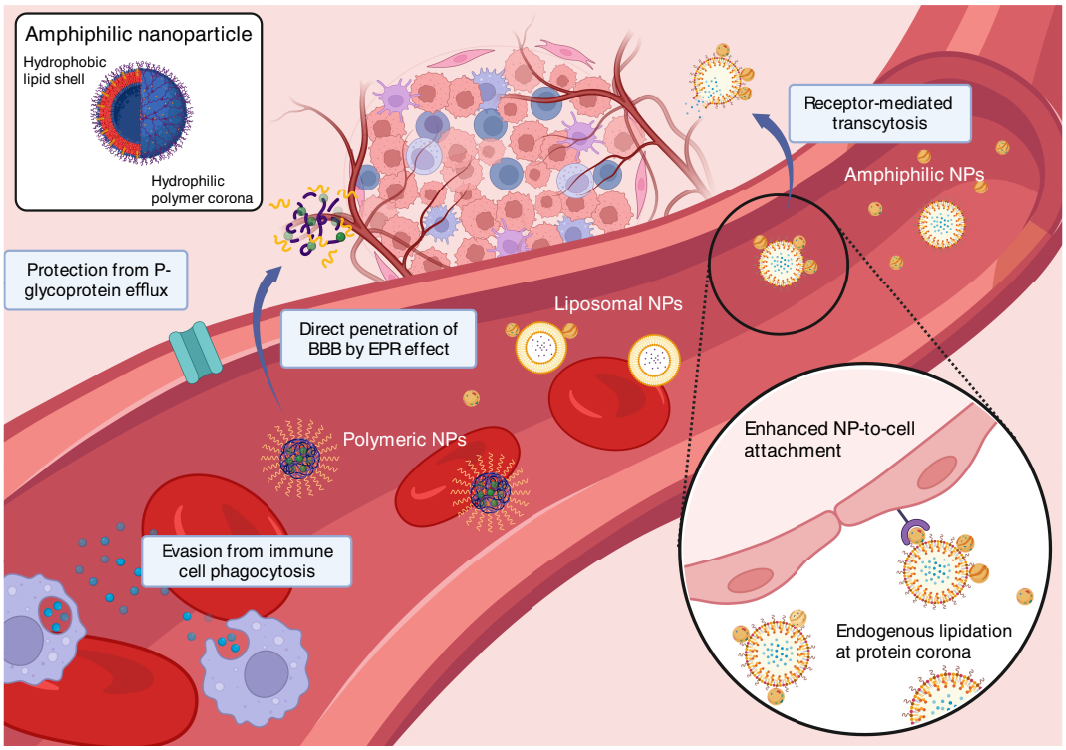

FIGURE 1 Different formulations of nanoparticles (NPs)—polymeric, liposomal and amphiphilic (inset image)—can enhance drug biodistribution against BCBM through several mechanisms. These mechanisms including improved penetration of the blood-brain barrier (BBB) due to the enhanced permeability and retention (EPR) effect and surface adsorption of circulating lipoproteins leading to receptor-mediated transcytosis (magnified image); reduction of drug efflux by active P-glycoprotein transport and avoidance of monocyte/macrophage destruction. Created with Biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

undetectable by 24 hours. Mice treated with PLD had a longer median survival (32 days) compared to mice treated with the free drug (23.5 days).[34]

Although, liposomal NPs have been more widely studied as drug carriers, polymer-based NPs have also been shown to be effective for drug delivery against BCBM. A study by Adkins et al, investigated the efficacy of irinotecan and a PEGylated irinotecan polymer conjugate (NKTR-102).[35] Specifically, it measured the levels of SN38—an active metabolite of irinotecan—where it was found that SN38 brain concentration decreased 30-fold after 24 hours in mice administered irinotecan, however in mice administered with NKTR-102 had only a decrease by 4-fold after 168 hours. This indicates a higher accumulation and slower elimination of the drug from the tumor, which correlated with extended survival of mice treated with NKTR-102 (74 days vs 35 days after treatment with unmodified irinotecan).

Using polymeric NPs containing camptothecin that were modified to target the transferrin receptor, Wyatt and Davis found that they were effective against different models of brain metastasis.[36] The authors also showed that the method for establishing BCBM, whether through intracranial, intracardiac or intravenous inoculation had a profound effect on the response to NP treatment, likely due to differences in the BBB/BTB. This finding raises an important implication for the design of preclinical studies, when testing NPs as a drug delivery system for BCBM.

6 | FUNCTIONALIZED NANOPARTICLES TO ENHANCE DRUG DELIVERY TO BCBM

Although the pharmacokinetic profile of NPs is favorable for increased drug delivery to the tumor, eliminating toxicity remains the holy grail for therapeutic drug design. One way to achieve this is by modifying the NPs to target the BCBM or its microenvironment. Khan et al proposed targeting luminal LRP1 on the endothelium, while avoiding clearance via abluminal LRP1-mediated transcytosis, to enhance drug delivery to BCBM. This was achieved by generating nanoparticles functionalized with a matrix metalloproteinase-1 (MMP1) cleavable fusion peptide that is bound to LRP1 on the luminal endothelium, but then releases the active agent upon crossing the BBB.[37] Consequently, the study authors showed that there was a nearly 5-fold increase in NPs accumulating in the BCBM compared to mice treated with unmodified NPs. Similarly, Guo et al showed that uplifting LRP1 expression could lead to enhanced NP influx across the BBB. Since P-gp function suppresses LRP1 expression and is dependent on higher cholesterol content in plasma membranes, Guo et al sought to inhibit cholesterol synthesis by blocking the enzymatic action of (3-hydroxy-3-methyl-glutaryl)-coenzyme A reductase (HMG-CoA reductase) directly in brain microvascular endothelial cells (BMECs). To that end, they used simvastatin/doxorubicin co-loaded poly(lactic-*co*-glycolic acid)-poly(ε-carbobenzoxy-L-lysine) (PLGA-PLL) NPs bound to

angiopep-2 (ANG), an oligopeptide that ligates LRP1, to augment LRP1 expression and, consequently, upregulate NP transcytosis through the BBB.[38] They showed that there was greater NP penetration with simvastatin pretreatment and significant improved survival in treated mice compared to free doxorubicin, functionalized NPs without doxorubicin or saline.

An alternative mechanism for enhancing NP transcytosis is through targeting the major facilitator superfamily domain-containing protein 2a (Mfsd2a), which is a key omega-3 fatty acid transporter that is exclusively expressed on brain endothelial cells.[39] Studies have shown that the Mfsd2a receptor is critical in the function of the BBB and a higher density of Mfsd2a expression inversely impacts on the transcytosis rate across the BBB.[40,41] Therefore, inhibition of Mfsd2a may be exploited as a method to increase NP penetration of the BBB. Ju et al took a two-step approach by first reducing Mfsd2a expression using systemically delivered PLGA-PLL NPs loaded with tunicamycin, followed by doxorubicin-loaded NPs coated with hyaluronic acid (HA), which targets CD44 expressed on BCBM cells. The authors found that pretreatment with the tunicamycin-loaded NPs led to a 4.3-fold increase uptake of doxorubicin-loaded NPs, compared to without priming.[42]

Taking a novel approach, Chen et al utilized a strategy that drew inspiration from the ability of *Escherichia coli* K1 (EC-K1) to invade BBB endothelial cells and cause bacterial meningitis.[43] The authors showed that biomimetic cell membrane-coated PLGA NPs could effectively cross the BBB and then target BCBM through interaction between outer membrane protein A (OmpA)—a component of the bacterial outer membrane—and gp96, a heat shock protein that is abundantly expressed in some intracranial malignancies. The outer membrane vesicles (OMV) were directly extracted from the bacterial outer membrane and purified to remove lipopolysaccharide (LPS), which is a component of gram negative bacteria cell membranes that potently activates the immune response. Compared to OMV, which is extracted from the bacterial culture supernatant, these LPS-free dOMVs were shown to have increased circulating time due to reduced macrophage uptake. Furthermore, dOMV-coated PLGA NPs could efficiently cross an intact BBB and deliver encapsulated doxorubicin to BCBM xenografts, with resulting significant improvements in survival compared to mice treated with free doxorubicin or vehicle only.

Modulating the BBB/BTB function has also been shown to facilitate brain-targeted drug delivery. Miao et al exploited the elevated expression of ATP-sensitive potassium channels (K_{ATP}) at the BTB compared to normal BBB to selectively induce BTB disruption at the BCBM.[44] To promote BTB disruption, the authors activated K_{ATP} using minoxidil sulfate loaded in PLGA-PLL polymer NPs that were surface decorated with BCBM-targeting HA and showed that minodoxil/doxorubicin dual-loaded NPs preferentially crossed the BTB rather than the normal BBB and delivered higher concentrations of cytotoxic drug to BCBM. Furthermore, it was shown that minodoxil sulfate promoted NP uptake by increasing transcellular endocytosis and downregulating tight junction protein expression, which then enhanced paracellular transport. Consequently, treatment with these functionalized, BTB-disrupting NPs led to greater accumulation of doxorubicin in BCBM and improved animal survival, compared to either free drug or vehicle only. There was also negligible accumulation in the uninvolved brain.

In a recent study conducted by Ni et al, it was found that the BCBM-BTB had upregulated expression of the protein, prostate-specific membrane antigen (PSMA).[45] Using nanoparticles modified to target PSMA and loaded with doxorubicin and lapatinib, the authors showed that the PSMA-targeted NPs had a 4.57-fold increase in tumor penetration compared to the unmodified NPs. Moreover, the median overall survival of mice treated with the PSMA-targeted NPs increased to 44 days vs 29 days for nontargeting NPs.

To enhance the specificity of NPs to the BCBM tumor microenvironment (TME), Ju et al manufactured PLGA-PLL-based NP shells that were co-functionalized with HA and transcytosis-targeting peptide (TTP).[46] These dual-targeting NPs were proposed to efficiently cross the BBB via TTP-mediated binding to heparin sulfate proteoglycans, followed by BCBM uptake through HA binding to CD44 expressed on BCBM cells. Furthermore, Ju et al loaded the dual-targeting NPs with a HA-doxorubicin conjugate that, after internalization by BCBM cells, would be cleaved and activated by hyaluronidase within the cytoplasm; thus, selectively inducing BCBM cell death while sparing normal tissue. Animals treated with these dual-targeting NPs that had been loaded with the HA-doxorubicin prodrug survived for significantly longer than animals treated with nontargeted NPs, single-targeting NPs or free drug.

A study generated polymer-lipid NPs conjugated to cyclic 9-amino acid internalizing peptide (iRGD) that were loaded with mitomycin C and doxorubicin.[47] Subsequently, the authors showed that treatment with these modified NPs not only reduced the brain metastatic burden of mice bearing triple-negative breast cancer (TNBC), but also had the dual benefit of reducing infiltration of tumor-associated macrophages, which are known to promote tumor growth.[48] Moreover, mice treated with the hybrid NP had more than a 50% increase in median survival compared to mice treated with the free form of the drugs. In a study conducted by Dancy et al, a PLGA-PEG polymer NP was formulated with a targeting moiety against the cell surface receptor, fibroblast growth factor-inducible 14 (Fn14), a tumor necrosis factor receptor that was shown to be overexpressed in different molecular subtypes of breast cancer, particularly TNBC.[49,50] Furthermore, besides Fn14-selective targeting, these functionalized NPs possessed minimal nonspecific binding to brain extracellular matrix proteins.[51] Thus, when loaded with paclitaxel, the so-called "decreased non-specific adhesivity, receptor targeted" (DART) NPs demonstrated enhanced tumor penetration, more efficient cell uptake and longer drug circulation compared to unmodified NP and NP albumin-bound paclitaxel (nab-paclitaxel)—an US Food and Drug Administration (FDA) approved paclitaxel NP conjugate.

In summary, the results from the aforementioned studies demonstrate that modifying NPs to selectively target a multitude of surface moieties in the TME could improve drug delivery to BCBM and enhance tumor control, while minimizing toxicity to uninvolved tissues. The different reported mechanisms for NP targeting are illustrated in Figure 2.

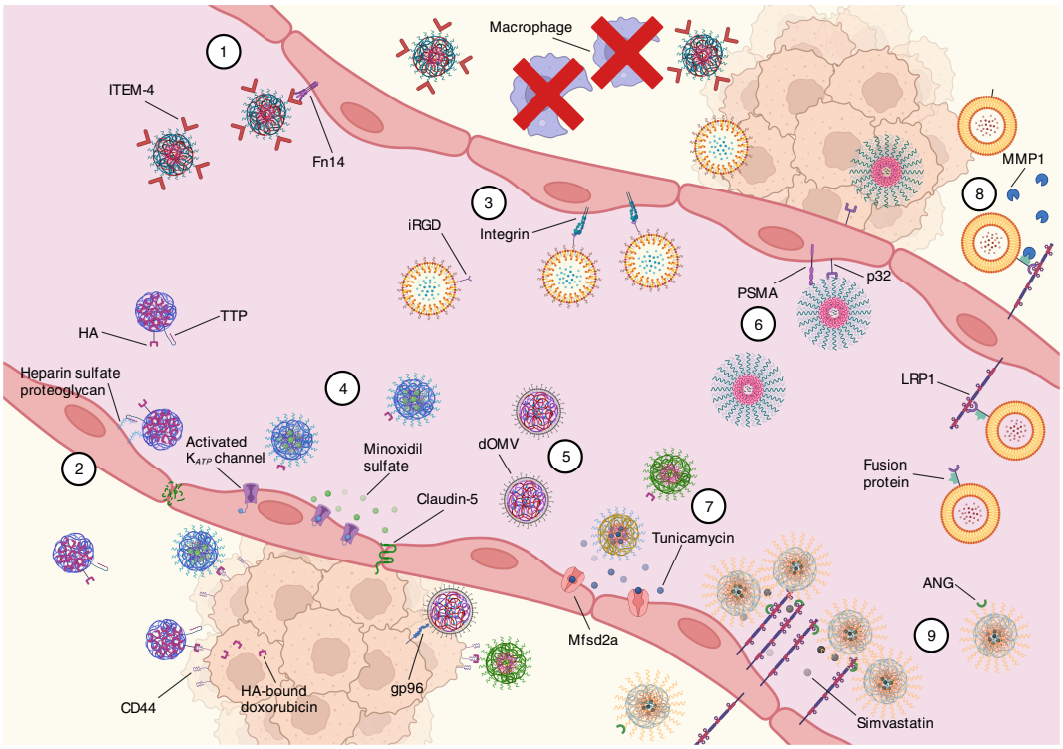

FIGURE 2 Functionalized NPs can enhance drug delivery to BCBM by several mechanisms: (1) paclitaxel-loaded polymer NPs conjugated with ITEM4 monoclonal antibody that targets fibroblast growth factor-inducible 14 (Fn14) on BCBM cells, while avoiding nonspecific binding to the brain extracellular matrix; (2) PLGA-PLL NPs co-functionalized with hyaluronic acid (HA) and transcytosis-targeting peptide (TTP) bind to heparin sulfate proteoglycans expressed on the blood-tumor barrier (BTB) and target the CD44-expressing BCBM cells, before releasing HA-conjugated prodrug that is cleaved and activated by intracellular hyaluronidase; (3) mitomycin C/doxorubicin dual-loaded polymer-lipid hybrid NPs conjugated to cyclic 9-amino acid internalizing peptide (iRGD) that are transported across the BTB, through an integrin-mediated process, and inhibits tumor growth and reduces macrophage infiltration; (4) HA-targeted polymer NPs release minoxidil sulfate, which activates ATP-sensitive potassium channels (K_{ATP}) expressed at the BTB and disrupts endothelial tight junctions, permitting BTB penetration by transcellular and paracellular routes; (5) doxorubicin-loaded PLGA NPs are encapsulated within a lipopolysaccharide-free bacterial outer membrane vesicle (dOMV) that permits BTB penetration and selective binding to tumor-expressed gp96; (6) doxorubicin/lapatinib dual loaded polymer NPs targeting endoluminal expressed prostate-specific membrane antigen (PSMA) with p32-assisted trafficking across the BTB; (7) tunicamycin-loaded NPs perform a priming strategy, by inhibiting BTB-expressed Mfsd2a function, allowing greater uptake of co-administered HA-targeted NPs to deliver doxorubicin; (8) fusion protein bound to drug-loaded liposomes that targets luminal low-density lipoprotein receptor-related protein-1 (LRP1) and is released in the abluminal side by matrix metalloproteinase-1 (MMP1) cleavage and (9) upregulation of BTB-expressed LRP1 is achieved using NP-released simvastatin, which permits selective penetration of angiopep-2 conjugated NPs and doxorubicin release. Created with Biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

6.1 | Therapeutic nanoparticles against HER2 positive BCBM

Given the high brain metastasis risk presented by HER2 overexpressing breast cancer, enhancing the brain penetrability of HER-targeted therapies has the potential to open new avenues for treating this subtype of breast cancer and dramatically improve survival. NPs have been shown to increased transportation of anti-HER2 medication, such as trastuzumab, across the BBB. An in vitro study demonstrated that lapatinib loaded in human serum albumin nanoparticles (LHNPs) inhibited the adhesion, migration and invasion of murine 4T1 mammary carcinoma cells more effectively compared to unbound lapatinib.[52] When tested in mice bearing intracarotid inoculated 4T1 brain metastases, besides improved brain penetration of LHNPs, the animals had more prolonged survival and reduced brain micrometastases when treated with LHNPs in a dose-dependent manner, compared to either orally or intravenously administered unbound lapatinib.

A study conducted by Patil et al, compared the use of nanotrastuzumab against the nonenclosed form and found that mice treated with NPs had an overall higher survival of 77.5 days compared to the control mice had a median survival of 49.5 days.[53] More complex nanocarrier systems have been tested for trastuzumab delivery in the form of hybrid nanoconstructs, comprising a two-stage assembly of a polysorbate 80 (PS 80) shell encasing a terpolymer (polymer, lipid, polymer)-conjugated trastuzumab (TRA-TPN).[54] The outer shell functions as a BBB-targeting moiety, while the inner nanoconstruct is released in the brain parenchyma to increase local bioavailability of trastuzumab at the tumor. Using these hybrid PS 80-TRA-TPN NPs, the study found that mice bearing a HER2 positive BT474 intracranial xenograft had higher accumulation of trastuzumab in the brain when

treated with PS 80-TRA-TPN and had greater tumor growth inhibition, compared to free trastuzumab or vehicle only.

NPs can be used in combination therapy, as demonstrated by Lu et al, who enclosed paclitaxel and lapatinib within a liposomal NP.[55] The NPs were shown to have a higher loading efficiency, and could easily cross the BBB and accumulate within BCBM. Wyatt and Davis M showed that a combination of camptothecin/trastuzumab contained within NPs had a greater effect in inhibiting BCBM tumor growth compared to the unmodified form of either drug.[56] Thus, NPs have the potential to dramatically alter the landscape of the treatment of BCBM from HER2-positive breast cancer by opening up additional therapeutic options. Figure 3 displays the aforementioned methods used to deliver anti-HER2 therapy via NPs.

6.2 | Nanoparticles for gene therapy against breast cancer brain metastasis

Gene therapy is an emerging field of treatment for BCBM. Currently, viral vectors are the most widely used tools to administer gene therapy in the clinic.[57] However, viral vectors have a number of disadvantages, including safety concerns, susceptibility to degradation by host nucleases, along with hindrance of cellular uptake due to the negative surface charge.[58] Viral vectors also have a relatively short circulating half-life that leads to unfavorable biodistribution.[59] Hence, nonviral vectors are emerging as a safer alternative for gene delivery; although, they have been limited by the comparatively low efficiency of gene delivery.[60] A recent research group demonstrated the feasibility of using NPs to deliver an artificial gene encoding the expression of the secretory protein promelittin, proMel. Furthermore, surface conjugation of a small molecule antagonist targeting CXCR4, AMD3100, to a PEG30-bound polymer was performed to generate functionalized NPs, or AP30NPs, which acted as carriers for the proMel gene. The study found that 52.4% of tumor cells were positive for NP uptake in mice bearing MDA231Br breast cancer xenografts that were treated with AP30NPs.[61] A study conducted by Yoo et al, has shown promising results by using gene therapy via NPs.[62] In this case, polymer nanoparticles were used to inhibit microRNA10b (miRNA10b), which has been shown to play a role in tumor cell invasion, migration and metastatic initiation. The study found that mice injected with NP had a reduced brain metastatic burden compared to controls. Thus, NPs can be used as a delivery system for gene modification, opening up the therapeutic avenues against BCBM.

6.3 | Special applications of drug-loaded nanoparticles in breast cancer brain metastasis

Nanobioconjugation is a method that involves chemically bonding two molecules, with at least one being a biomolecule. An in vivo study conducted by Mittapalli et al, tested a nanobioconjugate comprising a combination of paclitaxel and HA.[63] In mice bearing BCBM, when treated with the HA-paclitaxel nanobioconjugate, had significantly longer overall survival compared to the control and free paclitaxel group. This was due to the small size of HA-paclitaxel (5 kDA), allowing uptake up via CD44 receptor-mediated endocytosis and to bypass P-gp efflux through the cancer cell membrane.

Studies have shown that NPs have the ability to enhance imaging. Nanoconjugation can also occur between NPs and magnetic resonance imaging (MRI) contrast agents, such as gadolinium chelates, which permits passage through the BBB to broaden the utility of MRI. A study conducted by Du et al, found that lipid nanoparticles coated with BRBP1, a modified peptide, demonstrated significant enhancement of images produced by a T2 contrast MRI compared to non-

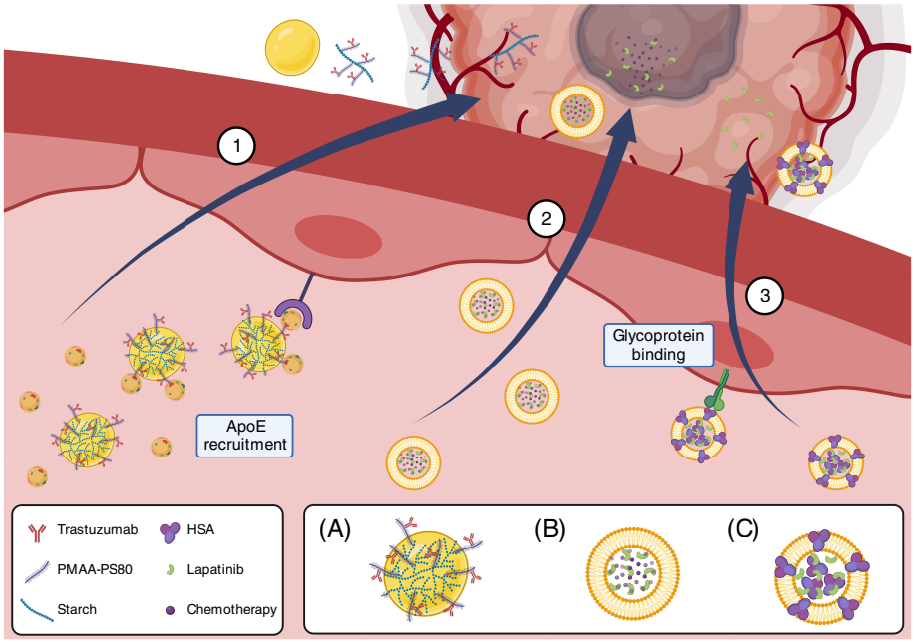

FIGURE 3 NPs can be used to deliver anti-HER2 therapy for HER2-overexpressed BCBM through the following mechanisms: (1) polysorbate 80 based-terpolymer NPs (A) conjugated with nanotrastuzumab recruit circulating ApoE, leading to endothelial attachment by LRP1, BTB penetration and finally HER2 blockade on tumor cells; (2) cross-BTB transportation, through the EPR effect, of liposomes loaded with chemotherapeutic agents and lapatinib (B) and (3) lapatinib-loaded human serum albumin (HSA) NPs (C) that transit across the BTB by endoluminal binding of the vascular expressed 60 kDa glycoprotein (gp60) receptor. Created with Biorender.com. [Color figure can be viewed at wileyonlinelibrary.com]

modified nanoparticles.[64] Similar results were generated by Kumar et al, who used a polymer NP coated with a near-infrared dye.[65] These examples demonstrate the diagnostic applications of NPs beyond drug delivery. Another study used a terpolymer containing poly(methacrylic acid) and PS 80 covalently engrafted onto starch (PMMA-PS 80-*g*-St) to deliver both an imaging contrast agent and cytotoxic chemotherapy to BCBM in mice.[66] They showed that gadolinium-loaded PMMA-PS 80-*g*-St NPs were capable of crossing the BBB, facilitated via ApoE adsorption onto the polysorbate 80 coated surface and internalization in the brain capillary endothelial cells. Moreover, when the same NP system was loaded with doxorubicin and administered in a BCBM xenograft model, there was greater accumulation of the cytotoxic drug in the BCBM and greater tumor control compared to free doxorubicin-treated mice. Consequently, multifunctional NPs can be used for direct imaging of the tumor, alongside delivery of therapeutic agents; thus, highlighting the theragnostic potential of NPs in the management of BCBM.

6.4 | In human studies of nanoparticles in breast cancer brain metastasis

A variety of clinical trials have shown an effective use of NPs for treatment of early and metastatic breast cancer. As an example, a clinical trial conducted by Gradishar et al, compared unbound paclitaxel with albumin nanoparticle-bound paclitaxel (nab-paclitaxel) in patients with metastatic breast cancer.[67] They found that patients treated nab-paclitaxel had a greater response rated compared to patients treated with standard paclitaxel (33% vs 19%, $P = .001$) and had a longer progression-free survival (23 weeks vs 16.9 weeks, $P = .006$). These outcomes were backed by another clinical trial that found similar results.[68] The evaluation of NPs for management of BCBM, however, has been less mature; largely due to the challenges in recruiting these patients into clinical trials and the systematic exclusion of this patient group from clinical studies. Nevertheless, a case study has reported the long-term therapeutic potential of nab-paclitaxel in combination with trastuzumab for a patient with heavily pretreated metastatic HER2-positive BCBM, with associated disease stabilization of greater than 13 months.[69] In a single center, phase II study, Xie et al, investigated the safety and efficacy of nab-paclitaxel in breast cancer patients with visceral metastases, specifically reported on patients with BCBM.[70] Of note, the BCBM patients formed a small subset of the study population (5 out of 80 patients) and were required to have had cranial irradiation before enrolment. Nevertheless, even these patients with stable and asymptomatic BCBM had significantly worse median progression-free survival (PFS) compared to the non-BCBM group (2.8 months vs 5.1 months).

In a pharmacokinetic study of NP biodistribution, by administering a HER2-targeted PEGylated liposomal doxorubicin labeled with ^{64}Cu (^{64}Cu-MM-302) followed by positron emission tomography (PET) imaging, Lee et al, showed that NPs accumulated within breast cancer metastatic tumors, including BCBM, by the EPR effect.[71] The study found that NPs accumulated in tumors more effectively than normal tissue, although high background levels were observed in the liver and spleen. The authors did find that NP uptake was heterogeneous across metastatic lesions and subsequent exploratory analysis showed a positive correlation between ^{64}Cu-MM-302 uptake and treatment response. These findings highlight the role of imaging in determining the response to NP therapy.

A phase I trial conducted by Sachdev et al, studied the effect of liposomal irinotecan on patients pretreated for metastatic breast cancer.[72] The study looked at patients with various forms of breast cancer and secondary tumors as well. It was found that a reduction in tumor between 7% and 55% of among seven patients with BCBM. The objective response rate was 30% for patients with BCBM and 50% of patients experienced visible clinical benefit. In another early phase I/II study, Koukourakis et al, showed that concurrent administration of radiolabelled ^{99}mTc-DTPA-stealth liposomal doxorubicin with radiotherapy was safe and resulted in drug accumulation between 7 and 13 times higher in metastatic brain tumors than normal brain tissue.[73] Out of the 10 patients with metastatic brain tumors, three had primary breast cancer. Of these three breast cancer patients, two showed a complete response to the treatment, while the third had a partial response in the brain metastasis.

A phase II trial (NCT05255666) is currently in progress that will assess the combination treatment of liposomal irinotecan and Pembrolizumab for the treatment of triple-negative BCBM. This study shall hopefully provide valuable information on the use of NPs in the treatment of BCBM. The trial will measure primarily the disease control rate, along with secondary outcomes such as overall survival (OS) and PFS.

The phase III BEACON study investigated the use of etirinotecan pegol (EP), a long-acting polymer conjugate of a topoisomerase-1 inhibitor, in locally recurrent or metastatic breast cancer. In a preplanned analysis of 67 BCBM patients, treatment with EP resulted in a significant reduction in risk of death and increase in median OS compared to treatment of physician's choice (TPC).[74] These findings gave hope that a new therapeutic agent would become an additional option for BCBM patients. However, the subsequent phase III ATTAIN study, which investigated EP vs chemotherapy of physician's choice in a brain metastasis only population of 178 women with breast cancer found that survival outcomes and treatment response were not significantly improved in the EP arm compared to TPC.[75] Despite the disappointing results, the ATTAIN study provided proof that large-scale randomized therapeutic studies could be performed in a BCBM population.

7 | DISCUSSION

Brain metastases are a major cause of morbidity and mortality in breast cancer patients. This problem is anticipated to grow in the future, as patients live longer due to improved extracranial disease control with the multitude of effective systemic agents available. Moreover, the more liberal use of neuroimaging, particularly in the context of clinical trials, will lead to higher detection of clinically asymptomatic BCBM. While local treatments over recent decades

have expanded, particularly with the availability of stereotactic radiotherapy or SRS for multifocal BCBM, the arsenal of systemic therapies that are efficacious against BCBM is growing, but at a slow pace. Chemotherapeutic and targeted agents that are known to be effective against extracranial breast cancer, such as trastuzumab, are limited in their ability to cross the BBB. Therefore, new options are needed that can overcome the therapeutic challenges related to BCBM, particularly in BBB penetration and tumor targeting. NPs are capable of overcoming these challenges due to their size and surface properties, coupled with the ability to add surface ligands. Therefore, NP drug formulations are expected to possess more favorable drug biodistribution and minimized systemic toxicity.

In this review, we focused on the application of drug-loaded therapeutic NPs for managing BCBM. Drugs conjugated to or enclosed within a NP have been found to have greater efficacy, reduced toxicity and greater brain bioavailability compared to their free form. Despite the promising results from preclinical studies, clinical translation of NPs for treatment of BCBM has so far been limited. One major factor is the historic practice of excluding BCBM patients from clinical trials, due to a combination of therapeutic nihilism and the dismal prognosis associated with BCBM. In more recent years, there has been a shift in perception regarding the management of BCBM, with several multicenter studies that have investigated systemic agents in BCBM patients.[75-77] Thus, agents with preclinical evidence of BCBM activity, including NPs, will prove attractive for clinical investigation in this growing cohort of patients.

More general problems associated with nanomedicines are the high cost and difficulty in manufacturing NPs that hinders scalable production necessary for clinical application. Technical challenges that need to be overcome by NPs include the risks of aggregation, fluid or protein adsorption, premature release of cargo, phase transition and contamination following contact with biological fluids.[78,79] Furthermore, the spontaneous coating of NPs by proteins, lipids and sugars, forming a protein corona, in the blood can inhibit the target specificity of functionalized NPs, as well as increasing susceptibility to degradation by the host innate immune system.[80,81]

Therapeutic NPs have been shown to be successful drug delivery systems that can overcome the constraints on systemic drug penetration across the BBB. Mostly these have been tested on standard cytotoxic chemotherapy agents. Given the propensity of HER2-positive breast cancer to spread to the brain, the ability of NPs to deliver anti-HER2 targeted therapies is a potential gamechanger in this disease. Beyond the role of NPs as vehicles for therapeutics, they have also been shown to be versatile tools for gene delivery and for theragnostic purposes against BCBM.

Future directions of therapeutic drug delivery NP research include the possibility of unlocking an antitumoral immune response against BCBM. Breast cancer is traditionally considered an immunologically inert cancer, although immune checkpoint inhibitors have demonstrated clinical efficacy against the triple-negative subtype.[82,83] As an example, bioengineered NPs have been used to target bone marrow-derived immune cells and to train them to target cancer.[84] Thus, additional therapeutic options may be opened up for patients with TNBC and brain metastasis. NPs have also been proposed to be used as artificial antigen-presenting cells (aAPCs). Carbon nanotubes have previously been engineered as aAPCs for optimal interactions with T cells in mice.[85] Moreover, NPs may be combined with extracorporeal technology to enhance drug delivery at the target site, for example using focused ultrasound to disrupt the BTB and enhance the delivery of liposomal NPs. A study conducted by Wu et al, showed that the use of pulsed-wave and low-dose ultrasound significantly enhanced the delivery and antitumoral effects of NPs in BCBM bearing mice compared to controls.[86]

With the projected rise in BCBM incidence, it is imperative that we begin to exploit the opportunity offered by NPs in enhancing drug delivery to the brain. The multitude of preclinical evidence for benefit of NPs in BCBM provides hope that additional systemic therapy options will soon become available for these patients.

AUTHOR CONTRIBUTIONS

Siddarth Kannan: Conceptualization, Methodology, Investigation, Writing - Original Draft, Visualization, Project administration. **Vinton W. T. Cheng:** Conceptualization, Methodology, Investigation, Writing - Reviewing & Editing, Visualization, Project administration, Supervision. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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