

Review Article

What Is the Role of Nanotechnology in Diagnosis and Treatment of Metastatic Breast Cancer? Promising Scenarios for the Near Future

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Metastatic breast cancer represents a diagnostic and therapeutic challenge due to tumor heterogeneity and to various physiological barriers that hinder drug delivery to the metastatic sites. To overcome these limitations, nanoformulated drugs have been developed and tested in preclinical studies, and few of them have been successfully translated into clinical practice. In particular, liposomal anthracyclines and nanoformulated albumin-bound paclitaxel have revealed an improved therapeutic index when compared to conventional chemotherapy, with significant reduction of drugs toxicity. Several strategies for nanoparticles engineering have more recently been explored to increase selectivity for tumor cells and to reach poorly accessible metastatic districts. Targeted nanoparticles, directed toward tumor markers and tissue-specific metastases, may provide effective devices in case of low-vascularized and small-sized metastases, thus paving the way for a real change in the natural history of metastatic disease. A number of targets have been identified and exploited for surface functionalization of different types of nanoparticles, which are currently undergoing preclinical studies. The aim of this review is to provide an overview of current nanotechnology applied to metastatic breast cancer diagnosis and treatment. Promising results encourage an upcoming translation of this research into clinical practice for an effective management of the disease in the near future.

1. Introduction

Metastatic breast cancer (MBC) is a major cause of cancer-related death among women in developed countries [1]. In recent years, some distinct biological portraits of breast cancer, characterized by different biomolecular profiles, behaviours, and clinical courses, have been described, and breast cancer has been defined as a heterogeneous disease [2, 3]. In this scenario, targeted therapy toward specific cellular receptors has gained a central role in breast cancer management, showing strongly improved clinical outcomes compared to older chemotherapy regimens. A paradigm of this concept was provided by the introduction of tamoxifen as adjuvant therapy for hormone receptors-positive breast tumors, which has led to a fall in cancer recurrence [4]. More recently, while some chemotherapy regimens have

failed to increase patients survival, the advent of the antibody trastuzumab has significantly improved the overall survival for human epidermal growth factor receptor 2- (HER2-) positive MBC, a highly aggressive cancer prone to brain metastases [5, 6]. However, onset of resistance to trastuzumab is not uncommon, and it leads to higher risk of local or distant recurrence and poor survival if therapy is not switched to other anti-HER2 strategies [6]. Moreover, HER2-positive cancers account for only 20–25% of breast malignancies, while other particularly aggressive subsets still represent an unsolved clinical challenge [7]. As an example, triple-negative breast cancer is a particular subset of cancer highly prone to local recurrence and distant metastases, characterized by the lack of expression of the estrogen receptor, progesterone receptor, and HER2, and no targeted therapy is currently available. Beyond targeted therapy, conventional

chemotherapy for MBC is generally based on anthracyclines and taxanes. Both these drugs have excellent cytotoxic activity. As a first-line single-agent chemotherapy, doxorubicin leads to response rates of 35–50% and reduces the risk of death by 22% with an increased median survival up to 18 months, when compared with nonanthracycline regimens [8, 9]. More recently, taxanes have been introduced in clinical practice with a substantial benefit in overall survival, time to progression, and cancer response [10]. However, despite their significant antitumor activity, doxorubicin and taxanes are associated with a number of severe side effects due to their toxicity profile. The most dreaded toxicity associated with doxorubicin is cumulative cardiotoxicity, which may lead to irreversible cardiomyopathy and subsequent congestive heart failure; taxanes induce significant neurotoxicity [10, 11]. These side effects are dose-dependent and mostly related to the lack of specificity of these drugs, which also affect healthy tissues. Severe toxicity slows down the therapeutic index of these therapies and makes the dose reduction or even the discontinuation of the chemotherapy necessary, with subsequent decreased efficacy. Therefore, MBC remains a largely incurable disease, and novel drug formulations able to achieve specific tumor delivery and to overcome major chemotherapy limitations are required. Moreover, various common sites of breast cancer metastases, such as the brain, are poorly accessible sanctuaries for cancer cells and require smart and innovative drug delivery systems [12]. In this context, nanotechnology represents a promising field of research, since nanoformulation of drugs may improve their bioavailability and allow the selective targeting of tumor cells, with subsequent increased efficacy and lower toxicity. Breast cancer management is the medical field with the most extensive clinical use and the most abundant preclinical research in nanotechnology, and more than 150 clinical trials are currently investigating the efficacy of nanoformulated chemotherapy [13]. The aim of this review is to provide a state of the art in nanotechnology applied to MBC treatment, from nanoformulated drugs already used in clinical practice to novel functionalized nanoparticles for targeted therapy and diagnosis. Ongoing preclinical and clinical studies are expected to provide a significant contribution to the development of new approaches for the management of MBC.

2. Nanotechnological Approaches for MBC Treatment

2.1. Nano-Drug-Delivery Systems: Functional and Structural Features. In the last decades, nanotechnology has made many efforts to design innovative and more effective drug delivery systems (DDS) in order to improve the pharmacological treatment of MBC. The main goal in DDS engineering is the achievement of an optimal therapeutic index, which is the combined result of drug release and efficacy, biocompatibility, and stability of the nanodevice and physiological features of the target tissue/organ [62]. The carrier should be nontoxic and easily produced on industrial scale to favour clinical translation [63]. Moreover, it is crucial that the nanodrug displays the highest specificity toward cancer cells in order to increase the delivery of active

drug to the tumor while avoiding side effects [64]. The amount of drug molecules loaded in the carrier needs to be adjusted and optimized in order to balance drug dosage and compatible DDS concentration per administration [62]. Generally, nanoparticles larger than 100 nm are easily recognized and cleared by the reticuloendothelial system; therefore, nanocarrier size refining is essential to provide stability in the bloodstream and proper pharmacokinetics upon parenteral administration [65, 66]. In the last twenty years, several nanoparticle platforms have been developed in order to improve pharmacokinetics and toxicity of anticancer drugs [67]. Among the first ones, we find liposomes, which are vesicles with a cave sphere structure constituted by single or multiple bilayers of natural or synthetic lipids surrounding an aqueous core. Liposomes are highly biocompatible and biodegradable, and their size can range from few tens of nanometers to micrometers. Since they are able to encapsulate hydrophilic molecules within the aqueous core and hydrophobic agents within their lamellae, liposomes are considered an excellent therapeutic carrier. Another kind of highly used DDS is the albumin-bound nanoparticle (Nab), which exploits the capability of albumin to bind and transport hydrophobic molecules. Moreover, albumin is able to recognize the glycoprotein receptor gp60 and mediate the endothelial transcytosis of Nab [68, 69]. Other extensively studied nanodevices for drug delivery include dendrimers, protein-based nanocages, and polymeric and metal nanoparticles. Dendrimers are regularly branched macromolecules produced starting from synthetic or natural elements such as amino acids, sugars, or nucleotides; they can be easily modified or conjugated with therapeutics and loaded with drugs using the cavities of their structure [35, 70]. Protein-based nanocages are biological nanoparticles characterized by easy catabolism, minimal toxicity, and immunogenicity. They are constituted by self-assembling protein subunits generally arranged in a hollow structure, which can be chemically or genetically engineered to insert pharmaceuticals and/or probes or to shape various and ordered functionalities, thus enabling the realization of multifunctional nanoparticles. The uniform cage of these nanoparticles allows the precise control of the amount of encapsulated drugs/probes, which is crucial in defining drug dosage. Moreover, their stability in physiological environment avoids macromolecular aggregation, thus increasing circulation time, protecting the cargo molecule from degradation, and improving bioavailability [71, 72]. Polymeric nanoparticles are made of biocompatible and biodegradable polymers consisting of two or more chains with different hydrophobicity. Through a self-assembling process, these chains form a core-shell structure that reduces the interactions of the hydrophobic blocks with the aqueous environment. These nanoparticles show high loading capacity and are well suited for delivery of hydrophilic or hydrophobic small drugs or macromolecules [36, 73]. Finally, inert metals, such as gold, iron, and titanium, have been used to generate multivalent and theranostic nanosystems, which couple in a single agent both cancer therapy and diagnostics. Indeed, thanks to their physicochemical properties, some inorganic nanoparticles can address other biomedical applications besides the drug delivery, such as the photothermal

therapy and the tumor imaging. They have been classified as being inert and biocompatible; however, metal nanoparticles retained in the organism after administration may potentially cause toxicity [67]. All nano-DDS developed for MBC management are described below and subdivided according to their use in clinical practice or preclinical research. A complete overview is provided in Table 1.

2.2. Nanoparticles in Clinical Use: From Liposomal Anthracyclines to Nanoformulated Paclitaxel. Among the first nanoparticles applied in medicine as drug delivery systems, we find three anthracycline-based nanoformulations: liposomal daunorubicin (DaunoXome), nonpegylated liposomal doxorubicin (Myocet), and pegylated liposomal doxorubicin (Doxil in USA and Caelyx in other countries). DaunoXome is composed of daunorubicin entrapped in a 45 nm unilamellar vesicle of distearoyl phosphatidylcholine (DSPC) and cholesterol, with a half-life of 4.4 hours [27]. While liposomal daunorubicin is widely approved for the first-line treatment of AIDS-related Kaposi sarcoma, only scarce literature reports on its role in MBC. In a phase I study, DaunoXome has been administered to 16 breast cancer patients with a planned dose escalation from 80 to 180 mg/m². Mild cardiotoxicity was observed in 3 patients only, but acute dose-limiting toxicity occurred as febrile neutropenia at 120 mg/m². Moreover, only 2 patients showed objective responses to treatment [27]. Therefore, further analyses are required to determine the safety and efficacy of this nanoformulation. Myocet is composed of doxorubicin loaded into a 180 nm vesicle of DSPC and cholesterol, with a half-life of 2-3 hours [74]. This nanoformulation is approved in combination with cyclophosphamide for the first-line treatment of MBC in Canada and Europe. Various randomized controlled trials have investigated Myocet efficacy and toxicity profile compared to conventional doxorubicin. Two phase III studies have compared nonpegylated liposomal doxorubicin versus doxorubicin as a first-line treatment: no differences were observed in anticancer efficacy and median survival, but a significant reduction of cardiotoxicity was evident with liposomal doxorubicin [18, 19]. Interestingly, nonpegylated liposomal doxorubicin was also compared to epirubicin, a well-known anthracycline analogue with different cardiotoxicity compared to doxorubicin. A phase III randomized trial showed similarly low cardiotoxicity rates, but Myocet showed increased efficacy compared to epirubicin [20]. A meta-analysis performed by the Cochrane Database of Systematic Reviews on the previously described trials confirmed a significant lower rate of cardiotoxicity with Myocet, and also significant reduction in grade 4 neutropenia, grade > 3 nausea/vomiting, and grade > 3 diarrhoea was observed [75]. These data strongly suggest that liposomal nanoformulation increases the therapeutic index of anthracyclines mainly by improving the toxicity profile, although keeping substantially comparable efficacy. The reason for decreased toxicity is that intravenously injected liposomes hamper drug exit from the circulation into healthy tissues, while they only extravasate at cancer sites where endothelial capillary junctions are leaky, thus accumulating specifically into the tumor [76]. Doxil is a 100 nm liposomal doxorubicin coated with protective

hydrophilic surface-bound methoxypolyethylene glycol [14]. Pegylation protects liposomes from uptake by the mononuclear phagocyte system, thus modifying drug pharmacokinetics and prolonging liposomes' blood circulation time. Doxil half-life is higher than that of other anthracycline-based nanoformulations (55 hours), and its biodistribution also differs from that of conventional doxorubicin, as shown by higher tumor concentration at lower dosage [14, 74]. Clinical trials have demonstrated again a reduced risk of cardiotoxicity but no changes in overall survival and response rates; moreover, Doxil led to a 48% incidence of hand-foot syndrome, a painful erythrodysesthesia that occurs on hand palms and feet soles [15, 16].

Beyond anthracyclines, taxanes (paclitaxel and docetaxel) traditionally represent another mainstay of MBC treatment, with well-established antitumor efficacy [21]. Since they are highly hydrophobic molecules, they are commercialized in combination with solvents (Cremophor EL and ethanol) that, while ensuring drugs solubility, are associated with hypersensitivity reactions; importantly, taxanes are associated with neurotoxicity and enhanced axonal degeneration [77]. To overcome these limitations, a 130 nm sized nanoformulated albumin-bound paclitaxel (Nab-paclitaxel, Abraxane) has been developed and subsequently approved by FDA, being nowadays in clinical use for various solid tumors, including MBC. After injection, Nab-paclitaxel particles benefit from albumin-mediated enhanced active transport to accumulate into the tumor [22]. A large number of randomized controlled trials have shown that Nab-paclitaxel could be administered at a higher dose than conventional paclitaxel and without any steroid premedication, which are normally used before infusion of taxanes. Moreover, a lower rate of grade 4 neutropenia was observed with Nab-paclitaxel, allowing a better therapy adherence with improved disease control and clinical outcomes [23, 24]. Due to these significant improvements in breast cancer therapy, a number of randomized trials are currently investigating Nab-paclitaxel in association with biologic agents used in the metastatic setting with encouraging results in terms of reduced neurotoxicity and higher overall response rates, although controversial findings were observed in progression-free and overall survivals [21, 25, 26]. Certainly, further large randomized trials are required to better clarify Nab-paclitaxel activity and optimal dosages in different subtypes of aggressive MBC, but Nab-paclitaxel has anticipated what we can expect from nanotechnology introduction in clinical practice, showing global improvements in both outcome and quality of life of MBC patients, allowing shorter infusion time, avoidance of steroid premedication, and potentially higher administered dosages [21, 22]. Other forms of nanoformulated paclitaxel are in phase II/III trials [78]. A cationic liposomal paclitaxel (EndoTAG) has been designed to enhance binding to negatively charged endothelial cells in tumor blood vessels, with an increased clinical benefit rate for cationic liposomal paclitaxel plus paclitaxel, although a slight increase in grades 3-4 neutropenia was observed [28]. Another nanoformulated taxane is polymeric-micellar paclitaxel (Genexol-PM), a compound of 20–50 nm diameter with excellent water solubility and stability. A phase II trial performed on 41 MBCs treated with

TABLE 1: Nano-DDS in MBC.

	Nanoparticle type	Cargo	Target	Size	Toxicity evaluation	Nanocompound
Clinical practice	Liposomes (pegylated)	Doxorubicin	—	100 nm	Skin toxicity, mucositis, stomatitis, hand-foot syndrome, and neutropenia	Doxil, Caelyx [14-17]
	Liposomes (nonpegylated)	—	—	180 nm	Myelosuppression (neutropenia, thrombocytopenia), congestive heart failure	Myocet [18-20]
	Albumin-bound nanoparticles (Nab)	Paclitaxel	—	130 nm	Grades 3-4 neutropenia	Abraxane [21-26]
Clinical studies	Liposomes	Daunorubicin	—	35-65 nm	Neutropenia, cardiotoxicity (decline in DaunoXome [†] [27] ejection fraction)	
	Paclitaxel	—	—	180-200 nm	Grades 3-4 neutropenia, infusion-related reactions (pyrexia and chills)	Endo-TAG ^{††} [28]
	Polymeric nanoparticles	Paclitaxel	—	20-50 nm	Sensory peripheral neuropathy, myalgia, and grades 3-4 neutropenia	Genexol-PM ^{*††} [29]
Preclinical research	Liposomes	Estrogen receptor (ER)	243 ± 4.6 nm (polydispersity index = 0.16)	Not evaluated	ER-targeted liposomal doxorubicin [30]	
	Doxorubicin	Tumor cell surface-bound nucleosomes	112 ± 7 nm	<i>In vivo</i> evaluation (auricular erythema manifestation)	Doxil-mAb 2C5 [31]	
	Mitoxantrone	—	$61 \text{ nm (polydispersity index = } 0.4295\text{)}$	<i>In vivo</i> evaluation (acute toxicity study)	Mitoxantrone solid lipid nanoparticles (MTO-SLN) [32]	
Lipid nanoparticles	Mitoxantrone	Clotted plasma protein p32	~ 130 to ~ 150 nm	Not evaluated	CREKA-Nab-Paclitaxel [33]	
	Paclitaxel	Y1 receptor	141.9 nm	<i>In vitro</i> cytotoxicity study	LyP-1-Nab-paclitaxel [33]	
	Doxorubicin	—	$10.8 \text{ nm (polydispersity index = } 0.16\text{)}$	<i>In vivo</i> evaluation (systemic and pulmonary tolerability)	PNBL-NPY albumin nanoparticles [§] [34]	
Dendrimers	Doxorubicin	—	281 ± 85 nm for OPN-AS; 294 ± 98 nm for BSP-AS	DOX-Pegylated PLL dendrimers [35]	AS-PLGA nanoparticles [35]	
Polymeric nanoparticles	Antisense (AS) against osteopontin (OPN) and bone sialoprotein (BSP)	—	320.60 ± 66.87 nm for siOPN; 293.40 ± 29.04 nm for siBSP	<i>In vitro</i> cytotoxicity study	AS-PLGA nanoparticles [36]	
	siRNA against osteopontin (siOPN) and bone sialoprotein (siBSP)	—		<i>In vitro</i> cytotoxicity study	siRNA-encapsulating polymeric biodegradable nanoparticles [37]	

TABLE I: Continued.

Nanoparticle type	Cargo	Target	Size	Toxicity evaluation	Nanocompound
Succinobucol	VCAM-1	53.0 ± 9.8 nm (polydispersity index = 0.196)		<i>In vitro</i> cytotoxicity study; <i>in vivo</i> evaluation of liver toxicity	Succinobucol self-assembled triblock polymer polyoxamer P188 nanoparticles [38]
Anti-miR-21, anti-miR-10b	uPA receptor	100 to 200 nm (polydispersity index = 0.09–0.264)		<i>In vitro</i> cytotoxicity study; <i>in vivo</i> evaluation of kidney and liver toxicity	uPA receptor-targeted antisense-loaded PLGA-b-PEG polymer nanoparticles (NPs) [39]
Curcumin, bortezomib	Bone	235.5 ± 71.30 nm		<i>In vitro</i> cytotoxicity study	Alendronate-coated PLGA nanoparticles [40]
Orlistat	Folate receptor	75.53 ± 1.029 nm (polydispersity index = 0.223)		<i>In vivo</i> evaluation of spleen, kidney, and liver toxicity	HEA-EHA copolymer micellar nanoparticles functionalized with folic acid [41]
Doxorubicin, gadolinium		61.9 ± 5.0 nm		<i>In vitro</i> cytotoxicity study	Multifunctional PMMA-PS 80-g-St terpolymer nanoparticles [§] [42]
Cetuximab or trastuzumab, gadolinium-DOTA	EGFR or HER2	16.0 ± 1.5 nm for cetuximab-NIA; 16.3 ± 1.6 nm for trastuzumab-NIA		Not evaluated	Anti-EGFR or anti-HER2 poly(b-l-malic acid) polymeric nanoimaging agents (NIAs) [§] ; $\alpha\text{v}\beta_3$ integrins [43]
Paclitaxel encapsulating liposomes, Silicon nanoparticles quantum dots, and iron oxide nanoparticles	E-selectin	1.6 ± 0.1 μm		<i>In vitro</i> and <i>in vivo</i> studies	E-selectin thioaptamer-conjugated porous silicon (pSi) particles (ESTA-PSP) [§] [44]

TABLE I: Continued.

Nanoparticle type	Cargo	Target	Size	Toxicity evaluation	Nanocompound
Composite nanoparticles	Paclitaxel, rapamycin	HER2	150–200 nm (polydispersity index ~0.2)	<i>In vitro</i> study (cytotoxicity and anti-inflammatory response)	Anti-HER2-glycerol monooleate coated magnetic nanoparticles (GMO-MNPs) [§] [45]
	$\alpha_1\beta_3$ integrins		137.2 ± 17.9 nm	<i>In vitro</i> cytotoxicity study	cRGD-iron oxide-based multicomponent nChain particles linked to liposomal doxorubicin [§] [46]
Doxorubicin					Herceptin-chitosan-conjugated pluronic-based nanocarriers (IONP/DOX-MFNC) [§] [47]

[†]Phase I; [‡]phase II; ^{*} clinical practice only in South Korea; [§] nanoparticles with theranostic application.

polymeric-micellar paclitaxel as single agent has revealed an objective response rate significantly higher if compared with that obtained at the same dosage with Nab-paclitaxel [29]. Polymeric-micellar paclitaxel is approved in South Korea for use in MBC [78].

3. A New Outlook from Preclinical Studies: The Active Nanotargeting of MBC

3.1. Why and How to Target Tumor Cells? Nanotechnological strategies have consistently improved the therapeutic index of anthracyclines and taxanes, mainly by ameliorating their toxicity profiles. However, improvements in clinical outcomes are controversial, and no substantial changes in overall survival have been observed compared to conventional chemotherapy in most cases. This piece of data probably reflects the fact that nanoparticles often accumulate into the tumor mass by enhanced permeability and retention (EPR) effect, while hardly entering the tumor cells. The EPR effect allows proteins larger than 30 kDa to passively extravasate from the blood vessels into the tumor interstitial space, thanks to the increased vascular permeability in correspondence with the tumor endothelium. Indeed, during tumor growth, neoangiogenesis is promoted in order to satisfy the increasing oxygen demand and, at the same time, the endothelium of the new blood vessels is tortuous, poorly differentiated, and leaky, thus allowing molecules extravasation. Moreover, solid tumors lack functional lymphatics and are unable to eliminate extravasated nanomaterials, thus contributing to increasing nanoparticles accumulation and prolonged retention within the tumor [79, 80]. Therefore, the EPR effect has become one of the most exploited biological phenomena for nanotherapeutic strategies. Nonetheless, it is a complex process depending on many factors such as tumor type, tumor microenvironment, and nanoparticle properties, and it does not ensure the intracellular delivery of the drug [79]. Certainly, the passive diffusion of nanoformulated drugs through leaky tumor vasculature may have a prominent role for the treatment of primary tumors with more than 100 mm³ in volume; however, it remains less effective in a metastatic setting. Metastases are only poorly accessible to molecular or nanoparticle agents because of their small size, high dispersion to organs, and low vascularization if compared to primary tumors [12, 81]. As a consequence, the EPR effect is not sufficient for proper drug nanodelivery to these sites, and the development of effective therapies toward metastases still remains a main challenge in cancer treatment. In this context, nanotechnologists have developed new systems meant to specifically target cancer cells, thus enabling a more effective recognition of the lesion, prolonged persistence at tumor site, and an increasing diagnostic and therapeutic efficacy. This strategy, called “active targeting,” involves the conjugation on the nanoparticle surface of targeting moieties, like antibodies or peptides, which specifically bind to tumor receptors or biomarkers and subsequently trigger nanoparticle internalization [80]. Targeted nanoparticles may benefit from the EPR effect but, thanks to the specific binding to the target, also improve tumor delivery

of therapeutics and uptake by cancer cells [67]. Liposomal anthracyclines such as Doxil have been functionalized with anticancer antibodies, and preclinical studies have demonstrated improved therapeutic index and reduced side effects when compared to original Doxil [31]. Nab-paclitaxel has also been functionalized with the peptide Lyp-1, which recognizes tumor lymphatics: this study has demonstrated an increased tumor growth inhibition after treatment with targeted Nab-paclitaxel in comparison with untargeted Nab-paclitaxel [33]. By delivering pharmacological agents more selectively into tumor cells, targeted nanoparticles modify the biodistribution of therapeutic drugs and guide them away from healthy tissues, further improving the efficacy-toxicity ratio when compared to untargeted nanocompounds [82]. Successful active targeting to MBC basically relies on a thorough understanding of the complex processes involved in tumor growth, invasion, and evolution toward metastasis and metastasis-specific features. Certainly, a major concern is the need of specific and reliable targets, with blown and persistent overexpression in cancer tissues. Recently, the neuropeptide Y1 receptor has been recognized as a novel target for breast cancer cells, since healthy breast tissue overexpresses only Y2 receptors. Therefore, albumin nanoparticles loaded with doxorubicin and functionalized with PNBL-NPY, a ligand of Y1 receptors, have been successfully used to properly address the nanodrug to breast cancer cells [34].

3.2. Targeting the Metastatic Primary Tumor. In the past few decades, significant progress has been made in understanding the genetics and the molecular principles contributing to malignant transformation and tumorigenesis. Gene expression profiling has been used to classify tumors, based on molecular fingerprints that correlate with histological subtypes and may predict the clinical outcome [83]. In particular specific molecules or pathways, either overexpressed or dysregulated in different types of MBC, have been identified and draw interest for targeted applications. HER2 is one of the most commonly targeted molecules in MBC therapy, since it is overexpressed in a large subset of aggressive breast cancers. Antibodies that recognize HER2, such as trastuzumab (Herceptin), represent a gold standard for the molecularly targeted therapy [84]. In this context, a variety of nanotherapeutic strategies based on the conjugation of Herceptin or fragments of it to nanoparticles surface have been explored for targeted delivery to HER2-positive breast cancer and have led to enhanced localization and treatment of tumors both *in vitro* and *in vivo* [45, 85–89]. Recently, HER2-targeted nanocarriers have been intensely explored to specifically deliver and release doxorubicin in HER2-positive cancer cells, with enhanced anticancer activity compared to nontargeted nanoparticles [47]. Besides HER2, more than two-thirds of breast cancer cells display upregulation of the estrogen receptor, which has therefore been selected as the most important target for hormone therapy of breast cancer [30]. Several drug delivery platforms have been successfully engineered in order to bind other specific receptors that are prone to endocytosis, such as the folate receptor, the transferrin receptor-1 (TfR-1), and the epidermal growth factor receptor (EGFR), thus enabling drugs to enter the

cytoplasm of cancer cells and to further exert their antitumoral effects [41, 90–92]. Biomolecules resembling receptors ligands or fragments of them have been studied and produced to be exploited in this context. This is the case for the aminoterminal fragment of the urokinase type plasminogen activator (uPA), which has been used as a targeting moiety for conjugation to the surface of iron oxide-based nanoparticle in order to achieve specific recognition of uPA receptor-expressing cancer cells [54]. A novel approach has been attempted with smart polymeric nanoparticles functionalized with uPA and loaded with antisense miRNAs to antagonize miR-21, responsible for apoptosis inhibition, and miR-10b, which induces metastatic features [39]. Interestingly, these nanoparticles have been investigated in murine model of triple-negative breast cancer, which is known to overexpress uPA receptor [93], and have provided significant reduction of tumor growth and metastases at a very low dose (0.15 mg/kg), thus proving to be a potential novel therapeutic option for MBC.

3.3. Targeting the Tumor Vasculature. In order to overcome drawbacks in reaching tumor cells, various endothelial-targeted nanodevices have been also developed [94]. These nanoparticles either bind and kill the endothelial target, stopping the flow of oxygen and nutrients to the tumor, or are designed to release the drug directly within the vessel, thus allowing it to go deep in the interstitium [95]. Several endothelial adhesion molecules involved in migration, invasion, and metastatic behaviour of cancer cells represent good targets for nanoparticles design. Ligands immobilized on nanoparticles surface to target tumor vasculature are the antibody fragment L19 and some derivatives of the RGD or NGR peptides, which recognize the EBD domain of fibronectin and the integrins $\alpha_2\beta_5$, $\alpha_v\beta_3$, and $\alpha_5\beta_1$, respectively [96, 97]. One interesting example is the multicomponent nanodevice developed by Peiris and coworkers, which consists of iron oxide-based nanospheres linked to a doxorubicin-loaded liposome. This device is functionalized on both liposome and iron oxide nanospheres with the cyclic RGD peptide that targets the $\alpha_v\beta_3$ integrins and cell adhesion molecules that mediate the metastatic site transition from tumor cell rolling on the endothelium to firm attachment for subsequent extravasation and tissue invasion. The active targeting provides the specific delivery of the nanoconstruct to tumor neovasculature and, together with size, shape, and flexibility of the construct, contributes to increasing the probability of homing to micrometastases [46]. Endothelial-targeted nanodevices have been shown to possess huge potential for improving antitumor efficacy when compared to tumor cell-targeted nanomedicines, and this is mostly due to the fact that they can more easily find their final target.

3.4. Targeting Selective Metastatic Sites and Overcoming Barriers to Cancer Reservoirs. Targeting nanomaterials specifically to the metastatic lesions is a major challenge for translation to clinical use. Expression profiling of metastases arising in different tissues has revealed that gene signature from metastases can be different from that of the original neoplasm [98]. As a consequence, some targeted approaches that generate

positive effects in primary tumors could be ineffective toward metastases. Moreover, targeting metastases depend on the specific features of different metastatic sites. Based on the identification of metastasis-specific features, strategies for improving drug delivery to metastatic sites have been developed. Different targets and conjugation strategies have been applied with respect to different types of tumor and metastasis location [12]. A major concern for MBC is the higher occurrence of brain metastases, particularly in some specific subsets [99]. Indeed, most chemotherapeutic drugs have not been generally considered an effective option for patients with central nervous system metastases due to the presence of the blood-brain barrier (BBB), which restricts the access of high-molecular weight molecules from the vasculature [100]. Within the BBB, the tight junctions in between brain microvascular endothelial cells and the P-glycoprotein efflux pumps hamper the filtration of therapeutic drugs, preventing their penetration into the brain. Nanotechnology could be successfully exploited to guarantee a proper addressing of anticancer drugs into the central nervous system, and various strategies are being investigated [101]. A multifunctional polymeric nanotheranostic system was designed in 2014 by Li et al. and tested in a murine model of breast cancer metastatic to the brain. This nanocarrier demonstrated a high permeability to BBB, with subsequent efficient release of doxorubicin into metastatic cancer deposits and proper gadolinium extravasation to enable an accurate imaging of metastases on magnetic resonance (MRI) [42]. Pegylated liposomal doxorubicin also demonstrated pharmacokinetics and efficacy advantage over nonliposomal doxorubicin in the treatment of an *in vivo* model of breast cancer brain metastases [17]. More recently, novel polymeric nanoparticles have been attached to gadolinium, functionalized toward HER2 or EGFR, and injected into mice bearing both lung and breast cancers metastatic to the brain. Nanoparticles were able to pass through the BBB and to selectively reach metastases; moreover, when gadolinium was replaced with selective inhibitors of HER2 or EGFR, a significant reduction of brain metastases and a longer survival of mice were observed [43]. Other attempts to reach brain tumors have been carried out by active targeting of the BBB, exploiting the overexpression of TfR-1 or apolipoprotein E (ApoE) receptors on its surface [102, 103]; promising results suggest that this approach could be of benefit even in MBC management.

Other intriguing progress in the field corresponds to the targeting of bone metastases, a common and devastating consequence of breast cancer that leads to alteration of osteoblast and osteoclast function, with resulting skeletal destruction [104]. E-selectin-targeted nanoparticles have proven to trigger bone marrow enrichment of therapeutics, thus suggesting a promising bone metastasis-specific device [44]. PLGA nanoparticles loaded with antisense oligonucleotides against osteopontin and bone sialoprotein have been successfully used in a rat model of triple-negative breast cancer to demonstrate a significant decrease in tumor bone metastasis incidence and in metastases size [36]. Similar polymeric-based biodegradable nanoformulation of siRNAs against bone-specific genes revealed significant efficacy against migration of breast cancer cells and osteolysis in a rat model of

skeletal metastases [37]. In 2012, PLGA nanoparticles for active targeting of MBC were developed by conjugation with alendronate, a bone seeking molecule able to bind to the bone and reduce bone resorption. Simultaneous encapsulation of two chemotherapeutic agents, curcumin and bortezomib, within these nanoparticles revealed antiosteoclastogenesis ability and significant decrease of tumor progression in an *in vivo* intraosseous model of bone metastasis [40]. Other biologic targets and pathways under investigation include breast cancer-derived interleukins, cytokines, prostaglandins, integrins, growth factors, and proteases that mediate cancer-related bone resorption [105].

Another serious problem for breast cancer patients is represented by lymph node metastases. Mitoxantrone solid lipid nanoparticles with mean size of less than 100 nm were prepared, characterized, and tested by subcutaneous injection in a model of lymph node metastases [32]. Results showed high targeting efficiency of the drug to the lymph nodes, enhanced therapeutic effect of the antitumor agent, and significant reduction in lymph node mean size.

Other researchers have exploited the vascular cell adhesion molecule-1 (VCAM-1) as a therapeutic target against lung metastasis of breast cancer. They have generated hydrophobic interaction-mediated self-assembled nanoparticles with succinobucol, a potent and selective VCAM-1 inhibitor, and have demonstrated improved drug bioavailability and biodistribution upon nanoformulation, together with efficacy in suppressing the lung metastasis of breast cancer in a 4T1 breast cancer murine model [38].

3.5. Targeting the Circulating Tumor Cells. Factors that promote the infiltration, survival, and colonization of distant organs are also attractive targets that could be used as prognostic markers for guiding the therapy and/or be themselves good therapeutic targets, to prevent metastases outgrowth. Numerous studies have evaluated the relevance of circulating tumor cells (CTCs) in the peripheral blood as markers of clinical progression in breast cancer and predictive indicators of response to therapy [106, 107]. Detecting CTCs, more than solid organ metastases, seems to offer an effective and reliable prediction of tumor behaviour; however, the lack of specific and robust molecular targets is a prominent limitation for this kind of approach. Galanzha and colleagues have developed gold nanoparticles to detect circulating tumor cells, by targeting CD44: such nanoconstructs have revealed high sensitive and noninvasive detection of cancer cells and their subsequent destruction by ultrasound or hyperthermia, thus preventing metastases formation [55]. More recently, magnetic nanogels based on magnetic nanoparticles and linear thermoresponsive polyglycerol were designed for CTCs capturing. Nanogel surface was decorated with transferrin-(Tf-) polyethylene glycol moieties, which provided capture of Tf receptors-positive CTCs [59].

4. Nanoparticles for MBC Diagnosis

In the last years, many studies have been directed to the design of new contrast agents allowing easy, reliable, and non-invasive identification of breast cancer [108]. In this context,

the development of target-specific nanostructured contrast agents has revealed optimal sensitivity for various imaging techniques, from the optical imaging (fluorescence and bioluminescence detection) to the radionucleotide-based imaging (positron emission tomography (PET) and computed tomography (CT)) or MRI. Magnetic iron oxide nanoparticles are able to enhance the T_2 -weighted negative contrast of target tissues in MRI and, to date, they represent the prevailing agent for breast cancer detection. Engineering the surface of this nanodevice with specific tumor markers has led to the generation of one of the most studied versatile platforms for site-specific tumor imaging and localization of primary breast cancer by MRI [50, 54, 61]. Nevertheless, the localization of peripheral metastasis still remains a key challenge, and only a limited number of studies have reported on this so far. Here, we describe preclinical nanotechnological research focused on MBC diagnostics and provide an overview of all developed nanoparticles for MBC imaging in Table 2.

In an interesting study, superparamagnetic iron oxide nanoparticles (SPIONs) have been functionalized with the luteinizing hormone/chorionic gonadotropin (LH/CG) and the luteinizing hormone releasing hormone (LHRH), whose receptors are expressed in >50% of breast cancers [51]. It was found that both types of these small (<50 nm hydrodynamic diameter) and highly soluble nanoparticles were actively internalized *in vitro* by the MDA-MB-435S breast cancer cells after binding to their receptors. *In vivo* investigation on nude mice bearing a MDA-MB-435S interscapular tumor showed a strong accumulation of intravenously injected LHRH-conjugated SPIONs (up to 59% of injected iron particles) within the primary tumor but also within lung metastases (up to 20%). MRI of breast cancers dissected after 20-hour exposure to LHRH-conjugated SPIONs showed that these nanoparticles were able to enhance the negative contrast of the xenografts [52]. Multi-CRAZED magnetic anisotropy images of isolated tissues confirmed the great potential of LHRH-conjugated SPION as contrast agent for lung metastases [52]. Kievit and colleagues have designed a SPION coated with a copolymer of chitosan and polyethylene glycol and functionalized with a monoclonal antibody against human HER2/neu [60]. This neu-conjugated nanoparticle (NP-neu) has been shown to be efficiently internalized by neu-expressing mouse mammary carcinoma cells *in vitro*. The ability of NP-neu to target MBC and to be detected by MRI was assessed in transgenic mice that spontaneously develop HER2/neu-positive tumors: a significant T_2 decrease was observed at the tumor site in NP-neu-injected mice as compared to the noninjected animals. Lung, liver, and bone marrow metastases were also detected by histological and cytofluorimetric assays upon NP-neu injection. Positive Prussian blue staining of histological sections indicated the presence of iron nanoparticles in lung and liver metastases. This targeting effect on liver and lung by NP-neu was further confirmed using flow cytometry analysis, which also provided a successful detection of metastatic cancer cells in aspirated bone marrow. Although able to selectively label early stage micrometastases by histology or flow cytometry, these neu-targeted nanoparticles have finally been shown to be useless for MRI, since the micrometastases were beyond

TABLE 2: Nanoparticles for MBC diagnostics[#].

Nanoparticle type	Target	Size	Toxicity evaluation	Nanocompound
Metal nanoparticles	$\alpha_v\beta_3$ integrins	107.8 ± 11.4 nm 25 nm	Not evaluated <i>In vitro</i> cytotoxicity study	cRGD-iron oxide nanochains (RGD-NC) [48]
HER2		185 nm	Not evaluated	Herceptin-MnO nanoparticles [49]
LH/CG or LHRH receptors		10 nm	Not evaluated	Anti-HER2 antibody-conjugated silica-coated magnetic-fluorescent gold nanoshells [50]
C-C chemokine receptor 5		21.5 ± 1.9 nm	<i>In vitro</i> cytotoxicity study	β CG- or LHRH-superparamagnetic iron oxide nanoparticles (SPIONs) [51, 52]
uPA receptor		18 nm	Not evaluated	d-Alal-peptide T-amide (DAPTA)-conjugated PdCu@Au tripods radiolabeled with ⁶⁴ Cu [§] [53]
CD44 or folic receptors		12.8 nm (diameter) × 91.7 nm (length) for GNTs; 30 nm for MNPs ^s	<i>In vitro</i> cytotoxicity study	uPA ATF-magnetic iron oxide (ATF-IO) nanoparticles ^s [54]
Silicon nanoparticles	CD105	175.3 ± 9.7 nm	Not evaluated	TRC105(Fab)-conjugated ⁶⁴ Cu-fluorescent labeled mesoporous silica nanoparticles (MSNs) ^s [56]
Composite nanoparticles	—	8.5 ± 0.8 nm (polydispersity index = 0.31 ± 0.11)	Not evaluated	⁸⁹ Zr-labeled high-density lipoprotein nanoparticles (⁸⁹ Zr-rHDL) [57]
		150 nm	Not evaluated	Positron-emitting magnetic nanoconstructs (PEMs): PLGA-phospholipid nanoparticles encapsulating ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) and ⁶⁴ Cu (DOTA) [§] [58]
		1,000 nm	Not evaluated	⁶⁴ Cu-discoidal polymeric nanoconstructs (DPNs) composed of PLGA chains, multiarm PEG acrylate chains, lipid-DOTA chains, lipid-Rhodamine B dye, and USPIOs ^s [58]

TABLE 2: Continued.

Nanoparticle type	Target	Size	Toxicity evaluation	Nanocompound
	Transferrin receptors	112 to 165 nm	Not evaluated	Transferrin-PEG-decorated polyglycerol magnetic nanogels (MNGs) [59]
		40 ± 1 nm (polydispersity index = 0.15 ± 0.06)	<i>In vitro</i> cytotoxicity study	Thiolated neu antibody-conjugated superparamagnetic iron oxide nanoparticles (SPIONs) coated with copolymer of chitosan and PEG (NP-neu) [60]
HER2		67 ± 5 nm	<i>In vitro</i> cytotoxicity study	Herceptin-dextran-coated magnetic iron oxide nanoparticles (SPIOs) [61]

[#] All these nanoparticles are in preclinical studies; ^{\$} nanoparticles with theranostic application.

the spatial resolution of a 3-Tesla MRI. In the same year, Pereis and colleagues developed a nanochain (100 nm hydrodynamic size) of four iron oxide nanoparticles functionalized with a cyclic tripeptide arginine-glycine-aspartic acid c(RGD), for the specific targeting of vascular $\alpha_v\beta_3$ integrins [48]. Fluorescence Molecular Tomography (FMT) imaging showed that these nanochain-RGD nanoparticles (RGD-NC) were able to actively target primary 4T1 mammary tumors in mice within 30 minutes from intravenous injection. Targeting of metastatic lesions by RGD-NC was also observed *in vivo* and *ex vivo* in liver, spleen, and lungs. MRI images of the liver in metastatic mice injected with RGD-NC showed a significantly higher negative contrast in this organ when compared to the preinjection contrast or to the postinjection background signal of healthy or uninvolved regions of the metastatic liver. Fluorescence microscopy observations of histological sections showed the microdistribution of RGD-NC in liver and lungs, indicating the colocalization of the nanoparticles with both cancer cells and $\alpha_v\beta_3$ integrins. Most recently, the addition of iron oxide nanoparticles to HER2-targeted doxorubicin nanocarriers allowed for obtaining a promising theranostic agent, suitable for both HER2-positive breast cancer treatment and MRI diagnosis [47].

Although SPION is still the most studied nanoparticle-based contrast agent for MRI detection of breast cancer and its metastases, some limitations in its use are associated with the negative contrast and the magnetic susceptibility artefacts provided by iron oxide. Therefore, some researchers have focused on a new class of contrast agent with positive (T_1 -weighted) contrast ability. In this context, Na and colleagues have developed manganese oxide (MnO) nanoparticles (25 nm diameter) functionalized with the anti-HER2 Herceptin, for MRI detection of breast cancer metastases in mice brain [49]. After intravenous injection of Herceptin-MnO nanoparticles, metastases were significantly enhanced in T_1 -weighted MRI as a result of the active targeting and the accumulation of nanoparticles into breast cancer cells. Nonfunctionalized MnO nanoparticles were also observed to reach the brain metastases by passing through the leaky BBB damaged by tumor formation within the brain. However, only functionalized nanoparticles were able to accumulate at the tumor site for an extended time thanks to their interaction with HER2.

Beyond MRI, PET imaging is indicated to complete the staging of MBC, due to its whole-body detection of tumor-related metabolic activity. However, its spatial resolution, its specificity, and sometimes uptake of ^{18}F -fluoro-2-deoxy-D-glucose are not optimal [109]. Recently, Pang et al. have demonstrated that PdCu@Au nanoparticles radiolabeled with ^{64}Cu and functionalized toward C-C chemokine receptor 5, a newly identified target of triple-negative breast cancer, were able to specifically recognize 4T1 mouse breast cancer cells increasing by 2- to 6-fold higher recognition compared to nontargeted nanoparticles, thus providing a tool for highly accurate PET imaging and photothermal treatment [53]. Interestingly, Pérez-Medina et al. have developed a ^{89}Zr -labeled liposome encapsulating a near-infrared fluorophore for both PET and optical imaging of breast

cancer. Intravenous injection of the nanotracer demonstrated its usefulness in bimodal imaging of cancer deposits by simultaneous PET and intraoperative optical imaging, which is an increasing field of interest in surgical oncology [57]. Mesoporous silica nanoparticles have been also investigated as dual-imaging tracer in murine models of metastatic breast cancer for both PET and near-infrared optical imaging with encouraging results regarding the targeting of both lung metastases and tumor vasculature [56, 58].

5. Conclusions

In MBC management, conventional chemotherapy shows major limitations in achieving a proper treatment. Although important improvements have been obtained with nanoformulated anthracyclines and paclitaxel, an accurate detection and a satisfying treatment of the metastatic disease still remain a key challenge. In this context, the active targeting of malignant cells appears as a promising strategy for a successful theranostic approach in MBC. Specific ligands or antitumor drugs conjugated on the surface of nanoparticles have demonstrated efficient interaction with cancer cells and improved drug delivery to tumor sites, even through physiological barriers. Active targeting nanostrategies are expected to reduce toxicity and chemoresistance and to enhance the anticancer activity. Certainly, further studies are necessary before introducing this new class of nanodrugs in clinical practice. However, active collaboration between nanotechnologists and physicians has provided satisfactory progress and should be strongly encouraged to achieve a clinical revolution for MBC management.

Competing Interests

The authors declare that there are no competing interests.

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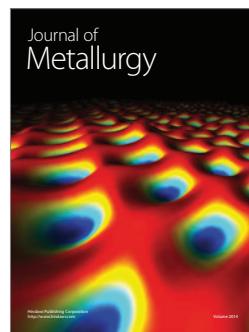
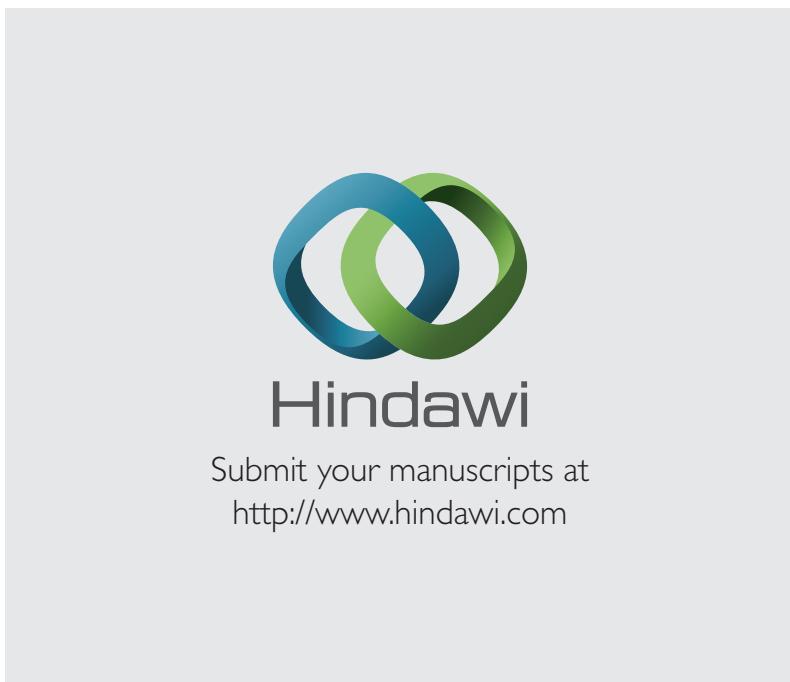
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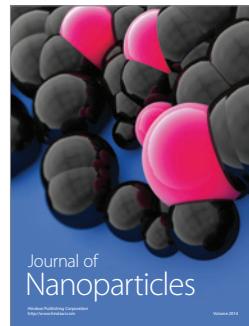
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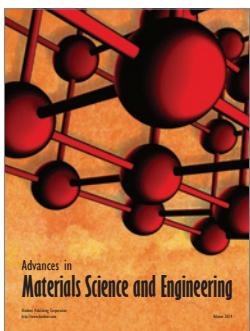
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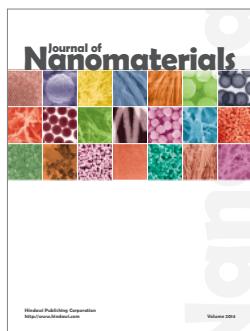
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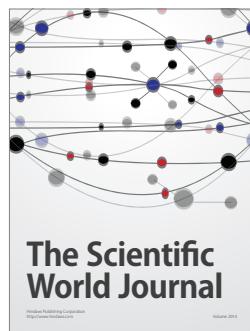
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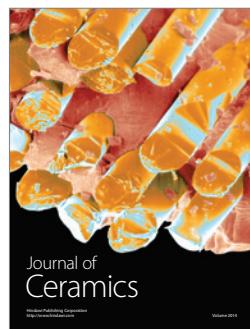
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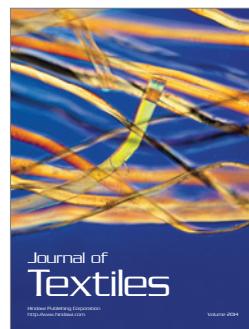
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