Novel strategies using sagacious targeting for site-specific drug delivery in breast cancer treatment: Clinical potentials and applications

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ABSTARCT

For more than a decade, researchers have been working to achieve new strategies and smart targeting drug delivery techniques and technologies to treat breast cancer. Nanotechnology presents a promising strategy for targeted drug delivery into the building of new therapeutics using the properties of nanomaterials. Nanoparticles are of high regard in the field of diagnosis and treatment of cancer. The use of these nanoparticles as a promising approach in the treatment of various cancers has attracted the attention of researchers in recent years. In order to achieve the maximum therapeutic efficacy in the treatment of breast cancer, combination therapy has also been adopted, leading to minimal side effects and thus, an improvement in the quality of life for patients. This review article compares, discusses and criticizes the approaches to treat breast cancer using novel design strategies and smart targeting of site-specific drug delivery systems.

Keywords: Breast cancer; Combination therapy; Nanoparticles; Site-specific drug delivery; Smart targeting; Triple-Negative Breast Cancer

List of Abbreviations

17-AAG: Tanespimycin (17-N-allylamino-17-demethoxygeldanamycin)

AKI: Aurora kinase inhibitor

Akt: Protein kinase B

AMD3100: A specific antagonist to the CXCR4 receptor

ATLAS: Adjuvant Tamoxifen: Longer Against Shorter

CT: Cancer/Testis

CXCL12: The stromal cell-derived factor 1 (SDF1), also known as C-X-C motif chemokine 12

CXCR4: C-X-C chemokine receptor type 4

DNA: Deoxyribonucleic acid

DOX: Doxorubicin

DPPE: 1,2-Bis(diphenylphosphino)ethane

dsRNA: double-stranded RNA

EGFR: Epidermal growth factor receptor

EPR: Enhanced permeability and retention

ER: Estrogen receptor

FITC: Fluorescein isothiocyanate

HER2: Human epidermal growth factor receptor 2

IL-6: Interleukin 6

IV: Intravenous

mAb: Monoclonal antibody

miRNA: Micro RNA

miRNAs: MicroRNAs

MRI: Magnetic resonance imaging

MSCs: Mesenchymal stromal cells

mTOR: Mammalian target of rapamycin

MTX: Methotrexate

N/A: Not Applicable

NPs: Nanoparticles

OS: Overall survival

PARP: Poly (ADP-ribose) polymerase

PARP: Poly (ADP-ribose) polymerase

pCR: Pathological complete response

PEG: Polyethylene glycol

PFS: Progression-free survival

PI3K: Phosphatidylinositol-3-kinase

PLA: Polylactic acid

PLN: Polymer-lipid hybrid NPs

PR: Progesterone receptor

PTX: Paclitaxel

RES: Reticuloendothelial system

RR: Response rate

siRNA: Small interfering RNA

SMTX: Short-term Methotrexate

sVEGF: Soluble VEGF

T-DM1: Trastuzumab emtansine

TMX: Tamoxifen

TNBC: Triple-negative breast cancer

TNF: Tumor necrosis factor

TTP: Time to progression

VEGF: Vascular endothelial growth factor

VEGFR2: Vascular endothelial growth factor receptor 2

WHO: World health organization

I. INTRODUCTION

Breast cancer is the most common cancer in females worldwide and the second most common cause of death in women.[1]. According to WHO (World Health Organization), breast cancer is the most recurrent cancer among women, affecting more than two million women each year.[2] Cancer statistics worldwide in 2020 show that 19.3 million new cases of cancer (18.1 million excluding non-melanoma skin cancer) have been identified, of which 2.3 million are related to female breast cancer (11.7%).[1]

Many reported studies focusing on the risk factors of breast cancer suggest that breast cancer is more common in young people. A lot of emphases are quite rightly placed on understanding the early stages of breast cancer. In recent years also, developments in novel design strategies based on nanoparticles have been directed towards achieving breast cancer drug delivery both in the detection at early stages and treatment.[3-5] Nanotechnology offers a potential solution for controlling and eradicating breast cancer, a disease with a very difficult historical challenge. One of the most effective strategies in improving cancer outcomes in the patient population and in the evolutionary changes of each individual is combination therapy.[6] The multiple pathways that drive cancer progression, the outset of resistance to a drug in the traditional treatment and poor distribution of injectable therapeutic agents, are reasons to support combination therapy.[7, 8] Metastatic breast cancer presents a diagnostic and therapeutic challenge due to the multiformity of tumors and many physiological barriers that hamper drug delivery to the metastatic sites.[9] To alleviate these limitations, nanoparticles containing drugs have been investigated and used in preclinical studies with a few of them successfully promoted into clinical practice.[10, 11] Over the years, numerous strategies have been used to treat several cases of breast cancer.[12] The intrinsic molecular subtype is necessary for clinical trials and a good understanding of cancer.[13-15] In

addition, new design strategies with specific site-targeting using nanoparticles and novel drug delivery have a huge potential for diagnosis and breast cancer treatment.

II. NEW STRATEGIES TO TARGET BREAST CANCER CELLS

The most effective receptors in the progression of breast cancer are the estrogen receptors. This is the reason for using estrogen in targeted delivery to prevent the estrogen signaling pathway in women with estrogen-positive breast cancer.[16] There are new strategies for targeted drug delivery in breast cancer treatment that have been suggested using anti-cancer tumor with increased compatibility for the human epidermal growth factor receptor 2 (HER2), estrogen receptor and progesterone receptor.[17] The HER2-positive breast cancer is set apart by other receptors with a high percentage of metastasis and drug resistance.[18] A new and effective strategy to target these 3 receptors (estrogen, progesterone and HER2) is to use recombinant monoclonal antibodies. Research suggests these 3 hormones to be expressed at high rates in most breast cancer cases.[19] For instance, about 30% of breast cancers are HER2 positive [20]. A tyrosine kinase realm located in the HER2 receptor plays a part in the occurrence of breast cancer. The HER2 protein shows more expression than the other receptors in breast cancer and is considered the main biomarker for treatment.[21] Among all of the anticancer drugs that target HER2, pertuzumab, trastuzumab, trastuzumab emtansine (T-DM1) and lapatinib have been shown to be more effective in HER2 positive patients in many clinical trials.[22, 23] Trastuzumab, the first cancer treatment drug, is a humanized monoclonal immunoglobulin G1 kappa antibody that has a great affinity in attaching to the extracellular dominion of HER2, which consecutively prevents the proliferation of cells in breast cancer and causes them to upregulate HER2.[24, 25] Trastuzumab can be administered as a single drug or in combination with one of the chemotherapy drugs (such as vinorelbine or

docetaxel) which brings about anti-cancer effects and noticeably responds to treatment and improves survival.[26]. Moreover, several randomizing control trials have reported that trastuzumab and chemotherapy drugs remarkably reduce the risk of reoccurrence and mortality and increase survival rate compared to chemotherapy drugs alone, thus potentially making trastuzumab a keystone of adjuvant treatments for breast cancer patients with HER2 positive receptors.[27-30] Conjugated monoclonal antibody T-DM1 may also be used in HER2 positive breast cancers as trastuzumab effectively transfers the DM1 drug (a microtubule inhibitor) directly into breast cancer to prevent growth. It has been reported that the relatively large molecular size of the antibodies and the occurrence of antigen-antibody binding at the tumor boundary impair the deep penetration of drugs into the tumor's dense clusters.[31-34] To facilitate the scattering of drugs into tumors, a cellular membrane penetration domain and a DNA binding motif are merged with a HER2 receptor binding area.[35-37] As divulged in a lately published patent (Table 1), this design allows drugs to pierce deep into HER2 positive cells and to specially target HER2 positive breast tumor cells.[38, 39]

Estrogens are a group of sex hormones that are mostly synthesized in the ovaries. It has been shown that there is a relationship between breast cancer and these hormones.[40, 41] Estrogens have a specific part in breast cancer both in pre-and postmenopausal women.[42] It has been reported that about 70% of breast cancers are estrogen receptor-positive.[43] Tamoxifen (TMX) is an antagonist of the estrogen receptor. It has a high affinity to the estrogen receptor and has been frequently used to treat breast cancer in women who are estrogen receptor-positive.[44, 45]. Nevertheless, TMX has no specificity to other tissues since it has outcomes on several transduction pathways and diverse ion channels.[46-48] To enhance the effectiveness of TMX, a polyethylene glycol (PEG)-based polymer

can be used to form nanoparticles on which the surface carriers have a molecular recognition element to target estrogen receptor-positive in breast cancer cells.[49, 50] Figure 1A displays the synthesis of TMX-loaded PLA/DPPE-PEG nanocapsules.[51] Figure 1B displays novel TMX nanoformulations for improving breast cancer treatment.[49] This novel drug delivery system has shown to be highly effective in delivering TMX to cancer cells.[49, 52] An adjuvant tamoxifen: longer against shorter (ATLAS) study recently indicated an advantage of 10 years rather than 5 years of TMX reducing the risk of breast cancer coming back both in postmenopausal and premenopausal women by 50% and also a reduction in the risk of new cancer developing in the other breast.[53] Another estrogen receptor antagonist is Fulvestrant which is effective in the treatment of estrogen receptor-positive breast cancer in postmenopausal women.[54, 55] The most used approach for breast cancer targeted therapy is the targeting of the HER2 protein which is overexpressed on the surface of cancerous breast cells.[56] A recent study showed that 99mTc-Radiolabeled silica nanoparticles containing Fluorescein isothiocyanate (FITC) functionalized by trastuzumab allowed the theranostic application through the binding HER2 in breast cancer cells (Figure 2).[57]

III. NEW STRATEGIES ON DRUGS DESIGNED TO TARGET TRIPLE-NEGATIVE BREAST CANCER

It has been reported that about 15% of all breast cancers are triple-negative breast cancer (TNBC).[58] A study at the phase II stage showed that a combination of the monoclonal antibody cetuximab with cisplatin chemotherapy appeared to be effective on cancer cells thereby indicating some subtypes of TNBC inhibition sensitivity.[59, 60] As it has been reported that about 15% of breast tumors do not express the HER2, estrogen or progesterone receptors, therefore, making some targeted drug delivery methods ineffective against triple-negative breast

tumor cells.[38] However, TNBC can proliferate very aggressively and can be quite difficult to eradicate, therefore the risk of recurrence is higher than non-triple negative breast cancer.[61, 62] Poly-(ADP-ribose)-polymerase (PARP) is connected with proteins that can be used in most cellular processes, especially in DNA repair and tumorigenesis.[63] PARP inhibitors like alkylating agents and benzamide (like 4-iodo-3-nitrobenzamide) or topoisomerase I inhibitors are therefore utilized to handle TNBC.[64, 65] Other drugs, like Epidermal Growth Factor Receptor (EGFR) inhibitors, antiangiogenic representative, docetaxel-oxaliplatin compound, and novel Taxane chemotherapy formulations have been used in clinical trials in the treatment of TNBC.[66-68] In several experiments, it was shown that both *in vitro* and *in vivo* studies using EGFR-homing strategy could kill most cancerous breast cells thereby improving mice survival after treatment. Other attempts have been made in the search for special markers that differentiate triple-negative breast cancer cells from the normal ones. These endeavours have led to the uncovering of many cancer genes that could be potentially used as gene markers for triple-negative cancerous breast cells.[69-71] For example, genes encoding cancer/testis (CT) antigens are mostly prevalent in human germline cells and different spiteful tumors. CT genes can be used as replacement markers for targeting triple-negative cancerous breast cells because of the constricted distribution of other genes in the testis and cancer cells.[72-75] MicroRNAs (miRNAs) are other molecular markers for diagnosis and targeted drug delivery. Many affirmations have shown that breast cancer pathogenesis is connected with RNA synthesis.[76, 77] miRNAs play decisive roles in cellular plasticity during breast tumorigenesis and metastasis.[78-80] It has been recently reported that several dysregulated miRNAs that can potentially function as indicators for triple-negative cancerous breast cells[81] The outline of multipurpose nanoparticles for transporting anticancer drugs has been discussed in a recent patent.[82, 83] The

foremost challenge for breast cancer combination therapy is to design a promising formula that is concurrently effective against the many subtypes of breast cancers.

IV. NEW STRATEGIES ON COMBINATIONAL DRUG THERAPY IN BREAST CANCER

The operation of combinational therapy goes back many years. Delivery of targeted combinational chemotherapy is likely to provide better efficacy and reduce the dose while reducing drug resistance.[84-86] For these outcomes, combinational chemotherapy has been set as the new strategy that can be applied in clinical practice.[87] New approaches to partitioning advancement and chemical synthetic capability, as well as omics and cell biology, have also played an essential role in increasing the application of combinational drug therapy in current healthcare practices.[88-90] Promising results from the use of combinational therapy of doxorubicin and cyclophosphamide, followed by docetaxel administered as a neoadjuvant chemotherapy regimen in patients with advanced breast cancer were announced at the National Surgical Adjuvant Breast and Bowel Project Protocol B27.[91, 92] The research announced that using 4 cycles of docetaxel after 4 cycles of doxorubicin and cyclophosphamide resulted in a noteworthy rise in clinical and pathologic response charge for feasible breast cancer.[93, 94] In another research, Ottaiano and co-investigators have evaluated the benefits of putting on gemcitabine to promote epirubicin with paclitaxel and cyclophosphamide. The authors also assigned the effect of sequencing the blocks of epirubicin and cyclophosphamide and paclitaxel alone or in combination with gemcitabine.[95] It was shown in other studies that including gemcitabine to paclitaxel and epirubicin and cyclophosphamide chemotherapy does not enhance the pathological complete response (pCR).[96, 97] However, sequencing chemotherapy in such a way that taxanes are accepted previous to anthracyclines could

ameliorate pCR in standard neoadjuvant chemotherapy for breast cancer.[98-100] The first drug which entered clinical trial was paclitaxel as early as the1980s.[101, 102] Another drug of the same class, docetaxel was presented owing to initial undersupply and difficulty in the paclitaxel manufacture.[103]. Assessment of paclitaxel in combination with other cytotoxic agents for the treatment of metastatic breast cancer was initiated simultaneously with phase I clinical trials of paclitaxel/doxorubicin combinations.[104, 105] The combination of paclitaxel and cisplatin showed less myelosuppressive effects compared to many other cytotoxic agents in clinical practice in the treatment of metastatic breast cancer.[106-108] Using this combination method, preliminary research showed an overall response of 85% success in the treatment with an admissible tolerance during cancer therapy.[109-111] Additionally, a combination of docetaxel with epirubicin was evaluated in the phase I/II program by the International Breast Cancer Study Group.[112, 113] It was noted that the epirubicin/docetaxel combination therapy could be used in progressive breast cancer patients with acceptable side effects.[114, 115] In addition, the regimen brings about severe falls in the tumor RNA integrity in some patients and these can be correlated with post-treatment pCR.[116, 117] A combination of capecitabine, gemcitabine and vinorelbine containing chemotherapy as mentioned in other studies also has been used in breast cancer therapy.[118-120] On the other hand, a combination of lapatinib with capecitabine, vinorelbine, or gemcitabine was tested in phase II in HER2 positive metastatic breast cancer patients after taxane treatment. Some of the combination therapy used in breast cancer are listed in Table 2.

V. NEW STRATEGIES ON USING NANOPARTICLES IN THE TREATMENT OF BREAST CANCER

Nanoparticles (NPs) are defined as particles (1–100 nm) with an outer layer surrounding different organic or inorganic coatings that set on the properties of NPs.[121] Even though it is not used regularly in clinical treatments, there are many studies presently being conducted to influence the prospective benefits of using NPs in cancer treatment as a drug delivery system.[122-124] NPs have been approved as nanocarriers mostly as a result of their properties such as biocompatibility, biodegradability and water dispersity.[125-128] NPs can increase the solubility, half-life and chemotherapeutics of drugs.[129-131] Furthermore, NPs can enlarge drug accumulation in the cancer tissues through enhanced permeability and retention (EPR).[132-134] Figure 3 shows passive targeting of TMX-loaded-nanoparticles to cancer cells via the EPR effect.[49]. Eventually, encapsulation of NPs with anti-cancer drugs can develop treatment efficacy by decreasing unpleasant effects through targeting specific cancer sites using target ligands.[135-137] Different types of NPs are accessible that have been used for site-specific targeted delivery.[138] NPs can be classified as polymer-based, metal-based, carbon-based, protein-based, liposomal, and mesoporous silica NPs(Table 3).[130, 139-143] Recent studies have shown that different targeted metabolic and physiological characteristics in combinational therapy could overcome drug resistance against cancer cells.[111, 144, 145] NPs have shown many advantages due to their specific properties while using combinational therapy in drug delivery. Some of these advantages include the possibility for functionalization to achieve a higher amount of loading in drug-delivery, tissue or organ-specific transport, decrease in administered dose and toxicity; the capability to carry and deliver multiple drugs of diagnostics and therapeutic loaded within nanoparticles, which can employ their numerous effects in a controlled manner and depletion in the repetition of administration.[129, 135,

[146-154] The ability of NPs in bearing multiple therapeutic agents is due to the fact that it is very convenient to administer drugs in combination with no need of increasing the frequency of administration.[150, 155] Hence, therapeutic agents of various classes can be used in combinational therapy with the same NP system to enhance the best therapeutic goal.[156-158] NPs can easily control the drug release which can help to modulate the pharmacokinetics, biodistribution, and stability of drugs with divergent chemical properties to trigger different pharmacological actions as shown in Figure 4.[131, 146, 159-161] NPs and nano delivery systems with long-acting features are able to continue the release of drugs in a controlled manner or permit independent modification of release rates of each drug which has more benefits to patients compared to conventional formulations.[11, 140, 162-164] NP formulations containing combination drugs from different therapeutic classes have also been used to treat breast cancer in clinical models. For example, the co-delivery of doxorubicin and mitomycin C in a polymer-lipid hybrid NPs (PLN) has exhibited effectiveness on human breast cancer cells and overcome combination drug resistance.[165, 166] Besides, a multiagent loaded NP micellar formulation was established for transporting rapamycin, paclitaxel and 17-AAG (triolimus) all at once.[167-170]. These NP formulations were estimated in tumor xenografts including MDA-MB-231 tumor-bearing mice. Combination drug treatments with a co-delivered chemotherapeutic agent and nucleic acid make use of NP arrangement and is also a promising master plan for the efficient treatment of breast cancer.[171-173] The ligand modified pH-responsive hyaluronic acid with paclitaxel and DNA loaded nanoparticles was tested *in vitro* and *in vivo* and has shown anti-cancer efficacy. Furthermore, the *in vitro* and *in vivo* efficacy of trastuzumab modified emtansine (DM1) loaded NP were investigated.[26, 174, 175] The researchers concluded that this NP system can have a great effect on the therapy of HER2 positive breast cancer. The effectiveness of docetaxel-loaded, trastuzumab functionalized nanostructured lipid loaded in

breast cancer cell lines has also been reported.[176, 177] The co-delivery of gadolinium and gemcitabine, a magnetic resonance imaging (MRI) difference agent, using self-assembled NPs has also been reported.[178] The application of NP-based drug delivery arrangements can be beneficial for combinational drug therapy in the treatment of breast cancer. However, there is a drive to find better strategies to increase the loading of combination drugs in delivery systems and receive the benefits in breast cancer therapy while avoiding unpleasant side effects.[179-181] A recent review described the use of combinational drug therapy and its beneficial approaches in metastatic breast cancer and the successful *in vivo* co-delivery of multidrug NP combinations used in breast cancer treatments.[182]. Different effects of biodistribution/pharmacokinetics of multi-drug combinations through different administration have been assigned to their inefficiency in a clinical trial.[183] This issue has been solved by the use of NPs for targeted delivery.[125] The special ability of multifunctional therapeutic NPs to target site-specific tumor, improve the solubility of anticancer drugs, synchronize the pharmacokinetics of entrapped drugs (drug combination), reduce drug resistance and achieve better anticancer activity of therapeutic drugs with concurrent use of chemotherapy with trastuzumab or pertuzumab, represents novel strategies in drug delivery.[124, 184, 185] The reticuloendothelial system (RES), plays an essential role in NP clearance. By getting into cells, NPs are vulnerable to resident phagocytic cell-mediated clearance and may accidentally trigger the excretion of cytokines such as tumor necrosis factor (TNF), interleukins, and interferons. This may incur regional inflammation which can damage tissues. Modifying the surface chemistry of NPs stops the absorption of NPs by serum protein which is censorious in reducing their lenient uptake into normal tissues. This, in turn, brings down the amount of the dose needed for achieving the same administered drugs to get therapeutic effects and reduce the side effects of the anticancer drugs.[186, 187] New strategies can be used such as the PEGylation on the

surface of NPs to reduce unwanted absorption of proteins to hamper opsonization. The polyethylene glycol (PEG) subunits can generate a hydrating layer that inhibits protein absorption. Some studies have shown that PEGylated NPs increase the circulatory half-life by increasing the ability to target tumor tissue in some experiments (*in vivo*). Thus, the possibility of new strategies in therapeutics can still increase the effectiveness of combinational therapy.[50, 188, 189] These combined systems can possibly lead to an increase in the need for NPs as drug transporters. By integrating a target-specific drug delivery system, the pharmacologically effective drug dosage can be reduced while drug effect on the target site is improved. This reduces the deleterious side effects of non-specific drug administration. Although not all these NPs have outstanding activity in clinical trials, the continuous evolution of drug delivery systems especially in the use of carbon-based NPs in conjunction with novel combination therapeutics can be encouraging and may be of great importance for breast cancer study in future.[190-193]

VI. OVERVIEW OF CURRENT STRATEGIES AND FUTURE DEVELOPMENT IN THE TREATMENT OF BREAST CANCER

The breast cancer treatments to date have been selected according to the needs of specific individual patients. All past findings can inform researchers with new strategies and designs that can lead to the development of the best approaches to breast cancer treatment.[194-196] Most of the clinical and molecular tests can aid in the choice of specific treatments for a subgroup of patients. Approaching the goal for the treatment of individual patients can be achieved by molecular patterns and specific molecular characteristics as a new strategy and design of cancer therapy.[38] Most probably after metastases in breast cancer, it may not be possible to fully treat patients with all the targeting described above, but there is a promise for survivors over ten years.[197, 198] Moreover, new

strategies and designs have focused on enhancing the survival of breast cancer patients in developed metastasis by investigating the roles of the adjacent tissues during breast cancer development. Therefore, there should be more efforts to promote breast cancer treatment by developing sagacious strategies for treatment.[199] For instance, Blache and his co-workers reported that intercellular interactivity between mesenchymal stromal cell (MSCs)[200] and cancerous breast cells contribute to the revival of breast cancer. These results led to the invention of a method for targeting the cellular interactions between MSCs and cancerous breast cells, making cancer cells more receptive to chemotherapy. Here, the authors explored the interrelationship between MSCs and breast cancer cells through membrane-bound CXCL12 and its receptor CXCR4. Consequently, reducing the binding of CXCR4 to CXCL12 using siRNA led to the hindrance of breast cancer cell proliferation when they were co-cultured with MSCs. Using a CXCR4 antagonist, AMD3100, in the co-culture of MSCs showed more sensitivity to carboplatin in cycling breast cancer cells.[201-204] This suggested that MSCs can be used as novel vehicles for transporting therapeutic drugs into cancerous breast tumors. The excretion of Interleukin 6 (IL-6) and Vascular endothelial growth factor (VEGF) from MSCs however can be observed as paracrine signals to assist the resettlement of breast cancer cells. The use of MSCs for the treatment of breast cancer, therefore, needs further research.[205-208] Triple-negative breast cancer regimens are extremely limited. There is still no verified agent that can effectively target triple-negative breast cancer cells.[209, 210] NPs as carriers for targeting cellular components could hypothetically help overcome this difficulty. Nevertheless, the immunogenicity of NPs remains unclear and needs to be fully characterized.[211, 212] Notably, the combinational therapy of multiple agents with several targets is more effective in the treatment of breast cancer. Bhullar *et al*. designed a technique by combining a cell signaling or angiogenesis blockage, specifically a VEGF receptors blocker, with an Aurora

kinase blocker (AKI) to treat cancerous tumors.[213] It is worth bearing in mind that the main obstacle in fighting cancer is its resistance to anticancer drugs. Developing sagacious strategies has shown that cancer cells can alter their microtubules and are able to modify cell morphologies after treatment with anticancer drugs. The morphologic change is correlated with chemoresistance, and the abrogate of PI3K/Akt/mTOR signaling network is responsible for chemoresistance in numerous cancers. Recent studies have emphasized that it extracts the best feature for the growth of breast cancer in regards to endothelial-carcinoma-myeloid interactions.[214-218] Conversely, albeit chemotherapy and radiation are capable of subduing or shrinking breast cancer tumors, they do not destroy breast cancer stem cells. These cancer stem cells are predicted to be in charge of breast tumor initiation and maintenance. They also operate metastasis, which is the major cause of death in women with developed breast cancer. Thus, eliminating breast cancer stem cells from the tumor is probably the clue to treat developed breast cancer.[219-223] The sagacious strategy which can prove the effectiveness of combinational therapy is to believe that one drug can kill cancer stem cells and the others will damage other cancer cells. For instance, recent studies have described a treatment technique to kill breast cancer cells by co-administering compounds that selectively target cancer stem cells along with the combination of anti-cancer drugs.[224-227] Another patent has revealed an immunotherapy method that involves the separation of cancer stem cells from the tumor tissue and the use of these cells to operate antigen-presenting cells, like dendritic cells which represent cancer stem cell antigens.[228]. Moreover, the effectiveness of bevacizumab and doxorubicin combination inhibits the growth of basal-like breast tumors than luminal-like breast cancer. This distinction was thrown back by a noteworthy change in the profile of metabolic and levels of gene expression.[229, 230] Therefore, biological differences in individuals with breast cancer

can help to identify personalized biomarkers for targeted drug delivery that improves patient response in cancer therapy.[231]

VII. CONCLUSION

This review summarizes a variety of studies that are either being used or have the potential to be used as drug delivery targets for the specific treatment of breast cancer (Figure 5). Recent findings have allowed researchers to contemplate new strategies in cancer therapy or aid as an accompaniment to current treatments such as combinational drug therapies to improve effectiveness and lessen the burden of breast cancer. Several new combinational drug therapies under development may bring great assurances to treat patients with breast cancer, thereby providing hope for new combinational therapy options in the near future.

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Table 1. Some patents of nanoparticles use in the treatment of breast cancer

Patent	Title	Brief description	Reference
WO2012138013A1	Paclitaxel loaded polymeric nanoparticles and preparation thereof	This process shows a method of development of poly(2-(dimethylamino)ethyl methacrylate-co-methacrylic acid (PDM) nanoparticles and efficacy of breast cancer treatment	[232]
US20060204443A1	Method of tumor treatment using dendrimer conjugates	This patent shows a method of development in generation 6-8 polyamidoamine (PAMAM) dendrimer conjugate with anticancer drugs for the treatment of different cancers like; breast cancer, brain and lung cancer	[233]
WO2017115301A1	Treatment of breast cancer using combination of cationic liposomal formulation of taxane, a non-liposomal formulation of taxane and a further active agent	This process shows treatment of triple negative breast cancer by using combination therapy of cationic liposomal formation of taxane, and non-liposomal formulation of taxane and an active agent gemeitabine	[234]
US9427466B2	Nanoparticles-assisted ultrasound for breast cancer therapy	This invention gives a method about use of antibody attached gold nanoparticles for the treatment of breast cancer using ultrasound irradiation	[235]
WO2016094402A1	Treatment of breast cancer with liposomal irinotecan	This process shows a method of development of irinotecan sucrosofate loaded in liposomes and their part in the treatment of triple negative breast cancer and estrogen receptor positive or progesterone receptor positive in breast cancer	[236]
WO2014039668A1	Non-pegylated liposomal doxorubicin combination for the treatment of triple negative breast cancer	This process reports a method for treatment of triple negative breast cancer using a combination of doxorubicin which is loaded in non-pegylated liposomes, a taxane and anticancer agent selected from gemcitabine, capecitabine and carboplatin	[237]
CN102225205B	Tripterine nano structure lipid carrier and prepration method and application thereof	This patent shows a method of development tripterin is loaded in nano structure lipid carrier for transdermal drug delivery in treatment of breast cancer	[238]
CN103655519A	Curcumin solid lipid nanoparticles with P-gp inhibiting effect and preparation method thereof	This process shows a method of preparation of SLN which contains (0.05%-1%) and lipidic material (5-15%) for effectiveness of breast cancer treatment	[239]

Table 2. Some of specific target drug combination uses in breast cancer treatment

Classes	Combination drugs	Advantages	Disadvantages	References
Tyrosine kinase inhibitor based	Lapatinib + Capecitabine Lapatinib + Paclitaxel Lapatinib + Letrozole	Improved RR, TTP, PFS	More toxicity from chemotherapy like, diarrhea, skin rash, nausea, pruritis.	[240, 241]
	Sunitinib + Docetaxel	No worsen toxicity	Nonsignificant combination activity	
	Erotinib + Cisplatin + Gemcitabine	Well tolerated	No survival benefit	
mAb based	Trastuzumab + Doxorubicin + Cyclophosphamide Trastuzumab + Epirubicin + Cyclophosphamide	Improved RR, PFS, and OS	Cardiomyopathy, hematologic toxicity	[242]
	Trastuzumab + other chemotherapy (Paclitaxel, Docetaxel, Vinorelbine, Capecitabine, Platinum compounds, and Gemcitabine)	Improved RR and PFS	Increased hematologic toxicity	
	Bevacizumab + Paclitaxel	Improved PFS	More toxicity (hypertension, proteinuria, bleeding, nasal septum perforation, thromboembolic event, heart failure, mortality)	
	Cetuximab + Cisplatin	Improved RR and PFS in patients with TNBC	More acne-like rash, neutropenia, dyspnea	
PARP inhibitor based	Iniparib + Gemcitabine + Carboplatin	Improved PFS and OS	Neutropenia, thrombocytopenia, anemia, fatigue or asthenia, leukopenia	[243, 244]
	Olaparib + Gemcitabine + Carboplatin	Improved RR		
Multiple targeted	Trastuzumab + Lapatinib	Improved PFS and Overcome Trastuzumab resistance	Additive toxicity from Trastuzumab and Lapatinib, patient compliance issue (IV and oral administration)	[245]

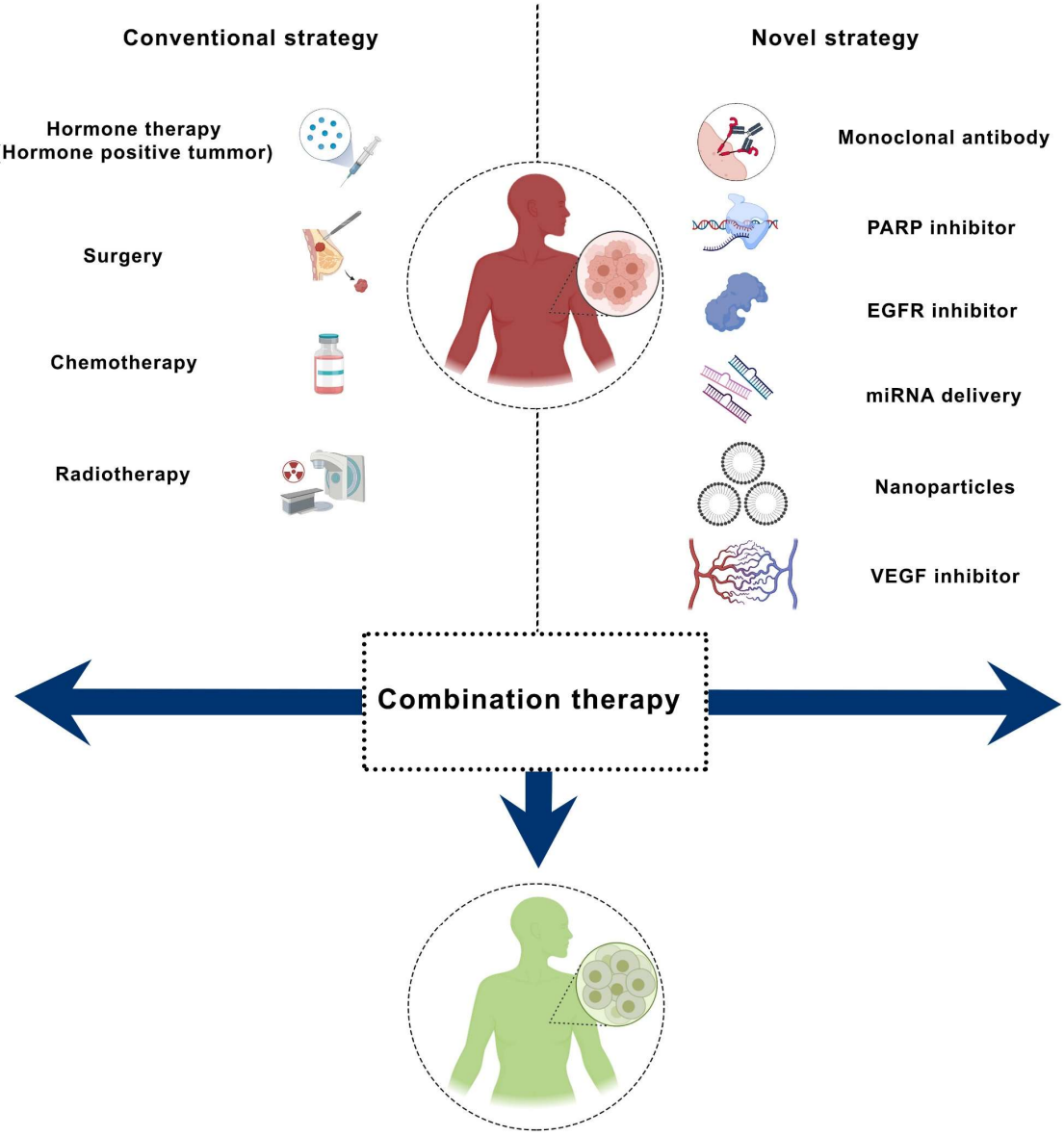
Note: IV: Intravenous; mAb: Monoclonal antibody; OS: Overall survival; PARP: Poly (ADP-ribose) polymerase; PFS: Progression-free survival; RR: Response rate; TNBC: Triple-negative breast cancer; TTP: Time to progression.

Table 3. Overview of some NPs for targeted drug delivery in cancer therapy [246]

Types of NPs	Particle size (nm)	Solubility	Drugs	Targeted receptors	Cell lines
1.Metal-based NPs					
1.1. Gold NPs	10-20	Hydrophilic	DOX, MTX, SMTX	EGFR, VEGFR2	MDA-MB231, MCF-7, MCF-10
1.2. Superparamagnetic Iron Oxide NPs	10-100	N/A	DOX	HER2	MDA-MB231, MCF-7
1.3. Quantum Dots	2-10	Resuspendable	Monoclonal antibodies	ER, PR, HER2, EGFR	MDA-MB231, MCF-7, BT474
2. Polymer-based NPs	100-300	Highly hydrophilic and permeable	DOX, PTX, trastuzumab, Cisplatin, TMX, siRNA	TNBC, HER2	MDA-MB231
3. Liposomal NPs	100-300	Amphiphilic	Vincristine, DOX, PTX, quercetin, cyclophosphamide, oligonucleotides, peptides, siRNA, miRNA, sVEGF	HER2	MDA-MB-231, MDA-MB435, MCF-7, JIMT-1
4. Mesoporous Silica NPs	N/A	N/A	DOX, siRNA	HER2	MCF7, BT474
5. Carbon-based NPs					
5.1. Carbon nanotubes	1-100	Low solubility	DOX, PTX	HER2	SK-BR-3, MCF7
5.2. Carbon dots	1-10	Resuspendable	N/A	N/A	MCF-7, MDA-MB231
6.Protein-based NPs	N/A	N/A	DOX, Trastuzumab	HER2	MCF-7, MDA-MB231

Note: DOX: Doxorubicin; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; miRNA: Micro RNA; MTX: Methotrexate; N/A: Not Applicable; PR: Progesterone receptor; PTX: Paclitaxel; siRNA: Small interfering RNA; SMTX: Short-term Methotrexate; sVEGF: Soluble VEGF; TMX: Tamoxifen; TNBC: Triple-negative breast cancer; VEGFR2: Vascular endothelial growth factor receptor 2.

Graphical Abstract



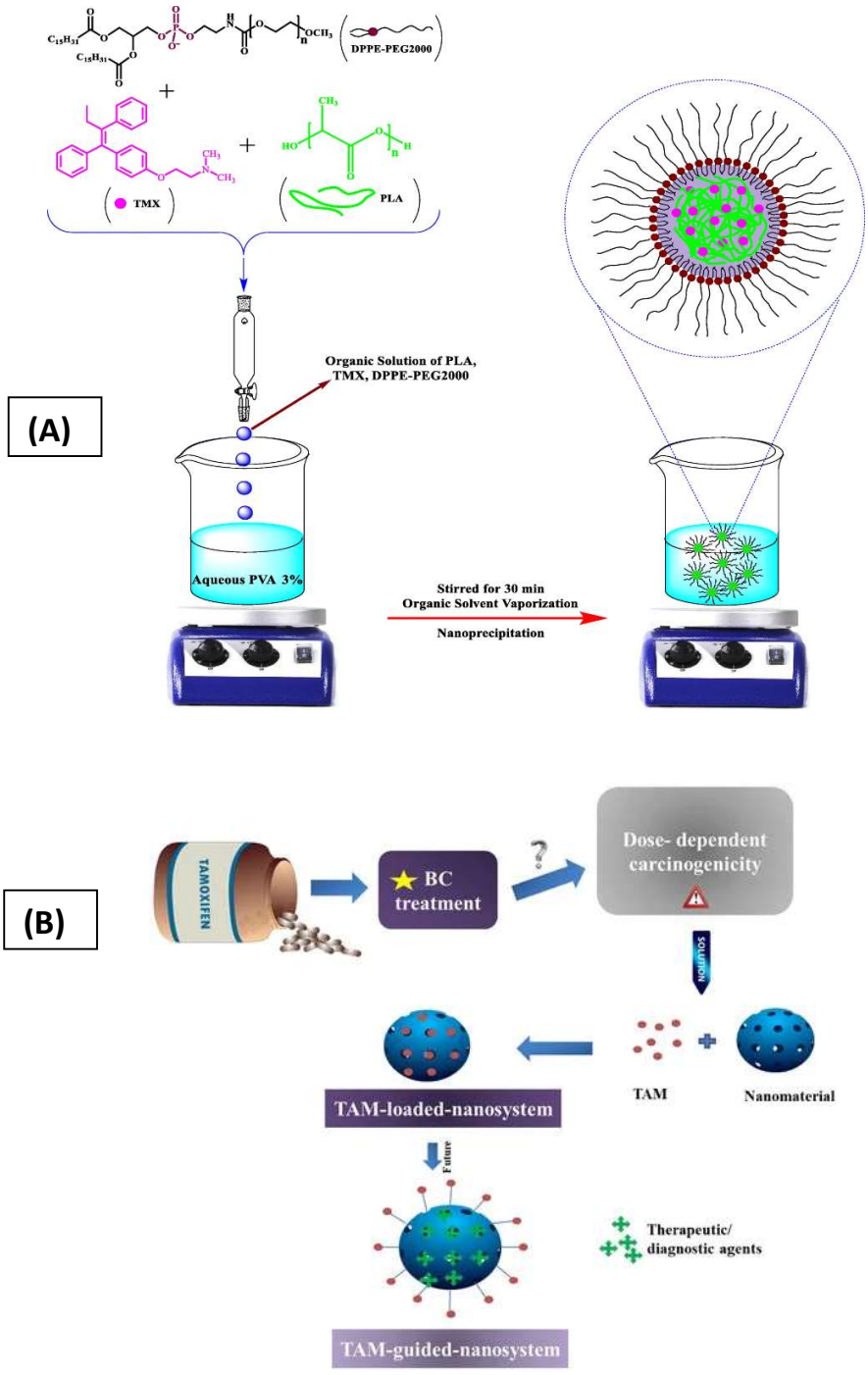


Figure 1. Synthesis of TMX-loaded PLA/DPPE-PEG nanocapsules (A). Adapted with permission from [247] Novel tamoxifen nanoformulations for improving breast cancer treatment (B). Image adapted from Day *et al*. [49].

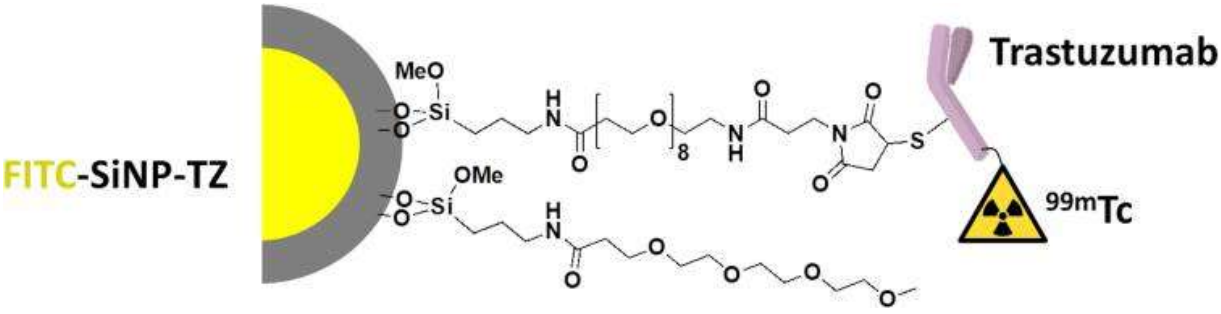


Figure 2. Graphic of 99mTc-Radiolabeled silica nanoparticles containing FITC (yellow) which were functionalized by trastuzumab. Image adapted from Rainone *et al*. [57].

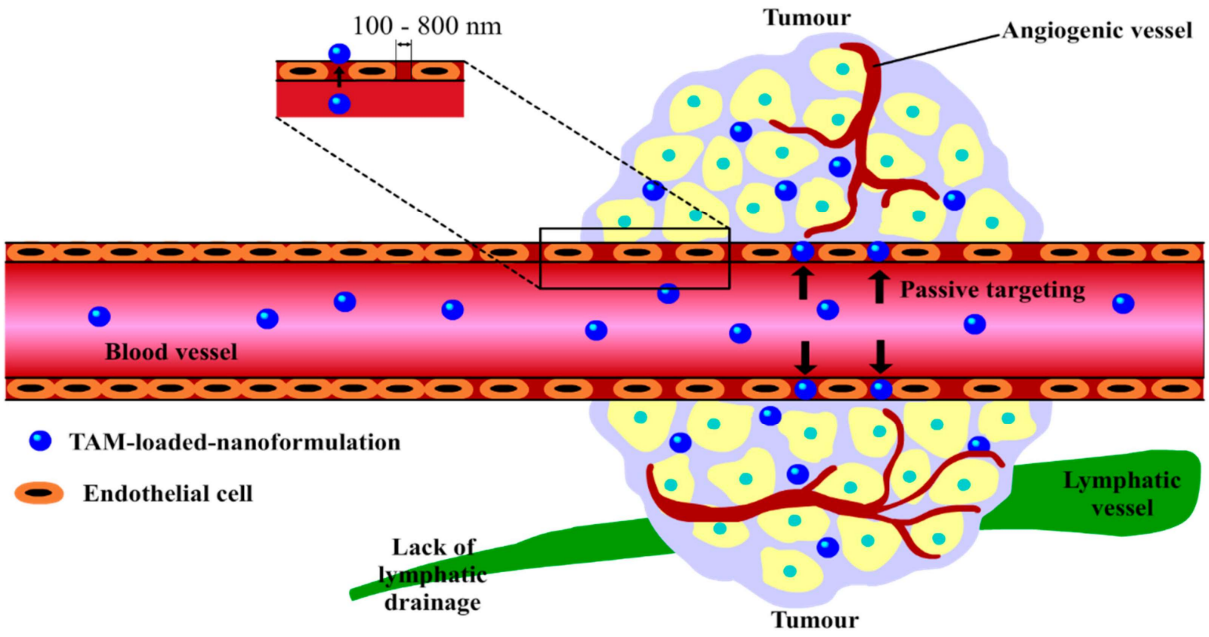


Figure 3. Passive targeting of tamoxifen-loaded nanoparticles to cancer cells via EPR effect Image adapted from Day *et al*. [49].

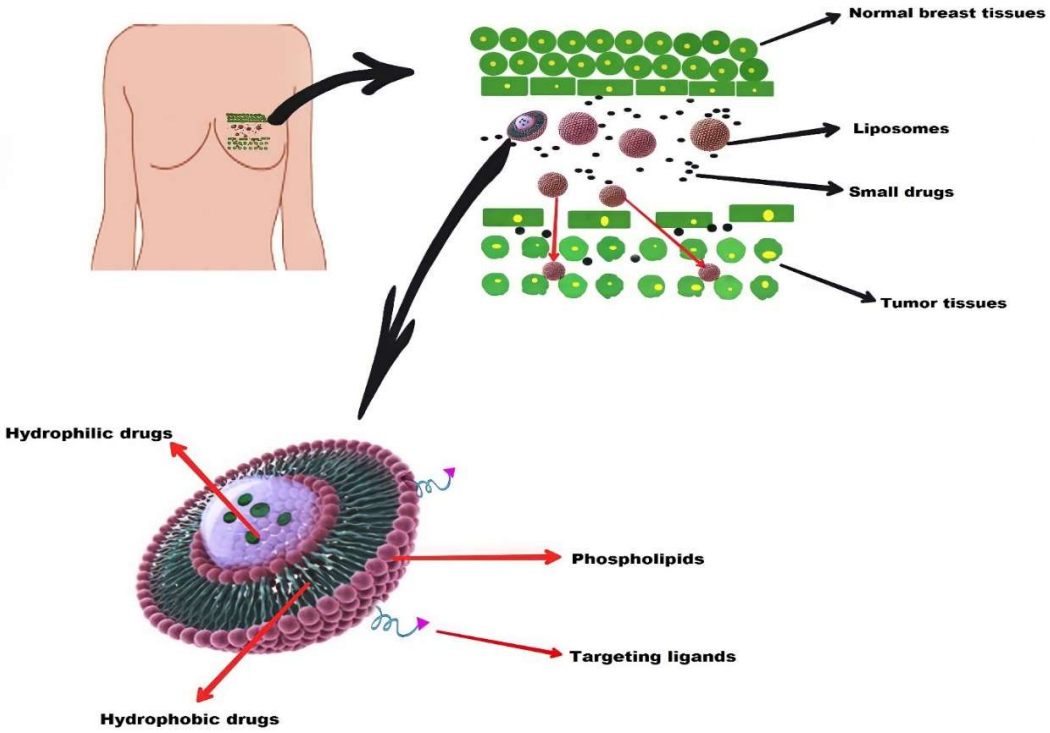


Figure 4. Design strategies and sagacious targeting for site-specific drug delivery in the tumor breast tissue.

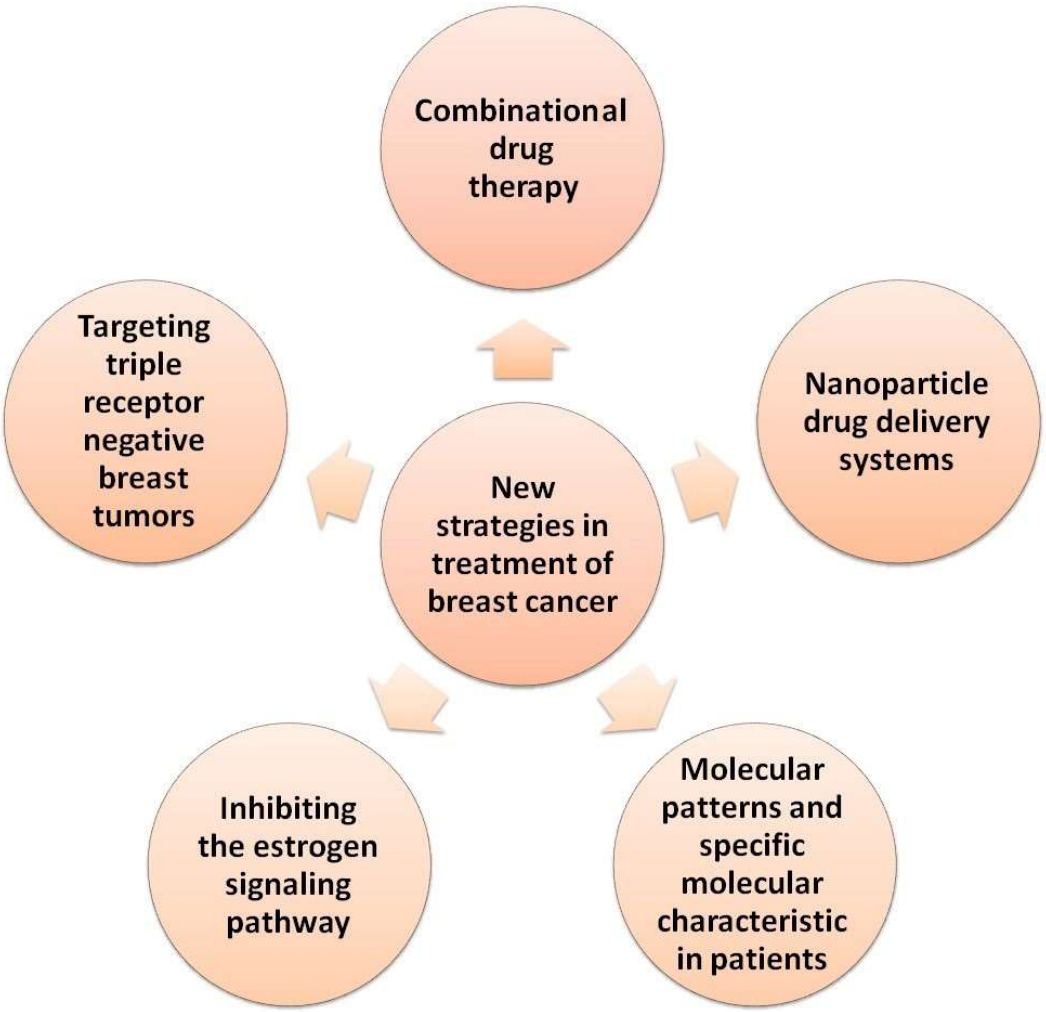


Figure 5. Development of design strategies and sagacious targeting for site-specific based on NPs drug delivery in breast cancer treatment.