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Review article

BREAST CANCER THERAPY AND NOVEL NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

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Abstract

Drug resistance is the major cause of drug treatment failure in breast cancer patients. Chemotherapy, as the dominant approach, is the mostly used treatment modality nowadays. Classical breast cancer drugs are still widely used however, they are being replaced by nanoparticle encapsulation drug formulations, due to their high toxicity. Nanoparticle drug delivery systems have a vast contribution in chemotherapy approach nowadays. Contemporary cancer treatment studies are progressively being focused on newly designed drug formulations, which exhibit lower toxicity in normal tissues and higher specificity for tumor tissues. Novel drug delivery systems are adapted either for delivery of existing, or newly designed anti-cancer agents. They come in various sizes, shapes, different encapsulating complexes and diverse drug loading efficiencies. Such drug designs are advantageous due to the reduced resistivity of cancer cells to such chemotherapeutic agents, thus increasing the treatment efficiencies. In addition, they are delivering anti-cancer agents within the tumor microenvironment, often with cancer cell-specific receptors. Some nanoparticle drugs are currently also being used for imaging purpose. Herein, we summarize different anti-cancer drug modalities and scientific findings acquired both from *in vitro* and *in vivo* studies, with a focus on breast cancer chemotherapeutic agents. We also introduce very recent nanomedicine-based drug designs, which tend to overcome the obstacles of old treatment strategies used to treat breast cancer patients.

Keywords: breast cancer, chemotherapy, topoisomerase inhibitors, drug delivery, nanoparticles

1. Introduction

One of the major challenges in cancer treatment has been the development of resistance in cancer cell towards anticancer agents. The intrinsic ability of cancer cells to resist therapies is comparable to stem cell properties. Cancer treatment is made more difficult because of the ability of such cells to induce tumor initiation and self-renewal mechanisms. One of the most widely used drugs to treat cancers include topoisomerase inhibitors such as camptothecin and doxorubicin. However, these conventional drugs and their derivatives have limitations in their usage, even though they have a wide range of application as anticancer agents. These drug regimens are now considered toxic due to their toxicity to normal cells, such as cardiotoxicity, mainly because of high reactive oxygen species (ROS) production (Meredith and Dass 2016). In newly designed chemotherapeutic drug delivery systems, nanotechnology has a significant contribution, especially during the recent years. The tendency of new anticancer drug design is focused on formulations which target specifically the cancer cells, without affecting the normal tissues (Al-lazikani, Banerji, and Workman 2012). Recent developments of multifunctional nanoparticle design include formulations of compact size, low cytotoxicity, strong photostability, good biocompatibility and high sensitization to ROS. By tracking the construction and disassembly of their cargo, their imaging abilities have demonstrated good use in observing and managing the delivery process (Bao et al. 2013). Doxorubicin and other chemotherapy medications can be delivered simultaneously in liposome-encapsulated formulations, as reported in a number of recent in vivo mouse studies and in phase II and phase III trial patients (Coltelli et al. 2017) (Harbeck et al. 2017). Nowadays various cancer types and stages are treated with nanoparticle drug regimens.

2. Body of Manuscript

2.1. Breast cancer drug resistance:

2.1.1. Molecular background in drug resistance: One of the major challenges in cancer treatment is the development of resistance in cancer cell towards anticancer agents. The intrinsic ability of cancer cells to resist therapies is comparable to stem cell properties. These properties consist of: the loss of expression of the target protein due to long and continuous treatment, the overexpression of certain peptides related to drug metabolism and efflux, induction of G0 phase, activation of pro-survival signaling, upregulation of some proapoptotic genes and regulation of DNA repair mechanism (Borst 2012) (Hassan et al. 2014) (Baxter et al. 2022). Additionally, cancer treatment is made more difficult because of the abilities of such cells have in inducing tumor initiation and self-renewal mechanisms. It is also observed that drug resistance can be caused from the resistance acquired as a selection mechanism from a small population of cells due to the molecular heterogeneity of tumors (Holohan et al. 2013).Other factors such as tumor microenvironment (consisting of immune cells, fibroblasts, blood vessels in tumors and extracellular matrix proteins) do induce drug resistance, growth and motility of metastatic cells in tumor mass (Tiwari, Trivedi, and Lin 2022) (Mcmillin et al. 2010).

2.1.2 Drug resistance according to breast cancer subtype: While drug resistance might be the main cause of incurability in advanced breast cancer, drug resistance acquired in early-stage breast cancer is of great interest because of higher chances of being cured. Resistance to endocrine therapy is categorized as intrinsic (not responding at all to endocrine therapy at all) and acquired (developed after a previous response), for the ER+ breast cancers (Selli, Dixon, and Sims 2016). However, hormonal therapy seems to depend on the drug, while cells develop resistance to one agent, another therapy might be effective to treat the same cancer cells (Wang et al. 2023). On the other hand, drug resistance in HER2+ patients include mechanisms that involve the loss of HER2 amplification during treatment, activation of other receptors of HER-family as a compensatory mechanism, absence of extracellular binding domain and deregulation of many signaling pathways (Wang et al. 2016). In order to overcome drug resistance, one of the strategies applied is the combination of HER2 inhibitors, which might show synergistic effects (Sirhan, Thyagarajan, and Sahu 2022) (Wilks 2015).

2.2. Breast cancer treatment by topoisomerase inhibition:

2.2.1. The biological function of topoisomerase enzymes: The double helix DNA needs to be uncoiled during the processes of DNA replication and transcription, however its structure restricts free rotation of DNA inside the cell nucleus. By the interference of helicase enzymes, the strand separation results in positive and negative supercoiling, at the front and back side of DNA transcription and replication (Leroy and James 1987). DNA replication and transcription is stalled by positive supercoiling, while supercoiling of the back side might induce the formation of aberrant DNA structure, which renders DNA unfunctional. The DNA tension caused during the processes of DNA replication and transcription is released by the help of large proteins/enzymes named as ‘topoisomerases’ (Mazouzi, Velimezi, and Loizou 2014). There are six topoisomerases encoded by human genome, classified either as Type I or Type II. Enzyme of Type I makes a single strand cut, while type II cleaves both strands of DNA during their catalytic functions (Mazouzi et al. 2014). Both enzymes function in a similar mode, by cutting the DNA via a nucleophilic attach and binding to the phosphate group after which DNA is re-ligated with the DNA sequence unchanged and the supercoiling relieved. TOP1mt for mitochondrial DNA, a topoisomerase subtype does perform the similar activity with topoisomerase I on DNA while uncoiling the mitochondrial DNA (Pommier et al. 2014).

2.2.2. The action of topoisomerase inhibitors: A further division of topoisomerases is based on their mode of activity. Topoisomerases show some other functions (such as splicing and promoter regulation of Top1), except for their role in DNA relaxation during the processes of transcription and translation (Elton et al. 2022). Almost all topoisomerases are clinical therapeutic targets, except for topoisomerase IA and IIB. In mammals, topoisomerase inhibitors bind to the enzyme and block their action during DNA relegation, inducing DNA single and double breaks (Okoro and Fatoki 2023).

2.2.3. Topoisomerase I inhibitors: The types of drugs included in the topoisomerase 1 inhibitor classification are camptothecin and non-camptothecin drugs. While attempting to find anticancer drugs by the screening of the natural products, M.E. Wall and M.C. Wani (1966), were the first to discover CPT from the wood bark of the Chinese tree Camptotheca acuminate. Nowadays there are at least three camptothecin derivatives already approved for clinical use, including irinotecan and topotecan (Takagi et al. 2007). The chemical instability at physiological pH caused by the presence of E-ring in their molecular structure is the reason why CPT derivatives have limitations in their usage, even though they have a wide range of application as anticancer drugs. This chemical instability of camptothecins couldn't be overcome even though some other CPT derivatives have been designed to improve its clinical tolerability. Drugs such as indenoisoquinolines, dibenzonaphthyridinones and aromathecins, examples of non-camptothecin synthetic topoisomerase I, have been developed as alternatives with improved drug stability and as more stable cleavage complexes (Cinelli et al. 2009).

2.2.4. Topoisomerase II inhibitors: Topoisomerase II inhibitors are responsible for the poisoning of Top2α and Top2β, resulting in the synthesis of TOP2cc (TOP2-DNA complex) which is an obstacle to the normal processes of DNA replication and transcription (Tammaro et al. 2013). TOPII inhibitors can also cause single strand breaks (SSB) in addition to the double strand breaks (DSB). They are classified into two main groups. The "poisons" are members of the first group, which are more frequently used, such as etoposide, doxorubicin and mitoxantrone. These agents elevate the level of TOP2-DNA covalent bond (Nitiss 2009). The second group members are classified as "catalytic inhibitors" such as bisdioxopiperazines. They do not increase the TOP2-DNA complex levels, even though they block the catalytic activity of TOPII. An example of a TOP2 poison, Doxorubicin, was firstly isolated from Streptomyces peucetius species. While it is widely used for many types of malignancies like breast cancer, leukemias and childhood solid tumors, it is also an anthracycline antibiotic. However, nowadays it is considered toxic because of its toxicity to normal cells which results frequently in cardiotoxicity because of high reactive oxygen species (ROS) production (Meredith and Dass 2016).

2.3. The role of camptothecin and doxorubicin in breast cancer studies and treatment modalities:

2.3.1 Camptothecin activity in in vitro breast cancer studies: The most dominant approach in the treatment of cancer is still chemotherapy with the usage of conventional drugs and their derivatives as the most widely used agents. In the research related to breast cancer therapy, there are many studies investigating the effect of camptothecin and doxorubicin on breast cancer cell lines. Lamparska et al. conducted a study in 2005 where it was observed that camptothecin treated MCF7 cells underwent apoptosis after 60min, whereas in the 24h drug treatment, autophagy was observed, but in a slower rate. Moreover, BID knockdown induced a shift from apoptosis to autophagy in the CPT treated MCF7 cells, suggesting the importance of BID in the mechanism of death. The same research group conducted another study in which a complex composition of cells with distinct morphological characteristics of apoptosis and autophagy was revealed by imaging of MCF7 cells after 6h of CPT treatment, by electron microscopy. The 8-16h exposure of MCF7 to 0.15μM CPT, resulted in accumulation of p53 protein in the nuclei of cells, with a rapid increase of ~20 fold during

S-phase (Deptala et al. 1999). Another study suggested that p53 might not be required for CPT-induced apoptosis because of the resistance CPT-treated cells showed to apoptosis as a response in MCF7 breast cancer cell lines which are p53 wild type (Nieves-Neira and Pommier 1999). Another study showed the P53-independent mode of action of CPT in several breast cancer cells. In this study CPT treatment induced degradation of WRN , which is a helicase enzyme with role in cellular senescence, genomic stability and DNA repair (Shamanna et al. 2016).

2.3.2. Doxorubicin activity in in vitro breast cancer studies: Doxorubicin studies, in a similar way to CPT, show not a single mechanism of breast cancer cell death induced by this drug. MDA-MB-231 as doxorubicin-resistant cell line, became more sensitive to doxorubicin treatment when exposed to an autophagy inhibitory molecule, exhibition cell death mode shift from apoptosis to necrosis (Aydinlik et al. 2016). NF-kB expression, as a metastasis inducer, has been linked to the resistance of MDA-MB-231 cell line to doxorubicin treatment (Dalmases et al. 2014). The impairment of NF-kB expression induced by doxorubicin, as a response to p53 restoration, implies p53-dependent cytotoxicity of this drug in MDA-MB-231 (Dalmases et al. 2014). Treatment of MCF7 cells with doxorubicin showed upregulation of p21 level and increase in cellular senescence (Mohammadrezaei, Movaghar, and Gharghabi 2016). However, in another study p53-status was shown as an independent effect of doxorubicin in inducing apoptosis both in MCF7 and MDA-MB-231 cell lines (Nestal et al. 2013). On the other hand, the uptake and drug response to doxorubicin in MCF7 cells was correlated to drug formulations as well as with cellular fluidity (Weber, Wagner, and Schneckenburger 2013). Several studies have been conducted to study the factors influencing efficacy and resistivity of breast cancer cells to chemotherapeutic effects of doxorubicin, including combined treatments of this drug with other molecules. When estrogen was coadministered with doxorubicin, an increase in apoptotic action was observed in estrogen-indipendent MCF7 cells via the suppression of NF-kB signaling (Scherbakov et al. 2011). Similarly, co-treatment with proteasome inhibitor, showed increase in the sensitivity to doxorubicin for different breast cancer cell lines (Shi et al. 2016). Additionally, in vitro and in vivo studies have reported reduced cardiotoxic effects and/or higher drug efficacy of doxorubicin, from many combinatorial treatments with natural products (Muhammad et al. 2016) (Muhammad et al. 2016).

2.4 Nanomedicine as a means of breast cancer therapy:

2.4.1 The properties of nanoparticles in cancer treatment : In chemotherapeutic drug delivery system, nanotechnology has a significant contribution, especially during the recent years. The tendency of recent anticancer drug designs is focused on formulations which target specifically the cancer cells and not affecting the normal tissues (Al-lazikani et al. 2012). Novel drug designs include formulations which incorporate either the already existing or newly developed drugs. The tendency of such therapeutic designs is to bypass the biological barriers (physiological and pharmacological) of classical therapies. Nanomedicine considers a good nanoparticle candidate, a formulation with small size, high drug loading efficiency and the ability to encapsulate different drug molecules in a single complex (Jin et al. 2016). Improved drug uptake by target cells and specificity to cancer cells are also characteristics of highly efficient formulations used for cancer therapy purpose (Parhi, Mohanty, and Sahoo 2012). Such nanoparticles are designed in nm dimensions since they should cross the gaps between the endothelial cells of tumor vascularization, which usually range from 100nm, to around 800nm (Haley and Frenkel 2008). In addition, NPs are usually coated by hydrophilic molecules to reduce binding to blood proteins and prevent clearance from the circulatory system (Sun, Yarovoy, and Capeling 2017). Different materials have been used to design NPs, including polymer, lipid, metal and ceramic. In addition, NPs are formulated in different shapes (i.e, spheres, nanotubes, liposomes) according to the purpose of use. They are also categorized into organic (e.g. micelles,

spheres) and inorganic NPs (e.g. iron oxide, gold). A good property of NPs used in nanomedicine is their degradability after they have released their cargo in cancer cells (Haley and Frenkel 2008). Recent nanocapsule designs do also have the advantage of sustained drug release as well as enhanced retention and permeability (EPR) and at the same time serving as imaging agents for cancer cells (Prados et al. 2012). Nowadays the gold standard of a NP formulation is its EPR effect. There are three approached of NPs targeting cancer cells: the active one (targeting the cancer cells by NP ligand), the passive one (passively incorporated into tumor cell), or targeting of tumor cells both actively and passively (Yan et al. 2017). Given the above characteristics, NPs are considered as formulations with high potential to improve and change current anticancer treatment modalities.

2.4.2. Conjugated Polymer Nanoparticles applications in medicine: Another category of nanoparticles is represented by conjugated polymer nanoparticles (CPNs), whose equivalent conjugated polymer (CP) is generated by reactions of the polymerization process, including oxidative polymerization, and Heck coupling, involving the utilization of various associated polymers such as PF, PPV, PPE, PT. Their features are influenced by two main factors, including charges in the surface and their functional groups. CNP's remarkable features involve light-harvesting and light-emitting qualities, which render them very useful and multi-purpose, in particular for the process of fluorescent target imaging, diagnostics, therapy of genes, and delivering of drugs (Feng et al. 2013). Recent developments in multifunctional nanoparticle design, exhibit compact size, low cytotoxicity, strong photostability, good biocompatibility and high sensitization to ROS. By tracking the construction and disassembly of their cargo (such as oligonucleotides), their imaging abilities have demonstrated good use in observing and managing the delivery process (Bao et al. 2013). The CNPs' recent applications are tightly related to destroying microorganisms, tumor cells, and in vivo and in vitro cell tagging. Moreover, conjugated oligomer associated/based nanoparticles (CONs), despite being outside of the literature focus, appear similar or superior compared to CPNs. CONs have shown similar cellular uptake and higher yields of fluorescent quantum and rapid delivery of cargo in comparison with their polymeric equivalents (Chen et al. 2014). The use of CONs as oligonucleotide nanocarriers for future drug delivery has also shown encouraging results. Nevertheless, due to their large positive charge, cellular toxicity is a significant issue in CON design. Hydrophobic moieties are added to the side chains of nanoparticle complexes to increase their interaction with cells, such as a macrocycle made up of glycoluril units called Cucurbituril (CB), that has two hydrophilic portals and a hydrophobic cavity (Gürbüz, Idriz, and Tuncel 2015). Pennakalathil et al. (2014) produced a CB7-capped, red-emitting CON that demonstrated pH responsiveness and had the capacity for both drug delivery and cell imaging (Pennakalathil et al. 2014) (Jahja 2017). The oligomeric nanoparticle, which is made up of amine groups, precipitated in human blood serum; however, CB7, a water-soluble CB, prevented this from happening, at least for the duration of a 24-hour incubation. Additionally, CB7-capping barely affected the oligomer NP size, maintaining its size-dependent characteristics (Cai et al. 2016). A multipurpose fluorescent oligomer with very auspicious results in real-time imaging of the sentinel lymph node (SLN) for preliminary identification of breast cancer metastasis and for photothermal therapy (PTT) by destroying metastatic cells, in particular, has been presented in a current study to show the great capacities of CONs (Pennakalathil et al. 2014)(Cai et al. 2016).

2.4.3. Nanoparticles as drug carriers in combinatorial formulations: Doxorubicin and other chemotherapy medications can be delivered simultaneously in liposome-encapsulated formulations, as reported in a number of recent in vivo mouse studies and in phase II and phase III trial patients (Coltelli et al. 2017) (Harbeck et al. 2017). Recently created liposomes, such as estrogen-anchored and pH-sensitive formulations, can carry and deliver active medicines by utilizing the pathophysiology of the tumor microenvironment, in addition to targeting individual receptors of cancer cells (Silva et al. 2016). Over the

last few years interest in drug formulations has grown to create drug formulations targeting a particular abnormal pathway in tumor cells. RNA interference (RNAi) method provides an option in the treatment of cancers since cells have developed highly effective survival mechanisms to withstand drug toxicity. siRNA therapy is delivered utilizing non-viral carriers such as NP-based formulations (used alone or in combination with other compounds). Studies have shown that siRNA library screens, which include high amount of siRNAs targeting cell cycle proteins, can be used in breast cancer therapy in combination with traditional anticancer medications in drug-resistant and drug-sensitive breast cancer cell lines as well as mice xenografts (Parmar et al. 2015).

2.4.4. Advancements in breast cancer treatment by nanomedicine drugs: NP-based medication formulations have undergone substantial investigation, and currently several of them have received FDA approval for either therapeutic or diagnostic use (Table 1). During the last years, various cancer types and stages are treated with cancer nanoparticle drugs. Additionally, the administration/delivery of small molecule medicines for the treatment of cancer via intravenously administered organic nanoparticle compositions has demonstrated significant effectiveness (Hald et al. 2022). Liposomal encapsulations of anticancer medications make up the majority of licensed nanoparticle medicines. Doxil (PEGylated Liposomal Doxorubicin) was the first liposomal cancer nanomedicine to receive FDA approval in 1995, proceeded by the medications DaunoXome, Myocet, and Abraxane (Albumin-bound Paclitaxel NP), which have the ability to preferentially assemble in the tumor microenvironment because of high retention and permeability, when compared to the free medication delivery procedure. Numerous nanoparticles are also being employed as imaging agents, including Optison, Definity and SonoVue (as an ultrasound contrast agent), Feridex and Resovist (for imaging of liver lesions), Ferumoxtran (for imaging of lymph node metastases). A number of additional formulations are recently undergoing human trials for approval (Table 2); most of which will be used for cancer treatment purpose (Sobhani et al. 2022) (Ding et al. 2022).

Novel drug conjugate designs such as Fam-trastuzumab deruxtecan and Sacituzumab govitecan have been recently approved by FDA (Table 1). As antibody conjugates, these formulations incorporate monoclonal antibodies targeting cancer cell receptors/antigens which overexpression is linked to various breast cancer cells. These drug conjugates are chemically linked to topoisomerase inhibitory drugs, which release into cancer cells is pH-dependent, inducing DNA breakage. This causes upregulation of several genes which result in cell cycle arrest and apoptosis (Fleming, Karpio, and Lombardo 2021).

In addition to the already approved ones, other drug formulations are on the way of approval (Table 2). An example is ThermoDox, which has high potential as chemotherapeutic platform, characterized by heat-triggered drug release. This drug was designed since 1998, which first clinical trial was in 2005, in combination with the radiofrequency ablation, in a patient with hepatocellular carcinoma (Regenold et al. 2022). Currently the second phase of Phase III clinical trial has terminated. Similarly, Cynviloq IG-001 as a temperature-responsive formulation (Nghan Le, Huynh, and Quyen Tran 2018), as well as other nanomaterial platforms, have shown successful progress on clinical trials (Anselmo and Mitragotri 2019) (Tagde et al. 2022). Novel tools in nanomedicine also include RNA-derived nanoparticles used for RNA immunotherapy, an example of which is IVAC_W_bre1_uID. This mRNA cancer vaccine is an individualized cancer treatment incorporating patient-specific tumor antigen targeted by on-demand RNA (based on tumor-specific mutations), which is embedded into a patient-specific liposomal complex. This design is based on the high tumor heterogeneity, thus it is specifically formulated according to each patient's tumor cell properties (Haque et al. 2021).

3. Tables

Table 1. Approved nanoparticle drug therapies or imaging agents, with application in breast cancer treatmen

Nanoparticle name / Company	Nanoparticle type	Specifications	Institution / Year of approval	Applications (other than in breast cancer)	Reference
Fam-trastuzumab deruxtecan / AstraZeneca / Daiichi Sankyo	Anti-HER2 antibody-drug conjugate	Cases with prior anti-HER2 therapies	FDA / 2022		(Rodriguez et al. 2022)
Sacituzumab govitecan / Immunomedics	Trop-2 directed antibody-drug conjugate	Metastatic triple negative breast cancer	FDA / 2020		(Rodriguez et al. 2022), (Yang et al. 2023)
Pazenir / Ratiopharm GmbH	Albumin-bound paclitaxel	Metastatic breast cancer	EMA / 2019	Pancreas & lung cancer	(Rodriguez et al. 2022)
Onivyde MM-398 / Merrimack	PEGylated-Liposomal irinotecan		FDA / 2015	Various cancers	(Anselmo and Mitragotri 2019)
Cadcyla / Roche Genentech	DM1-linked trastuzumab	HER2+ breast cancer	FDA / 2013; EMA / 2013		(Rodriguez et al. 2022)
Lipodox / Taiwan Liposome	Liposome doxorubicin		FDA / 2013	Ovarian cancer, Kaposi sarcoma	(Yang et al. 2023), (Kafle, Agrawal, and Dash 2022)
Abraxane / Celgene	Albumin-particle bound pacitaxel	Secondary metastatic breast cancer	FDA / 2005; EMA / 2008	Various cancers	(Yang et al. 2023)
Genexol-PM / Samyang Biopharmaceuticals	Paclitaxel polymeric micelle nanoparticle		FDA / 2007	Head and neck	(Anselmo and Mitragotri 2019), (Yang et al. 2023)
Lipusu / Nanjing Luye Sike Pharmaceutical	Paclitaxel liposome		FDA / 2006	Advanced solid tumors	(Yang et al. 2023)

Nanoparticle name / Company	Nanoparticle type	Specifications	Institution / Year of approval	Applications (other than in breast cancer)	Reference
Nanoxel	Polymeric micelle paclitaxel		FDA / 2006	Non-small cell lung cancer and pancreatic cancer	(Yang et al. 2023)
Definity / Lantheus Medical Imaging	Perflutren lipid microspheres	Ultrasound contrast agent	FDA / 2001	Various cancers	(Anselmo and Mitragotri 2019)
SonoVue / Bracco Imaging	Phospholipid stabilized microbubble	Ultrasound contrast agent	EMA / 2001	Various cancers	(Anselmo and Mitragotri 2019)
Myocet / Teva	Non-pegylated liposomal doxorubicin	Primary metastatic breast cancer	EMA / 2000	Various cancers	(Yang et al. 2023)
Doxil Ccaelyx / Janssen	PEGylated-Liposomal doxorubicin		FDA / 1995; EMA / 1996	Various cancers	(Anselmo and Mitragotri 2019)
Doxil / Sequus Pharmaceuticals I	PEGylated-Liposomal doxorubicin	Advanced stage breast cancer	FDA / 1995		(Tagde et al. 2022)
LipoDox / Sun Pharmaceutical Industries	Doxorubicin hydrochloride liposome	Metastatic breast cancer	FDA / 1995	Advanced ovarian cancer	(Tagde et al. 2022)

Table 2. Nanoparticle drug therapies or diagnostic agents not yet approved, with application in breast cancer treatment

Nanoparticle name / Company	Nanoparticle type	Specification	Applications (other than in breast cancer)	Reference
ThermoDox / Celsion	Lyso-thermosensitive liposomal doxorubicin	Breast cancer recurrence	Various cancers	(Regenold et al. 2022)
Mitoxantrone hydrochloride liposome / CSPC ZhongQi	Mitoxantrone liposome		Lymphoma	(Anselmo and Mitragotri 2019)

Nanoparticle name / Company	Nanoparticle type	Specification	Applications (other than in breast cancer)	Reference
Pharmaceutical Technology				
MM-302 / Merrimack Pharmaceuticals	PEGylated HER2-targeted liposomal doxorubicin	Breast-cancer specific		(Anselmo and Mitragotri 2019)
Cynviloq IG-001 / Serronto	Paclitaxel polymeric micelle nanoparticle	Breast-cancer specific		(Nghan Le et al. 2018)
NK105 / Nippon Kayaku	Paclitaxel micelle nanoparticle	Breast cancer-specific		(Anselmo and Mitragotri 2019)
Anti-EGFR-IL-dox / Swiss Group for Clinical Cancer Research; University Hospital Basel	Doxorubicin-loaded anti-EGFR immunoliposomes	Advanced triple negative EGFR positive breast cancer	High grade gliomas	(Anselmo and Mitragotri 2019)
IVAC_W_bre1_uID / BioNTech SE	Patient-specific liposome (tumor antigen-specific) complexed RNA	Triple negative breast cancer		(Anselmo and Mitragotri 2019)
dHER2+AS15 / GlaxoSmithKline	dHER2 antigen-Specific Immunotherapeutic with lapatinib	Metastatic breast cancer		(Tagde et al. 2022)
Lipoplatin / Regulon	Liposomal cisplatin		Non-small cell lung cancer, pancreatic, head and neck cancer	(Tagde et al. 2022)
EndoTAG1 / MediGene	Liposomal paclitaxel		Pancreatic caner	(Tagde et al. 2022)
DPX-0907 / ImmunoVaccine Technologies	Multicancer-incorporated antigens		Ovarian and prostate cancer	(Karkada, Berinstein, and Mansour 2014)
LEM-ETU / NeoPharm	Liposomal mitoxantrone		Leukemia, stomach, liver and ovarian cancer	(Bulbake et al. 2017)
LEP-ETU / NeoPharm	Liposomal paclitaxel		Broad range of advanced cancer	(Slingerland et al. 2017)

4. Conclusion

Free drug treatments are now being replaced by nanoparticle drug designs, due to the many advantages they offer. On the other hand, nanoparticles as drugs are continuously facing challenges due to technological, biological, and clinical limitations, as well as long term potential toxicity and pharmaceutical stability. However, nanomedicine is expected to make ongoing breakthroughs in medicine due to their active targeting of cancer cells, overpassing drug toxicity and drug resistance to chemotherapeutic agents. Nanomedicine alone, or in combination with other therapeutic strategies, are revolutionizing cancer treatment due to their significantly lower toxicity compared to the traditionally formulated drugs and their cancer-specific treatment efficiency.

References

[1]. Al-lazikani, Bissan, Udai Banerji, and Paul Workman. 2012. "Combinatorial Drug Therapy for Cancer in the Post-Genomic Era." Nature Biotechnology 30(7):1–13. doi: 10.1038/nbt.2284.

[2]. Anselmo, Aaron C., and Samir Mitragotri. 2019. "Nanoparticles in the Clinic: An Update." Bioengineering and Translational Medicine 4(3):e10143. doi: 10.1002/btm2.10143.

[3]. Aydinlik, Seyma, Merve Erkisa, Buse Cevatemre, Mehmet Sarimahmut, Egemen Dere, Ferda Ari, and Engin Ulukaya. 2016. "Enhanced Cytotoxic Activity of Doxorubicin through the Inhibition of Autophagy in Triple Negative Breast Cancer Cell Line." BBA - General Subjects. doi: 10.1016/j.bbagen.2016.11.013.

[4]. Bao, Biqing, Nanjiao Tao, Dongliang Yang, Lihui Yuwen, Lixing Weng, Quli Fan, Wei Huang, and Lianhui Wang. 2013. "A Controllable Approach to Development of Multi-Spectral Conjugated Polymer Nanoparticles with Increased Emission for Cell Imaging." Chemical Communications 49(90):10623-5. doi: 10.1039/b000000x.

[5]. Baxter, Joseph S., Diana Zatreanu, Stephen J. Pettitt, and Christopher J. Lord. 2022. "Resistance to DNA Repair Inhibitors in Cancer." Molecular Oncology 16(21):3811-3827. doi: 10.1002/1878-0261.13224.

[6]. Borst, Piet. 2012. "Cancer Drug Pan-Resistance : Pumps , Cancer Stem Cells , Quiescence , Epithelial to Mesenchymal Transition , Blocked Cell Death Pathways , Persisters or What?" Open Biology 2(5):120066. doi: DOI: 10.1098/rsob.120066.

[7]. Bulbake, Upendra, Sindhu Doppalapudi, Nagavendra Kommineni, and Wahid Khan. 2017. "Liposomal Formulations in Clinical Use : An Updated Review Development." Pharmaceutics 9(2):12. doi: 10.3390/pharmaceutics9020012.

[8]. Cai, Xiaolei, Xiaofeng Liu, Lun-de Liao, Aishwarya Bandla, Ji Min Ling, and Yu-hang Liu. 2016. "Encapsulated Conjugated Oligomer Nanoparticles for Real-Time Photoacoustic Sentinel Lymph Node Imaging and Targeted Photothermal Therapy." Small 12(35):4873-4880. doi: 10.1002/smll.201600697.

[9]. Chen, Jing, Fangyingkai Wang, Qiuming Liu, Jianzhong Du, and Jing Chen. 2014. "Antibacterial Polymeric Nanostructures for Biomedical Applications." Chemical Communications. doi: 10.1039/C4CC03001J.

[10]. Cinelli, Maris A., Brenda Cordero, Thomas S. Dexheimer, Yves Pommier, and Mark Cushman. 2009. "Bioorganic & Medicinal Chemistry Synthesis and Biological Evaluation of 14- (Aminoalkyl-Aminomethyl) - Aromathecins as Topoisomerase I Inhibitors : Investigating the Hypothesis of Shared Structure – Activity Relationships." Bioorganic & Medicinal Chemistry 17(20):7145–55. doi: 10.1016/j.bmc.2009.08.066.

[11]. Coltelli, Luigi, Andrea Fontana, Sara Lucchesi, Laura Ginocchi, Guido Bocci, Mario Filidei, Marco Scalese, Giada Arrighi, Chiara Finale, Lorenzo Marcucci, Orlando Goletti, Barbara Salvadori, Ilaria Ferrarini, Eleonora Bona, Alfredo Falcone, and Giacomo Allegrini. 2017. "Cardiac Safety of Adjuvant Non-Pegylated Liposomal Doxorubicin Combined with Cyclophosphamide and Followed by Paclitaxel in Older Breast Cancer Patients." The Breast 31:186–91. doi: 10.1016/j.breast.2016.11.006.

[12]. Dalmases, Alba, Irene González, Silvia Menendez, Oriol Arpí, Josep Maria, Sonia Servitja, Ignasi Tusquets, Cristina Chamizo, Raúl Rincón, Joan Albanell, and Federico Rojo. 2014. "Deficiency in P53 Is Required for Doxorubicin Induced Transcriptional Activation of NF-KB Target Genes in Human Breast Cancer." Oncotarget 5(1):196-210. doi: 10.18632/oncotarget.1556.

[13]. Deptala, A., X. L. Bedner, W. Cheng, F. Traganos, and Z. Darzynkiewicz. 1999. "Differences in Induction of P53 , P21 WAF1 and Apoptosis in Relation to Cell Cycle Phase of MCF-7 Cells Treated with Camptothecin." International Journal of Oncology 15(5):861-71. doi: 10.3892/ijo.15.5.861.

[14]. Ding, Yi-nan, Ming Xue, Qiu-sha Tang, Li-jun Wang, Hui-yan Ding, Han Li, Cheng-cheng Gao, and Wei-ping Yu. 2022. “Immunotherapy-Based Novel Nanoparticles in the Treatment of Gastrointestinal Cancer: Trends and Challenges.” World Journal of Gastroenterology 28(37):5403–19. doi: 10.3748/wjg.v28.i37.5403.
[15]. Elton, Terry S., Victor A. Hernandez, Jessika Carvajal-moreno, Xinyi Wang, Deborah Ipinmoroti, and Jack C. Yalowich. 2022. “Intronic Polyadenylation in Acquired Cancer Drug Resistance Circumvented by Utilizing CRISPR / Cas9 with Homology-Directed Repair : The Tale of Human DNA Topoisomerase II α.” Cancers 14(13):3148. doi: 10.3390/cancers14133148.
[16]. Feng, Liheng, Chunlei Zhu, Huanxiang Yuan, Libing Liu, Fengting Lv, and Shu Wang. 2013. “Conjugated Polymer Nanoparticles: Preparation, Properties, Functionalization and Biological Applications.” Chemical Society Reviews 42(16):6620-33. doi: 10.1039/c3cs60036j.
[17]. Fleming, Patrick, Sylvia Karpio, and Nicholas Lombardo. 2021. “Sacituzumab Govitecan for Treatment of Refractory Triple-Negative Metastatic Breast Cancer.” Journal of the Advanced Practitioner in Oncology 12(7):747–52. doi: 10.6004/jadpro.2021.12.7.8.
[18]. Gürbüz, Sinem, Muazzam Idriz, and Dönüs Tuncel. 2015. “Cucurbituril-Based Supramolecular Engineered Nanostructured Materials.” Organic and Biomolecular Chemistry 13(2):330-47. doi: 10.1039/c4ob02065k.
[19]. Hald, Camilla, Jayesh A. Kulkarni, Dominik Witzigmann, Marianne Lind, Karsten Petersson, and Jens B. Simonsen. 2022. “The Role of Lipid Components in Lipid Nanoparticles for Vaccines and Gene Therapy.” Advanced Drug Delivery Reviews 188:114416. doi: 10.1016/j.addr.2022.114416.
[20]. Haley, Barbara, and Eugene Frenkel. 2008. “Nanoparticles for Drug Delivery in Cancer Treatment.” Urologic Oncology 26(1):57-64. doi: 10.1016/j.urolonc.2007.03.015.
[21]. Haque, Sakib, Kiri Cook, Gaurav Sahay, and Conroy Sun. 2021. “RNA-Based Therapeutics : Current Developments in Targeted Molecular Therapy of Triple-Negative Breast Cancer.” Pharmaceutics 15;13(10):1694. doi: 10.3390/pharmaceutics13101694.
[22]. Harbeck, Nadia, Steffen Saupe, Marcus Schmidt, Elke Ja, Burkhard Joerg Otremba, Dirk Waldenmaier, Rolf Kreienberg, Lothar Mu, Julia Dorn, Mathias Warm, Michael Scholz, Michael Untch, Philipp Harter, Maike De Wit, Jana Barinoff, Hans-joachim Lu, Doris Augustin, Paul Harnett, and Matthias W. Beckmann. 2017. “A Randomized Phase III Study Evaluating Pegylated Liposomal Doxorubicin versus Capecitabine as First-Line Therapy for Metastatic Breast Cancer : Results of the PELICAN Study.” Breast Cancer Research and Treatment 161(1):63-72. doi: 10.1007/s10549-016-4033-3.
[23]. Hassan, Mohamed, Hidemichi Watari, Ali Abualmaaty, Yusuke Ohba, and Noriaki Sakuragi. 2014. “Apoptosis and Molecular Targeting Therapy in Cancer.” BioMed Research International 150845. doi: 10.1155/2014/150845.
[24]. Holohan, Caitriona, Sandra Van Schaeybroeck, Daniel B. Longley, and Patrick G. Johnston. 2013. “Cancer Drug Resistance : An Evolving Paradigm.” Nature Publishing Group 13(10):714–26. doi: 10.1038/nrc3599.
[25]. Jahja, Ermira. 2017. “Investigation of Novel RNAi and Nanoparticle Approaches for Their Anti-Proliferative and Drug-Sensitizing Effects in Breast Cancer.” Bilkent University.
[26]. Jin, Xun, Bingwen Zou, Li Lou, Chuanhong Zhong, Peilan Zhang, Hao Cheng, Yanfang Guo, and Maling Guo. 2016. “Codelivery of Thioridazine and Doxorubicin Using Nanoparticles for Effective Breast Cancer Therapy.” International Journal of Nanomedicine 4545–52. doi: DOI: 10.2147/IJN.S104635.
[27]. Kafle, Urmila, Satish Agrawal, and Alekha Dash. 2022. “Injectable Nano Drug Delivery Systems for the Treatment of Breast Cancer.” Pharmaceutics 14(12):2783. doi: 10.3390/pharmaceutics14122783.
[28]. Karkada, Mohan, Neil Berinstein, and Marc Mansour. 2014. “Therapeutic Vaccines and Cancer : Focus on DPX-0907.” Biologics; Targets and Therapy 8:27-38. doi: 10.2147/BTT.S55196.
[29]. Leroy, F. Liu, and C. Wan. James. 1987. “Supercoiling of the DNA Template during Transcription.” Proceedings of the National Academy of Sciences of the United States of America 84:7024–27. doi: 10.1073/pnas.84.20.7024.
[30]. Mazouzi, Abdelghani, Georgia Velimezi, and Joanna I. Loizou. 2014. “DNA Replication Stress : Causes , Resolution and Disease.” Experimental Cell Research 329(1):85-93. doi: 10.1016/j.yexcr.2014.09.030.
[31]. Mcmillin, Douglas W., Jake Delmore, Ellen Weisberg, Joseph M. Negri, D. Corey Geer, Steffen Klippel, Nicholas Mitsiades, Robert L. Schlossman, Nikhil C. Munshi, Andrew L. Kung, James D. Griffin, Paul G. Richardson, Kenneth C. Anderson, and Constantine S. Mitsiades. 2010. “Tumor Cell-Specific Bioluminescence Platform to Identify Stroma-Induced Changes to Anticancer Drug Activity.” Nature Medicine 16(4):483–89. doi: 10.1038/nm.2112.
[32]. Meredith, Ann-marie, and Crispin R. Dass. 2016. “Increasing Role of the Cancer Chemotherapeutic Doxorubicin in Cellular Metabolism.” The Journal of Pharmacy and Pharmacology 68:729–41. doi: 10.1111/jphp.12539.
[33]. Mohammadrezaei, F. Mir, A. Fayyaz Movaghar, and M. Gharghabi. 2016. “The Effect of Caffeine and Chk2 Inhibitor on Doxorubicin-Induced Cellular Senescence in MCF-7.” Drug Research 66(9):450-454.
[34]. Muhammad, Yusran Abdul Aziz, Nadiah Abu, Swee Keong Yeap, Wan Yong Ho, Abdul Rahman Omar, Nor Hadiani Ismail, Syahida Ahmad, Mehdi R. Pirozyan, Nadeem M. Akhtar, and Noorjahan Banu Alitheen. 2016.

"Combinatorial Cytotoxic Effects of Damnacanthal and Cells in Vitro." Molecules 21(9):1228. doi: 10.3390/molecules21091228.

[35]. Nestal, Gabriela, De Moraes, Flavia C. Vasconcelos, Deborah Delbue, Giuliana P. Mognol, Cinthya Sternberg, João P. B. Viola, and Raquel C. Maia. 2013. "Doxorubicin Induces Cell Death in Breast Cancer Cells Regardless of Survivin and XIAP Expression Levels." European Journal of Cell Biology 1–10. doi: 10.1016/j.ejcb.2013.08.001.

[36]. Nghan Le, Phung, Chan Khon Huynh, and Ngoc Quyen Tran. 2018. "Advances in Thermosensitive Polymer-Grafted Platforms for Biomedical Applications." Materials Science and Engineering. C, Materials for Biological Applications. doi: doi: 10.1016/j.msec.2018.02.006.

[37]. Nieves-Neira, Wilberto, and Yves Pommier. 1999. "Apoptotic Responsse to Camptothecin and 7-Hydroxystaurosporine (UCN-01) in the 8 Human Breast Cancer Cell Lines of the NCI Anticancer Drug Screen." International Journal of Cancer 82(3):396-404. doi: 10.1002/(sici)1097-0215(19990730)82:3<396::aid-ijc13>3.0.co;2-z.

[38]. Nitiss, John L. 2009. "Targeting DNA Topoisomerase II in Cancer Chemotherapy." Nature Reviews Cancer 9(5):338-50. doi: 10.1038/nrc2607.

[39]. Okoro, Cosmas O., and Toluwase Hezekiah Fatoki. 2023. "A Mini Review of Novel Topoisomerase II Inhibitors as Future Anticancer Agents." International Journal of Molecular Sciences 24(3):2532. doi: 10.3390/ijms24032532.

[40]. Parhi, Priyambada, Chandana Mohanty, and Sanjeeb Kumar Sahoo. 2012. "Nanotechnology-Based Combinational Drug Delivery : An Emerging Approach for Cancer Therapy." Drug Discovery Today 17(17–18):1044–52. doi: 10.1016/j.drudis.2012.05.010.

[41]. Parmar, Manoj B., Hamidreza Montazeri Aliabadi, Parvin Mahdipoor, and Cezary Kucharski. 2015. "Targeting Cell Cycle Proteins in Breast Cancer Cells with SiRNA by Using Lipid-Substituted Polyethylenimines." 3(February):1–14. doi: 10.3389/fbioe.2015.00014.

[42]. Pennakalathil, Jousheed, Ermira Jahja, E. Sila Özdemir, Özlen Konu, and Dönüs Tuncel. 2014. "Red Emitting, Cucurbituril-Capped, PH-Responsive Conjugated Oligomer-Based Nanoparticles for Drug Delivery and Cellular Imaging." Biomacromolecules. doi: 10.1021/bm500839j.

[43]. Pommier, Yves, Shar-yin N. Huang, Rui Gao, Benu Brata Das, Junko Murai, and Christophe Marchand. 2014. "Tyrosyl-DNA-Phosphodiesterases (TDP1 and TDP2)." DNA Repair 19:114-29. doi: 10.1016/j.dnarep.2014.03.020.Tyrosyl-DNA-phosphodiesterases.

[44]. Prados, Jose, Consolación Melguizo, Raul Ortiz, Celia Vélez, Pablo J. Alvarez, Jose L. Arias, Maria A. Ruíz, Visitacion Gallardo, and Antonia Aranega. 2012. "Doxorubicin-Loaded Nanoparticles : New Advances in Breast Cancer Therapy." Anti-Cancer Agents in Medical Chemistry (1):1058–70. doi: 10.2174/187152012803529646.

[45]. Regenold, Maximilian, Pauric Bannigan, James Evans, Adam Waspe, Michael Temple, and Christine Allen. 2022. "Turning down the Heat: The Case for Mild Hyperthermia and Thermosensitive Liposomes." Nanomedicine, Nanotechnology, Biology and Medicine 40:102484. doi: https://doi.org/10.1016/j.nano.2021.102484.

[46]. Rodriguez, Francisco, Pablo Caruana, Noa De Fuente, P. Español, and Josep Balart. 2022. "Nano-Based Approved Pharmaceuticals for Cancer Treatment : Present and Future Challenges." Biomolecules 12(6):784. doi: 10.3390/biom12060784.

[47]. Scherbakov, Alexander M., Yulia S. Lobanova, Olga E. Andreeva, Valentina A. Shatskaya, and Mikhail A. Krasil Nikov. 2011. "Oestrogen Treatment Enhances the Sensitivity of Hormone-Resistant Breast Cancer Cells to Doxorubicin Bioscience Reports." Bioscience Reports 31(2):137-43. doi: 10.1042/BSR20100052.

[48]. Selli, Cigdem, J. Michael Dixon, and Andrew H. Sims. 2016. "Accurate Prediction of Response to Endocrine Therapy in Breast Cancer Patients : Current and Future Biomarkers." Breast Cancer Research 1–10. doi: 10.1186/s13058-016-0779-0.

[49]. Shamanna, Raghavendra A., Huiming Lu, Deborah L. Croteau, Arvind Arora, Devika Agarwal, Graham Ball, Mohammed A. Aleskandarany, Ian O. Ellis, Srinivasan Madhusudan, and Vilhelm A. Bohr. 2016. "Camptothecin Targets WRN Protein : Mechanism and Relevance in Clinical Breast Cancer." Oncotarget 7(12):13269-84. doi: 10.18632/oncotarget.7906.

[50]. Shi, Yonghua, Yang Yu, Zhenyu Wang, and Hao Wang. 2016. "Second-Generation Proteasome Inhibitor Carfilzomib Enhances Doxorubicin-Induced Cytotoxicity and Apoptosis in Breast Cancer Cells." Oncotarget 7(45):73697-73710. doi: 10.18632/oncotarget.12048.

[51]. Silva, Juliana O., Renata S. Fernandes, Sávia C. A. Lopes, Valbert N. Cardoso, Elaine A. Leite, Geovanni D. Cassali, Maria Cristina Marzola, Domenico Rubello, Monica C. Oliveira, Andre Luis, and Branco De Barros. 2016. "PH-Sensitive, Long-Circulating Liposomes as an Alternative Tool to Deliver Doxorubicin into Tumors : A Feasibility Animal Study." Molecular Imaging and Biology. doi: 10.1007/s11307-016-0964-7.

[52]. Sirhan, Zaid, Anita Thyagarajan, and Ravi P. Sahu. 2022. "The Efficacy of Tucatinib - Based Therapeutic Approaches for HER2 - Positive Breast Cancer." Military Medical Research 1–9. doi: 10.1186/s40779-022-00401-3.

[53]. Slingerland, Marije, Henk-jan Guchelaar, Hilde Rosing, Max E. Scheulen, Laurence J. C. Van Warmerdam, Jos H. Beijnen, and Hans Gelderblom. 2017. “Bioequivalence of Liposome-Entrapped Paclitaxel Easy-To-Use (LEP-ETU) Formulation and Paclitaxel in Polyethoxylated Castor Oil : A Randomized , Two-Period Crossover Study in Patients With Advanced Cancer *.” Clinical Therapeutics 35(12):1946–54. doi: 10.1016/j.clinthera.2013.10.009.

[54]. Sobhani, Navid, Bruna Scaggiante, Rachel Morris, Dafei Chai, and Martina Catalano. 2022. “Therapeutic Cancer Vaccines: From Biological Mechanisms and Engineering to Ongoing Clinical Trials.” Cancer Treatment Reviews 109:102429. doi: 10.1016/j.ctrv.2022.102429.

[55]. Sun, Haotian, Iven Yarovoy, and Meghan Capeling. 2017. “Polymers in the Co-Delivery of SiRNA and Anticancer Drugs for the Treatment of Drug-Resistant Cancers.” Topics in Current Chemistry 1–30. doi: 10.1007/s41061-017-0113-z.

[56]. Tagde, Priti, Agnieszka Najda, Kalpana Nagpal, Giriraj T. Kulkarni, Muddaser Shah, Obaid Ullah, Sebastian Balant, and Habibur Rahman. 2022. “Nanomedicine-Based Delivery Strategies for Breast Cancer Treatment and Management.” International Journal of Molecular Sciences 23(5):2856. doi: 10.3390/ijms23052856.

[57]. Takagi, Kazutaka, Thomas S. Dexheimer, Christophe Redon, Olivier Sordet, Keli Agama, Gilbert Lavielle, Alain Pierre, Susan E. Bates, and Yves Pommier. 2007. “Novel E-Ring Camptothecin Keto Analogues (S38809 and S39625) Are Stable , Potent , and Selective Topoisomerase I Inhibitors without Being Substrates of Drug Efflux Transporters.” Molecular Cancer Therapeutics 6:3229–39. doi: 10.1158/1535-7163.MCT-07-0441.

[58]. Tammaro, Margaret, Peri Barr, Brett Ricci, and Hong Yan. 2013. “Mechanisms of DNA Double-Strand Break Induction by the Topoisomerase 2-Targeting Drug Etoposide.” PLoS ONE 8(11):1–14. doi: 10.1371/journal.pone.0079202.

[59]. Tiwari, Aadhya, Rakesh Trivedi, and Shiaw Yih Lin. 2022. “Tumor Microenvironment : Barrier or Opportunity towards Effective Cancer Therapy.” Journal of Biomedical Science 1–27. doi: 10.1186/s12929-022-00866-3.

[60]. Wang, Ruo-xi, Sheng Chen, Xi Jin, and Can-ming Chen. 2016. “Weekly Paclitaxel plus Carboplatin with or without Trastuzumab as Neoadjuvant Chemotherapy for HER2-Positive Breast Cancer : Loss of HER2 Amplification and Its Impact on Response and Prognosis.” Breast Cancer Research and Treatment. doi: 10.1007/s10549-016-4064-9.

[61]. Wang, Y., H. Xu, Y. Han, Y. Wu, Q. Sa, and J. Wang. 2023. “Identifying the Optimal Therapeutics for Patients with Hormone Receptor- Positive , HER2-Positive Advanced Breast Cancer : A Systematic Review and Network Meta-Analysis.” ESMO Open 8(3):1–9. doi: 10.1016/j.esmoop.2023.101216.

[62]. Weber, Petra, Michael Wagner, and Herbert Schneckenburger. 2013. “Cholesterol Dependent Uptake and Interaction of Doxorubicin in MCF-7 Breast Cancer Cells.” International Journal of Molecular Sciences 14(4):8358-66. doi: 10.3390/ijms14048358.

[63]. Wilks, Sharon T. 2015. “Potential of Overcoming Resistance to HER2-Targeted Therapies through the PI3K / Akt / MTOR Pathway.” The Breast 4–11. doi: 10.1016/j.breast.2015.06.002.

[64]. Yan, Guoqing, Jun Wang, Liefeng Hu, Xin Wang, Guanqing Yang, Shengxiang Fu, Xu Cheng, Panpan Zhang, and Rupei Tang. 2017. “Stepwise Targeted Drug Delivery to Liver Cancer Cells for Enhanced Therapeutic Efficacy by Galactose-Grafted , Ultra-PH-Sensitive Micelles.” Acta Biomaterialia. doi: 10.1016/j.actbio.2017.01.031.

[65]. Yang, Fan, Qingjie He, Xiangpeng Dai, and Xiaoling Zhang. 2023. “The Potential Role of Nanomedicine in the Treatment of Breast Cancer to Overcome the Obstacles of Current Therapies.” Frontiers in Pharmacology 14:1143102. doi: 10.3389/fphar.2023.1143102.