

# Recent Advancements of Anti-cancer Nanomedicine in Breast Cancer

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**Keywords:** Nanomedicine, Cancer, Anti-Cancer, Cancer Treatment.

**Abstract:** Nanomedicine is a novel type of cancer treatment that has been applied to clinical practice for its identified safety and potency against cancer cells and safety. Conventional cancer treatments such as surgery, radiation, and chemotherapy work generally well but inevitably bring severe adverse reactions and sometimes unsatisfying results. Breast cancer is one of the most major cancer with high incidence rate and mortality rate, characterized by high risks and a great reduction in of life quality of life with high incidence rate and mortality rate. In the past three decades, nanotechnology emerged to giving rise to novel forms offer anti-cancer drug delivery systems and offering greater therapeutic therapeutical advantages than traditional cancer treatments can do. With the incorporation of nanocarriers, higher drug loading efficiency, targeted delivery, enhanced bioavailability, and stronger cytotoxicity, and less side effects can be achieved. This paper shows the recent developments of nanocarrier-incorporated anti-cancer drugs with specific to breast cancer. Ways of newly synthesized drug loaded nanoparticles alleviating side effects from conventional treatments and improving therapeutic effects are stressed in this paper.

## 1 INTRODUCTION


Cancer, the second leading cause of death, is a group of diseases induced by uncontrollable abnormal cell division and replication. According to the World Health Organization's International Agency for Research on Cancer Global Cancer Observatory (GLOBCAN), in 2018, there were 18 million new cancer incidences and 9.5 million related deaths worldwide, and by 2040 the number of new cases will rise to 29.5 million and the number of related deaths would be 16.4 million (Hulvat, 2020).

Conventional treatments for cancer are surgery, radiation, and chemotherapy. For cancers in early stage, surgery and radiation work well. Surgery is an important approach to tumors for the ability to remove the lower grade benign tumors. Surgery, however, becomes extremely difficult when the tumor is located on unreachable sites. Moreover, side effects like headaches, fatigue, and further damage to the brain tissue may happen after the surgery. Radiation is a cancer therapy applying high energy radiation to eliminate cancer cells, which is not an ideal approach because there is an annual and a lifetime exposure limit, and it inevitably affects adjacent normal cells. Radiation may also bring

adverse symptoms such as nausea, hair loss, and diarrhea. The other side effect is that when metastasis occurs, the surgery and radiation become ineffective. Metastasis refers to that the secondary cancer develops and spreads to different sites in the body far from its initial site. When the tumor is metastasized, surgical removal may enhance tumor recurrence (Tohme, Simmons, Tsung, 2017). Similarly, radiation promotes metastasis and increases the possibility of recurrence, suggesting by abundant clinical data (Vilalta, Rafat, Graves, 2016).

Later, since 1940s, chemotherapy has been utilized as a treatment of cancers. Chemotherapy is characterized by fast killing of cancer cells by delivering chemical agents that disturb cancer cell's replication. It is used to treat metastatic cancer, which has spread to other parts of the body. The drugs are delivered through the bloodstream and reach cancer cells; however, chemotherapy has some severe problems. Chemotherapy eliminates normal cells along with cancer cells. Moreover, nausea, vomiting, and neutropenia are commonly observed after receiving chemotherapy.

Breast cancer is one of the major cancers with high incidence and mortality rate (DeSantis, Ma, Gaudet, et al 2019). Female breast cancer has become the leading cause of global cancer incidence

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in 2020, in which unhealthy lifestyle plays a role in it other than hormonal factors. The risk of breast cancer is associated with personal lifestyle. Obesity, insufficient physical activity, and high alcohol consumption are risk factors of breast cancer which are many people are currently having.

The specific cause of cancer is still under investigation. Up until now, scientists believe that the formation of cancer is associated with oncogenes and tumor suppressor genes. Oncogenes are found to be expressed at a high level in cancer cells. They emerge when proto-oncogenes, which promotes positive cell growth, mutate to become activated oncogenes (Lam, Schmidt, 2012). As a result, the cell starts to uncontrollably divide and promotes carcinogenesis (Lam, Schmidt, 2012). On the contrary, tumor suppressor genes, also called anti-oncogenes, regulate normal cell division and inhibit cell proliferation (Krasin, Davidoff, 2012). The inactivation of tumor suppressor genes leads to their malfunction, inducing infinite cell replication, or the development of malignancy. (Lam, Schmidt, 2012). Most current anti-cancer drugs or therapies either kill fast-growing cancer cells along with normal cells (e.g., chemotherapy, radiation) or target specific proteins inside or outside cancer cells. (e.g., small molecule drugs and monoclonal antibodies). Target therapies can be identified through the examination of highly expressed proteins in cancer cells; while in normal cells, the amount of the same kind of proteins remains low (Kampen, 2011). For example, human epidermal growth factor receptor 2 (HER2) is a protein overexpressing on the surface of approximately 20-30 % of breast cancer cells. (Mitri, Constantine, O'Regan, 2012). Trastuzumab and Pertuzumab are antibodies that target HER2. (Kunte, Abraham, Montero, 2020). Another difference between cancer cells and normal ones that inspire novel drugs is that cancer cells require large supply of oxygen to sustain cell replication and to spread. Cancer cells often experience hypoxia, the decreased level of oxygen (McKeown, 2014), so the average oxygen level is lower in cancer cells. Angiogenesis, the formation of new blood vessels, is observed a large increase when benign tumor transforms into malignant one (Brustmann, Riss, Naudé, 1997), which is the induced response of hypoxia (Chen, Endler, Shibasaki, 2009). Under such circumstances, angiogenesis inhibitors are applied to restrain the cancer blood vessel growth (Klagsburn, Moses, 1999). Clinically approved drugs are Trastuzumab and Pertuzumab for advanced breast cancer, only to name a few. Along with conventional treatments, anti-tumor target drugs alone such as Trastuzumab

and Pertuzumab could bring serious side effects (Bines, Clark, Barton, et al, 2021) Given such situation, a less painful approach with higher therapeutic efficiency is needed.

In recent years, people have gained greater understanding of nanomedicine as a novel approach to cancer treatment. Nanomedicine is the application of nanotechnology for medical therapeutics by using nano-scaled agents to treat diseases. Nanomedicine possesses properties of targeted delivery, small-scale size, decent permeability, and bioavailability (Patra, Das, Fraceto, et al, 2018). Nanodrugs synthesized by materials such as liposomes, polymers, inorganic particles, and peptides are proved to be feasible ways to enhance the effectiveness of cancer treatments by the clinical data. They target specific to prevent the damage to normal tissues and cells, thereby exhibiting high cytotoxic concentration in tumors. The encapsulation of drugs into nanocarriers protects anti-cancer drugs from degradation, improving the drug delivery efficiency (Patra, Das, Fraceto, et al, 2018).

Previous researches have done to integrate the advantages and clinical practices of nanocarriers with a broad focus on several cancers. However, within the rapid development of nanomedicine in past ten years, new forms of nanodrugs and clinical applications emerge; therefore, an update that includes the analysis of past nanomedicine and how they evolve within times with more specific focus is needed.

This paper provides a description of recent nanomedicine-incorporated cancer treatments with specific to breast cancer. The specific advantages and working mechanisms of common nanoparticles: liposome, porous silicon, and dendrimer are described. Disadvantages of traditional drugs such as Tamoxifen, Doxorubicin, and Trastuzumab, and how newly synthesized drug loaded nanoparticles address these problems and offers therapeutic effects are stressed in this paper.

## 2 COMMON NANOMEDICINE FOR BREAST CANCER TREATMENT

Nanomedicines has been applied to clinical practice and they are still under intensive investigation, for its potential and effectiveness of anti-tumor. Liposome, porous silicon, and dendrimer are commonly used nanocarriers to treat breast cancer. Their working mechanisms and advantages are

briefly described below, for which are core concepts in understanding later introduction of nanoparticle-incorporated drugs.

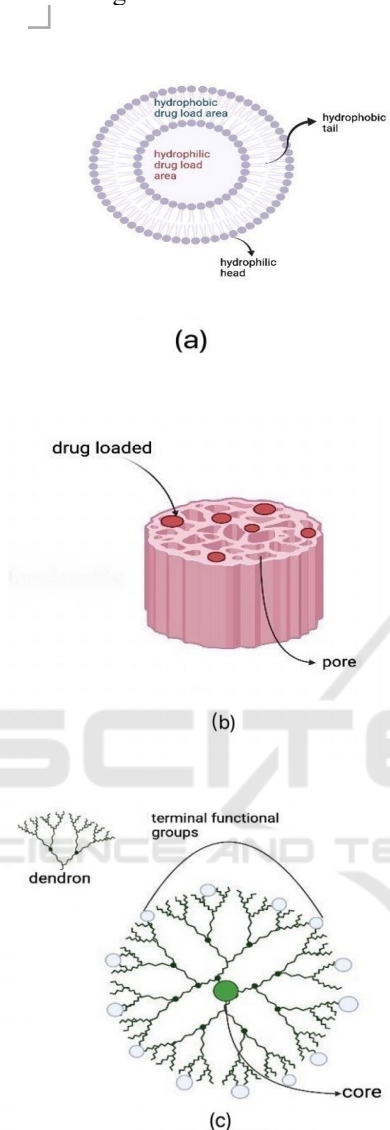


Figure 1: Scheme diagram for six nanocarriers: (a) Liposome, (b) Porous Silicon, (c) Dendrimer.

## 2.1 Liposome

Liposome is a spherical nanosized vesicle that consists of an aqueous core and phospholipid bilayers. The bilayer is composed of hydrophilic heads and hydrophobic tails, making it amphipathic. As a result, liposomes can carry both hydrophilic and hydrophobic drugs without degeneration.

Normally, drug-loaded liposome works in four patterns: (Sharif, Fazle, Nazir, 2006)

1. Endocytosis by phagocytic cells, absorbing substances by cell membrane's engulfment (Phagocytosis and Intracellular Killing, 2012). Adsorption to the surface of the cell by interactions with components on the surface.
2. Fusion with the plasma membrane by the interaction between phospholipid bilayers and plasma membrane, releasing the contents loaded in the core of liposome.
3. Transfer of liposomal membranes to cellular membranes.

## 2.2 Porous Silicon (pSi)

Porous silicon is a sponge-like nanostructure in which microstate crystalline silicon is introduced. The pSi has proved to possess excellent biocompatibility and biodegradability due to its unique porous structure and chemical properties (Kumeria, McLinnes, Maher, Santos, 2017). Porous silicon is identified by large surface area and internal volume, allowing high loading capacity and enhanced adsorption ability (Santos, Mäkilä, Airaksinen, Bimbo, Hirvonen, 2014). Once pSi arrives at the targeted site and releases the loaded drug, it degrades into silicic acid which is harmless to human body and easily removed by kidneys (Manj, Chen, Rehman, Zhu, Luo, Yang, 2018).

## 2.3 Dendrimer

Dendrimers are ordered, branched three dimensional polymeric molecules. They have symmetric and monodisperse structure which consists of a core, branched, symmetric dendrons, and terminal functional groups (Abbasi, Aval, Akbarzadeh, et al, 2014) The internal cavities of dendrimers enable the encapsulation of drugs, making excellent stability and solubility (Santos, Veiga, Figueiras, 2020). Dendrimers' properties can be possibly modified and controlled, for various terminal groups attached are responsible for the interaction of dendrimers and external molecules (Han YL, Kim SY, Kim T, Kim KH, Park JW, 2020).

# 3 BREAST CANCER

## 3.1 Tamoxifen

Tamoxifen (TMX), an antiestrogen, is a traditional clinically proved hormonal treatment for breast cancer (Yang, Nowsheen, Aziz, Georgakilas, 2013).

It has dual mechanism of action: (1) inhibiting estrogen action and blocking the binding of estradiol ( $E_2$ ), (2) binding with DNA after metabolic activation and initiating carcinogenesis (Yu, Bender, 2001, Craig Jordan, 1992). TMX is reported to reduce the incidence of oestrogen positive breast cancer by 38% among high-risk patients (Singh, 2021). It decreases the taker's death rate and recurrence rate (Gray, Rea, Handley, et al, 2013). TMX, however, induces side effects (Osborne, 1998). Besides those common adverse reactions such as hot flashes, sleep problems, and vaginal dryness, it stays on estrogen receptors in tumor tissue for several months after the treatment is stopped and gives false negative results (Osborne, 1998). Moreover, TMX treatment promotes the development of endometrial cancer and increases the risk of it (Bergman, Beelen, Gallee, Hollema, Benraadt, Van Leeuwen, 2000).

Porous silicon (pSi) based nanomaterials have been identified the potential to be excellent carriers for cancer treatment. Inspired by the side effects of TMX and the advantages of pSi, researchers synthesized TMX-loaded pSi nanoparticle to further improve the bioavailability of TMX (Haidary, Mohammed, Córcoles, Ali, Ahmed, 2016). The drug release is controlled by the rate of degradation of pSi due to its biodegradable property (Haidary, Mohammed, Córcoles, Ali, Ahmed, 2016). Biocompatible, non-toxic material chitosan and silica xerogel hybrid is used on surface coating to prevent infection, and the hybrid coating produces outstanding drug release results (Haidary, Mohammed, Córcoles, Ali, Ahmed, 2016).

The price of chemicals needed for preparation, hydrosilylation, and bioactive coating is moderate. For instance, 2.5 L 37% hydrochloric acid is about \$112 on Sigma Aldrich, while only 0.5 mL diluted HCl (2%) is needed for silica xerogel preparation, similar situation to other chemicals required. Obstacles of industrial production of TMX-loaded pSi nanoparticle, however, still remain. The process of preparation of pSi particle, the hydrosilylation, and the bioactive coating, is complicated, making the large production expensive and time-consuming.

### 3.2 Doxorubicin

Doxorubicin (DOX), an antibiotic derived from bacterium *Streptomyces peucetius*, is another commonly used anti-breast cancer agent with strong effectiveness (Christowitz, Davis, Isaacs, Van Niekerk, Hattingh, Engelbrecht, 2019). The primary working mechanism of DOX involves intercalation

of DNA pairs, breaking the DNA strand and inhibiting the DNA and RNA synthesis (Agrawal, 2007). DOX brings severe adverse effects like other widely applied agents. For instance, DOX is highly toxic and it increases the risk of potentially fatal cardiotoxicity; therefore, its dose should be limited strictly (Zhao, Ding, Shen, Zhang, Xu, 2017). Other deleterious side effects include myocardial damage and heart failure (Redfors, Shao, Råmunddal, et al, 2012).

When treating tumors, DOX alone is of rather low drug loading efficiency due to the hamper of abnormal, tortuous blood vessels; only 5-10% of drugs enter the tumor tissue and take effect (Chang, Li, Lu, Jane, Wu, 2013). To increase the higher drug load efficiency and to achieve better therapeutic effects, PEGylated liposomal doxorubicin (PLD), a formulation of doxorubicin packed into liposome with polyethylene glycol outer coating, was created by reseachers (Green, Rose, 2006). With nanocarrier's encapsulation, 15,000 DOX molecules per vesicle with over 95% drug loading efficiency is achieved (Chang, Li, Lu, Jane, Wu, 2013, Gabizon, 2001). Small size of liposomal carrier contributes to better tumor accumulation; the smaller the size, the better tumor accumulation (Gabizon, 2001). Moreover, PLD is observed to have longer half-life and slower clearance than non-PEGylated liposome and free DOX, which means that PLD has the ability to achieve longer circulation time (Gabizon, 2001). All in all, PLD has revealed great potential in making a perfect anti-cancer practice.

The therapeutic value of DOX is further improved by the encapsulation of nanocarriers on which modified by other tumor target chemical agents. For example, after the Clot-binding pentapeptide Cys-Arg-Glu-Lys-Ala (CREKA) has gained the recognition of the ability to recognize fibrin-fibronectin complexes that overexpress in tumor vessel endothelium and stroma rather than normal cells, making CREKA a target peptide of effectiveness and precise target delivery (Shi, Zhang, Liu, et al, 2018, Jiang, Song, Yang, et al, 2018). In a recent study, CREKA modified liposomal DOX (CREKA-Lipo-DOX) has been synthesized and proved its therapeutic effects (Jiang, Song, Yang, et al, 2018). Compared to free DOX with rapid release, the drug release of CREKA-Lipo-DOX is more sustained with little burst; the release of CREKA-Lipo-DOX is slightly faster than those of PLD.[40] Though PLD improves the anticancer efficiency of free DOX, CREKA-Lipo-DOX can significantly inhibit cancer cell growth and metastasis *in vivo*. Furthermore, CREKA-Lipo-DOX

is safer than PLD and DOX (Attia, Anton, Wallyn, Omran, Vandamme, 2019). Study demonstrates that CREKA-Lipo-DOX shows no severe cardiotoxicity and all other organs are of normality without obvious histopathological lesions (Jiang, Song, Yang, et al, 2018).

The needed chemicals and materials in this study are of large amount and overall price of all material is high. The researchers implemented the thin-film hydration method to prepare liposomes for its simplicity; however, this method may result in no controlled size in production of liposomes and poor encapsulation efficiency of hydrophilic drugs (Nkanga, Bapolisi, Okafor, Krause, 2019). Also, this study mainly focuses on anti-metastasis efficacy; more data specifically about anti-tumor is needed for further development.

### 3.3 Trastuzumab

Trastuzumab is a traditional anti-breast cancer monoclonal antibody targeting HER2 (a gene that activates the growth factor signal) positive cells (Bines, Clark, Barton, et al, 2021). Trastuzumab binds to the juxtamembrane portion of the domain of HER2 receptor and prevents the overexpression of HER2 (Hudis, 2007). In general, patients who receive Trastuzumab improves all clinical outcome parameters including overall survival rate of patients. Despite these benefits, Trastuzumab induces serious cardiac and gastrointestinal side effects after investigating the toxicity associated with it (Huszno, Leś, Sarzyczny-Słota, Nowara, 2013). In addition, diarrhea, fever, nausea is commonly observed after treatment.

A new form of Trastuzumab treatment has been invented to improve its therapeutic efficiency. By covalently attaching fluorinated dendrimer to Trastuzumab, Trastuzumab-dendrimer-fluorine drug delivery system targeting the HER2 receptor on breast cancer cells is synthesized by researchers (Bartusil-Aebisher, Chrzanowski, Bober, 2021). The incorporation of  $^{19}\text{F}$  increases the lipophilicity and hydrophobicity of drug delivery system, while the use of PAMAM-G5 dendrimer enhances the cellular uptake of the drug delivery system and increases biocompatibility (Bartusil-Aebisher, Chrzanowski, Bober, 2021). In addition, Trastuzumab-dendrimer drug delivery systems have shown enhanced solubility and controlled release of Trastuzumab in comparison to the pure drug alone (Bartusil-Aebisher, Chrzanowski, Bober, 2021).

The Trastuzumab-dendrimer drug delivery research was done *in vitro*, which means that further

study must be done to prove its safety and feasibility before clinical use, but with long and complicated synthesis to obtain the final product, the *in vivo* stage test might face more challenges.

## 4 CLINICAL APPROVALS OF NANOMEDICINE

Nanomedicine has been the frontier technology in medicine. Since 1990s, large amounts of designed nanoparticles were created and entered clinical trial. However, few of them were able to be approved for clinical use. Nanoparticles being declined exhibit extra strong cytotoxicity, unwanted adverse effects, and low efficiency of targeted delivery (Seok, Bae, 2018).

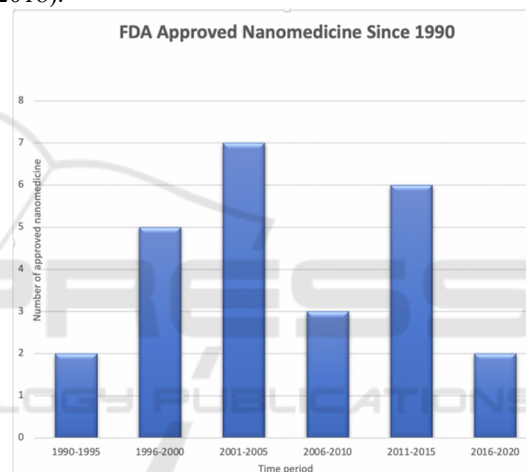


Figure 2: FDA approved nanomedicine since 1990s (Anselmo, Mitragoti, 2019).

Since the approval of Doxil® in 1995, more newly made nanomedicine emerge in 2000s with significant breakthrough of drug delivery efficiency gained approval (Seok, Bae, 2018). Although the number of approved nanomedicines is not satisfying compared to the fact that numerous novel nanoparticles are ongoing for clinical trial, scientists continue to make progresses towards improving synthesis strategies.

## 5 CONCLUSIONS

The presence of nanoparticles provides an alternative way to more effective cancer treatments other than conventional therapies. This paper includes the working mechanisms and advantages of

partial common nanoparticles, including pSi, liposome, polymeric materials, and peptide drugs.

They possess the characterization of small size, high drug loading capacity and efficiency, enhanced bioavailability, and harmlessness to human body, making them ideal approaches to anti-cancer practice. Nanotechnology is still evolving rapidly; current existing nanoparticle-based drug delivery systems will be refined, and newly designed ones will emerge in the future. Although huge amounts of nanocarrier incorporated drug delivery system with excellent therapeutical effects and clinical values have been successfully synthesized in laboratory and entered the clinical trial, clinically approved ones are relatively fewer. While the majority of them are passive targeting nanoparticles, there are no active targeting ones approved from 2007 to 2017 (Narum, Le T, Le DP, et al, 2019). From future perspective, active targeting nanoparticles need to be further investigated, for they can be applied to the situation where therapeutic drugs have difficulties crossing the cell membrane (Attia, Anton, Wallyn, Omran, Vandamme, 2019). Throughout the paper, we know that the choice of nanoparticle depends on specific cancer type, the cost of production, prior studies on possible adverse reactions and research parameters, and studied nanodrug-induced response *in vivo*, to ensure the nanodrug's safety and effectiveness (Attia, Anton, Wallyn, Omran, Vandamme, 2019). Given that, much efforts should be devoted to investigate safe and feasible nanoparticle-based drug delivery system for cancer treatments.

The synthesis procedures of previously described nanomedicine are generally at high cost: expensive chemicals, bioreactors, equipment, and instruments are required, and more animal and clinical testing will need to be completed before clinical approval. The use of organic solvents and complicated steps to synthesize nanoparticles cannot ensure the purity of the product. Future investigations can focus on the alternative ways of creating nanoparticles with fewer steps and lower price when the yield, purity and stability can be sustained.

All in all, this paper stresses recent advance anti-cancer nanomedicine within a short time frame with specific focus on breast cancer treatments. This paper possesses potential time limitations due to the fact that nanomedicine continues to advance. Future investigation can cover lower cost nanomedicine production methods, new clinical practices of nanodrugs on different types of cancer and treatments, and safer, more therapeutically effective synthesis design for the time being.

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