



# ADVANCES IN NOVEL DRUG DELIVERY STRATEGIES FOR BREAST CANCER THERAPY

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## ABSTRACT

Breast cancer is one of the world's most devastating diseases. However, better understanding of tumor biology and improved diagnostic devices can lead to improved therapeutic outcomes. Nanotechnology has potential to revolutionize cancer diagnosis and therapy. Various nanocarriers have introduced to improve the therapeutic efficacy of anticancer drugs, including liposomes, polymeric micelles, quantum dots, nanoparticles, and dendrimers. Recently, targeted drug delivery systems for anti-tumor drugs have demonstrated great potential to lower cytotoxicity and increase the therapeutic effects. Various approaches have been explored for targeting breast cancer. This article provides an overview of breast cancer, conventional therapy, potential of nanotechnology in management of the breast cancer, and rational approaches for targeting breast cancer.

**Key words-**breast cancer, drug targeting, liposomes, nanoparticles, growth factor receptor

## INTRODUCTION

Breast cancer is one of the world's most devastating diseases with more than 7,600,000 deaths and 1,301,867 new cases every year.

Breast tumors are categorized into 4 different stages based upon their size, location, and evidence of metastasis. Mode of treatment depends upon stage and expression of MDR transporters that actively pump chemotherapeutic drugs out of the cell and reduce the intracellular drug doses below lethal threshold levels. The treatment of primary breast cancer is mainly consisted of initial surgery followed by radiation and various forms of systemic adjuvant therapy

Conventional drug delivery approaches suffer from some limitations like lack of selectivity and cytotoxicity by non-targeted cells. Therefore targeting strategies must be determined to overcome non-specific uptake by non-targeted cells. The new signaling networks that regulate cellular activities include membrane growth factors receptors, cytoplasmic signaling molecules, nuclear cell cycle proteins, modulators of apoptosis and molecules that promote angiogenesis, which were determined by molecular and genetic approaches in the late 1980s and after that many drugs targeted at these key proteins result in the cancer drug development with the beginning of a new "targeted therapy era".

Specific molecular targets having critical roles in cancer proliferation that are interfered by targeting drugs. Some important therapeutic targets in breast cancer are HER-2(Human epidermal growth factor receptor 2), VEGF (vascular endothelial growth factor), IGFBP-3 (insulin-like growth factor binding proteins-3), ER (estrogen receptor), gene silencing by siRNA . These targeted therapies should be able to show action with high efficacy and less toxicity. Several nanotechnological approaches have been used to improve targeted delivery of a potent anticancer drug to breast cancer cells with minimum toxic effects on healthy tissues and also maintaining efficacy. Nanotechnology is developing a new generation of more effective therapies by using nanocarriers that have the capacity of overcoming the biological, biophysical, and biomedical barriers in treatment of breast cancer. Nanocarriers shows promising breast cancer therapy by selectively reaching the desired specific sites due to their small size and surface modifying properties with multifunctionality. This article highlights recent approaches that can be targeted and have clinical applicable for treatment of breast cancer.

## ***BREAST CANCER***

Breast cancer is the second leading common cancer seen in women in the United States and it begins in breast tissue, usually the ducts and lobules. Breast cancer do not show any symptoms in the early stages; therefore screening tests often fail to detect the disease at this time. The following changes may occur with breast cancer growth:

- \*A lump in or near the breast.
- \*A change in the size or shape of the breast.
- \*A change in the skin of the breast, areola, or nipple.

The main cause of breast cancer are still unknown, but there is a combination of risk factors including lifestyle factors, environmental factors, genetic factors, and hormonal factors which may be responsible for breast cancer. Although many risk factors are associated with breast cancer, it is not yet known how these risk factors cause normal breast cells to become cancerous.

The molecular biology of breast cancer is complex as multiple factors are responsible for the development of breast cancer such as genetic mutations in BRCA1, BRCA2 and p53 and cross-talks between different signaling pathways. Cell-signalling pathways allow normal programs of proliferation, transcription, growth, differentiation and death in the normal cell. But in the breast cancer cells, these normal programs are altered by altering cell-signalling pathways. Various signalling pathways that has important impact in development and progression of breast cancer are initiated by the interaction between growth factors and their receptors, such as human epidermal growth factor receptors (HER-2 and VEGF) and their ligands, as well as insulin-like growth factor (IGF) and IGF-1R.

## ***CONVENTIONAL BREAST CANCER THERAPY***

Now a days various conventional therapies like radiation therapy, chemotherapy, hormonal therapy, and immunotherapy are used for the treatment of breast cancer. Cancer cells that are not be seen during surgery can be killed by radiation to reduce the risk of local recurrence of cancer. Radiation therapy is a therapy in which cancer cells are exposed to high levels of radiation directly. Radiation therapy after surgical operation shrinks the tumor in combination with chemotherapy. But there are some side-effects of radiation therapy, such as decreased sensation in the breast tissue , skin problems in the treated area (including soreness, itching, redness) and at the end of treatment the skin may become moist.

The purpose of hormonal therapy Is either to add or block hormones. The female hormones estrogen and progesterone promotes the growth of some breast cancer cells. Therefore hormone therapy is necessary to block or lower the levels of estrogen and progesterone to prevent growth of cancer cells. Types of hormonal drugs used for primary breast cancer include Tamoxifen, Toremifene, Arimidex, Zoladex, etc. Tamoxifen is a selective

estrogen-receptor modulator (SERM), which blocks estrogen from attaching to estrogen receptors on breast cancer cells. Tamoxifen increases the risks of uterine cancer, thromboembolism and tamoxifen resistance. Aromatase inhibitors block estrogen production.

The National Institute for Health and Clinical Excellence (NICE) in November 2006 published that aromatase inhibitors after surgery for early breast cancer in postmenopausal women and recommended Anastrozole, Exemestane, Letrozole, etc. for treatment of breast cancer.

In chemotherapy cytotoxic drugs are administered to kill various cancer cells. Chemotherapy can be recommended as adjuvant chemotherapy or neoadjuvant chemotherapy. Adjuvant chemotherapy is the systemic therapy which is given to patients after surgery to treat undetected breast cancer cells. Neoadjuvant chemotherapy is given before surgical operation to shrink large cancers so that they can easily be removed by lumpectomy. It is reported clinically that chemotherapy is very effective when given in combinations of more than one drug. Common combinations used for treatment of breast cancer are listed below in table 1. Common side-effects are hair loss, mouth sores, loss of appetite, nausea, vomiting, increased chance of infections (due to low white blood cell counts), easy bleeding (due to low blood platelet counts), and fatigue.

### ***NANOCARRIERS FOR BREAST CANCER THERAPY***

Nanocarriers is considered as powerful tools for delivery of drugs, imaging, and diagnosis due to their size, ease to design and surface modification characteristics. Various nanocarriers, including liposomes, dendrimers, nanocrystals, magnetic nanoparticles and biodegradable nanoparticles, increase drug bio-availability and reduce side-effects. The surface of these carriers can be modified to achieve desirable properties and to make them suitable for several different functions such as diagnosis, prognosis, controlled and sustained delivery of therapeutic agents at specific targeting sites. Surface modification of various nanocarriers can be achieved by using moieties such as ligands. The surface modifier may be soluble polymer, pH or temperature-sensitive lipids, specific ligands, such as antibody, peptide, folate, transferrin, etc. Such kind of surface modifications provide functionality, which in turn makes nanocarriers an efficient delivery system. Different surface modifiers used are shown in below table. Targeting of nanocarriers is of 2 types: Active targeting and Passive targeting. Passive targeting is achieved by incorporating the therapeutic agent into a nanocarrier which passively reaches the target organ. It is the accumulation of active ingredient in a specific site due to various physicochemical, pathophysiological and anatomical attributes. This can be explained in cancerous tissues, as these tissues have poor lymphatic drainage which means it enhanced permeability and retention (EPR) effect, resulting in the accumulation of nanoparticles at the tumor site. The various large gaps between adjacent endothelial cells in tumor neovasculature allows for passive targeting to the tumor site, while poor lymphatic drainage leads to enhanced retention of macromolecular therapeutics within the tumor mass. For passive targeting, the size and surface properties of drug delivery nanoparticles must be controlled in order to avoid the uptake by the reticuloendothelial system (RES). The desired size, less than 100 nm in diameter, enhances the circulation times and targeting ability. The hydrophilic surface of nanoparticles prevents engulfment by macrophages and that can be achieved through hydrophilic polymer coatings such as polyethylene glycol, poloxamines, poloxamers,

polysaccharides or through the use of branched or block amphiphilic co-polymers. PEG is biocompatible, non-toxic, non-immunogenic with desired molecular weight

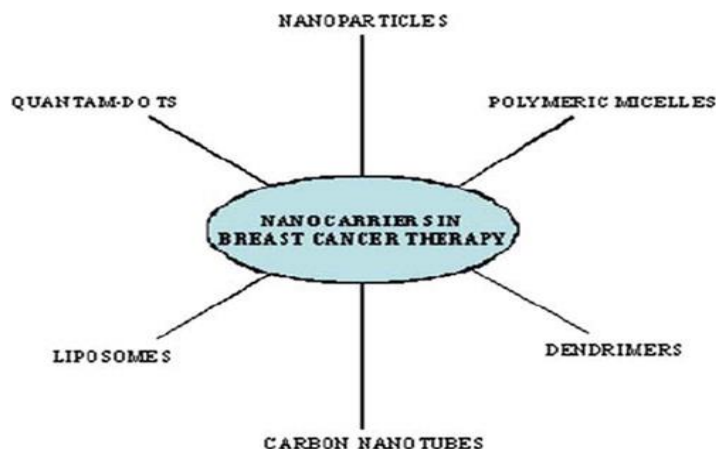


Figure 1. Various types of nanocarriers used in breast cancer therapy

and binding capacity to proteins and antibodies. Active targeting is usually achieved by conjugating a specific targeting ligand to the surface of the nanoparticles which provide accumulation of nanoparticles at the desirable targeting site. This way is based on specific interactions of ligand-receptor and antibody-antigen. An expression of receptors or antigens in cancer acts as a potential target to achieve efficient drug uptake via receptor-mediated endocytosis. Depending on the design of the cleavable bond, the drug may be released intracellularly on exposure to lysosomal enzymes or lower pH.

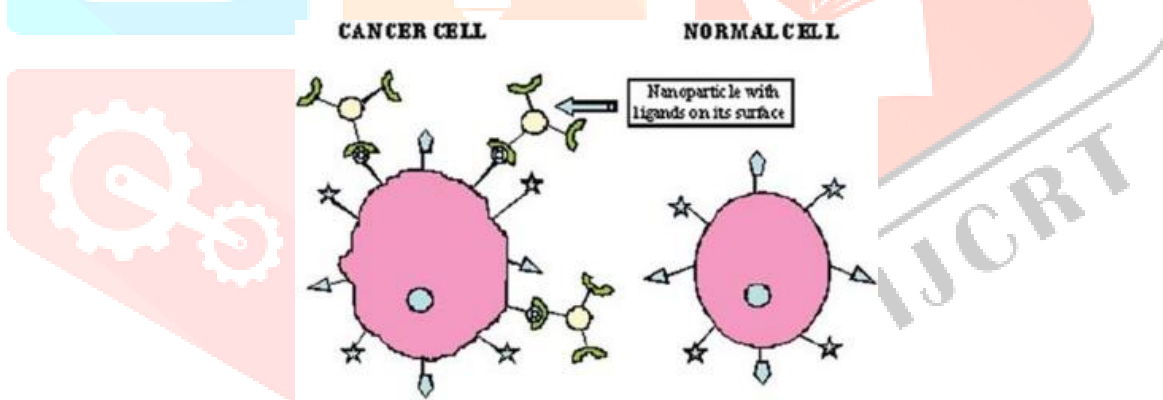


Figure 2. Trail of active targeting.

## LIPOSOMES

Both lipophilic and hydrophilic drugs can be entrapped into liposomes because of presence their biphasic character. Lipophilic drugs are very poorly soluble in water, hence entrapped in the lipid bilayers of liposomes. Hydrophilic drugs may be entrapped inside the aqueous core of liposomes or located in the external water phase. The preparation procedure and bilayer composition of liposome affects the percentage entrapment of hydrophilic drug. Conventional liposomes have major limitations as they are rapidly cleared by RES due to adsorption of opsonin proteins on the phospholipid membrane of liposomes. Drug-containing liposomes of diameters approximately 50–200 nm are easily escaped from the blood into the tumor interstitial space through gaps between discontinuous endothelial cells.

Liposomal drug delivery to tumor is affected by long circulation time, stability (drug retention), and small vesicle size of liposome.

The prolonged circulation achieved by pegylated doxorubicin liposomes (Doxil®, Caelyx®) of size less than 100 nm proved that surface coating of a hydrophilic polymer PEG provides favorable in vivo pharmacokinetic properties. Pegylated liposomes, also known as sterically stabilized or “stealth” liposomes, prevent opsonization, therefore engulfment by mononuclear phagocytes is avoided and prolonged circulation is achieved. Anthracyclines have been encapsulated in different kinds of liposomes and cardio-toxic effects of anthracyclines can be reduced by liposomal biodistribution. Myocet® is a non-pegylated liposomal formulation of doxorubicin and is approved for the treatment of metastatic breast cancer in Europe in combination with Cyclophosphamide. Caelyx® is a pegylated liposomal formulation of Doxorubicin and is approved for the treatment of metastatic breast cancer, Kaposi’s sarcoma, and refractory ovarian cancer in Europe and U.S.

Developed systems have demonstrated highly specific binding and internalization into the mammary epithelial cells that overexpress the human epidermal growth factor receptor 2 (HER-2). Antibody conjugated liposomes delivered 22-fold greater concentration of calcein to the mammary epithelial cells compared to the conventional approach. Combined delivery of quercetin and vincristine via liposomal delivery has been delivered for enhanced estrogen-receptor-negative breast cancer treatment. Studies demonstrated that synergistic effect of both encapsulated chemotherapeutic drugs. Recently, ligand (ATN-161 (N-acetyl-proline-histidine-serine-cysteine-asparagine-amide, PHSCN) of integrin receptor has been synthesized and their targeting potential was determined on human umbilical vein endothelial cells and breast cancer cells. After study it is revealed that liposomal conjugated PHSCN demonstrated significantly enhanced cell uptake and cytotoxicity of doxorubicin on both cell lines, due to the integrin-mediated endocytosis. Topotecan encapsulated liposomes have been prepared using transmembrane gradients of triethylammonium salts of polyphosphate or sucrose octasulfate. Studies revealed that in vivo circulation and uptake of topotecan encapsulated liposomal was significantly enhanced. Also, anti-EGFR and anti-HER2-immunoliposomal formulations dramatically increased uptake of topotecan compared to conventional liposomal formulation and poorly permeable free topotecan in HER2-overexpressing human breast cancer (BT474) xenografts. Plasmid pcDNA3.1-IP10 loaded cationic liposomes have demonstrated the antitumor and antimetastatic effects in BALB/c mice model with 4T1 breast cancer. Plasmid complexed liposomal systems significantly inhibited the growth of tumors and also formation of lung metastasis neoplasm. PE38KDEL-loaded anti-HER2 PEGylated liposomes have been developed by incorporation of pyridylthiopropionylamino-PEG-distearoylphosphatidylethanolamine into thiolated PEGylated liposomes. Flow cytometry and confocal microscopy have shown that PE-HER-liposomes possessed receptor-specific binding and internalization for HER2-overexpressing SK-BR3 cells and were more cytotoxic than non-targeted PE-liposomes in HER2-overexpressing breast cancer cells. Nanoliposomal short-chain ceramide inhibits agonist-dependent translocation of neurotensin receptor 1 (NTSR1) to structured membrane microdomains in breast cancer cells. Generally, it reduces NTSR1 interaction with Galphaq/11 subunits within structured membrane microdomains, consistent with diminished NTS-induced translocation of NTSR1 into membrane microdomains. Ceramide-based liposomal formulations have the potential to inhibit NTS-dependent breast cancer progression.

## ***DENDRIMERS***

Dendrimers are highly branched molecules having size range 1–15 nm with a well-defined core, an interior region, and a large number of terminal groups. Dendrimers contain three different regions: core, branches, and surface. The monodispersity, water solubility, encapsulation ability, and a large number of functionalizable peripheral groups of dendrimers makes an ideal carrier for drug delivery.

There are three architectural domains in dendrimers:

- (i) the core of the dendrimer
- (ii) that is attached by branch cell layers, i.e. dendrons
- (iii) having the multivalent surface with larger number of reactive sites.

Because of the presence of unimolecular structures, dendrimer-drug conjugates are more stable, easy to formulate and sterilize as compared to liposomes and micelles. The ability to get attach to cell-specific targeting groups, solubility modifiers, stealth moieties and imaging tags in a well controlled manner on a dendritic surface differentiates dendrimers from other drug delivery carriers such as micelles, liposomes, and emulsion droplets. In dendrimers, the drug may be covalently attached to the periphery of the dendrimer to form dendrimer prodrugs or the drug may be attached to the outer functional groups by ionic interactions or the drug may be encapsulated through the formation of a dendrimer-drug supramolecular assembly as like a unimolecular micelle. In 1990, Lauterbur demonstrated the first *in vivo* diagnostic imaging applications using dendrimer-based MRI contrast agents. Wiener et al. reported the first *in vivo* "cell-specific active targeting" with dendrimers against breast cancer. To treat of breast carcinoma with overexpression of tumour neovasculatures, PAMAM dendrimers modified with vascular endothelial growth factor could be targeted.

Polypropylenimine based dendrimers have been developed for delivering of 31 nt triplex-forming oligonucleotide (ODN) in breast, prostate, and ovarian cancer cell lines. Dendrimers enhanced the uptake of ODN by approximately 14-fold in MDAMB-231 breast cancer cells. A biocompatible polyester dendrimer composed of the natural metabolites, glycerol and succinic acid has been developed for the encapsulation of camptothecins, and their derivatives. Cellular uptake and efflux measurements in MCF-7 cells have shown an increase of 16-fold for cellular uptake and an increase in drug retention within the cell when using the dendrimer vehicle. Magnetic nanoparticles (MNP) have been modified with different generations of polyamidoamine (PAMAM) dendrimers and complexed with antisense survivin oligodeoxynucleotide (asODN). AsODN-dendrimer-MNP composites showed better uptake of ODNs into cancer cells that may caused marked down-regulation of the survivin gene and protein and have potential applications in cancer therapy and molecular imaging diagnosis. Surface modified 1,3,5-tris(3-aminopropyl)benzene dendrimers have been developed using amino acids like phenylalanine (Phe), methionine (Met), aspartic acid (Asp), and diaminopropionic acid (Dap). Developed systems provide better stability against proteolytic enzymes and deliver the therapeutic molecules into cytosol of MCF-7 cells. Studies have revealed that cellular uptake of the dendrimers into the MCF-7 cells is depended on surface modification (Phe>Met unmodified>>Dap=Asp) and the generations (G(0)>G(1)). A 4<sup>th</sup> generation polyamidoamine dendrimers loaded with vascular endothelial growth factor antisense oligodeoxynucleotide (G4PAMAM/VEGFASODN) has been developed for the inhibition of site specific mRNA of breast cancer cells and vascular endothelial cells. Developed dendrimer complex is about 10 nm in diameter with high buffering capacity have showed high trasfection efficiency without any cytotoxicity.

## **MICELLES**

Polymer micelles have been widely used for delivery of hydrophobic drugs into cells and tumors. Polymeric micelles have been utilized to increase the accumulation of drugs in tumor tissues via enhanced permeability and retention effect and to incorporate various kinds of drugs into the inner core by chemical conjugation or physical entrapment with relatively high stability. Recently, multifunctional block copolymer micelles for the delivery of <sup>111</sup>In have been prepared from MePEG(2500)-b-PCL(1200) and <sup>111</sup>In-DTPA-PEG (3000)-b-PCL(1600) with or without hEGF-PEG(2900)-b-PCL(1400) (<sup>111</sup>In-hEGF-BCMs or <sup>111</sup>In-BCMs). Studies demonstrated that <sup>111</sup>In-hEGF- block copolymer micelles were significantly bound, internalized, and transported to the nuclei of EGFR-positive BC cells. It can be considered as promising delivery system for targeted radiotherapy of breast cancer. Diblock copolymers of methoxy poly(ethylene glycol)-block-poly(delta-valerolactone) have utilized for conjugation of epidermal growth factor (EGF) for targeted delivery to EGF receptor over expressing cancer cells. Developed polymeric miceller systems were nanometric in size (below 45 nm) with prolonged release of anticancer drugs. Ligand anchored targeted micelles have revealed nuclear-specific localized delivery in the perinuclear region with higher cell uptake to EGFR-overexpressing cancers .

**VARIOUS APPROACHES FOR TARGETING BREAST CANCER**

Some specific molecular targets having significant role in breast cancer proliferation are interfered by targeting drugs to achieve higher specificity and minimum toxicity. Various therapeutic targets in breast cancer are HER-2, VEGF (vascular endothelial growth factor), IGFBP-3 (insulin like growth factor binding proteins-3), ER (estrogen receptor), etc. VEGF is responsible for angiogenesis and ER plays an important role in breast cancer by expressing growth factors as a transcription activator. Similarly, HER-2 and IGFBP-3 have important roles in proliferation of breast cancer and so act as targets for treatment of breast cancer. Other approaches such as siRNA may also target breast cancer. Various approaches for targeting breast cancer are shown below table.

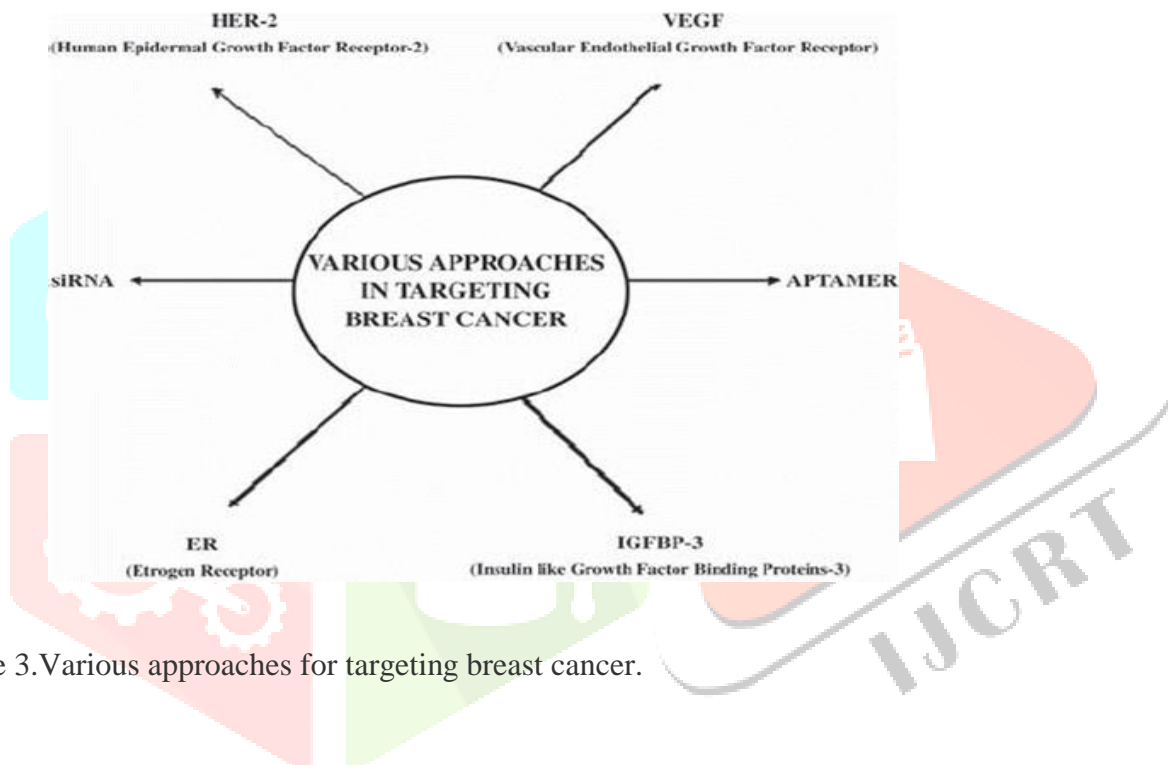


Figure 3. Various approaches for targeting breast cancer.

***HER-2 (Human Epidermal Growth Factor Receptor-2)***

HER-2 impact is observed in 20–25% of all breast cancer patients. So, HER-2 receptor may act as a potential target for HER-2 positive breast cancer. HER-2 is a member of the epidermal growth factor receptor (EGFR) family. EGFR consists of 4 members: EGFR (ErbB1), HER-2 (ErbB2), HER-3 (Erb3) and HER-4 (Erb4). These consist of extracellular ligand-binding region, a transmembrane region, and a cytoplasmic tyrosine-kinase-containing domain. All of these have receptor-specific ligand, except HER-2.

HER-2 in breast cancers has made it a target for breast cancer therapy, such as herceptin and pertuzumab antibodies. Therefore monoclonal antibodies directed against HER-2 offer a strategy for targeted anticancer therapy. The very first approved monoclonal antibody for treatment of HER-2 overexpressing metastasis breast cancer is Trastuzumab. Trastuzumab was approved by the US. FDA in 1998. In clinical studies, it was found that antitumor effect was produced by trastuzumab as a single agent that produces synergistic effect in advanced breast cancer in combination with anthracycline or taxane or chemotherapy. Patients treated with trastuzumab were found to have increased risk for cardiac dysfunction, characterized by symptoms of congestive heart failure.

Seidman et al. (2002) described seven clinical trials with trastuzumab in metastatic breast cancer patients, where the patients received trastuzumab and anthracyclines simultaneously have the greatest incidence of cardiac

dysfunction (27%). This risk in large amount lower patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3–7%).

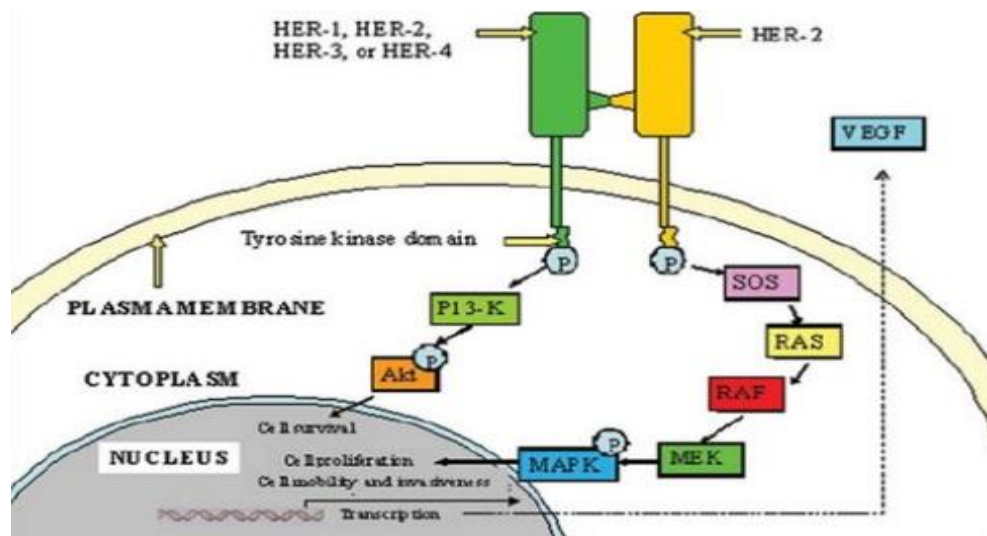


Figure 4. Molecular mechanism underlying HER-2 action in breast cancer.

### ***ER (Estrogen Receptor)***

Estrogen plays a significant role in the development of breast cancer, because it can stimulate the growth of breast tissues by expressing growth factors via the function of estrogen receptor (ER) as a transcription activator. Anti-estrogen therapy has been successful in ER-positive breast cancer therapy targeting ER receptors. Receptors of estrogen are: ER $\alpha$  and ER $\beta$ . ER $\alpha$  is a transcription repressor upon binding of certain antagonists such as tamoxifen. But the patients with advanced breast cancer will develop resistance to tamoxifen after a period of time. By selective estrogen receptor modulators (SERM) or selective estrogen receptor down-regulators (SERD), the targeting effects of estrogen on ER receptor may be blocked at the cellular level. The efficacy of anti-estrogens and aromatase inhibitors is limited because only 60–70% of the breast cancers are ER-positive. As ER-negative breast cancers are more aggressive, other targeted therapies are required.

Other therapies targeting breast cancer like anti-EGFR and anti-ErbB-2/HER-2 can be used in treatment of breast cancer. EGFR and ErbB-2/HER-2 are examples of growth factor signaling molecules that are being targeted for breast cancer. There is “cross-talk” between growth factor and estrogen receptor signaling. EGFR and HER-2 targeting strategies include anti-receptor antibodies and receptor antisense molecules. ER regulation is unrestricted to direct ligand binding but it can also be deviated by other pathways like the epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF1) mitogenic pathways. Activation of these pathways affects ER transcriptional activity either by targeting the receptor directly or regulating the activities of receptor coregulators. PI3K-AKT-mTOR is the major signaling pathway. mTOR is a key kinase downstream of PI3K/AKT, which regulates tumor cell proliferation, growth, survival and angiogenesis. Estrogen binds to the ER, inducing a homodimerization. The receptor pair then acts on DNA and activate genes involved in cell growth.



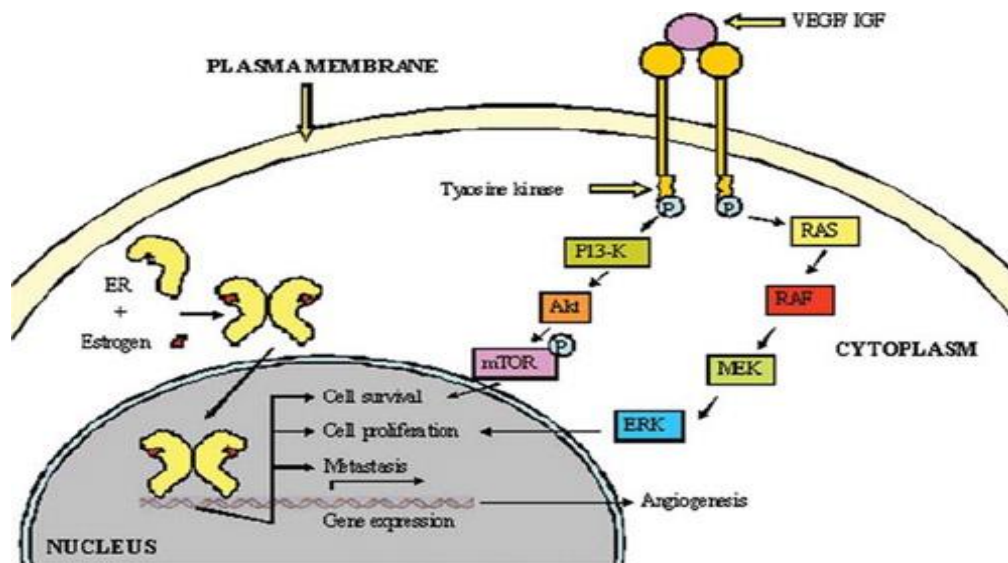


Figure 5. Molecular mechanism underlying VEGF, IGF, and ER in breast cancer

### VEGF (Vascular Endothelial Growth Factor)

VEGF and its receptor have been shown major role and reported as a potential target in breast cancer. The VEGF family and their corresponding receptors are known to play an important role in angiogenesis. Inhibition of VEGF induced angiogenesis significantly inhibits tumor growth in vivo. It has been proposed that a naturally occurring soluble form of VEGFR-1 called sVEGFR-1 may be an important negative regulator of VEGF in breast cancer. In breast cancer patients, notably higher plasma levels of VEGF and lower plasma levels of sVEGFR-1 are found as compared to healthy controls. As VEGF has a critical role in tumor growth and metastasis, the anti-VEGF blocking antibody bevacizumab showed remarkable results in the treatment of metastatic colorectal cancer and also it has recently been approved by the FDA. Recently, bevacizumab has been assessed in Phase III trials of metastatic breast cancer and renal cell carcinoma. Bevacizumab, a humanized monoclonal antibody, acting as an anti-angiogenesis agent against VEGF offers a strategy for targeted therapy against breast cancer. Other targeted therapy includes small-molecule VEGF receptor inhibitors such as PTK787, SU11248, etc.

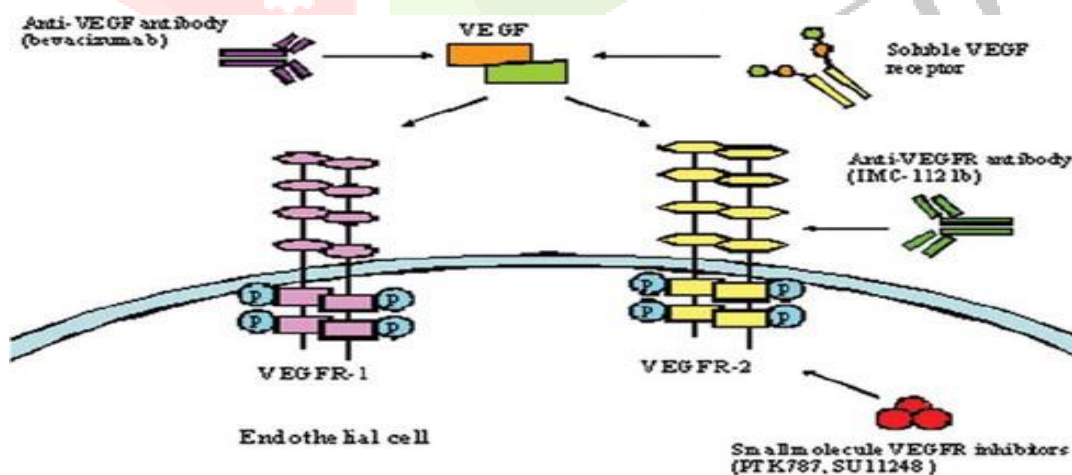


Figure 6. VEGF pathway

### **IGFBP-3 (Insulin-like Growth Factor Binding Proteins-3)**

Members of the insulin-like growth factor (IGF) plays an important role in the occurrence of cancer at various sites, including the breast. The IGF family consists of ligands (IGF-I and IGF-II), receptors (IGF-1R and IGF-2R), and several insulin-like binding proteins (IGFBPs). IGF-I and IGF-II are peptide mitogens in human breast cancer cells. The biological effects of both IGF-I and IGF-II are mediated through IGF-I receptor as IGF-I receptor has a high affinity for ligands. For potentiating IGF-I action, the mechanism may be cell surface binding of IGFBP-3, which facilitates the binding of IGF-I to its receptor. In premenopausal women, the levels of IGF-I and its main binding protein (IGFBP-3) are associated with breast cancer risk. From the recent epidemiologic studies, it is possible that plasma levels of IGF-I are directly associated and those of IGFBP-3 are inversely associated with subsequent risk of breast cancer in premenopausal women.

### **CONCLUSION**

Nanotechnology offers various opportunities to achieve drug targeting with the help of newly discovered breast-cancer-specific targets. Effective targeting would require a better understanding of the target and a development of the targeting system. Nanotechnology provides various nanocarriers, which vary with respect to many properties, such as particle size, shape, charge, and surface modification. Nanocarriers enable the solubilization of substandard soluble anticancer drugs and increasing their bio-availability. Specially designed nanocarriers allow controlled drug release and enhanced permeability and retention effect because of leaky vasculature of cancerous tissue. Specific targeting can be achieved by the attachment of ligand molecules to the carrier surface. The growing field of nanotechnology in combination with advanced molecular biology of cell signaling pathways shows tremendous improvements to the field of breast cancer.

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