

# Development In Nanomedicines Targeting Triple Negative Breast Cancer

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## Abstract

This review covers combination of all aspects from Triple negative breast cancer (TNBC) that were missed by some articles. Most of review study focus on epidemiology and management of disease but rarely on types of formulation used, so by proper awareness about disease and its management, the burden of disease and its ill effect can be reduced. TNBC is one of the most common malignancies in women and girls. It has several therapeutic benefits for treating TNBC. Small scale (nanometric), active and passive targeting, the potential to attach multiple centered on moieties, managed launch, and region-specific centered on are only some of the precise characteristics provided via nanotechnology. The conventional pharmacological therapy, modern-day control techniques, and novel healing modalities for TNBC are the main topics of this evaluate. The treatment of TNBC and breast cancers stem cells with a number of chemotherapeutic agents brought using nanocarriers, including polymeric nanoparticles/micelles, metal/inorganic NPs, and lipid-based totally NPs (Liposome, stable-lipid nanoparticles (SLNs), and nanostructured lipid vendors (NLCs), and so on., has been thoroughly discussed. Additionally, the use of nanomedicine for the remedy of TNBC, which includes the usage of CRISPR nanoparticles, as well as extra molecular goals such poly (ADP-ribose) polymerase (PARP) for in addition research, were discussed.

**Keywords:** Breast Cancer, Nanomedicine, Nanotechnology, TNBC.

## INTRODUCTION

Breast tissue can develop breast cancers, a malignant condition. most usually, emergence occurs from the milk duct, while there are a few rarer conditions wherein it occurs from lobules. Ductal carcinoma refers to most cancers of the ductile vicinity, at the same time as lobular carcinoma refers to most cancers of the mammary lobules [1–3]. The World Health Organization (WHO) reviews that breast cancers are the second one maximum common place sickness in the international. in the U.S.A. and Europe, breast cancer has been located to be the second one foremost purpose of circumstances of life after lung cancers. In plenty much less evolved countries, the is likewise customary [4,5]. TNBCs, additionally known as triple-negative breast cancers, are notion to be the maximum competitive styles of breast cancers and are because of exceptional progesterone, estrogen, and human epidermal growth hormone receptor 2 [6]. TNBCs are commonly first-rate cell expression of progesterone and estrogen receptors of 1% and human epidermal growth receptor 2 amongst zero and 1+, as determined immune histochemistry, consistent with the yank Society of clinical Oncology/university of yankee Pathologists (ASCO/CAP) tips [7]. TNBCs have scientific behavior that is more aggressive than those of different breast cancer subtypes. these tumors also have regular metastatic patterns and a depressing prognosis [8]. TNBCs account for 24% of newly identified breast cancers, and their occurrence has been shown to be gradually growing [9].

### 1. Triple- negative breast cancer (TNBCs)

The most excessive and damaging form of breast cancer, triple-negative breast cancer (TNBC), is characterized by way of the absence of any ER, PR, or HER2 protein and is typically mutated in younger humans [10–12]. It well-known shows aggressive development, a high mitotic index, a high fee or probability of metastasis, a high degree of histology, and relapse those encompass mesenchymal, basal-like immune-suppressed (ER-/PR-/HER2-/IM low), basal-like immune activated (ER-/PR-/HER2-/IM+), mesenchymal stem-like, luminal/androgen receptor (HER2-/PR-/AR+), metaplastic (zero.2-five%), and immunomodulatory [13–15].

### 2. TNBC Histological Classification

Most TNBC is histologically categorized as being of no specific type (IDC-NST) [16]. Pleomorphic cells with suggested nucleoli are the most important form of IDC. The cells are prepared as ductal differentiated diffuse sheets, cords, and nests. The last malignancies are divided into forty-seven wonderful subtypes, together with the least frequent glycogen-rich clear cellular carcinoma, invasive lobular carcinoma, metaplastic carcinoma, medullary carcinoma, mucinous carcinoma, adenoid cystic carcinoma, secretory carcinoma, and acinic cellular carcinoma [17,18].

The glandular factor of metaplastic carcinoma can be partially or completely replaced via one or greater non-glandular component(s). Based totally on their differentiation fame, metaplastic carcinoma is further divided into three kinds: (i) squamous kind (tumor with keratinization and squamous differentiation); (ii) matrix-producing type (tumor with extra cells within the outer edge); and (iii) blended type (tumor with each squamous differentiation and these metaplastic tumors have a distinct pattern of reproduction variety alteration and deliver mutations within the PIK3CA and Wnt (Wingless-kind MMTV Integration website own family) signaling pathway genes [19–21]. An emphasis at the presence of WBCs has led to the identification of TILs and TAMs, that are the parameters defining analysis and therapy for TNBC even though the histological checks were pointing to the lifestyles of WBCs in and surrounding the TNBC subtypes. because of mutations that result in atypical protein expression on the cell membrane, the TNBCs may be immunogenic [22–24]. White blood cells referred to as tumor-infiltrating lymphocytes (TILs) move from the bloodstream to the tumor newly created blood vessels (angiogenesis), which most cancers cells appoint to meet their dietary and oxygen needs [25].

### 3. TNBC Molecular Classification

TNBC is divided into six types: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), luminal androgen receptor (LAR), mesenchymal stem mobile-like (MSL), and mesenchymal (M).

#### 3.1. BL-1 AND BL-2:

The basal subtype is prominent with the aid of the overexpression of DNA harm response and cellular cycle-related genes, and this subtype has a sturdy proliferative capability as a result. Strong expression of the Ki-67 gene is likewise visible within the basal-like subtype, and excessive proliferation is appeared as one in all this subtype's key characteristics [26,27]. The EGFR, MET, NGF, Wnt/-catenin and IGF-1R signaling pathways are abnormally activated within the BL2 subtype, and mTOR inhibitors and growth issue inhibitors (lapatinib, gefitinib, and cetuximab) are promising targeted remedy drugs [26,27].

#### 3.2. M Subtype:

The M subtype, also known as metaplastic breast most cancers, consists of quite activated differentiation pathways (Wnt route, anaplastic lymphoma kinase pathway, and TGF- signaling), extracellular matrix-receptor interplay pathways, and mobile migration-associated signaling pathways (controlled with the aid of actin) [26,27]. The M subtype is vulnerable to growing drug resistance and possesses tissue functions equivalent to sarcomas or squamous epithelial cells. consequently, mTOR inhibitors or medications that target the epithelial-mesenchymal transition may be used to deal with M-subtype patients [28].

#### 3.3. MSL Subtype:

The groupings that Lehmann and Burstein previously called the M and MSL subtypes and the MES subtype are sincerely blanketed inside the mesenchymal-like TNBC subtype. TGF-beta, mTOR, Rac1/Rho, Wnt/beta-catenin, FGFR, PDGFR, and VEGFR signaling pathways are rather expressed in the M and MSL subtypes. Moreover, the EMT procedure and stem cellular-like traits are related to these signaling pathways. Mainly, the MSL subtype and the CL subtype proportion a few molecular traits, together with a sizeable enrichment for EMT markers, immune reaction-related genes, and trends just like most cancers stem cells [29,30].

#### 3.4. IM Subtype:

Tumors classified as IM type, BLIA type, or basal-enriched Genes & Genomics 1 3 with a robust immune reaction and few M2-like macrophages are included inside the IM subtype. The immoderate expression of genes concerned in immune cellular activities is a defining feature of the IM subtype. Immunological mobile signaling, cytokine signaling, antigen presentation, and immune sign transduction pathway (together with NF-B, JAK/STAT, and tumor necrosis element (TNF) signaling) are a number of the enriched gene clusters of the IM subtype. This subtype has prominent lymphocytic infiltrate within the stroma on histologic findings, and medullary characteristics are often seen in addition. [30–32].

#### 3.5. LAR Subtype:

In spite of the truth that the LAR subtype lacks ER, its well-known gene expression traits just like those of the luminal subtype and a mile's better hormone-regulated pathway[30]. This subtype is specialized for steroid biosynthesis, porphyrin metabolism, androgen/estrogen metabolism, as well as the peroxisome proliferator-activated receptor (PPAR) signaling pathway [33]. Although IHC staining indicates that this subtype belongs to the organization, the subtype's gene expression pattern revealed an improved estrogen signaling pathway [30–33].

#### 3.6. NBC AND BRCA:

Most people of BRCA gene mutation sufferers fall into the basal-like subtype category. due to the fact the homologous recombination repair pathway is defective due to BRCA gene mutation, genomic instability develops within the basal-like subtype, the genomic instability characteristics are displayed no matter BRCA gene mutation [30]. it could be deduced that people with the basal-like subtype might also benefit clinically from treatments that concentrate on proliferative tumors primarily based on the specific molecular traits of the basal-like type. patients with the basal-like subtype confirmed a greater PCR price than those with other subtypes, helping this concept [34]. Moreover, restoration outcomes can also additionally result from anti-most cancers medicinal capsules that focus on DNA harm reaction pathways (such as platinum-based chemotherapy and PARP inhibitors).

#### 4. Triple-Negative Breast Cancer Risk Factors and Its Epidemiology

Age, race, genetics, waist-to-hip ratio, breastfeeding practices, and parity all have an impact on the hazard of getting TNBC. The occurrence of breast cancers subtypes interior racial and menopausal subsets, in addition to the relationship among numerous pathological variables and breast cancers-unique survival, had been installation inside the Carolina breast cancers research (1993–1996). Premenopausal African-American women's (39%) as compared with postmenopausal African-American women (14%) and non-African-American women's (sixteen%) of any age had a better prevalence of the basal like breast cancers subtype than did non-African-American women (0.001) the usage of populace-primarily based definitely data from the California most cancers Registry, Bauer et al. diagnosed 6370 women's with TNBC and compared them to 44704 girls with specific breast cancers in terms of age, race/ethnicity, socioeconomic characteristic, degree at diagnosis, tumor grade, and relative survival [35]. Ghanaians had the best occurrence of TNBC (82%), observed through African-people and white Americans, according to a observe that as compared breast cancer patients within the US and Ghana. those variations in occurrence among racial businesses suggest that those women may be predisposed to TNBC with the aid of genes or genetic alterations [36].

#### 5. Epigenetic Modification in TNBC

In several malignancies, which consist of breast cancer, numerous epigenetic changes with diagnostic, prognostic, or healing significance have already been documented [37]. DNA methylation and post-transcriptional modifications of histones are the primary and most considerable epigenetic changes which have been defined and are normally typical [38,39]. Noncoding RNAs (ncRNAs) [37,38], chromatin remodeling [38,39], nucleosome placement, and chromosomal looping are additional more these days defined and stated adjustments.

##### 5.1 Methylation of DNA in TNBC

Based totally on differentially methylated areas (DMRs), one of the most thorough investigations of the TNBC methylome divided affected person information into three methylation clusters [40,41]. The WT1 gene and its antisense counterpart, WT1-AS, are some of the genes tested, and high ranges of methylation for those genes have been associated with excessive levels of expression and negative survival. despite the fact that WT1 and WT1-AS expression is reduced and survival is better while the bidirectional promoter is hypermethylated, those consequences need to be showed on a bigger cohort [41]. within the context of overall hypomethylation, the look at additionally cited that hypermethylation events by and large take area in CpG islands. The regions of human mammary epithelial cells tagged with H3K27me3, a marker of epigenetic silencing, and the hypermethylated regions showed an excessive correlation.

##### 5.2 Role Of Long Non-Coding RNAs in TNBC

**Long non-coding RNAs in TNBC:** By way of combining the profiles of mRNAs and lincRNAs, created a completely unique categorization approach for TNBC. The Lehmann subtypes which have previously been defined have been partially connected with the four clusters that have been diagnosed—IM, LAR, MES, and BLIS—and the BLIS subtype has also been defined as having the most competitive phenotype [42].

**Long non-coding RNAs in Basal-like Breast Cancer:** In MCF-7-TNR cells, the basal-like descendant of the luminal-like MCF-7 cells, a lincRNA known as HOTAIR has been suggested to be elevated. HOTAIR has been associated to aggressive breast cancer progression via H3K27 methylation [43]. When either HOTAIR or EZH2 have become inhibited, the dysregulated expression of luminal-like and basal-like markers end up attenuated, and the proliferation of MCF-7-TNR cells turned into inhibited. This suggests that HOTAIR and its associate enhancing of zeste homolog 2 (EZH2) play an important role in preserving the basal like phenotype (decide 3).

##### 5.3 Role of Micro RNAs in TNBC

Small non-coding RNAs referred to as miRNAs, which are 20 nucleotides lengthy, can post-transcriptionally alter gene expression [44]. A four-miRNA signature in TNBC became discovered by using Gasparini et al. and authorized the category of patients into high-chance and occasional-chance corporations. MiR-30e and miR-27a downregulation was associated with a poorer affected person result, whereas miR-493 and miR-155 upregulation changed into associated with a higher affected person destiny [45]. Additionally cited as capability TNBC indicators are miRNAs. In breast cancer cellular strains, miR-10b, miR-26a, miR-146a, and miR-153 were tested, and they had been linked to BRCA1 expression. BRCA1 expression is suppressed in MDA-MB-231 cells through miR-10b and miR-26a. while miR-153 can upregulate BRCA1 expression in MDA-MB-231 cells, miR-146a is markedly overexpressed in TNBCs without converting BRCA1 expression [46]. MiR-590-5p and miR-4417 have been located to be hyper expressed in TNBC in a have a look at with

the aid through interacting with the two ESR1 mRNA regions, miR-590 could have an impact on ER regulation, whereas miR-4417 can manipulate BRCA1 mRNA [47]. Epithelial-to-mesenchymal transition (EMT), a critical step inside the starting of metastasis, is likewise regulated via miRNAs. A recent take a look at that proven the relationship between epigenetic pathways gave perception into the mechanism that governs their expression in TNBC and affiliation to node metastasis. Low miR-200c expression and lymph node invasion in TNBC are related with miR-200c/miR-141 locus methylation, selling metastasis and converting the analysis for TNBC [48]. The miR-200c/ZEB1 axis has been proposed as an ability healing goal in metastatic TNBC because of its affiliation with excessive degrees of ZEB1 transcription factor, that is involved in EMT.

#### 5.4 Role Of Modification of Histone in TNBC

Eight critical histone changes, inclusive of four TNBCs (MDA-MB-231, MDA-MB-436, MDA-MB468, and HCC1937), had been analyzed throughout 13 mobile strains. those modifications are H3K4me1, H3K4me3, H3K9me3, H3K9ac, H3K27me3, and H3K79me2. Additionally, subtype-particular histone changes profiles, including special H3K36me3 patterns in TNBC cellular strains, have been determined. In MDA-MB-231 and HCC1937 cells, AFAP1-AS1 knockdown small interfering RNA led to reduced proliferation and colony formation [49]. BCL11A, these days characterized transcription element, is crucial for mammary stem and progenitor cells [50] and is overexpressed in TNBCs, along with basal-like subtypes [51]. It promotes tumor formation by interacting with a common subunit (RBBP4/7) of the histone methyltransferase (percent) and histone deacetylase (NuRD, SIN3A) complexes to modify transcription and promote tumorigenesis.

### 6. Current Diagnostic Options For TNBC

Imaging and immune histochemistry (IHC) are typically utilized in a -step technique to discover TNBC [52–54]. A mammography, ultrasound, and magnetic resonance imaging are all examples of imaging [54].

#### 6.1 Mammography:

A mammography best desires a small amount of radiation, that is tough to penetrate breast tissues [55]. at some point of mammography, the presence of calcifications (white spots), growths, or tumors—also called hundreds—determines the analysis of breast maximum cancers [56]. The key trouble is the possibility of false-fine and false-terrible outcomes influencing the path of remedy for the identified patient. Moreover, in excessive-risk people such BRCA gene carriers or people with a circle of relatives document of the disorder, the radiation from mammography aspect consequences also can promote the improvement of breast most cancers [57]. The effectiveness of mammography is operator-mounted, which can have an impact at the imaging effects [58].

#### 6.2 Ultrasound:

When a lump or swelling cannot be seen on a mammography however can still be felt, an ultrasound analysis is made. If a sample is taken from the proper place and tested for most cancers, this diagnosis is the number one technique for differentiating among breast cysts (a fluid-stuffed sac) and tumors. Breast cysts and strong tumors vary in that breast cysts are commonly benign, whereas a solid tumor needs additional confirmation to determine its malignancy [59].

#### 6.3 Magnetic resonance imaging (MRI):

Contrarily, MRI is used to diagnose breast cancer while a patient is deemed to be at excessive hazard (circle of relative's history/BRCA gene mutation) and to assess the severity of the carcinoma because of MRI's advanced capacity to detect breast most cancers in its earliest tiers whilst as compared to breast ultrasound and mammography [60,61]. The most important drawback of MRI is that it could handily verify the presence of breast most cancers and cannot distinguish among wonderful forms of breasts maximum cancers [62].

### 7. Triple-Negative Breast Cancer Treatment Availability

Anthracyclines, taxanes, and/or platinum compounds are often given as a part of chemotherapy, that is the mainstay of treatment, to interfere with the functioning of cancer cells. due to the fact most, patients do not experience a PCR following chemotherapy, there may be dialogue on the kind of chemotherapy and whether remedy alternatives for exclusive TNBC subtypes ought to alternate. whilst the quantity of TNBC sufferers who reap a PCR has extended whilst platinum compounds had been introduced to conventional remedy [63,64]. Those difficulties have sparked extensive look at to find a hit therapeutic method for TNBCs.

### Exploiting BRCA Status For Targeted Therapy In TNBC Using Poly-ADP Ribose Polymerase Inhibitors (PARPi).

Currently, PARP inhibition has drawn loads of interest as a likely effective intention for treating cancers with BRCA1 mutations via a technique referred to as artificial lethality, in which the simultaneous lack of two genes causes cell lack of life however the deletion of both gene by has no effect on cell viability. BRCA1 is every now and then mutated in sporadic TNBCs, even though a few TNBC patients display a pattern like that of a BRCA1 mutation provider whilst BRCA1 is inactivated in some other manner [65,66]. Cancers or cell lines with BRCA1 or BRCA2 mutations or inactivation have bad HR and must rely upon the PARP1-required opportunity non-homologous quit-joining (alt-NHEJ) and base excision restore (BER) pathways for DNA harm restore. As a result, cells in BRCA poor tumors which have PARP1 inhibition are

not able to repair their DNA and are forced to go through apoptosis. for you to higher in shape patients with these drug treatments, tests have been devised to assess the HR popularity of malignancies [67–70].

**Refined Expression Signatures Suggest Novel Molecular Targets in TNBC:** A modest range of potentially druggable targets were evaluated in each cellular lines and preclinical models because of massive-scale gene silencing the usage of small interfering RNAs (siRNAs) and/or quick hairpin RNAs (shRNAs) in breast cancer mobile line models [71]. As an example, mobile cycle checkpoint manipulates and mitogenesis [group 1: checkpoint kinase 1 (CHK1), budding uninhibited by benzimidazoles 1 (BUB1), monopolar spindle 1-like 1 (MPS1/TTK), and adenylate kinase 2 (AK2)] were separated into four awesome clusters of kinases [72].

**Proteomics-Based Breast Cancer Classifiers and Novel Therapeutic Target Identification:** Extensively, a recent look at that mixed RPPA and mRNA expression information from TCGA to map transcription factors (TFs) controlling gene expression styles in breast cancer subtypes identified unique TFs that regulate oncogenic signaling networks in basal-like breast most cancers and highlighted capacity drug targets within those networks [73]. We lately pronounced overexpression and activation of a non-canonical MAPK signaling pathway involving mitogen-activated protein kinase 7 (MAPK7/ERK5), which, along with warmth surprise protein 90 (HSP90) inhibition, supplied a capability therapeutic alternative in TNBCs [74]. This turned into carried out by way of profiling the kinome and related signaling molecules in TNBCs. due to the fact TNBC tumors had higher stages of several kineme signaling molecules implicated in boom, focal adhesion, stress signaling, and protein folding, these molecules can be useful as objectives.

**RTKs and Non-RTK Signaling Targets in TNBC:** In addition, several studies have located regular signaling molecules, RTKs, which might be frequently improved during tumors and can be usable targets in TNBCs . RTKs serve critical roles in both autocrine and paracrine mobile-to-cellular conversation and are vital elements of sign transduction pathways. RTKs adjust mobile improvement and metabolism, manage cell proliferation and differentiation, and promote cell survival and dying [75,76].

## 8. Constraints in TNBC Therapy

TNBCs make up an incredibly tiny proportion of breast cancer diagnoses, yet they're disproportionately answerable for affected person mortality. at the least four molecularly distinct subtypes of TNBCs were discovered through sizeable genomic and proteomic analyses, and they have made it feasible to pick out putative objectives unique to every subtype, supporting the encouragement of preclinical trials with novel remedies [77]. Oncogenes and other "sickness-associated" genes are regularly an aspect of larger networks; for this reason, it can be beneficial to target the close by proteins in the network to disrupt their signaling without inflicting drug resistance [78].

## 9. Nanomedicine in Triple-Negative Breast Cancer: Current Status

Numerous strategies for imaging, tracking, diagnosing, and handing over chemotherapy medicines to the tumor website are made feasible by using nanotechnology. Nanoparticles can go organic barriers and aid inside the transport of medicinal drugs with elevated efficacy and reduced toxicity, which improves anticancer interest. Engineering, molecular biology, remedy, material science, and data technology are all blended in nanomedicine. The software of nanoscience to medicine makes it possible to look at the biological gadget more thoroughly and allows to understand the numerous mechanisms at play.

## 10. Organic Material Based Nanomedicines

### 10.1 Lipid Based Nanomedicines:

Lipid-based totally nanomedicines may also enhance remedy shipping to tumor tissue, lessen facet outcomes, and useful resource within the reversal of multidrug resistance, in line with certain theories [79]. One-of-a-kind varieties of materials may be used to create lipid-based colloids, which have a spread of healing and diagnostic makes use of within the observe of most cancers. when formed as nanostructured lipid companies (NLCs), self-micro/nano emulsified drug delivery systems (SMEDDS/SNEDDS), and many others., they've benefits like biodegradability, biocompatibility, and targeting [80].

### 10.2 Liposomes:

First said in 1964 [81], liposomes are a type of round, closed vesicles crafted from a membrane lipid bilayer and an aqueous inner center. Gregoriadis et al. posted the first have a have a look at the utilization of liposomes in 1971 [82]. Hydrophobic medicinal drugs may be contained inside the lipid bilayer of liposomes, which may be generally 50–a hundred nm in length, on the same time as hydrophilic prescribed drugs, genes, and siRNA (small interfering RNA) may be contained within the aqueous center. Decreased systemic toxicity, longer circulate instances, biocompatibility, and a low incidence of identification and next clearance with the aid of the reticuloendothelial gadget are all benefits of liposomes [82–84]. The first FDA-widely wide-spread nanomedicine become DOX loaded PEGylated liposomes (Doxil). Doxil is typically used to deal with ovarian most cancers, Kaposi sarcoma, and refractory breast cancers [85]. Under segment II trials, a liposomal method of the anthraquinone spinoff mitoxantrone hydrochloride became clinically tested for the remedy of metastatic or recurrent BC. patients received an intravenous injection of this liposome to govern or lessen the progression of BC and lower the danger.

### 10.3 Solid Lipid Nanomaterials

Expanded effectiveness towards MCF-7 and MCF 10-A cells became visible in SLNs containing tamoxifen citrate and camptothecin [86]. whilst in comparison to the single drug, cytotoxicity, cell uptake, and SLN retention had been all higher. SK-OV3 cellular lines and their multi-drug resistance variations had been also said to be objectives of NLCs encapsulating DOX and PTX [87].

### 10.4 Nanostructured Lipid Carriers

Quercetin-loaded NLCs have been created with the aid of [88] the usage of soy lecithin, glyceryl tridecanate, glyceryl tripalmitate, and Kolliphor HS15. considering that quercetin has a low oral bioavailability, placing it onto NLCs solves the solubility troubles. In MCF-7 and MDA-MB-231 cells, the entrapment performance was stated to be 95%, and quercetin's prolonged launch promoted powerful mobile demise [89].

### 10.5 Self Micro-Emulsifying Drug Delivery System

Self-emulsified drug shipping systems have the wonderful gain of making quite lipophilic medicines greater soluble via a factor of a couple of. One such example turned into the coaching and trying out of DTX-loaded SMEDDS to decide their effectiveness in opposition to breast most cancers cells. SMEDDS containing DOX and LyP-1 confirmed behind schedule metastasis and tumor boom. studies on the in-vitro cytotoxicity of p32-expressing BC cells, 4T1 cellular strains brought about a vast amount of mobile death. Malignant BC cells have excessive LyP-1 expression tiers, that's a selected peptide for the p32 receptor [90].

## 11. Polymer Based Nanoparticles

### 11.1 Polymeric Micelles:

Amphiphilic block copolymers are assembled into center-shell systems in aqueous conditions to shape polymeric micelles, that are supramolecular delivery systems. The polymer micelle, which has a semi-strong hydrophobic middle product of biodegradable polymers like poly(L-lactide), poly(-caprolactone), and PLGA and has a diameter of 10 to a hundred nm, is perfect for assisting some of water-insoluble chemotherapies [91]. Polymer micelles had been created via to defend the medication from phagocyte aggregation and degradation [92]. The artificial PTX micelles (Genexol-PM) confirmed more advantageous healing consequences when used to deal with metastatic BC [93]. used methoxyl poly (ethylene glycol)-poly (d, L-lactide) copolymer micelles to study the results of resveratrol (RES) and DTX in mixture on MCF-7 cells. The simultaneous management of each medicines discovered capability synergism in breast cancer cells.

### 11.2 Polymeric Nanoparticles:

An incredible gain of polymeric nanoparticles are their biocompatibility. A DNA hypermethylation inhibitor called Decitabine (DAC) became encapsulated in PEG-NPs by using [94], which stepped forward the reaction to chemotherapy and assisted BCSCs and MDA-MB-231 cells in overcoming drug resistance. Salinomycin and PTX had been added synergistically into the BCSCs the use of poly (d, L-lactide-co-glycolide)/hyaluronic acid-based totally self-assembled block copolymer nanocarriers. Hyaluronic acid showed improved in-vitro pastime and complements drug absorption by way of CD44+ receptors. comparable systems encasing sulforaphane (SFN), a -catenin inhibitor, gradual down BCSCs' potential to self-renew. Through the use of photodynamic action, the multifunctional core-shell nanomedicine can restriction the unfold of malignancies on the equal time as increasing cytotoxicity. Malarvizhi et al. announced the advent of middle-shell nanomedicine, which consists of PLGA nanocore encapsulating Dasatinib (a tyrosine kinase inhibitor) with 20 nm of particle diameter and albumin nano shell encapsulating m-tetra (hydroxyphenyl)chlorin (mTHPC) as a photosensitizer [95, 106].

### 11.3 Dendrimers:

Dendrimers are of interest as nanocarrier primarily based systems in most cancers chemotherapy, especially through ligand or receptor-mediated endocytosis, as it offers many benefits over traditional therapy through introducing concentrated on houses. With a diameter starting from 2 to ten nm, dendrimers have a definitely described, homogenous, and monodisperse high branching nanoscale symmetrical structure. they're the ideal vendors for the centered transport of therapeutic and diagnostic materials because they possess unique characteristics [96]. Focused on the MDR1 gene, that is liable for the development of drug resistance in MCF-7 cells, is achieved the use of PAMAM dendrimers which have been loaded with beneficial siRNA. Dendriplexes, a nano complex referred called PAMAM-siMDR1 complex, were created via phospholipid (PL) exchange. This mixture confirmed exceptional gene silencing, increased siMDR1 uptake, reduced P-gp expression, and for this reason accelerated cell DOX accumulation [97].

## 12. Inorganic Based Nanoparticles

### 12.1 Metallic Nanoparticles:

The steel-primarily based NPs offer exquisite flexibility in medication shipping and diagnostic applications further to polymeric NPs. Gold nanoparticles loaded with DOX were created by means of sun et al. to greater correctly deal with cancer through delivering the drugs to BCSCs [98]. The take a look at concerned the rational design of DOX-tethered gold NPs with PEG and an acid-labile hydrazine bond, which has a bigger functionality to move DOX to BCSCs and to lessen mammosphere formation and most cancers initiation interest through P-gp efflux evasion mechanism. even as

compared to the manage organization and the group that received best free DOX, this nanocarrier displayed tumor quantity reductions of 32 and 18 instances, respectively.

**12.2 Silver Nanoparticles:** In keeping with Ghosh et al., GSTE became used to create silver nanoparticles (AgNPs). The cytotoxicity of MCF-7 cells was proven to be increased by using each AgNPs [99]. Gloriosa superba leaf extract with AgNPs changed into created synthetically by Muthukrishnan et al. and examined against DLA tumor cells [100]. thus, the investigations confirmed that NPs were an eco-friendly way to supply potential active medicines in opposition to TNBC.

### 13. Carbon Based Nanomedicines

#### 13.1 Carbon Nanotubes:

Researchers had been intrigued with the aid of carbon nanomaterials inclusive of carbon nanotubes (CNTs), fullerenes, and graphene because of their biocompatibility, adaptable chemical functionalization, green drug delivery approach, and stable physio-chemical residences. latest research has validated that these materials can be employed for both regulated healing drug management and as assessment sellers for tumor imaging, diagnosis, and medicine localization. in line with Fiorillo et al., BCSCs are greater amenable to graphene oxide-based carbon nanotube remedy and have a higher ability for targeting them [101].

#### 13.2 Fullerenes:

To discover and remedy cancer, fullerenes will have imaging sellers and chemotherapeutics functionalized on their surfaces [102]. first-rate fluorescence and smooth in-vitro penetration of BC cells (MCF-7) are each feature of the amine-functionalized fullerene nanocarrier [103].

#### 13.3 Graphene Nanospheres:

Advanced carboxyl functionalized graphene as a likely imaging agent of tumors in deep tissue the usage of a non-invasive method that turned into non-poisonous to the tumor cells but showed stepped forward cellular uptake through mixture photodynamic and photo-thermal outcomes [104,105].

### 14. Advanced Nanotherapeutics In TNBC

#### 14.1 CRISPR/CAS9:

Drug resistance is an enormous barrier to BC therapy, in keeping with clinical proof. The elevated mortality and recurrence charges in cancer sufferers are because of this chemo resistance. A trade inside the genetic make-up of tumor cells is frequently one issue that contributes to the development of remedy resistance. The Clustered regularly interspaced quick palindromic repeats (CRISPR)/related (Cas9) generation, which may be beneficial in overcoming drug resistance, has these days been advanced genome modifying is getting interest. Drug-resistant breast most cancers therapy is substantially aided by using CRISPR/Cas9 because it reverses genetic abnormalities and identifies potential goal regions for BC that can be using drug resistance [106].

## CONCLUSION

Main improvements in the detection and treatment of both hormone-tremendous and hormone-bad BC are made possible by using nanomedicine. The disease is presently being dealt with the usage of a diffusion of nanoparticle-primarily based formulations that integrate therapeutic pills, molecular concentrated on, and imaging competencies. these formulations are the subsequent-technology TNBC therapeutics. To growth the focused-on effectiveness, NPs are coupled with an inhibitor of the cell signaling pathway. these days, techniques for developing nanomedicine the use of green chemistry also are being investigated. PtNPs and PdNPs showed strong anticancer interest towards MCF-7 cells and are utilized in photothermal therapy and remedy delivery. both progressive medicinal medicines and diagnostic tools can be made from carbon nanostructures. Based medicinal drug distribution to cancer cells is more impacted by manner of BisBAL NPs than transport to non-cancerous cells. MSNs have transformed the medication delivery enterprise and are also utilized for targeted therapy. there are numerous unique forms of recovery compounds which have been diagnosed as sturdy TNBC inhibitors, but there can be no evidence in the literature that the ones drug treatments are being investigated as nanomedicine. destiny tendencies in nanomedicine for treatment of TNBC will certainly gain from a deeper information of organic methods and nanotechnology upgrades.

## REFERENCES:

1. Almansour NM. Triple-Negative Breast Cancer: A Brief Review About Epidemiology, Risk Factors, Signaling Pathways, Treatment and Role of Artificial Intelligence. *Front Mol Biosci* 2022;9. <https://doi.org/10.3389/fmolb.2022.836417>.
2. Medina MA, Oza G, Sharma A, Arriaga LG, Hernández Hernández JM, Rotello VM, et al. Triple-Negative Breast Cancer: A Review of Conventional and Advanced Therapeutic Strategies. *Int J Environ Res Public Health* 2020;17:2078. <https://doi.org/10.3390/ijerph17062078>.
3. Muneer I, Ahmad S, Naz A, Abbasi SW, Alblihy A, Aloliqi AA, et al. Discovery of Novel Inhibitors From Medicinal Plants for V-Domain Ig Suppressor of T-Cell Activation. *Front Mol Biosci* 2021;8. <https://doi.org/10.3389/fmolb.2021.716735>.
4. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and Mortality and Epidemiology of Breast Cancer in the World. *Asian Pacific Journal of Cancer Prevention* 2016;17:43–6. <https://doi.org/10.7314/APJCP.2016.17.S3.43>.

5. Suleman M, Tahir ul Qamar M, Saleem S, Ahmad S, Ali SS, Khan H, et al. Mutational Landscape of Pirin and Elucidation of the Impact of Most Detrimental Missense Variants That Accelerate the Breast Cancer Pathways: A Computational Modelling Study. *Front Mol Biosci* 2021;8. <https://doi.org/10.3389/fmolb.2021.692835>.
6. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nat Rev Clin Oncol* 2016;13:674–90. <https://doi.org/10.1038/nrclinonc.2016.66>.
7. Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *Arch Pathol Lab Med* 2014;138:241–56. <https://doi.org/10.5858/arpa.2013-0953-SA>.
8. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. *Clinical Cancer Research* 2007;13:4429–34. <https://doi.org/10.1158/1078-0432.CCR-06-3045>.
9. Tsai J, Bertoni D, Hernandez-Boussard T, Telli ML, Wapnir IL. Lymph Node Ratio Analysis After Neoadjuvant Chemotherapy is Prognostic in Hormone Receptor-Positive and Triple-Negative Breast Cancer. *Ann Surg Oncol* 2016;23:3310–6. <https://doi.org/10.1245/s10434-016-5319-8>.
10. Farheen J, Hosmane NS, Zhao R, Zhao Q, Iqbal MZ, Kong X. Nanomaterial-assisted CRISPR gene-engineering – A hallmark for triple-negative breast cancer therapeutics advancement. *Mater Today Bio* 2022;16:100450. <https://doi.org/10.1016/j.mtbio.2022.100450>.
11. Dai J, Cimino PJ, Gouin KH, Grzelak CA, Barrett A, Lim AR, et al. Astrocytic laminin-211 drives disseminated breast tumor cell dormancy in brain. *Nat Cancer* 2021;3:25–42. <https://doi.org/10.1038/s43018-021-00297-3>.
12. Xu P, Xiong W, Lin Y, Fan L, Pan H, Li Y. Histone deacetylase 2 knockout suppresses immune escape of triple-negative breast cancer cells via downregulating PD-L1 expression. *Cell Death Dis* 2021;12:779. <https://doi.org/10.1038/s41419-021-04047-2>.
13. Huang Y, Zhang H-L, Li Z-L, Du T, Chen Y-H, Wang Y, et al. FUT8-mediated aberrant N-glycosylation of B7H3 suppresses the immune response in triple-negative breast cancer. *Nat Commun* 2021;12:2672. <https://doi.org/10.1038/s41467-021-22618-x>.
14. Djomehri SI, Gonzalez ME, da Veiga Leprevost F, Tekula SR, Chang H-Y, White MJ, et al. Quantitative proteomic landscape of metaplastic breast carcinoma pathological subtypes and their relationship to triple-negative tumors. *Nat Commun* 2020;11:1723. <https://doi.org/10.1038/s41467-020-15283-z>.
15. Dai M, Yan G, Wang N, Daliah G, Edick AM, Poulet S, et al. In vivo genome-wide CRISPR screen reveals breast cancer vulnerabilities and synergistic mTOR/Hippo targeted combination therapy. *Nat Commun* 2021;12:3055. <https://doi.org/10.1038/s41467-021-23316-4>.
16. Weigelt B, Reis-Filho JS. Histological and molecular types of breast cancer: is there a unifying taxonomy? *Nat Rev Clin Oncol* 2009;6:718–30. <https://doi.org/10.1038/nrclinonc.2009.166>.
17. Malhotra GK, Zhao X, Band H, Band V. Histological, molecular and functional subtypes of breast cancers. *Cancer Biol Ther* 2010;10:955–60. <https://doi.org/10.4161/cbt.10.10.13879>.
18. Balkenhol MCA, Vreuls W, Wauters CAP, Mol SJJ, van der Laak JAWM, Bult P. Histological subtypes in triple negative breast cancer are associated with specific information on survival. *Ann Diagn Pathol* 2020;46:151490. <https://doi.org/10.1016/j.anndiagpath.2020.151490>.
19. Geyer FC, Weigelt B, Natrajan R, Lambros MB, de Biase D, Vatcheva R, et al. Molecular analysis reveals a genetic basis for the phenotypic diversity of metaplastic breast carcinomas. *J Pathol* 2010;220:562–73. <https://doi.org/10.1002/path.2675>.
20. Hennessy BT, Gonzalez-Angulo A-M, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee J-S, et al. Characterization of a Naturally Occurring Breast Cancer Subset Enriched in Epithelial-to-Mesenchymal Transition and Stem Cell Characteristics. *Cancer Res* 2009;69:4116–24. <https://doi.org/10.1158/0008-5472.CAN-08-3441>.
21. Hayes MJ, Thomas D, Emmons A, Giordano TJ, Kleer CG. Genetic Changes of Wnt Pathway Genes Are Common Events in Metaplastic Carcinomas of the Breast. *Clinical Cancer Research* 2008;14:4038–44. <https://doi.org/10.1158/1078-0432.CCR-07-4379>.
22. Kuroda H, Sakamoto G, Ohnisi K, Itoyama S. Clinical and pathological features of glycogen-rich clear cell carcinoma of the breast. *Breast Cancer* 2005;12:189–95. <https://doi.org/10.2325/jbcs.12.189>.
23. Geyer FC, Pareja F, Weigelt B, Rakha E, Ellis IO, Schnitt SJ, et al. The Spectrum of Triple-Negative Breast Disease. *Am J Pathol* 2017;187:2139–51. <https://doi.org/10.1016/j.ajpath.2017.03.016>.
24. Degnim AC, Brahmabhatt RD, Radisky DC, Hoskin TL, Stallings-Mann M, Laudenschlager M, et al. Immune cell quantitation in normal breast tissue lobules with and without lobulitis. *Breast Cancer Res Treat* 2014;144:539–49. <https://doi.org/10.1007/s10549-014-2896-8>.
25. Aaltomaa S, Lipponen P, Eskelinen M, Kosma V-M, Marin S, Alhava E, et al. Lymphocyte infiltrates as a prognostic variable in female breast cancer. *Eur J Cancer* 1992;28:859–64. [https://doi.org/10.1016/0959-8049\(92\)90134-N](https://doi.org/10.1016/0959-8049(92)90134-N).
26. Yin L, Duan J-J, Bian X-W, Yu S. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Research* 2020;22:61. <https://doi.org/10.1186/s13058-020-01296-5>.
27. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. *J Pathol* 2014;232:142–50. <https://doi.org/10.1002/path.4280>.
28. Gibson GR, Qian D, Ku JK, Lai LL. Metaplastic breast cancer: clinical features and outcomes. *Am Surg* 2005;71:725–30.
29. Lee Y-M, Oh MH, Go J-H, Han K, Choi S-Y. Molecular subtypes of triple-negative breast cancer: understanding of subtype categories and clinical implication. *Genes Genomics* 2020;42:1381–7. <https://doi.org/10.1007/s13258-020-01014-7>.
30. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *Journal of Clinical Investigation* 2011;121:2750–67. <https://doi.org/10.1172/JCI45014>.
31. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SAW, et al. Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-Negative Breast Cancer. *Clinical Cancer Research* 2015;21:1688–98. <https://doi.org/10.1158/1078-0432.CCR-14-0432>.
32. Jézéquel P, Loussouarn D, Guérin-Charbonnel C, Campion L, Vanier A, Gouraud W, et al. Gene-expression molecular subtyping of triple-negative breast cancer tumours: importance of immune response. *Breast Cancer Research* 2015;17:43. <https://doi.org/10.1186/s13058-015-0550-y>.
33. Liu Y-R, Jiang Y-Z, Xu X-E, Yu K-D, Jin X, Hu X, et al. Comprehensive transcriptome analysis identifies novel molecular subtypes and subtype-specific RNAs of triple-negative breast cancer. *Breast Cancer Research* 2016;18:33. <https://doi.org/10.1186/s13058-016-0690-8>.
34. Yin L, Duan J-J, Bian X-W, Yu S. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Research* 2020;22:61. <https://doi.org/10.1186/s13058-020-01296-5>.
35. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. *Cancer* 2007;109:1721–8. <https://doi.org/10.1002/cncr.22618>.
36. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, Takyi V, et al. African ancestry and higher prevalence of triple-negative breast cancer. *Cancer* 2010;116:4926–32. <https://doi.org/10.1002/cncr.25276>.
37. Millikan RC, Newman B, Tse C-K, Moorman PG, Conway K, Smith L v., et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008;109:123–39. <https://doi.org/10.1007/s10549-007-9632-6>.
38. Kanwal R, Gupta K, Gupta S. *Cancer Epigenetics: An Introduction*, 2015, p. 3–25. [https://doi.org/10.1007/978-1-4939-1804-1\\_1](https://doi.org/10.1007/978-1-4939-1804-1_1).
39. Basse C, Arock M. The increasing roles of epigenetics in breast cancer: Implications for pathogenicity, biomarkers, prevention and treatment. *Int J Cancer* 2015;137:2785–94. <https://doi.org/10.1002/ijc.29347>.
40. Temian DC, Pop LA, Irimie AI, Berindan-Neagoe I. The Epigenetics of Triple-Negative and Basal-Like Breast Cancer: Current Knowledge. *J Breast Cancer* 2018;21:233. <https://doi.org/10.4048/jbc.2018.21.e41>.
41. Stirzaker C, Zotenko E, Song JZ, Qu W, Nair SS, Locke WJ, et al. Methylome sequencing in triple-negative breast cancer reveals distinct methylation clusters with prognostic value. *Nat Commun* 2015;6:5899. <https://doi.org/10.1038/ncomms6899>.

42. Liu Y-R, Jiang Y-Z, Xu X-E, Yu K-D, Jin X, Hu X, et al. Comprehensive transcriptome analysis identifies novel molecular subtypes and subtype-specific RNAs of triple-negative breast cancer. *Breast Cancer Research* 2016;18:33. <https://doi.org/10.1186/s13058-016-0690-8>.
43. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010;464:1071–6. <https://doi.org/10.1038/nature08975>.
44. Palazzo AF, Lee ES. Non-coding RNA: what is functional and what is junk? *Front Genet* 2015;6. <https://doi.org/10.3389/fgene.2015.00002>.
45. Gasparini P, Cascione L, Fassan M, Lovat F, Guler G, Balci S, et al. microRNA expression profiling identifies a four microRNA signature as a novel diagnostic and prognostic biomarker in triple negative breast cancers. *Oncotarget* 2014;5:1174–84. <https://doi.org/10.18632/oncotarget.1682>.
46. Fkih M'hamed I, Privat M, Ponelle F, Penault-Llorca F, Kenani A, Bignon Y-J. Identification of miR-10b, miR-26a, miR-146a and miR-153 as potential triple-negative breast cancer biomarkers. *Cellular Oncology* 2015;38:433–42. <https://doi.org/10.1007/s13402-015-0239-3>.
47. Murria R, Palanca S, de Juan I, Alenda C, Egoavil C, Seguí FJ, et al. Immunohistochemical, genetic and epigenetic profiles of hereditary and triple negative breast cancers. Relevance in personalized medicine. *Am J Cancer Res* 2015;5:2330–43.
48. Damiano V, Brisotto G, Borgna S, di Gennaro A, Armellini M, Perin T, et al. Epigenetic silencing of miR-200c in breast cancer is associated with aggressiveness and is modulated by ZEB1. *Genes Chromosomes Cancer* 2017;56:147–58. <https://doi.org/10.1002/gcc.22422>.
49. Xi Y, Shi J, Li W, Tanaka K, Allton KL, Richardson D, et al. Histone modification profiling in breast cancer cell lines highlights commonalities and differences among subtypes. *BMC Genomics* 2018;19:150. <https://doi.org/10.1186/s12864-018-4533-0>.
50. Khaled WT, Choon Lee S, Stingl J, Chen X, Raza Ali H, Rueda OM, et al. BCL11A is a triple-negative breast cancer gene with critical functions in stem and progenitor cells. *Nat Commun* 2015;6:5987. <https://doi.org/10.1038/ncomms6987>.
51. Moody RR, Lo M-C, Meagher JL, Lin C-C, Stevens NO, Tinsley SL, et al. Probing the interaction between the histone methyltransferase/deacetylase subunit RBBP4/7 and the transcription factor BCL11A in epigenetic complexes. *Journal of Biological Chemistry* 2018;293:2125–36. <https://doi.org/10.1074/jbc.M117.811463>.
52. Dass SA, Tan KL, Selva Rajan R, Mokhtar NF, Mohd Adzmi ER, Wan Abdul Rahman WF, et al. Triple Negative Breast Cancer: A Review of Present and Future Diagnostic Modalities. *Medicina (B Aires)* 2021;57:62. <https://doi.org/10.3390/medicina57010062>.
53. Penault-Llorca F, Viale G. Pathological and molecular diagnosis of triple-negative breast cancer: a clinical perspective. *Annals of Oncology* 2012;23:vi19–22. <https://doi.org/10.1093/annonc/mds190>.
54. Schoub PK. Understanding indications and defining guidelines for breast magnetic resonance imaging. *South African Journal of Radiology* 2018;22. <https://doi.org/10.4102/sajr.v22i2.1353>.
55. Sechopoulos I, Suryanarayanan S, Vedantham S, D'Orsi CJ, Karellas A. Radiation Dose to Organs and Tissues from Mammography: Monte Carlo and Phantom Study. *Radiology* 2008;246:434–43. <https://doi.org/10.1148/radiol.2462070256>.
56. Gosling S, Scott R, Greenwood C, Bouzy P, Nallala J, Lyburn ID, et al. Calcification Microstructure Reflects Breast Tissue Microenvironment. *J Mammary Gland Biol Neoplasia* 2019;24:333–42. <https://doi.org/10.1007/s10911-019-09441-3>.
57. Pal T, Vadapampil ST. Genetic Risk Assessments in Individuals at High Risk for Inherited Breast Cancer in the Breast Oncology Care Setting. *Cancer Control* 2012;19:255–66. <https://doi.org/10.1177/107327481201900402>.
58. Wengert GJ, Helbich TH, Leithner D, Morris EA, Baltzer PAT, Pinker K. Multimodality Imaging of Breast Parenchymal Density and Correlation with Risk Assessment. *Curr Breast Cancer Rep* 2019;11:23–33. <https://doi.org/10.1007/s12609-019-0302-6>.
59. Berg WA, Sechtin AG, Marques H, Zhang Z. Cystic Breast Masses and the ACRIN 6666 Experience. *Radiol Clin North Am* 2010;48:931–87. <https://doi.org/10.1016/j.rcl.2010.06.007>.
60. Zhang Z. Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk. *JAMA* 2012;307:1394. <https://doi.org/10.1001/jama.2012.388>.
61. Dogan BE, Turnbull LW. Imaging of triple-negative breast cancer. *Annals of Oncology* 2012;23:vi23–9. <https://doi.org/10.1093/annonc/mds191>.
62. Zhou Z, Qutaish M, Han Z, Schur RM, Liu Y, Wilson DL, et al. MRI detection of breast cancer micrometastases with a fibronectin-targeting contrast agent. *Nat Commun* 2015;6:7984. <https://doi.org/10.1038/ncomms8984>.
63. Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric-Bernstam F, et al. Differential Response to Neoadjuvant Chemotherapy Among 7 Triple-Negative Breast Cancer Molecular Subtypes. *Clinical Cancer Research* 2013;19:5533–40. <https://doi.org/10.1158/1078-0432.CCR-13-0799>.
64. Petrelli F, Coiu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2014;144:223–32. <https://doi.org/10.1007/s10549-014-2876-z>.
65. Lips EH, Mulder L, Onk A, van der Kolk LE, Hogervorst FBL, Imholz ALT, et al. Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. *Br J Cancer* 2013;108:2172–7. <https://doi.org/10.1038/bjc.2013.144>.
66. Anders CK, Winer EP, Ford JM, Dent R, Silver DP, Sledge GW, et al. Poly(ADP-Ribose) Polymerase Inhibition: “Targeted” Therapy for Triple-Negative Breast Cancer. *Clinical Cancer Research* 2010;16:4702–10. <https://doi.org/10.1158/1078-0432.CCR-10-0939>.
67. Birkbak NJ, Wang ZC, Kim J-Y, Eklund AC, Li Q, Tian R, et al. Telomeric Allelic Imbalance Indicates Defective DNA Repair and Sensitivity to DNA-Damaging Agents. *Cancer Discov* 2012;2:366–75. <https://doi.org/10.1158/2159-8290.CD-11-0206>.
68. Naipal KAT, Verkaik NS, Ameziane N, van Deurzen CHM, ter Brugge P, Meijers M, et al. Functional *Ex Vivo* Assay to Select Homologous Recombination-Deficient Breast Tumors for PARP Inhibitor Treatment. *Clinical Cancer Research* 2014;20:4816–26. <https://doi.org/10.1158/1078-0432.CCR-14-0571>.
69. Watkins JA, Irshad S, Grigoriadis A, Tutt AN. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. *Breast Cancer Research* 2014;16:211. <https://doi.org/10.1186/bcr3670>.
70. Peng G, Chun-Jen Lin C, Mo W, Dai H, Park Y-Y, Kim SM, et al. Genome-wide transcriptome profiling of homologous recombination DNA repair. *Nat Commun* 2014;5:3361. <https://doi.org/10.1038/ncomms4361>.
71. Xu H, Eirew P, Mullaly SC, Aparicio S. The Omics of Triple-Negative Breast Cancers. *Clin Chem* 2014;60:122–33. <https://doi.org/10.1373/clinchem.2013.207167>.
72. Speers C, Tsimelzon A, Sexton K, Herrick AM, Gutierrez C, Culhane A, et al. Identification of Novel Kinase Targets for the Treatment of Estrogen Receptor-Negative Breast Cancer. *Clinical Cancer Research* 2009;15:6327–40. <https://doi.org/10.1158/1078-0432.CCR-09-1107>.
73. Osmanbeyoglu HU, Pelosoff R, Bromberg JF, Leslie CS. Linking signaling pathways to transcriptional programs in breast cancer. *Genome Res* 2014;24:1869–80. <https://doi.org/10.1101/gr.173039.114>.
74. Al-Ejeh F, Miranda M, Shi W, Simpson PT, Song S, Vargas AC, et al. Kinome profiling reveals breast cancer heterogeneity and identifies targeted therapeutic opportunities for triple negative breast cancer. *Oncotarget* 2014;5:3145–58. <https://doi.org/10.18632/oncotarget.1865>.
75. Zhang J, Hochwald SN. Targeting Receptor Tyrosine Kinases in Solid Tumors. *Surg Oncol Clin N Am* 2013;22:685–703. <https://doi.org/10.1016/j.soc.2013.06.010>.
76. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer* 2004;4:361–70. <https://doi.org/10.1038/nrc1360>.
77. Sandmann T, Boutros M. Screens, maps & networks: from genome sequences to personalized medicine. *Curr Opin Genet Dev* 2012;22:36–44. <https://doi.org/10.1016/j.gde.2012.02.001>.
78. Barabási A-L, Gulbace N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011;12:56–68. <https://doi.org/10.1038/nrg2918>.
79. Miller AD. Lipid-Based Nanoparticles in Cancer Diagnosis and Therapy. *J Drug Deliv* 2013;2013:1–9. <https://doi.org/10.1155/2013/165981>.

80. Fontana G, Maniscalco L, Schillaci D, Cavallaro G, Giammona G. Solid Lipid Nanoparticles Containing Tamoxifen Characterization and *In Vitro* Antitumoral Activity. *Drug Deliv* 2005;12:385–92. <https://doi.org/10.1080/10717540590968855>.
81. Torchilin VP. Liposomes as targetable drug carriers. *Crit Rev Ther Drug Carrier Syst* 1985;2:65–115.
82. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nat Rev Drug Discov* 2005;4:145–60. <https://doi.org/10.1038/nrd1632>.
83. Gurunathan S, Kang M-H, Qasim M, Kim J-H. Nanoparticle-Mediated Combination Therapy: Two-in-One Approach for Cancer. *Int J Mol Sci* 2018;19:3264. <https://doi.org/10.3390/ijms19103264>.
84. Barenholz Y (Chezy). Doxil® — The first FDA-approved nano-drug: Lessons learned. *Journal of Controlled Release* 2012;160:117–34. <https://doi.org/10.1016/j.jconrel.2012.03.020>.
85. Zhang L, Chan JM, Gu FX, Rhee J-W, Wang AZ, Radovic-Moreno AF, et al. Self-Assembled Lipid–Polymer Hybrid Nanoparticles: A Robust Drug Delivery Platform. *ACS Nano* 2008;2:1696–702. <https://doi.org/10.1021/nn800275r>.
86. Acevedo-Morantes CY, Acevedo-Morantes MT, Suleiman-Rosado D, Ramírez-Vick JE. Evaluation of the cytotoxic effect of camptothecin solid lipid nanoparticles on MCF7 cells. *Drug Deliv* 2013;20:338–48. <https://doi.org/10.3109/10717544.2013.834412>.
87. Zhang L, Chan JM, Gu FX, Rhee J-W, Wang AZ, Radovic-Moreno AF, et al. Self-Assembled Lipid–Polymer Hybrid Nanoparticles: A Robust Drug Delivery Platform. *ACS Nano* 2008;2:1696–702. <https://doi.org/10.1021/nn800275r>.
88. Sun M, Nie S, Pan X, Zhang R, Fan Z, Wang S. Quercetin-nanostructured lipid carriers: Characteristics and anti-breast cancer activities in vitro. *Colloids Surf B Biointerfaces* 2014;113:15–24. <https://doi.org/10.1016/j.colsurfb.2013.08.032>.
89. de Sousa Cunha F, dos Santos Pereira LN, de Costa e Silva TP, de Sousa Luz RA, Nogueira Mendes A. Development of nanoparticulate systems with action in breast and ovarian cancer: nanotheragnostics. *J Drug Target* 2019;27:732–41. <https://doi.org/10.1080/1061186X.2018.1523418>.
90. Timur SS, Yöyen-Ermiş D, Esendağlı G, Yonat S, Horzum U, Esendağlı G, et al. Efficacy of a novel LyP-1-containing self-microemulsifying drug delivery system (SMEDDS) for active targeting to breast cancer. *European Journal of Pharmaceutics and Biopharmaceutics* 2019;136:138–46. <https://doi.org/10.1016/j.ejpb.2019.01.017>.
91. Lensen D, Gelderblom EC, Vriezema DM, Marmottant P, Verdonschot N, Versluis M, et al. Biodegradable polymeric microcapsules for selective ultrasound-triggered drug release. *Soft Matter* 2011;7:5417. <https://doi.org/10.1039/c1sm05324h>.
92. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *The Lancet* 2012;379:432–44. [https://doi.org/10.1016/S0140-6736\(11\)61625-5](https://doi.org/10.1016/S0140-6736(11)61625-5).
93. Guo X, Zhao Z, Chen D, Qiao M, Wan F, Cun D, et al. Co-delivery of resveratrol and docetaxel via polymeric micelles to improve the treatment of drug-resistant tumors. *Asian J Pharm Sci* 2019;14:78–85. <https://doi.org/10.1016/j.ajps.2018.03.002>.
94. Li S-Y, Sun R, Wang H-X, Shen S, Liu Y, Du X-J, et al. Combination therapy with epigenetic-targeted and chemotherapeutic drugs delivered by nanoparticles to enhance the chemotherapy response and overcome resistance by breast cancer stem cells. *Journal of Controlled Release* 2015;205:7–14. <https://doi.org/10.1016/j.jconrel.2014.11.011>.
95. Malarvizhi GL, Chandran P, Retnakumari AP, Ramachandran R, Gupta N, Nair S, et al. A rationally designed photo-chemo core-shell nanomedicine for inhibiting the migration of metastatic breast cancer cells followed by photodynamic killing. *Nanomedicine* 2014;10:579–87. <https://doi.org/10.1016/j.nano.2013.10.006>.
96. Gu J, Fang X, Hao J, Sha X, Sha X. Reversal of P-glycoprotein-mediated multidrug resistance by CD44 antibody-targeted nanocomplexes for short hairpin RNA-encoding plasmid DNA delivery. *Biomaterials* 2015;45:99–114. <https://doi.org/10.1016/j.biomaterials.2014.12.030>.
97. Liu J, Li J, Liu N, Guo N, Gao C, Hao Y, et al. In vitro studies of phospholipid-modified PAMAM-siMDR1 complexes for the reversal of multidrug resistance in human breast cancer cells. *Int J Pharm* 2017;530:291–9. <https://doi.org/10.1016/j.ijpharm.2017.06.026>.
98. Sun T-M, Wang Y-C, Wang F, Du J-Z, Mao C-Q, Sun C-Y, et al. Cancer stem cell therapy using doxorubicin conjugated to gold nanoparticles via hydrazine bonds. *Biomaterials* 2014;35:836–45. <https://doi.org/10.1016/j.biomaterials.2013.10.011>.
99. Ghosh S, N Harke A. Gloriosa superba Mediated Synthesis of Silver and Gold Nanoparticles for Anticancer Applications. *J Nanomed Nanotechnol* 2016;7. <https://doi.org/10.4172/2157-7439.1000390>.
100. Muthukrishnan S, Vellingiri B, Murugesan G. Anticancer effects of silver nanoparticles encapsulated by *Gloriosa superba* (L.) leaf extracts in DLA tumor cells. *Futur J Pharm Sci* 2018;4:206–14. <https://doi.org/10.1016/j.fjps.2018.06.001>.
101. Fiorillo M, Verre AF, Iliut M, Peiris-Pagés M, Ozsvári B, Gandara R, et al. Graphene oxide selectively targets cancer stem cells, across multiple tumor types: Implications for non-toxic cancer treatment, via “differentiation-based nano-therapy.” *Oncotarget* 2015;6:3553–62. <https://doi.org/10.18632/oncotarget.3348>.
102. Liu Y, Chen C, Qian P, Lu X, Sun B, Zhang X, et al. Gd-metallofullerenol nanomaterial as non-toxic breast cancer stem cell-specific inhibitor. *Nat Commun* 2015;6:5988. <https://doi.org/10.1038/ncomms6988>.
103. Xie R, Wang Z, Yu H, Fan Z, Yuan F, Li Y, et al. Highly Water-soluble and Surface Charge-tunable Fluorescent Fullerene Nanoparticles: Facile Fabrication and Cellular Imaging. *Electrochim Acta* 2016;201:220–7. <https://doi.org/10.1016/j.electacta.2016.03.198>.
104. Nurunnabi M, Khatun Z, Huh KM, Park SY, Lee DY, Cho KJ, et al. *In Vivo* Biodistribution and Toxicology of Carboxylated Graphene Quantum Dots. *ACS Nano* 2013;7:6858–67. <https://doi.org/10.1021/nn402043c>.
105. Casais-Molina ML, Cab C, Canto G, Medina J, Tapia A. Carbon Nanomaterials for Breast Cancer Treatment. *J Nanomater* 2018;2018:1–9. <https://doi.org/10.1155/2018/2058613>.
106. Meghavati R, Badwar, Atul R. Bendale, Vasim Pathan, Vaishali D. Naphade, Sandhya L. Borse, Hemant Chikhale, & Laxmikant B. Borse. (2022). Nanoencapsulation An Approach for Targeting Nasal Drug Delivery. *Journal of Pharmaceutical Negative Results*, 13, 2169–2178. <https://doi.org/10.47750/pnr.2022.13.S05.341>
107. Chen Y, Zhang Y. Application of the CRISPR/Cas9 System to Drug Resistance in Breast Cancer. *Advanced Science* 2018;5:1700964. <https://doi.org/10.1002/advs.201700964>.