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Chapter 5: Nanotechnology in Triple-Negative Breast Cancer: Overcoming Drug Resistance and Tumor Aggressiveness

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Abstract

Triple-negative breast cancer (TNBC) is one of the most challenging malignancies in oncology, characterized by aggressive biological behavior, limited therapeutic targets, and poor clinical outcomes. This chapter provides a comprehensive examination of nanotechnology-based approaches to overcome the fundamental barriers limiting therapeutic success in TNBC treatment. The unique molecular heterogeneity of TNBC, encompassing distinct sub-types with varying resistance mechanisms and aggressive phenotypes, necessitates innovative therapeutic strategies beyond conventional chemotherapy approaches. Advanced nanomedicine platforms, including lipid-based nanocarriers, polymeric systems, inorganic nanoparticles, and hybrid formulations, offer unprecedented opportunities to address drug resistance mechanisms through targeted delivery, controlled release, and combination therapeutic approaches. Strategic co-delivery of sensitizing agents, ABC transporter inhibition, cancer stem cell targeting, and stimuli-responsive drug release systems demonstrate remarkable efficacy in reversing multi-drug resistance and preventing therapy-induced enrichment of resistant populations. Nanotechnology enables sophisticated targeting of tumor aggressiveness factors, including epithelial-Mesenchymal transition, angiogenesis, and immunosuppressive microenvironments, through precise modulation of signalling pathways and cellular interactions. Theranostic platforms integrating diagnostic and therapeutic functionalities provide real-time monitoring capabilities that enable personalized treatment optimization and adaptive therapy protocols.

Clinical translation progresses steadily, with multiple nanomedicine formulations advancing through clinical trials while demonstrating manageable safety profiles and encouraging efficacy results. Future directions emphasize artificial intelligence-guided design optimization, personalized nanomedicine approaches, and sophisticated combination therapies targeting multiple resistance pathways simultaneously. The convergence of nanotechnology with emerging therapeutic modalities promises to transform TNBC treatment from empirical approaches to precision medicine strategies, ultimately improving survival outcomes and quality of life for patients facing this devastating disease.

Keywords: *Triple-negative breast cancer, Nanotechnology, Drug resistance, Nanomedicine, Theranostics, Tumor aggressiveness*

1. Introduction

Triple-negative breast cancer (TNBC) is a clinically aggressive subtype defined by the absence of estrogen and progesterone receptors and the lack of HER2 overexpression, accounting for 10–15% of all breast cancers yet responsible for disproportionately poor outcomes(Kadi *et al*., 2023). Characterized by rapid proliferation, early distant metastasis, and limited therapeutic targets, TNBC carries a five-year survival rate of approximately 77%, dropping to 11–12% in the metastatic setting(Lu *et al*., 2023). Conventional chemotherapy—anthracyclines, taxanes, and platinum agents—yields pathological complete responses in only 30–50% of patients and is hampered by systemic toxicities and the near-inevitable emergence of multidrug resistance(Xiong *et al*., 2024). Mechanisms such as ATP-binding cassette (ABC) transporter–mediated drug efflux, heightened DNA repair capacity, cancer stem cell survival, and EMT collectively thwart sustained treatment efficacy and drive rapid relapse. Nanotechnology offers transformative potential to surmount these challenges through precision delivery, controlled drug release, and combinatorial targeting within a single platform(Obidiro *et al*., 2023). Lipid-based nanocarriers—including liposomes and solid lipid nanoparticles—enhance drug solubility, extend circulation time, and reduce off-target effects. Polymeric systems and dendrimers enable modular design for stimuli-responsive release and surface conjugation of targeting ligands, promoting tumor-specific uptake and endosomal escape. Inorganic nanoparticles such as gold and iron oxide combine drug delivery with photothermal or imaging capabilities, facilitating theranostic applications that integrate treatment and real-time monitoring. Hybrid “smart” nanosystems leverage multiple stimuli and biomimetic coatings to navigate the complex tumor microenvironment, overcome drug efflux pumps, eradicate resistant stem-like cells, and exploit tumor hypoxia for on-demand activation of prodrugs. By integrating therapeutic and diagnostic functions, nanomedicine stands poised to shift TNBC management from broad-spectrum cytotoxic regimens to adaptive precision strategies tailored to overcome both drug resistance and tumor aggressiveness(Obidiro *et al*., 2023). TNBC is molecularly heterogeneous, with transcriptional profiling defining distinct subtypes that exhibit unique vulnerabilities. The most widely adopted

TNBCtype-4 classification comprises on the basis of their moleular sub-types(Yadav & Leon-Ferre, 2024):

- Basal-like 1 (BL1): High cell-cycle and DNA damage response activity, frequent TP53 mutations, and sensitivity to DNA-damaging agents.
- Basal-like 2 (BL2): Enriched in growth factor signaling and metabolic pathways, sharing proliferative features with BL1.
- Mesenchymal (M): Marked by epithelial-mesenchymal transition pathways, enhanced invasiveness, and mesenchymal gene expression.
- Luminal androgen receptor (LAR): Driven by androgen signaling despite ER negativity, often harboring PIK3CA mutations and responsive to AR antagonists.
- Alternative schemes include the Burstein system (LAR, MES, BLIS, BLIA) and the FUSCC classification (IM, LAR, MES, BLIS), each refining subtype-specific prognostic and therapeutic implications. A schematic diagram of these classifications and their defining features will be presented to illustrate subtype relationships and key molecular hallmarks(Yadav & Leon-Ferre, 2024).

2. Characteristics of Triple-Negative Breast Cancer

2.1. Molecular Subtypes of TNBC

The molecular heterogeneity of triple-negative breast cancer has been extensively characterized through transcriptomic analyses, revealing distinct subtypes with unique biological properties and therapeutic vulnerabilities (Battogtokh *et al*., 2024;Wang *et al*., 2024;Mao, L., & Zeng, F.,2025). The pioneering work by Lehmann and colleagues established the first comprehensive molecular classification system, identifying six distinct TNBC subtypes through gene expression profiling of 587 cases: two basal-like subtypes (BL1 and BL2), an immunomodulatory subtype (IM), a mesenchymal subtype (M), a mesenchymal stem-like subtype (MSL), and a luminal androgen receptor subtype (LAR) (Shan *et al*., 2024;Giaquinto *et al*., 2024;Liu *et al*., 2024;Zhang *et al*., 2025).

The effect of the tumor microenvironment and stromal cell infiltration as well as overlapping of tumor-infiltrating lymphocytes and mesenchymal cells with the original IM and MSL classifications play a major role in classification of TNBC into four stable transcriptional sub-types: BL1, BL2, M, and LAR (Liu *et al*., 2024;Zhang *et al*., 2025). The basal-like 1 (BL-1) subtype is the most proliferative TNBC subtype with a higher cell cycle regulatory genes expression and DNA damage response pathways (Loizides & Constantinidou, 2023; Chen *et al*., 2018). BL-1 also has the highest rate of TP53 mutation(almost 92%), and has common amplifications at MYC, CDK6, and CCNE1 and deletions of BRCA2, PTEN, MDM2, and RB1 (Liu *et al*., 2024; Zhang *et al*., 2025; Weng *et al*., 2024). The basal-like 2 (BL2) subtype is characterized by growth factor

pathway and myoepithelial marker enrichment. It is also highly proliferative phenotype as BL-1 with improved rates of pathological complete response for mitotic inhibitors like taxanes (Liu *et al*., 2024; Zhang *et al*., 2025; Weng *et al*., 2024).Both basal-like subtype are highly sensitive to cisplatin-based adjuvant therapy in spite of their intrinsic DNA repair loss and high proliferation rate (Weng *et al*., 2024). The luminal androgen receptor (LAR) subtype, is ER negative with an over-expression of androgen receptor with a luminal pattern of gene expression (Li *et al*., 2024). LAR subtype has common PIK3CA mutations and amplifications at CCND1 and FGFR2 and has characteristic sensitivity at androgen receptor antagonists like that of bicalutamide (Mao, L., & Zeng, F. 2025; Giaquinto *et al*., 2024; Weng *et al*., 2024). The LAR subtype has distinct clinical features, which are characterized by advanced age at diagnosis, low histological grade, and specific bone metastasis tropism, from other TNBC subtypes (Liu *et al*., 2024; Li *et al*., 2024). The mesenchymal (M) subtype has over-expression of epithelial-mesenchymal transition (EMT) networks and motility genes, indicating major lung metastases (Liu *et al*., 2024; Zhang *et al*.,2025; Weng *et al*.,2024). Alternative classification methods have generated complementary information regarding TNBC heterogeneity like the Burstein classification identified four subtypes such as LAR, mesenchymal (MES), basal-like immune-suppressed (BLIS), and basal-like immune-activated (BLIA), and certain features related particularly to differences in immune signal transduction (Mao, L., & Zeng, F.,2025). The BLIS subtype shows immune pathway down-regulation and is the most immunologically inert subtype, where as the BLIA subtype show increased immune activation and STAT signaling. The Fudan University Shanghai Cancer Center (FUSCC) classification has developed the concepts for use among Asian populations and has characterized four sub-types (LAR, BLIS, IM, and MES) defined by characteristic changes in genomic predispositions and therapy-related characteristics for the Asian demographic (Mao, L., & Zeng, F.,2025; Li *et al*., 2024).

2.2. Genetic and Epigenetic Alterations

Triple-negative breast cancer has a unique combination of high mutation rates, significant changes in copy number, as well as unique epigenetic changes (Hou *et al*., 2022; Wang *et al*., 2024; Mao, L., & Zeng, F., 2025). Of the mutations disrupting TP53, the most common involve changes in the gene's DNA-binding domain; this mutation interrupts the cell cycle regulation and DNA damage response mechanisms in over 80% of cases. These changes lead to the production of defective proteins that drive genomic instability and make treatment difficult. The Evolutionary Action Score (EAp53) classification system predicts clinical impact of specific TP53 alterations on chemotherapy sensitivity. Homologous recombination deficiencies are critical in TNBC, driven by BRCA1/2 mutations (Battogtokh *et al*., 2024).While only 19% harbor germline BRCA1 mutations and 2.7% carry BRCA2 mutations, most exhibit "BRCAness" - a

BRCA-like HRD phenotype. This results from alterations in HR-related genes (PALB2, CHEK2, ATM, NBN), with 14.6% of TNBCs carrying HRD-related mutations. HRDetect classification enables three subgroups: HR Detect-high (better prognosis, high chemotherapy sensitivity), HR Detect-intermediate (CCNE1 amplification), and HR Detect-low (PIK3CA/AKT1 abnormalities). EGFR/FGFR2 amplifications and PTEN loss alter growth factor signaling and promote resistance. Whole-genome duplication occurs in ~45% of patients, buffering mutation burden effects and mitigating Muller's ratchet, particularly in BLIS subtypes. Epigenetic alterations encompass DNA methylation changes, histone modifications, and microRNA dysregulation. TNBC-specific methylation patterns emphasize tumor suppressor silencing. TET1 DNA demethylase overexpression in ~40% of patients associates with hypomethylation of 10% of CpG sites, worse survival, and activation of PI3K, EGFR, and PDGF pathways. Histone deacetylation patterns influence gene regulation, leading to HDAC inhibitor investigations(Sarkar *et al*., 2024).

2.3. Tumor Microenvironment in TNBC

The tumor microenvironment of TNBC is characterized by complex interactions between malignant cells, immune infiltrates, and stromal components that collectively influence disease progression and therapeutic response (Mitri *et al*., 2022; Liu *et al*., 2024; Chen *et al*., 2018). TNBC demonstrates significantly higher levels of tumor-infiltrating lymphocytes (TILs) compared to other breast cancer subtypes, with this enhanced immunogenicity attributed to increased neoantigen generation resulting from defective DNA repair mechanisms (Liu *et al*., 2024; Chen *et al*., 2018;Zolota *et al*., 2021). The composition and density of immune infiltrates vary considerably. Among the other TNBC subtypes, IM and BLIA types showing the highest levels of immune cell infiltration (Mitri *et al*., 2022; Liu *et al*., 2024; Chen *et al*., 2018). In TNBC, Tumor-infiltrating lymphocytes or TIL represent a rather heterogeneous population of cells (Lehmann, 2024; Mahendran et al., 2024; Wang et al., 2023). These include CD8+ cytotoxic T cells, which constitute an estimated 11.1% of the immune infiltrate and which are associated with enhanced survival and immunotherapy efficacy (Lehmann, 2024; Mahendran et⁻ al., 2024; Wang *et al*., 2023). The helper T cells, which are CD4+, constitute 14.1 % of TILs, and the Th2 subtype (11.7 %) demonstrates a specific prognostic value of both relapse-free and overall survival (Lehmann, 2024). Recent reports have demonstrated that Th2-infiltration can in fact better predict survival compared to the total TIL count; high-Th2 levels are associated with better results in multivariate analyses (Lehmann, 2024). The existence of antigen-presenting cells, such as dendritic cells and macrophages (combine to 8.4 percent) also constitute 8.4 percent of the immune microenvironment that promotes a better relapse-free survival (Lehmann, 2024; Mahendran *et al*., 2024). One of the most important stromal elements is cancer-associated fibroblasts (CAFs), which have a potent influence on cancer advancement

and resistance to therapy (Wang *et al*., Loizides and Constantinidou, 2023). TNBC exhibits the highest rates of CAF infiltration of other subtypes of breast cancer, and such cells are better equipped to promote tumor growth and invasion (Chen *et al*., 2018; Loizides and Constantinidou, 2023). CAFs in TNBC can be classified into distinct subtypes based on their functional characteristics as CAFs-I,CAF-II,CAF-III AND CAF-IV. CAF-I involve in remodeling of extracellular matrix and associated with poor immunotherapy response.Inflammatory CAFs-II (iCAFs) contributing to tumor microenvironment inflammation. Myofibroblastic CAFs-III express α-SMA and promoting tissue remodeling, and Antigen-presenting CAFs-IV potentially influence immune responses (Loizides & Constantinidou, 2023). The interaction between CAFs and immune cells creates an immunosuppression condition that facilitates tumor immune evasion and contributes to therapeutic resistance(Wang *et al*., 2023;Loizides & Constantinidou, 2023). The immunological landscape of TNBC has been further refined through multi-omics approaches that classify tumors into distinct microenvironment phenotypes (Mitri *et al*., 2022). These include "immune-desert" tumors with poor immune cell infiltration, "innate immune-inactivated" tumors with limited innate immune cells and predominant non-immune stromal infiltration, and "immune-activated" tumors with robust immune cell presence (Mitri *et al*., 2022). The immune-activated phenotype correlates with better prognosis and enhanced response to immune checkpoint inhibitors, while immune-desert tumors demonstrate resistance to immunotherapy approaches (Mitri *et al*., 2022). Myeloid-derived suppressor cells (MDSCs) also play crucial roles in TNBC immune evasion, with both monocytic and granulocytic subtypes contributing to immunosuppression through distinct mechanisms involving IL-6, TGF-β, and other cytokine pathways (Fan & He, 2022).

2.4. Clinical Presentation and Prognosis

Triple-negative breast cancer presents distinct clinical characteristics that distinguish it from other breast cancer sub-types, with unique demographic patterns, aggressive biological behavior, and challenging prognostic outcomes(Huertas-Caro *et al*., 2023;Brousse *et al*., 2023;Oshi *et al*., 2023). TNBC accounts for approximately 10-15% of all invasive breast cancers globally but demonstrates disproportionate representation among younger women, particularly those under 40 years of age(Xiong *et al*., 2024;Sarkar *et al*., 2024). The clinical presentation of TNBC is characterized by rapid tumor growth, high histological grade, and early propensity for distant metastasis (Huertas-Caro *et al*., 2023;Brousse *et al*., 2023). Most TNBC tumors (78.2%) present as grade 3 lesions, reflecting their highly proliferative and poorly differentiated nature(Zhang *et al*., 2023). The disease demonstrates a unique pattern of recurrence risk, with the highest probability of relapse occurring within the first 3 years following diagnosis, after which the risk declines substantially below that of hormone-positive breast cancers(Brogna *et al*., 2025). Approximately 40% of patients with stage I-III

TNBC experience disease recurrence despite standard treatments, with rapid-relapse TNBC (RR-TNBC) representing a particularly aggressive subset characterized by marked chemoresistance and poor survival (Brogna *et al*., 2025). The recurrence patterns favor visceral metastases, with lung and liver representing common sites of distant spread (Brogna *et al*., 2025). Prognostic stratification in TNBC relies on multiple clinicopathological and molecular factors that collectively determine patient outcomes(Brousse *et al*., 2023;Oshi *et al*., 2023). The overall 5-year relative survival rate for TNBC across all stages is approximately 77%, significantly lower than the 90% survival rate for all breast cancer subtypes combined(Zhang *et al*., 2023;Brogna *et al*., 2025). Stage-dependent survival rates reveal the impact of disease extent, with localized TNBC demonstrating 87% 5-year survival, regional disease showing 68% survival, and distant metastatic disease exhibiting only 11-12% 5-year survival(Zhang *et al*., 2023;Brogna *et al*., 2025). Key prognostic factors include tumor size, lymph node involvement, histological grade, and molecular characteristics such as BRCA1/2 mutation status and PD-L1 expression (Brousse *et al*., 2023;Oshi *et al*., 2023;Brogna *et al*., 2025). Patients with BRCA mutations demonstrate improved response to platinum-based chemotherapy and PARP inhibitors, with hazard ratios of 0.68 for overall survival and 0.72 for disease-free survival(Garrido-Castro *et al*., 201;Brousse *et al*., 2023). The clinical management of TNBC has evolved significantly with the incorporation of neoadjuvant chemotherapy and novel targeted therapies(Brousse *et al*., 2023;Zhang *et al*., 2023)The rates of pathological complete response (pCR) at the conclusion of the neoadjuvant chemotherapy lie between 30 and 50 percent based on the tumor type and on the treatment regime (Brousse *et al*., 2023; Zhang *et al*., 2023). Achieving patients pCR demonstrates astonishing 91% event-free survival rate 5 years later, while patients who still have residual disease have a 57% probability of survival (Zhang et al., 2023). Recent improvements include the application of immune checkpoint inhibitors, e.g., pembrolizumab, in metastatic triple-negative breast cancer (TNBC) PD-L1-expressing, yet response rates are still low, and only a small percentage of patients report long-term effects (Brousse et al., 2023).Inclusion of molecular subtyping created potential for personalized treatment methods, since numerous subtypes exhibit unique responses for targeted therapy methods (Wang *et al*., 2024; Mao, L., & Zeng, F., 2025; Li *et al*., 2024).

3. Drug Resistance Mechanisms in TNBC

3.1. Intrinsic and Acquired Resistance Pathways

The management of triple-negative breast cancer (TNBC) is one of the most difficult challenges in cancer treatment because of its ability to become resistant to both conventional and targeted therapy. This is due to the diverse molecular mechanisms of resistance pathways in TNBC as described in (Jiao *et al*., 2024; Jie *et al*., 2025). Within the context of TNBC, resistance pathways have been widely categorized as intrinsic (de

novo) or acquired, which possess distinct molecular features contributing to treatment failure and advancement of disease (Kesireddy *et al*., 2024). Of note, intrinsic resistance describes the features tumor possess that defy treatment, due to prior alteration arising genetically in the majority of tumor cells prior to intervention (Lucas *et al*., 2024). These mechanisms of resistance that are often included as intrinsic comprise the overexpression of efflux receptors, dysregulated apoptotic pathways, and inherent deficiencies in DNA repair pathways which inextricably undermine treatment and its therapeutic value from the start of therapy (Cai *et al*., 2023).

The molecular basis of intrinsic resistance of TNBC is often attributed to upregulation of survival networks, e.g., PI3K/AKT/mTOR and MAPK signal cascades that impose cell survival and growth in the presence of cytotoxic insult(Huang & Stoppler, 2024;Lim *et al*., 2023). Constitutively active NF-κB signaling is also a significant mediator of intrinsic resistance and has an expression level seen several times higher in TNBC tissues than it does in normal mammary tissue (De Francesco *et al*., 2022). The pathway inhibits apoptosis, controls inflammatory responses, and promotes angiogenesis, and all of them collectively lead to the development of TNBC and poor prognoses(De Francesco *et al*., 2022;Marra *et al*., 2020). Additionally, intrinsic heterogeneity of tumors also contributes significantly since there are pre-existing resistant populations that dominate once treatment-sensitive cells are removed by pushing for treatment failure and disease relapse(Yi, 2023).When patients are exposed to treatment over a prolonged period of time are likely to develop acquired resistance through mechanisms that favor survival and growth of tumor cells despite consistent therapeutic pressure(Zheng *et al*., 2023;Bui *et al*., 2023). This form of resistance generally develop through treatment-driven selection of resistant clones or through epigenetic adaptations favoring cancer cells evading drug-induced cytotoxicity(Błaszczak *et al*., 2025). The name Receptor tyrosine kinase (RTK) emerges as one of the primary alternative pathways that induce targeted drug resistance in triple-negative breast cancer (TNBC); the most interesting fact about it is that it does not rely on the typical genetic mutations (Chen *et al*., 2022).This entire process is based on a complex cascade of signalling networks, which vary among RTKs and multiple important crosspoints in central pathways such as MAPK (Błaszczak *et al*., 2025; Chen *et al*., 2022).

The development of acquired resistance is a pitfall in the treatment of TNBC: there are mechanisms that become active immediately after the initial drug intake, and those that creep in during the later stages of tumor evolution through its evolutionary adjustments (Chen *et al*., 2022).The primary perpetrators in this scenario are the epigenetic alterations, i.e., the presence of the changes in the DNA methylation and histone modifications that direct the gene expression related to drug metabolism, DNA repair, and apoptosis (Zheng *et al*., 2023).Also, the tumour microenvironment is also capable of

adapting: the release of cytokines triggered by hypoxia, the remodeling of the extracellular matrix, and so on all contribute to the survival of the cancer amid the drug attack (Xu *et al*., 2023).Therefore, it is necessary to map all these multi-pathways of resistance when we aim to develop therapies capable of overcoming the tumours of TNBC patients (Nedeljkovic *et al*., 2021).

3.2. ABC Transporters and Drug Efflux

ATP -binding cassette (ABC) transporters are members of that giant family of membrane-spanning proteins and have an immense impact on TNBC drug resistance as they can actively transport various therapeutic agents out of cancer cells (Fultang *et al*., 2021; Singh *et al*., 2021). With ATP hydrolysis they can effectively maintain intracellular drug levels below the cytotoxic threshold by enabling unidirectional movement across membranes (Gupta *et al*., 2020). The primary actors of the chemo resistance in TNBC are the big three ABC transporters, including ABC1 (multidrug resistance-associated protein 1), ABCB1 (P-glycoprotein 1/MDR1), and ABCG2. These transporters are in fact more often and more expressed in TNBC compared to other subtypes of breast cancer (Nedeljkovic *et al*., 2021; Gupta *et al*., 2020). The process of drug efflux in ABC transporter involves a substrate binding, which induces conformational changes in the trans-membrane domains (Gupta *et al*., 2020). ATP binds to the nucleotide-binding domains, triggers dimerization, and closes the high-affinity drug-binding site to a low-affinity state that expels the drug into the extracellular environment (Chen *et al*.,2024).ABC transporters efficiently protect the intracellular environment from different chemotherapeutic agents by removing their substrates from the inner layer of the plasma membrane bilayer and pumping them out of the cell (Chen *et al*., 2024). According to recent data, ABC transporter activity of the chemotherapy resistant cancer cells is primarily powered by mitochondrial-derived ATP, forming a vital connection between drug efflux capacity and cellular metabolism (Feyzizadeh *et al*., 2022). While ABCG2 is closely linked to the chemoresistance of cancer stem cell populations, while ABCB1 expression is linked to metastatic spread among TNBC molecular sub-types (Feyzizadeh *et al*., 2022; Gomes *et al*., 2020). Interestingly, in certain TNBC sub-types, elevated ABCG2 expression is correlated with better disease-free interval and overall survival despite its association with drug resistance. This suggests that these transporters play complex and context-dependent roles in the progression of the disease (Gomes *et al*., 2020). To address ABC transporter-mediated resistance in TNBC, a number of treatment approaches have been created (Giddings *et al*., 2021). These comprise of RNA interference methods which target transporter expression, in turn inhibiting the transporter function, thus nanomedicine-based strategies to get around efflux mechanisms (Modi *et al*., 2022).

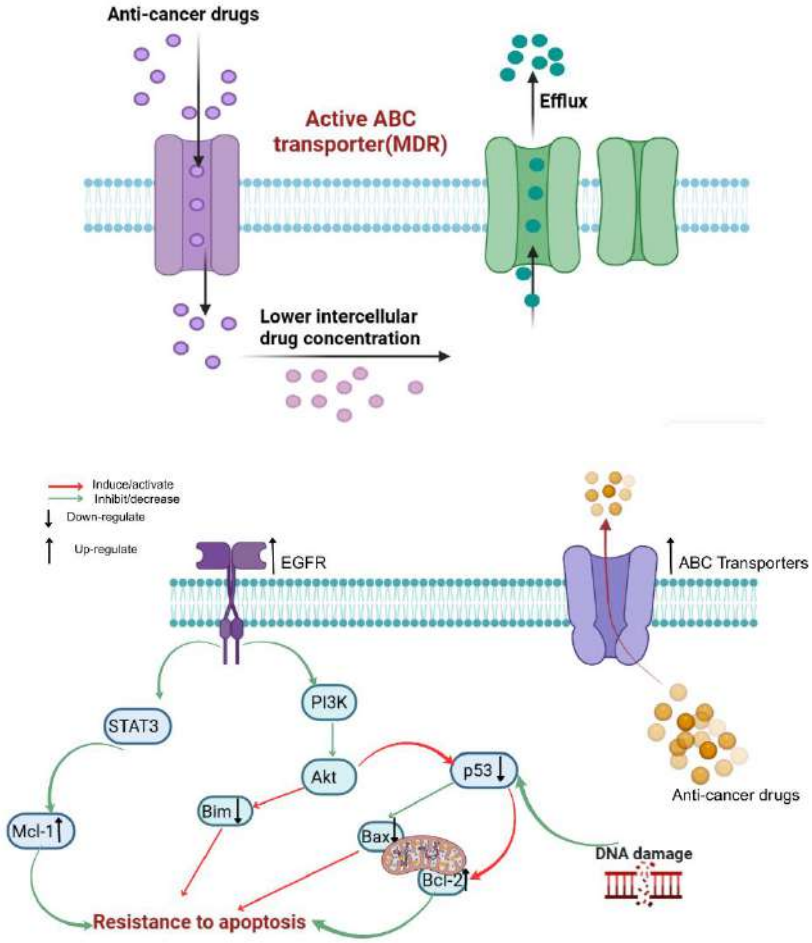

Figure 5.1: ABC transporter-mediated drug efflux in cancer cells; Mechanisms of drug resistance involving ABC transporters and apoptosis regulation in cancer cells.

3.3. Cancer Stem Cells and Resistance

Cancer stem cells (CSCs) represent a class of tumor cells with self-renewing capacity and the ability to generate heterogeneous tumor cell populations, playing an important role in TNBC progression, therapeutic resistance, and disease recurrence(Modi *et al*., 2022;Babu *et al*., 2022). These cells are enriched in TNBC compared to non-TNBC subtypes, with multiple studies revealing that TNBCs harbor the highest percentage of CD44+CD24-ALDH1+ CSCs, a feature that negatively correlates with chemotherapy response, disease-free survival, and overall survival and emerging approaches utilizing

nanoparticle-based drug delivery systems, gene-editing technologies, and immunotherapies directed against CSC-specific antigens offer promising strategies for overcoming CSC-mediated resistance in TNBC(Makuch-Kocka *et al*., 2023;Bhola *et al*., 2014). The phenotypic and functional characteristics of breast cancer stem cells (BCSCs) enable them to survive conventional therapies through multiple resistance mechanisms, including enhanced drug efflux capacity, increased DNA repair efficiency, and resistance to apoptosis(Makuch-Kocka *et al*., 2023). The molecular basis for intrinsic resistance in TNBC often involves survival pathway upregulation, for example, that observed in PI3K/AKT/mTOR and MAPK pathways, and that drives cell survival and proliferation despite cytotoxic insult(Huang & Stoppler, 2024;Lim *et al*., 2023). The molecular definition of BCSCs often relies on distinctive surface markers and functional assays and that CD44+/CD24-/low and ALDH1+ are utilized most often for TNBC(Modi *et al*., 2022;Bhola *et al*., 2015). The CD44+/CD24-/low phenotype almost exclusively localizes to basal/mesenchymal breast cancer cell lineages, while ALDH1 activity is more prevalent among HER2 overexpressing and basal/epithelial lineages of breast cancer cells(Bhola *et al*., 2014). A simultaneous CD44/CD24 ratio and ALDH1 positivity is a more effective means for outlining CSC populations most responsible for TNBC aggression(Dey *et al*., 2023).Multiple signal transduction pathways that maintain CSC phenotype in TNBC and that underlie therapy resistance(Srivastava *et al*., 2023). The Notch pathway plays an integral part in BCSC maintenance and has a very strong association for chemotherapy resistance and constitutively active Notch signaling promotes oncogenic programs among basal TNBC lineages(Nedeljković & Damjanović, 2019;Ricardo *et al*., 2011). Notch-1 activation induces the expression of ABCC1 in mammary cancers, and γ-secretase inhibitors that diminish Notch pathway activation suppress this upregulation and that promotes chemosensitization(Ricardo *et al*., 2011). In a comparable way, the Wnt/β-catenin pathway plays a prominent role for TNBC growth and maintenance of stemness based upon observed findings of severely comprised populations of stem cells and decreased tumor growth upon β-catenin knockdown(Bhola *et al*., 2014). Additional essential pathways encompass Hedgehog signaling, transforming growth factor-beta (TGF-β), and the Hippo-YAP/TAZ pathway that collectively govern the self-renewal, growth, and therapy response of BCSCs(Dey *et al*., 2023). Novel observations in CSC biology have revealed new therapy vulnerabilities in TNBC(Nedeljković & Damjanović, 2019). Inhibition of CSC-specific signal transduction through small molecule inhibitors has demonstrated promise in preclinical models, and a cocktail of pathway inhibitors has demonstrated synergistic potential for eradicating CSC populations(Bhola *et al*., 2014). An illustration is suppressing the FGFR-mitochondrial metabolism-Notch1 axis that suppresses resistance to TORC1/2 inhibitors by eradicating drug-resistant CSCs in preclinical models of TNBC(Dey *et al*., 2023). In addition, epigenetic regulators like the long non-coding RNA BMP/OP-Responsive Gene (BORG) enhance BCSC phenotypes by engaging the E3 SUMO ligase TRIM28 and thus hold promise for intervention(Ricardo *et al*., 2011).

3.4. DNA Repair Mechanisms and PARP Inhibitor Resistance

With complex interactions between multiple repair pathways affecting treatment response and disease progression, DNA repair deficiencies in TNBC represent both a vulnerability and a source of therapeutic resistance (Dey *et al*., 2023). About 10–20% of TNBCs have germline BRCA1/2 mutations, but a higher percentage have a "BRCAness" phenotype, which is defined by poor homologous recombination (HR) repair without detectable BRCA mutations (Nedeljković & Damjanović, 2019; Ricardo *et al*., 2011). These HR deficiencies have been exploited therapeutically through synthetic lethality approaches, most notably with poly(ADP-ribose) polymerase (PARP) inhibitors that selectively kill HR-deficient cells by preventing the repair of DNA single-strand breaks, leading to replication fork collapse and double-strand break formation(Bhola *et al*., 2014).Despite initial responsiveness to PARP inhibitors, resistance inevitably emerges in most patients through multiple mechanisms that restore DNA repair capacity or enable tolerance of DNA damage(Giddings *et al*., 2021). The most frequent and clinically relevant mechanism of PARP inhibitor resistance involves restoration of HR function through secondary "revertant" mutations in BRCA1/2 genes(Modi *et al*., 2022). These mutations restore the open reading frame of previously defective BRCA genes, reestablishing functional protein expression and HR proficiency(Babu *et al*., 2022). This phenomenon has been documented in various tumor types, including breast, ovarian, and prostate cancers, representing a general mechanism of PARP inhibitor resistance that extends beyond BRCA1/2 to other HR pathway genes such as PALB2, RAD51C, and RAD51D(Makuch-Kocka *et al*., 2023;Bhola *et al*., 2015;Bhola *et al*., 2014).Beyond genetic reversion, additional mechanisms contribute to PARP inhibitor resistance in TNBC(Bhola *et al*., 2014). Loss of p53-binding protein 1 (53BP1) or its downstream effectors REV7/SHLD1-3 removes a barrier to DNA end resection in BRCA1-deficient cells, partially restoring HR and causing PARP inhibitor resistance(Dey *et al*., 2023). Mechanistically, 53BP1 loss in BRCA1-deficient cells promotes end resection of DNA double-strand breaks, enabling RAD51 recruitment and subsequent HR despite BRCA1 deficiency(Nedeljković & Damjanović, 2019;Ricardo *et al*., 2011). Similarly, reduced PARP trapping through mutations affecting PARP1 function or decreased PARP1 expression can confer resistance by limiting the cytotoxic lesions induced by PARP inhibitors(Dey *et al*., 2023). Loss of PARG (poly(ADP-ribose) glycohydrolase) activity represents another resistance mechanism, as it results in reduced DNA retention of PARP1 in PARP inhibitor-treated cells and partial amelioration of PARP1-induced DNA damage(Giddings *et al*., 2021). Replication fork stabilization has emerged as a critical mechanism of PARP inhibitor resistance that functions independently from HR restoration(Modi *et al*., 2022). Nucleases like MRE11 and MUS81 can pathologically degrade stalled replication forks, but BRCA1/2 proteins prevent this from happening (Babu *et al*., 2022). Loss of fork-degradation-promoting factors, such as PTIP, EZH2, and CHD4, in PARP inhibitor-resistant cells inhibits excessive nucleolytic processing

of stalled forks and permits cell survival in the face of chronic HR deficiency (Makuch-Kocka *et al*., 2023; Bhola *et al*., 2015).

Table 5.1: Key Drug Resistance Mechanisms in TNBC and Their Molecular Basis

Resistance Mechanism	Molecular Basis	Drug Classes Affected	Resistance Type	References
ABC Transporters and Drug Efflux	Overexpression of ABCB1 (P-gp/MDR1), ABCC1 (MRP1), ABCG2 (BCRP); ATP-dependent efflux of chemotherapeutic drugs; Mitochondrial ATP fueling drug pumps	Anthracyclines, taxanes, platinum agents, PARP inhibitors	Intrinsic and Acquired	(Pote & Gacche, 2023; Choi & Yu, 2014)
Cancer Stem Cell Maintenance	Enrichment of CD44+/CD24-/low and ALDH1+ populations; Activation of stemness signaling (Notch, Wnt/β-catenin, Hedgehog); Self-renewal capacity	Most conventional chemotherapeutics, targeted therapies	Intrinsic and Acquired	(Fultang *et al*., 2021; Huang *et al*., 2024)
Homologous Recombination Restoration	Secondary BRCA1/2 mutations; Loss of 53BP1/RIF1/REV7; Restoration of RAD51 loading; Reversal of promoter hypermethylation	PARP inhibitors, platinum agents	Primarily Acquired	(Chopra *et al*., 2020; Belli *et al*., 2019)
Enhanced DNA Repair	Upregulation of NER/BER pathways; Increased PARP1/PARG expression; Enhanced	DNA-damaging agents, platinum compounds, PARP inhibitors	Intrinsic and Acquired	(Lee *et al*., 2020; Kang *et al*., 2025)

	ATM/ATR/CHK1 signaling; Error-prone NHEJ pathway dominance			
Replication Fork Stabilization	Loss of MRE11/MUS81 nuclease recruitment; Decreased fork degradation; EZH2/PTIP/CHD4 loss; Protection of nascent DNA strands	PARP inhibitors, platinum compounds	Primarily Acquired	(Liao *et al*., 2018)
Epithelial-Mesenchymal Transition (EMT)	Loss of epithelial markers; Acquisition of mesenchymal phenotype; Increased cell motility and invasion; TGF-β pathway activation	Taxanes, conventional chemotherapeutics	Intrinsic and Acquired	(Kepuladze *et al*., 2024)
Apoptosis Evasion	Dysregulation of death receptors (DR-5); Overexpression of anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1); Reduced caspase activation	Most cytotoxic agents, targeted therapies	Intrinsic and Acquired	(Kamalabadi-Farahani *et al*., 2019; Adinew *et al*., 2023)
Tumor Microenvironment Interactions	Hypoxic niche formation; Cancer-associated fibroblast recruitment; Immunosuppressive microenvironment; Extracellular matrix remodeling	Immune checkpoint inhibitors, conventional chemotherapeutics	Primarily Intrinsic	(Fan & He, 2022; Furukawa *et al*., 2023; Sabit *et al*., 2025)

Intratumoral Heterogeneity	Pre-existing resistant subclones; Distinct molecular subtypes within tumor; Genetic and epigenetic diversity; Treatment-induced selection pressure	Most therapeutic approaches	Intrinsic	(So *et al*., 2022; Yang *et al*., 2017)

4. Tumor Aggressiveness Factors

Compared with different breast cancer subtypes, triple-negative breast cancer (TNBC) is particularly aggressive, with rapid growth, early metastatic dissemination, and poor clinical outcomes (Mir *et al*., 2020; Passalacqua *et al*., 2022). TNBC shows a characteristic biological behavior, emerging as a result of a combination of mutually reinforcing cellular and molecular mechanisms that jointly promote tumour growth and selective resistance to therapy. Here, the main factors contributing to the aggressiveness of TNBC are described, including immunosuppressive tumour microenvironment, hypoxic angiogenesis, the possibility of metastatic spread, the mechanisms of invasion, and epithelial-mesenchymal transition (Mir *et al*., 2020; Kim *et al*., 2024). This understanding of the fundamental processes is essential to developing new treatments that will challenge the innate aggressiveness of the cancer (Grasset *et al*., 2022).

4.1. Epithelial-Mesenchymal Transition (EMT)

Epithelial-mesenchymal transition (EMT) is fundamentally a characteristic process within triple-negative breast cancer (TNBC). During EMT, epithelial cells also lose their typical characteristics and cell-cell connectivity in order to develop mesenchymal features that enable them to become more motile, invasive, and resistant to programmed cell death (Mir *et al*., 2020; Xu *et al*., 2023). Recent single-cell transcriptomics findings have revealed that TNBC tumors in fact have a high fraction of hybrid epithelial-mesenchymal (E/M) cells that can simultaneously express both sets of markers, challenging the old binary EMT model (Mir *et al*., 2020; Son *et al*., 2024). These E/M hybrid cells are unexpectedly invasive yet preserve sufficient epithelial properties to colonize remote locations (Mir *et al*., 2020; Haque *et al*., 2024). At the molecular level, SNAIL, TWIST, ZEB1, and ZEB2 are the key transcription factors in EMT. These conditions suppress the activity of adhesion proteins, such as E -cadherin, and at the same time, stimulate the expression of mesenchymal proteins, including vimentin, N -cadherin, and fibronectin (Xu *et al*., 2023; Chen *et al*., 2022). The role of Vimentin, notably, in TNBC itself is paradoxical, as it increases invasion but suppresses metastatic expansion, with the complex dynamics of EMT at various metastasis stages emphasized (Nie *et al*., 2024). Signaling pathways TGF-B, Notch, Wnt/-catenin and TNF-alpha/NF-

KB are essential to EMT in TNBC, and their cross-talk and redundancy present genuine therapeutic challenges (E. Kim, 2025; Peddi *et al*., 2011). Additionally, EMT is directly associated with cancer stem cell (CSC) phenotypes in TNBC. EMT cells oftentimes gain stem-like functions, which increase tumor formation, resistance to therapy, and metastatic capacity (Grasset *et al*., 2022; Li *et al*., 2024). This connection is enhanced by tumor-associated macrophages discharging chemokines like CCL2, which stimulates AKT signaling, enhances 2 8 -catenin nuclear translocation, and stimulates both CSC phenotype and EMT (2024, Kim *et al*.; 2024, Son *et al*.; 2022, Chen *et al*.).

4.2. Metastatic Potential and Invasion Mechanisms

About 40% of patients with stage I-III disease experience recurrence despite standard treatments, which is largely due to TNBC's exceptional metastatic propensity (Nie *et al*., 2024; Grasset *et al*., 2022).TNBC demonstrates distinctive metastatic patterns with preferential spread to visceral organs including lungs, liver, and brain, differing from hormone receptor-positive breast cancers that frequently metastasize to bone(Nie *et al*., 2024; Z. Chen & Zhao, 2025). Comprehensive genomic and transcriptomic profiling has revealed that metastatic TNBC tumors adapt their metabolic signatures to resemble those of their destination organs while retaining core TNBC-specific features, highlighting the remarkable plasticity of these cancer cells(Li *et al*., 2024;Z. Chen & Zhao, 2025). Matrix metalloproteinases (MMPs) serve as critical mediators of TNBC invasion by degrading extracellular matrix components and activating growth factors that facilitate tumor cell migration(Haque *et al*., 2024;O'Reilly *et al*., 2021). MMP-1, MMP-7, MMP-9, and MMP-13 are significantly upregulated in TNBC compared to adjacent normal tissue, with expression levels correlating with invasive potential and poor clinical outcomes(Haque *et al*., 2024; Bokhari *et al*., 2024). The degradation of basement membranes by MMPs creates pathways for tumor cell invasion and enables the release of pro-angiogenic factors that promote neovascularization at primary and metastatic sites(O'Reilly *et al*., 2021;García-Hernández *et al*., 2024). Intracellular signaling pathways driving TNBC invasion include the PI3K/AKT/mTOR, MAPK, and Wnt/β-catenin cascades, which converge to enhance cell motility, cytoskeletal remodeling, and production of proteolytic enzymes. Recent evidence indicates that dysregulated calcium signaling through BBOX1-IP3R3 interaction contributes to TNBC aggressiveness by promoting cell progression, migration, and survival pathways . The JAK-STAT and TNF signaling pathways have been identified as key drivers of TNBC progression through multi-omics network analyses, representing potential targets for therapeutic intervention(O'Reilly *et al*., 2021;García-Hernández *et al*., 2024).

4.3. Angiogenesis and Hypoxia

Hypoxia represents a defining feature of the TNBC microenvironment that drives tumor progression through multiple mechanisms including metabolic adaptation, angiogenesis,

and metastasis(Haque *et al*., 2024; García-Hernández *et al*., 2024). The hypoxic tumor niche is characterized by oxygen tensions below 2%, which trigger the stabilization and activation of hypoxia-inducible factor 1-alpha (HIF-1α), a master transcriptional regulator that orchestrates the cellular response to oxygen deprivation(García-Hernández *et al*., 2024;Liu *et al*., 2023)[95][99]. HIF-1α activation in TNBC upregulates numerous genes involved in glycolysis, angiogenesis, cell migration, and immune evasion, collectively enhancing tumor aggressiveness and therapeutic resistance(García-Hernández *et al*., 2024;W. Wu *et al*., 2021). Angiogenesis in TNBC is stimulated through hypoxia-mediated upregulation of vascular endothelial growth factor (VEGF), angiopoietins, platelet-derived growth factor, and fibroblast growth factor, which promote endothelial cell migration and proliferation (García-Hernández *et al*., 2024;W. Wu *et al*., 2021). These pro-angiogenic factors increase vascular permeability and facilitate the formation of abnormal, tortuous blood vessels that are characterized by structural and functional deficiencies, further exacerbating tumor hypoxia and creating a self-reinforcing cycle [13][16]. In addition to conventional angiogenesis, TNBC exhibits vasculogenic mimicry, wherein tumor cells form vessel-like structures that contribute to blood perfusion independently of endothelial cell-mediated angiogenesis (Chen & Zhao, 2025;W. Wu *et al*., 2021). Hypoxia-induced therapeutic resistance in TNBC occurs through multiple mechanisms including reduced drug delivery due to impaired vasculature, activation of drug efflux transporters, decreased proliferation of hypoxic cells, and enhanced DNA repair capacity(Haque *et al*., 2024; Srivastava *et al*., 2023). The bromodomain and extra-terminal domain inhibitor JQ1 has demonstrated efficacy in impairing the TNBC response to hypoxia by modulating hypoxia-regulated genes, particularly carbonic anhydrase 9 (CA9) and VEGF-A, offering a promising approach to simultaneously target angiogenesis and hypoxic adaptation(Chen & Zhao, 2025;Liu *et al*., 2023). Novel therapeutic strategies leverage tumor hypoxia as a targeting mechanism, exemplified by nanosystems that combine anti-angiogenic agents with hypoxia-activated prodrugs to enhance treatment efficacy through oxygen deprivation-dependent drug activation(O'Reilly *et al*., 2021; Bokhari *et al*., 2024).

4.4. Immunosuppressive Tumor Microenvironment

The tumor microenvironment of TNBC demonstrates a complex immune landscape characterized by extensive immune cell infiltration that paradoxically fails to control tumor growth due to predominant immunosuppressive mechanisms(W. Wu *et al*., 2021;Karagoz *et al*., 2015). Despite having higher levels of tumor-infiltrating lymphocytes (TILs) compared to other breast cancer subtypes, the functional capacity of these immune cells is frequently compromised through multiple immunoregulatory pathways(Liu *et al*., 2023;Kim, 2025). The TNBC immune microenvironment exhibits considerable heterogeneity, with distinct phenotypes ranging from "immune-desert" tumors with minimal immune infiltration to "immune-activated" tumors with robust but

functionally impaired immune cell presence (Xu *et al*., 2023; Fan & He, 2022). Tumor-associated macrophages (TAMs) represent a major component of the TNBC microenvironment, with M2-polarized macrophages promoting tumor progression through secretion of immunosuppressive cytokines, induction of regulatory T cells, and stimulation of angiogenesis(Grasset *et al*., 2022;W. Wu *et al*., 2021). These TAMs facilitate epithelial-mesenchymal transition and enhance cancer stem cell properties in TNBC through CCL2-mediated activation of AKT/β-catenin signaling, creating a positive feedback loop that amplifies tumor aggressiveness (Lu *et al*., 2023;Chaudhuri *et al*., 2022). Recent single-cell protein profiling has identified phenotypically distinct subpopulations of cancer and stromal cells associated with TNBC progression, with CD97 expression demonstrating significant prognostic potential(Karagoz *et al*., 2015;Ossovskaya *et al*., 2011). Hypoxia contributes significantly to immune suppression in TNBC through multiple mechanisms including impaired T-cell function, enhanced regulatory T-cell activity, and increased expression of immune checkpoint molecules(Haque *et al*., 2024). Recent research indicates that hypoxia, in fact, suppresses expression of immune effector genes in T -cells and NK -cells through an HIF1alpha -driven epigenetic program involving HDAC1 and PRC2, which results in chromatin remodeling and ultimately immune dysfunction (Pratelli *et al*., 2023). CXCL5 and IL-8 secretion by cancer cells and adipocytes interact to produce a unique inflammatory-inducing and pro-tumorigenic microenvironment in the triple-negative breast cancer (TNBC) microenvironment; serum amyloid A1 (SAA1) has been associated with a specific controller of adipocyte activity (Liu *et al*., 2023;Ossovskaya *et al*., 2011).

5. 5. Nanotechnology Platforms for TNBC Treatment

Table 5.2: A comprehensive overview of different nanotechnology systems used for triple-negative breast cancer treatment.

Platform Category	Subtype	Key Features	Advantages	Representative Examples & Status	References
Lipid-Based Nanocarriers	Liposomes	Self-assembling phospholipid bilayers forming aqueous core and lipid shell for hydrophilic	Excellent biocompatibility, controlled/pH-responsive release, reduced off-target toxicity	Pegylated liposomal doxorubicin (Doxil/Caelyx); matrix metalloprotease-responsive immunoliposomes with	(Anwar *et al*., 2024; Dasari *et al*., 2024; Llaguno-

		and hydrophobic drugs		paclitaxel + anti-CD47	Munive *et al*., 2024; Nel *et al*., 2023)
	Solid Lipid Nanoparticles	Crystalline lipid core at body temperature enabling high drug loading and stable matrix for hydrophobic agents	Enhanced colloidal stability, predictable release kinetics, minimal drug leakage, high entrapment efficiency (>70%)	Folic acid-functionalized SLNs loaded with diallyl trisulfide; dual-aptamer (EGFR + CD44) SLNs	
Polymer-Based Nanocarriers	Polymeric Micelles	Amphiphilic block copolymer self-assembly into core–shell micelles for hydrophobic drug encapsulation	Small size (~20–100 nm), deep tumor penetration, prolonged circulation, stimuli-responsive release	pH- and glutathione-responsive glutamine-PEG-b-PAE micelles delivering doxorubicin; halofuginone-loaded TPGS micelles12	(Zhao *et al*., 2020; Chaudhuri *et al*., 2022) (Zhang *et al*., 2016; Pulukuri *et al*., 2025; Alven & Aderibigbe, 2020)
	Dendrimers	Precisely branched PAMAM or PEGylated peptide scaffolds with multivalent	Atom-by-atom synthetic control, high payload capacity, facile ligand attachment,	PAMAM dendrimers delivering TWIST1 siRNA; PD-L1 antibody-conjugated PDK1	

		surface for drug/siRNA conjugation	theranostic functionality	siRNA dendrimers12	
Inorganic Nanoparticles	Metal & Metal Oxide NPs	Gold NPs with surface plasmon resonance; iron oxide NPs superparamagnetic for MRI contrast	Multifunctional: photothermal therapy, radiosensitization, magnetic targeting/imaging, theranostics	Folate-targeted AuNPs co-loaded with curcumin + docetaxel; endoglin-binding peptide Fe_3O_4 NPs with doxorubicin + poly I:C12	(Vikal *et al*., 2025; Sidhic *et al*., 2025; Mongy & Shalaby, 2024) (Eftekharifar *et al*., 2025; Rahchamandi *et al*., 2024; Guha *et al*., 2022)
	Carbon-Based Nanomaterials	Carbon nanotubes, graphene oxide, carbon dots offering hollow cores and large surface area for multi-drug loading	Intrinsic photothermal/photodynamic activity, high loading capacity, immunomodulatory effects	Ginsenoside Rg3-loaded CNTs suppressing PD-1/PD-L1; arginine-glycine-aspartic acid-modified GO for paclitaxel delivery	
Hybrid & Smart Nanocarriers	Exosome-Polymer Hybrids	Biomimetic exosome shell with PLGA or polymeric core enabling tumor-homing and controlled release	Natural targeting, immune evasion, reduced immunogenicity, enhanced tumor accumulation	Mesenchymal stem cell-derived exosome–PLGA hybrid platforms	(Banerjee & Rajeswari, 2023; O'Brien *et al*., 2013; Joshi *et al*., 2023)

	Stimuli-Responsive Systems	Multi-stimuli triggers (pH, redox, enzyme) for sequential or on-demand payload release in TME	Adaptive precision release, combined chemo-immuno-photothermal modalities, real-time monitoring	pH/enzyme/redox-responsive nanoparticles co-encapsulating chemotherapy + immunomodulator + photosensitizer	(Jha *et al*., 2025; Zandieh *et al*., 2023)

Nanotechnology is regarded as a game-changer of treating triple-negative breast cancer, providing new opportunities in addressing traditional troubles in TNBC treatment (Liu *et al*., 2021; Peddi *et al*., 2011; Zhang *et al*., 2021). The physical and chemical characteristics of nanotech drug carriers enhance tumor targeting, enhance pharmacokinetics, and reduce systemic toxicity relative to traditional chemotherapy (Dewi *et al*., 2022; Vozgirdaite *et al*., 2024; Chen *et al*., 2021). These nano-systems take advantage of the increased permeability and retention (EPR) effect of tumor vessels and overcomes the biological barriers that are peculiar to the treatment of TNBC (Chen *et al*., 2021; Lu, J., 2025; Dinakar *et al*., 2023). Advanced nanocarrier systems have enabled an alternative shift towards personalized nanomedicine of aggressive forms of breast cancer sub-types, which entails a strong control over drug release kinetics, cellular uptake pathways, and therapeutic targeting (Dinakar *et al*., 2023; Pradhan *et al*., 2023; Fatima *et al*., 2022). Site-specific immunogenic targeting and delivery nanotech-based therapeutics in the treatment of triple-negative breast cancer have experienced significant progress in the last decade. The field has evolved to adopting advanced nanocarrier systems such as lipid-based systems, polymeric nanoparticles, inorganic nanomaterials, and hybrid formulations due to the aggressive biology of TNBC. A paradigm shift toward precision nanomedicine approaches can be seen in the development of multifunctional theranostic platforms that can perform simultaneous therapy and real-time monitoring, as opposed to simple drug encapsulation systems.

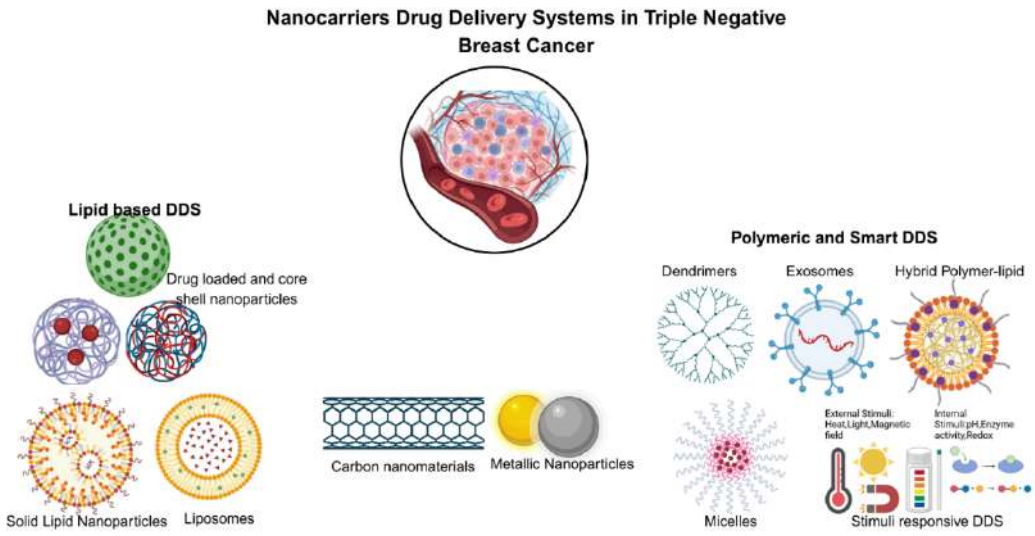

Figure 5.2: Structure and Properties of Key Nanocarriers for TNBC Drug Delivery

6. Clinical Translation and Regulatory Considerations

Nanotechnology-enabled therapeutics for triple-negative breast cancer have advanced to over 100 active clinical trials worldwide as of September 2024, reflecting a shift from early exploratory research to late-stage clinical validation. Among these, 58 address metastatic disease and 50 focus on non-metastatic settings, with Phase II studies comprising 81% (87 trials) and Phase III trials accounting for the remaining 19% (21 trials). In the United States alone, 1,230 study sites are engaged—217 hosting a single trial, 529 hosting two to four, and 484 hosting five or more—underscoring both the geographic breadth and variability in trial access. Liposomal doxorubicin remains the most clinically mature nanomedicine platform; the OCTANE trial of liposomal doxorubicin combined with carboplatin in early-stage TNBC patients achieved a pathological complete response rate of 30.2% and a two-year recurrence-free survival of 90.3%, with tolerability comparable to standard chemotherapy regimens. Combination immunotherapy approaches have likewise shown promise: the LAE005 study, pairing PD-L1 antibody therapy with afuresertib and nab-paclitaxel, yielded a median progression-free survival of 5.4 months, an objective response rate of 35.7%, and a disease control rate of 64.3%, with manageable toxicity profiles extending treatment durations up to 73 weeks. Innovative strategies incorporating CD40 agonists and Flt3 ligands alongside liposomal doxorubicin are underway to amplify antigen-presenting cell activation and dendritic cell expansion in metastatic TNBC, addressing the limited durable responses seen with PD-1 blockade alone.Regulatory evaluation of nanomedicines follows existing drug approval pathways in both the United States and

European Union, with no dedicated legal frameworks for nanoscale products. In the U.S., new nanomedicine applications may pursue Section 505(b)(1) for novel active ingredients, Section 505(b)(2) to leverage existing safety and efficacy data, or the abbreviated Section 505(j) for generics. The FDA emphasizes rigorous physicochemical characterization, stability profiling, and manufacturing control to ensure consistent safety and efficacy, noting that "liposome drug products are sensitive to changes in manufacturing conditions, including scale." European oversight by the EMA has evolved through specialized working groups and the Regulatory Science to 2025 strategic framework, which prioritizes integration of nanotechnology and new materials. The European Pharmacopoeia Commission has issued monographs on liposomal preparations and pegylated liposomal doxorubicin concentrate, and regulatory flexibility programs are emerging to expedite promising nanomedicines for diseases with high unmet need. Expedited device pathways, such as the Breakthrough Devices Program, demonstrate the potential for accelerated timelines—achieving decisions in as few as 152 days for 510(k) clearances—highlighting opportunities for analogous drug pathways.Safety and toxicology assessments for TNBC nanomedicines must address the unique interactions of nanoparticles with biological systems. Critical parameters—size distribution, surface properties, aggregation state, and long-term stability—require specialized analytical methods and standardized protocols. Preclinical evaluations reveal that minor variations in nanomaterial properties can lead to substantial differences in in vivo behavior, mandating formulation-specific characterization. Clinical safety monitoring has documented manageable adverse events for liposomal doxorubicin regimens: grade 1 fatigue in 92.6% of patients, grade 1 anemia in 81.5%, grade 3/4 neutropenia in 29.6%, and notably reduced alopecia (18.5% grade 1) compared to conventional doxorubicin, indicating improved patient quality of life.Manufacturing and scale-up of multicomponent nanosystems remain formidable challenges. Traditional pharmaceutical production methods are inadequate for precise control of three-dimensional nanoparticle architectures, necessitating specialized equipment and advanced process analytics. Key manufacturing parameters—polymer-to-drug ratios, solvent systems, emulsification conditions, temperature, pressure, and pH—must be tightly controlled to preserve product consistency. Processes often involve solvent use, high-speed homogenization, sonication, milling, emulsification, crosslinking, solvent evaporation, centrifugation, filtration, and lyophilization. Reproducibility is sensitive to environmental and process variations, and ensuring sterility while preventing harmful airborne nanoparticle exposure requires robust containment and worker protection. FDA guidance underscores the need to identify and evaluate critical scale-dependent manufacturing parameters, with advanced process analytical technology and real-time monitoring essential for batch-to-batch consistency and regulatory compliance.

Table 5.3: Clinical Trials of Nanomedicines for TNBC Treatment: Status and Outcomes

Trial Name/ID	Nanomedicine Platform	Phase	Status	Primary Endpoint	Key Outcomes	Safety Profile	References
OCTANE Trial (NCT05949021)	Liposomal doxorubicin + carboplatin	II	Active	Recurrence-free survival	Primary objective: effectiveness in reducing recurrence risk; Secondary: safety assessment using CTCAE v5.0	Evaluation ongoing	https://clin.larvol.com/trial-detail/NCT05949021
NCT05029999	Liposomal doxorubicin + CDX-1140 + CDX-301	I	Active	Recommended Phase II dose	Enrollment up to 45 patients; Multiple sites including UT Southwestern, Johns Hopkins	DLT evaluation in progress	(Reddy *et al.*, 2024)
LAE005 Combination (NCT05390710)	Nab-paclitaxel + afuresertib + LAE005	I/II	Active	Safety and efficacy	22 subjects enrolled; Median PFS 5.4 months; ORR 35.7%; DCR 64.3%	Manageable AEs; Most common: rash (90.9%), neutropenia (77.3%)	(Xu *et al.*, 2024)

Neoadjuvant DOX+CAR Study	Liposomal doxorubicin + carboplatin	II	Completed	Pathological complete response	pCR rate 30.2%; 2-year RFS 90.3%; 62 patients enrolled	Grade 1 fatigue (92.6%), anemia (81.5%); Low alopecia rates (18.5%)	(Chan *et al.*, 2022)
DAT/DAE Trial	Liposomal doxorubicin + bevacizumab + mTOR inhibitor	I/II	Completed	Objective response rate	ORR 21% in metaplastic TNBC; CBR 40%; Enhanced response with PI3K pathway activation	Well-tolerated combination therapy	(Bardia *et al.*, 2024)
NCT02456857 (ARTEMIS)	Liposomal doxorubicin + bevacizumab + everolimus	II	Completed	pCR/minimal residual disease	Targeted mesenchymal TNBC with chemotherapy insensitivity	Study design with molecular profiling integration	(Moulder *et al.*, 2017; Damodaran *et al.*, 2017)
Genexol-PM Trial (NCT00876486)	Polymeric micelle paclitaxel	III	Completed	Efficacy vs conventional	Comparison in recurrent/ metastatic	Established safety profile	(Park *et al.*, 2016)

				paclitaxel	breast cancer		
NCT02530489	Albumin nanoparticle (atezolizumab + paclitaxel)	II	Active	Immunotherapy combination efficacy	Anti-PD-L1 + chemotherapy nanomedicine approach	Ongoing safety evaluation	(Yam *et al.*, 2023)

7. Future Directions and Emerging Trends

The landscape of nanotechnology-based therapeutics for TNBC continues to evolve rapidly, driven by advances in molecular biology, materials science, and computational technologies. The amalgamation of these disciplines has created platforms to address the fundamental challenges that have limited the therapeutic success in this aggressive cancer subtype. Approaches such as personalized nanomedicine drug design and delivery, artificial intelligence-driven design optimization, RNA therapeutics and gene delivery systems, and advanced combination therapies that target multiple pathways at one go and are likely to be the four main areas of focus for future advancements in TNBC nanomedicine.

7.1. RNA Therapeutics and Gene Delivery

RNA-based therapeutics is currently one of the most cutting edge in TNBC treatment, offering the potential to target the proteins and pathways through precise genetic modulation which were difficult to target (Vikal *et al*., 2024). Recent advances in small interfering RNA (siRNA) and microRNA (miRNA) delivery systems have demonstrated remarkable efficacy in silencing oncogenic targets that are responsible for TNBC progression and resistance(Bhalla *et al*., 2024). Therapeutic interventions through targeted gene silencing approaches is supported by the discovery of critical RNA-binding proteins such as ZCCHC24, which promotes tumorigenicity in TNBC through mRNA stabilization mechanisms(Bhalla *et al*., 2024).Innovative antisense oligonucleotide (ASO) strategies have shown potential in targeting oncogenic long non-coding RNAs (lncRNAs) that responsible for TNBC aggressiveness(Mazumdar *et al*., 2024). The development of LNA GapmeRs that targeting TROLL-2 and TROLL-3 lncRNAs shows the potential for RNA-based therapeutics to overcome AKT-driven resistance to conventional chemotherapeutics, PARP inhibitors, and targeted therapies(Mazumdar *et al*., 2024). These therapeutic approaches both enable us to directly engineer the molecular biology underlying drug resistance, and reduce the off-target side effects that are experienced with conventional small-molecule inhibitors. Another accurate and

upcoming option of dealing with TNBC is CRISPR gene editing, which is coupled with a fancy delivery system (Lu *et al*., 2023). The combination of CRISPR and nanotech renders it feasible to conduct precise editing of genomes, due to the fact that the delivery is focused directly on tumor cells (Xu *et al*., 2024). In order to adjust oncogenes, reactivate tumor suppressors or enhance immunotherapy of TNBC cells, recent studies are regarding the construction of nano-carriers capable of delivering CRISPR components effectively (Vikal *et al*., 2024). CircRNA therapies provide new avenues to intervene in TNBC since they can control the expression of genes and cell metabolism, and assist us in understanding the efficacy of drugs (Mao *et al*., 2024). High-tech nano-formulations are being developed to provide circRNA therapies capable of modulating the immune microenvironment and metabolic interconnections that cause TNBC (Benderski *et al*., 2025).

7.2. Personalized Nanomedicine Approaches

In fact, the future of TNBC treatment is simply the personalization of nanomedicine to the specific molecular composition of a patient and molecular characteristics of their tumor (Bhalla *et al*., 2024). Emerging advances in liquid-biopsy technology combined with full genomic profiling enable us to identify patient-specific biomarkers that guide the selection and control of the nanotherapeutics we develop (Linde *et al*., 2024). In combination with circulating tumor DNA and nanoparticle delivery systems, this allows monitoring the state of the patient in real time and adjusting the therapies as need be on demand (Linde *et al*., 2024). A new treatment involves patient-derived organoid (PDO) models that personalize nanomedicine therapies. Such organoids allow us to screen drugs on tumor settings that are indeed patient-specific (Xu *et al*., 2024). Next, there is the immune-organoid co-culture model that anticipates the strength of an individual TNBC patient response to immunotherapy. This makes customized combo therapies with immunomodulators and nanomedicine technology easier to make, and it assists us in making real-time treatment decisions, as we can rapidly test nanoparticle efficacy at clinically pertinent time points (Xu *et al*., 2024). Another giant leap in personalized medicine is the selection of nanotherapies depending on biomarkers that enable us to categorize patients properly and to select the most suitable treatment. All this is being done via radiomics and AI-based imaging biomarker creation (Cabezas et al., 2024). Proposals in recent AI-based imaging research can assist us in identifying molecular profiles that forecast the intensity of a tumor to respond to nanotherapy, thus we can adjust the treatment regimen to the specific characteristics of the tumor (Bhalla *et al*., 2024; Cabezas *et al*., 2024). Population-specific targets also need to be considered in personalized nanomedicine. To provide an example, studies of racial and ethnic disparity in TNBC have reported increased Hedgehog signaling in non-Hispanic black females. These results underscore the necessity of tailored therapeutic approaches that emphasize

the development of nanomedicine platforms capable of being tailored to the therapeutic issues and resistance mechanisms of each group (Mazumdar et al., 2024).

7.3. Artificial Intelligence in Nanomedicine Design

Artificial intelligence is an important aspect in the development of nanomedicine because nanoparticles lack logical design, optimization, and behavior prediction (Ali *et al*., 2022). Machine learning algorithms have been used to predict drug loading efficacy, release dynamics, and patterns of cellular uptake to develop nanoparticles (Ali *et al*., 2022; Sheikh and Jirvankar, 2024). Recent studies using artificial neural networks are more accurate in prediction compared to the conventional response-surface methodology and thus, this allows them to optimize its parameters toward nanoformulations more effectively (Sheikh and Jirvankar, 2024). The analysis of drug uptake and nanoparticle–cell interaction using deep learning-based methods have proven to have remarkable potential in automating the evaluation(Benderski *et al*., 2025). The models based on convolutional neural networks have the potential to transform the methods of drug development since they could accurately predict the drug uptake and release processes in TNBC cells (Sheikh and Jirvankar, 2024). The AI-based automation of cellular uptake analysis is a crucial solution to critical problems in nanomedicine development and ensures better reproducibility and minimizes human bias. The AI-enabled nanoparticle design platforms are advancing newer nanomaterials with enhanced therapeutic properties, with a greater efficiency in drug delivery than a traditional formulation. The collaboration between Cardiff University and AstraZeneca conducted this study (Sheikh *et al*., 2024; Benderski *et al*., 2025; El-Sahli *et al*., 2021). These approaches use machine learning to optimize targeting blocks, surface modification, and nanoparticle composition on the basis of intensive analysis of biological interactions and therapeutic results. A novel method is a combination of artificial intelligence and biomolecular corona analysis to gain a deeper insight into and enhance the behavior of nanoparticles in biological systems (Dumbrava *et al*., 2024). When developing corona-resistant or corona-exploitative nanoformulations, advanced AI algorithms will have the capacity to forecast protein corona formation and its effect on targeting efficiency (Dumbrava *et al*., 2024). Such a high level of bio-nano interactions promises to create nanomedicines more effective and to decrease immunogenic responses.

7.4. Combination Nanotherapies

In the recent past, scientists have been refining novel nanotherapy combination therapies that have the potential to strike a tumor pathway across the board, and are gradually gaining acceptance as the treatment of choice when it comes to TNBC (El-Sahli *et al*., 2021). Multi-drug nanomedicines tend to be more successful, according to meta-analyses, than single-drug strategies; in one study, the combination was reported to be

43% more effective than single-drug therapy and even 29% more effective than conventional combinations of drugs (El-Sahli *et al*., 2021). These data emphasize the importance of developing combined nanotechnology systems to treat aggressive cancers such as TNBC Three drug nanoformulations which actually change the paradigm (Linde *et al*., 2024). Combinations of polymer-lipid hybrid nanoparticles containing combretastatin, verteporfin, and paclitaxel are dual-targeted to tumor blood vessels, cancer stem cells, and bulk tumor (Chaudhuri *et al*., 2022). Blocking the Hippo/YAP pathway, preventing the accumulation of the stem-cell result of chemotherapy, and fiddling with angiogenesis counter this messy biology of TNBC (Linde *et al*., 2024). There are clear limitations to single-agent checkpoint blockade, and it can be overcome using combo immunotherapies that rely on nanoparticle-based delivery. You are able to cut systemic toxicity but combine PD-1/PD-L1 inhibitors with immunomodulators, chemotherapy, or targeted agents with advanced nano platforms (Dumbrava *et al*., 2024). Combination therapy with lenvatinib and pembrolizumab has real potential in a combination to treat brain metastases in TNBC patients. Most recent TNBC therapies include sequential multi-modal blows on immunological vulnerabilities. Combination of checkpoint blockers, chemo, macrophage-reprogramming agents as well as epigenetic modulators have demonstrated full tumor control in preclinical TNBC models. These strategies involve the state-of-the-art understanding of tumor-immune interactions to target multiple pathways simultaneously, avoid resistance, and generate long-term responses.

Conclusion and Perspectives

Nanotechnology has begun to convert triple-negative breast cancer (TNBC) from a chemoresistant, highly aggressive malignancy into a disease tractable by precision medicine. Lipid, polymeric, inorganic and hybrid nanosystems now co-deliver cytotoxics, sensitizers and immunomodulators to bypass ABC-transporter efflux, eradicate stem-like clones and remodel the hostile tumor microenvironment, producing superior response rates in pre-clinical and early-phase trials. Further speeding up the search for enhanced, stimulus-responsive carriers with ideal loading and release profiles is formulation design guided by artificial intelligence. Tumor heterogeneity, scale-up complexity, and the long-term safety of certain inorganic platforms are still challenges, but the combination of immuno- and gene-editing therapies with adaptive nanocarriers is set to overcome lingering resistance mechanisms and slow the spread of metastatic disease. Nanotechnology is poised to transform TNBC's lethality into a manageable condition with consistent interdisciplinary collaboration and thorough clinical validation, significantly increasing the survival and quality of life for afflicted patients. Major breakthroughs in overcoming drug resistance mechanisms have been accomplished through innovative strategies including co-delivery of sensitizing agents, ABC transporter targeting, cancer stem cell elimination, and stimuli-responsive drug

release systems. These advances have demonstrated remarkable efficacy in reversing multi-drug resistance and preventing therapy-induced enrichment of resistant cell populations. The development of combination nanotherapies targeting multiple pathways simultaneously has shown superior therapeutic outcomes compared to conventional approaches, with meta-analyses demonstrating consistent improvements in tumor growth inhibition and overall survival. The integration of artificial intelligence with nanomedicine development has accelerated the discovery and optimization of novel nanoformulations while reducing development timelines and costs. AI-driven methods have made it possible to rationally design nanoparticles with better drug loading efficiency, optimized release kinetics, and increased targeting specificity. Numerous nanomedicine formulations have advanced through clinical trials and shown manageable safety profiles with promising initial efficacy results, indicating a significant advancement in clinical translation.

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