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Nanotechnology in triple-negative breast cancer: a review of nanocarrier systems for enhanced efficacy and reduced toxicity

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The aggressive and extremely diverse subtype of breast cancer known as triple-negative breast cancer (TNBC) lacks HER2, progesterone, and oestrogen receptors, which limits treatment options and increases the risk of metastasis and recurrence. Because of TNBC's complex tumour microenvironment (TME), genetic variety, and innate drug resistance, conventional therapies like chemotherapy and radiotherapy frequently cause severe systemic toxicity and have poor efficacy. By improving targeted delivery, reducing off-target effects, and facilitating multimodal therapy options, nanocarrier-based drug delivery devices provide a revolutionary strategy for TNBC. The ability of several nanocarrier platforms, such as liposomes, dendrimers, polymeric nanoparticles (NPs), and quantum dots, to target TNBC's distinct TME *via* passive and active mechanisms is thoroughly examined in this review. Stimulus-responsive systems enable regulated drug release, and nanocarriers functionalised with ligands, peptides, and antibodies have shown enhanced selectivity and decreased immune recognition. Furthermore, theranostic nanocarriers optimise therapeutic outcomes by enabling simultaneous diagnostic and treatment monitoring. Clinical translation is still hampered by important issues like scalability, regulatory obstacles, and possible immunogenicity. The relevance of nanotechnology in improving TNBC treatment is highlighted in this publication, which also addresses these obstacles and new developments intended to overcome them. Nanocarrier-based strategies have the potential to improve patient outcomes in TNBC management with precise control over drug cargo delivery sites and suitable engineering to mitigate the disease.

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1. Introduction

Triple negative breast cancer (TNBC) is the cause of around 40% of breast cancer-related deaths and makes up 10% to 15% of all breast cancers worldwide. Over 50% of patients experience recurrence within three to five years, indicating a significant recurrence risk,[1] and have about a 75% 5-year survival rate, which is much less than the 95% observed in ER/PR+, HER2-tumors. About 62% of TNBC tumours have nodal metastases, and 75% of them are grade III, with tumour diameters ranging from 0.4 to 8.0 cm (median ~2.5 cm).[2] Numerous subtypes are identified by molecular profiling, such as mesenchymal-like (MES, 11.2%) and luminal androgen receptor (LAR, 28.6%), with PD-L1 positivity seen in 76.6% of cases, particularly in grade III tumours with Ki67 ≥14%.[3] The immunological phenotypes of TNBC tumours vary: 16.3% are immune-inflamed, 21.1% are immune-excluded, and 62.6% are immune deserts. Positive results for SOX10 (33.3%), GCDFP15 (28.3%), mammaglobin (22.1%), GATA3 (46.3%), and TRPS1 (53.7%) are shown in protein expression data.[2] The 5-year survival rate for stage II and stage III TNBC is 76% and 45%, respectively, according to survival data. There is no discernible difference in 2-year survival rates between PD-L1+ and PD-L1− individuals (84.1% *vs.* 92%, $P = 0.512$).[4] RRAS2 overexpression is reported to significantly contribute towards lower survival rates in TNBC. However

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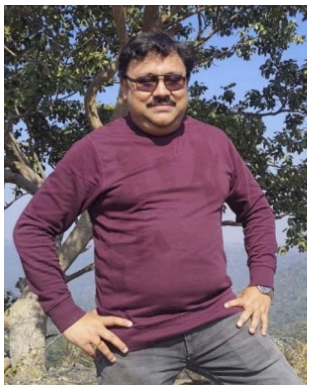

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factors like TP53 dysfunction, BRCA1/2 deficiency, activation of the P13K/AKT/mTOR axis and EMT/stemness transcriptional programs (TWIST, SNAIL, and ZEB1) which promote invasion and drug resistance[5–7] are also key determinants of TNBC prognosis. The use of PD-L1 inhibitors, such as pembrolizumab and atezolizumab, which exhibit therapeutic advantages in PD-L1+ TNBC patients, is an example of treatment advancements. The mesenchymal stem-like (MSL) subtype and epithelial–mesenchymal transition (EMT) activity are associated with RRAS2 overexpression. Notably, according to the METABRIC study, postpartum women between the ages of 30 and 40 exhibit a greater proportion (~50%) of TNBC cases.[8]

TNBC is a very aggressive and diverse subtype of breast cancer that has a poor prognosis and is limited by traditional hormonal and HER2-targeted treatments since it lacks ER, PR, and HER2 amplification.[9] Chemotherapy, immunotherapy, targeted medicines, and novel molecular techniques are therefore the mainstays of TNBC treatment. Anthracyclines (doxorubicin [DOX] and epirubicin) and taxanes (paclitaxel [PTX] and docetaxel) are common components of standard chemotherapy regimens. They are frequently used with platinum drugs like cisplatin or carboplatin, which are especially useful for patients with BRCA mutations or homologous recombination deficiency (HRD-positive) TNBC.[10] Pathologic complete response (pCR) is greatly improved by neoadjuvant chemotherapy (NCT),[11] and EGFR inhibitors (*e.g.*, lapatinib and erlotinib) in conjunction with DOX induce synergistic tumour apoptosis.[12] In BRCA-mutated TNBC, platinum medicines and PARP inhibitors such as olaparib and talazoparib take advantage of synthetic lethality and exhibit promise in both neoadjuvant and metastatic contexts.[13] When paired with chemotherapy, immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as pembrolizumab and atezolizumab, has improved outcomes in PD-L1-positive TNBC; nevertheless, despite comparable therapeutic responses, access gaps still exist.[14] Additionally, in relapsed or metastatic TNBC, new treatments such as antibody–drug conjugates (ADCs), such as sacituzumab govitecan and trastuzumab deruxtecan, which target Trop-2 and HER2-low expressions respectively, show improved overall survival (OS) and progression-free survival (PFS). Trials investigating ADC–ICI combinations are currently underway.[15]

Additionally, metabolic dependencies in TNBC have been discovered using metabolomics-based classification, providing new targets like lipid metabolism modulators, CDK4/6 inhibitors, and PI3K/mTOR inhibitors.[16] As demonstrated by the effectiveness of DOX-based regimens, functional precision medicine employing patient-derived organoids and xenograft (PDX) models helps customise therapy based on drug sensitivity.[17] Key oncogenes such as MDM2, CDK11, CK2, TWIST, c-Myc, PLK1, and EGFR can be silenced by siRNA-based therapies, including antibody–siRNA conjugates, providing a multigene approach to combat drug resistance.[18] Delivering siRNA, miRNA, chemotherapeutics, immunotherapeutics, and CRISPR-based tools is made easier by nanotechnology, which aids in the preclinical and clinical development of novel combination medicines.[19] To further customise TNBC treatment, molecular pathway-targeted treatments targeting EGFR, TGF-β, Notch, Wnt/β-catenin, EMT indicators, miRNAs and lncRNAs are being researched.[10] In order to predict pCR and long-term outcomes and assist in therapy optimisation, genomic profiling tools such as TNBC-DX combine immune gene signatures and tumour characteristics; ongoing trials like OptimICE-pCR and SCARLET seek to validate these predictive models.[11] Furthermore, inhibiting mitotic kinases like BUB1 and using drugs like pevonedistat to target post-translational modifications like neddylation and sumoylation offer promising ways to overcome chemoresistance and improve sensitivity to radiation and chemotherapeutics, even in BRCA wild-type TNBC.[13,20]

The absenteeism of receptors makes TNBC irresponsive towards the conventional hormonal or HER2-targeted therapies, hence making chemotherapy the predominant therapeutic option.[21] However, chemotherapy often suffers from poor specificity, leading to significant systemic toxicity and undesirable side effects. TNBC's unique tumor microenvironment (TME) further complicates treatment, as it includes high stromal density, increased interstitial fluid pressure, and immunosuppressive factors, all contributing to drug resistance and limited drug penetration within the tumor tissue.[22] Nanocarriers offer a unique and sophisticated method of drug administration that overcomes many of the drawbacks of conventional therapies, marking a revolutionary breakthrough in the treatment of cancer.[23] Conventional radiation and chemotherapy frequently have poor specificity, which can cause serious systemic toxicity and unfavorable side effects. Because of their nonspecific nature, these treatments can damage healthy tissues in addition to cancer cells, which can have a devastating effect on the patient and typically restrict the dosage and length of treatment.[24,25]

On the other hand, nanocarriers are designed at the nanoscale to take advantage of the special qualities of malignant tissues, improving the accuracy of medication administration. Usually measuring between one and one hundred nanometers, these minute delivery vehicles can be engineered to concentrate specifically in tumor tissues by means of the enhanced permeability and retention (EPR) effect. This phenomenon occurs when the leaky vasculature of tumors permits nanocarriers to enter and stay in the tumor microenvironment for a longer period of time than they do in normal tissues.[26] Furthermore, targeting ligands like peptides, antibodies, or small molecules that bind selectively to receptors overexpressed on cancer cells can be added to nanocarriers to functionalize them and enhance the specificity of drug delivery. This approach allows for active targeting.[27]

The variety of nanocarrier systems, such as metallic NPs, liposomes, polymeric NPs, and dendrimers [Table 1], provides an adaptable platform for the administration of a broad range of therapeutic medicines. These chemicals, which can be conjugated, adsorbed, or encapsulated onto the nanocarrier, can include conventional chemotherapeutic medications, nucleic acids for gene therapy, or even therapeutic proteins. Because of their adaptability, multifunctional nanocarriers that can co-deliver numerous therapeutic drugs can be designed, potentially leading to combination therapies on a single platform and producing a synergistic impact.[28] Furthermore, it is possible to design nanocarriers that include diagnostic imaging agents, making it possible to track drug delivery and tumor

Table 1 Nanocarrier: characteristics, novelty, merits and demerits

Nanocarrier design	Advantages	Disadvantages	Innovation window	References
Lipid-based NPs	Easy to formulate, self-assembly, biocompatible, highly bioavailable, and adjustable physicochemical properties	Traditional LNP formulation methods like pipette mixing, ethanol injection, vortexing and thin-film hydration yield homogeneous particles but with low efficiency and reproducibility	Forms micellar structures within the particle core, a morphology that can be altered based on formulation and synthesis parameters	30 and 31
Spherical platforms with at least one interior aqueous compartment surrounded by a lipid bilayer	High drug entrapment, regulated release, and scalable	Microfluidic techniques create uniform LNPs but are expensive and also face challenges with biodistribution, accumulating excessively in the liver and spleen		32
Liposomes	Low toxicity, biocompatible and biodegradable	Quick identification and removal by the MPS, brief half-life in	Can encapsulate both lipophilic and hydrophilic drugs	31
Spherical vesicles with an aqueous core encircled by bilayers of amphiphilic phospholipids	Encapsulates both lipophilic and hydrophilic drugs Improved targeted drug delivery	circulation, quick drug release, inadequate drug loading, and unstable qualities		32
Solid lipid NPs	Least hazardous and safely absorbed by the brain	Limited by the need for hydrophilic polymer or surfactant coating for improved bioavailability	Provide improved protection against degradation as they immobilise sensitive lipophilic drug molecules within the solid lipid matrix	33–35
Stable colloidal carrier system with a solid hydrophobic core	Small size, controlled release, higher drug entrapment efficiency and scalable			
Nanocapsules	Improved stability and cargo-retention efficiency	Limited control over drug release and reduced absorption by tumors	Nanocapsules have a liquid or oily core encased in a polymeric or lipid shell which enables reservoir-based delivery of drugs	30 and 36
Hollow spaces encased in a polymeric shell or membrane	Useful for delivering medicines into the cytosol			
Dendrimers	Surface-facing active groups aid drug encapsulation	Presence of amine groups	Unlike many NPs that depend on a single loading method, drugs	37
Highly branching molecules with distinct, uniform, and monodispersed architectures	Biocompatible, water-soluble, and stable	Difficulty in controlled drug release	can be chemically attached to surface groups or physically enclosed within interior cavities ensuring high entrapment	30
	Potential as smart nanocarriers	Rapid clearance by macrophages Reduced absorption of pharmaceuticals by tumors		
Polymeric micelles	Suitable for poorly soluble medicines	Dependent on strong cohesive force between drug and core polymer segments	Polymeric micelles have greater thermodynamic stability when diluted in the bloodstream due to their extremely low CMC values when compared to surfactant micelles	32 and 38
Nanoscopic core–shell structures formed by the self-assembly of amphiphilic di/tri-block copolymers	Multifunctional for drug administration and imaging and prolonged circulation			
Quantum dots	Small size and tag biological macromolecules	Sensitivity to environmental conditions and potential toxicity	Serve as a single platform, integrating photothermal or photodynamic therapy, drug delivery, and diagnostics	39
Colloidal semiconductor nanocrystals with distinctive optical and fluorescent characteristics	Improved photostability and fluorescence			
Gold NPs	Simple, affordable synthesis, effective targeting and engulfing of tumors	Variable photostability and need for surface modification to improve water solubility	In contrast to most polymeric or lipid NPs, AuNPs display Surface Plasmon Resonance (SPR) which can aid easy detection apart from their ability to conjugate with drug cargo	40–42
Used in medical applications, excellent for targeting tumors and preventing angiogenesis	Inhibit angiogenesis			

Table 1 (*Contd.*)

Nanocarrier design	Advantages	Disadvantages	Innovation window	References
Iron oxide NPs	Superparamagnetic characteristics and effective in drug and gene delivery	Limited by the need for appropriate surface coating to improve stability and bioavailability	An external magnetic field can be used to direct and concentrate IONPs to targeted locations, minimizing off-target toxic effects	43
Composed of magnetite or maghemite and used in contrast agents, drug delivery systems, and thermal therapies	FDA-approved			39

response at the same time. This theranostic ability helps optimize treatment plans and enhance patient outcomes by enabling real-time monitoring of treatment efficacy and offering vital insights into the pharmacokinetics and biodistribution of the therapeutic drugs.[29]

Notwithstanding these encouraging qualities, there are still a number of obstacles standing in the way of the clinical use of nanocarriers, such as issues with large-scale production, obtaining regulatory permission, and possible immunogenicity. However, continuous research and development is underway to improve nanocarrier technologies in an effort to overcome these challenges and bring these ground-breaking treatments from the lab to the clinic.

2. Challenges in triple negative breast cancer (TNBC)

2.1. Tumour microenvironment (TME) and immunosuppression in TNBC

TME components can interact with each other, altering the tumor's internal environment (Fig. 1) and promoting resistance in TNBC. The TME's non-cancerous cells are essential to the development of cancer because they support the tumor's survival, growth, metastasis, and resistance to treatment. Cancer growth and medication resistance are associated with interactions between the stromal cells and the cancer cells within the TME.[44] Oxidative stress, acidosis, and hypoxia can result from TNBC tumour cells' proliferation, metabolic remodelling, and cell death. These conditions can induce lysyl oxidase (LOX) activation, reshaping the ECM and promoting drug resistance.[45] Reactive oxygen species (ROS) and oxidative phosphorylation levels are decreased when the collagen prolyl 4-hydroxylase P4H-α1/HIF-1 axis is activated, increasing the stemness of TNBC cells.[46] By releasing cytokines, chemokines, and ECM remodelling factors, cancer-associated fibroblasts (CAFs) accelerate the spread of cancer and treatment resistance.[47] Lipid-associated macrophages (LAMs) generated by CAFs mediate immunological suppression in breast cancer, especially TNBC.[48] This metabolic change contributes to immunosuppression by affecting immune cell activity and causing a phenotypic change in macrophages.

The activation of immunological checkpoint pathways such as the CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) pathway and the PD-1/PDL1 (programmed death ligand-1) axis, among other factors, results in immunosuppressive responses at the tumour site.[49] ACSL3 in TNBC protects TNBC cells from ferroptosis induced by maternal adipocytes. M2 macrophages activate PCAT6 and release VEGF, promoting cancer cell growth and metastasis through VEFGR2 modulation. Different myeloid cell subtypes of TNBC exhibit distinct mechanisms of immunotherapy resistance.[50]

In general, TNBC is not significantly affected by the chemotherapeutic medications included in cholesterol liposomes. Interleukin-10 (IL-10), IL-6, IL-4, IL-1β, IL-17, and tumour necrosis factor-alpha (TNF-α) are all produced by CAFs in the tumour microenvironment (TME), which creates a complex milieu that affects immune cells, stromal cells, and cancer cells.[51] These factors combine to build an impenetrable physical barrier. Immune cells, such as regulatory T cells (Tregs), CD8+ T cells that target cancer cells directly, and CD4+ T cells that organise immune responses, which express the Foxp3 transcription factor, play a crucial role in infiltrating tumor sites.[52,53] In TNBC, M2-like Tumor-Associated Macrophages (TAMs) secrete cytokines, chemokines, and growth factors, contributing to immunosuppression. M2 TAMs expressing CD163+ infiltrate stromal fibroblasts and the mesenchymal transition stage causes aggressive phenotypes and low survival rates in TNBC patients.[54] In human breast invasive ductal carcinoma xenografts, ginsenoside Rg3, a ginseng component, prevents growth and angiogenesis and has antitumor properties.[50] Rg3 has been utilised to create a docetaxel-loaded Rg3 liposome that can enter the tumour more deeply, inhibit collagens, TGF-β, and CAFs, and increase the cytotoxicity of chemotherapeutic agents in TNBC. These liposomes have outstanding drug-loading and encapsulation capabilities.[55] Because of immune evasion strategies, TNBCs frequently feature dysfunctional tumor-infiltrating lymphocytes (TILs), whilst myeloid-derived suppressor cells (MDSCs) lessen the immunological response by preventing T-cell activation and proliferation. Compared to receptor-positive breast tumours, TNBCs frequently express more MDSCs, which activates the chemokines CCL22 and CXCL2, leading to considerable metastatic cascades.[56]

Cancerous cells can cause a shift in macrophages, promoting an M2-like immunosuppressive phenotype in tumor-associated macrophages (TAMs). This is facilitated by metabolites like lactate and adenosine. By attaching to certain receptors (A2A and A2B) on T cell surfaces, the purine nucleotide adenosine can limit T cell activation, cytokine generation, and cytotoxicity.[51]

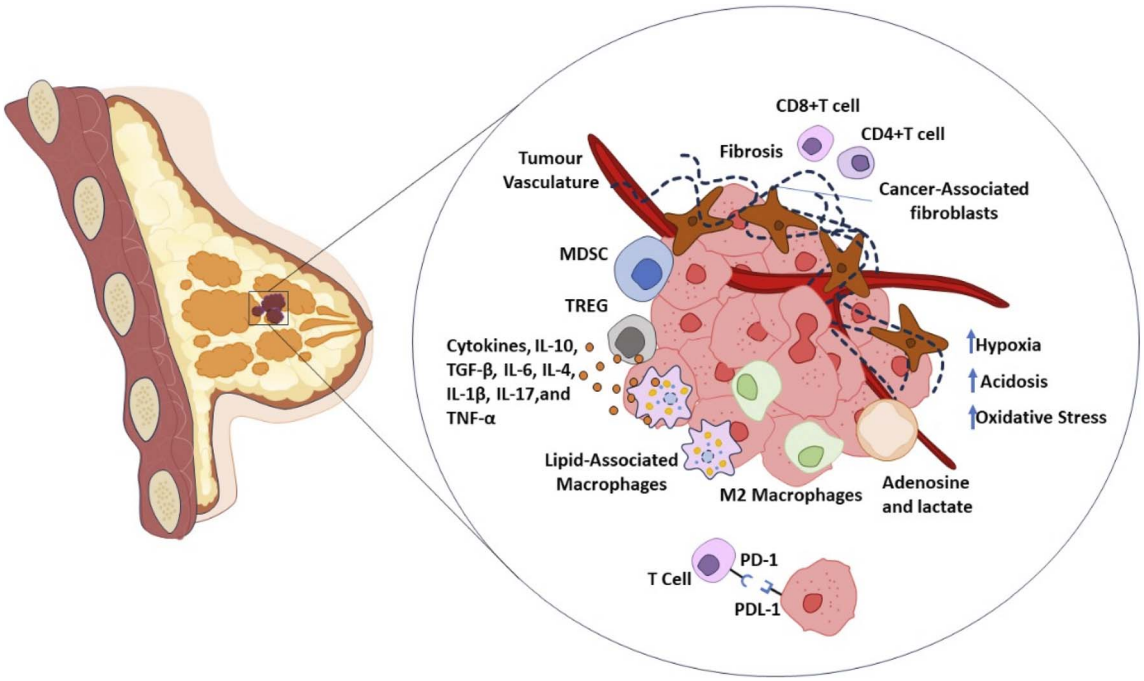

Fig. 1 TNBC tumour microenvironment.

2.2. Lack of target receptors

TNBC is the most aggressive and diverse subtype of breast cancer; it does not express the ER, PR, or HER2 markers. TNBC is identified in 15–20% of all breast cancers.[18] TNBC, often linked to BRCA1 mutations, lacks estrogen and progesterone receptors due to mutations or epigenetic changes. Hormone therapies like tamoxifen or aromatase inhibitors can block cancer growth by interfering with hormone-driven signaling pathways. However, in TNBC, the lack of ER and PR receptors makes it difficult to control the tumor with hormonal treatments, making it more challenging to treat.[57] TNBC does not overexpress HER2, a growth-promoting protein found on some breast cancer cells, unlike other types of breast cancer. This is due to the cancer's unique molecular characteristics, which typically show normal HER2 gene expression or lack of amplification. Targeted therapies like trastuzumab and pertuzumab are ineffective without HER2 overexpression, limiting treatment options.[58]

2.3. Drug-resistance

MYC and MCL1 oncogenes are frequently found in therapy-resistant TNBC cells post-neoadjuvant chemotherapy. They increase mitochondrial oxidative phosphorylation (mtOXPHOS) and ROS generation, regulating drug-resistant cancer stem cells (CSCs). This stimulates HIF-1α, which is related to CSC enrichment in TNBC. Inhibiting MYC and MCL1-targeting siRNA is one possible strategy to prevent chemotherapy resistance in TNBC by focussing on mitochondrial respiration and HIF-1α.[59] Twist-related protein (TWIST) increases the risk of disease recurrence and poor prognosis in TNBC patients by stimulating the EMT, promoting CSCs, and decreasing apoptosis.[60]

The discovery that neo-adjuvant chemotherapy enhanced ABCC1 protein expression in TNBC lends greater credence to the involvement of ABCC1 in TNBC chemo-resistance. Furthermore, TNBC cells developed drug resistance as a result of the hedgehog pathway's activation because ABC transporters were upregulated. The chemo-resistance of stem cells in TNBC is significantly influenced by ABCG2.[61]

Drug resistance is linked to the PI3K system, and intrinsic tolerance is a common side effect of inhibitors, especially PI3K inhibitors. Regarding the problem of medication resistance in TNBC patients, several advancements have been made. The primary cause of PI3K/AKT inhibitor resistance was PTEN insufficiency, which is present in 35% of TNBCs.[62]

2.4. Drug bioavailability

The ideal loading and release profiles for nanocarrier TNBC therapy are still elusive despite effective drug loading inside nanocarriers and regulated release kinetics. Stability and bioavailability must be guaranteed by carefully designing the encapsulation procedure. Furthermore, toxicity and biocompatibility are important variables affecting the clinical feasibility of nanocarriers.[63] Table 2 gives the summary of various NP based drugs under clinical trials for the treatment of TNBC.

2.5. Heterogeneity in TNBC

Triple-negative breast cancer (TNBC) presents unique challenges to conventional chemotherapy due to its inherent molecular and genetic heterogeneity. The current agreement is that BLIA (20–30%), BLIS (25–40%), LAR (15–25%), and mesenchymal (15–20%) are four primary molecular subtypes, which are classified based on independent DNA and RNA level investigations[78]

2.5.1. Basal-like immune activated (BLIA) subtype. The BLIA subtype of TNBC shows over 80% TP53 mutations with numerous low-frequency mutations and is marked by DNA

Table 2 Therapeutic regimens for TNBC management in the clinical trial phase[a]

Drug	CT phase	Outcome	Ref.
Pembrolizumab (MK-3475) + chemotherapy	Phase 3, randomized, double-blind, placebo-controlled	Pembrolizumab plus chemotherapy significantly improved progression-free survival in patients with a PD-L1 combined positive score of 10 or more, reducing the risk of death by 27% compared to chemotherapy alone	64
Atezolizumab + PTX	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Compared to PTX alone, atezolizumab with PTX did not increase PFS or OS	65
Sacituzumab govitecan	Phase 3, randomized, open-label, multicenter trial	For patients with metastatic TNBC, sacituzumab govitecan significantly extended both the progression-free and overall survival unlike single-agent chemotherapy. A higher frequency of diarrhea and myelosuppression was seen	66
Ipatasertib + atezolizumab + PTX	A phase 3, double-blind, placebo-controlled, randomized study	The combination of ipatasertib, atezolizumab, and PTX showed some improvement in PFS for PD-L1 non-positive participants	67
Atezolizumab + PTX	Phase 3, randomized, double-blind, placebo-controlled clinical trial	The combination of atezolizumab with chemotherapy post-surgery does not significantly improve survival outcomes for patients with operable stage II–III triple-negative breast cancer	68
Atezolizumab + Nab-PTX	Phase III, double-blind, randomized, placebo-controlled study	The addition of atezolizumab to neoadjuvant chemotherapy for early-stage TNBC improved pathologic complete response without increasing patient treatment burden	69
Pembrolizumab + capecitabine + eribulin	A randomized open-label phase III study	Pembrolizumab demonstrated efficacy and was well-tolerated in pre-treated patients, indicating its potential in treating TNBC patients with limited options	70
Bevacizumab + standard adjuvant chemotherapy	An international multi-centre open-label 2-arm phase III trial	In both the groups, overall survival remained similar, and the study found no statistically significant difference in invasive disease-free survival (IDFS) between the chemotherapy-alone and bevacizumab groups	71
Bevacizumab + PTX + docetaxel	Open-label study phase 4	The Bev-Tax-Cap regimen, which included capecitabine, taxanes, and bevacizumab, outperformed other regimens in terms of progression-free survival when compared to taxanes alone or in other combinations	72
DOX + cyclophosphamide + Ixabepilone (Ixempra) + PTX (Taxol)	Phase III study with triple-negative breast cancer (early-stage)	Both the AC/Ixabepilone and AC/PTX regimens had comparable overall survival at 48 months and 5-year disease-free survival. The PTX group also experienced a higher rate of discontinuations and dose changes. Peripheral neuropathy was also prevalent	73
Capecitabine + carboplatin + cisplatin	A randomized phase III post-operative trial	According to the TITAN research, platinum drugs exhibited more severe toxicities and did not increase 3-year invasive disease-free survival in basal subtype TNBC post-NAC when compared to capecitabine. Due to improbable dominance, the trial was terminated early	74
Capecitabine	Multicenter, open-label, randomized phase III	Low-dose capecitabine maintenance therapy significantly increased early-stage TNBC patients' 5-year disease-free survival (82.8%), with a 0.64 hazard ratio for recurrence or death, according to the SYSUCC-001 trial	75
Ipatasertib + PTX	A double-blind, placebo-controlled, randomized phase III study	In advanced TNBC, the combination of ipatasertib, PTX, and atezolizumab demonstrated encouraging disease control; nevertheless, 19% of patients had significant	76

Table 2 (*Contd.*)

Drug	CT phase	Outcome	Ref.
		side effects that needed to be carefully managed	
Nab-PTX + carboplatin + gemcitabine	A phase 2/3, multi-center, open-label, randomized study	It lowered the chances of disease progression or mortality in metastatic TNBC patients by 40%, providing a safer first-line therapy option and improved progression-free survival	77

[a] PFS – performance free survival, OS – overall survival, PD-L1 – programmed cell death-ligand 1, "AC" refers to a combination of two chemotherapy drugs: DOX (Adriamycin) and cyclophosphamide, and "post NAC" refers to "post-neoadjuvant chemotherapy" neoadjuvant chemotherapy.

damage repair activity and immense instability of chromosomes.[79] CDK1 amplification is also common in BLIA.[80] This subtype is characterized by strong immune response, with high expression of immune-related genes (T cell activity, antigen processing, and checkpoint molecules like CTLA4, PD1, and PDL1).[81] Histologically, BLIA shows significantly higher intratumoral and stromal lymphocyte counts compared to other TNBC subtypes, making it a prime candidate for immune checkpoint inhibitors.[78]

2.5.2. Basal-like immune suppressed (BLIS) subtype. BLIS, unlike BLIA, shows minimal immune activity, making it less responsive to immunotherapy.[82] BLIS tumors express VTCN1 (B7-H4), which suppresses T cell activation,[83] and SOX family transcription factors that promote tumor proliferation and invasion.[80] These tumors are enriched in metabolic reprogramming pathways, which contribute to cell proliferation and resistance to immunotherapy.[78] BLIS is also linked to high recurrence rates and shows enrichment in Homologous Recombination Deficiency (HRD) signatures and genomic scars. Tumors with high-HRD have a better prognosis,[84] and RAD51-low scores during the S/G2 phase of the cell cycle are predictive of response to platinum-based chemotherapy.[85] However, increased RAD51 foci after treatment indicate resistance to PARP inhibitors, and the utility of RAD51 as a biomarker for BLIS remains under investigation.[86]

2.5.3. Luminal androgen receptor (LAR) subtype. The LAR subtype of TNBC, while negative for ER by IHC, shows high expression of estrogen-related genes (*e.g.*, FOXA1 and GATA3) and increased androgen receptor signaling.[87] These tumors are often categorized as non-basal (luminal or HER2-enriched) by PAM50 and frequently carry ERBB2 mutations in the kinase domain, which can lead to resistance to trastuzumab.[84] Instead, tyrosine kinase inhibitors may be more effective.[88] LAR tumors commonly harbor PIK3CA mutations (40–55%) and show hyperactivation of the PI3K/AKT pathway, with preclinical models suggesting that PI3K-AKT inhibitors combined with CDK4/6 inhibitors are more effective, especially in PIK3CA-mutant tumors.[89] In addition to losing CDKN2A, LAR tumours also maintain RB1, which increases their susceptibility to CDK4/6 inhibitors. They exhibit modest levels of immunological activity, HRD, and chromosomal instability, yet they are associated with apocrine characteristics, lipid metabolism, and advanced age.[78]

2.5.4. Mesenchymal subtype. The mesenchymal subtype of TNBC is characterized by the activation of pathways related to the epithelial–mesenchymal transition (EMT), extracellular matrix, and angiogenesis.[90] These tumors express markers like NOTCH1/3, EGFR, IGF-1, and osteocyte markers (OGN).[78] Their PAM50 profiles are mixed, showing both basal-like and non-basal features.[84] Mesenchymal tumors also have more genomic instability, copy number alterations and tumor mutation burden but exhibit low immune cell infiltration and PD-L1 expression, which suggests immune evasion and resistance to immunotherapy.[91] These tumors show increased MAP3K1 and PDGFRA deletions, mutations in antigen presentation and DNA repair genes, and epigenetic alterations, like mutations in the ASXL gene family and BAF SWI/SNF complex, which affect antigen presentation and make them potentially sensitive to EZH2 inhibitors. Mesenchymal tumors also exhibit DNA hypermethylation and breast cancer stem cell-like properties with upregulation of JAK1/STAT3 signaling. Although JAK1 inhibitors have shown limited success, they may be effective specifically for mesenchymal tumors.[78,91–93] The mesenchymal stem-like (MSL) subtype displays non-basal profiles and is enriched in angiogenesis pathways, with high expression of VEGF and PDGFR.[92,94] Anti-angiogenic therapies, which have been ineffective in unselected TNBC patients, may hold promise for MSL, given its angiogenic profile and the presence of innate immune cells like mast cells, which promote tumor angiogenesis.[78]

2.6. Obstacles to nanotechnological interventions in TNBC

Polymeric NPs, like liposomes, face biological barriers in clinical studies. For instance, CT-2103, a poly-L-glutamic acid conjugated PTX NP, administered IV produced a higher PTX AUC in the liver than in the primary tumor.[95] Additional obstacles to tumour targeting may arise from the passive filtering of small polymeric particles through the glomerulus. Large polymeric particles may concentrate in renal cells and tissues, according to a new study, underscoring the need for comprehending drug carrier biodistribution for efficient tumour targeting.[96] Pharmaceutical drug carriers in clinical studies often face biological barriers before reaching tumors. Combination therapy could improve efficacy or decrease toxicity, but sequential infusions limit drug synchronicity. To optimise the cytotoxic impact, the perfect carrier would target and provide a therapeutically appropriate mix of chemotherapeutic medications.[97] Fig. 2 illustrates the various challenges in TNBC.

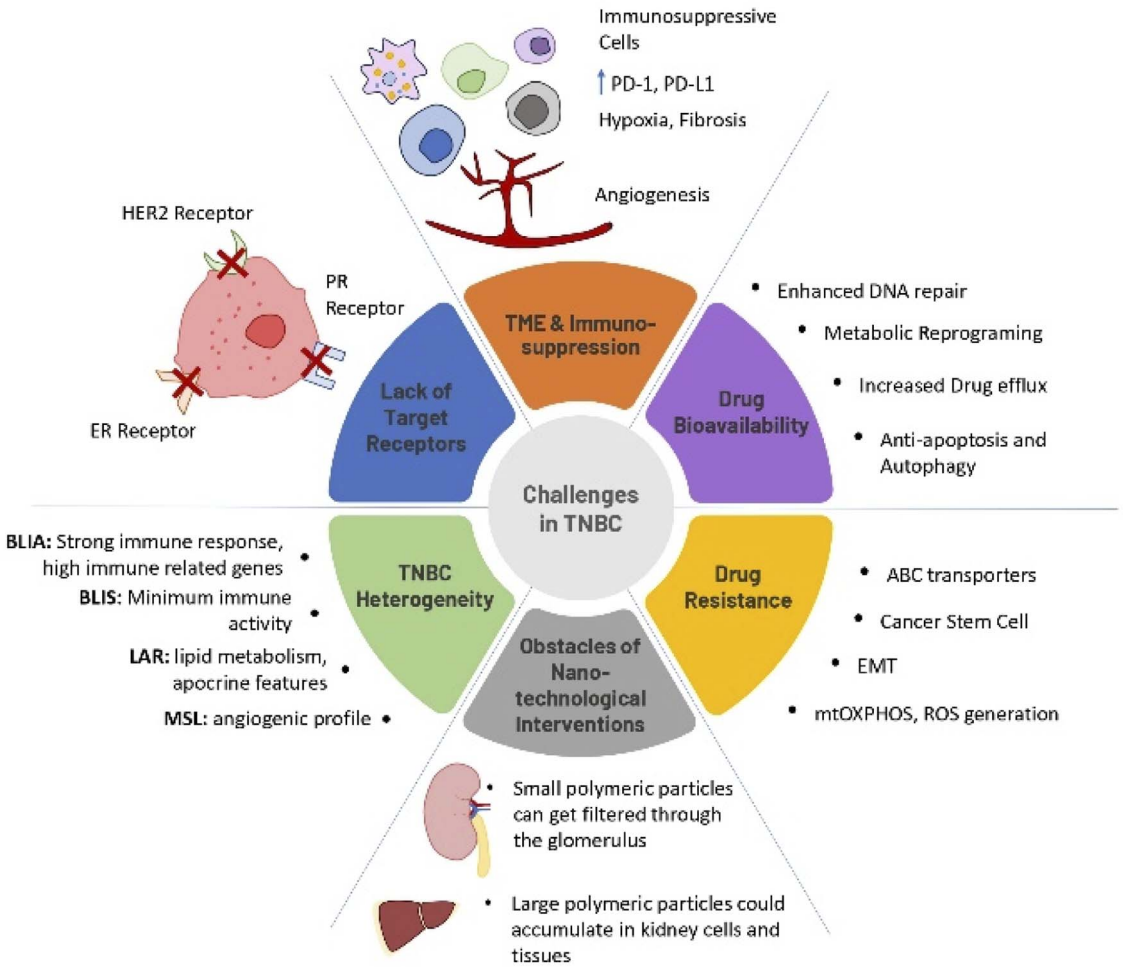

Fig. 2 Illustration of the complex challenges in treating triple-negative breast cancer (TNBC), highlighting factors such as tumor heterogeneity, drug resistance and the immunosuppressive tumor microenvironment.

3. Strategies for nanocarrier mediated cancer targeting

3.1. Surface modification and stealth techniques

3.1.1. PEGylation. PEGylation decreases the toxicity of peptides, proteins, hydrophobic polymers, medications, or NPs while improving their pharmacokinetic characteristics. With more than 20 PEGylated liposomes or RNA licensed by the FDA for clinical use, it is extensively utilised in biomedical research, especially in the treatment of cancer and neovascular age-related macular degeneration.[98] PEGylation improves NP targeting by:

- Decreased immune detection: PEG's hydrophilic and neutral properties conceal nanocarriers from the immune system, extending circulation duration.[99]
- Reduced protein adsorption: the PEG coating creates a barrier that prevents plasma protein binding, reducing rapid body removal.[100]
- Enhanced pharmacokinetics: PEGylation improves drug pharmacokinetics for more efficient delivery by avoiding immune detection and reducing protein adsorption.[101]

PEGylation strategies for NPs

- Physical adsorption: this conventional method involves functionalizing NP (NP) surfaces with PEG through simple operation and control. It is suitable for low PEG density and strong adsorption between PEG and substrates.[102] However, it suffers from low adsorption strength, causing PEG chains to detach under certain conditions.[98]
- Chemical conjugation: covalent coupling of PEG to NPs prevents PEG separation from the NP surface.[98] This strategy offers mild reactions, high yield, and stable bonds between PEG and the substrate. PEG is only on the surface, avoiding presence in the NP core.[103] However, the grafting is limited by the position and density of surface-active sites, causing issues with meeting application requirements. Space hindrance and reaction rate differences can lead to batch variations in the graft ratio.
- Molecular self-assembly: PEGylated NPs can be self-assembled using nanoprecipitation or emulsification. Amphiphilic polymers form spherical NPs, with fluorescence-labeled polymers used for drug delivery and bioimaging. Copolymers provide high surface graft density, but synthesis is complex and requires precision.[104] Emulsification results in higher PEG coverage but may damage shear force- or heat-sensitive drugs and biological agents.[98]

3.1.2. Biomimetic coatings. Disguising nanocarriers as "self" using proteins or cell membranes is a novel drug delivery strategy, particularly for cancer treatment.[105,106] Coating NPs with natural cell membranes or proteins offers several benefits. The natural cell membrane components, such as CD47 and CD44 proteins and glycans, help NPs evade immune clearance by signaling as "self".[107] These nanocarriers mimic donor cells' characteristics, enhancing their targeting to specific tissues or tumors through homotypic interactions.[108] The cell membrane coatings reduce recognition by phagocytic cells, lowering clearance by the mononuclear phagocyte system (MPS) and reticuloendothelial system (RES), thus improving distribution and delivery.[109]

3.1.3. Zwitterionic coatings. Zwitterionic polymers, with equal cationic and anionic groups, are popular in biomedical fields for their resistance to nonspecific protein adsorption and high biocompatibility. Types like phosphorylcholine, carboxybetaine, and sulfobetaine have proven effective for NP coatings.[110] However, linear zwitterionic polymer chains often lack sufficient density to fully mask the NP surface. A zwitterionic polymer membrane coating could bridge the gap between polymer and cell membrane coatings. Zwitterionic coatings, including those from polymethacryloyloxyethyl phosphorylcholine (pMPC), enhance NP stability and ingestion by reducing protein adsorption and particle aggregation, thus improving cellular absorption and suspension stability.[111] Certain zwitterionic coatings are pH-sensitive, aiding in tumor targeting. For example, applying a pH-sensitive zwitterionic coating to gold nanocages balances systemic circulation needs with cellular internalization.[112]

3.2. Targeting ligands

3.2.1. Antibodies and aptamers. Aptamer-conjugated nanomaterials offer a promising, less hazardous approach to cancer treatment by combining nanomaterials' properties with aptamers' unique recognition capabilities.[113] Recent advancements include using aptamer-conjugated NPs and aptamer-tethered DNA nanostructures for cancer cell recognition.[114] Cutting-edge strategies such as photothermal therapy (PTT) and photodynamic therapy (PDT) also employ these nanomaterials.[115,116] This aptamer-targeted approach shows high efficacy and minimal adverse effects, making aptamer-conjugated nanomaterials attractive for future cancer treatments.

Aptamers, with their strong affinity and selectivity for tumor cells, are used to develop anti-tumor medications, minimizing cell toxicity and enhancing therapeutic efficacy. They can be used alone or with other compounds to create targeted drug delivery systems. Prominent aptamers include Sgc8 (targeting protein tyrosine kinase 7; PTK7), AS1411 (targeting nucleolin), EpCAM (targeting epithelial cell adhesion molecule), and A10 (targeting prostate-specific membrane antigen; PSMA).[117] SELEX has evaluated these for tumor targeting. Aptasensors, which use aptamers as bio-receptors, have gained interest for cancer biomarker detection.[118] Aptamers can act as agonists or antagonists to tumor-specific surface indicators, producing tumoricidal effects. Aptamer–drug nanoconjugates, aptamer-modified nanocarriers, and aptamer-mediated immunotherapy are examples of therapeutic uses.

3.2.2. Peptides and small molecules. Peptide-based delivery systems used for CRISPR/Cas9 components have gained significant interest. Peptides can serve as carriers and targeting ligands, providing an effective alternative for targeted cargo delivery. They are cost-effective and low in toxicity and can be tailored to couple with NP vectors, ensuring specific payload delivery to target cells.[119] NP-based delivery techniques now incorporate the CRISPR/Cas9 system to target cancer-related receptors.

For example, Chen *et al.* conjugated the receptor-targeting ligand iRGD peptide to liposome-templated hydrogel NPs (LHNPs) in order to introduce CRISPR/Cas9 components into U87 cells and brain tumors.[120]

Cell targeting peptides (CTPs) are designed to target specific proteins on cell membranes, like the epidermal growth factor receptor (EGFR), integrin, and G protein-coupled receptors, which are tumor markers. The receptor must express at least three times as much as normal cells in order for targeting to be effective. Drug–antibody conjugates have successfully targeted the EGFR in TNBC.[121]

Cell-penetrating peptides (CPPs), short positively charged peptides comprising five to thirty amino acids, facilitate intracellular CRISPR/Cas9 delivery. Numerous studies have assessed CPPs' ability to deliver CRISPR/Cas9 components.[122–124] Dendrons and dendrimers are examples of cationic peptides that have been explored as CRISPR/Cas9 carriers.

Gene editing effectiveness up to 80% was achieved in HEK293T cells by Gustafsson *et al.*[124] when they studied the RNA-delivery CPP PepFect14 (PF14) for transporting a Cas9 RNP *via* a non-covalent interaction between the sgRNA and Cas9 RNP.

The development of targeted medications has accelerated, especially following the FDA's 2001 approval of imatinib, the first small-molecule tyrosine kinase inhibitor (TKI). In the past 20 years, FDA-approved targeted cancer treatments have significantly increased.[125]

3.3. Stimuli-responsive systems

3.3.1. Internal stimuli. Recent advances in nanocarriers for tumor theranostics focus on responses to internal stimuli like enzymes, redox, pH and hypoxia within the TME, potentially enhancing drug release and therapy efficacy.[126]

3.3.1.1. pH-sensitive nanocarriers. Metal–Organic Frameworks (MOFs), with larger surface area and high porosity, are effective drug delivery systems. pH-sensitive MOFs developed for cancer immunotherapy have shown enhanced anti-cancer activity by disrupting intracellular IL-6 and TNFα levels.[127] Similarly, Au NPs, known for high surface area and easy functionalization, have been developed as pH-sensitive carriers (Fig. 3). DOX (DOX)-loaded KFG-Au NPs demonstrated lower cell viability and reduced tumor volumes in human breast cancer cells.[128] Branched polymeric nanostructures, called dendrimers, have high drug loading capacity and antitumor activity at different pH

levels. They have shown effectiveness in imaging-guided anticancer therapy in HeLa cells.[129] Y. Han *et al.* reported a pH-sensitive polymeric micellar system for the delivery of PTX. The study reports that the PEG shell and optimal micelle size allow prolonged circulation and strong tumor accumulation, while their positive charge enhances uptake by TNBC cells. Once inside the tumor environment, the hydrazine bonds cleave and rapidly release PTX, leading to potent antitumor activity.[130] Polymeric Micelles (PMs) are self-assembling NPs with a hydrophobic core and hydrophilic shell, while liposomes are spherical vesicles with amphiphilic phospholipids. Both are biocompatible, biodegradable, non-toxic, and non-immunogenic, making them successful drug delivery systems.[126]

3.3.1.2. Enzyme-responsive carriers. Enzyme-responsive NPs: designed with an enzyme-responsive core, these NPs can entrap and release active drugs upon structural changes. Matrix metalloproteinases (MMPs) are crucial for developing these systems due to their role in cancer cell invasion and metastasis.[126] Activatable protein NPs (APNPs) have been developed for targeting therapeutic peptides, achieving extended circulation, reduced systemic toxicity, and controlled release.[131] Incorporating materials like proteins, peptides, and hyaluronic acid (HA) into NPs increases water solubility and facilitates cell uptake. Enzyme-cleavable peptides functionalized with hydrophobic drugs and MMP-responsive peptides are prioritized for these applications.[132] Enzyme-responsive linkers attach drugs to the NP core, connect the core to the hydrophilic crown, or modify the surface with targeting ligands. Peptides specific to proteases are common candidates for fabricating NPs with enzyme-responsive linkers.[133] Peptides and HA are used to develop targeting ligands with enzyme-responsive abilities, enhancing retention in brain tumors.

Hypoxia, or low oxygen levels in solid tumors, contributes to cancer progression and treatment resistance. Strategies to address hypoxia include increasing oxygen levels and using hypoxia-activatable prodrugs.[134] Various nanocarriers, such as liposomes, silica NPs, and polymeric micelles, have been engineered to target hypoxic tumors and deliver cargos like imaging agents and anticancer drugs.[135] Hypoxia-sensitive nanocarriers, made from hypoxia-sensitive materials, have shown high performance in tumor imaging and therapy.[136,137] Future studies should focus on modulating the hypoxic TME, enhancing drug penetration, and translating hypoxia-responsive nanocarriers to clinical use. Redox-responsive nanocarriers, with unique reduction potentials, are widely used for drug delivery in tumors. These include nanocapsules, mesoporous silica NPs, and polymeric micelles.[138] Disulfide bonds in these nanocarriers can be cleaved by glutathione (GSH), while diselenide bonds are also redox-sensitive but with lower bond energy.[139–141] Nanocarriers responsive to hydrogen peroxide (H_2O_2) have been developed for treating hypoxic and multidrug-resistant tumors. These nanocarriers can release cargo inside cancer cells through redox-sensitive bonds, leading to the degradation and dissociation of the nanocarriers. They also show potential in treating hypoxic tumors by targeting cancer cells with ligands like cRGD and releasing therapeutic agents for intracellular imaging and apoptosis.[142]

3.3.2. External stimuli. External stimuli such as magnetic, thermal, electronic, ultrasound, and light can influence nanocarrier behaviour in biological systems, enhancing accumulation, controlled release, intracellular delivery, and imaging and therapy activation. These methods offer precise control and multifunctionality in cancer theranostics but are less practical for metastatic lesions.[143]

3.3.2.1. Ultrasound. Ultrasound (US), a high-frequency sound wave, can control drug release at diseased sites like tumors. It is versatile, allowing imaging at low frequencies or disrupting nanocarriers for cargo release and enhancing cell membrane permeability at high frequencies. Commercialized microbubbles are used for US imaging, drug delivery, and cancer theranostics.[144] US-sensitive nanocarriers, incorporating gases or contrast agents such as air, N_2, and perfluorocarbons, can be used for tumor imaging, controlled cargo release, and enhanced tumor accumulation and intracellular delivery.[145] US creates transient pores in cell membranes, increasing the cytosolic delivery of released drug. In TNBC models, US in microbubbles has been shown to affect signalling pathways (*e.g.* JNK/c-Jun) and reverse drug resistance. Use of low intensity pulsed US with microbubbles improved chemo responsiveness in TNBC *via* JNK/c-Jun pathway modulation.[146]

3.3.2.2. Temperature-sensitive nanocarriers. Temperature-sensitive nanocarriers, stable at normal temperatures but responsive to higher temperatures, include liposomes, polymeric micelles, nanocomposites, nanocapsules, nanogels, and vesicles. Thermosensitive materials include poly(*N*-isopropylacrylamide) (PNIPAM), poly[2-(2-methoxyethoxy)ethyl methacrylate], poly(2-oxazoline) (POxs) (PMEOMA) and poly(*N*-vinyl isobutyramide) (PAMAM), which change their physicochemical properties with temperature variations.[126] However, there is a limited range of thermosensitive materials, and some have transition temperatures outside the biological range, complicating their use. Non-biodegradable polymers like PNIPAM pose challenges for clinical translation.[147] Future development should focus on biodegradable, thermosensitive materials and enhancing tumor accumulation for precise thermally triggered drug release and therapy. Natural Phase Change Materials (PCMs) like fatty acids and alcohols are preferred for their low toxicity, biodegradability, and cost. Combining PCMs with hyperthermia stimulation can enhance anticancer effects. Researchers suggest mixing fatty acids to match human body temperature for improved therapy.[148] A phase change fiber (PCF)-based scaffold has been developed for collaborative mild photothermal-chemotherapy. Hollow carbon fibers (HCFs) with high porosity and photothermal performance were soaked in methanol with apoptozole and DOX hydrochloride, showing optimal performance and temperature-responsive drug release under near-infrared laser irradiation.[149]

3.3.2.3. Magnetic-responsive nanocarriers. Magnetic-responsive nanocarriers target tumors to employ an alternating magnetic field to cause localized hyperthermia in order to release medication and ablate tumors. Incorporating magnetic materials like iron oxide NPs and graphene/Au/Fe_3O_4 hybrids, these nanocarriers can be used for MRI tumor imaging

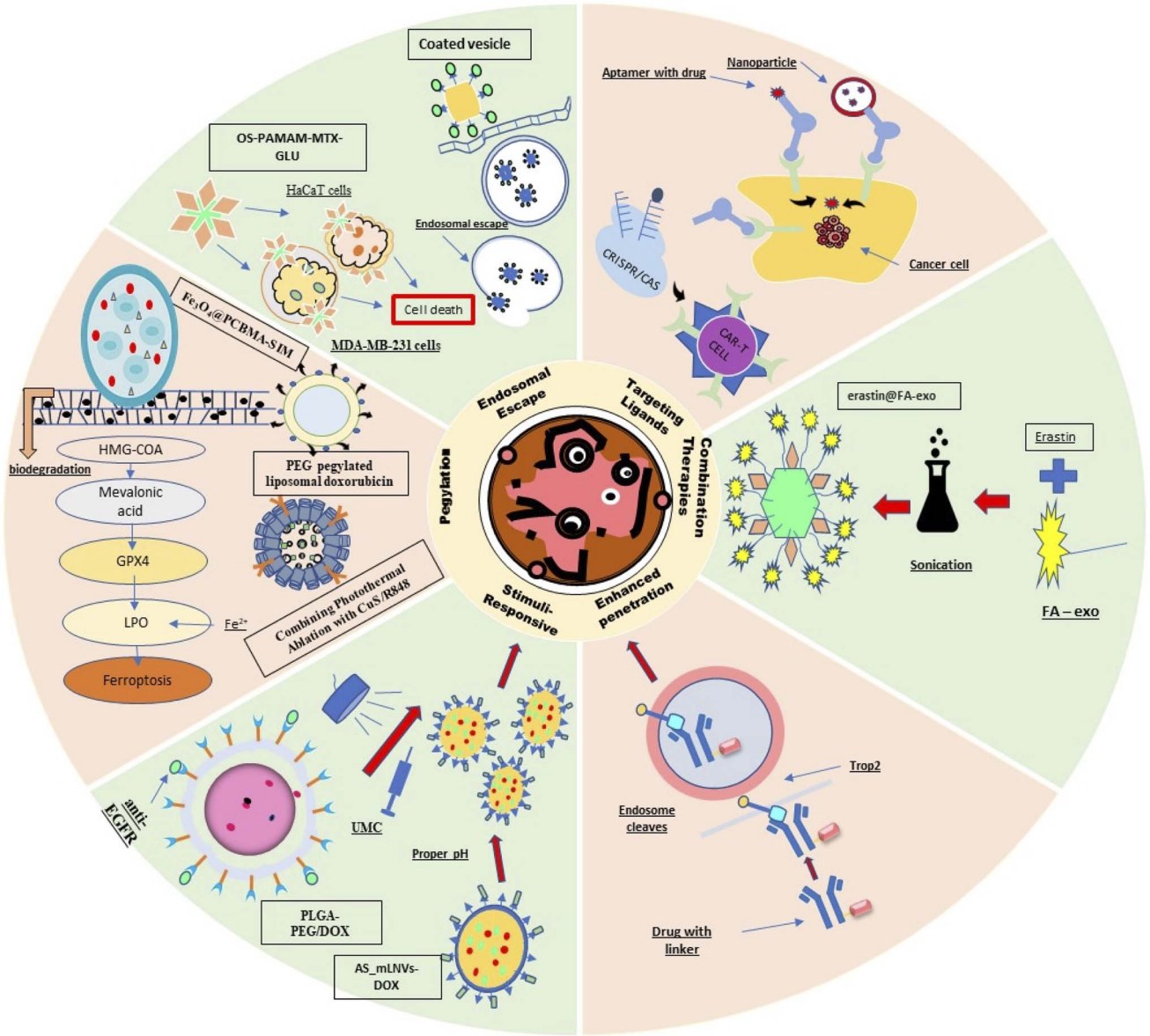

Fig. 3 Illustration of strategies for nanocarrier-mediated cancer targeting, featuring active targeting ligands, stimuli-responsive systems, and biomimetic coatings to enhance drug delivery precision and therapeutic efficacy in tumors.

and passive or active tumor targeting through the EPR effect.[150] The interaction with a magnetic field guides nanocarrier accumulation in tumors. Hyperthermia generated by magnetic-sensitive nanocarriers induces on-demand cargo release, promoting bioactive compound accumulation in tumors and treating hyperthermia-resistant and multi-drug resistant (MDR) cancers.[151–153] In an alternating magnetic field (AMF), these particles generate localized heat (magnetic hyperthermia). A study showed that dasatinib-loaded magnetic nanomicelles showed higher drug release and 1.35× greater cytotoxicity against MDA-MB-231 cells. Magnetic hyperthermia leads to dehydration of polymer chains and destabilization of the micelle structure, resulting in the boost of drug release from the hydrophobic core.[154] This approach shows promise for treating metastatic tumors and improving survival rates. High concentrations of magnetic-sensitive nanocarriers in specific areas and tumor-specific administration are prerequisites for the magnetic field-guided approach.

3.3.2.4. Light-responsive nanocarriers. Light-responsive nanocarriers have been developed for drug delivery, controlled release, and cancer therapy. They can be manipulated by adjusting the wavelength, power, and affected area of light. Examples include polyplexes, polyion complex vesicles (PICsomes), NPs, polymeric micelles, liposomes, upconverting NPs (UCNPs), polymersomes, nanogels, nanorods, and nanorattles. These can trigger therapeutic release, enable light-activated imaging, and generate singlet oxygen for photodynamic therapy (PDT) and tumor ablation.[155,156] Near-infrared (NIR) light can externally heat photoabsorbing nanocarriers, inducing drug release. For instance, a study used thermosensitive DPPC

liposomes loaded with indocyanine green (ICG) dye which upon NIR irradiation released an immunotherapy peptide payload and also generated local heat to kill TNBC cells.[157] Light-sensitive nanocarriers are highly promising for cancer theranostics, controlled release, and medication administration, particularly in accessible tumours.

3.4. Enhanced penetration techniques

3.4.1. Size and shape optimization. Size enlargement – NPs (NPs) in biomedical applications, like gold NPs (AuNPs), quantum dots and carbon magnetic NPs, have small sizes that enable good tumor penetration but can be quickly cleared, limiting their accumulation and therapeutic effect. Techniques to increase the size of NP at the tumor location utilize unique tumor tissue properties like acidic pH, upregulated enzymes, temperature, and exogenous stimuli.[158]

Size enlargement triggered by pH – in an acidic environment, pH-triggered enlargement depends on the dissolution of charge balance. To create pH-sensitive, mixed-charge zwitterionic AuNPs, researchers modified AuNPs using mixed self-assembled monolayers of weak and strong electrolytic chemicals.[159] Proteins containing acidic or basic amino acid residues serve as natural pH-sensitive nanoplatforms for enhanced tumor retention.[160]

Enzyme-induced size enlargement – overexpressed enzymes in tumors can trigger drug release or enhance targeting. Legumain, a conserved aspartate endonuclease, is useful for prodrug initiation and responsive nano-drug delivery. Hu *et al.* using highly expressed HAase in tumours developed a nanocarrier (CS-NG) that aggregates outside the cells and forms extracellular depots that prevent internalisation and extend tumour retention, increasing cytotoxicity and effectiveness.[161]

Temperature-responsive size enlargement – polymer solutions with adjustable LCST and UCST can form temperature-responsive NPs that cluster and self-assemble in the cells. Qiao *et al.* developed polymeric peptide conjugates (PPCs) that self-assemble in cells, ensuring stability and monitoring cell death and treatment response. Photothermal molecules and exogenous light enhance responsiveness to different temperatures.[162]

Light-mediated drug delivery – light-mediated drug delivery is noninvasive, spatiotemporal, and highly efficient for tumor treatment. NP cross-linking can result from the isomerization or dimerization of polymers conjugated with light-sensitive compounds such as azobenzene, spiropyrans, and salicylideneaniline at particular wavelengths. However, UV, visible, and blue light's weak tissue penetration limits *in vivo* application. Near-IR light is converted into short-wavelength light by rare-earth metals like lanthanide ions, enabling the development of up-conversion NPs (UCNPs) with potential in light-sensitive aggregation.[163,164]

Click-chemistry-mediated size enlargement – click chemistry is efficient and selective, promoting covalent crosslinks on NPs. A study used $CuSO_4$ and $C_6H_7NaO_6$ to enlarge NP size and improve tumor retention, though biotoxicity was a concern. By using strain-promoted alkyne–azide cycloaddition (spAAc), a more biocompatible, copper-free click chemistry has been developed for tumor-targeted drug delivery, responsive to intracellular lysosomes and acidic tumor microenvironments.[165]

3.4.1.1. Size shrinkage. pH-triggered size shrinkage – size shrinkage is facilitated by pH-responsive polymers and acid-labile chemical linkages. iCluster/Pt, a nano-system developed by Li *et al.*, releases small PAMAM prodrugs for deep penetration. This system shrinks from 100 nm in acidic tumor environments.[166] Polymers with ionizable groups transition between hydrophilic and hydrophobic states at different pH values, causing size shrinkage or disintegration. A size-shrinkable dual-pH-sensitive micelle system targets deep and perivascular tumor areas.[167]

Enzyme-triggered size shrinkage – tumor-associated enzymes like MMPs and HAase degrade the extracellular matrix, aiding cancer progression. A QD gelatin NP (QDGelNP) was designed to release smaller 10-nm QDs upon MMP-2 degradation for deeper penetration into the tumor. DGL/GEM@PP/GA is a multipurpose size-shrinkable nanoplatform that targets deep tumor penetration and TAF regulation.[168] Another NP (HSA-PTX@CAP-ITSL) responds to the fibroblast activation protein-α (FAP-α) and NIR laser irradiation. The dual receptor-targeting "cluster bomb" (DA-tMN) uses HA nanogel and DOX/AP-18 co-loaded micelles.[169] However, enzyme expression heterogeneity limits NP applications.

Redox-induced size shrinkage – intracellular glutathione (GSH) in tumor microenvironments is promising for reduction-sensitive delivery. Guo *et al.* created a size-shrinkable micellar system (PELEss-DA) for direct nuclear drug administration in MDR cancers,[139] whereas Wang *et al.* employed disulfide bonds in a pH- and redox-sensitive nano-system (PSPD).[169]

ROS-triggered size shrinkage – high ROS levels in tumor cells trigger size shrinkage. Cao *et al.* developed a ROS-sensitive nanocarrier (TK-PPE@NPCe6/DOX) for light-activated, controlled drug release. Combining ROS-responsive materials with photodynamic therapy (PDT) holds significant potential for enhanced tumor drug delivery.[158]

3.4.2. Extracellular matrix (ECM)-degrading enzymes. Hyaluronic acid (HA), a major ECM component, increases interstitial fluid pressure in tumors, hindering nanomedicine diffusion. It interferes with cell contact, recruits tumor-associated macrophages, promotes the epithelial–mesenchymal transition, and is linked to tumor resistance. HA modulates cancer biology by affecting intracellular signaling, cell proliferation, and invasiveness. Hyaluronidase (HAase) degrades HA, increasing tissue permeability. A study on NPs-EPI/HAase NPs showed enhanced tumor growth inhibition and deeper penetration in HepG2 tumors by embedding hyaluronidase to alter the TME, increasing NP penetration effectiveness.[170]

3.4.3. Active transport mechanisms. Receptor-mediated transcytosis (RMT) is a delivery technique that moves NPs into tumor tissue by binding to specific endothelial cell receptors. This process involves targeting receptors, creating ligand- or antibody-modified NPs, and transporting them through vesicles. RMT can reduce side effects, enhance efficacy, and

increase the NP concentration in tumor tissue. Lipid-based NPs have shown effectiveness in crossing the blood–brain barrier (BBB) *via* RMT.[171] While NPs can utilize the enhanced permeability and retention (EPR) effect under certain conditions, RMT is crucial for BBB crossing in therapeutic transport to the central nervous system.[172]

Surface modification with ligands like antibodies, peptides, or aptamers improves NP targeting specificity to BBB endothelial cell receptors or transporters, facilitating barrier transport.[173] Controlled release properties of NPs ensure long-term therapeutic concentrations in the brain, reduce adverse reactions, and enhance outcomes.

3.5. Endosomal escape mechanisms

3.5.1. Proton sponge effect. Understanding how drugs or nanocarriers escape endosomes is crucial for designing efficient delivery systems. The proton sponge effect, though controversial, suggests that cationic polymers like polyamidoamine (PAMAM) dendrimers can resist the pH decrease in endosomes. This leads to osmotic pressure buildup and endosomal rupture, releasing the contents into the cytosol. However, efficient quantification methods for endosomal escape remain lacking, often relying on reporter protein expression as an indirect measure. Mechanisms include pore formation, pH-buffering, flip-flop, and conformational changes. Despite their potential, biomimetic agents and synthetic peptides face challenges such as immune stimulation and poor stability.[174,175]

3.5.2. Membrane-disruptive polymers. An innovative approach in nanomedicine involves using polymers that disrupt endosomal membranes upon acidification, enhancing the direct cytoplasmic delivery of therapeutic agents. Polymers sensitive to acidic pH, such as those with tertiary amine groups, break down within cancer cells, releasing the therapeutic payload directly into the cytoplasm. This method bypasses the lysosomal degradation pathway, significantly increasing delivery efficiency. Safety concerns include ensuring biocompatibility and avoiding damage to non-target cells. This strategy is particularly beneficial for delivering nucleic acid-based therapies like antisense oligonucleotides (ASOs).[176,177]

3.6. Combination therapies

3.6.1. Multimodal approaches. Combining chemotherapy with immunotherapy, gene therapy, phototherapy, or other treatments can enhance the effectiveness of nanocarriers in tumor delivery through synergistic effects.

Phototherapy and nanomaterials synergy – combined photothermal and phototherapy for cancer shows that while phototherapy alone may be insufficient, it can be synergistic when combined with immunotherapy, radiation, chemotherapy, and gene therapy.[178]

Photo-immunotherapy – light-triggered multifunctional nanoplatforms for cancer photo-immunotherapy demonstrate that combining immunotherapy and phototherapy significantly increases therapeutic efficacy. NPs with high drug loading capacity and laser-triggered photodynamic and photothermal activity enhance the stability and biocompatibility of the cargo, reducing side effects.[179,180]

Integration of gene therapy – combining gene therapy with treatments like chemotherapy can improve outcomes for advanced-stage malignancies. Nanovectors play a crucial role in this integration by efficiently loading and delivering drugs to targeted organs and the cytoplasm.[181]

Chemotherapy-based synergy – intelligent nano-platforms combine chemotherapy with photothermal treatment (PTT), photodynamic therapy (PDT), and chemodynamic therapy (CDT) for enhanced anti-cancer effects. These platforms address various biological elements in tumors, resulting in improved therapeutic outcomes.[182]

These studies suggest that integrating multiple therapeutic modalities using nanocarriers can lead to more effective cancer treatments by targeting tumor sites and delivering drugs in a controlled manner.

3.6.2. Co-delivery systems

3.6.2.1. Multi-drug resistance (MDR) in cancer treatment. Mechanisms such as increased irregular drug uptake and efflux, elevated detoxification enzyme levels, intracellular redistribution, altered drug target enzymes, accelerated DNA repair, and survival/apoptosis signalling imbalances make MDR a major issue in the treatment of cancer. Co-delivery of medicinal agents employing NPs (NPs), precise ratiometric control of medications such as DOX adjudin (ADD) and (DOX), and programmed drug release are methods to overcome MDR.[183] When first- and second-generation P-gp inhibitors are ineffective, tetrandrine, quercetin (QUE), kaempferol, and icaritin are examples of natural alkaloids that can be used in conjunction with pharmaceutical medications.[184,185]

3.6.2.2. Inducing cell apoptosis. One intriguing method for causing cancer cells to undergo apoptosis is the co-delivery of several therapeutic drugs using NPs. For instance, liposomes loaded with curcumin (CUR) and cisplatin (CDDP) can enhance HepG2 cell apoptosis. Combining chemotherapy and photothermal therapy (PTT) in NPs is another effective method to induce cell apoptosis.[186]

3.6.2.3. Limiting tumor metastasis. Strategies to limit tumor metastasis involve preventing tumor growth, secondary tumor formation, and pulmonary metastasis. For example, P85-PEI/TPGS complex NPs can achieve effective RNA interference and cellular absorption in 4T1 cells, inhibiting tumor growth and pulmonary metastasis. High drug loading self-assembled nanodrugs, such as DOX and a berberine derivative (Ber), are effective in treating metastatic breast cancer.[187]

3.6.2.4. Inhibiting angiogenesis. Inhibiting angiogenesis, which is essential for cancer growth, can be achieved by targeting vascular endothelial growth factor (VEGF). Candesartan (CD) and angiostatin (ANG) plasmids were co-delivered into MCF-7 cells using an amine-functionalized silica NP, which effectively combined angiogenesis for the treatment of breast cancer.[188]

3.6.2.5. Inducing ferroptosis. The non-apoptotic programmed cell death mechanism ferroptosis has a lot of promise for cancer treatment.[189] Combining ferroptosis with chemotherapy, sonodynamic therapy, and phototherapy enhances

Table 3 Recent patents approved in NP based TNBC targeting[a]

Potential targets/targeting methods	NP engineering	Application in TNBC	Ref.
ICAM 1 (overexpression in TNBC)	ICAM 1 antibody conjugated iron oxide NPs as an MRI probe	Targeting agent and imaging agent	192
Active targeting capability with internal stimuli triggered	Bismuth-manganese-based composite particle comprises a TNBC cell membrane wrapping the core loaded with ICG	High drug loading rate, unique shape, easy preparation, and ability to modify the TME	193
CD44 (overexpression in TNBC)	Hyaluronic acid-appended PEG–PLGA polymer coated mesoporous silica NPs (MSNs) for the co-delivery of miR-34a-mimic and antisense-miR-10b	High specificity in targeting TNBC tumors and retardation of metastasis	194
Endosomal escape and release in cytoplasm	A pH activated NP containing a gas bound to a substrate by a pH sensitive interaction which releases the gas to disrupt the endosome	Significant suppression of tumor growth in TNBC models, especially those with deletions or mutations in the TP53 gene	195
Fibroblast growth factor-inducible 14 (Fn14) (overexpression in TNBC)	PTX loaded decreased nonspecific adhesivity, receptor targeted (DART) polymeric formulation with Fn14 specific binding	Enhances uptake by cancer cells, increases tumor retention, and reduces toxicity to surrounding healthy cells	196
Multitherapy approach including gene therapy, chemotherapy and photodynamic therapy	Electrostatic combination of an RNA hydrogel and manganese dioxide NPs that delivers miRNA-205, miRNA-182 and DOX	Improves the TME and administers PDT in addition to targeted gene therapy, chemotherapy, and on-demand drug release	197

[a] IACM-intercellular adhesion molecule; PDT-photodynamic therapy; ICG-indocyanine green.

antitumor immunity. Co-delivery systems in tumor immunotherapy can transport multiple therapeutic agents to immune effector cells or the TME, mutually boosting the anticancer immune response by improving antigen presentation, immune cell recruitment, stimulation of immune responses, and reducing immune suppression.[190,191]

3.6.2.6. Combination therapy. Combination therapy is a major trend in cancer treatment due to its benefits of enhancing treatment outcomes, overcoming metastasis, lowering toxicity, triggering ferroptosis and apoptosis, angiogenesis inhibition, tumour metastasis limitation, and antitumor immunity enhancement. Effective combination therapy involves choosing agents with different mechanisms, synergistic therapeutic effects and minimal adverse effects on normal tissues.[183] Table 3 enlists the patents approved in NP based targeting of TNBC in the past 15 years.

4. Nanocarrier design principles for optimizing cancer therapy

4.1. Functionalization of NPs with biomimetic materials derived from biological entities

Erythrocyte membrane – red blood cells (RBCs) are excellent NP carriers due to their biocompatibility, extended circulation, and biodegradability. RBCs' CD47 "marker-of-self" proteins prevent immune cells from phagocytosing them, extending circulation time.[198] Drug-delivery systems often use RBC membranes (RBCMs) to coat NPs (RBCM-NPs). Hu *et al.* first encased poly(lactic-*co*-glycolic acid) (PLGA) NPs in RBCMs, achieving a 64% reduction in macrophage engulfment by preserving CD47 orientation.[199] In contrast to other surface-modified NPs, RBCM-NPs have superior elimination half-life. For example, rapamycin-loaded RBCM-coated PLGA NPs specifically targeted atherosclerotic plaques, significantly delaying disease progression without substantial adverse effects in a mouse model.[200]

Leukocyte membrane – surface proteins found on white blood cells (WBCs) can identify inflammatory and sick tissues. T-cells, which have higher quantities of targeting proteins, accumulate more easily at tumor sites. T-cell membranes are used to camouflage NPs, prolonging circulation and enhancing cancer targeting.[201] Azide-modified T cell membrane-coated NPs showed excellent fluorescence intensity and photothermal response for bioimaging.[202] The T-cell receptor-peptide-major histocompatibility complex interaction is crucial for destruction of cancer cells, though it proved ineffective against solid tumors lacking tumor-specific biomarkers.[203]

Virus-derived strategies – virosomes and virus-like particles (VLPs) mimic viral structures without genetic material. VLPs resemble virus capsid structures, while virosomes are particles that resemble liposomes and have incorporated glycoproteins. Both can enclose various payloads, retaining viral traits like immune evasion and cellular entry. Encasing NPs in viral coating proteins enhances cellular absorption. For example, hepatitis B core VLPs encapsulated magnetic NPs efficiently, showing potential for magnetic resonance imaging applications.[204,205]

Bacterial membranes – using bacterial membranes as NP coatings is still under research, requiring extensive cytotoxicity studies. The size of outer membrane vesicles (OMVs) influences their entry into host cells. Lipopolysaccharide-neutralizing peptides can reduce BM-NPs' inflammatory response but only for specific cell types. Addressing these issues is crucial for developing BM-NP-based vaccines and treatments.[200,206]

Cancer cell membranes – cancer cell adhesion molecules (CCAMs) are crucial for metastasis. Cancer cells also express CD47, helping them evade the immune system. NPs coated with

cancer cell membranes (CCMs) exploit these properties, targeting homologous malignant areas and evading immune detection. CCM-NPs show strong homotypic attraction to source cancer cells, resulting in higher cellular uptake compared to uncoated NPs and RBC membrane-NPs. Using CCMs from the same cancer cells enhances selective targeting and self-recognition by source cancer cell lines.[207,208]

4.2. Functionalization of NPs *via* surface modification techniques

PEGylation – PEGylation involves adding PEG molecules to polymeric NPs to extend their half-lives in the bloodstream by reducing aggregation, opsonization, and phagocytosis.[209] PEGylation creates a hydrating layer by grafting PEG on NP surfaces, which hampers protein adsorption and MPS clearance. For instance, PEGylation of liposomal DOX extended its half-life significantly, from minutes to hours. PEG-decorated lipid NPs are crucial in developing mRNA-based COVID-19 vaccines, enhancing target mRNA transfection.[210] While PEG has numerous benefits, it can also cause hypersensitivity reactions. Alternatives like poloxamers, polyvinyl alcohol, poly(-amino acids), and polysaccharides have been explored, but PEG remains the most widely used material.[211]

Zwitterions (ZWs) – ZWs are a promising alternative to PEG, combining cationic and anionic groups to form a dense hydration layer under aqueous conditions. ZWs prevent protein adhesion, reducing immune absorption and prolonging NP circulation. However, ZWs do not actively interact with target proteins or cell membrane receptors, necessitating the grafting of biologically active groups (BAGs) for effective targeting. Functionalization of biocompatible SiO_2-NPs with amino (ANH_2), mercapto (ASH), and carboxylic (–COOH) groups facilitates electrostatic interactions with cell membranes, protein binding, and catalytic activity. Dual surface functionalization with ZWs and BAGs ensures NP stability in biological media and enables interaction with biosystems.[200,212,213]

Surface electric charge – the surface charge of NPs influences their fate and cellular absorption. Positively charged NPs are attracted to negatively charged cell membranes, enhancing cellular uptake, while negatively charged NPs have less cellular absorption.[214] In the body, NPs encounter a complex microenvironment with various proteins that can adsorb onto their surfaces, forming a protein corona. This can alter the NP's biological properties and functionality, leading to nonspecific internalization. The conjugation of functional groups to NP surfaces allows for the study of the surface charge effect and exposing them to different micropatterned environments. Both total surface charge and charge density should be carefully examined *in vitro* and *in vivo* to understand their impact.[215–217]

4.3. Functionalization of NPs with geometric property variations

4.3.1. Particle size. The size of NPs is a crucial design factor that influences *in vivo* behaviour, including circulation half-lives, extravasation, and macrophage absorption. NPs can be manufactured with high precision and monodispersity. For instance, NPs around 200 nm can pass through interendothelial slits of 200 to 500 nm, while larger particles (2–5 μm) accumulate in lung capillaries, which is beneficial for targeting metastatic sites.[218] Resident macrophages in the liver, spleen, and lungs also facilitate particle uptake. Generally, NPs under 100 nm exhibit prolonged circulation times, increasing their chances of extravasation through 380–780 nm tumor vasculature fenestrations. The enhanced permeability and retention (EPR) effect varies with tumor vascularity, but sub-100 nm polymer micelles (30–100 nm) efficiently penetrate highly permeable tumors.[219]

4.3.2. Shape. Shape-changing nanomedicines can balance retention and accumulation. A dual-stimulus responsive nanosystem, sensitive to acidic pH and light, was designed using a cytolytic peptide (melittin) with photothermal agents (cypate) and surface functionalized with HA. As a result of the EPR effect, these nanosystems ($\approx$35 nm) accumulated well at tumor sites. In acidic TMEs, they get transformed into nanofibers, remaining in tumor tissues for up to 72 hours. Upon laser illumination, these nanofibers changed into smaller NPs ($\approx$25 nm) for better penetration, dispersing throughout the tumor. This programmable shape transformation achieved effective cancer inhibition by balancing penetration and retention.[213,220]

4.4. Functionalization of NPs using materials used for preparation

Functionalization of NPs involves tailoring their composition to enhance specific therapeutic effects, particularly in targeting challenging cancers like triple-negative breast cancer (TNBC). Organic NPs, including lipid-based types like liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs), are widely used for their biocompatibility, controlled drug release, and reduced toxicities. They also provide high drug encapsulation and targeted delivery, while dendrimers and lipid-pol enhance drug stability and loading. Biomimetic carriers such as cell-derived cellular vesicles offer immune evasion and improved bioavailability. Inorganic NPs like metallic and carbon-based types have loading and multifunctional applications, with superparamagnetic NPs aiding in imaging and magnetic hyperthermia. Table 4 summarises the various types of NPs and their role in TNBC.

5. Clinical and translational perspective of nanocarriers

A small but growing number of NP formulations have reached clinical testing in breast cancer and some have been evaluated in TNBC cohorts. Established nanomedicines such as PEGylated liposomal DOX and albumin-bound PTX (nab-PTX) are clinically used in breast cancer and have been trialed in TNBC settings while targeted liposomal constructs (EndoTag-1 a cationic liposomal PTX, for *e.g.*) and PEGylated liposomal combinations continue to be assessed in TNBC trials (ClinicalTrials.gov identifiers: NCT00448305 and NCT02315196; ongoing adjuvant trials are also registered). These studies show that nanocarriers can improve tolerability and enable novel

Table 4 Overview of NPs: composition and applications in TNBC treatment

Types of NP			Composition	Role in TNBC	Ref.
Organic NPs	Lipid based	Liposomes	Phospholipids and cholesterol	Controlled release, non-hemolytic, non-toxic, non-immunogenic, biodegradable, and hydrophobic drug loading	221
		Nanoemulsions	Oil, surfactants, and co-surfactants	Hydrophobic drug loading, enzyme-resistant drug protection, improved bioavailability, enhanced drug solubility, and controlled release	222
		SLNs	Solid lipids, surfactants, and co-surfactants	Greater physical/chemical stability, biocompatible and biodegradable, and controlled release	223
		NLCs	Solid lipids, liquid lipids, and surfactants	Increased entrapment efficiency and reduced drug leakage during storage	224
		Exosomes	Cholesterol, diacylglycerol, surface proteins, heat shock proteins, lysosomal proteins, and nucleic acids	Low immunogenicity and toxicity	225
	Polymer based	Polymeric NPs	Cellulose, chitosan, PLL, PCL, PGA, PLA, and PLGA	High drug encapsulation, higher solubility & permeability, controlled release, and remarkable biocompatibility	221
		Polymeric micelles	Hydrophilic part: PEG, PVP and PTMC Hydrophobic part: PPO, polyesters, or copolymers of glycolic and lactic acids	Increased bioavailability, controlled release, and target specific action	154
		Dendrimers	Polyamidoamine (PAMAM), poly-lysine, PPI, phosphorus, and carbosilane	Enhanced drug efficacy, improved drug biocompatibility, reduced drug toxicity, and controlled/sustained drug release	226
	Lipid polymer hybrid		Polymers and lipids	High biocompatibility and stability, improved drug loading, and controlled release	227
	Biomimetic	Cell-derived NPs	Platelets, stem cells, RBCs, macrophages, and microorganisms	Lymphocyte and dendritic cell activation, homotypic targeting, and immune escape	228
		Extracellular vesicles	Exosomes, microvesicles or ectosomes, and apoptotic bodies	Enhanced drug penetrance, stability, solubility, lifespan, and cellular uptake	229
		Nucleic acid-based nanostructures	DNA, RNA, and aptamers	Smart cargo loading and release, targeted delivery, and combinatorial therapy	230
		Protein-based biomimetic nanocarriers	Albumin, ferritin, lipoproteins, and peptides	High cargo capacity, biodegradable, and easy surface modification	231
Inorganic NPs	Carbon based		Graphene and graphene oxide, carbon nanodots, oxidized carbon NPs, carbon nanotubes, and nanodiamonds	High drug loading, biocompatibility, low toxicity, multifunctionality, and controlled release	232 and 233
	Metallic/metal oxide NPs		Gold NPs, silver NPs, platinum NPs, zinc oxide, bismuth/manganese oxide, and yttrium oxide	ROS generation, theranostic applications, high drug loading, and low toxicity	234–237
	Superparamagnetic NPs		Magnetite (Fe_3O_4)	Magnetic hyperthermia and MRI	238
	Quantum dots		Multiple metal and non-metal based	Targeting system, cytotoxic activity, and diagnostics	239
Hybrid NPs			Combination of two or more NP systems	Extraordinary diagnostics, treatment, drug loading, and targeting capabilities	240

combination regimens (*e.g.* chemo-immunotherapy), but clear superiority in long-term outcomes over standard regimens remains limited in many instances.

5.1. Key translational challenges

Translating TNBC-targeted nanocarriers from bench to bedside involves several interconnected obstacles like major hurdles in nanocarrier fabrication, high-cost, scale-up and reproducibility. Laboratory scale synthesis especially for complex hybrid or biomimetic coatings is difficult to reproduce under GMP conditions impacting batch-to-batch consistency and leading to altered pharmacokinetics and therapeutics.[241] Safety and immunogenicity concerns also remain significant as intravenous nanomedicines can activate the complement system and trigger complement activation-related pseudo allergy (CARPA), infusion reactions or unpredictable immune responses, complicating clinical dosing and monitoring.[242] In addition, heterogeneous TNBC biology and the lack of strong predictive biomarkers for NP accumulation or treatment response lead to suboptimal patient selection in clinical trials, reducing measurable therapeutic benefit across diverse cohorts.[243]

Global market capture by nanomedicines is around 150 billion USD supported by an accelerating growth rate of 26.7%. But still entry into clinical application is constrained by several factors like cytocompatibility, *in vivo* stability, unfavourable routes of administration (as most nanocarriers are introduced through the parenteral route) and degree of selectivity especially in the case of targeted nanocarriers.[244] Additionally, the fabrication of most nanomedicines is a multi-step affair so in a large scale setting reproducibility, high-cost and time consumption become major burdens.[245]

Regulatory and clinical pathway uncertainty further slows translation because guidance specific to sophisticated nanomedicines is still evolving and differs across regulatory bodies adding cost time and uncertainty to clinical translation.[246]

5.2. Strategies to enhance clinical translation

Recent clinical and preclinical efforts highlight several strategies that may accelerate translation of nanocarriers in TNBC. Biomimetic and immune-compatible coatings such as cell membranes or exosome covering are being explored to improve immune evasion, reduce opsonization and extend time for systemic circulation.[247] Another promising direction is simplifying and modularizing nanocarrier design so that a single scalable manufacturing platform can deliver different therapeutic payloads that can improve reproducibility and reduce regulatory complexity while maintaining flexibility for personalized treatment approaches. Early integration of companion diagnostics and patient-selection biomarkers may further strengthen translation. Imaging-based predictors of NP accommodation or molecular biomarkers such as PD-L1 or EMT signatures could assist in identification of responsive TNBC subgroups and improve trial outcomes.[243] Combination strategies are also gaining momentum with nanocarriers increasingly being designed to co-deliver chemotherapeutics alongside immune modulators or targeted therapies, capitalizing on synergy and supporting improved clinical responses in TNBC.

5.3. Causes of failure of nanocarriers in clinical translation

Many nanocarriers fail before or during clinical development due to a combination of biological, technical and regulatory limitations. A major factor is the insufficient predictive power of preclinical models like rodent xenografts that often overestimate NP tumor uptake and treatment efficacy compared with human tumors, leading to clinical results that do not reproduce the strong preclinical activity.[248] Pharmacokinetic and bio-distribution discrepancies also contribute to failure as human plasma protein corona formation and variable tumor perfusion can alter NP behavior in ways not observed in animals. Immunological liabilities, in particular, complement activation and CARPA-like reactions, sometimes force dose reductions or compromise trial continuity while also potentially interfering with antitumor effects.[242,249] Manufacturing and quality-control barriers remain significant; complex multicomponent structures including biomimetic surfaces are challenging to standardize under GMP which leads to increasing regulatory risk and production cost.[241] Finally, many nanocarrier systems failed to demonstrate clear clinical advantages such as improved survival or markedly reduced toxicity over existing therapies in spite of cost escalation, which is essential for regulatory approval and clinical adoption.

6. Challenges

Nanotechnology has significantly advanced, but few NPs (NPs) reach clinical trials, often halting at *in vivo* and *in vitro* stages. The challenges in clinical translation of NPs are broadly categorized into biological, technological, and study-design-related issues.

NPs face difficulties with routes of administration, biodistribution, crossing biological barriers, degradation, and toxicity.[250] Intravenous injection is common, but NPs are quickly cleared from the bloodstream, requiring high drug concentrations that may not yield desired effects.[251] Magnetic NPs, controlled by 3D magnetic fields, show promise, but their effects on the human body need more research. NPs, despite being made of biosafe materials, can cause lung, liver, and kidney damage due to factors like surface area, particle size, and solubility.[252] They can accumulate in the lungs, causing inflammation and cytotoxicity,[251] and generate harmful free radicals.[253] Using biocompatible materials like chitosan and NIR-responsive substances might mitigate these issues. Avoiding the mononuclear phagocytic system (MPS) is another challenge. In biological fluids, NPs form a protein corona (PC) that prompts MPS uptake. Coating NPs to prevent PC formation has had limited success. Targeting macrophages as drug carriers or using strategies like preventing macrophage recruitment, depleting TAMs, and blocking CD47-SIRPα pathways are potential solutions.[254]

Scaling up NP synthesis and ensuring consistent optimization and performance are crucial for clinical success. Most NPs used in studies are produced in small batches, making large-scale production difficult. Lead clinical candidates often lack

Table 5 Performance overview of nanocarriers in TNBC: efficacy enhancement and minimization of off-target toxicity

Nanocarrier type	Improved outcomes	Mitigation of toxicity/side effects	Ref.
FZD7-targeted PLGA NPs	Increased TNBC cytotoxicity Downregulated Wnt/beta-catenin signaling and enhanced cell killing	Improved therapeutic window	260
DOX-Fe/RSL3 co-loaded lipososmes	Synergistic anti-cancer effect	Reduced DOX toxicity due to the DOX–Fe complex	261
C-peptide conjugated solid lipid NPs (SLNs)	SLNs loaded with an integrin (α-vβ-3)-binding C-peptide showed much higher 4T1 cell kill ($IC_{50} \sim 1.2$ μg ml^{-1}) than the untargeted ($IC_{50} \sim 3.4$ μg ml^{-1}) or free drug ($IC_{50} \sim 1.2$ μg ml^{-1}) *In vivo* showed ∼82% tumor volume reduction and abolition of lung metastases	Preserved normal tissue despite high drug dose	262
PAMAM dendrimer-camptothecin (PD-Campto) conjugate	PD-Campto showed markedly higher uptake by TNBC cells and much stronger cytotoxicity than the free drug	Enhanced camptothecin's aqueous solubility and provided sustained release Reduces off-target exposure	263
Magnetic iron-oxide mesoporous NPs (DOX-loaded HFON)	Hollow mesoporous iron oxide DOX loaded NPs (with external magnet targeting) induced high ROS and ferroptosis in MDA-MB-231 cells	External magnets facilitated drug-NPS tumor selective delivery ensuring unharmed normal tissues	264
Poly(glutamic acid) crosslinked DOX nanogels	Demonstrated anti-metastatic efficacy, strongly inhibiting lung nodules and almost completely suppressing lymph node metastases	Showed no evident additional toxicity. Improved safety margins by leading DOX to metastatic sites	265

systematic optimization. Testing numerous nanoformulations and iteratively selecting the best one can help, but such candidates shouldn't go directly to human trials. Because it is difficult to replicate *in vivo* data in human trials, predicting NP efficacy and performance is a hard task. Combining computational modeling with experimental results, such as using organs-on-chips, can improve predictions.[255–257]

Study size, intent, and timing of NP therapies impact clinical outcomes. Numerous research studies use animal and cell models, which might not translate to trials involving humans. Single models struggle to replicate human reactions. Research on cancer metastasis models is crucial due to metastasis being a key cancer property. Clinical studies are necessary for personalized medicine, considering genetic, medical history, and environmental factors.[258,259] NPs are rarely first-line therapies. Approved nanoformulations are often used when disease progression is detected, typically in patients with multiple prior treatments or drug resistance, skewing clinical trial results and reducing NP treatment's perceived effectiveness. Despite these challenges, advances in NP technology and study designs continue to hold promise for more effective cancer treatments. In view of these translational challenges it is essential to evaluate how different nanocarrier designs perform across therapeutic outcomes and safety profiles. Table 5 summarizes these comparative insights with a focus on multifunctional biomimetic and next generation TNBC nanocarriers.

7. Conclusion

By enhancing the delivery of chemotherapeutic medications straight to tumors and reducing systemic toxicity and adverse effects, nanocarriers have become a promising strategy for targeted cancer treatment. One of their main advantages is their capacity to target cancer cells using both active and passive techniques. Nanocarriers can aggregate in tumour tissue by passive targeting, which takes advantage of the tumour vasculature's increased permeability and retention effect. To enable precise drug administration, active targeting entails functionalizing the surfaces of nanocarriers with ligands or antibodies that attach to overexpressed receptors on cancer cells. A complete approach to cancer treatment that may involve immunotherapy, gene therapy, chemotherapy, and real-time imaging is made possible by the adaptability of nanocarriers, which enables them to co-deliver a variety of therapeutic drugs and diagnostic instruments. Because cancer is complex, this multifunctionality is essential for providing individualised and adaptable treatments.

Innovations in nanocarrier design are expected to prioritise stimuli-responsive systems that can release drugs only upon tumor-specific cues, biomimetic coatings that improve immune compatibility and modular architectures that allow rapid customisation for different cancer subtypes. Engineering nanocarriers with improved intratumoral penetration, real-time tracking abilities and predictable pharmacokinetics will be essential for achieving consistent clinical outcomes. On the translational side, advances in scalable manufacturing, standardized quality control frameworks and early integration of regulatory considerations will accelerate movement from laboratory development to clinical use. Combining nanocarriers with patient-specific molecular profiling and AI driven optimization also represents a growing opportunity to design personalized, adaptable and more effective cancer therapies.

In conclusion, even if nanocarriers present a groundbreaking method of treating cancer, their full potential in

clinical oncology depends on resolving present issues through ongoing research and development. More specialised and improved therapeutic outcomes with nanomedicines will be possible by bridging the gaps in their clinical translation, structured regulatory network and better comprehension of the cancer microenvironment.

Author contributions

Qazi Saifullah: conceptualization, writing – original draft. Sajid Mondal: writing – original draft. Amartya Nandi: writing – original draft. Yeduvaka Madhuri: writing – original draft. Suvadra Das: conceptualization, writing – review & editing. Partha Roy: conceptualization, supervision, writing – review & editing.

Conflicts of interest

The authors confirm the absence of conflict of interest.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this work.

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