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Bioactive nanotherapeutic trends to combat triple negative breast cancer

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Bioactive nanotherapeutic trends to combat triple negative breast cancer

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ABSTRACT

The management of aggressive breast cancer, particularly, triple negative breast cancer (TNBC) remains a formidable challenge, despite treatment advancement. Although newer therapies such as atezolizumab, olaparib, and sacituzumab can tackle the breast cancer prognosis and/or progression, but achieved limited survival benefit (s). The current research efforts are aimed to develop and implement strategies for improved bioavailability, targetability, reduce systemic toxicity, and enhance therapeutic outcome of FDA-approved treatment regimen. This review presents various nanoparticle technology mediated delivery of chemotherapeutic agent(s) for breast cancer treatment. This article also documents novel strategies to employ cellular and cell membrane cloaked (biomimetic) nanoparticles for effective clinical translation. These technologies offer a safe and active targeting nanomedicine for effective management of breast cancer, especially TNBC.

1. Introduction

Breast cancer (BC) remains the most commonly diagnosed cancer among women and is the second leading cause of death after lung cancer in the United States [1]. In 2020, it was estimated that 276,480 new cases of BC will be diagnosed among women and 42,170 women will be expected to die due to this disease. Breast cancer begins when the malignant epithelial cells accumulate and grow out. Depending on the region they grow out from, it is classified into non-invasive and invasive. Non-invasive (carcinoma *in-situ*) is when the carcinoma is confined in the lobules and duct. Invasive carcinomas occur when the carcinoma diffuses to the surrounding connective tissues and metastasize to distant sites. These carcinomas are divided into ductal and lobular carcinoma, depending on where the tumor is formed. Ductal carcinomas comprise two-third of the total BC and arise from the epithelial cells of the ducts, whereas the lobular carcinoma arises from the lobules and is about one-third of the total BC cases [2].

Triple negative breast cancer (TNBC) represents the most aggressive and heterogeneous subtype of BC. Clinically, it is characterized by negative for expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) protein. Typically, TNBC demonstrates an increased mitotic activity, increased expression of proliferation markers, high nuclear atypia, high nuclear-cytoplasmic ratio, scant stromal content, central necrosis, multiple apoptotic cells, invasive, and stromal lymphocytic infiltration [3,4]. Additionally, these tumors are also characterized by rapid growth rate, higher grade, greater chance of lymph node involvement/progression, and metastasize mostly to the viscera, especially the lungs and the brain [5]. The distinct cellular phenotype, aggressive nature, metastatic potential, and lack of receptor or target [6], makes chemotherapy as a prefered treatment option for TNBC. However, TNBC with the worst prognosis and high recurrence rate within the first 5 years of therapy and shorter overall survival to only 9–13 months [7], in contrast to other subtypes of BC, which makes therapeutic intervention for TNBC is an unmet need.

2. Therapeutic strategies for TNBC

As described above, TNBC due to heterogeneity, molecular variability, and stemness [8] has no specific treatment protocol. Although

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the relentless efforts of researchers have led to improvements in the therapy of TNBC, and newer targets are discovered by studying the genomic variability. Therapies that have shown promising outcomes in TNBC, either alone or in combination with neoadjuvant therapy have been evaluated by clinical trials, are summarized below. Fig. 1 describes the schematic representation of the various conventional treatment strategies and emerging treatment trends for TNBC. Although chemotherapy remains the backbone treatment option for most TNBC patients, emerging trends are evolved which includes immunotherapy (checkpoint inhibitors), targeted therapy (inhibitors of various pathways), antibody conjugates, and novel nanotherapeutic formulation.

2.1. Conventional chemotherapy

Chemotherapy remains the mainstay treatment for TNBC. These agents are usually anthracycline, platinum, and/or taxanes. Anthracyclines such as doxorubicin (DOX) and epirubicin (EP) have shown enhanced response rate and survival by 22 months [9–12]. These agents have proven to be beneficial and have shown enhanced sensitivity when used as a single agent [10,11] as well as in neoadjuvant setting [12]. Phase III clinical trial of anthracyclines as an adjuvant agent versus CMF (cyclophosphamide, CP; methotrexate, MTX; and 5-fluorouracil, 5-FU) [13] demonstrates a 23% decrease in the recurrence rate. A 17% pathological complete response (PCR) in Phase II clinical trial was observed in a neoadjuvant setting with anthracyclines agents in combination with others such as CP, 5-FU, and epirubicin (ER) [14]. A Phase III clinical trial demonstrate that a 5-year disease-free survival was achieved in 71% of the TNBC patients treated thrice every week in contrast to only 26% improvement with treated twice weekly when anthracyclines are used in combination [15–17]. Although, a higher response rate is achieved with this therapy [16,17] yet higher recurrence rate and overall low survival rate [18] has limited usage of this type of therapy. Other associated side effects include acute toxicity such as irreversible cardiotoxicity myelotoxicity, alopecia, nausea, and vomiting [18–20].

Platinum agents have proven to be beneficial for the treatment of TNBC patients when used in combination or as single agents [21]. These agents are effective in patients with a breast cancer gene (*BRCA*) mutation. A Phase II clinical trial (NCT00148694) suggests that 21% of patients received PCR with single-agent cisplatin and 15% response when excluding the BRCA1 mutations. This indicates the importance of platinum agents as adjuvant or neoadjuvant therapy in BRCA mutants [10]. BRCA1 mutant has shown increased sensitivity to platinum agents because of the ability to repair DNA; however, it may become resistant and may be required to be used in homologous combination [11]. Another Phase II clinical trial suggests carboplatin and paclitaxel (PTX) with or without trastuzumab showed a 67% increase in PCR [22]. In another Phase II clinical trial, cisplatin (CIS) combination with ER and 5-FU in addition to PTX versus without the PTX treatment improved the response rate by 40% [23]. A higher response rate of 34% was observed in women treated with platinum and docetaxel (DTX) [24]. Thus, a combination of platinum agents has been shown to have higher efficacy than when used alone. Therapy with platinum agents are of special interest when treating a TNBC patient with a BRCA defect.

Taxanes either as a single agent or in combination with anthracyclines have shown to be beneficial in TNBC in contrast to other subtypes of BC, attaining PCR of up to 40% [25]. Cancer and Leukemia Group B

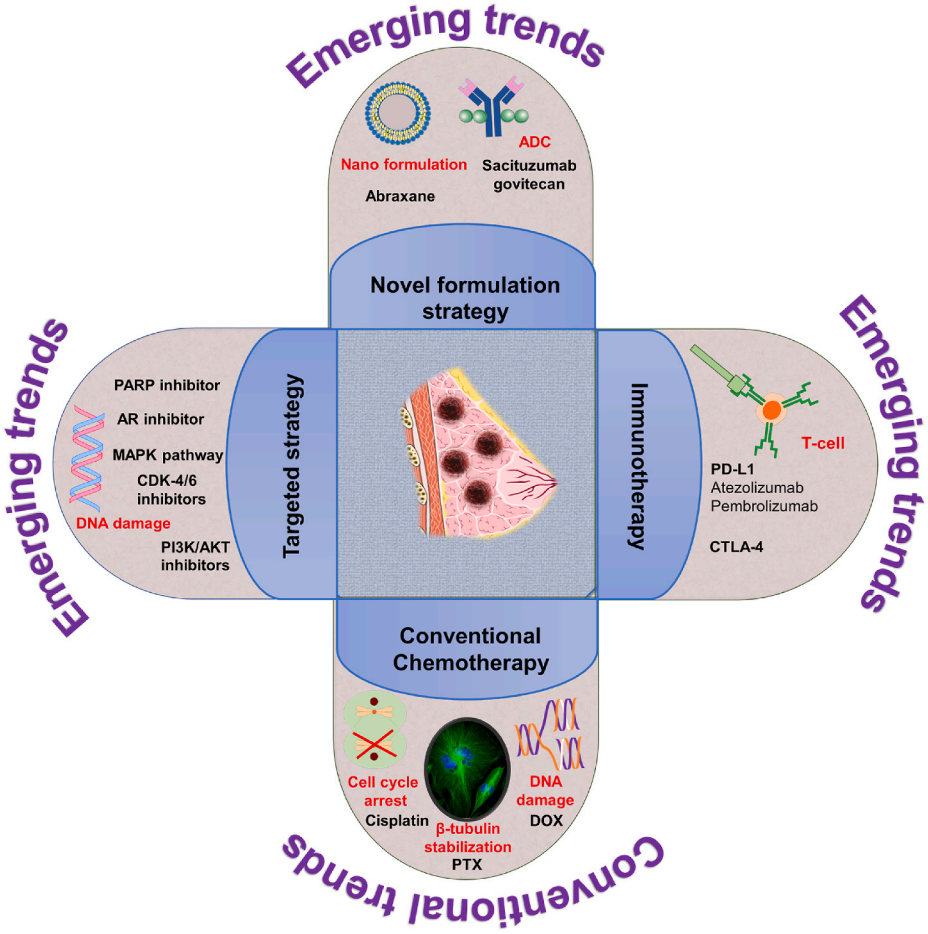

Fig. 1. Schematic illustration of various treatment strategies for TNBC. Conventional strategies with chemotherapeutic agents (doxorubicin, paclitaxel, and cisplatin), targeted strategies includes specific pathway inhibitors, immunotherapies, and nanotechnology (drug loaded nanoparticles or antibody drug conjugates).

(CALGB) team conducted a trial on 9344 subjects, demonstrate disease-free survival among TNBC patients treated with PTX, versus all other subtypes of BC [26]. BC International Research Group (BCIRG) reported a clinical trial report that indicated an advantage in the group that was co-treated with PTX over cyclophosphamide on the TNBC cohort [27]. Further, a non–platinum-based neoadjuvant therapy with CP-DOX-vincristine-prednisolone shows a 15% increase in the PCR in comparison to all the other regimen, suggesting TNBC apart BRCA mutation subset, has greater response to taxanes in comparison to other regimens [28].

2.2. Targeted therapies

The molecular heterogeneity of TNBC [6] makes it difficult for physicians and clinicians to have a standard care guided approach for the treatment. Advancement in the molecular classification and genome sequencing has led to the development of targeted therapy [6,8]. From a variety of gene expression analysis, six main subtypes of TNBC have been proposed, *viz.* basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor (AR) [29]. Numerous clinical trials are underway to develop targeted therapy for TNBC using inhibitors of poly ADP ribose polymerase (PARP), phosphatidylinositol 3-kinase/Protein kinase B (PI3K/AKT), mitogen-activated protein kinases (MAPK), and cyclin-Dependent Kinase (CDK).

Among these therapies, PARP-1 inhibitor(s) leads to enhanced DNA double-strand breaks causing an increase in apoptosis [30–32]. PARP-1 inhibitor has been particularly beneficial in BRCA1 and BRCA2 mutant cells because of their ability to sensitize cells [31,32]. Although BRCA mutations account for only 20% of TNBC population, yet several PARP inhibitors have gained clinical approval such as olaparib, veliparib, niraparib, rucaparib, and talazoparib. Phase III clinical trial in TNBC patients with BRCA mutation report that oral PARP inhibitor olaparib increases the progression-free survival to 7 months in contrast to 4.2 months in the placebo group. US Food and Drug Administration (FDA) approved the first PARP inhibitor (olaparib in 2018) for the treatment of advanced-stage BRCA mutant TNBC [33]. Talazoparib treatment confirmed that about 53% of patients achieved PCR in a phase II clinical trial NCT02282345 [34]. A larger single-arm Phase II study (NCT03499353) proved that talazoparib is highly effective in HER2 negative advanced BC with an overall survival of 24.3 months, in contrast to only 6.3 months in patients receiving only chemotherapy. This lead to the approval of the second PARP inhibitor for germline BRCA mutation [34].

The PI3K/AKT regulates cell growth and glucose metabolism. There are complexities associated with the activated PI3K/AKT pathway, although activated PI3K/AKT pathway is high in TNBC [34]. Ipatasertib, an oral AKT inhibitor is used with PTX demonstrated improved progression-free survival from 9 months to 4.9 months in TNBC patients (phase II NCT02162719) [35] and improvement in overall survival of 23.1 months versus 18.4 months [36]. Inhibition of epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor by PI3K/AKT pathway has proven to be useful in the treatment of TNBC. However, cetuximab a humanized monoclonal antibody used in combination with other taxanes failed to show significant improvement in the TNBC subtype [37]. Similarly, another phase II multicenter clinical trial by the Translational BC Research Consortium demonstrates that cetuximab used alone or in combination with platinum agents such as cisplatin and carboplatin, failed to show any impressive result by the anti-EGFR antibody [38]. This is probably because only 50% of the TNBC cases are EGFR positive [39].

AR accounts for 13–37% among TNBC patients and it is more prevalent among older [40,41] people. However, the role of AR as a prognostic marker in TNBC is not clear, as there are contradictory reports about the characteristics of AR in TNBC. It is also associated with low nuclear grade, and low proliferative rate and is unrelated to be a prognostic marker [42], whereas some suggest they have a higher nuclear grade, high lymph node metastasis, and higher mortality rate [43]. Enzalutamide is a novel targeted AR inhibitor that competitively binds to the AR and prevents translocation to the nucleus [44]. NCT02750358 is a Phase II ongoing clinical trial for determining the compliance rate of enzalutamide as adjuvant therapy for a 1-year dose [45]. In another Phase II clinical trial, superior benefits are achieved with enzalutamide indicating this may be a therapeutic option for patients. To further evaluate the efficiency of enzalutamide with PTX a phase IIB is currently ongoing. Bicalutamide also an AR inhibitor, has shown to have promising results in a phase III clinical trial for metastatic TNBC patients [46].

The role of activation MAPK was initially investigated *in vitro*, which causes loss or downregulation of various genetic and epigenetic functions that are associated with chemoresistance. MEK inhibitors are known to cause efficient suppression of chemoresistance either alone or in combination with other chemotherapeutic drugs. Significant inhibitory effects were seen with combination treatment of cobimetinib with PTX [47]. Another study demonstrates, MEK inhibitor selumetinib given in combination with either buparlisib or the platelet-derived growth factor receptor inhibitor pazopanib, showed effective inhibition of brain metastases in TNBC patients [48]. An ongoing clinical trial shows MEK inhibitor trametinib in combination with gemcitabine showed complete response in the patient with metastatic TNBC [49]. However, there have been serious toxicities prohibiting phase II clinical study of MEK inhibitor with mTOR or PI3K inhibitors [50,51].

CDK is responsible for hyperphosphorylation of retinoblastoma protein (RP) and causes G1-S phase transition in the cell cycle [52]. CDK inhibitors thus were explored as a potential target for TNBC. Palbociclib is a selective inhibitor of CDK and was explored in clinical trials for TNBC with positive RP expression, that demonstrated a partial response in 50% of the patients, improving disease-free survival for 6 months or more [53]. There are several other clinical trials conducted either alone or in combination with other chemotherapy.

2.3. Antibody-drug conjugates

Antibody-drug conjugates (ADCs) are also considered as targeted therapy where the toxic anticancer drug targets the cancer cells through the specific binding of an antibody that has specificity for receptors on the surface of the cancer cell. There have been lot of ongoing research using ADCs for TNBC with some of them discussed below. Trophoblast antigen 2 (Trop2) [54] is target *via* ADC for TNBC. IMMU-132, also known as sacituzumab govitecan is an ADC that targets Trop2 and have been used in combination with three PARP inhibitor; olaparib, rucaparib and talazoparib and have shown improved overall response [55]. Another compelling ADC, glembatumumab vedotin that combines the monomethyl auristatin E (MMAE) (a potent microtubule-disrupting agent) shows improvement in disease-free progression in Phase I/II clinical trial [56]. However, data suggests that a 100 mg dose caused some toxicity of grade 3 and 4, which may limit the usage of these agents [57]. Ladiratuzumab vedotin is another ADC explored for targeting TNBC and is composed of a humanized IgG1, MMAE and a monoclonal antibody for targeting oestrogen-regulated gene (LIV-1). LIV-1 is overexpressed in 90% TNBC tumors but is not significantly expressed in normal tissues. In a phase I study with ladiratuzumab vedotin a 25% overall response rate was achieved. Although there are toxicity issues such as alopecia, neutropenia and peripheral neuropathy. Ongoing studies are still conducted to evaluate the efficiency of ladiratuzumab vedotin as monotherapy or in combination with chemotherapy for TNBC [58].

2.4. Immunotherapy

TNBC is known to have the highest mutations among all other types of BC. The role of tumor-infiltrating lymphocytes play a major role in disease progression in TNBC. Thus, activation of these cytotoxic T cells

would be initiating an antitumor immune response. T cells show the expression of immune checkpoint inhibitors: cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1). PD-1 inhibitors are the most extensively studied checkpoint and is a cell surface protein expressed on the infiltrating tumor lymphocytes that induce inhibition of T cells by binding to two ligands: PD-L1 and PD-L2 [59]. Researchers are actively involved in evaluating the role of these checkpoint inhibitors and have shown some encouraging results for the treatment of TNBC. Among PD-1 inhibitors, pembrolizumab was evaluated as a first-line therapy in PD-L1 positive TNBC patients. In which 87% of the patients had received either neoadjuvant or adjuvant chemotherapy, with overall survival outcome being 16.1 months [60]. In another phase II trial, I-SPY 2 trial (NCT01042379), 69 HER- and 29 TNBC patients were received either neoadjuvant PTX and/or pembrolizumab, followed by dose-dependent doxorubicin and cyclophosphamide. The raw PCR was improved to 71% with pembrolizumab compared to 19% in the control arm, whereas the estimated PCR was 62% with pembrolizumab versus 22% in the control arm [60]. The beneficial results achieved through I-SPY 2 trial led to the phase III trial, KEYNOTE-552 (NCT03036488) and KEYNOTE-355 (NCT02819518) which are currently ongoing. Another PD-L1 inhibitor that has achieved impressing outcomes among TNBC patients is, atezolizumab. Impassion130 trial, NCT02425891 which was a phase III trial, among metastatic or advanced stage TNBC patients receiving Abraxane with/without atezolizumab plus placebo. A 1.4 fold improvement was achieved among patients receiving atezolizumab, with progression-free survival of 2.5 months, versus 1.7 months who did not receive atezolizumab. Overall survival was also improved to 9.5 months, with no significant improvement observed among patients without atezolizumab [61]. Based on these results, the FDA accelerated the approval of atezolizumab with Abraxane for the treatment of metastatic TNBC patients who are PD-L1 positive. Further ongoing phase III trial NCT03125902 is being evaluated with patients receiving either atezolizumab and PTX versus PTX and placebo for first-line therapy in TNBC.

Due to the heterogeneity and the inherent nature of TNBC to develop multi drug resistance (MDR) to conventional chemotherapeutics, several ongoing clinical trials with combination therapies or targeted therapies or immunotherapies or ADC, are being evaluated to identify predictable biomarkers that will improve treatment outcomes among TNBC patients. Although, the paradigm is shifting and lots of attention is being given to the development of novel and nano-based therapies for TNBC.

3. Nanotechnology based therapies for TNBC

The lack of specific (ER, PR, and HER2) cellular receptors on TNBC tumors, makes drug delivery to the tumor challenging. So researchers are extensively focused on targeted delivery to TNBC. In this regard, nanotechnology-based delivery systems have been beneficial to provide significant tumor delivery by following active- and passive-targeting mechanisms [62]. Passive targeting occurs by a phenomenon known as the enhanced permeability and retention (EPR) effect. This phenomenon occurs because of the tumor vasculature that is hyper vascularized with enhanced vascular permeability causing fluid retention and lack of lymphatic drainage. This results in extravasation within tumor tissues and increased accumulation of therapeutics at the intertumoral site, whereas they get cleared into the lymphatic system of healthy tissues [63]. However, achieving therapeutic concentrations inside the tumor site is a challenge with passive targeting and, as a result of which compromises are usually made on the biotherapeutic window of the drug. Active targeting relies on conjugating the surface of the nanoparticle to biocompatible targeting moieties such as aptamers, antibodies, and peptides, that have specificity to the antigens or receptors at the tumor site [64,65]. This approach provides a myriad of advantages over conventional therapeutic approaches, such as target specific delivery, minimizes systemic or non-specific toxicities, increases biodistribution and therapeutic window with intravenous administration, resulting in transport of maximal payload, improving half-life and systemic circulation, less immunogenic reaction, controlled drug release, increase in drug solubility, and stability of poorly water-soluble chemotherapeutic agents (which compromises the majority of available, approved, and marketed chemotherapeutics). Alongside taking advanatage of synergistic effects, combined therapy has been able to deliver multiple therapeutic agents for multimodal functions, such as imaging and/or theranostic agent [66–68]. Some of the commonly employed nanoparticles [62] that have been explored for delivery of therapeutics are polymeric nanoparticles, micelles, liposomes, dendrimers, nanoconjugates, albumin nanoparticles, and carbon nanotubes (Fig. 2).

These unique nanostructures can be generated following various synthetic methods [69,70]. Hydrothermal, sonochemical, polyol, microwave synthesis, inert gas condensation, ultrasound, laser ablation, thermal decomposition, electrochemical, gamma radiation, spark discharge, sputtering, template synthesis, sol-gel, biological building, co-precipitation, microemulsion process are commonly used approaches to construct these nanostructures [69,71]. It is possible to achieve dry nanoparticle powders or nanoparticles dispersed in liquid medium. Researchers have employed other techniques such as polymer precipitation, emulsion-solvent diffusion, emulsion-reverse salting out, interfacial condensation, polyelectrolyte complexation, ionic gelation and many other similar techniques for drug loaded NPs [72]. The super critical fluid technology (rapid expansion of supercritical solution, supercritical anti solvent, aerosol solvent extraction system, solution enhanced dispersion by supercritical fluid, and particles from gas-saturated solutions/suspension) is highly considered to generate pharmaceutical based particles [73,74]. This new technology overcome the drawbacks of spray drying and milling techniques. All these systems are further modified for delivering not only drugs but also oligonucleotides, DNA or proteins [75].

3.1. Polymeric nanoparticles

Polymeric nanoparticles are nanosized range materials that are synthesized using either natural or synthetic biodegradable and biocompatible polymers. Depending on the characteristics of the polymer of choice, both hydrophilic and hydrophobic drugs can be encapsulated into these nanoparticles that can be released by surface or bulk erosion, swelling or diffusion mechanisms. Studies have shown that polymeric nanoparticles made of poly(ε-caprolactone)-*b*-poly(ethyleneglycol)-*b*-poly(ε-caprolactone) encapsulating DTX successfully improved the *in vivo* survival rate of mice in contrast to marketed docetaxel formulation due to the prolonged circulation of the nanoparticles for the EPR effect [76]. Similarly, poly(lactic-*co*-glycolic acid)-poly(ethyleneglycol) nanoparticles were utilized to deliver cisplatin in TNBC xenograft mouse model with significant tumor inhibition and prolongation of half-life, although systemic toxicities were observed in normal organs such as kidney and liver [77].

Inadequate therapeutic dose reaching the tumors *via* passive targeting has led to the utilization of nanoparticles by decorating the surface with active moieties allowing longer circulation and causing higher concentration accumulating in tumor tissues compared to normal tissues. For instance, a novel peptide (Gly–Ile–Arg–Leu–Arg–Gly) conjugating onto polymeric nanoparticles containing PTX, exhibited a significant delay in tumor growth in contrast to untargeted nanoparticles [78]. A protein polymer called elastin-like polypeptides was used to form nanoparticles that assemble into <100 nm and was surface decorated with FK506 binding protein 12, which is a cognate receptor for potent yet poorly soluble rapamycin (RPM). These nanoparticles prolonged circulation time and increased the half-life by 26 folds, with enhanced anti-tumor efficacy, and lower cytotoxicity than free drug in TNBC xenograft mouse model [79]. Enhancer of zeste homolog 2 (EZH2) was found to be overexpressed in TNBC and is found to be responsible for poor overall patient survival. Delivery of siRNA *via* chitosan

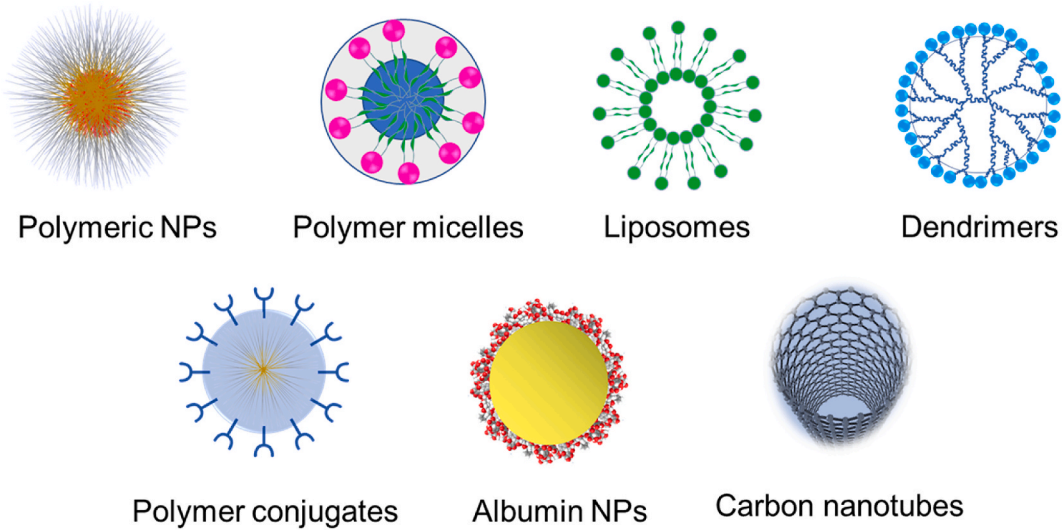

Fig. 2. Graphic representation of structurally varied nanoformulations, polymer nanoparticles, polymer micelles, liposomes, dendrimers, polymer conjugates, albumin nanoparticles, and carbon nanotubes used in cancer therapeutics including TNBC. These nanostructures are able to accommodate small/biomacromolecular therapeutics, contrast/imaging, and other agents that imparts therapeutic and/or theranostic properties.

nanoparticles directed to target the EZH2 in the orthotopic MDA-MB-231 mouse model has shown to cause a significant reduction in tumor growth [80].

3.2. Polymeric micelles

Polymeric micelles are developed by using hydrophilic and hydrophobic chains of polymers, that form Van der Waals bonds to form a hydrophobic core which usually encapsulates the drug either by physical entrapment or chemical bonds. The outer shell on the other hand being hydrophilic, aids prolong circulation and prevents rapid clearance by the reticuloendothelial system (RES) [81]. A block copolymer of poly (ethylene glycol) (PEG) and poly(glutamic acid) conjugated to the active metabolite of topoisomerase I inhibitor irinotecan (SN-38) forms ~ 20 nm spherical polymeric micelles. Significant tumor inhibition in an orthotopic mouse model has suggested this could be a promising candidate and is in Phase II clinical trial for treatment in TNBC patients [82]. Active targeting by polymeric micelles using D-tocopheryl PEG succinate polymer, encapsulating DTX conjugated to cetuximab, that specifically targets EGFR on the TNBC tumors by 205.6 and 223.8 folds in contrast to Taxotere® (marketed formulation of docetaxel) [83].

Various polymer micelle-based PTX formulations exist for clinical use. Genexol-PM® (Cynviloq™) was developed by Samyang Biopharmaceuticals Corporation (South Korea) for the treatment of several types of cancer, such as breast, ovarian cancer, and NSCLC. It is made up of monomethoxy-PEG-*b*-poly($_{D,L}$-lactide) diblock copolymer that entraps PTX in polymeric micelles (20–50 nm) with a drug loading capacity of 16.7% w/w. The absence of albumin reduces the risk of microbial contamination in comparison to Abraxane. A phase III clinical trial (NCT00876486) of the formulation in contrast to the Abraxane in metastatic BC, shows enhanced efficacy and reduced toxicity issues [84]. Other clinical trials demonstrate that the MTD of this formulation was lowered to 180 mg/m^2 than that of Abraxane®, although both the regimens showed a similar incidence of neutropenia and less severe non-hemotoxicity [85,86]. Although, the higher-dose regimen of 390 mg/m^2 has a higher incidence of neutropenia and neuropathy [87]. In phase II clinical trial at a dosing regimen of 300 mg/m^2 in metastatic BC patients, 58.5% of them demonstrate response rates. However, the response rate of Taxol® was similar but conducted in a much larger group. Also, greater incidence of neutropenia (68.3%), neuropathy (51.2%), and hypersensitive reaction (19.5%) was observed [88]. Overall, Genexol-PM® showed a similar response to Taxol®, which initiated the fast track approval through 505(b)(2) for new drug application (NDA) regulatory pathway for Cynviloq® in the U.S [89]. Paclical® developed by Oasmia Pharmaceuticals, which is composed of XR-17, a vitamin A derivative which is made of N-(all-trans retinoyl)-L-cysteic acid methyl ester sodium salt and N-(13-cis retinoyl)-L-cysteic acid methyl ester sodium salt. It forms micelles of 20–60 nm which encapsulates PTX and is available as a lyophilized powder, administered as infusion [90]. Pharmacokinetic profile of Paclical® and Abraxane® are similar, suggesting the opportunity for approval of Paclical in the treatment of metastatic BC [91]. Nanoxel® from Dabur Pharma Limited (India) is available for the treatment of metastatic BC, ovarian cancer, NSCLC, and AIDS-related Kaposi's sarcoma in India. It is a micellar solution of size range 80–100 nm, is composed of a pH-sensitive copolymer of *N*-isopropyl acrylamide and vinylpyrrolidone monomers which is stable at physiological pH and drug release in an acidic environment as tumor microenvironment [92]. Ranade et al. [93] demonstrates in phase I clinical trial the MTD to be 375 mg/m^2 with a linear pharmacokinetic behavior with grade 3 diarrhea and grade 4 neutropenia adverse effects. However, the same group conducted a phase II trial in anthracycline failed advanced metastatic BC patients and show though the formulation in comparison to the generic formulation Taxol® has improved overall response rate, being 40% and 32.3%, the higher incidence of neutropenia of 56.3% versus 50%, higher incidence of neuropathy of 12.5% versus 6.3, respectively [92]. Triolimus® from Co-D Therapeutics is a polymeric micellar formulation (30–40 nm) composed of PEG-PLA and encapsulates three drugs, PTX, RPM (mTOR inhibitor), and tanespimycin (17-AAG, Hsp90 inhibitor) [94]. After showing promising preclinical results in xenograft models by the synergistic activity of the three actives, this formulation is in the process of phase I clinical trial for breast, NSCLC, and angiosarcoma [95]. NK105 is a micellar formulation composed of polyethylene glycol and modified polyaspartate by esterification with 4-phenyl-1-butanol and is about 85 nm in diameter [96]. The core encapsulates 23% (w/w) of PTX and demonstrates good drug retention after intravenous. administration. This formulation has MTD of about 180 mg/m^2 in phase I clinical trial with grade 3 neutropenia as the adverse dose-limiting toxicity. Pharmacokinetic profile of this formulation in comparison to the marketed generic formulation Taxol® has 15 folds higher AUC at the recommended dose of 150 mg/m^2. However, in phase III clinical trial against metastatic BC enrolled patients failed to meet the primary endpoint of the study [97].

3.3. Liposomes

Liposomes are composed utilizing the lipid bilayer characteristics, which allows the formation of spherical vesicles as large as 100–400 nm, enclosing an aqueous core. The lipid bilayer being amphiphilic allows the interaction of the hydrophilic surface of the lipid with the central aqueous core-forming lipid spheres, whereas the hydrophobic region can be modified as per drug delivery needs. The ability of drug loading both in the aqueous core or lipid bilayer and the possibility of active and passive targeting makes liposomes an attractive alternative for researchers. A liposomal PTX-formulation called Lipusu® is communalized by LuyePharma Group in China consists of lyophilized powder of PTX solubilized in liposomes made of lecithin and cholesterol in a ratio of 87:13 w/w % and is 400 nm in diameter. It is approved in China as first-line chemotherapy for ovarian cancer, first-line therapy for NSCLC patients not suitable for radiotherapy or surgery, and for BC. Wang et al. [98] investigates the anaphylactic effect of the formulation in contrast to Taxol® and showed adverse responses such as piloerection, anhelation, and syncope, which were not seen in animals treated with Lipusu®. Lipusu® showed some milder hypersensitivity reactions [98]. There are several ongoing clinical trials (NCT02142790 for metastatic BC and NCT02142010 for Lipusu with cisplatin in BC) [99] to evaluate the efficacy in comparison to other standard regimen. Another liposomal PTX formulation (LEP-ETU®) developed by NeoPharm cardiolipin, cholesterol, and D-α-tocopheryl acid succinate (in the molar ratio 5:5:90) and are about 150 nm in diameter. Phase I clinical trial to study the dose-limiting toxicities at 325 mg/m^2 associated with the treatment of LEP-ETU® shows peripheral neuropathy, myelosuppression, and even neurotoxicity [100]. Slingerland et al. demonstrate that the pharmacokinetic profile (AUC and C_{max}) of *LEP-ETU*® were similar to Taxol® [101]. A phase II clinical trial has conducted to determine the safety and efficacy of LEP-ETU® in thirty-five subjects show sensory polyneuropathy (3%) and neutropenia (6%). Other than that no significant reactions were observed [102].

EndoTAG-1® is a PTX formulation developed by MediGene and later taken over by SynCore Biotechnology. It is comprised of liposomes composed of phospholipid DOTAP and neutral phospholipid DOPC in a 53:47 M ratio and are about 200 nm in diameter and positive zeta potential of 25–100 mV in a 0.05 mM KCl solution at pH 7.5 [103]. The positively charged liposomes promote the PTX uptake into the tumor endothelial cells. As a result of which combining antivascular effects with conventional chemotherapy may result in increased permeability within the tumors [104]. However, preclinical and clinical trial conducted on other types of cancer such as adenocarcinoma, pancreatic cancer is shown to cause neutropenia and thrombocytopenia. Efficacy in TNBC was evaluated by Awada and coworkers [105], showing results from a phase II clinical trial comparing the safety and efficacy of EndoTAG-1® with Taxol® in 140 patients, receiving either weekly EndoTAG-1® with Taxol® or EndoTAG-1® (twice a week) or weekly Taxol®. However, there was no significant improvement in the overall survival between the treatment groups (13.0, 11.9, and 13.1 months, respectively). Other adverse effects include pyrexia and chills and about 17.8% discontinued the therapy due to unbearable adverse events. Ongoing clinical trials evaluating EndoTAG-1® for treatment of TNBC (NCT01537536 and NCT00448305) [106,107]. CAR, a homing peptide modified liposomal with fasudil or fasudil-DETA NONOate combination, can efficiently concentrate in the lungs [108,109] for the treatment of pulmonary arterial hypertension. Additionally, this construct and methodology can also be applied with other cancer drugs for the treatment of TNBC that are metastasized to the lungs.

Researchers have utilized lipid-based nanocapsules to entrap lipophilic drug ferrocenyl tamoxifen derivative FcOHTAM and demonstrated improved antitumor effects in TNBC xenograft model that is resistant to tamoxifen treatment [110]. Lipid-based nanoparticles were constructed from chemically modified cholesterol-terminated poly (acrylic acid) and cross-linked with diamine linkers for active targeting. This modification allows a high drug loading capability of doxorubicin via this approach exhibiting superior tumor growth inhibition and no systemic toxicity in comparison to the free drug in orthotopic TNBC murine model [111]. Similarly, liposome vesicles can efficiently encapsulate arsenic trioxide (which has dose-limiting toxicity and rapid clearance) resulted in enhanced antitumor efficacy than the parent drug in an orthotopic murine model with pharmacokinetic parameters and efficacy profile [111]. PEGylated liposomal formulation of DOX and gemcitabine showed remarkable responses in TNBC patients, however adverse effects such as metastasis to the skin have limited its use [112]. In an attempt of active targeting, integrin α3 that is overexpressed in TNBC models and is known to cause tumor angiogenesis, proliferation, therapeutic resistance, and poor prognosis, is attached to the surface of PEG-PCL based liposomes. The authors attach a cyclic octapeptide LXY (Cys–Asp–Gly–Phe(3,5-DiF)–Gly–Hyp–Asn–Cys) and achieve enhanced accumulation of co-administered drugs (DOX and RPM) at the tumor site, resulting in improved antitumor efficacy in *in vivo* TNBC model [113]. Active targeting of eEF-2K which has shown to cause tumorigenesis and is associated with a poor prognosis in TNBC, by neutral liposomal siRNA formulation leads to a significant inhibition in tumor growth in orthotopic TNBC mouse model [114]. EndoTAG-1 is a PTX-loaded liposome formulation for targeting the activated tumor endothelial cells has entered Phase III clinical trial after showing promising results in contrast to plain drug in TNBC patients [105].

Paclitaxel injection concentrate for nanodispersion (PICN) is a nanoparticle-based formulation composed of polymer and lipid, polyvinyl-pyrrolidone, cholesteryl sulfate, and caprylic acid-forming nanoparticle of 100–110 nm, developed by Sun Pharma and approved in India for the treatment of metastatic BC. This formulation is castor oil- and albumin-free formulation of paclitaxel and alternative for Taxol® and Abraxane®. Jain et al. evaluated the efficacy of this formulation in comparison to Abraxane in phase II/III clinical study and demonstrate similar efficacy and tolerability profile at MTD of 260 mg/m^2. Although the incidence of most common side effects such as neutropenia, peripheral neuropathy, and leukopenia was the least at MTD 260 mg/m^2 versus PICN 295 mg/m^2 and Abraxane 260 mg/m^2, yet there was no statistically significant difference between them [115]. In U.S. PICN is in phase III clinical trial for the treatment of biliary tract carcinoma (NCT02597465) [116] and just finished phase I trial when administered alone or in combination with carboplatin (NCT01304303), the results are yet to be disclosed [117].

3.4. Dendrimers

Dendrimers are repeating branched monomers arising radially from the central core, formed by the polymerization reaction. These dendrimers are usually 10–100 nm in size with an amphiphilic nature having a hydrophobic core and a hydrophilic outer periphery [118]. Due to the polyvalent nature of dendrimers like micelles, gene delivery, active targeting can also be possible by conjugating ligands or imaging compounds. Wang et al. [119] utilizes a fourth-generation poly(amidoamine) dendrimers conjugated to antisense oligodeoxynucleotides for targeting the vascular endothelial growth factor expressed in TNBC cells. The authors report an increased accumulation of dendrimers in TNBC-xenograft mouse model with significant reduction in expression of vascular endothelial growth factor, in comparison to unconjugated nanoparticles. Gene delivery using dendrimers was further displayed, in which a third-generation poly(amidoamine) dendrimer was used to deliver YTZ3-15 that can knockdown the TWIST1 transcription factor and is associated with aggressive behavior, metastasis, and cellular migration through an epithelial-mesenchymal transition in TNBC cells [120].

3.5. Nanoconjugates

Nanoconjugates are nanoplatforms that are covalent complexes that

can bind to multifunctional groups, providing an opportunity to a conjugate protein(s) or peptide(s) of interest such that cell- or tissue-specific targeting can be achieved [121]. Mittapalli et al. [122] construct an ultra-small hyaluronic acid-PTX nanoconjugates of 2–3 nm that can target CD44 receptor located on the surface of metastatic cancer. CD44 receptor-mediated endocytosis results in 10 folds increase in cellular uptake and significant improvement in overall survival of animals in a TNBC mouse model of the brain metastasized in contrast to the plain drug. The multifunctionality of nanoconjugates was further explored and demonstrated poly (β-$_{L}$-malic acid) nanoplatforms was formed by conjugation of a 2C5 monoclonal antibody and for active targeting: anti-mouse transferrin receptor (TfR) antibody and oligonucleotides (MASONs). This approach allows active targeting of EGFR-positive TNBC cells, resulting in significant tumor inhibition via the EGFR pathway thus controlling tumor progression [123]. A similar nanoconjugate was constructed utilizing such nanoplatforms and produces significant tumor inhibition with no systemic toxicity in TNBC xenograft mice. This strategy was employed for active targeting of three oligonucleotides, leading to a significant arrest of EGFR and laminin-411 which are known to cause tumor growth and angiogenesis [124,125]. A folate-drug nanoconjugate of folic acid and tubulysin B hydrazide entered into clinical trial for many types of aggressive cancer including TNBC subtype [126]. HPMA copolymer–PTX is the first polymer-drug conjugate of PTX, developed by Pharmacia Corporation, conjugating PTX to HPMA by a tetrapeptidil linker of glycylphenylalanylleucylglycine. Although the formulation has a good aqueous solubility and about 5% w/w drug loading capacity, it failed to have any difference in pharmacokinetic behavior, illustrating that the conjugation did not have any significant impact on the drug behavior, though a partial response was observed in one of the twelve patients with advanced BC. However, clinical studies in phase I was discontinued earlier due to severe neurotoxicity observed [127]. Opaxio™ is a polymer drug conjugate of PTX conjugated to the poly(L-glutamic acid) at the 2′-hydroxyl position of the drug by an ester linkage. It is available as a lyophilized powder and has shown beneficial results in preclinical studies. In ovarian tumors, uptake of Opaxio™ was about 5-fold higher than Taxol® with prolonged circulation time [128]. After promising preclinical results, pharmacokinetic profiling of this compound in comparison to the original drug shows prolonged half-life and low renal clearance, however, the achieved C_{max} was 3 times lower than Taxol® [129]. Also, similar dose-limiting toxicity such as neuropathy and neutropenia similar to taxane(s) was observed. CT-2103 completed phase II trial for metastatic BC [130] and is also being evaluated in combination with carboplatin versus PTX and carboplatin in NSCLC patients [131]. ANG 1005 is a drug peptide conjugate of angiopep-2 and PTX that binds to the low-density lipoprotein receptor-related protein (LRP)-1 which facilities movement across the blood-brain barrier (BBB), as LRP-1 is highly overexpressed in BBB. In a preclinical model, ANG 1005 has shown therapeutic efficacy which has progressed its application in a clinical trial. In phase II trial among metastatic BC patients promising results have been achieved with the application of ANG1005 to treat peripheral metastatic BC and brain metastasis [132]. It is now in phase III clinical trial (NCT03613181) [133].

3.6. Albumin-based nanoparticles

The disadvantages associated with Taxol® caused another nanotechnology based PTX formulations to be marketed by Abraxis/Celgene with the tradename “Abraxane”. It is a solvent-free colloidal suspension that is lyophilized, including six or seven PTX molecules non-covalently bonded to form aggregates of 4–14 nm which further aggregates to form 130 nm in diameter. It was initially approved by FDA in 2005 for metastatic BC but has eventually been approved for treating NSCLC, metastatic adenocarcinoma and pancreatic cancer, either as a single agent or used in combination with other first-line treatment [134]. The pharmacokinetic profile of Abraxane suggests that clearance and volume of distribution are significantly higher than the traditional formulation. It is well distributed and binds to the tissue and extravascular proteins [135]. Preclinical studies demonstrate an improvement in efficacy, in contrast to Taxol® and 33% higher tumor accumulation and less toxicity [136]. Advantages such as the ease of administration, reduction in some of the adverse effects like hypersensitivity reactions, better overall response, and survival were achieved. Although, Abraxane shows a reduced risk of neutropenia yet increased incidence of neurotoxicity is overserved in combination with gemcitabine in pancreatic cancer [137]. Additionally, a randomized clinical trial CALGB 40502, suggests that toxicity profile for both the treatment groups receiving either PTX or nab-PTX weekly has no improvement, in fact, more neuropathy and myelosuppression were observed with nab-PTX [138].

Clinical trials on BC patients receiving weekly Abraxane shows it is well-tolerated and has higher antitumoral activity in contrast to PTX. However, grade 4 neutropenia and grade 3 peripheral neuropathy were observed as dose-limiting toxicities [139,140]. Gradishar et al. [141] conducted a phase III clinical trial on metastatic BC patients with Abraxane showing a significantly higher response rate of 33% versus 19% improvement with Taxol®. However, no significant difference in overall survival, which is considered one of the most important parameters to evaluate clinical efficacy. Another phase III trial treated with Abraxane® (125 mg/m^2) or Taxol® (80 mg/m^2) each given weekly, followed by epirubicin/cyclophosphamide, shows significant higher PCR especially in the TNBC cohort in comparison to Taxol® (38% *vs* 29%). However, Abraxane® was associated with significantly greater toxicities such as peripheral sensory neuropathy compared with Taxol® (10% *vs* 3%) [142].

3.7. Carbon nanotubes

Carbon tubes are cylindrical structures made from benzene rings and are insoluble in any solvent and thus can be modified chemically to become water soluble or can be functionalized with multiple groups. This unique nanoneedle shaped and the monolithic structure allows passive diffusion to the lipid layer can be multi-functionalized and can be considered an important drug carrier for cancer therapeutics [143,144]. Carbon nanotubes could be single-walled (around 1–2 nm, one layer) or multi-walled (around 5–100 nm, multiple layers), depending upon the number of cylindrical layers. Chemical modification of single-walled carbon nanotubes via an ester bond yielded a branched polyethylene glycol chain to which PTX was conjugated to the water-soluble carbon nanotubes. This conjugate exhibited 10 times higher tumor uptake than the conventional Taxol® and little toxicity in murine 4T1 breast TNBC model. The improved circulation is probably because of the PEGylation that resulted in more suppression in tumor growth due to the enhanced permeation and retention [145]. Another interesting application of these carbon nanotubes is based on photo thermal-induced ablation, where nanotubes promote cell membrane permeabilization and necrosis, eliminating both tumor mass and BC stem cells, suggesting this could be an effective treatment option for tumor resistant and preventing recurrence [146].

4. Biological and biomimetic nanomedicine

Active targeting by attaching ligands on nanoparticles enables to recognize and bind to receptors on target cancer cells. Such techniques were reported conjugating the nano-carrier systems to biomolecules including small molecules, peptides, aptamers, and antibodies [147,148]. Biological cells such as lymphocytes, macrophages, exosomes, erythrocytes, and platelets are used as whole-cell carriers to depot the free drug(s) or drug-loaded nanoparticles for a better tumor targeting and causing detrimental effects on the cancerous cells (**Fig. 3**). Fig. 3 depicts cell and cell-derived drug loaded delivery system efficiently deliver therapeutic load to the tumor cells. In the case of whole cell-mediated drug delivery, the activated cells or natural cells often

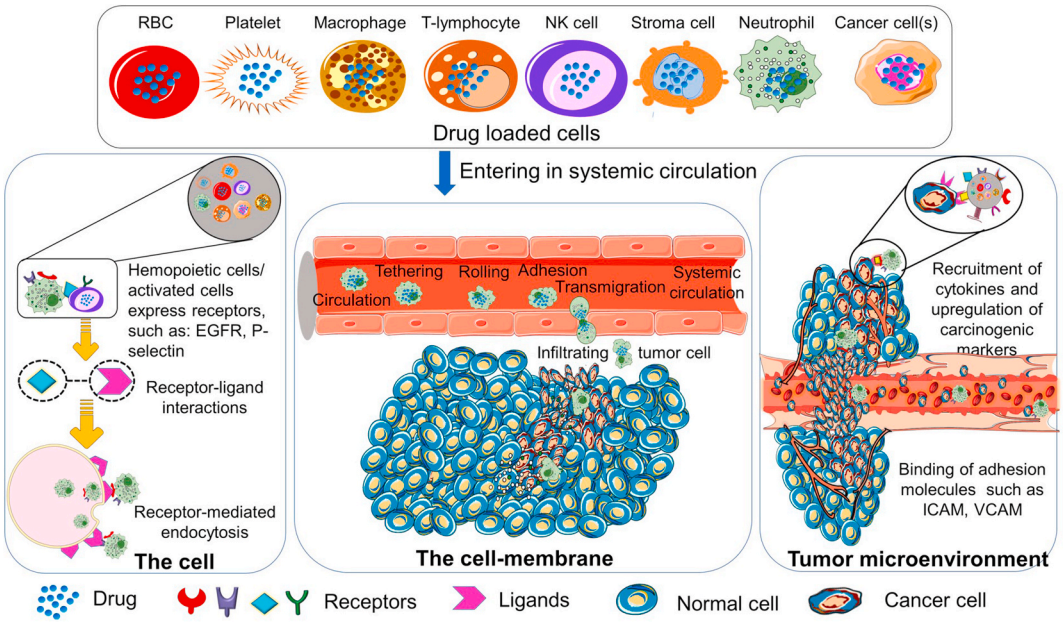

Fig. 3. Schematic representation of possible delivery options of therapeutic agents *via* whole cell recruitment at the tumor sites. Improved interaction, circulation, penetration, and recruitment of cells/cellular vehicles in tumors.

recruited at the site of the injury/tumor, express receptors on their surfaces, that has affinity for ligands present on the tumor. This process causes receptor-ligand interactions that aid in the uptake of the drug loaded delivery system by receptor-mediated endocytosis. On the other hand, the cell membrane-mediated drug delivery, for example, neutrophils are recruited readily at the tumor site as an inflammatory stimulus and permeates the endothelium near the tumor site naturally by a multistep process: circulation, tethering, rolling, adhesion, and transmigration [149] into the circulation, finally infiltrating the tumor cells causing activation due to the concentrated cytokines environment. This can cause binding of the adhesions molecules, present on the surface of the tumors to undergo binding with the receptors on the surface of the cell-derived delivery systems. The upcoming sections focus on cells as therapeutic carriers and biomimetic (cell membrane clocked) nanoparticles for tumor directed delivery applications.

4.1. Hematopoietic stem cells as carrier for targeted delivery

The remarkable characteristics of hematopoietic stem cells give rise to other blood cells. It makes them an appropriate fit for an efficient drug delivery system in nanomedicine. These blood cells can be broadly divided into three main categories: erythrocytes or red blood cells (RBCs), leukocytes (WBCs), and thrombocytes (platelets). These hemocytes play an important role in the defense mechanism of the body against a wide range of pathogens and foreign particles. The biological drug delivery system (using blood cells as drug carriers) ensures the biocompatibility and biodegradability of the nanoparticle-loaded cell carriers. The biochemical characteristics favor the non-immunogenicity of blood cells guaranteeing successful drug delivery at target sites [150]. Thus, blood cells serve as the natural biological carriers that can bypass the immune surveillance and efficiently deliver the drugs to target cells. Some of the hematopoietic stem cells based nanocarriers that have shown clinical potential in various cancer model has been summarized in Table 1, with closer attention given to BC and their associated metastatic regions [151].

4.1.1. Erythrocytes

Erythrocytes or RBCs are the ideal biological carriers for nanomedicine that can operate without inducing immunological response and provide numerous advantages such as long circulation time, abundant surface ligands, and flexible morphology. RBCs are the most abundant cells in the blood (a quarter of the total volume) readily transporting oxygen and carbon dioxide throughout the body. These biconcave discoid cells (diameter, ~7 μm) have high drug loading capacity. Due to their extremely high half-life (over 100 days), it is highly distinguished from macromolecular structure-based drug delivery systems. The presence of carbohydrates, proteins, and phospholipids on the outer member layer provides stability and deformability allowing to target even extremely small vascular structures [152–154]. The erythrocyte membrane undergoes reversible changes between expanded and tight network structural integrity and aids in the process of evading intravascular hemolysis [155].

This delivery system involves the controlled opening of the RBC membrane, the encapsulation of the nano-carrier loaded anti-cancer drugs, and the subsequent resealing of the outer membrane. For example, it encapsulates anti-cancer drugs such as daunorubicin for leukemia treatment, 5-fluorouracil (methotrexate) [156], and l-Asparaginase (l-ASNase) [157]. Erythrocytes encapsulate and protect l-ASNase from degradation, exhibits a longer half-life, increasing the efficiency by ten-fold, and reduce the severity of side effects. In another study, asparaginase-loaded RBCs serve as 'bio-reactors' to deplete asparagine, an amino acid required for cancer cell growth, from the blood with a tendency of low coagulation disorders and minimum allergic reactions [158,159]. A MTX-loaded erythrocyte treatment approach can increase the average survival time of mice bearing hepatoma ascites tumors by 28.5–42.8% than native MTX [159]. Magnetic targeting using an external magnetic field was applied to DOX-loaded RBCs which are bound to iron-oxide nanoparticles pre-coated with a photosensitizer in the chemotherapy of cancer [160]. The modification of the pharmacokinetic and pharmacodynamics parameters of the drug by carrier erythrocytes maintains a relatively inert intracellular environment, decreased fluctuations in concentration, reduces drug side effects. Thus, the molecular mechanisms of erythrocytes make them perfect candidates as carriers of convention and new anti-cancer drugs [155,161].

4.1.2. Leukocytes

White blood cells (WBCs) or leukocytes are an integral part of the

Table 1
Summary of various hematopoietic cells based nanocarriers for breast cancer treatment.

Cell type	Nanoparticle Core	Intended use	Targeted cancer type and benefits achieved
Lymphocytes membrane [236]	Membrane coated on PLGA nanoparticles, low-dose irradiation.	Subcutaneous model using: MKN45 cells.	Nanoparticles caused 56.68% tumor inhibition, liver accumulation in 96 h while LDI caused more tumor accumulation with ~89% tumor inhibition.
Monocytes [132]	pH-responsive amphiphilic copolymer, polyethylene glycol-block-poly [(1,4-butanediol)-diacrylate-ß-N,N-diisopropylethyl-enediamine] (PDB) and phagocyting this in Ly6Chi monocyte isolated from peripheral blood.	Metastatic 4T1 BC.	2 folds increase in tumor accumulation was observed with the monocyte loaded nanoparticles, with relatively less nonspecific uptake in lung and liver, compared to blank nanoparticles (no monocytes). Also, highest AUC was observed 7.20-folds higher than PTX, with highest tumor suppression of 96.8% over only 50.4% inhibition was attained with nanoparticles (without monocytes). Also, lung metastasis decreased by 99.2% with these nanoparticles, over 50% decrease with non-monocytes nanoparticles.
Platelet membrane [237]	A synthetic peptide with dendritic disulfide conjugate of PTX coupled with PEG via click reaction, to yield a redox-responsive micelle that could capture internally activated platelets	Xenograft TNBC tumors: MDA-MB-231 cells.	The micelles were recruited to the surface of the activated platelets, due to overexpression of P-selectin on the platelets and adhere to it. Relative to PTX these targeted micelle exhibits enhanced targeting to the primary TNBC tumors as well as lung and liver metastasis. This is due to the interaction between activated platelets and ICAM overexpressed at the metastatic sites, by tumor cell receptor-targeting strategies.
Platelet membrane [238]	Nanogel with TNF- α, RGD peptide (Nanoparticle 1). Dextran nanoparticles with coated with platelet membrane with PTX (Nanoparticle 2)	TNBC tumor using MDA-MB-231 cells.	Nanoparticle1 induces tumor vascular inflammation and RGD peptide caused significant accumulation in the tumor by 5 folds, relative to nanoparticles without RGD. Whereas nanoparticle2 cause greater tumor accumulation by 5 folds relative to the nanoparticles without coating.
RBC membrane [214]	Thermo-responsive hybrid nanoparticle composed of poly (caprolactone)-ester endcap polymer (PCL), dipalmitoylphosphatidylcholine (DPPC) poloxamer 188 and membrane coating.	4T1 orthotropic tumor mimicking metastasis BC.	A 12.3, 2.6- and 3-folds increase of fluorescent dye (DiR) at the tumors, liver and lung metastasized sites, respectively in comparison to free DiR. 69.2% and 12.6% tumor inhibition were achieved by the nanoparticles, PTX respectively, in comparison to control. Also, 98.6% lung metastasis was achieved.
RBC membrane [239]	PCL, poloxamer 188, co-administrated with the tumor penetrating peptide, iRGD and membrane coating.	Metastatic 4T1 breast tumor model.	The half time of the cell membrane nanoparticles was 32.8 h (5.8 and 16.9 folds higher than that of polymeric nanoparticles and Taxol, respectively). These nanoparticles in combination with iRGD yield 2.89, 3.02 folds higher tumor fluorescence uptake, 90% tumor growth inhibition and 94.8% lung metastasis were achieved. All comparisons were with uncoated nanoparticles with iRGD and cell membrane nanoparticles (without iRGD).
RBC membrane [240]	Ferric oxide (Fe_3O_4) and O-carboxymethyl chitosan (CMC) nanoparticles co-encapsulated PTX and doxorubicin with Arg-Gly-Asp (RGD) and membrane coating.	Subcutaneous xenograft model of lung carcinoma.	Synergistic effect of RBC membrane magnetic nanoparticles and RGD ligand, on the application of magnetic field, increased fluorescent uptake at the excised tumors by ~17 times and significant tumor reduction in contrast to naked nanoparticles (without membrane coating and RGD).
RBC membrane [241]	DSPE-PEG-MAL coupled with tumor-penetrating bispecific recombinant protein (anti-EGFR-iRGD) with RBC membrane coating.	Subcutaneous tumors of gastric cancer cells: MKN45.	RBC membrane coating prolonged nanoparticle circulation in the tumors from 2 to 48 h. The synergistic effect of anti-EGFR-iRGD along with membrane coated nanoparticles caused tumor inhibition by 61% in contrast to only 21% inhibition with the PTX, relative to the control.
RBC membrane [236]	RBC membrane coated nanoparticles.	Mammalian intestinal mucosal cells (MDCK-MDR1)	Permeability was enhanced by 3.5-& 16.2 folds than free PTX in MDCK-MDR1 cell monolayers and intestinal mucosa, respectively. The presence of the RBC membrane prolonged the circulation time by increasing the mean residence time of the nanoparticles by 1.81 folds, AUC by 14.2 folds and C_{max} by 6 folds, relative to free PTX.
Macrophage membrane [241]	pH sensitive polymer cationic 2- aminoethyldiisopropyl with IGF1R targeting peptide, after PEGylation and macrophage membrane.	Orthotopic BC: MDA-MB-231 cells.	Significantly tumor accumulation and towards the center of the tumor was achieved, relative to group without the non-pH sensitive polymer and without macrophage coating, due to membrane coated tumor homing effect and pH-sensitive drug release by the polymer. The peptide also enhanced the fluorescence intensity due to IGF1R mediated uptake pathway.
Neutrophil [242]	CXCL1 chemokine laden thermosensitive hydrogel of PLGA-PEG-PLGA nanoparticles, encapsulated by the endogenous neutrophils.	B16F10 murine melanoma cells.	Neutrophils sequester the nanoparticles and in 8 h shows 82.2% uptake implying viability of neutrophils were not affected by the PTX loaded nanoparticles. Fluorescent dye (DiD)increased significantly at the tumor site with CXCL1 from 1 to 8 h, unlike without the CXCL1 group, suggesting the presence of the chemokine was primarily causing

(*continued on next page*)

Table 1 (*continued*)

Cell type	Nanoparticle Core	Intended use	Targeted cancer type and benefits achieved
			recruitment of the neutrophil loaded nanoparticles. Synergistic effect of CXCL1 and neutrophil loaded nanoparticles caused the most tumor inhibition of 67.28%, 2.13 folds higher without the CXCL1 group (46.95%).
Neutrophil [243]	Cationic liposomes made of 1,5-dioctadecyl-N-histidyl-L-glutamate (HG2C18), internalized in mouse bone marrow derived neutrophils.	G422 glioblastoma cells.	Highest fluorescent intensity of DiR dye was observed with neutrophil nanoparticles in the tumor region of the brain collected from surgically treated glioma tumors. The nanoparticles migrated to the infiltrating glioma cells GFP-G422 cells, up to 96 h, suggesting enhanced targeting due to neutrophil which causes inflammatory response after surgery. AUC_{brain} was the highest suggesting highest targeting efficiency due to neutrophils.
Neutrophil [244]	Commercially available PTX formulation: Abraxane dispersed within human NEs in combination with radiotherapy by 5-Gy.	Gastric cancer: SNU719 tumor-bearing mice.	Tumor reduction was maximum when radiotherapy and neutrophil nanoparticles were combined. The radiation disrupts the tumor and allows the neutrophils to be homed at the tumor site, due to the release of inflammatory cytokines. Radiation therapy with only neutrophil (no nanoparticle) did not produce any significant anti-tumor effect.

innate immune system of the body in response to pathogen invasion. When tissue damage, bacterial, and viral infections occur, leukocytes are deployed in circulation to combat those changes. Therefore, inflammation can be defined as a defense mechanism of the body to fight foreign invaders (physical, chemical, antigens) and maintain homeostasis [162]. Owing to their aiming movement and transmigration ability, leukocytes are specifically targeted to deliver nanotherapeutics into diseased tissues. The pathogenesis of most types of cancers is in correlation to uncontrolled inflammation. Thus, hijacking leukocytes and deploying them as delivery vehicles to transport anti-cancer therapeutics across blood vessel barriers directly to the tumor microenvironment are explored [163–165].

4.1.3. Neutrophils

Neutrophils are first-line defenders reaching at the inflammatory site (s) migrating across the endothelial layer (neutrophil transmigration) to fight pathogens and initiate a phase of repair. They are the most abundant white blood cells (50–70%) in humans and are associated with tumor progression as well as tumor inhibition process. The neutrophils that infiltrate tumor sites are called tumor-associated neutrophils (TANs) [165,166]. The recruitment of TANs into tumor environment is mediated by their surface protein composition and chemokine activity. TANs are classified as Pro-tumorigenic (N2, produced in the tumor microenvironment) and anti-tumorigenic (N1, ability to kill tumor cells) which are phenotypically distinct from normal circulating neutrophils. Targeting these neutrophils would allow better specificity and enhanced therapeutic efficacy of anti-cancer nanotherapeutics [167,168]. Studies have shown that inhibition of BM and ECM breakdowns by TANs derived NE and MMP-9 can dramatically reduce tumor angiogenesis and lung adenocarcinoma in a murine model [169]. In another study, the successful downregulation of a murine model tumor ICAM-1 expression *via* shRNA reduced colorectal adenocarcinoma by 45%. In cancer treatments, where surgical resection has negative outcomes, anti-TAN therapy serves a potential approach with higher disease-free survival rates [170,171]. In a recent study, Chu et al. [172] demonstrated gold nanorods (GNRs) linked with anti-CD11b Abs were able to exponentially decrease tumor growth and increased survival rates in a lung carcinoma model of mice. Photothermal therapy was undertaken as the therapeutic method because GNRs can absorb infrared light to generate local heat to destroy the tumor [172]. In one of their previous studies, they combined TA99 monoclonal antibodies and albumin nanoparticles to treat melanoma in a mouse model. This was achieved through the mechanism of antibody-dependent cellular cytotoxicity, wherein the albumin NPs were loaded with photodynamic therapy agents which activated the infiltration of neutrophils into tumor sites markedly reducing tumor growth and thus emerging as a novel strategy for immunotherapy in cancer treatment [173]. Neutrophils have been heavily employed as immune cell carriers for delivering nanoparticles to inflammation sites. For example, piceatannol-loaded and TCPA-1/cefoperazone acid-loaded albumin nanoparticles with neutrophils as delivery vehicles are used as treatment approaches for acute lung injury and pyropheophorbide-a loaded albumin nanoparticles are targeted against melanoma [165].

Therefore, neutrophil-mediated delivery of nanotherapeutics has immense potential to dramatically increase target specificity, therapeutic efficacy, and provide a translational effect. Their intrinsic properties of transmigration, ability to infiltrate in huge numbers in response to inflammation, and their first responder nature makes them appropriate biological carriers to deliver nanotherapeutics [165].

4.1.4. Monocytes/macrophages

Monocytes are an integral part of immune-oncology with the unique characteristic to be able to differentiate into tissue macrophage, known as tumor-associated macrophages (TAMs), after crossing the endothelial barrier. The ability of TAMs to reach the hypoxic areas of the tumor microenvironment makes them excellent targets for a biomimetic based delivery system. TAMs constitute 70% of the cell mass in breast carcinoma and can be classified into M1 and M2 types. M2-like macrophages are responsible for tumor growth and progression whereas M1 phenotype is associated with killing tumor cells. Owing to their innate phagocytotic capability, monocytes can be loaded with a variety of nanotherapeutics and serve as “Trojan Horse” delivery vehicles reaching otherwise inaccessible tumor regions. Once these cells reach the tumor sites, they differentiate into macrophages and their nanoparticle-based therapeutic function could be initiated by near-infrared illumination, henceforth destroying the TAMs associated with tumor metastasis [165,174–177]. In a recent study, Choi et al. [178] demonstrated that the tumor’s natural recruitment of monocytes may be exploited for nanoparticle-based drug delivery and therapeutics. To avoid any harm to surrounding cellular entities of the host, the drug was loaded in Au nanoshells, nanoparticles consisting of a silica core surrounded by a thin Au shell. Human breast tumor spheroids (T47D) were utilized as a model to examine the therapeutic efficacy and cellular uptake of the Au nanoshells. They successfully demonstrated the potential of monocytes as delivery vehicles into hypoxic tumors and established a foundation for a novel drug delivery system [178].

Poor efficiency of conventional drug delivery systems into the sites of metastases leads to high mortality rates of BC. In a recent anti-metastasis therapy study, He et al. [179] demonstrated that loading

legumain-activated nanoparticles into inflammatory monocytes can actively target lung metastases of BC and inhibit tumor progression. The self-assembled poly(styrene-*co*-maleic anhydride) nanoparticles were conjugated with a legumain-sensitive peptide and loaded into Ly6c + inflammatory monocytes (M-SMNs). In this biomimetic delivery system, the SMNs would remain inactive until they come in contact with the metastatic niche. This prevents early drug release and ensures the living state of monocytes which is required for the efficient anti-metastatic effect. Upon reaching the tumor microenvironment, the monocytes differentiate into macrophages to release the anti-cancer drug as free drug molecules by destroying the macrophages. The study shows plausible evidence of inhibition of the proliferation, migration, and invasion activities of metastatic 4T1 TNBC cells [179]. In another study, a mouse macrophage-like cell line was used to demonstrate the anti-cancer efficacy of lung metastasis of BC (4T1 cells). A mouse macrophage-like cell line (RAW 264.7) with similar functions to primary macrophage cells were used as delivery vehicles and loaded with DOX to serve as an anti-cancer biomimetic delivery system. The DOX loaded macrophage system showed tumor suppression, metastasis inhibition, with an increased life span of the host and reduced toxicity to other healthy tissues and organs as compared to their control groups. Thus, DOX encapsulating macrophages proved to be an efficient delivery system into tumor sites and showed an enhanced therapeutic effect by inhibiting tumor growth to a great extent [180]. Exploiting autologous macrophages (MΦ) for anti-cancer therapy has been developed in the late 20th century and it still has unexplored areas to venture upon. Tumors, however, promote normal MΦ functions of tissue repair, resulting in tumor growth, over inflammatory responses. In the tumor microenvironment, the replacement of MΦ with genetically engineered monocytes or drug-loaded monocytes can be potential delivery vehicles for nanotherapeutics [181–183]. The encapsulation of drugs in MΦ has an added advantage of an extended half-life, protected from clearance by the endogenous RES system. The multi-faced benefits of utilizing MΦ as delivery vehicles have been demonstrated in a study by Escobar et al. [182] They used a spontaneous BC mouse model (MMTV-PyMT), wherein they performed hematopoietic stem cell transplants with selective expression of IFNα in TIE2+ tumor-associated MΦs in the model. The highly localized TIE2+-MΦ-mediated delivery of IFNα reduced lung metastatic areas 5-fold and primary tumor size 3-fold without apparent toxic effects to the host organism. The plasticity and versatility of autologous macrophages make them ideal candidates for novel drug delivery systems to enhance the specificity of cell therapeutics [181–183].

4.1.5. Thrombocytes

Platelets are nucleated, small subcellular fragments of megakaryocytes with a half-life of 7–10 days that circulate in the bloodstream and are activated during a vascular endothelial dysfunction or damage [184]. They are associated with inflammatory cells and play a central role in the cancer microenvironment by cell-cell communication and ability to uptake a plethora of different molecules [185–187]. Activated platelets are key contributors to tumorigenesis, metastasis, tumor growth, and angiogenesis. B-thromboglobin and P-selectin, markers of platelet activation, are abundant in patients with BC/TNBC, suggesting tumor cell-induced platelet aggregation [188]. Once activated, these platelets facilitate cancer cell survival and their adhesion to the endothelium. Thus, tumor-associated platelets can be potential therapeutic targets and serve as effective delivery vehicles in anti-cancer treatment modalities [188,189]. Targeting specific platelet receptors and tumor-associated platelets has become an emergent field of delivery of anti-tumor therapeutics. Zhang et al. [190] designed a biocompatible liposomal nanoparticle with a tumor-homing peptide on the surface and loaded with the reversible platelet inhibitor ticagrelor, known as CREKA-Lipo-T, to demonstrate its ability to block tumor cell acquisition of an invasive phenotype and tumor cell adhesion of platelets. The target specificity and therapeutic efficiency of CREKA-Lipo-T was sucessfully acheived using 4T1 solid tumors [190]. In another study by the same group, they constructed a polymer-lipid-peptide-based drug delivery system (comprised of matrix metalloproteinase 2 (MMP2)-cleavable peptides, lecithins, and PEGylated phospholipids to form an enzyme-responsive drug release known as PLP-D-R) to co-deliver a platelet-depleting antibody (R300) and chemotherapeutic drug, DOX. They successfully demonstrated the anti-cancer efficacy of PLP-D-R in an MCF7 tumor-bearing nude mouse model that showed enhanced tumor suppression with minimal bleeding complications. Moreover, they also showed enhanced nanoparticle retention (almost thrice as compared to control groups), tumor regression, and metastasis inhibition in tumor-associated platelet depleted models of mice [146,147].

Novel strategies involving anti-platelet therapeutics are gathering momentum and emerging as an alternative approach to conventional anti-cancer modalities. In a recent study, it was demonstrated that the administration of low-dose aspirin, a member of nonsteroidal anti-inflammatory drugs which inhibit prostanoid biosynthesis by inhibiting the action of COX-1 and COX-2, reduced the formation of lung metastases [148,191]. It was also shown that in P2Y12-deficient mice, which is an ADP platelet receptor, the co-administration of the drug clopidogrel with aspirin attenuates the development of hepatocarcinoma and improves survival rates of the host [192,193]. In a murine model of lung cancer, it was shown that how blocking the platelet GPIIb/IIIa receptor, using the monoclonal antibody 10E5, prevented the cells from metastasizing [194,195]. The curative effect of heparin and fondaparinux against tumor cells was demonstrated by indirect inhibition of thrombin and Factor Xa, thereby inhibiting the activation of platelets by BC cells [151]. Additional studies [196–198] designed nano construct that can bind simultaneously to GPIIb-IIa like integrins and P-selectin on the high-metastatic MDA-MB-231 human BC cells. They successfully achieved their goal of killing the tumor cells and enhanced the therapeutic efficiency by their platelet-inspired metastasis-targeted drug delivery approach. All the above studies establish the potential of utilizing platelets as delivery vehicles and the promising future of platelet-inspired anti-cancer therapeutics.

4.2. Cell-membrane coated nanoparticles for targeted delivery

Cell membranes isolated from the parent cells are subjected to a continuous process, to isolate the various cellular components. Cells are previously treated with hypotonic buffer under the protection of protease inhibitors are followed by series of ultracentrifugation. This enables the removal of cell contents, including enzymes, nucleus, and other cellular components. The membranes are then coated on the surface of the nanoparticle core, *via* extrusion, sonication, and/or electroporation techniques (**Fig. 4**).

An array of various techniques that could be employed to isolate membranes from the source cells by different methods: sonication, the freeze-thaw method, extrusion by differential centrifugation, hypotonic lysis buffer and/or Dounce homogenization to generate the empty cell membrane vesicles. Such strategies would also efficiently minimize off-targeting problems, maximize the therapeutic window and would ensure maximum survival rate and improve the quality of the patient's life. These systems can show enhanced specificity for cancer cells with minimal side-effects, increasing the therapeutic efficacy up to 100-fold against drug-resistant cancer stem cells [148]. The reappearance of cancer after a post-treatment and disease-free period is the result of inappropriate drug targeting and low cancer selectivity [192,194]. Thus, the application of nano-carriers for active targeting in cancer drug delivery will exponentially alleviate the non-specific accumulation offering enhancement of therapeutic efficiency [147,151]. The distinguished physical and chemical properties of these nanoparticles make them the appropriate drug delivery carriers. These include their rigidity, hydrophobicity, size, and charge, which facilitates their penetration into biological barriers and effectively delivers the drug at tumor sites [196, 199,200]. These approaches have allowed alteration in the

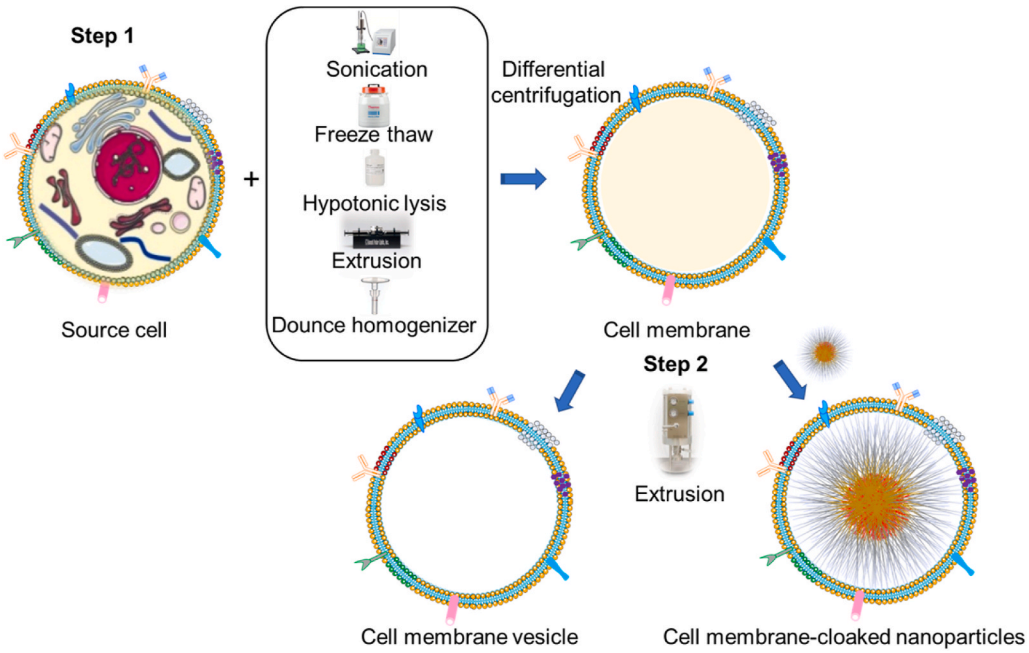

Fig. 4. Schematic illustration of the preparation of cell membranes and cellular membrane-cloaked nanoparticles. Step 1 requires selection of appropriate cell type and extraction method (sonication, freeze thaw, hypotonic lysis, extrusion, or dounce homogenization). Step 2 needs removal of inherent cellular components. After Step 2 it is often required to incorporate the nanoparticle into the cellular membrane immediately, to prevent the cellular membrane lacking the intercellular components from collapsing.

pharmacokinetics and biodistribution of the drug [199]. The previous issues of poor solubility and low bioavailability of the conventional anticancer drugs have been overcome by nano-formulating them [201]. They can not only conjugate the required targeting therapeutic agents but can also deliver it without compromising its activity [202]. This makes nanotechnology one of the best man-made achievements of recent times. It has changed the face of diagnosis and treatment of fatal diseases. The upcoming sections focus on cells as therapeutic carriers and biomimetic (cell membrane cloaked) nanoparticles for tumor directed delivery applications.

Different types of source cells are employed to generate empty cell membrane nanovesicles that are extracted from either erythrocytes/RBC, leukocytes: neutrophils, monocytes/macrophages, T-lymphocytes, thrombocytes/platelets, mesenchymal stem cells, and cancer cells. These membrane-derived vesicles retain the surface protein, antigens from the source cells when coated on the surface of nanoparticles, can directly target or bind to the target site of cancer (Fig. 5). The cellular biomembranes impart a double layer, owing to the structure of the lipid bilayer and are about 50–800 nm in size [203,204]. The transmembrane proteins and all the relevant membrane-bound antigen required for imparting a biological characteristic are preserved on the cell membrane, with no loss in functionality during or after translocating the membrane onto the surface of the nanoparticles [205]. This allows the nanoparticles to be camouflaged by the cell membranes, preventing degradation by the patient's immune system [206]. The cell membrane coated nanoparticles can interact with cells of the targeted site, due to

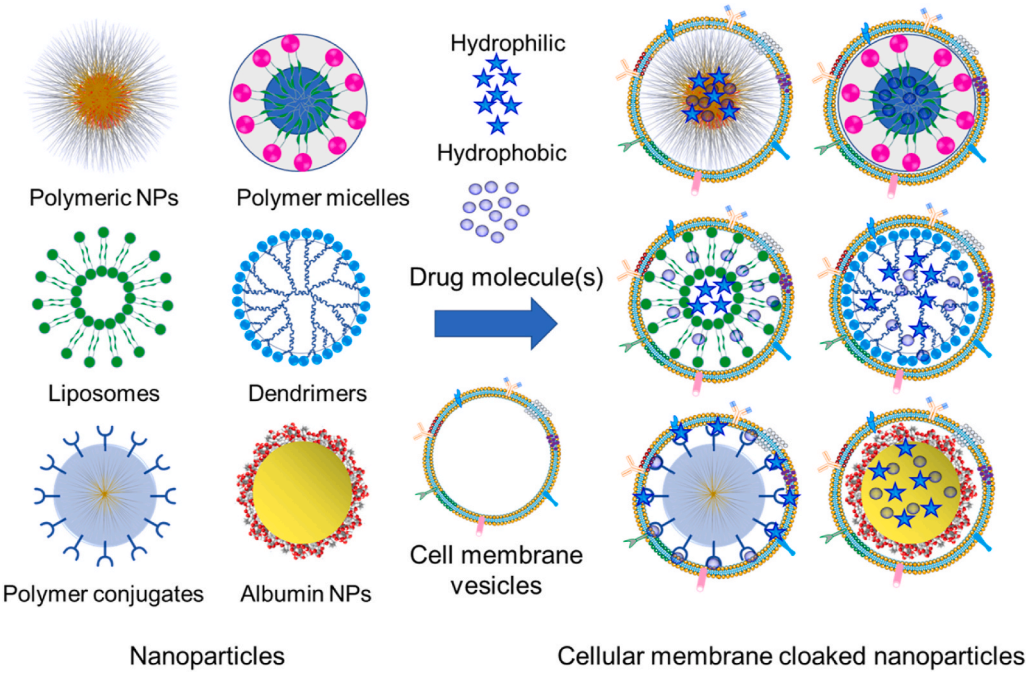

Fig. 5. Schematic representation of bioengineering of the cell membrane cloaked drug loaded nanoparticles. Various methods (co-extrusion, microfluidic electroporation, cell membrane template polymerization) are present to coat or decorate cellular membranes on nanoparticles (not shown in this schematic). Depending on the nature and type of cell membrane carrier that is used the choice of drug could be made, ranging from both hydrophilic or hydrophobic drug molecules (eg: liposomes).

the presence of receptors originated from the derived parent cells that make them able to deliver therapeutics at these targeted sites [207]. Thus, cellular membranes coated nanoparticles offer advantages in contrast to plain nanoparticles; such as i) prolonged circulation [208] ii) cell targeting [209], iii) circumventing the immune system clearance [210], iv) detoxification [211], and v) mediating intracellular communications *via* endocytosis, which can be used to deliver microRNA, mRNA [212]. However, scalability, production, isolation of these membranes for a bulk manufacturing process needs to be addressed for better clinical applications.

4.2.1. Erythrocyte membrane-coated nanoparticles

Erythrocytes are the most common cell component with a unique biconcave discoidal shape, allowing a large volume of therapeutic cargo to be loaded. They bear high mechanical flexibility allowing them to be able to squeeze through very small blood capillaries even when maintaining the constant surface area. It can circulate about over 100–120 days and eventually cleared by the RES [160]. Additionally, they prevent unwanted macrophage uptake, provides specificity to the target, extend biocompatibility, biodegradability, and non-immunogenic nature, and limits activation of other competitor cellular components [213]. Erythrocytes membrane coated nanoparticles are prepared by extracting the membrane from the cellular components, yet preserving their original protein antigens, that provides the innate natural targeting ability. Researchers have utilized hypotonic solution to extract the cellular contents and used the membrane to coat PLGA polymer nanoparticles. This construct demonstrated the prolonged circulation of 72 h over non coated PLGA nanoparticles [208] and suppress 98% lung metastasis in metastatic BC model. Su et al. [214] demonstrated similar results, erythrocytes membrane coated PLGA nanoparticles prolong circulation due to protein receptors present on the surface of these membranes and also in combination with integrating iRGD that provide specific targeting of metastatic breast tumor model. The authors show inhibition of more than 90% tumor growth and 95% of the lung metastasis with these nanoparticles as they can escape clearance by RES and circulate longer.

Additionally, the presence of tumor penetrating peptide iRGD serves as a receptor for lung metastatic sites that overexpress αvβ3 integrin and neuropilin-1, which allows the nanoparticle to specifically target and penetrate tumors. The authors also report enhanced retention of membrane coated nanoparticles at the metastatic regions, without the iRGD peptide, indicating the innate tendency of the erythrocytes membrane proteins to accumulate near the metastatic and tumor region [214]. Guo et al. [215] developed a nano vaccine utilizing the ability of erythrocytes coated nanoparticles to target antigen-presenting cells (especially dendritic cells) for induction of cytotoxic T lymphocyte-mediated response against tumors. The authors developed PLGA nanoparticles, coated with erythrocyte membrane entraps melanoma-associated antigenic peptide and targets dendritic cells because of their ability to specifically target tumor antigens that promote the secretion of pro-inflammatory cytokines such as TNF-α and IFN-γ and causes enhanced $CD8^+$ T-cell response. This novel antigenic peptide delivery system retarded tumor growth and suppressed tumor metastasis in a prophylactic, therapeutic, and metastatic melanoma model. This illustrates the possibility of using erythrocytes derived membranes in the development of biomimetic nanoparticles to demonstrate tumor-specific immune response. Hybrid nanoparticle infusing two types of bioinspired membranes: erythrocytes and platelets for prolonging circulation time and the other for expression of adhesion proteins, respectively increases site-specific targetability and prevents unwanted macrophage uptake [216]. This study demonstrates the ability to fuse two different types of cell membrane into one nanoparticle construct that will possess individual properties of each type of membrane and the endless number of possibilities that could be further explored. RBC membrane derived membrane-coated nanoparticles are extensively studied for various applications. A detailed overview of advantages and limitation of membrane-coated nanoparticles over erythrocytes as carriers has been documented by Xia et al. [217].

4.2.2. Neutrophil membrane-formed nanoparticles

Neutrophils are the most commonly found leukocytes in humans. They are the first immune cells that migrate to any infected site caused by bacteria and virus, to prevent the pathogens from spreading, by the release of cytokines/chemokines and ROS production. This response is called acute inflammation and involves neutrophil infiltration, which is regulated by intercellular interaction due to the presence of adhesion molecules on the neutrophils and vascular endothelium [218]. For example, researchers have demonstrated how activated neutrophils which express integrin β_2 binds to the inflamed vasculature that overexpress ICAM-1 [219]. A similar approach of conjugating nanoparticles to anti-ICAM-1 has also been explored by various researchers, however, the conjugation process did not show significant targeting improvement due to the complex tumor microenvironment [220]. Also, the cost ineffectiveness makes this strategy less useful and makes avenue for exploring the other potential options for novel targeting approach, such as cell membrane-based or whole-cell nanoparticles. Gao et al. [221] shows how human leukemia HL-60 cells were utilized for generating nanovesicles by nitrogen cavitation method, which highly express integrin β_2 and binds to the inflamed vascular endothelium due to the overexpression of ICAM-1 on them. The authors loaded the nanovesicles with an anti-inflammatory drug (TPCA-1) to show the ability of these nanovesicles to reduce the expression of cytokines TNF-α and IL-6, demonstrating their ability to bind to the inflamed vasculature and producing an anti-inflammatory effect. Red blood cells were used as a control to generate nanovesicles that lacked the expression of integrin β_2 and does not bind to the endothelium, elucidating the utilization of neutrophils to deliver therapeutics specifically at inflamed vasculature. Another similar study was demonstrated by Kang et al. [222] utilizing polymeric nanoparticles coated with the neutrophil membrane to target tumor vasculature and metastatic tumor cells in 4T1 BC with lung metastasis model. The authors demonstrate PLGA nanoparticles when coated with neutrophil membrane and loaded with carfilzomib, a proteasome inhibitor targets the circulating tumor cells or the metastatic niche and the inflamed endothelium. Thus, demonstrating the potential of polymeric nanoparticle coated with neutrophil membrane can be used to inhibit early metastasis and preformed metastasis.

4.2.3. Monocyte-derived nanoparticles

Monocytes are circulating white blood cells and play a crucial role in the inflammatory response and represent around 10% of leukocytes. They differentiate into macrophages or dendritic cells, with the latter mainly occurring during the active infection [223]. They also have similar roles as neutrophils and platelets in maintaining homeostasis and inflammatory response. Monocytes have 1–3 days half-life and could be exploited due to their intrinsic targeting ability especially at the inflamed vasculature or injury site [224]. Researchers have explored monocytes derived nanovesicles and have shown that these serve as better drug delivery tools over drug-loaded exosomes for various disease conditions. Jang et al. [225] loaded doxorubicin in exosome derived nanovesicles and show similar inhibition in tumor growth as a 20-fold higher dose of the same drug without causing any systemic adverse effects. The exosomes nanovesicles possess counter receptors such as LFA-1 that has specificity for cell adhesion molecules such as ICAM-1, VCAM-1, and E-selectin that is overexpressed on the inflamed endothelium cells, enabling the monocytes to target the circulating cells causing the maximal release of the therapeutic cargo at the targeted site [225]. On a similar approach, PLGA nanoparticles loaded with doxorubicin and coated with monocytes that express α4β1 integrin and binds to the cell adhesion molecules such as VCAM-1 that is overexpressed on the metastatic cancer cells have also been explored [226]. Further application of monocytes derived vesicles for the theranostic purpose has also been explored and has shown to cause significantly higher

uptake in the brain for upto 5 h, in contrast to non coated nanoparticles [227]. This type of construct has also been explored for delivery of siRNA and RNAi, due to the failed attempts to deliver naked RNA which gets degraded and cannot pass through the membranes to make it to the targeted site. Thus, this construct has improved delivery of RNA molecules which further can go through the process of RNA interference and suppress overexpressed oncogenes especially in cancer [228,229]. The ability of circulating monocytes to target tumor cells due to the expression of protein molecules on the surface of these monocytes, make them specific to the cells that prevent cancer progression, metastasis, angiogenesis, invasion, migration, and resistance to chemotherapy [230].

4.2.4. Platelet membrane-coated nanoparticles

Platelets are small and non-nucleated cytoplasmic body that are present actively circulating in the blood. They express a wide variety of immune cell receptors and adhesion molecules on their surface, responsible for mediating immune response. The platelets have the unique ability to be recruited instantaneously at the site of injury or after an infection which allows them to bind to the antigens and release blood clotting factors that would heal the wound. The presence of these various protein antigens on their surface allow immunomodulatory and cell adhesion capability. Researchers have utilized platelet membrane coated PLGA nanoparticles in two disease models of coronary restenosis and systemic bacterial infection to deliver docetaxel and vancomycin, respectively. Enhanced therapeutic efficacy was achieved via these novel biomembranes inspired polymeric nanoparticles in contrast to uncoated nanoparticles. Also, the authors demonstrate the coating shields the polymeric nanoparticles from unwantedly up taken by macrophages, thus enhancing nanoparticle deposition at the target site [231]. DOX loaded in platelet coated liposomes with two peptides: GPIIb-IIIa-like integrins and P-selectins expressed on their surface. This construct shows enhanced targetability to bind and destroy specifically metastatic BC cells over nonmetastatic BC cells in *in vitro* and *in vivo* models [232]. Platelet coated PLGA nanoparticles that have overexpression of P-selectin was also used to deliver tumor-specific apoptosis-inducing ligand cytokine (TRAIL) and doxorubicin to tumor cells due to specificity for CD44 receptors, expressed on the surface of tumor cells. Due to the enhanced targetability between the platelet membrane and cancer cells, the therapeutic efficacy of TRAIL due to activated extrinsic apoptosis is enhanced resulting in increased apoptosis. This way the authors synergistically deliver active therapeutics to the tumor cells by targeting via both intrinsic and extrinsic pathways, eliminating metastatic cells too [233]. Similar approaches were made by synthesizing silica nanoparticles that were further functionalized with activated platelet membranes and decorated with tumor-specific peptides such as TRAIL. This construct was able to specifically target circulating tumor cells and prevents unwanted phagocytosis, due to the expression of CD47 on the surface of the activated platelets that extends the half-life of the nanoparticles. This targeting strategy binds to circulating metastatic cells and shows significant decrease of lung metastases in metastatic orthotopic BC mouse model [234].

Platelets coated magnetic nanoparticles were applied for theranostic applications for both cancer therapy and cancer diagnosis. The authors, fabricated Fe_3O_4 nanoparticles coated with platelet membranes that express protein moieties which allows longer circulation and prevents immunogenicity. The application of magnetic nanoparticles allow optical absorption that extends to tumor magnetic resonance imaging as well as photothermal therapy. This allows enhanced tumor targetability along with intrinsic targeting ability from the membrane proteins of the platelets also reducing macrophage uptake. Thus, this strategy provides the application of bioinspired nanoparticle for personalized medicine in various disease states [235].

5. Conclusions and future perspectives

To date, TNBC remains a disease with a poor prognosis and poorer patient outcomes because of the disparity in molecular and genomic profiles among TNBC patients. Although major advancement has been made with targeted therapy for other types of BC, such as for HER2 positive trastuzumab has proven to be a blessing, yet in the case of TNBC, chemotherapy remains the backbone treatment regimen. A ray of hope in the advancement of therapy for TNBC had emerged when FDA approved the first-ever targeted therapy: PARP inhibitors, olaparib and talazoparib in 2018. Although it is only restricted among patients with BRCA1/2 mutation, which accounts for only 10–15% among TNBC population, extensive research is ongoing leading to positive preclinical and clinical outcomes with combination therapy or targeted therapy or immunotherapy or ADC. However, a lot of improvement could be achieved with other novel and/or nano formulation-based therapies that could lead to greater hope in enhancing treatment options and health outcomes among TNBC patients.

We present our views and recent development of cell membrane cloaked nanoparticles and illustrated their application in cancer therapeutics, particularly in BC and TNBC. These bioactive systems can also be tested or applied for other tumor types. The selection of cell membrane and composition is critical to achieve a superior tumor targeting. The unique properties (escaping the immune system and achieve long circulation time, inherent biocompatibility and biodegradability, avoid use of pharmaceutical excipients/additives, prolong life span, adhesion, and homologous targeting, etc.) of source cells (RBCs, WBCs, platelets, stem cells, immune cells, and cancer cells, etc.) can be extended as a carrier for delivery of therapeutics. However, these whole cells suffer from poor drug/therapeutic loading and its structure is destroyed during loading process. Thus, nanoparticles coated with appropriate cellular membranes can lead to the development of biomimetic nanoplatforms which offers low immunogenicity and superior biocompatibility. The prime advantage of these biomimetic nanosystems is retaining the cellular vesicle structures (membrane proteins, glycans, and lipids) which introduces the whole cell properties to the nanosystems. Such biomimetic nanoplatforms have been widely adopted in drug delivery, imaging, and anti-cancer research. These data laid a foundation for designing personalized medicine. Together, membrane cloaked nanoparticle technology has been matured to improve preparation, yields, stabilization, and scaling up process. The futuristic approach may be to introduce mixed types of cell membranes on nanoparticles rather from a cell as coating components for effective tumor targeting. The reviewed literature suggests that therapeutic formulations of membrane cloaked bioactive nanoformulations do not show systemic toxicities over free drugs. It may be possible that extensive and repeated use of such bioactive nanosystems can induce inflammation and alteration of the immune system. However, their long term systemic toxicity has not been studied in humans. Thus for effective implementation of these biomimetic nanoplatforms in drug delivery systems, it is important to focus on their future translation into the clinic.

Declaration of interest

Authors declare no potential conflict of interests.

CRediT authorship contribution statement

Pallabita Chowdhury: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision. **Upasana Ghosh:** Writing – original draft, Writing – review & editing, Supervision. **Kamalika Samanta:** Writing – original draft, Writing – review & editing, Supervision. **Meena Jaggi:** Methodology, Resources, Writing – original draft, Supervision. **Subhash C. Chauhan:** Methodology, Resources, Writing – original draft, Supervision. **Murali M. Yallapu:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review &

editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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