Proceedings of Anticancer Research, 2025, Volume 9, Issue 3
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Advances in Biomimetic Nanotechnology for Triple-Negative Breast Cancer Therapy

Lezhang Mao, Furen Zeng*

The First Affiliated Hospital of Hunan Normal University, Hunan Provincial People's Hospital, Changsha 410000, Hunan, China

***Author to whom correspondence should be addressed.**

Abstract: This article systematically reviews the application of biomimetic nanotechnology in targeted therapy for triple-negative breast cancer (TNBC). TNBC poses significant challenges for conventional treatments due to the lack of defined therapeutic targets, chemotherapy resistance, and a complex immunosuppressive microenvironment. Biomimetic nanotechnology, by mimicking the functional properties of biological structures (e.g., cell membranes, exosomes), has significantly enhanced drug delivery efficiency, targeting precision, and anti-tumor immune responses. This review focuses on the design strategies of biomimetic nanocarriers (including cell membrane-coated nanoparticles, engineered exosomes, and biomimetic synthetic materials) and their innovative applications in TNBC therapy: (1) Targeted delivery systems that overcome tumor barriers and reduce systemic toxicity; (2) Photothermal therapy combined with immunomodulation for precise treatment and immune activation; (3) Tumor microenvironment regulation (e.g., vascular normalization, pH neutralization, immunosuppression reversal). Studies demonstrate that biomimetic nanotechnology significantly improves TNBC treatment efficacy through multimodal synergistic mechanisms (e.g., chemo-photothermal-immunotherapy). However, challenges such as scalable production, long-term safety, and personalized adaptation remain for clinical translation. Future research should integrate artificial intelligence for optimized design and dynamic imaging technologies to advance biomimetic nanomedicines toward clinical applications.

Keywords: Biomimetic nanotechnology; Triple-negative breast cancer; Targeted therapy; Photothermal therapy; Immunomodulation; Tumor microenvironment

Online publication: June 5, 2025

1. Introduction

Triple-negative breast cancer (TNBC) is a highly aggressive breast cancer subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression [1]. Due to the lack of actionable therapeutic targets, TNBC management primarily relies on chemotherapy (e.g., anthracyclines and taxanes), which is limited by drug resistance, tumor heterogeneity, and

frequent recurrence [2]. Molecular heterogeneity further subdivides TNBC into basal-like, mesenchymal, and immunomodulatory subtypes, each exhibiting distinct therapeutic responses, complicating precision treatment [3]. Additionally, the immunosuppressive tumor microenvironment (TME) in TNBC, driven by PD-L1 upregulation and regulatory T cell (Treg) recruitment, further diminishes anti-tumor immunity [2]. While immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies) show promise in some TNBC patients, their efficacy is hindered by dynamic TME regulation and inefficient drug delivery [1]. Thus, novel strategies to overcome heterogeneity, remodel the TME, and penetrate biological barriers are urgently needed.

Biomimetic nanotechnology, inspired by natural biological structures (e.g., cell membranes, exosomes, or pathogens), offers transformative solutions for TNBC. Core design strategies include coating synthetic nanoparticles with cell membranes (e.g., red blood cells, cancer cells, or immune cells) to confer immune evasion, prolonged circulation, and active targeting [4]. For instance, macrophage membrane-coated nanocarriers exploit chemokine receptors (e.g., CCR2) to target tumor-associated inflammatory sites while co-delivering chemotherapeutics and immunomodulators to reverse immunosuppression [5]. Hybrid membrane technology (e.g., fusing red blood cell and cancer cell membranes) integrates multiple functionalities: CD47-mediated immune evasion, homologous targeting for tumor accumulation, and stimuli-responsive drug release [4]. Compared to conventional nanocarriers, biomimetic systems reduce off-target toxicity and enhance interactions with host biology, such as crossing the blood-brain barrier or inducing immunogenic cell death [6]. These advantages position biomimetic nanotechnology as a powerful tool to address chemotherapy resistance, metastasis, and theranostic integration [7].

This review summarizes the design strategies of biomimetic nanomedicines, current applications of biomimetic nanotechnology, and its role in TNBC therapy, aiming to explore its clinical potential and guide the development of next-generation TNBC treatments.

2. Design strategies of biomimetic nanocarriers

2.1. Cell membrane-coated nanoparticles

Cell membrane-coated nanoparticles (CNPs) encapsulate synthetic nanoparticles with natural cell membranes (e.g., tumor cells, macrophages, or leukocytes), inheriting the source cells' surface antigens and targeting capabilities. Tumor cell membrane-coated nanoparticles achieve homologous targeting for precise tumor localization [8]. Macrophage membrane-coated nanoparticles leverage inflammation targeting and immune evasion to penetrate physiological barriers and evade clearance [9]. Leukocyte membrane-coated nanoparticles mimic leukocyte rolling and adhesion, enhancing tumor vascular retention [10]. Recent advances include genetic engineering of membranes (e.g., overexpressing calreticulin to enhance antigen presentation) to synergize with checkpoint inhibitors [11]. This hybrid "natural-synthetic" strategy improves targeting efficiency and reduces immunogenicity, offering new avenues for precision drug delivery [12].

2.2. Exosomes and extracellular vesicles

Exosomes are naturally secreted nanovesicles (30–150 nm) with lipid bilayers, capable of carrying proteins, nucleic acids, and drugs while mediating intercellular communication. Their advantages include low immunogenicity, biocompatibility, and intrinsic targeting. Tumor-derived exosomes utilize integrins for organ-specific metastasis, serving as anti-metastatic carriers [13]. Exosome-encapsulated siRNA effectively silences S100A4, inhibiting

premetastatic niche formation in breast cancer [14]. Engineered exosomes enhance targeting via ligand conjugation (e.g., folate) or membrane protein fusion. For example, mesoporous silica nanoparticles combined with exosomes deliver chemotherapeutics to reverse cancer stem cell-driven epithelial-mesenchymal transition (EMT) [15]. Exosomes also serve as multifunctional carriers for photodynamic therapy or immunomodulators, enabling synergistic anti-tumor effects [16].

2.3. Biomimetic synthetic materials

Biomimetic synthetic materials mimic natural biomolecules for stimuli-responsive and dynamic targeting. Hyaluronic acid (HA)-modified nanoparticles target CD44-overexpressing tumor cells and release drugs via enzymatic degradation in acidic microenvironments [17]. Peptide-based supramolecular materials undergo structural rearrangement in response to TME cues (e.g., low pH, ROS) for controlled drug release [18]. Stimuli-responsive polymers (e.g., pH-sensitive ZIF-8) encapsulate glucose oxidase (GOx) and hemin to amplify ROS generation, enhancing immunogenic cell death (ICD) [19]. Prussian blue nanocomposites combine chemotherapy and photothermal therapy to induce pyroptosis and activate anti-tumor immunity [20]. These smart materials address limitations of traditional nanocarriers [21].

3. Applications of biomimetic nanotechnology in cancer therapy

3.1. Photothermal therapy (PTT) and biomimetic nanotechnology

PTT employs near-infrared light to activate nanoparticles for localized hyperthermia. Biomimetic designs enhance PTT precision and efficacy. For example, Wu *et al*. developed erythrocyte membrane-coated nanocrystals (AE@RBC/Fe NCs) containing aloe-emodin and ferritin. This system prolongs circulation, induces ferroptosis via Fe^{3+} release, and activates anti-tumor immunity, achieving 90% tumor suppression in breast cancer models [22]. Li *et al*. designed platelet membrane-coated Prussian blue nanocomposites (PB/PM/HRP/Apt) that target tumor sites, enhance penetration, and release PD-L1 aptamers under photothermal activation, suppressing primary and metastatic tumors [23]. Biomimetic membranes (e.g., tumor or leukocyte membranes) reduce immune clearance and improve tumor accumulation [24].

3.2. Biomimetic delivery systems for chemo-immunotherapy

Biomimetic nanocarriers enhance chemotherapy targeting and TME modulation. Geng *et al*. constructed mesenchymal stem cell (MSC) membrane-coated nanoparticles to deliver metronidazole and doxorubicin, eliminating intratumoral *Fusobacterium nucleatum* and synergizing with PD-L1 inhibitors to prolong survival in 4T1 models [25]. Zhang *et al*. developed tumor cell membrane-lipid hybrid nanoparticles (CLip-PC@CO-LC NPs) for spatiotemporal co-delivery of docetaxel and siRNA, suppressing non-small cell lung cancer growth [26]. Xiao *et al*. engineered anti-PD-L1 antibody-conjugated gold nanostars (PDA/GNS@aPD-L1 NPs) that combine photothermal ablation with immune checkpoint blockade, enhancing $CD8^+$ T cell infiltration in colorectal cancer [27].

3.3. Innovative combination strategies and clinical translation

Multimodal therapies integrate diverse mechanisms to overcome treatment limitations. Wang *et al*. designed lactoferrin/albumin-coated nanoparticles (Alb/LF NPs) loaded with copper/iron diethyldithiocarbamate to induce ferroptosis and metalloimmunity in gliomas [28]. Cao *et al*. developed MSC membrane-camouflaged black

phosphorus nanosheets (BP NSs) for photothermal-chemotherapy, delaying BP degradation and enhancing tumor accumulation [29]. Challenges in clinical translation include scalable production, long-term safety, and personalized design. For instance, platelet membrane-coated nanoparticles (PNP-R848) achieved complete tumor regression in colorectal cancer models, highlighting clinical potential [30,31].

4. Biomimetic nanotechnology in TNBC therapy

4.1. Innovations in targeted delivery systems

Biomimetic nanocarriers enable precise drug release and enhanced tumor accumulation. Bhullar *et al*. engineered exosomes co-loaded with Survivin siRNA, gemcitabine, and paclitaxel, achieving tumor-specific delivery via CD44 aptamers and reducing systemic toxicity in TNBC models [32]. Chowdhury *et al*. utilized neutrophil membrane-coated nanoparticles (PVT-NEU NPs) to enhance paclitaxel delivery, increasing tumor cell uptake by 2.3-fold and improving suppression rates by 40% [33]. Zhang *et al*. developed macrophage membrane-coated magnetic nanoparticles (MMNPs) targeting CD163 to promote M1 polarization and immune activation [34].

4.2. Integration of photothermal and immunotherapy

Biomimetic platforms combine photothermal materials (e.g., gold nanoparticles) with immunomodulators for synergistic effects. Liu *et al*. designed platelet membrane-coated silver metal-organic frameworks (PM@MOF-Ag NPs) that induce ROS-mediated apoptosis and enhance Bax/Bcl-2 ratios in TNBC [35]. Jiang *et al*. developed gadolinium-doped carbon dots (Gd@CDs) for MRI-guided photothermal-chemotherapy, suppressing 4T1 tumor growth and metastasis [36]. Wang *et al*. conjugated IR792 photosensitizers and PD-L1 antibodies to silica nanoshells, boosting $CD8^+$ T cell infiltration and survival in TNBC models [37].

4.3. Tumor microenvironment (TME) modulation

Biomimetic nanotechnology regulates TME components to improve treatment outcomes. Gong *et al*. developed ternary heterostructure nanoparticles (AZG) that generate ROS under near-infrared light, inducing apoptosis and angiogenesis inhibition in MDA-MB-231 models [38]. Li *et al*. designed hyaluronic acid-functionalized hydrogels delivering VEGF siRNA and CCL2 inhibitors to reduce M2 macrophages and vascularization in TNBC [39].

5. Conclusion and perspectives

Biomimetic nanotechnology offers unique advantages for TNBC therapy: Targeted delivery reduces systemic toxicity; photothermal-immunotherapy overcomes heterogeneity and immune tolerance [40,41]; TME modulation transforms “cold” tumors. However, clinical translation requires addressing scalable production, long-term safety, and personalized design. Future research should integrate AI-optimized materials, multifunctional systems, and advanced imaging. With advancements in single-cell sequencing and dynamic imaging, personalized biomimetic nanotherapies may become the cornerstone of TNBC precision medicine.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Obidiro O, Battogtokh G, Akala EO, 2023, Triple Negative Breast Cancer Treatment Options and Limitations: Future Outlook. Pharmaceutics, 15(7): 1796.

[2] So JY, Ohm J, Lipkowitz S, et al., 2022, Triple Negative Breast Cancer (TNBC): Non-genetic Tumor Heterogeneity and Immune Microenvironment: Emerging Treatment Options. Pharmacol Ther, 237: 108253.

[3] Singh DD, Yadav DK, 2021, TNBC: Potential Targeting of Multiple Receptors for a Therapeutic Breakthrough, Nanomedicine, and Immunotherapy. Biomedicines, 9(8): 876.

[4] Chen HY, Deng J, Wang Y, et al., 2020, Hybrid Cell Membrane-coated Nanoparticles: A Multifunctional Biomimetic Platform for Cancer Diagnosis and Therapy. Acta Biomater, 112: 1–13.

[5] Lopes J, Lopes D, Pereira-Silva M, et al., 2022, Macrophage Cell Membrane-Cloaked Nanoplatforms for Biomedical Applications. Small Methods, 6(8): e2200289.

[6] Oroojalian F, Beygi M, Baradaran B, et al., 2021, Immune Cell Membrane-Coated Biomimetic Nanoparticles for Targeted Cancer Therapy. Small, 17(12): e2006484.

[7] Tong Q, Qiu N, Ji J, et al., 2020, Research Progress in Bioinspired Drug Delivery Systems. Expert Opin Drug Deliv, 17(9): 1269–1288.

[8] Fang R, Gao W, Zhang L, 2023, Targeting Drugs to Tumours Using Cell Membrane-coated Nanoparticles. Nat Rev Clin Oncol, 20(1): 33–48.

[9] Khatoon N, Zhang Z, Zhou C, et al., 2022, Macrophage Membrane Coated Nanoparticles: A Biomimetic Approach for Enhanced and Targeted Delivery. Biomater Sci, 10(5): 1193–1208.

[10] Wang D, Wang S, Zhou Z, et al., 2022, White Blood Cell Membrane-coated Nanoparticles: Recent Development and Medical Applications. Adv Healthc Mater, 11(7): e2101349.

[11] Li Z, Cai H, Li Z, et al., 2023 A Tumor Cell Membrane-coated Self-amplified Nanosystem as a Nanovaccine to Boost the Therapeutic Effect of Anti-PD-L1 Antibody. Bioact Mater, 21: 299–312.

[12] Ning S, Dai X, Tang W, et al., 2022, Cancer Cell Membrane-coated C-TiO2 Hollow Nanoshells for Combined Sonodynamic and Hypoxia-activated Chemotherapy. Acta Biomater, 152: 562–574.

[13] Shao J, Zaro J, Shen Y, 2020, Advances in Exosome-based Drug Delivery and Tumor Targeting: From Tissue Distribution to Intracellular Fate. Int J Nanomedicine, 15: 9355–9371.

[14] Zhao L, Gu C, Gan Y, et al., 2020, Exosome-mediated siRNA Delivery to Suppress Postoperative Breast Cancer Metastasis. J Control Release, 318: 1–15.

[15] Sarkar R, Biswas S, Ghosh R, et al., 2024, Exosome-sheathed Porous Silica Nanoparticle-mediated Co-delivery of 3,3'-Diindolylmethane and Doxorubicin Attenuates Cancer Stem Cell-driven EMT in Triple Negative Breast Cancer. J Nanobiotechnology, 22(1): 285.

[16] Zhang M, Hu S, Liu L, et al., 2023, Engineered Exosomes from Different Sources for Cancer-targeted Therapy. Signal Transduct Target Ther, 8(1): 124.

[17] Zhou X, He C, Liu M, et al., 2021, Self-assembly of Hyaluronic Acid-mediated Tumor-targeting Theranostic Nanoparticles. Biomater Sci, 9(6): 2221–2229.

[18] Zhang W, Yu L, Ji T, et al., 2020, Tumor Microenvironment-responsive Peptide-based Supramolecular Drug Delivery System. Front Chem, 8: 549.

[19] He Q, Chen J, Yan J, et al., 2020, Tumor Microenvironment Responsive Drug Delivery Systems. Asian J Pharm Sci, 15(4): 416–448.

[20] Long Y, Fan J, Zhou N, et al., 2023, Biomimetic Prussian Blue Nanocomplexes for Chemo-photothermal Treatment of

Triple-negative Breast Cancer by Enhancing ICD. Biomaterials. 303: 122369.

[21] Ding H, Tan P, Fu S, et al., 2022, Preparation and Application of pH-responsive Drug Delivery Systems. J Control Release, 348: 206–238.

[22] Wu M, Ling W, Wei J, et al., 2022, Biomimetic Photosensitizer Nanocrystals Trigger Enhanced Ferroptosis for Improving Cancer Treatment. J Control Release, 352: 1116–1133.

[23] Li W, Li F, Li T, et al., 2023, Self-actuated Biomimetic Nanocomposites for Photothermal Therapy and PD-L1 Immunosuppression. Front Chem, 11: 1167586.

[24] Gallo J, Villasante A, 2023, Recent Advances in Biomimetic Nanocarrier-Based Photothermal Therapy for Cancer Treatment. Int J Mol Sci, 24(20): 15484.

[25] Geng S, Guo P, Li X, et al., 2024, Biomimetic Nanovehicle-Enabled Targeted Depletion of Intratumoral Fusobacterium nucleatum Synergizes with PD-L1 Blockade against Breast Cancer. ACS Nano,18(12): 8971–8987.

[26] Zhang W, Gong C, Chen Z, et al., 2021, Tumor Microenvironment-activated Cancer Cell Membrane-liposome Hybrid Nanoparticle-mediated Synergistic Metabolic Therapy and Chemotherapy for Non-small Cell Lung Cancer. J Nanobiotechnology, 19(1): 339.

[27] Xiao Y, Zhu T, Zeng Q, et al., 2023, Functionalized Biomimetic Nanoparticles Combining Programmed Death-1/Programmed Death-ligand 1 Blockade with Photothermal Ablation for Enhanced Colorectal Cancer Immunotherapy. Acta Biomater, 157: 451–466.

[28] Wang R, Song W, Zhu J, et al., 2024, Biomimetic Nano-chelate Diethyldithiocarbamate Cu/Fe for Enhanced Metalloimmunity and Ferroptosis Activation in Glioma Therapy. J Control Release, 368: 84–96.

[29] Cao J, Qi J, Lin X, et al., 2021, Biomimetic Black Phosphorus Nanosheet-Based Drug Delivery System for Targeted Photothermal-Chemo Cancer Therapy. Front Bioeng Biotechnology, 9: 707208.

[30] Chan M, Chang Z, Huang C, et al., 2022, Integrated Therapy Platform of Exosomal System: Hybrid Inorganic/Organic Nanoparticles with Exosomes for Cancer Treatment. Nanoscale Horiz, 7(4): 352–367.

[31] Bahmani B, Gong H, Luk B, et al., 2021, Intratumoral Immunotherapy Using Platelet-cloaked Nanoparticles Enhances Antitumor Immunity in Solid Tumors. Nat Commun, 12(1): 1999.

[32] Bhullar AS, Jin K, Shi H, et al., 2024, Engineered Extracellular Vesicles for Combinatorial TNBC Therapy: SR-SIM-guided Design Achieves Substantial Drug Dosage Reduction. Mol Therapy, 32(12): 4467–4481. https://doi.org/10.1016/j.ymthe.2024.09.034

[33] Chowdhury P, Bhusetty Nagesh PK, Hollingsworth TJ, et al., 2022, Coating a Self-assembly Nanoconstruct with a Neutrophil Cell Membrane Enables High Specificity for Triple Negative Breast Cancer Treatment. ACS Appl Bio Mater, 5(9): 4554–4566. https://doi.org/10.1021/acsabm.2c00614

[34] Zhang L, Chen W, Wang X, et al., 2024, Macrophage Membrane-coated Magnetic Nanoparticles Enhance Chemoimmunotherapy via CD163-Targeted Delivery and M1 Polarization. Nano Today, 52: 102122.

[35] Liu H, Cai G, Yuan S, et al., 2024, Platelet Membrane-Camouflaged Silver Metal-organic Framework Biomimetic Nanoparticles for the Treatment of Triple-negative Breast Cancer. Mol Pharm, 21(7): 3577–3590.

[36] Jiang Q, Liu L, Li Q, et al., 2021, NIR-laser-triggered Gadolinium-doped Carbon Dots for Magnetic Resonance Imaging, Drug Delivery and Combined Photothermal Chemotherapy for Triple Negative Breast Cancer. J Nanobiotechnology, 19(1): 64. https://doi.org/10.1186/s12951-021-00811-w

[37] Wang Y, Li X, Zhang Z, et al., 2024, Dual-modality NIR-II Photothermal/Immune Checkpoint Blockade Therapy Using IR792-conjugated Silica Nanoshells. Adv Mater, 36(15): 2311285.

[38] Dong S, Huang Y, Yan H, et al., 2024, Ternary Heterostructure-driven Photoinduced Electron-hole Separation Enhanced

Oxidative Stress for Triple-negative Breast Cancer Therapy. J Nanobiotechnology, 22: 240. https://doi.org/10.1186/s12951-024-02530-4

[39] Li J, Qiu Y, Xu C, et al., 2024, Hyaluronic Acid-functionalized Hydrogel Nanocarriers for Dual Targeting of TAMs and VEGF in Triple-negative Breast Cancer. Biomaterials, 310: 122345.

[40] Wang Y, Wang H, Song Y, et al., 2022, IR792-MCN@ZIF-8-PD-L1 siRNA Drug Delivery System Enhances Photothermal Immunotherapy for Triple-negative Breast Cancer Under Near-infrared Laser Irradiation. J Nanobiotechnology, 20: 96. https://doi.org/10.1186/s12951-022-01255-6

[41] Yin H, Xiong G, Guo S, et al., 2019, Delivery of Anti-miRNA for Triple-negative Breast Cancer Therapy Using RNA Nanoparticles Targeting Stem Cell Marker CD133. Mol Ther, 27(7): 1252–1261. https://doi.org/10.1016/j.ymthe.2019.04.018