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REVIEW

Biomimetic Nanoparticles for Targeted and Efficient Cancer Therapy: Progress, Challenges and Perspectives

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Abstract: Cancer remains a prominent cause of global mortality, with over 200 identified forms, and is projected to have a 25% increase in fatalities by 2030. Early diagnosis and treatment are crucial, but current therapy, which includes surgery, chemotherapy, immunotherapy, hormonal therapy, targeted therapy, and radiotherapy, faces challenges such as non-targeted drug distribution, toxicity, and limited efficacy. In recent years, biomimetic nanoparticles have emerged as a promising nanocarrier with great potential that enables site-specific drug release, improves biocompatibility, prolongs circulation time, and minimizes immune responses. Among various biomimetic nanoparticles, nanoparticles coated with cell membranes, such as those from cancer cells, immune cells, and stem cells, have been shown to have great potential for cancer treatment. The cell membrane-coated nanoparticles, further functionalized with tumor-specific ligands, demonstrated potential in improving half-life, drug specificity, and overall therapeutic efficacy. In this comprehensive article, we have reviewed recent advances in cell membrane-coated biomimetic nanoparticle systems for cancer therapy. We discussed the biomimetic nanoparticles coated with membranes of red blood cells, cancer cells, platelet cells, macrophages, exosomes, hybrid cells, and protein/serum albumin for cancer therapy. This review also highlights challenges associated with large-scale production, maintaining structural integrity during drug loading, clinical and biosafety aspects, regulatory requirements, and the clinical translation of the cell membrane-coated biomimetic nanoparticle systems.

Keywords: targeted delivery, cell membrane-coated nanoparticles, biomimetic nanoparticles, cancer therapy

Introduction

Cancer is a formidable worldwide health concern and remains a substantial contributor to worldwide mortality. Cancer can be defined as the uncontrolled division or growth of cells that can easily evade and destroy their surroundings and can also spread to other parts of the body. The grim statistics on cancer-related deaths underscore its profound impact on individuals and societies. According to the 2020 report from the World Health Organization's Global Cancer Observatory, malignancies hold the unenviable position of being the foremost cause of global mortality. Carcinoma cells, responsible for this devastating disease, exhibit marked morphological abnormalities, including pleomorphism, loss of cellular polarity, and anaplasia, characteristics that enable their aggressive spread to distant anatomical sites.[1] More than 200 distinct cancer forms have been identified worldwide to date. The WHO projects a worrisome 25% increase in cancer-related fatalities from 2020 to 2030, underscoring the pressing need for effective prevention and treatment

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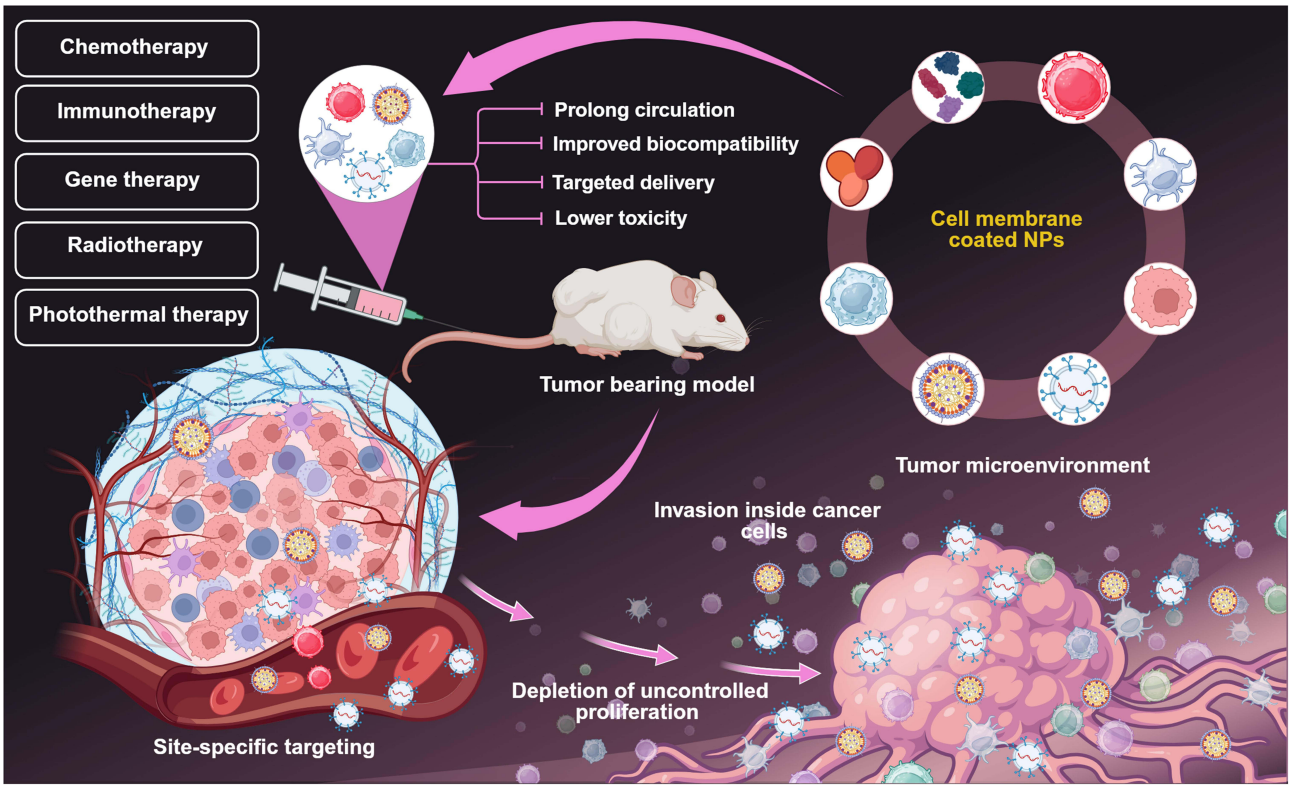
Graphical Abstract



strategies.[2] Despite advancements in medical science, cancer remains an imposing challenge and continues to be one of the world's most deadly diseases, casting a heavy burden on both individuals and communities.[3]

It is possible to treat early-stage cancers surgically, but it is challenging to eradicate all neoplasms through surgery alone. In most cases, adjunctive therapies such as chemotherapy or radiotherapy are indispensable.[1] The primary strategy for achieving a cure lies in the early diagnosis of cancer, a task facilitated through various diagnostic modalities, including X-ray,[4] Endoscopy,[2] Colonoscopy, Ultrasonography, Blood Serum analysis, etc.[5] Despite advancements in therapeutic agents over the decades, issues persist with their non-targeted distribution throughout the body. This inherent lack of precise targeting, limited bioavailability, rapid excretion, and substantial toxicity necessitate the administration of high dosages to attain the desired therapeutic concentration at the intended site.[6] Consequently, refining drug delivery mechanisms to facilitate specificity and reduce adverse effects remains a critical focus in oncological research.[7] In this regard, due to their site-specific delivery and biomimetic nature, biomimetic nanoparticles have recently garnered significant interest in cancer therapy. Over the past few decades, these nanoparticles (NPs) have undergone substantial cutting-edge research, especially for cancer, trauma, cardiovascular disease, acute kidney injury, rheumatoid arthritis, etc. NPs are tiny particles that range between 1 and 100 nm.[8] Biomimetic nanoparticles are a novel frontier in the fight against cancer. These nanoparticles were meticulously crafted to mimic the complex operations of biological systems, adopting nature's elegance as their primary design influence. Biomimetic nanoparticles hold the potential to make cancer therapy a more targeted and successful attempt by mimicking physiological processes, including cell targeting and drug transport.[1] The latest methods for preparing biomimetic materials include 3D printing, electrospinning, biological templating, and surface coating.[9] These preparation processes aim to mimic the functional and biological properties. Recent progress focuses on advanced fabrication of these biomimetic nanomaterials for tissue engineering, drug delivery,

and the development of scaffolds.[10] The development of these methods focuses on multi-scale design of nanostructures and integration with native cells or tissues for specific applications.

The limitations of conventional therapies, such as rapid clearance by the immune system and poor drug targeting, can be overcome by using new technologies.[11] And one of them includes the use of cellular components to mimic the natural cellular structures. Biomimicking offers improved biocompatibility and reduced toxicity, which allows efficient drug delivery to disease-specific targeted sites.[12] Immune evasion provides an extended circulation time and allows the biomimetic nanoparticles to reach the target site.[13] The surface modification with the cell membrane enables the nanoparticle to mimic the self-recognition on the cell surface, leading to more precise drug delivery, and a similar biostructure also makes the biomimetic nanoparticles more compatible with biological systems and reduces the potential toxic side effects associated with conventional nanoparticles.[14] These abilities provide a significant enhancement in the therapeutic efficacy of the drug carrier and overcome biological barriers. Biomimetic nanoparticles act as an interlink between the synthetic materials and the complex biological environment, making a sophisticated mechanism for the development of a particular and compelling drug delivery system.[15]

Thus, biomimetic nanoparticles offer a diverse array of applications, including targeted drug delivery, photothermal therapy, gene delivery, antimicrobial treatments, vaccines, tissue engineering, and the monitoring of the phenotypic evolution of cancer cells, all while minimizing undesirable immune responses.[16] One of the key strategies in developing these nanoparticles involves camouflaging them with cell membranes, which opens innovative avenues for research. Red blood cell-coated nanoparticles, for instance, exhibit an improved half-life. This biomimetic approach allows nanoparticles to evade the immune system's surveillance and effectively express their targeting properties. Additionally, surfaces engineered with nanoparticles that have natural ligands or plasma membranes obtained from cancer cells significantly improve drug specificity by attaching to specific biological markers on the surface of cancer cells (Figure 1). However, challenges like robust clinical translation and ensuring biocompatibility of purified cell membranes for clinical application remain unresolved.[17]

This review explores the nature of biomimetic nanoparticles, how they revolutionize cancer therapy by mimicking biological activities, and provides targeting and immunomodulatory strategies. Exploring the latest advancements in biomimetic nanoparticles synthesized from natural cells and shedding light on their potential in cancer therapy management. The collaborative information about the basics and recent development of biomimetic nanoparticles, their immune response, and their clinical translation in cancer treatment and diagnosis will help the researchers, scientists and young individuals to exploit the advanced developments of this field. This review also offers an insight into how these innovative technologies may reshape the landscape of cancer treatment, providing more targeted and effective therapeutic options.

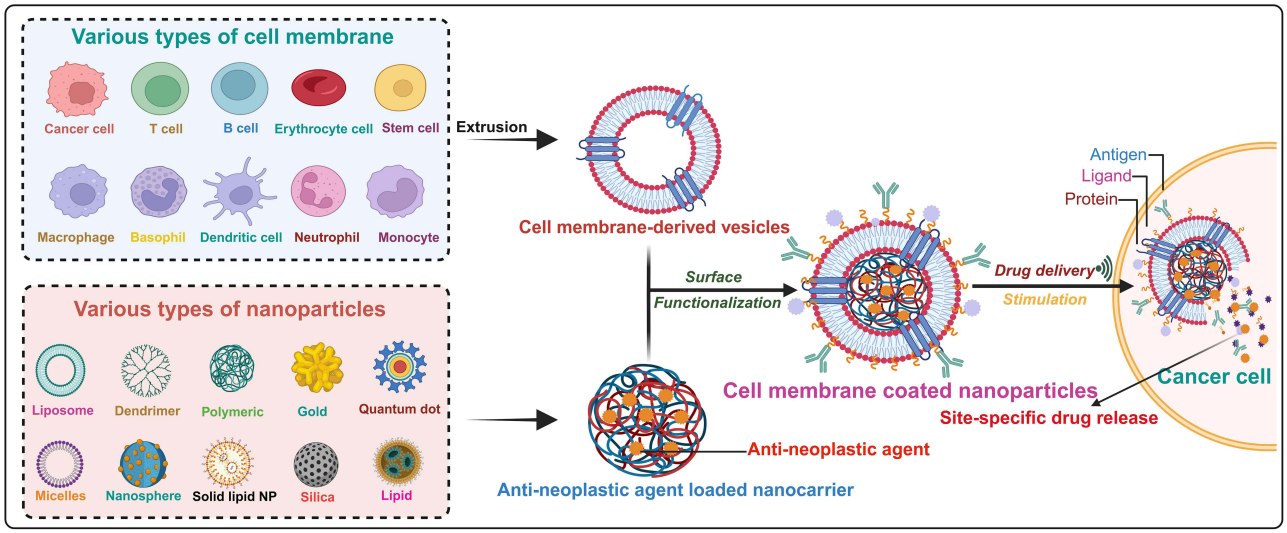


Figure 1 Schematic illustration of a biomimetic nanoparticle encapsulated antineoplastic agent and its surface functionalization for targeting cancer cells to site-specific cargo release.

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Cancer: Development, Immune Response and Its Clinical Aspects

Development of Cancer Cells

The disease of cancer is characterised by abnormal cell proliferation with the ability to infiltrate or spread to other sections of the body.[5] Symptoms include unusual bleeding, a persistent cough, a lump, weight loss, and a change in bowel habits, which should be investigated promptly.[18] The hormones or other chemicals released by the tumor cause some systemic symptoms of cancer, like paraneoplastic disorder, which consists of hypercalcemia, causing altered mental status, constipation, dehydration, and hyponatremia, causing altered mental status along with headache and seizures. The process by which the cancer cells migrate to different body parts is called metastasis. A metastatic tumor is a cancer that has migrated beyond its original location, whereas a primary tumor is a cancer that has not spread to other parts of the body.[6] The immune cells of the body, such as CD8+ T cells and natural killer cells, identify the tumor cells in the initial stage and fight to eliminate them from the body.[19] While the others, such as macrophages, neutrophils, and B cells, not only help to counter the tumor progression but also support and promote its growth. With this, tumor cells can also escape the immune response by avoiding immunorecognition and initiating an immune-suppressive tumor microenvironment (TME).[19]

The uncontrolled growth of cancer cells leads to a proliferation of irregularities that disrupt various cellular regulatory mechanisms, adversely impacting the patient's immune system.[7] Cancer treatments, such as chemotherapy and radiation therapy, can harm the bone marrow, leading to a reduction in blood cell production. Consequently, the immune system becomes weaker, and the body is less able to fight infections. The origin of cancer comprises both the disease itself and the external agents that induce disruptions within the body. The precise cause of cancer is still unknown, even after years of research. However, new developments in cytogenetics and molecular biology give hope that the underlying causes of cancer may eventually be understood. The second component of cancer causation is challenging to understand and involves a complex interaction of variables that are related to the growth of human cancer. Ionizing radiation stands out as one of the most widely recognized causes of cancer in humans. Notably, ionizing radiation emerges as a prominently acknowledged contributor to cancer in humans among these factors.

Immune Response

Cancer cells can spread out from where they started, infiltrating neighboring tissues and developing masses at other parts of the body, known as tumors. Tumors are particularly dangerous when the tissues and organs essential for the organism's overall survival are damaged. In genetically altered cells, tumors form when a single cell within a healthy population has a genetic mutation that enhances its proclivity to multiply when it should be resting. In hyperplasia, the altered cell and its descendants appear normal, but they reproduce excessively. After years, one in a million of these cells suffers another mutation that further loosens controls on cell growth. The abnormal growth of cells is said to be malignant when genetic changes allow it to invade underlying tissue and shed cells into the blood or lymph. Cancer also weakens our immune system, which is crucial for fighting cancer. It spreads into the bone marrow and reduces the amount of blood cells (mainly in leukaemia or lymphoma), thus weakening the immunity to eradicate the cancer cells.[20] Sometimes, the cancer treatment itself temporarily affects the immune system, which also includes some immunotherapies like monoclonal antibodies, vaccines, cytokines, and CAR T-cell therapy.[20] Burnet and Thomas gave the immunological surveillance theory, suggesting the recognition of malignant cells by assessing the presence of tumor-associated antigens or tumor-specific antigens.[21] But these cancer cells learned and adapted to survive by evading the immune system. Indoleamine 2,3-dioxygenase, an immunomodulatory enzyme, is a significant factor in malignant cell growth and immune suppression. Inhibiting this enzyme may overcome the effects of traditional chemotherapeutic treatments. Immunity not only helps to eradicate the cancer development or proliferation but also enhances its progression in some cases, eg, Chronic gastritis caused by *Helicobacter pylori* can be associated with gastric cancer.[21] Thus, failure in the elimination of a foreign substance may further lead to malignant progression and cancer expansion.

Clinical Aspects

Cancer treatment encompasses a multifaceted range of clinical approaches, including advanced diagnostic techniques, standardized staging systems, diverse treatment procedures, and comprehensive patient care. Continuous evolution in

cancer's clinical management emphasizes multidisciplinary collaboration, precise medication, and patient-centred support services to optimize the treatment outcomes. Diagnostic approaches, such as biomarker identification and imaging technology, involve the detection of genetic mutations, protein levels, and circulating tumor DNA (ctDNA), which provides valuable information to identify malignancies at various stages. Several traditional and novel biomarkers expanded the capabilities of tumor diagnosis. Traditional tumor marker examples include AFP, PSA, CA-125, and CEA markers for liver, prostate, ovarian, and colorectal cancer, respectively.[22] Whereas microRNA, synthetic biomarkers, circulating nucleosomes, and tumor cells are examples of novel biomarkers.[23]

Standardized staging systems, primarily the TNM system, can help to guide the prognosis and treatment of tumors. The TNM staging system is an internationally accepted standard for the classification of cancer, regulated by the American Joint Committee on Cancer and the Union for International Cancer Control.[24] T describes the primary tumor size and local tissue invasion, N indicates the involvement of lymph nodes, and M determines the distant metastatic spread. The TNM classification collaboratively describes the overall cancer stages from 0 to IV.[25] Furthermore, the treatment procedures and clinical approaches include surgery, chemotherapy, radiation, targeted therapy, and immunotherapy, depending on cancer type, stage, and patient-related factors.[26] Modern surgical approaches involve the removal of the tumor with minimal invasive techniques.[27] Advances in chemotherapy focus on improving side effects, including nausea, fatigue, hair loss, and immunosuppression, with optimized drug combinations.[28] And, radiation therapy for tumor shrinkage before surgery and sometimes post-operatively to eliminate the residual cancer cells.[29] Still, with such effective available treatment options, more precise, safer, and patient-oriented advanced therapies are needed. Targeted therapy, immunotherapy, and combination therapies are some of the most recently used advanced techniques.[30] Unlike chemotherapy's broad cellular effect, targeted therapy offers the use of a specific drug targeting a specific molecular pathway to inhibit cancer cell survival.[4] Thus, offering a personalized treatment with potentially reduced side effects. Immunotherapy boosts the patient's immune system against cancer, and recent clinical trials also demonstrate improvements in cancer patients with 67% shrinkage in metastatic non-small cell lung cancer, better than 50% shrinkage with standard therapy.[31] Another example showed that pembrolizumab immunotherapy after bowel cancer surgery eliminates the signs of cancer in over 50% of patients.[32] And, combination therapies mean the integrated use of multiple treatment procedures instead of relying on a single approach to maximize the therapeutic efficacy while managing the toxic profile of therapies.[33]

Participation in cancer treatment trials has improved, with 7.1% of cancer patients enrolling in treatment trials. However, NCI-designated cancer centres alone achieved 21.6% enrolments, while only 4.1% enrolments were achieved by community programs.[34] Overall, 21.9% of cancer patients participate in at least one or more clinical research study, contributing 12.9% in biorepository studies, 7.3% in registry studies, 3.6% in genetic studies, and 2.8% in quality of life research studies.[34] Active participation of physicians and availability of digital platforms can serve as a streamlined tool for identification and acceleration of clinical trial recruitment. Studies also demonstrated that around 73% of cancer patients learn about clinical trial opportunities through their physician or healthcare provider.[35] Cancer survivors also experience some of its long-term effects that include persistent fatigue, chronic pain, musculoskeletal problems, cognitive dysfunction, depression, and fear of recurrence.[36] These long-term survival challenges present physical and psychosocial effects even after the completion of treatment. Studies showed that breast cancer survivors experience the lowest functioning levels, which hampers their quality of life as compared to prostate cancer survivors, who have high functioning with minimal symptoms.[37] Therefore, clinical research is necessary to form and enhance the clinical guidelines, leading to improved patient-centred care, safety, and quality of life.

Biomimetic Nanoparticles

The architecture and functionalities of these NPs are intended to resemble those of real biological entities.[38,39] Their application in medicine is quite promising, especially in therapeutic drug delivery systems based on biomimetic nanoparticles. These systems can change how individuals treat and identify illnesses.[40] Biomaterials that can replicate the biological characteristics and functions of natural cells are integrated or synthesized into the surface of an emerging class of nanoparticles known as biomimetic nanoparticles.[41] They possess a greater biocompatibility, higher site-specific targeting, better bioavailability, and minimal side effects.[42] In medicine, the three parts of bionic refer to: Directly

extracting, isolating, and purifying endogenous chemicals from people, animals, or microorganisms; Creating goods that are comparable to the endogenous substances in terms of their composition and operation; and that resemble the disease's microenvironment.[43] Since they are more effective at targeting and retaining cargo, biomimetic nanoparticles have been used as drug delivery vehicles for many years.[44] Whereas, non-targeted cargo can impact healthy cells or organs rather than the desired site.[45] In recent times, nanotechnology and nanoscience have been widely applied in biomedical research.[46] Due to its ability to resist phagocytosis, it successfully passed as an endogenous molecule and achieved prolonged blood circulation.[47] Although nanoparticles have become a promising drug delivery system, there are several factors that hamper their capacity. To overcome them, nanocarriers are being cloaked with different types of cell modifications. It helps the vehicle to bypass the cell membrane and reach the target site. And, for the development of cancer therapy, biomimetic nanoparticles have been proven to be an innovative drug delivery platform for enhancing the drug payload and biocompatibility.[48]

Developing appropriate carriers is crucial in achieving high targeted efficiency and low overall toxicity.[49,50] Enhancing the accumulation of chemotherapeutic agents at the targeted locations can improve therapeutic effectiveness in certain areas and reduce drug resistance.[44] To increase the therapeutic efficacy at targeted sites and minimize drug resistance, it is essential to develop suitable carriers that can improve the accumulation of chemotherapy agents at targeted locations.[51] Biomimetic nanoparticles, such as cell membrane-coated, RBC-coated, stem cell-coated, and platelet-coated carriers, can help achieve this goal.[52] The liposomal drug carrier has also proven to be an effective delivery vehicle. Its phospholipid bilayer can generate a nanostructure that imitates natural cells, but the instability caused by the absence of a fully developed membrane structure continues to be a significant drawback.[53] Rather than that, nanoparticles with surface modification by incorporating natural ligands or a cancer-derived plasma membrane significantly increase the drug's specificity by attaching to specific biological markers found on the membranes of cancer cells.[41,53] To date, several nanoparticle-based drugs have been formulated to counter cancer.[54–57] Nanotechnology and nanomedicine have a very high scope in biomedical research and applications.[43] Nanoparticle-embedded drugs have better affinity to reach the target site and provide therapeutic effects.[58] From the literature, it is clear that biomimetic functionalization of nanoparticles and other materials can resolve many biomedical conditions.[59] A comparative overview of biomimetic nanoparticulate platforms representing their drug-encapsulation strategies, tumor-targeting features, in vivo models, and therapeutic outcomes is presented in Table 1. Studies have also mentioned that coating nanocarriers with modified membranes helps prolong blood circulation and enhances tumor tissue penetration.[38,41,55]

Red Blood Cell-Coated Nanoparticles

RBC-coated nanoparticles' excellent payload efficiency, biocompatibility, deformability, and deterrability make them one of the most potent biomimetic drug carriers.[94,95] RBC-membrane camouflaged nanoparticles have been demonstrated to possess a significantly improved capability for evasion from the mononuclear phagocytic system.[96] Designing nanoparticles for in vivo medicinal uses requires determining their hemocompatibility.[60] This, in turn, enhances the delivery of therapeutics to the tumor location, thereby alleviating systemic undesired effects. And, due to the highly flexible RBC structure, cells can move through relatively small capillary networks, including factors such as cell surface-to-volume ratio, cell content viscosity, and membrane viscoelasticity. Glycocalyx, a thick polysaccharide covering on the surface of RBCs, is crucial for immunological escape properties and cell stability. These complex polysaccharides on the cell surface are comparable to a hydrophilic coating in achieving spatial stability. In contrast, the stabilized RBC-NP surface can effectively block further membrane interactions. Even in the presence of extra RBCs, this stabilizing mechanism ensures the formation of a monolayer film coating. From the literature, it was found that nanoparticles modified with RBC membrane show high affinity towards the specific site and have high drug loading capacity.[97] The RBC membrane-coated nanoparticles have an improved half-life, making them a more accepted modification type of cargo vehicles.[98] The preparation of RBC camouflaged nanocarriers can be carried out through both physical and chemical methods.[41] Firstly, the desired type of nanovesicle is prepared, which is further coated with the RBC membrane.[99] The techniques used to carry it out include the cell membrane-templated polymerization, microfluidic electroporation, co-extrusion, etc.

In response to the rising issue of lung metastasis, a group of researchers developed the M@AP nanoplatform to activate immune cells in the spleen, thereby enhancing anti-carcinogenic activity.[100] Furthermore, quantitative analysis of

Table 1 Comparative Summary of Various Biomimetic Nanoparticulate Platforms, Highlighting Drug Encapsulation Strategies, Tumour-Targeting Properties, in vivo Models and Corresponding Therapeutic Outcomes

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
RBC-coated NPs	MSN, DOX	iRGD- Modified RBC membrane	Breast cancer	Mice model	The DOX-loaded iRGD-RM -(DOX/MSNs) with DOX forming the core shows a high degree of malignancy & aggressiveness.	[60]
	ICG, GA	RBC-m-coated BSA nanoparticle	HeLa	Nude mice bearing a subcutaneous HeLa tumor	RBC-m-coated BSA NPs exhibit a greater specificity towards ICG and GA, resulting in increased loading efficiency.	[61]
	SPN	SPN@RBC-m coated nanoparticle	4T1	BALB/c mice model with 4T1 cancer cells lines	SPN@RBC-m functions as a targeted chromotropism nanoplatform, allows precise photoacoustic (PA) signals for tumor imaging. Additionally, it penetrates deeply into the tumor site and is readily cleared from the body.	[62]
	DOX	Polymeric nanoparticles coated with human RBC membranes for targeted theranostics (TT-RBC NPs)	MCF-7 breast cancer cells	–	The TT-RBC-NPs exhibited a greater cytotoxic effect on EpCAM-expressing MCF-7 cells compared to non-targeted NPs, thereby providing a superior platform for targeted cargo delivery.	[63]
	Curcumin, TPZ	Cur+TPZ@RB nanoparticle	MCF-7, A375, HEK293, L132	–	The RBC-membrane-coated NPs displayed excellent curbing response in MCF7 and A375 cancer cells.	[64]
Cell membrane-coated NPs	DOX, siRNA	Lipid nano vector	Esophageal cancer	–	Cell membrane coated biomimetic nanoparticles focuses mainly on bionic research due to their multiple natural function.	[65]
	Porphyrin	MnO_2 nanosheet coated metal-organic framework core and cancer cell membrane coated nanoparticle.	HeLa	–	The CM-MM nanoparticle displayed good stability and integrity in the process of cellular endocytosis and strong site specificity.	[57]
	–-	–-	–-	–-	–-	–-

(*Continued*)

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Table 1 (Continued).

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
Platelet membrane-coated nanoparticles	Bufalin	Platelet membrane coated biomimetic hollow MnO_2	–	ICR female mice	It indicates that platelet membrane coated biomimetic $HMnO_2$ nanoparticles are promising cargo delivery system for MRI monitoring and enhanced targeted treatment of tumor.	[66]
	DTX	VAR2CSA peptide (rVAR2)-modified activated platelet-mimicking nanoparticles	Primary metastatic cancer	Female C57BL/6 mice and female Sprague-Dawley rats	The developed nanoparticle possesses GSH-responsive drug release characteristics and actively targets the primary tumor site and metastatic foci.	[67]
	Combretastatin A4 (CA4), and apatinib (Apa)	Mesoporous silica nanoparticles, camouflaged with platelet membrane	CA4 cell line	BALB/c mice	The designed nanocarrier delivered VDA and AAD with tumor vascular targeting function, with an excellent biocompatibility and intertumoral self-amplified accumulation property.	[68]
	DOX	DLMSN@DOX/IR780 (DDI) NPs	4T1, RAW 264.7	BALB/c mice	The prepared LPHM@DDI nanoparticle had shown effective targeting of TNBC and a significant increase in in vitro and in vivo PTT/PDT performance.	[55]
	DOX	HLDZ@PM Nanoparticle	4T1 cell line	BALB/c mice	The multifunctional nano carrier, HLDZ@PM nanoparticle, showed enhanced tumor targeting ability and enhanced biocompatibility.	[69]
Cancer cell membrane-coated nanoparticles	DOX	Cancer cell-coated DOX-loaded PLGA nanoparticle	Human hepatoma, RAW 264.7	BALB/c mice	Cancer cell membrane coating enhanced the stability of PLGA/DOX and inhibited pre-release of cargo. It also amplified cellular endocytosis of DOX and showed more coherence.	[70]

(*Continued*)

Table 1 (Continued).

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
	PTX	CSiFePNs	MDA-MB-231 cell	–	The prepared nanoparticle aids in inhibiting the growth of MDA-MB-231 cells using the combination method of chemotherapy and magnetic hypothermia.	[71]
	DOX, Mefuparib hydrochloride	MSN supported PEGylated liposome yolk and CCM coating	MCF-7 cells	BALB/c mice	The prepared nanocarrier loaded with DOX showed greater tumor suppression compared with Doxil.	[16]
	DTIC	DTIC@CMSn	Melanoma tumor	C57BL/6 mice	The prepared nanoparticle DTIC@CMSN exhibited high stability for drug retention, tumor acidic environment responsiveness, and good biocompatibility.	[72]
	DOX, Curcumin	PEG-TE10 @PLGA@DOX-Cur nanoparticle	TE10 cell line	BALB/c mice	The prepared targeted biomimetic NDDS, PMNs, was able to overcome the multidrug resistance in oesophageal cancer via co-administration of DOX and curcumin.	[73]
Exosome membrane-coated nanoparticles	Trypsin, Penicillin, and Streptomycin	CBSA/ SiS100A4@exosome coated nanoparticle	Triple-negative breast cancer, 4T1 cell lines.	BALB/c mice	The prepared CBSA/ SiS100A4@exosome camouflaged nanoparticles provides a platform that holds capacity to protect SiRNA from enzymatic degradation and showed notable results in tumor targeting.	[74]
	DOX	ID@E-MSNs	4T1 cell line	BALB/c mice	The prepared ID@E-MSNs nanoparticle loaded with ICG and DOX cloaked with 4T1 cells showed promising results in targeting, long-term retention, and biocompatibility.	[75]

(*Continued*)

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Table 1 (Continued).

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
	Let-7a	NN/NKEXO cocktail	MDA-MB231 and 293T cell line.	Female NOD/ SCID mice	The natural killer cell exosome-coated nanoparticles targeted the site very specifically and interacted via endocytosis. Then the therapeutic agent was released from it and regulated the transcriptome batch.	[76]
	Curcumin	ECaC	CT26 Colon cancer cell line	BALB/c mice	ECaC with exosome membrane coating specifically targeted the cancerous site, evaded clearance, and accumulated more effectively at the site.	[77]
	DOX	DOX@E-Psi nanoparticles	H22, Bel 7402, B16-F10 cell line	C57BL/6 mice	The prepared nanoparticle, cloaked by an exosome obtained through the exocytosis of the endocytosed DOX-loaded Psi nanoparticle from tumor cells, showed promising results in targeting tumors.	[78]
Hybrid biomimetic coated nanoparticles	Panaxytriol	PDIP membrane (PB, Dopamine, ICG, Panaxytriol)	Breast cancer	Female nude mice	After 24 hours of PDIP and PDIPM treatment, substantial aggregation was seen in tumors.	[79]
	PTX	PLGA NPs encapsulated PTX and coated with 143B-RAW hybrid membrane (PTX-PLGA@[143B RAW] NPs)	Osteosarcoma	Tumor-bearing mice	It showed targeting ability towards osteosarcoma. NPs demonstrated superior cellular uptake and the highest cytotoxicity toward 143B cells	[80]
	DOX	Au@Pt nanoparticles	Chemo/ Photothermal cancer	BALB/c female mice	The DOX/ Au@Pt-M can significantly reduce the DOX-induced oxidative damage to the organs and tissues.	[81]
	Gboxin	(HM-NPs@G) nanoparticles	Glioblastoma	Nude mice	The prepared HM-NPs@G nanoparticle has enhanced BBB crossing capacity and also overcomes limitations of gboxin treatment.	[82]

(*Continued*)

Table 1 (Continued).

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
	Interferon-γ	HPDA@[OMV-CC] nanoparticles	B16-F10 cell line	C57BL/6 mice	The prepared nanoparticle displayed homogenous melanoma targeting capacity and immune response activation by quickly inducing DC maturation in lymph nodes. The melanoma is completely eradicated with no perceptible side effects when OMV immunotherapy is used in conjunction with HPDA-mediated photothermal treatment.	[83]
Macrophage membrane-coated	Saikosaponin D	RAW 264.7 cell membrane	Breast cancer	4T1 tumor-bearing mice	SCMNPs can not only destroy the local tumor but can also produce a predominant abscopal antitumor effect to prevent the tumor metastasis	[84]
	Gemcitabine and Erlotinib	PLGA NPs with a macrophage membrane coating (MPGNPs)	Pancreatic cancer	Male BALB/c nude mice (6 weeks old)	The combination treatment of MPGNPs and erlotinib markedly inhibited the tumor growth in vivo, resulting in highly diminutive tumors.	[85]
	DOX	Cabazitaxel-loaded PLGA nanoparticles camouflaged with RAW-4T1 hybrid membrane (DPLGA@[RAW-4T1] NPs)	4T1Breast cancer cell membrane	Mice	DPLGA@[RAW-4T1] NPs enhanced anti-metastatic therapy in breast cancer patients with lung metastases, leading to prolonged survival without overt cardiotoxicity.	[86]
	Cabazitaxel	IL-4-stimulated M2 macrophage membrane–camouflaged polyfluorocarbon nanoparticle.	Breast cancer	MCF-7 and 4T1 breast cancer mouse models	This leads to an increase in intratumoral permeation and targeting ability to the tumor, ultimately resulting in a decrease in tumor growth and progression.	[87]
	Emtansine	RAW 264.7 macrophage cell membrane.	4T1 breast cancer With lung metastasis	4T1 breast cancer mouse model	This leads to an increase in biocompatibility and drug accumulation in metastatic 4T1 cells in the lungs.	[88]

(*Continued*)

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Table 1 (Continued).

Types of Biomimetic Nanoparticles	Drug Encapsulated	Engineered Platform (Type of NPs)	Tumor Targeted	In vivo Models Examined	Remark/Outcome	Reference
Serum albumin fabricated nanoparticles	Quinacrine and DTX	BSA decorated lipidic core nanoparticles	Lung Cancer	–	Quin was studied as a potential adjuvant to help treat the side effects of DTX's high-dose toxicity.	[89]
	PTX	SP-HSA-PTX Nanoparticles	Glioblastoma multiforme	Mice	The results show favorable biocompatibility, enhanced stability, and low medication leaking while in vivo circulation	[90]
	DOX	HSA–DMDOX nanoparticles	Breast, bladder, ovary, and livercancers	Female nude mice	HSA-DMDOX exhibited anticancer activity comparable to that of free DOX, but with reduced cardiotoxicity and systemic toxicity.	[91]
	Bufalin and nintedanib	BF-ND-BUP-sMPs	Cancer therapy	Mouse	The combination use of ND significantly improved the effectiveness of the therapy by remodeling TME function and tumor inhibition efficacy.	[92]
	PTX	Liposome-albumin composite nanoparticles (Lip-PTX/BSA NPs)	4T1 cell line	BALB/c mice	Increased in vitro cytotoxicity towards 4T1 cells was also demonstrated by Lip-PTX/BSA NPs, which was caused by remarkable NPs internalization efficiency.	[93]
Protein-based biomimetic nanoparticles	DOX	S-CM-HPAD nanoparticles	Malignant tumor	Mice	S-CM-HPAD NPs were able to inhibit tumor growth and tumor metastasis.	[59]

Abbreviations: ICG, Indocyanine green; GA, Gambogic acid; RBCs, Red blood cells; SPN, Semiconducting polymer network; MSN, Mesoporous silica nanoparticles; NPs, Nanoparticles; DOX, Doxorubicin; iRGD, internalizing RGD peptide; GA, General anesthesia; ICG, Indocyanine green; BSA, Bovine serum albumin; RBC-m, Red blood cell membrane; DSPE-mPEG, 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy[poly(ethylene glycol)]; SPN, Semiconducting conjugated polymeric nanoparticles; PA signals, Pulse active signals; BALB, Bagg albino; MCF-7, Michigan cancer foundation-7; TT, Targeted theranostic; EpCAM; Epithelial cell adhesion molecule; TPZ, Tirapazamine; HEK293, Human embryonic kidney 293; siRNA, Small interfering ribo nucleic acid; MRI, Magnetic resonance imaging; TNBC, Triple negative breast cancer; DTIC, Dacarbazine.

M@AP nanoparticles revealed their ability to directly damage local tumor cells and stimulate immune cells to generate cytokines, thereby presenting cellular damage against tumor cells. In B16-F10 tumor-bearing mice, the in vivo anti-tumor activity was examined. The observed levels of CD4 and CD8 in M@AP (Light+) were approximately 40% higher than those of the other groups. Similarly, RBC membrane-coated (TPC-PTX) nanoparticles were synthesized for synergistic chemo- and photodynamic therapy (PDT). It involved a combination of chemotherapy and photodynamic therapy, thereby enhancing anti-cancer therapeutic activity and light-triggered drug release, which reduces systemic toxicity. After 23 hours, it also showed a difference of ~4.6-fold higher absorption when loaded with PTX_2-TK.

Moreover, to overcome the barrier of internalization in breast cancer treatment, RBC-4T1@DOX/CS-NPs were prepared and evaluated for cellular toxicity effects and in vitro nanoparticle uptake in cells. The drug loading efficiency of the mentioned nanoparticle was evaluated for doxorubicin (DOX), which showed a positive result of 72–73% loading

of the drug. Thus, the prepared nanoparticle showed notable cellular uptake and cellular damage in the 4T1 breast cancer cell line.[99] Similarly, molybdenum disulfide nanocomposites-RBC were prepared by another researcher's group for breast cancer treatment. The in vivo fluorescence imaging and in vivo photothermal imaging test of molybdenum disulfide nanocomposites-RBC nanoparticle confirmed the promoted accumulation of carrier materials at the tumor site after RBC membrane modification. The in vivo analysis also showed that the nanocomposite loaded with Adriamycin hydrochloride/DOX has over 98% drug loading capacity and provided better efficacy.[101] Despite having high potential, RBC-coated biomimetic nanoparticles face several challenges. Scalability and reproducibility tend to be the main concerns in the manufacturing of biomimetic nanoparticles.[64]

Nanoparticles coated with RBC membrane, believed to have very low immunogenicity, may be prone to an immune response.[102] By encapsulating porous magnetic biomimetic nanoparticles in salvianolic acid B, researchers developed a biomimetic approach for synergistically targeting triple-negative breast cancer.[103] The PMNP-SAB@RTM is prepared through altering the tumor-associated fibroblast membrane and red blood cell membrane (RBCM) (Figure 2A). The maximum encapsulation efficiency rate of SAB was found to be approximately 97.28%, with the mass ratio of 1:2 for SAB to PMNPs. Additionally, in vitro assays on the 4T1 cell line and in vivo studies showed reduced cell viability and the overcoming of tumor-associated physical barriers upon the application of magnetic field, respectively. This enhances drug penetration, increases tumor cell apoptosis and necrosis, and suppresses cell proliferation more effectively than the drug alone, demonstrating strong synergistic antitumor effects.

Conventional drug delivery systems have several limitations, including a short systemic circulation time and poor tumor accumulation of conventional nanocarriers used in cancer therapy. Apart from this, most nanocarriers are rapidly cleared from the bloodstream by the mononuclear phagocyte system, which limits their ability to reach tumor sites effectively. Additionally, their rigid structures often hinder their ability to navigate through narrow capillaries and tumor vasculatures. To overcome these limitations, designing a deformable, erythrocyte membrane-camouflaged nanocarrier that mimics the natural flexibility and immune-evasive properties of RBC, can prolong circulation time and improve tumor targeting efficiency. RBC membrane camouflage nanocarriers accelerate circulation and enhance cancer therapy.[104] In CLSM findings, RBC membrane-coated elastic poly (ethylene glycol) diacrylate hydrogel nanoparticles displayed a visible fluorescence signal; however, RBC-SNVs and RBC-HNPs only displayed low-level fluorescence in the central tumor area throughout the entire tumor (Figure 2B and C), and very little fluorescence by PEG-Lipo was visible in the tumor tissue's periphery. The intensity of fluorescence emitted by RBC-ENPs within the tumor showed an approximately 1.8-, 2.4-, and 13.8-fold increase compared with RBC-SNVs, RBC-HNPs, and PEG-Lipo, respectively. Thus, the findings encourage future research to focus on optimizing the deformability and targeting specificity of these biomimetic nanocarriers to enhance their clinical applicability in personalized cancer therapy.[104]

Recently, RBCVs modified with iRGD-TRP-PK1 were also engineered to function as a targeted vehicle for anticancer drug delivery in head and neck tumors.[105] Notably, the RBCVs functionalized with iRGD-TRP-PK1 displayed a characteristic ring-like formation on their outer layer. Following drug encapsulation, noticeable dark spots appeared within the vesicles, indicating successful drug loading. And the loading efficiencies for cisplatin and DOX were found to be 58.63% and 64.34%, respectively. Therapeutic efficacy via in vivo model showed notably higher accumulation of formulation in tumor tissues for all iRGD-TRP-PK1–functionalized vesicle groups compared to controls (Figure 2D), indicating that the DOX or cisplatin-loaded RBCVs conjugated with iRGD-TRP-PK1 have the highest drug targeting ability than other groups. Overall, the iRGD-TRP-PK1-RBCVs represent a significant advancement in targeted chemotherapeutic delivery, offering enhanced efficacy and safety profiles for the treatment of head and neck cancers.

Platelet Membrane-Coated NPs

Platelets exhibit distinct surface moieties responsible for modulating their adhesion to various disease-relevant substrates, involving vascular damage, immune evasion, and pathogen interactions.[106] Due to the extensive bio-interfacing properties of platelets, drug carriers that imitate platelets have been created to selectively deliver drug payloads in disease areas for increased therapeutic effectiveness.[107] Platelets are essential for hemostasis and wound healing, and their membranes contain a wealth of bioactive molecules that can be capitalized on for therapeutic purposes.[108] Platelet membrane-coated nanoparticles tend to possess tumor-homing and circulating tumor cells targeting and metastasis-targeting properties

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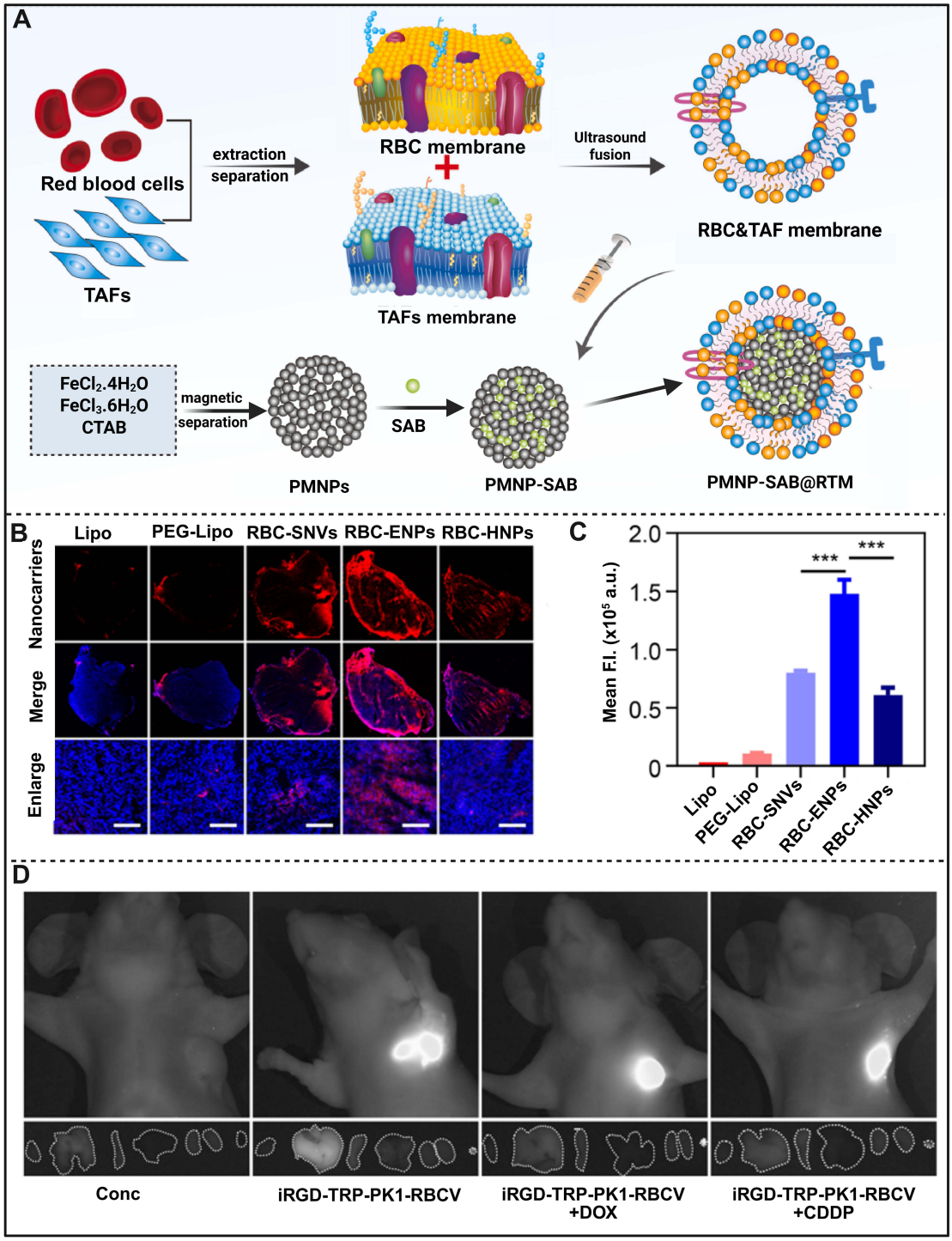

Figure 2 (**A**) Schematic representation of the synthesis of PMNP-SAB@RTM. Reproduced with permission from Cheng N, Zhou Q, Jia Z et al. Functionalized biomimetic nanoparticles loaded with salvianolic acid B for synergistic targeted triple-negative breast cancer treatment *Material Today Bio.*[103] Copyright 2025, Elsevier. (**B**) Illustration of CLSM imaging with DiI labeling nanocarriers (red) and DAPI staining nuclei (blue), scale bar 100μm. Reproduced with permission from Miao Y, Yang Y, Guo L et al. Cell Membrane-Camouflaged Nanocarriers with Biomimetic Deformability of Erythrocytes for Ultralong Circulation and Enhanced Cancer Therapy. *ACS Nano.*[104] Copyright 2022, American Chemical Society. (**C**) Fluorescence intensity analysis of nanocarrier distribution in tumor 4T1 cells (*** for p<0.001). Reproduced with permission from Miao Y, Yang Y, Guo L et al. Cell Membrane-Camouflaged Nanocarriers with Biomimetic Deformability of Erythrocytes for Ultralong Circulation and Enhanced Cancer Therapy. *ACS Nano.*[104] Copyright 2022, American Chemical Society. (**D**) Tumor-targeted delivery of Dox and CDDP (cisplatin) via iRGD-TRP-PK1-engineered RBCVs in an HN4 cell-derived xenograft (CDX) model. Reproduced with permission from Bai S, Wang Z, Zhang Yet al iRGD-TRP-PK1-modified red blood cell membrane vesicles as a new chemotherapeutic drug delivery and targeting system in head and neck cancer. *Theranostics.*[105] Copyright 2025, Creative Commons Attribution Non-Commercial License 4.0 (CC BY-NC).

during multiple steps in the metastatic cascade.[67] They also possess a variety of surface moieties with broad bio-interfacing capabilities, which are used for targeting various diseased tissues.[109] Due to their ability to detect and react to changes in blood flow and endothelial cell disturbance, platelets serve as sentinels of vascular integrity.[110] Platelet-membrane-coated nanoparticles have recently been demonstrated to have better biological characteristics than other nanoparticles, as well as to protect nanoparticles against rapid blood clearance and immune system activation.[111] When a tissue is injured, platelets quickly create fibrin to clot the bleeding.[112] They do act as a temporary scaffold for inflammatory cells, and store cytokines, chemokines, and growth factors that help to initiate the early stages of repair, including the activation of neutrophils functioning as the body's initial defence mechanism against microbes.[113] Indeed, during 12–24 hours of damage, neutrophils make up around 50% of all the cells in the wound, but macrophages take over after 3–5 days.[114] The fragmentation of megakaryocytes initiates the biogenesis of platelets, which are enucleated cells. Platelets are currently the focus of numerous research groups worldwide due to their immense potential to alter our fundamental understanding of how various diseases originate. And, due to their involvement during cancer progression, angiogenesis, along with metastasis, platelets are a significant area of study interest in the current scenario.[115]

Platelet vesicles were used to modify the surface of cuprous oxide nanoparticles with TBP-2 cuproptosis sensitization system (PTC) via the extrusion method.[116] This surface modification of PTC, additionally, improves circulation time and cancer targeting, along with the release of copper ions, hydrogen peroxide, and inhibition of copper efflux. This biomimetic PTC system promotes GSH consumption and cell membrane damage through type-1 photodynamic therapy, thereby leading to cuproptosis in tumor cells. In vivo results demonstrated the higher presence, higher growth inhibition and tumor necrosis by the group treated with PCL and light therapy. Also, the group has higher concentration of central memory T cells with minimal or no hepatorenal toxicity.

Direct receptor binding or protein-mediated receptor bridging (such as von Willebrand factor or fibrinogen) are the two ways that platelet-cancer cell interactions can take place. For instance, the C-type lectin-like receptor 2, which binds with podoplanin located at the surface of tumor cells, is a key platelet receptor involved in cancer spread.[117] Platelet membrane-coated superparamagnetic oxide nanoparticles loaded with paclitaxel showed a synergistic effect, enhancing cancer treatment through combined chemotherapy and magnetic hyperthermia (Figure 3A).[118] The drug release of Paclitaxel loaded SPIONP/PTX/PM was 1.4-fold higher than others at pH 5.5. However, confocal microscopy combined with flow cytometry study findings reveal an increase in uptake of cells in SPION/PTX/PM NPs. Furthermore, Quantitative evaluation of haemolytic activity for various samples, expressed as mean ± SD with three independent measurements (n = 3), indicates that alginate-coated magnetic iron oxide NPs exhibit lower haemolysis than other treated samples (Figure 3B and C). In vivo study findings suggest that the SPION/PTX/PM formulation under AMF treatment revealed the maximum inhibition of tumor growth, which was about 92.14%.

Addressing the major problems of acidosis and hypoxia in tumors during cancer therapy, a group of scientists formulated an Hb-LOX-DOX-ZIF8 system, camouflaged with platelet membrane nanoparticles, which accelerates chemotherapeutic strategy through modulation of acidosis and alleviation of hypoxia.[69] The particle size and zeta potential of ZIF8-based and H-L-D-Z@PM nanoparticles were about 447nm and 964 nm, and 18.7mV and −3.35 mV, respectively. The in vivo study was performed in a 4T1 tumor-induced BALB/c mouse model, and among all treatment groups, the H-L-D-Z@PM nanoparticles-treated group exhibited the smallest tumor size and lowest tumor weight (Figure 3D). Most of these nanoparticles were found within the mononuclear phagocyte system, connected to the phagocyte system (such as the liver and spleen). These observations showed that PM coating significantly increases the tumor accumulation efficiency of H-L-D-Z@PM nanoparticles. The application of lactate oxidase effectively increases oxidative stress and sufficiently reduces intra-tumoral lactate. Meanwhile, used haemoglobin increased the catalytic activity of lactate oxidase, relieved hypoxia, and mediated O_2 transport. These nanoparticles had strong biocompatibility and the capacity to actively target tumors due to the coated PM.[69]

Transmission electron microscopy (TEM) image of PDA@Cu and PDA@Cu/PM revealed that the nanoparticles were spherical, and after coating with platelet membrane, a thin film boundary appeared. The XPS analysis of PDA@Cu validates the presence of Cu, N, and C elements, and these elements are dispersed throughout the NPs (Figure 3E and F).[119] Furthermore, antitumor activity was assessed in the 4T1 tumor-bearing mouse model by injecting PCM NPs through the tail vein method. Quantification of copper was measured using ICP-AES, and PC+RT therapy validates that

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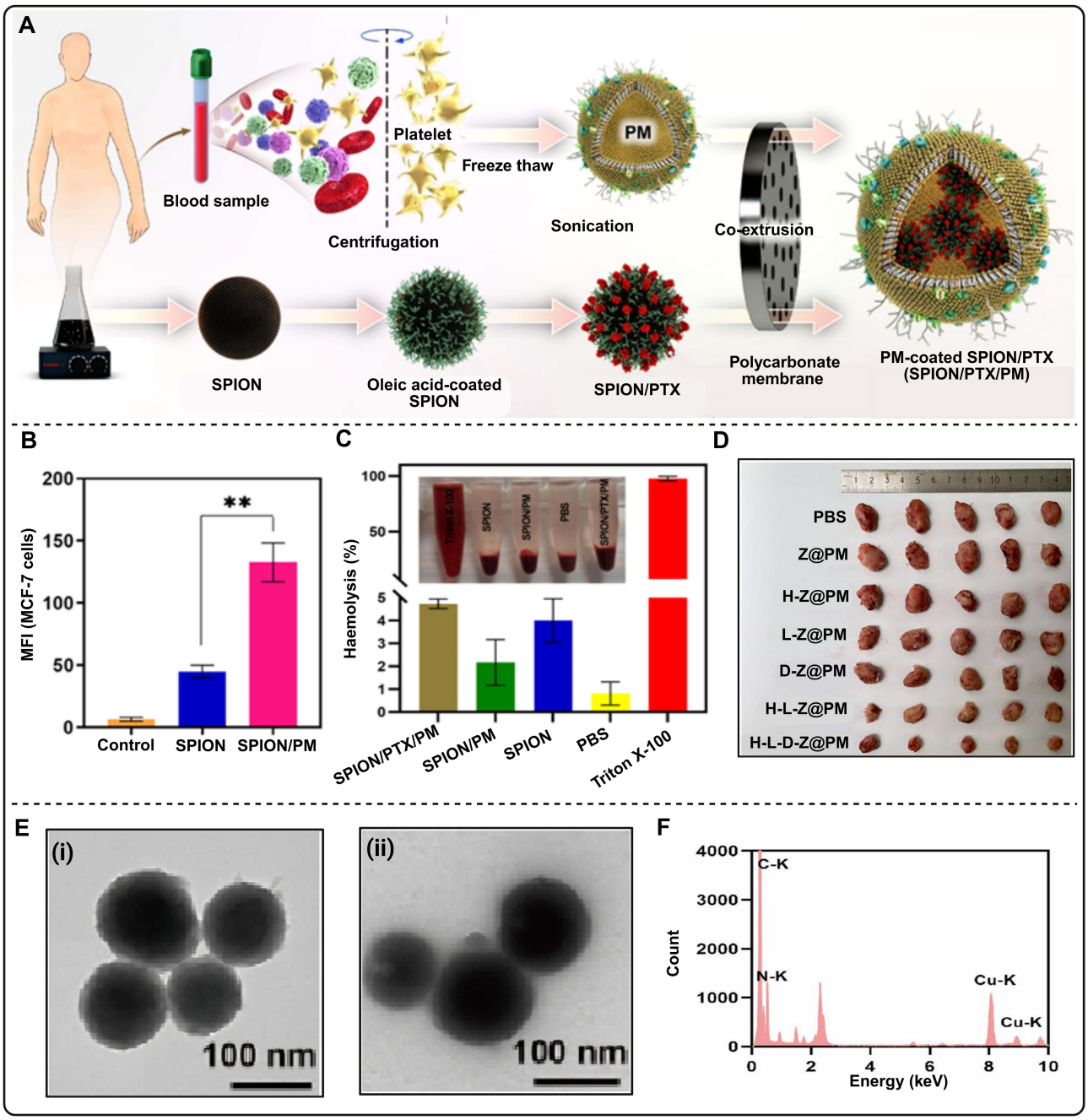

Figure 3 (**A**) Schematic representation of SPION/PTX/PM NPs using the co-extrusion process. Reproduced with permission from Tavakoli M, Maghsoudian S, Rezaei-Aderiani A et al. Synergistic effects of paclitaxel and platelet-superparamagnetic iron oxide nanoparticles for targeted chemo-hyperthermia therapy against breast cancer. *Colloids Surfaces B Biointerfaces*.[118] Copyright 2025, Elsevier. (**B**) Mean fluorescent intensity (MFI) of control, SPION NPs, and SPION/PM NPs against MCF-7 cells (** for $p<0.01$). Reproduced with permission Tavakoli M, Maghsoudian S, Rezaei-Aderiani A et al. Synergistic effects of paclitaxel and platelet-superparamagnetic iron oxide nanoparticles for targeted chemo-hyperthermia therapy against breast cancer. *Colloids Surfaces B Biointerfaces*.[118] Copyright 2025, Elsevier. (**C**) Quantitative evaluation of hemolysis induced by SPION/PTX/PM NPs, phosphate buffer solution, and Triton X-100 (Positive control) group. Reproduced with permission from Tavakoli M, Maghsoudian S, Rezaei-Aderiani A et al. Synergistic effects of paclitaxel and platelet-superparamagnetic iron oxide nanoparticles for targeted chemo-hyperthermia therapy against breast cancer. *Colloids Surfaces B Biointerfaces*.[118] Copyright 2025, Elsevier. (**D**) Captured photographs of the tumor dissection of the BALB/c mice model after 14 days. Reproduced with permission from Luo X, Cao J, Yu J et al. Regulating Acidosis and Relieving Hypoxia by Platelet Membrane-Coated Nanoparticle for Enhancing Tumor Chemotherapy. *Front Bioeng Biotechnol*.[69] Copyright 2022, Frontiers. The Authors. (**E**) TEM imaging of (i) copper-doped nanoparticles (PDA@Cu NPs), (ii) Platelet cell membrane-coated nanoparticles (PC@PDA@Cu NPs). Reproduced with permission from Xin L, Ning S, Wang H, Shi R. Tumor Microenvironment Responsive and Platelet Membrane Coated Polydopamine Nanoparticles for Cancer Radiosensitization by Inducing Cuproptosis *Int J Nanomedicine*.[119] Copyright 2025, The Authors. (**F**) Elemental composition of PDA@Cu NPs. Reproduced with permission from Xin L, Ning S, Wang H, Shi R. Tumor Microenvironment Responsive and Platelet Membrane Coated Polydopamine Nanoparticles for Cancer Radiosensitization by Inducing Cuproptosis. *Int J Nanomedicine*.[119] Copyright 2025, The Authors.

this approach was most efficient among all treatment groups. The amalgamation of Cu + RT leads to severe curoptosis, further accelerates the in vitro immunogenic cell death effect, and enhances dendritic cell maturation. Platelet integrin GPIIb/IIIa, also known as αIIbβ3 integrin, stands out among platelet-cancer cell interactions because it promotes cancer spread through direct and indirect pathways.

Cancer Cell Membrane-Coated Nanoparticles

Modification of nanoparticles using a coating technique via a biological cell is one of the most essential and advanced techniques for targeting a specific cancerous tissue.[120] This technique helps in improved targeting when compared to other cell membranes via prolonged systemic circulation and target delivery to the tumor cell.[73] On the other hand, immune escape is one of the crucial aspects of these nanoparticles due to the presence of membrane proteins (CD47, E-cadherin, Thomsen-Friedenreich antigens, galectin-3, N-cadherin, and EpCAM). When compared to the other membrane donors, cancer cells can self-target homologous cells, making them robust and straightforward to culture in large numbers.[121] Due to the cancer cell membrane coating, nanoparticles can adhere uniformly to early cancer cells, extending their blood circulation and reducing systemic clearance, which further improves tumor targeting.[72] Above all, this membrane-coated nanoparticle can target primary tumors and metastatic nodules with the ability of self-recognition within cancer cells.[121] Implementation of the biomimetic nanoparticles approach for cancer targeting has revolutionized anticancer therapy, with high therapeutic efficacy, lower toxicity, and relative biosafety.

Many studies have been conducted to advance cancer cell membrane-coated nanoparticles for the efficient delivery of drugs.[122–124] Notably, the rise of multidrug resistance in esophageal cancer has negatively impacted the effectiveness of chemotherapy, and this has led to a decreased survival rate of patients. To subdue these issues, a group of researchers developed PEG-TE10@PLGA@DOX-Cur nanoparticles to successfully limit the growth of DOX-resistant esophageal cancer through targeting cells of TE10 and TE10/DOX cells xenografted tumor.[73] The solvent evaporation approach was used to synthesize DOX and curcumin-loaded biodegradable poly (lactic-co-glycolic acid) nanoparticles, followed by the addition of TE10 cancerous cell membrane and DSPE-PEG to make them biomimetic nanoparticles. It has been found that the utilization of poly (lactic-co-glycolic acid) as an encapsulating polymer has successfully retarded the leakage of cargo from the membrane. Further, the results of the cytotoxicity study of PLGA@Cur+DOX on TEX10/DOX cells have shown less toxicity, and the cell viability was about 90% when compared to the TE10-PLGA@Cur+DOX and PEG-TE10 -PLGA@Cur+DOX nanoparticles. Curcumin and DOX have shown a potent anti-tumor effect when used together in vitro. Additionally, in vivo findings reveal that the anti-tumor effect of PEG-TE10-PLGA@Cur+DOX was better than that of TE10-PLGA@Cur+DOX. This was found to be due to the surface modifications of these nanoparticles with PEG, which results in prolonged blood circulation and prevents their early excretion. On the other hand, the anti-tumor effect of PLGA@Cur+DOX is only better than the control group ($p<0.05$), indicating the possible use of PLGA in sustained release of cargos.

Similarly, DOX-loaded polylactic glycolic acid nanoparticles were developed through the double emulsion solvent evaporation method to inhibit the development of Hepatocellular carcinoma.[70] The results indicated that comparing CC/PLGA/DOX to free DOX, the former showed strong tumor suppression and greater safety. The results showed quick distribution of free DOX throughout the body and elimination within 24 hours. In contrast, DOX, when combined with PLGA/DOX and CC/PLGA/DOX, takes a much longer time for its elimination. In vivo results showed that the anti-tumor effect of free DOX was low when compared to the control group. The tumor reduction rate of PLGA/DOX coating is lower than that of CC/PLGA/DOX, with rates of 20.1% and 52.0%, respectively.

Metformin, an FDA-approved antidiabetic agent, with cancer cell-membrane-coated liposome (TMFL) was used by researchers to inhibit the postoperative recurrence of breast cancer.[125] TMFL, under the light irradiation produce singlet oxygen, promotes immunogenic cancer cell death and promotes T cell immunity. The group treated with TMFL and light irradiation during the in vivo study showed the highest inhibition of cancer cells, along with the maturation of dendritic cells to produce a strong anti-cancer immune memory response.

According to the data of Cancer Statistics 2022, the most common cancer in women, accounting for 30% of the total, is breast cancer.[126] Although Paclitaxel is a standard treatment for breast cancer, cancer cell membrane nanoparticles can be a good alternative to paclitaxel due to their high hydrophobicity and low tumor selectivity.[127] Excellent

biocompatibility and built-in targeting modalities of human serum albumin nanoparticles make it an ideal carrier for chemotherapeutic agents.[127] 4T1 cancer cells were attached with HSA-PTX to enhance their anti-cancer effect and biocompatibility. Compared to HSA-PTX, CM-HSA-PTX exhibited a reduced cell survival rate due to the coating of 4T1 cancer cells. CM-HSA-PTX provides homologous targeting due to its excellent stability in serum, storage, and dilution stability; thus, more PTX might enter the cell and exert its anti-cancer effects.

Another disease is Pancreatic ductal adenocarcinoma, which is one of the most hostile cancers, and the survival rate of 5 years is only 9%.[128] Due to the poor treatment outcomes at the progression of the disease and the sensitivity of traditional chemotherapeutic agents, cancer cell membrane nanoparticles are also used for disease treatment. This disease requires ROS-based therapies like photodynamic, chemodynamic, and sonodynamic to overcome the challenges faced through pancreatic ductal adenocarcinoma.[129] ROS causes the demise of a cancer cell's mitochondria by interfering with the electron transport chains.[130] The nanoparticle was prepared through the fabrication of core-shell nanoparticles firstly with ZnxMn1-xS (abbreviated as ZMS) and further coated with the pancreatic cancer cell membrane BxPC-3.[129] BUC@ZMS core-shell nanostructure has proven to be an efficient therapy for reducing the GSH expression linked to pancreatic ductal adenocarcinoma and showed enhanced blood circulation with a tumor retention effect. It was proposed to work on the principle of ROS accumulation that leads to the death of pancreatic cancer cells, as this therapy for pancreatic ductal adenocarcinoma looks promising. The results of the cytotoxicity study done on BxPC-3 cells reveal that when the concentration of the drug was beyond 100μg/mL, the cell viability of BUC@ZMS and UC@ZMS was found to be ~65% and ~79% respectively.

One of the research focuses on visualization and multi-modeling imaging, magnetic resonance imaging, fluorescence imaging, and photoacoustic imaging altogether for the disease progression. A549 lung cancer cells were coated with nanoparticles to promote their diagnostic efficiency.[131] PP@ICGNPs having a cancer cell membrane coating allow them to potentially accumulate at tumor-specific sites. Inhibition of tumor development was attained after AM-PP@ICGNPs administration in a mouse model during in vivo studies. Gastric cancer is considered the prevalent cancer across the world, where Platinum has been selected as the first-line chemotherapy drug for GC patients.[126,132] So, the Manganese-coated mesoporous silica nanoparticle shows time-dependent biodegradable behavior. CCM@Mn@MSN-Pt(IV) shows homologous targeting abilities with suitable size distribution and enhanced biocompatibility, and so has in vitro a more substantial impact on the immune regulation.[132] Biosafety was checked for the CMnMPt by measuring the cytotoxicity in normal cells, and it was found that when applied to cancer cells, CMnMPt NPs showed selective cytotoxicity, whereas normal cells were only mildly affected.

Sulindac dimer linked via an ortho-ester bond and co-assembled with DOX forms a pH-sensitive nanodrug. These SU-OE@DOX NPs camouflages with the tumor cell membrane for inhibiting COX-2 expression and chemo-photo thermal synergistic anticancer therapy.[133] The prepared biomimetic nanoparticle enhances H22 cellular uptake via homologous targeting and effectively alleviates macrophage internalization. The Biomimetic nanodrugs use sulindac-ortho ester small molecule prodrugs for cancer cell membrane targeting: A synergistic chemo-phototherapy approach analyzed in both in vitro and in vivo (Figure 4A). Combining NIR-range irradiation, the nanoparticles also induce heat, enabling photothermal therapy. The cell viability of SU-OE@DOX NPs incubated with H22 cells dropped from 83% to 20%. In contrast, the H22 cell survival after exposure to free DOX H22 cells dropped decreased from 88% at 16 μg/mL to 32% at 0.5 μg/mL, which indicates significant dose-dependent cytotoxicity. Apart from this, antitumor activity was performed in a mouse model via the intravenous route, demonstrating that HM@I/NPs treated with NIR laser exhibit the highest remarkable antitumor activity, as shown in the graph (Figure 4B). The dual approach of chemotherapy and photothermal therapy worked synergistically to significantly inhibit tumor growth in animal models, with minimal side effects, underscoring the potential of this strategy for effective and targeted cancer treatment.[133]

Another approach of research in biomimetic nanoparticles for cancer treatment includes cancer-associated factor (CAF) and cancer cell membrane (CCM) hybrid membrane biomimetic nanoparticles loaded with carboplatin (CBP) and siRNA (PH20/CCM@PMCS), a cancer-associated combined targeted multidimensional treatment for ovarian cancer. In SEM and TEM images, MXene appears as stacked layers, whereas after extended sonication, the TEM images display a well-dispersed morphology of MXene sheets (Figure 4C). Furthermore, the entrapment efficiency of CBP and siRNA was 82.98% and 71.79%, and the drug loading capacity was 71.34% and 1.75%, respectively. The DLS analysis detected

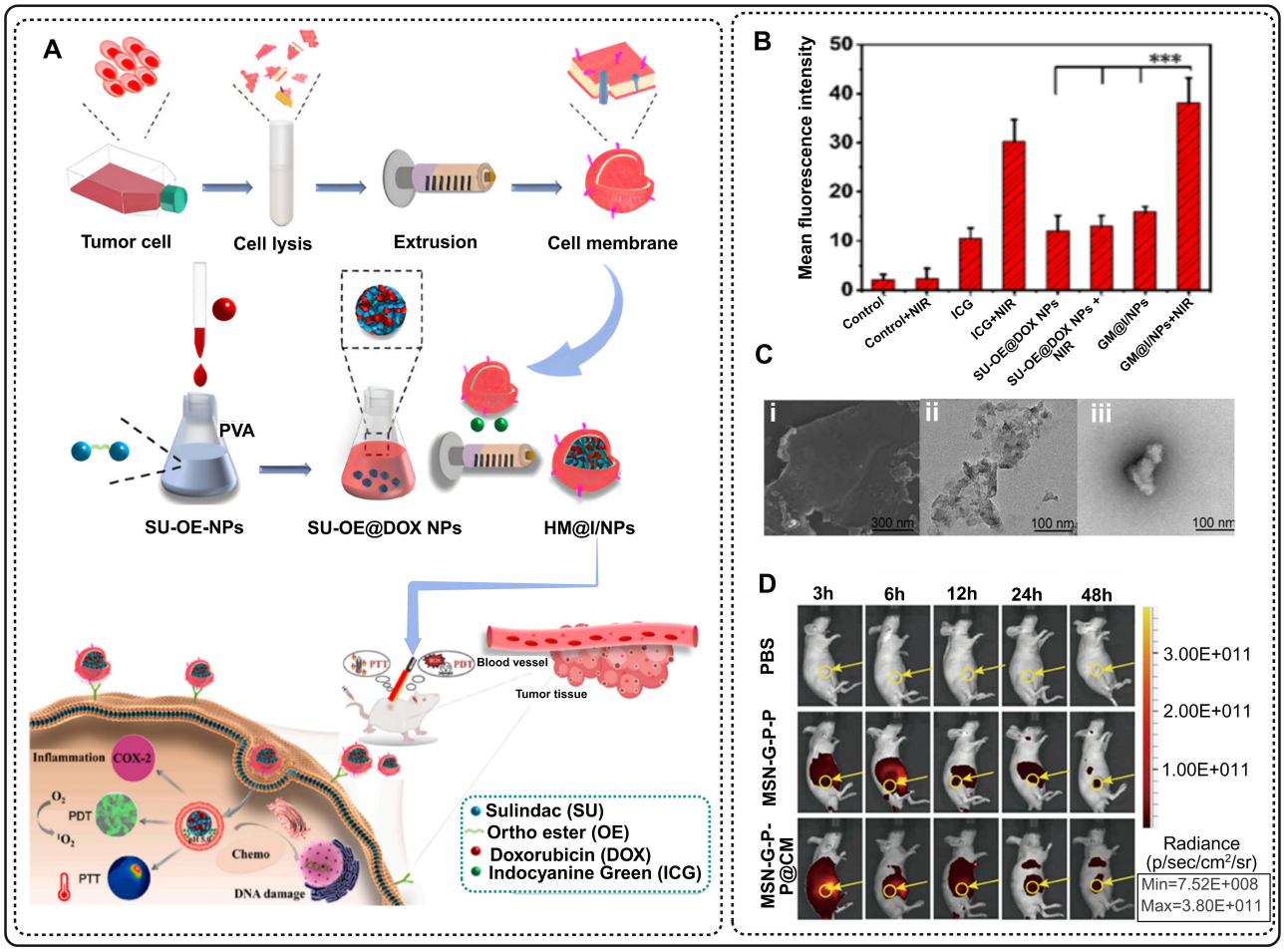

Figure 4 (**A**) Schematic illustration of the construction and evaluation of biomimetic SU-OE@Dox NPs. Reproduced with permission from Zhang J, Yang Q, Zhang Y et al. Cancer cell membrane-coated sulindac-ortho ester nanoprodrug for inhibiting COX-2 expression and chemo-photothermal synergistic antitumor therapy. *Int J Pharm*.[133] Copyright 2025, Elsevier. (**B**) Graphical representation of tumor profiles of different groups of mice from the antitumor study (*** for $p<0.001$). Reproduced with permission from Zhang J, Yang Q, Zhang Y et al. Cancer cell membrane-coated sulindac-ortho ester nanoprodrug for inhibiting COX-2 expression and chemo-photothermal synergistic antitumor therapy. *Int J Pharm*.[133] Copyright 2025, Elsevier. (**C**) (i) SEM image showing stacked block-like structures of MXene (scale bar: 300 nm). (ii) TEM imaging of MXene blocks (scale bar: 100 nm). (iii) TEM imaging of dispersed MXene sheets (scale bar: 100 nm). Reproduced with permission from Yao Y, Zhang J, Huang K et al. Engineered CAF-cancer cell hybrid membrane biomimetic dual-targeted integrated platform for multi-dimensional treatment of ovarian cancer. *J Nanobiotechnology*.[134] Copyright 2025, The Authors. Creative Commons Attribution Non-Commercial License 4.0 (CC BY-NC). (**D**) Biodistribution of M-G-P/P and M-G-P/P@CM in lung tumor-bearing mice at various time intervals. Reproduced with permission from Yang K, Zhang C, Wang Z et al. CRISPR-dCas9-Mediated PTEN Activation via Tumor Cell Membrane-Coated Nanoplatform Enhances Sensitivity to Tyrosine Kinase Inhibitors in Nonsmall Cell Lung Cancer. *ACS Appl Mater Interfaces*.[135] Copyright 2025, American Chemical Society.

that after loading the CBP, the surface charge of PH20/CCM@PMCS was −13.3 ± 4.3 mV, and this negatively charged nanoparticle enhances the blood circulation time of NPs.[134]

A tumor cell membrane-coated nanoplatform to deliver CRISPR-dCas9 for targeted activation of the PTEN tumor suppressor gene in non-small cell lung cancer (NSCLC) was analyzed by research scientists to combat cancer. Reactivation of PTEN expression enhances the sensitivity of cancer cells to tyrosine kinase inhibitors (TKIs), which helps to eradicate drug resistance.[135] However, both in vitro and in vivo experiments demonstrated significant tumor growth inhibition, improved apoptosis, and increased therapeutic efficacy when combined with TKIs. This approach offers a promising gene-based strategy to boost the effectiveness of targeted therapies in NSCLC. Indocyanine (ICN) dye was used to mark the drug carrier to visualize the drug distribution within the animals. It was found that M-G-P/P and M-G-P/P@CM were distributed in the tumor sites, liver, and lung, and their fluorescence intensity remained strong for 48 hours (Figure 4D). Additionally, long-term safety, immune response, and scalability of the tumor cell membrane-coated nanoplatform remain to be fully evaluated before clinical translation. The limitation of the study is the potential off-target effects and delivery efficiency challenges associated with the CRISPR-dCas9 system in complex in vivo environments.[135]

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Exosome Membrane-Coated NPs

Exosome membrane-coated nanoparticles, or Exo-NPs, have emerged as a groundbreaking approach in cancer treatment by leveraging exosomes' natural ability to transport drugs precisely and selectively. This novel strategy leverages the inherent qualities of exosomes to address challenges associated with traditional cancer therapy methods.[136] One of the key benefits of Exo-NPs in tumor therapy lies in their ability to achieve targeted drug delivery. The surface proteins on exosome membranes can be tailored to interact with specific receptors overexpressed on cancer cells, enabling precise localization of therapeutic payloads and minimizing damage to healthy tissues.[137] Exosome membrane-coated nanoparticles are uniquely positioned to navigate the complex biological barriers encountered in cancer treatment. Their biomimetic nature allows them to exploit endogenous cellular uptake mechanisms and facilitate efficient penetration through the TME, thus enhancing drug delivery to cancer cells. Exo-NPs offer a framework for customized cancer treatment by enabling the combination of specific targeting ligands and therapeutic agents tailored to the molecular profile of individual cancers.[138] This precision medicine approach may reduce side effects while improving treatment outcomes.

Recently, researchers addressed limitations in ultrasound diagnosis and drug delivery by developing exosome-fused microbubbles.[139] These exosome membrane-coated microbubbles exhibit enhanced stability and active targeting capabilities. And, under ultrasound exposure, they display favorable targeting properties to their original cells. Also, loading of the photosensitizer chlorin e6 into exosome-fused microbubbles resulted in improved therapeutic efficacy for enhanced photodynamic therapy and cancer immunotherapy. This innovative platform represents a novel ultrasound image-guided drug delivery system, thus overcoming conventional limitations and enabling dual-mode therapy. As discussed above, cancer treatment has undergone significant improvements and modernizations using biomimetic nanoparticles. Among them, exosome membrane-coated biomimetic nanoparticles have been a prominent approach in targeting cancerous cells.[75] Its biocompatibility, stability, and ability to act as a biological barrier reflect its aptitude as a novel modification in targeted drug delivery.[140] Furthermore, researchers addressed the recurrence and metastasis progression of post-surgery triple-negative breast cancer, and utilized autologous breast cancer cell-derived exosomes to prepare biomimetic NPs due to their efficient targeting capabilities.[74] Thus, biomimetic nanoparticles (CBSA/siS100A4@Exosome) were engineered by combining cationic bovine serum albumin conjugated siS100A4 with an exosome membrane coating. These self-assembled nanoparticles, approximately 200 nm in size, effectively protect siRNA from degradation. In vitro cellular uptake on mouse embryonic lung fibroblast cells and ex vivo imaging indicates significant cellular uptake, revealing distribution patterns with excellent biocompatibility. The CBSA/siS100A4@Exosome nanoparticles demonstrated significant S100A4 gene silencing, which leads to a substantial inhibition of malignant breast cancer cell growth. These data suggested that self-assembled CBSA/siS100A4-loaded exosomes represent an effective method for suppressing postoperative breast cancer metastasis.

Glucose oxidase-based starvation therapy, another approach in cancer treatment, faces limitations due to its low tumor accumulation and weak catalytic activity. And, to resolve these issues, biomimetic nano-platform was engineered with an exosome-sheathed magnetic mesoporous structure.[141] Further, this nanoformulation was modified with glucose oxidase for tumor-specific targeting, enhanced retention, and effective starvation therapy (Figure 5A). The exosome shell, derived from tumor cells, provided excellent homing ability, allowing the nanoparticles to accumulate in tumor tissue selectively. Once localized, the glucose oxidase catalyzes glucose consumption and generates hydrogen peroxide, which effectively induces starvation in cancer cells. Figure 5B shows a TEM image of MNPs@$mSiO_2$-GOx@EM, revealed the successful coating of Silicon dioxide at a scale bar of 100 nm. Furthermore, in vitro cell viability test of MNP@$mSiO_2$-GOx@EM in the 4T1-bearing mouse model revealed that the biomimetic nanoformulation exhibits low cell viability after treatment. However, high capture efficiency was achieved toward various breast cancer cell lines, completing 85.6% for MCF-7 cells, 78.3% for MDA-MB-231 cells, and 81.2% for 4T1 cells. These results indicate that the nanoparticles' effective recognition and selective binding to tumor cells of similar origin enhance their tumor-targeting potential. Additionally, the magnetic core enabled external magnetic guidance and imaging capabilities, improving targeting precision.

Another starvation therapy, tumor glutamine starvation, was also researched by the scientists. Exosomes derived from tumor cells were used in the modification of aggregation-induced emission luminogens for the suppression of cellular glutathione in cancer cells by photodynamic therapy.[144] The enhanced Calreticulin fluorescence of cancer cells and the

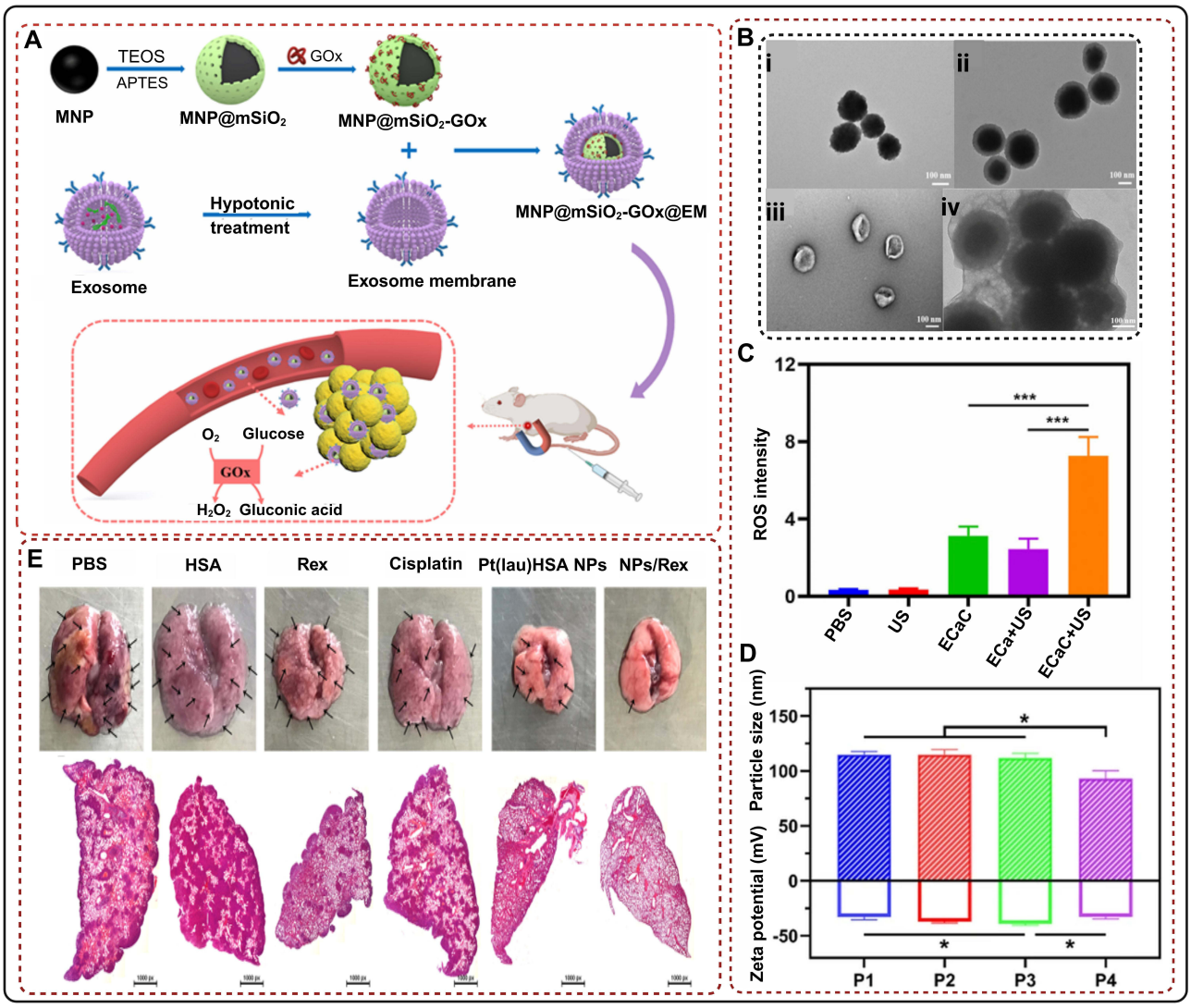

Figure 5 (**A**) Illustration of the MNPs@mSiO$_2$-GOx@EM system for synergistic targeting of tumor cells. Reproduced with permission from Li M, Tai Q, Shen S, Gao M, Zhang X. Biomimetic Exosome-Sheathed Magnetic Mesoporous Anchor with Modification of Glucose Oxidase for Synergistic Targeting and Starving Tumor Cells. *ACS Appl Mater Interfaces*.[141] Copyright 2024, American Chemical Society. (**B**) TEM images showing (i) MNPs, (ii) MNPs@mSiO$_2$ nanoparticles, (iii) exosomes obtained from MCF-7 cells, and (iv) MNPs@mSiO$_2$-GOx@EM nanostructure at 100 nm scale bar. Reproduced with permission from Li M, Tai Q, Shen S, Gao M, Zhang X. Biomimetic Exosome-Sheathed Magnetic Mesoporous Anchor with Modification of Glucose Oxidase for Synergistic Targeting and Starving Tumor Cells. *ACS Appl Mater Interfaces*[141] Copyright 2024, American Chemical Society. (**C**) ROS fluorescence intensity of different treated groups (*** for p<0.001). Reproduced with permission from Li Y, Huang C, Xu Y. Colon cancer exosome-derived biomimetic nanoplatform for curcumin-mediated sonodynamic therapy and calcium overload. *Front Bioeng Biotechnol*.[77] Copyright 2022, The Authors. Creative Commons Attribution License (CC BY). (**D**) Size distribution and surface charge measurements of four types of Lut-NPs (P1, P2, P3, P4) (* for p<0.5). Reproduced with permission from Ye S, Pan X, Zou L et al. HepG2 exosomes coated luteolin nanoparticles remodeling hepatic stellate cells and combination with sorafenib for the treatment of hepatocellular carcinoma. *Cancer Nanotechnol*.[142] Copyright 2024, The Authors. Creative Commons Attribution Non-Commercial License 4.0 (CC BY-NC). (**E**) Lung tissue imaging of 4T1 tumor-bearing BALB/c mice, and H&E-staining for displaying metastatic nodules (scale bar 1000). Reproduced with permission from Xiong F, Ling X, Chen X et al. Pursuing Specific Chemotherapy of Orthotopic Breast Cancer with Lung Metastasis from Docking Nanoparticles Driven by Bioinspired Exosomes. *Nano Lett*.[143] Copyright 2019, American Chemical Society.

increased release of HMGB1 in culture medium show immunogenic cell death by AIEgens and PPI co-loaded exosomes under light irradiation. In MGC803 subcutaneous gastric cancer model, this photodynamic glutamine starvation therapy showed improved tumor inhibition and immunogenic cancer cell death.

To evaluate the effect of biomimetic nanoparticles on colon cancer and its model, colon cancer-derived biomimetic nanoparticles were formulated by experts for curcumin-mediated sonodynamic therapy and calcium overload. In this research, engineered nanoparticles loaded with curcumin, a natural sonosensitizer, and calcium carbonate were encapsulated within exosomes derived from colon cancer cells.[77] The clinical efficacy of sonodynamic therapy is limited by the

https://doi.org/10.2147/IJN.S579622

poor water solubility of sonosensitizers and the suppressive TME. To overcome these hurdles, researchers designed a biomimetic nano-system (ECaC) that uses tumor-derived exosomes to encapsulate hydrophobic curcumin and $CaCO_3$ nanoparticles. This biomimetic approach ensured enhanced tumor targeting and immune evasion with synergistic therapeutic effects through calcium-induced mitochondrial damage and improved sono-dynamic therapy. On ultrasound irradiation, curcumin generated reactive oxygen species, while the acidic TME triggered the decomposition of $CaCO_3$, releasing calcium ions. This dual action induced mitochondrial dysfunction, calcium overload, and amplified oxidative stress, leading to enhanced apoptosis of cancer cells. And, Figure 5C shows enhanced sonodynamic therapy via oxidative stress, which is responsible for cancer cell apoptosis. Overall, the findings suggest that biomimetic nanoplatforms offer a promising and safe strategy for synergistic sono-dynamic therapy and calcium-mediated cancer treatment.

In another study, where found that HepG2-based exosome-wrapped luteolin NPs loaded with sorafenib for the treatment of hepatocellular carcinoma. The size distribution and surface charge measurements of four types of Lut-NPs (P1, P2, P3, P4) prepared with varying PLGA solution concentrations and PLGA/luteolin ratios were found in the range of 93–115nm and −33 to −39mV, respectively (Figure 5D).[142] Bio-inspired exosome-driven nanoparticle for targeted chemotherapy in orthotopic breast cancer with lung metastasis overcomes the various challenges of conventional chemotherapy, such as poor drug targeting, systemic toxicity, and limited efficacy against disseminated metastatic lesions. The limitations of synthetic nanoparticles, such as immune clearance and insufficient tumor homing, accelerate the potential of bioinspired exosomes as natural carriers for improved biocompatibility and active targeting. Exosome-driven nanoparticles enhance precise drug delivery, reduce off-target effects, and overcome the aggressive nature of lung metastases, ultimately aiming to improve therapeutic outcomes in advanced breast cancer. The significant reduction in lung metastatic nodules (average 15 ± 3 nodules in treated groups vs 32 ± 5 in controls) is due to enhanced tumor-specific drug delivery. Furthermore, H&E staining revealed reduced tumor cell proliferation and increased apoptosis in treated lung tissues, with preserved standard alveolar architecture compared to extensive metastatic infiltration in controls. This research study suggests future directions focusing on scaling up this strategy for clinical translation and exploring combinational therapies for enhanced efficacy against metastatic cancers.[143]

Hybrid Biomimetic Coated NPs

The development of hybrid biomimetic coated nanoparticles (Hybrid-BCNPs) signifies a pioneering approach in cancer therapy, combining the advantages of biomimicry and multifunctionality. This innovative strategy draws inspiration from natural biological entities and integrates diverse functionalities to address the intricacies of cancer treatment. In this note, we explore recent advancements in Hybrid-BCNPs and their potential applications in the field of cancer therapy. Hybrid-BCNPs typically incorporate biomimetic coating derived from natural sources, such as exosomes or cell membranes, offering enhanced biocompatibility and the ability to target cancer cells with precision. This biomimetic surface modification enables specific interactions with cancer cell receptors, facilitating a site-specific drug delivery system (DDS) with minimal unintended effects.[145,146] The hybrid nature of these nanoparticles allows the incorporation of diverse therapeutic payloads. Hybrid-BCNPs can carry chemotherapeutic agents, nucleic acids, imaging agents, and other therapeutic modalities, providing a multifunctional platform for comprehensive cancer treatment. Recently, in this regard, RBCM and 4T1 cancer cell-erythrocyte hybrid membranes (RBC-4T1CMs), and 4T1 cancer cell membranes were used to develop cell-membrane-coated nanoparticles loaded with DOX.[99] These biomimetic nanoparticles demonstrated improved immune evasion, homotypic targeting, and circulation. Studies conducted in vitro on 4T1CM-coated breast cancer cells showed enhanced NP absorption and cytotoxicity. The findings highlight the critical function of 4T1-CM in tumor homotypic targeting and anti-tumor efficacy.

Cancer therapy is undergoing a paradigm shift, with innovative nanotechnology-based approaches emerging as promising strategies.[147] One such approach is the development of hybrid membrane-coated biomimetic nanoparticles for cancer therapy.[148,149] In addressing the challenges of hepatocellular carcinoma, researchers proposed a strategy utilizing platelet membrane-coated polypyrrole nanoparticles encapsulating DOX (PLT-PPy-DOX) for specific and controllable chemo-photothermal therapy.[150] Platelet membranes facilitate immune evasion and tumor targeting, thereby aiding in HCC accumulation. Intravenous injection of PLT-PPy-DOX nanoparticles in a mouse model results in the selective accumulation of biomimetic nanoparticles in tumor tissues. Photothermal assessment at 808 nm reveals PLT-

PPy's efficacy, reaching 50 °C, while PBS experiences minimal temperature rise. Elevated temperatures induce membrane rupture, thereby facilitating the release of DOX. PLT-assisted photo-chemotherapy effectively inhibits tumor growth and metastasis, highlighting the potential for personalized therapy biodegradable photothermal agents. Hybrid biomimetic nanoparticles, with potential for advancing cancer therapeutics, offer benefits such as targeted drug delivery, minimized side effects, and enhanced interactions with biological systems. The incorporation of a biomimetic approach not only helps nanoparticles evade the immune system but also enables specific targeting of cancer cells. In summary, hybrid biomimetic-coated nanoparticle presents an innovative and state-of-the-art strategy in the pursuit of more efficient and personalized approaches to cancer treatment.

The co-delivery of a Focal Adhesion Kinase (FAK) inhibitor and bismuth-embedded biomimetic metallic organic framework (MOF) nanoplatform for improved radiosensitivity and tumor targeting in cervical cancer (Figure 6A), works on the TME, which consists of cancer-associated factors that are the major contributor to drug resistance due to their phenotypic adaptation and radio resistance.[151] To address these resistances, researchers developed a MOF nanoplatform for the co-delivery of FAK suppressor IN10018 and Bismuth (Bi) to accelerate radiosensitivity in cervical cancer. Bismuth consists of high atomic number elements, which remarkably increase X-ray absorption and thus radio sensitization. At the same time, the FAK inhibitor suppresses the DNA damage repair pathway and cell survival signaling post-irradiation. Additionally, in vitro study findings showed improved cellular uptake, accelerated DNA double–strand break, and apoptosis when cells were treated with the nanoplatform and radiotherapy. Furthermore, female BALB/c nude mice model treated with the nanoplatform combined radiotherapy showed the most significant tumor inhibition compared to other groups (Figure 6B).

Development of a hybrid cell membrane is another biomimetic nanoplatform. An example of this include porphyrin-DOX nanoparticles coated with RBC and 4T1 hybrid cancer cell membrane to overcome the previous cancer treatment challenges.[152] Due to the complex tumor environment, limited drug delivery, low blood circulation, and poor drug targeting at the tumor site, scientists developed these nanoparticles. Upon characterization, DLS revealed that the size distribution of DOX-Por@TRM was slightly increased compared to uncoated DOX-Por, indicating successful coating of nanoparticles with the membrane. Moreover, zeta potential measurement exhibits that the surface charge of coated nanoparticles closely matches that of the hybrid membrane. Among all ratios, the ratio 4:1 exhibited a significant negative zeta potential value, which indicates good stability (Figure 6C and D). Flow cytometry analysis further demonstrated that DOX-Por@TRM induces significantly higher intracellular ROS level in 4T1 cells, when compared to other formulations (Figure 6E). The study also showed that the hybrid membrane facilitated homologous targeting, leading to improved cellular uptake by 4T1 tumor cells. During in vivo analysis, a single intravenous administration of DOX-Por@TRM followed by three laser irradiations led to complete tumor eradication in the breast cancer mouse model, with minimal systemic toxicity. These findings revealed the effectiveness of combination chemotherapy and photodynamic therapy within a membrane-camouflaged nanoparticle system, offering enhanced tumor targeting, increased ROS generation, and superior therapeutic outcomes.

The hybrid membrane-coated nanoparticles exhibited approximately 2.5-fold higher tumor accumulation compared to uncoated nanoparticles, owing to their dual-targeting capability derived from tumor and immune cell membranes. In previous treatment approaches, some impediments were found, such as local recurrence and low efficacy. Scientists designed a dual membrane-coated biomimetic nanoparticle with erythrocyte membrane and WEHI-164 fibrosarcoma cell membrane. The biomimetic system was then embedded with poly (lactic-co-glycolic acid) NPs containing imiquimod (R837) and Indocyanine green for synergistic immunotherapy and photothermal therapy of fibrosarcoma.[153] The 808 nm near-infrared laser irradiation demonstrated a high photo-thermal conversion efficiency of 42.3%, affective localized tumor heating and ablation. In vivo data revealed that the combination treatment achieved a tumor inhibition rate exceeding 85%, which was markedly higher than the <40% suppression observed with monotherapies. Furthermore, the immune response was also remarkably improved, with a 2.5-fold increase in $CD8^+$ T cell infiltration and a 2-fold decrease in regulatory T cells within the TME, indicating a shift toward robust anti-tumor immune activation. The cumulative release rate of PIR and PIR@WRV at pH 5.0 and pH 7.4, and temperatures 60°C and 37°C, respectively, was shown in Figure 6F. Notably, throughout the treatment, no significant changes in body weight or histological abnormalities in major organs were observed, confirming the biosafety of the nanoplatform. Collectively, these findings

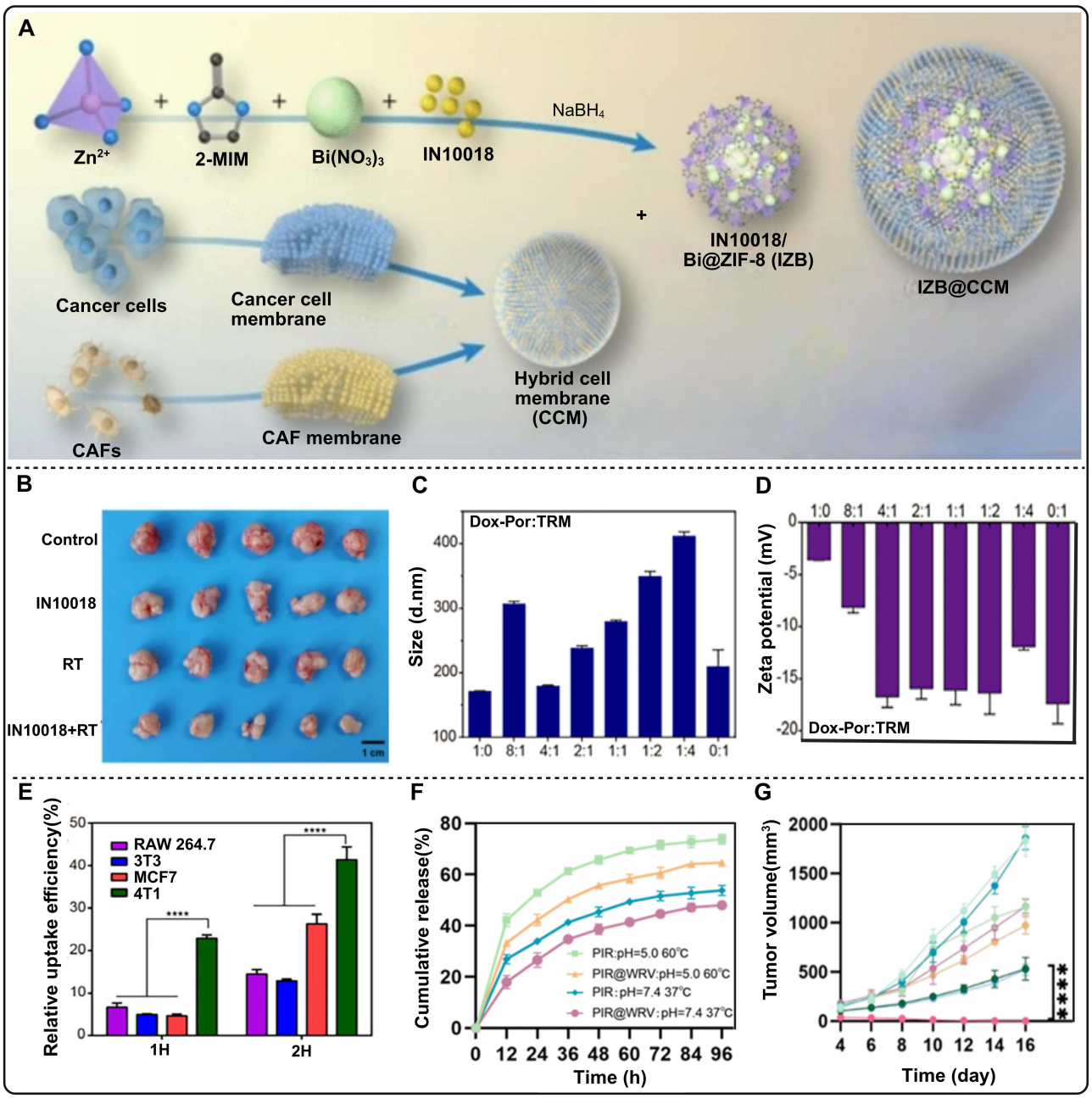

Figure 6 (**A**) A schematic representation of IZB synthesis using a one-pot method. Reproduced with permission from Chang Y, Huang K, Tang H et al. Biomimetic MOF nanoplatform for dual-targeted co-delivery of FAK inhibitor and bismuth to enhance cervical cancer radiosensitivity. *Advanced Composites and Hybrid Materials*.[151] Copyright 2025, The Authors. (**B**) Tumor imaging of different treated groups. Reproduced with permission from Chang Y, Huang K, Tang H et al. Biomimetic MOF nanoplatform for dual-targeted co-delivery of FAK inhibitor and bismuth to enhance cervical cancer radiosensitivity. *Advanced Composites and Hybrid Materials*.[151] Copyright 2025, The Authors. (**C** and **D**) Particle size and zeta potential measurements of DOX-Por. Reproduced with permission from Wang S, Lan J, Ren Z et al. Molecular Dynamics Simulations of Hybrid Cell Membrane-Coated Porphyrin Nanoparticles for Enhanced Photochemotherapy of Breast Cancer. *Adv Funct Mater*.[152] Copyright 2025, Wiley VCH-GmbH. (**E**) Flow cytometry evaluation of RAW 264.7, 3T3, MCF7, and 4T1 cells after treatment with Dox-Por@TRM (**** for $p<0.0001$). Reproduced with permission from Wang S, Lan J, Ren Z et al. Molecular Dynamics Simulations of Hybrid Cell Membrane-Coated Porphyrin Nanoparticles for Enhanced Photochemotherapy of Breast Cancer. *Adv Funct Mater*.[152] Copyright 2025, Wiley VCH-GmbH. (**F**) Cumulative release rate of PIR and PIR@WRV at pH 5.0 and pH 7.4, 60°C and 37°C, respectively. Reproduced with permission from Ma Y, Wang Z, Xia X et al. Biomimetic Hybrid Membrane-Cloaked Nanoparticles Assisted with Laser Irradiation for Synergistic Photothermal Immunotherapy of Fibrosarcoma. *ACS Appl Nano Mater*.[153] Copyright 2025, American Chemical Society. (**G**) Changes in primary tumor volume (n = 5), with statistical significance denoted as **** for $p<0.0001$. Reproduced with permission from Ma Y, Wang Z, Xia X et al. Biomimetic Hybrid Membrane-Cloaked Nanoparticles Assisted with Laser Irradiation for Synergistic Photothermal Immunotherapy of Fibrosarcoma. *ACS Appl Nano Mater*.[153] Copyright 2025, American Chemical Society.

demonstrate the potent synergistic effect of combining photothermal therapy with immune stimulation using biomimetic hybrid membrane-coated nanoparticles for the effective treatment of fibrosarcoma. Figure 6G shows the changes in primary tumor volume (n = 5), with statistical significance denoted as ****P < 0.0001. Also, there was no significant toxicity to major organs, indicating good biocompatibility and safety of this DDS.

Macrophage Membrane-Coated NPs

Although the discovery of nanoparticles has improved the delivery of drugs primarily for cancer, their efficacy has been enhanced after the development of macrophage cell membrane coating of nanoparticles.[154] So, developing macrophage membrane-coated nanoparticles has unlocked various therapeutic possibilities in cancer therapy.[155] The cells that are most prevalent in the TME are macrophages, which are responsible for the development and spread of the tumor, as M1 macrophage inhibits the growth of tumor cells while M2 macrophages promote the growth of tumor cells.[84] M1 macrophages can target and easily permeate inside the tumor cells, and hence, coating of the membrane leads to the accumulation of nanoparticles in the TME.[154] By taking advantage of macrophages' repolarization to the protumorigenic M2 phenotype, macrophage is also implicated in early diagnosis of cancer through in vivo sensors to detect 4T1 breast tumor.[87] This sensor may potentially address the limitations of traditional cancer diagnosis methods in terms of sensitivity and specificity. An innovative treatment strategy for treating pulmonary metastasis that originates from breast cancer involves the use of biomimetic nanoparticles coated with a hybrid membrane of macrophage-4T1 cancer cells.[86] The approach of coating macrophages to the core of nanoparticles has opened up a new ideal for the delivery of drugs across vascular boundaries, and can be done through processes like coextrusion, electrostatic interaction, electroporation, in situ production, and sonication.[53,156]

Modifying nanoparticles with membrane proteins of macrophages enhances their circulation time, immune evasion, elimination half-life, and selective targeting, which ultimately increases therapeutic potency. Through the technique of macrophage membrane-coated nanoparticles, the ability of the formulation's adherence to the tumor can be improved while maintaining drug-loading capability.[157] In terms of cancer treatment, the macrophage cell membrane is applied for various purposes, including therapy for metastatic and primary tumors, antiangiogenic therapy, antiproliferative cancer therapy, photothermal therapy, and photodynamic therapy.[158] Besides being used for cancer therapy, macrophage-coated membrane nanoparticles have also proven beneficial for diseases like Alzheimer's, bacterial and viral infections, stroke, inflammatory osteolysis, atherosclerosis, sepsis, and age-related macular degeneration.[107] It also works as an immunomodulator, a photosensitizer, a photothermal agent, as well as a cancer bioimaging and therapy.[159] One of the researchers focused on the coating of macrophage membrane decorated on Poly lactic glycolic acid (PLGA) NPs with loading of Saikosaponin D drug to show its efficacy against breast cancer with fewer side effects.[84] Here, T7peptide-conjugated PEGylated phospholipids are fused with Saikosaponin D-loaded Poly lactic glycolic acid nanoparticle (SCMNPs) to demonstrate targeted action against cancer cells. Besides showing its anti-tumor effect, SCMNPs are also known for their abscopal anti-tumor effect, which can further prevent metastasis effectively.

Pancreatic cancer is considered a very deadly cancer, with a 5-year survival rate of 6% and an average survival duration of only around 15 months.[160] Gemcitabine is a drug of choice for treating pancreatic cancer, but due to its toxicity and chemotherapeutic effect, it needs to be encapsulated into a nanoparticle.[161] Therefore, the researcher synthesized the gemcitabine-loaded Poly lactic glycolic acid nanoparticles with macrophage membrane-coated nanoparticles for treating pancreatic cancer.[162] Coating of the macrophage membrane on the nanoparticle leads to the reduction of phagocytosis and formation of antigen-antibody complexes. The comparison of free gemcitabine and gemcitabine-loaded macrophage membrane-coated nanoparticles reveals that the former is more toxic to cell lines than the latter.[85] So, this concludes that coating of the macrophage membrane on the nanoparticles can enhance the therapeutic value of a drug and its targeting capacity towards the tumor.

Macrophage membrane-coated biomimetic nanoparticle that encapsulates DOX and tetradrine NPs effectively reverse multidrug resistance in breast cancer cells (Figure 7A).[163] To combat this challenge, researchers devised DOX and Tetradrine loaded liposomes, which were surface-coated with macrophage membrane. MM@DOX-TT NPs inhibit DOX efflux by binding to p-glycoprotein, thereby increasing DOX release at the tumor site. Additionally, MM@DOX-Tet NPs exhibit a higher survival rate than DOX-Tet NPs in MCF-7 cells alone compared to MCF-7/ADR cells across all

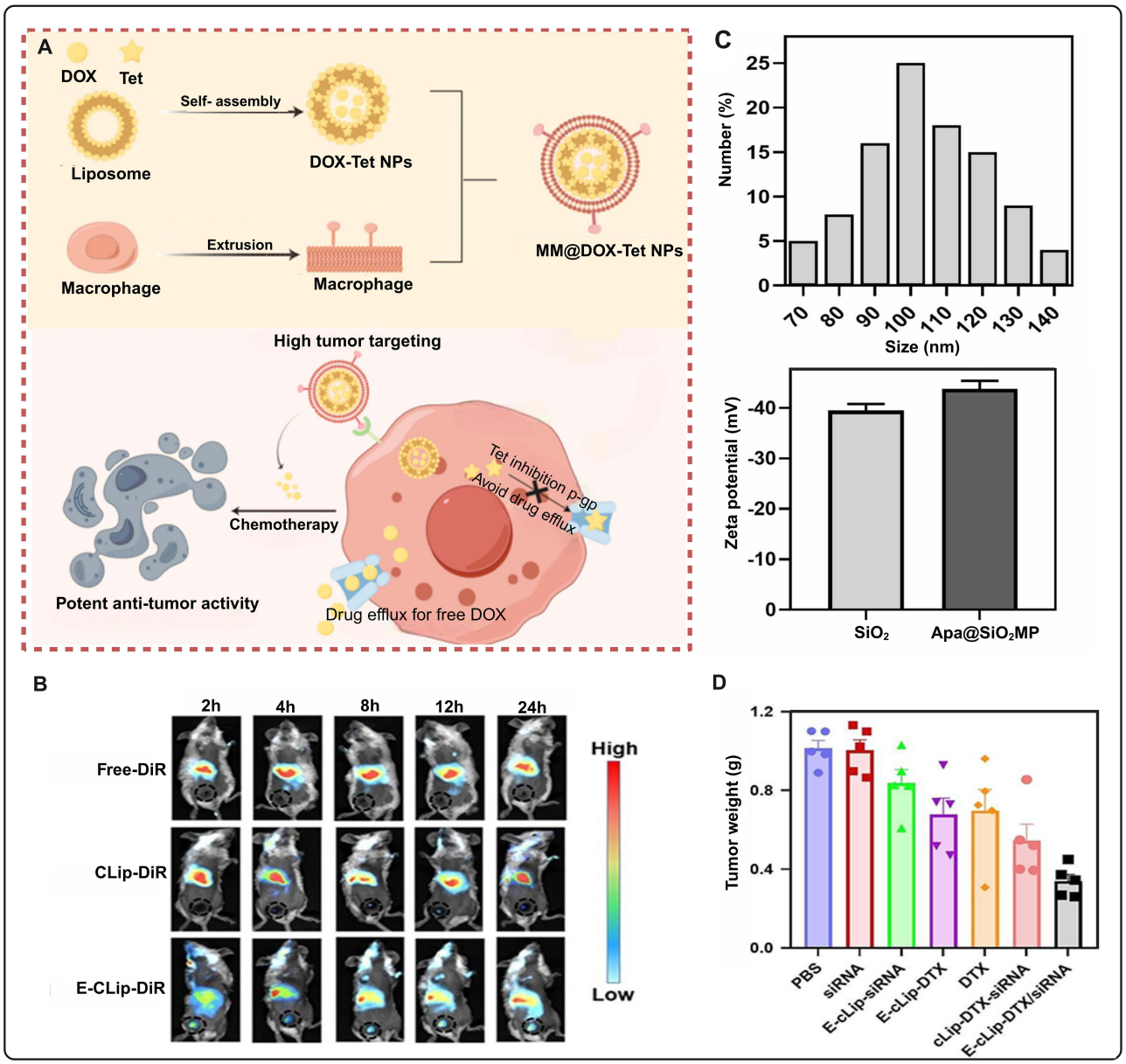

Figure 7 (**A**) Fabrication of MM@DOX-Tet NPs and their potential to target the tumor. Reproduced with permission from Lai Y, Pang S, Li C et al. Breast cancer-targeted therapy and doxorubicin multidrug resistance are reversed via macrophage membrane-camouflaged liposomes. *Colloids* Surfaces (**B**) Biointerfaces.[163] Copyright 2025, Elsevier. (**B**) In- vivo fluorescence imaging of Docetaxel biodistribution in cLip-DiR, Free DiR, and E-cLip-DiR over time. Reproduced with permission from Xu M, Bai L, Sun M et al. ROS-Responsive Biomimetic Nanocomplexes of Liposomes and Macrophage-Derived Exosomes for Combination Breast Cancer Therapy. *Int J Nanomedicine*.[164] Copyright 2025, The Authors. (**C**) Graphical representation of the DLS analyzing the size and zeta potential of SiO_2NPs and Apa@SiO_2NPs@MP. Reproduced with permission from Li H, Wang Y, Zhou S, Liu J, Jin Y. Apatinib-loaded silicate nanoparticles coated with macrophage membranes and PD-1 antibody for enhanced chemo-immunotherapy in ovarian cancer via VEGFR2 and PD-1 dual inhibition *Colloids Surfaces B Biointerfaces*.[164,165] Copyright 2025, Elsevier. (**D**) Tumor weight assessment in breast cancer model mice treated with PBS, E-cLip-DTX/siRNA, and other prepared formulations. Reproduced with permission from Xu M, Bai L, Sun M et al. ROS-Responsive Biomimetic Nanocomplexes of Liposomes and Macrophage-Derived Exosomes for Combination Breast Cancer Therapy. *Int J Nanomedicine*.[164] Copyright 2025, The Authors.

concentrations. Among all groups, in vivo anti-tumor activity in the tumor-bearing mice model indicated that MM@DOX-TT NPs exhibited the highest tumor suppression rate of 59.57 ± 6.86%, compared to groups treated with free DOX, free TT, and DOX-TT mixture. In another research study, scientists developed biomimetic nanocomplexes made with macrophage membranes loaded with docetaxel and Bcl-siRNA, along with reactive oxygen species-responsive cationic liposomes for dual delivery.[164] TEM showed spherical nanoparticles measuring between 55 and 80 nm and a surface charge of 36 mV. In vitro studies demonstrated controlled release with a 65% release over 24 hours, and

showed apoptosis rate of 66.4%. These E-cLip-DTX/siRNA nanocomplexes showed efficient cellular uptake and effective siRNA delivery, significantly enabling lysosomal escape for more effective gene silencing. In vivo fluorescence imaging using the Alliance Q9 chemiluminescence system revealed biodistribution patterns of different DTX formulations over time (Figure 7B). In breast cancer mouse model, E-cLip-DTX/siRNA nanocomplexes effectively targeted tumor sites, reduced liver clearance, and accumulated more in TME. The co-delivery system significantly inhibited tumor growth by decreasing Bcl-2 and Ki67 expression and induced strong tumor apoptosis without affecting body weight or causing organ damage. And, these findings demonstrate the excellent anticancer activity and biosafety of E-cLip-DTX /siRNA, highlighting its potential as a promising treatment strategy.

Apatinib-encapsulated mesoporous silica nanoparticles coated with a macrophage membrane (MM) and a PD-1 antibody represent another targeted strategy to accelerate chemoimmunotherapy through the dual suppression of VEGFR2 and PD-1 in ovarian cancer. Dynamic light scattering showed that the average particle diameter of SiO2NPs and Apa@SiO2NPs@MP was 101.2 ± 6.5 nm and 112.7 ± 4.6 nm, respectively, with surface potentials of about −39.5 ± 1.3 mV and −43.8 ± 1.6 mV (Figure 7C and D). Cytotoxicity study with CCK-8 assay indicated a greater reduction in cell viability for groups treated with Apatinib, Apa@SiO_2@MP, and Apa@SiO_2. However, SiO_2 did not cause any cytotoxicity, and Apa@SiO2 showed minimal effects. Both Apatinib and APD1 enhance drug delivery and therapeutic impact while also reducing toxicity, helping to overcome limitations such as low bioavailability and immune invasion seen in traditional cancer therapies.[161]

Serum Albumin-Fabricated Nanoparticles

Serum albumin-fabricated nanoparticles have garnered significant interest in the realm of cancer therapy due to their potential as drug-delivery vehicles. These nanoparticles, also known as albumin-bound or albumin-nanoparticles, are often designed to take advantage of the properties of serum albumin (a naturally occurring protein present in significant amounts in human blood), to enhance therapeutic outcomes and enable targeted drug delivery in the context of cancer treatment. Albumin is a versatile protein frequently utilized as a carrier in synthesizing albumin-derived nanocarriers (ADNCs) for the targeted delivery of cancer medicines. Improved tumor selectivity, reduced drug-induced cytotoxicity, and the ability to maintain therapeutic agents such as drugs, peptides, proteins, and genes at active concentrations for extended periods are just a few benefits of these ANCs. In addition to cancer treatment, ANCs find applications in cancer diagnosis, imaging, and multimodal therapy.[166] In this regard, researchers demonstrated that hydrophobic carbon nanodots encapsulated in human serum albumin (CDs-HSA) are used as a staining agent on HeLa tumor cells.[167] The study suggests that the proposed CDs-HSA technique can inspire the development of novel approaches for the next preparation of multimodal nanoparticles for various applications in the future. Furthermore, researchers reported the synergistic antitumor efficacy of DOX and gambogic acid-encapsulated albumin nanocomposites.[168] The researchers synthesized and characterized the nanocomposites and tested them on various types of cancer cells in vitro *and* in vivo. The results showed that the combination of DOX and gambogic acid-encapsulated albumin nanocomposites led to more significant tumor inhibition than single full-dose treatment while reducing organ toxicity at reduced doses. The researchers conclude that this strategy is promising for cancer treatment. Moreover, dysregulated protein kinases contribute to cancer and drug resistance. Despite small molecule kinase inhibitors, drug resistance remains a challenge, as seen in chronic myeloid leukaemia. To address this, a personalized nanomedicine, "holo-transferrin (Tf) conjugated albumin-bound sorafenib," targeting refractory CML with elevated STAT5 signalling and transferrin receptors (TfR) overexpression was studies.[169] The nanomedicine showed effective antileukemic activity, highlighting the potential of a dual-targeting approach to overcome molecular drug resistance.

Furthermore, the research conducted aimed to enhance the therapeutic effectiveness of Paclitaxel by overcoming its inherent limitations, primarily focusing on stability and targeting efficiency. This was achieved through the utilization of nanoparticulate drug carriers. The methodology involved the incorporation of PTX into human serum albumin using a disulfide reduction approach to formulate HSA-formulated PTX nanoparticles (HSA-PTX NP).[170] The study encompassed both in vitro and in vivo investigations, yielding significant key findings. The in vitro cytotoxicity of various PTX formulations against MDA-MB-231 tumor cells was assessed at different concentrations and the results demonstrated that the developed serum biomimetic nanoparticles exhibit promising potential for improving cancer treatment. The

incorporation of biomimetic elements in their design enhances compatibility with biological systems, enabling targeted drug delivery while minimizing adverse effects.

Another group of researchers formulated biomimetic nanoparticles using 4T1 cancer cell membranes encapsulated with HSA and PTX NPs for the site-specific delivery of PTX for the treatment of breast cancer.[127] Marketed formulation Abraxane has several limitations, including poor stability and inadequate tumor targeting ability. To overcome these issues, scientists developed biomimetic NPs using 4T1 cancer cell membranes loaded with HSA and PTX for targeted delivery of PTX for treatment of breast cancer (Figure 8A). CM-HSA-PTX demonstrated promising dilution stability, storage stability, and serum stability, which may facilitate the extension of blood circulation and enable cargo to reach the disease site. Additionally, cytotoxicity analysis was performed on MCF-7, B16-F10, and HepG2 cell lines, which exhibit robust cytotoxicity. However, Future research could focus on combining this cancer cell membrane-coated albumin nanoparticle platform with photodynamic therapy or immune adjuvants to enhance precision treatment and immune activation. This multifunctional strategy holds promise for improving targeted drug delivery and synergistic therapeutic outcomes in breast cancer and other solid tumors.

Gefitinib/albumin NPs coated with RBCM for tumor imaging and targeted tumor therapy against lung cancer, tried to overcome the serious side effects of conventional cancer treatment, including hepatotoxicity, renal toxicity, and poor drug targeting.[172] To address these limitations, scientists built gefitinib-encapsulated NPs coated with cRGD-modified cell membrane (R-RBC@GEF-NPs). The surface charge of RBC membrane suspension, BSA solution, and GEF-NPs was −14.66 ± 0.32 mV, −22.14 ± 0.96 mV, and −20.21 ± 0.92 mV, along with the values −16.99 ± 1.49 mV and −16.65 ± 0.88 mV for RBC@GEF-NPs and R-RBC@GEF-NPs, respectively. Cell viability remained above 90% following treatment with a dose of 1000 μg/mL without drug BSA nanoparticles, indicating minimal cytotoxicity. In contrast, treatment with 10 μg/mL of GEF in R-RBC@GEF-NPs reduced the cell survival to 38%, which was significantly lower than the viability observed in other formulations, highlighting the R-RBC@GEF-NPs induced cytotoxicity (Figure 8B). Furthermore, the hemolysis rates in normal saline (NS, GEF, GEF-NPs, R-RBC@GEF-NPs, and RBC@GEF-NPs) were 3.41%, 7.85%, 5.49%, 3.8%, and 4.69%, respectively, demonstrating that R-RBC@GEF-NPs exhibit significant biocompatibility among all groups. Additionally, in vivo hepatotoxicity and nephrotoxicity findings reveal the biosafety of liver and kidney functions after the induction of R-RBC@GEF-NPs.

Conventional photothermal treatment is hindered by adaptive immune resistance and poor tissue penetration of external light. To address these hurdles, researchers formulated serum albumin-based chemiexcited photodynamic biomimetic cancer cell membrane nanoreactor (CC@HSA/GOX@Z(Arg/1-MT)m), which accelerates antitumor therapy by overcoming adaptive immune resistance.[171] The diameter of these NPs was 195.7 ± 3.6 nm, and after coating with a tumor cell membrane, it increased to 201.4 ± 4.4 nm. After coating, the particle surface charge decreased from 34.6 ± 0.6 mV to 15.7 ± 0.7 mV. TEM images of CC@HSA/GOX@Z(Arg/1-MT) exhibit a spherical morphology, which demonstrates the Ce6/CPPO@HSA loaded into ZIF-8 without any toxic effect (Figure 8B). Additional evidence of the selective CC@HSA/GOX@Z(Arg/1-MT) m accumulation within tumor tissues was provided through ex vivo live imaging fluorescence system of both tumors and major organs. The findings highlighted the strong tumor-targeting capability of these nanoparticles, which can be credited to their optimal particle size, high colloidal stability, pH-sensitive behavior, and modification with tumor cell membranes that enhance homotypic targeting. Additionally, Enzyme Linked Immunosorbent assay (ELISA) results showed a significant increase in interferon-gamma (IFN-γ) secretion within tumor tissues in both CC@HSA/GOX@Z(Arg/1-MT)m and CC@HSA/GOX@Z(Arg)m treatment groups. B16F10 and 4T1 cancer cells, both prone to lung metastasis, were used to develop a murine model to evaluate anti-metastatic efficacy (Figure 8C). The findings indicate that CC@HSA/GOX@Z(Arg/1-MT)m achieved a synergistic antitumor effect by integrating chemiexcited photodynamic therapy (CRET-PDT) with IDO inhibition.[171] This combined approach significantly enhanced therapeutic outcomes and demonstrates strong potential for future clinical applications in cancer treatment.

Protein-Based Nanoparticles

A protein-mediated nanocarrier can be defined as a nanocarrier that is either modified by a protein or composed entirely of protein components. Protein-based biomimetic nanoparticles have attracted significant attention in the

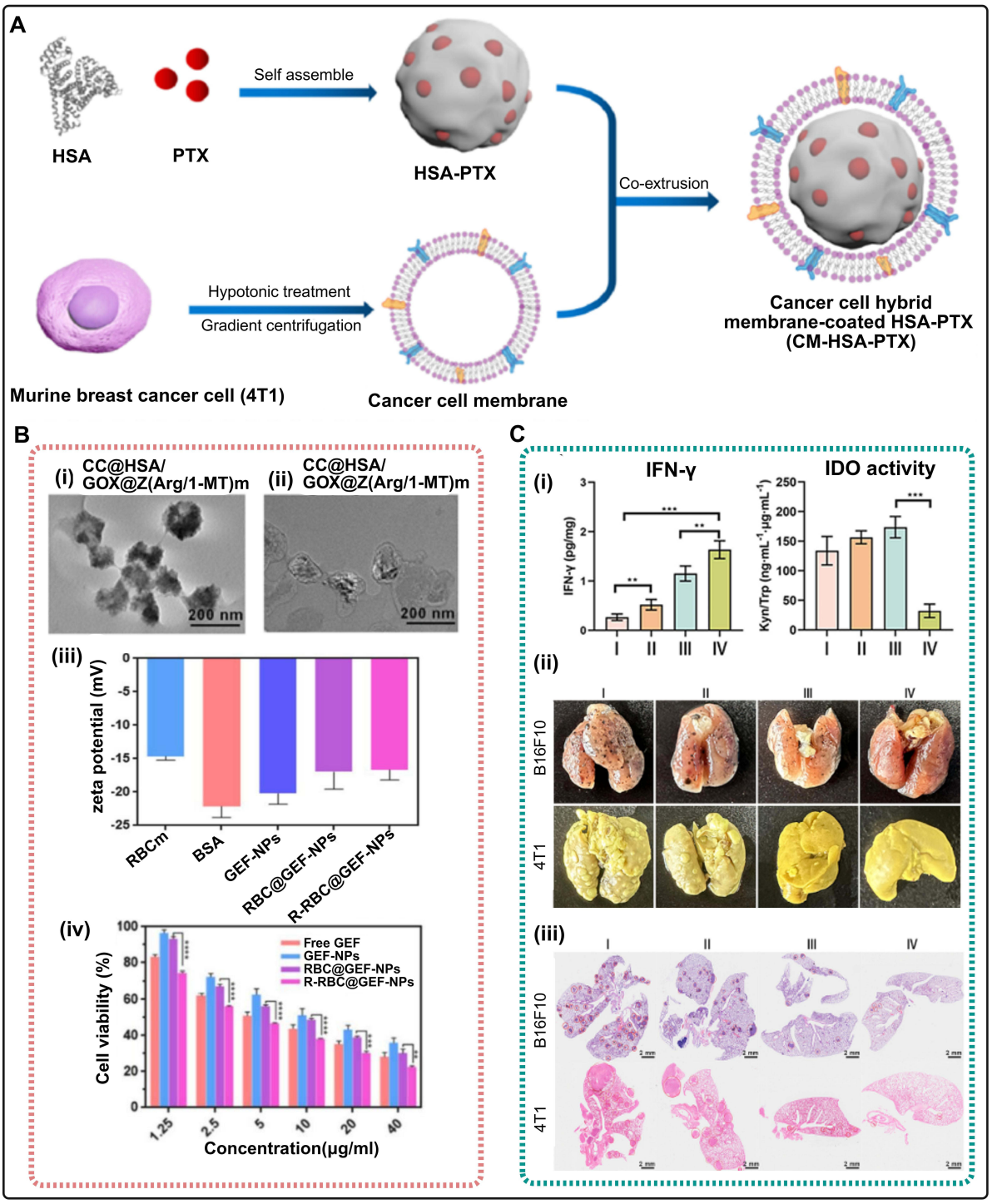

Figure 8 (**A**) Representation of the fabrication of HSA and PTX encapsulated cancer cell hybrid membrane. Reproduced with permission from Cao Y, Yang Y, Feng S, Wan Y. Biomimetic cancer cell-coated albumin nanoparticles for enhanced colloidal stability and homotypic targeting of breast cancer cells. *J Drug Deliv Sci Technol.*[127] Copyright 2022, Elsevier. (**B**) TEM images of (i) CC@HSA/GOX@Z(Arg/1-MT) and (ii) CC@HSA/GOX@Z(Arg/1-MT)m (scale bar 200 nm). Reproduced with permission from Li K, Su Y, Zhao W et al. Albumin-based synergistic chemiexcited photodynamic biomimetic nanoreactor overcoming adaptive immune resistance for enhanced cancer immunotherapy. *Int J Biol Macromol.*[171] Copyright 2025, Elsevier. (iii) Particle charge measurements of BSA-NPs, GEF-NPs, RBC@GEF-NPs, and RGDRBC@GEF-NPs, and (iv) In vitro cytotoxic effects on A549 cells of free gefitinib, GEF-NPs, RBC@GEF-NPs, and R-RBC@GEF-NPs (** for p<0.01), (*** for p<0.001), (**** for p<0.0001). Reproduced with permission from Wen Q, Zhang Y, Muluh TA et al. Erythrocyte membrane-camouflaged gefitinib/albumin nanoparticles for tumor imaging and targeted therapy against lung cancer. *Int J Biol Macromol.*[172] Copyright 2021, Elsevier. (**C**) (i) Graphical representation of IFN-γ and Kyn/Trp presence in tumor control and CC@HSA@Z(Arg)m (** for p<0.01), (*** for p<0.001). (ii) Image showing the development of a murine model to evaluate anti-metastatic efficacy using B16F10 and 4T1 cancer cells. (iii) Hematoxylin and eosin (H&E) staining of lung tissue sections (scale bar 2 mm). Reproduced with permission from Li K, Su Y, Zhao W et al. Albumin-based synergistic chemiexcited photodynamic biomimetic nanoreactor overcoming adaptive immune resistance for enhanced cancer immunotherapy. *Int J Biol Macromol.*[171] Copyright 2025, Elsevier.

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field of cancer therapy due to their potential for tailored drug delivery, reduced side effects, and greater therapeutic efficacy. These nanoparticles are designed to mimic biological processes and structures, such as proteins or cell membranes, to improve their interaction with the body and specific cancer cells. They have demonstrated remarkable efficacy in co-delivering anticancer drugs and conducting gene therapy for tumors, with a particular emphasis on their performance in tumor imaging.[41] Protein biomimetic-based nanoparticles are nanoscale structures designed with surfaces incorporating or constructed using natural proteins. These nanoparticles are gaining attention in targeted drug delivery due to their exceptional adaptability and compatibility with biological systems. Various protein types, including serum albumin, ferritin, lipoproteins, and virus-like particles, find applications in constructing these versatile nanoparticles.[173]

Research studies highlight the effectiveness of natural proteins in targeted drug delivery systems. They demonstrate considerable potential in achieving targeting specificity, pH, or stimulus-induced conformational changes for sustained drug action, improved drug stability, and synergistic effects. For instance, Abraxane employs albumin-bound paclitaxel nanoparticles for cancer therapy.[174] Furthermore, recently, researchers have introduced a novel recombinant high-density lipoprotein nanoparticle designed for the accurate co-encapsulation and co-delivery of two established anti-cancer agents.[175] Their hypothesis revolved around the potential synergy of these drugs to enhance their effectiveness against cancer. This co-loaded rHDL system was engineered by first passively incorporating the hydrophobic drug PTX and subsequently remotely encapsulating the hydrophilic drug DOX into the same NPs. Notably, co-loaded rHDL nanoparticles demonstrated exceptional effectiveness in increasing the ratio of drug accumulation within cancer cells, thereby augmenting the anti-tumor response, particularly when employing synergistic drug ratios. These nanoparticles exhibited superior anti-cancer effects, as evidenced by their performance in in vitro cell viability assessments and in a comparison with traditional free drug cocktail solutions in a hepatoma xenograft tumor model. Protein-based biomimetic nanoparticles have enormous potential to overcome present barriers in cancer treatment as research in this area advances. The optimisation of novel nanocarriers, alongside clinically approved and investigational protein-based therapies, marks a significant step toward more potent, precise, and patient-friendly cancer treatments (Table 2).

Table 2 A Summary of Clinically Approved Protein-Based Therapies for Cancer Therapy

Title Clinical Trial	Company Name	Name	Type	Clinical Approved Phase	Website Link	Ref.
Phase III Study of ABI-007(Albumin-bound Paclitaxel) Plus Gemcitabine Versus Gemcitabine in Metastatic Adenocarcinoma of the Pancreas	Celgene	Abraxane (ABI-007)	Paclitaxel HSA-bound NP	Approved	https://clinicaltrials.gov/study/NCT00844649	[176]
A Phase I/II Trial of ABI-008 (Nab-Docetaxel) in Patients With Hormone-Refractory Prostate Cancer.	Abraxis BioScience, Inc.	ABI-008	Docetaxel-albumin NP	Phase II	https://adisinsight.springer.com/trials/700022179.	[177]
A Phase 2 Study of Nab-sirolimus (ABI-009) in Patients With Advanced Malignant PEComa (AMPECT)	Aadi Bioscience, Inc.	ABI-009	Rapamycin-albumin NP	Phase II	https://www.clinicaltrials.gov/study/NCT02494570	[178]
Injection of 99mTc-nanocolloid and ICG to Identify, Retrieve and Qualify TDLN in Early-stage NSCLC (INITIATE) (99mTc-nanoscan)	Radboud University Medical Center	Nanoscan	^{99m}Tc-labelled HAS	Early Phase I		[179]

(*Continued*)

Table 2 (Continued).

Title Clinical Trial	Company Name	Name	Type	Clinical Approved Phase	Website Link	Ref.
Phase 3 Study to Treat Patients with Soft Tissue Sarcomas (Aldoxorubicin)	ImmunityBio, Inc.	Aldoxorubicin	Doxorubicin–maleimide conjugate	Phase III	https://clinicaltrials.gov/study/NCT02049905	[180]
Erbitux Metastatic Colorectal Cancer Strategy Study (Erbitux)	Merck KGaA	Erbitux	Cetuximab	Approved	https://clinicaltrials.gov/study/NCT02484833?tab=table	[181]

Biosafety Hurdles, Regulatory Requirements, and Clinical Translation

The clinical implementation of biomimetic NPs for cancer therapy confronts a multitude of complex obstacles that must be surmounted before these promising nanomaterials can be widely integrated into clinical practice. Prolonged timelines, inherent biases, and a considerable rate of unsuccessful endeavours characterise the journey of translating nanomedicines into the clinical realm. These challenges encompass the absence of established standardized protocols, insufficient characterization of materials and biological components, and inconsistencies in statistical analyses, all of which present formidable barriers in the development of nanomedicine. Additionally, the substantial heterogeneity in the selection of experimental models, a hesitancy to share research findings, and methodological inaccuracies have collectively hindered progress toward advanced clinical trial phases. Discrepancies between publicly available data and industry-acquired results, coupled with the intricate task of identifying suitable commercial partners due to translational disparities, have resulted in the premature termination of ongoing research initiatives.[182] Moreover, several challenges during clinical translation of biomimetic NPs for cancer therapy revolve around the absence of Good Manufacturing Practice (GMP) protocols, the need for a scalable manufacturing procedure to generate consistently stable and sterile products, and the time-consuming, less efficient manufacturing processes associated with bio membrane-based nanostructures like exosomes and outer membrane vesicles (OMVs). Furthermore, although preclinical data indicate an emerging trend in applying nanotechnology to immunotherapy, numerous concerns and unresolved issues must be tackled to facilitate the path of nano-vaccines into clinical practice.[183]

Limitations in clinical transformation of biomimetic nano DDS include content during drug loading, premature drug leakage at off-target locations during circulation, immunogenicity, and possible toxicity hazards of the carrier materials. Additionally, it is mentioned that during the scale-up production process, it is crucial to avoid uneven or incomplete coverage of the cell membrane on nanoparticles to prevent unnecessary side effects in blood circulation. The repeatability of the manufacturing process and preservation of functional surface proteins require adequate control and monitoring for critical measures. Thus, several challenges limit the clinical transformation of biomimetic nanomaterials, such as biological barriers like immune clearance, blood-brain barrier, and extracellular matrix, along with some quality and regulatory issues like scalability, encapsulation efficiency, lack of standardized guidelines, and commercial cost regulations.[184] Still, there is a lot of work remaining to address issues in biomimetic DDS for a better understanding of how they work and pave the way for immunotherapy in developing more effective bionic DDS with minimal side effects.[185] In addition, Regulatory approval requirements pose a significant challenge in the clinical translation of biomimetic NPs for tumor treatment. The regulatory pathway for introducing biomimetic nanoparticles into clinical practice is intricate and demanding. Regulatory agencies like the FDA and EMA have stringent guidelines that necessitate comprehensive preclinical and clinical results to indicate safety and efficacy. Before advancing to human trials, biomimetic nanoparticles must undergo thorough preclinical testing. The guidelines provide a risk-based quality by design framework approach in the development of biomimetic nanoparticles for cancer therapy. ICH Q8 focuses on designing and manufacturing of biomimetic nanoparticles, considering the quality target product profile, critical quality

attributes, design space and process parameters for these biomimetic nanoparticles in cancer therapy.[186] Whereas ICH Q9 focuses on quality risk management, ICH Q10 on quality management for GMP, ICH Q11 for development in manufacturing and risk control, and Q12 focuses on the lifecycle management.[186] Also, biological evaluation of products, medical devices, along with their sterility and endotoxin tests, should also be considered for these biomimetic nanoparticles for cancer therapy.[186–189] These studies, which evaluate toxicity, pharmacokinetics, and biodistribution, require extensive resources and can be time-consuming. Regulatory requirements prioritize patient safety and ethical conduct. While this is essential, it can lead to added complexities in patient recruitment, informed consent procedures, and monitoring to ensure the well-being of trial participants. In conclusion, regulatory approval requirements represent a formidable challenge in clinical translation of biomimetic NPs for tumor treatment. While these regulations are in place to validate patient safety and efficacy of treatment, they necessitate significant investments in terms of time, resources, and stringent compliance, often prolonging the journey from research to clinical application.

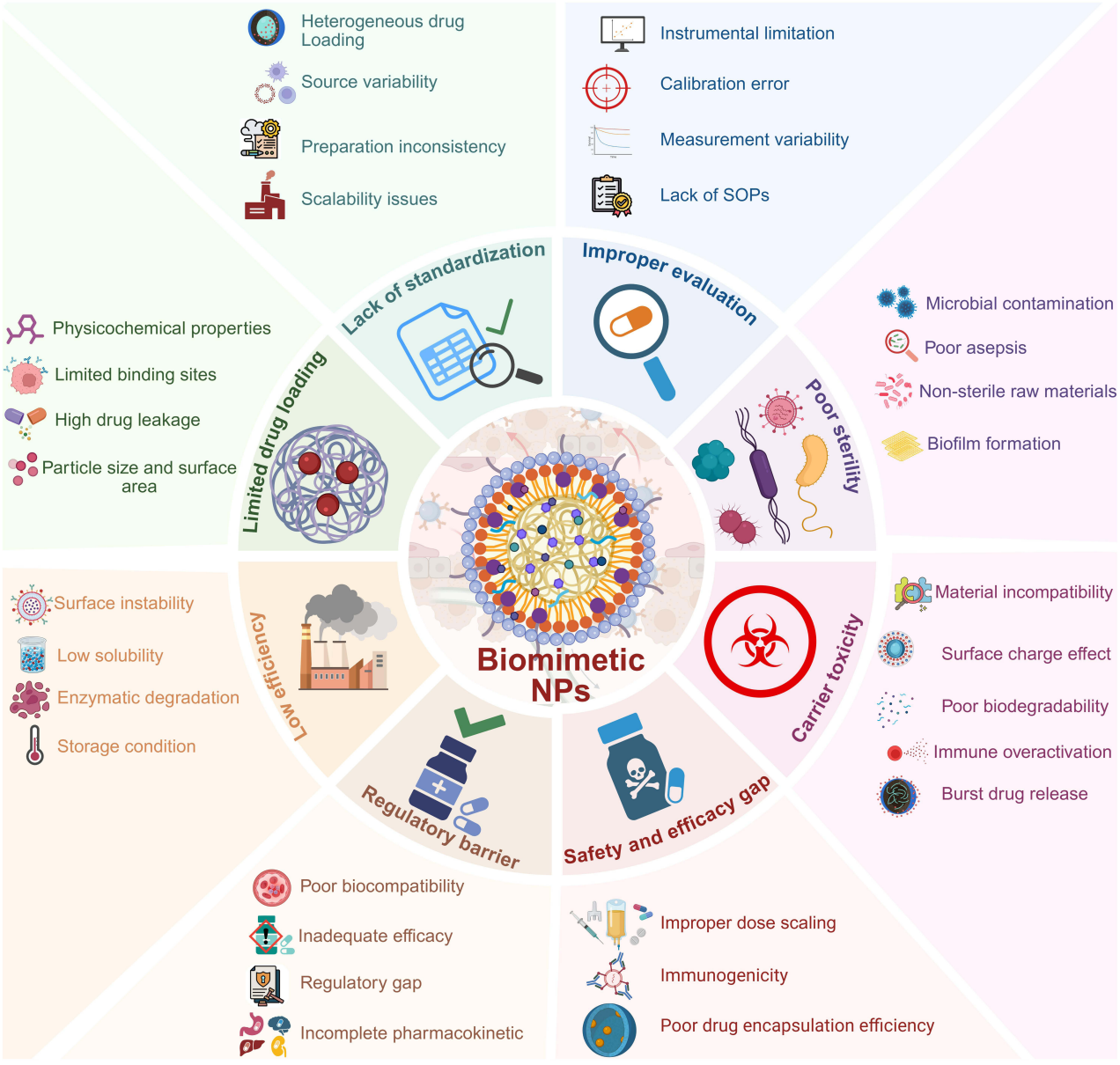

Figure 9 Schematic illustration of various hurdles and their causes in biosafety, regulatory requirements, and clinical translation of biomimetic nanoparticles.

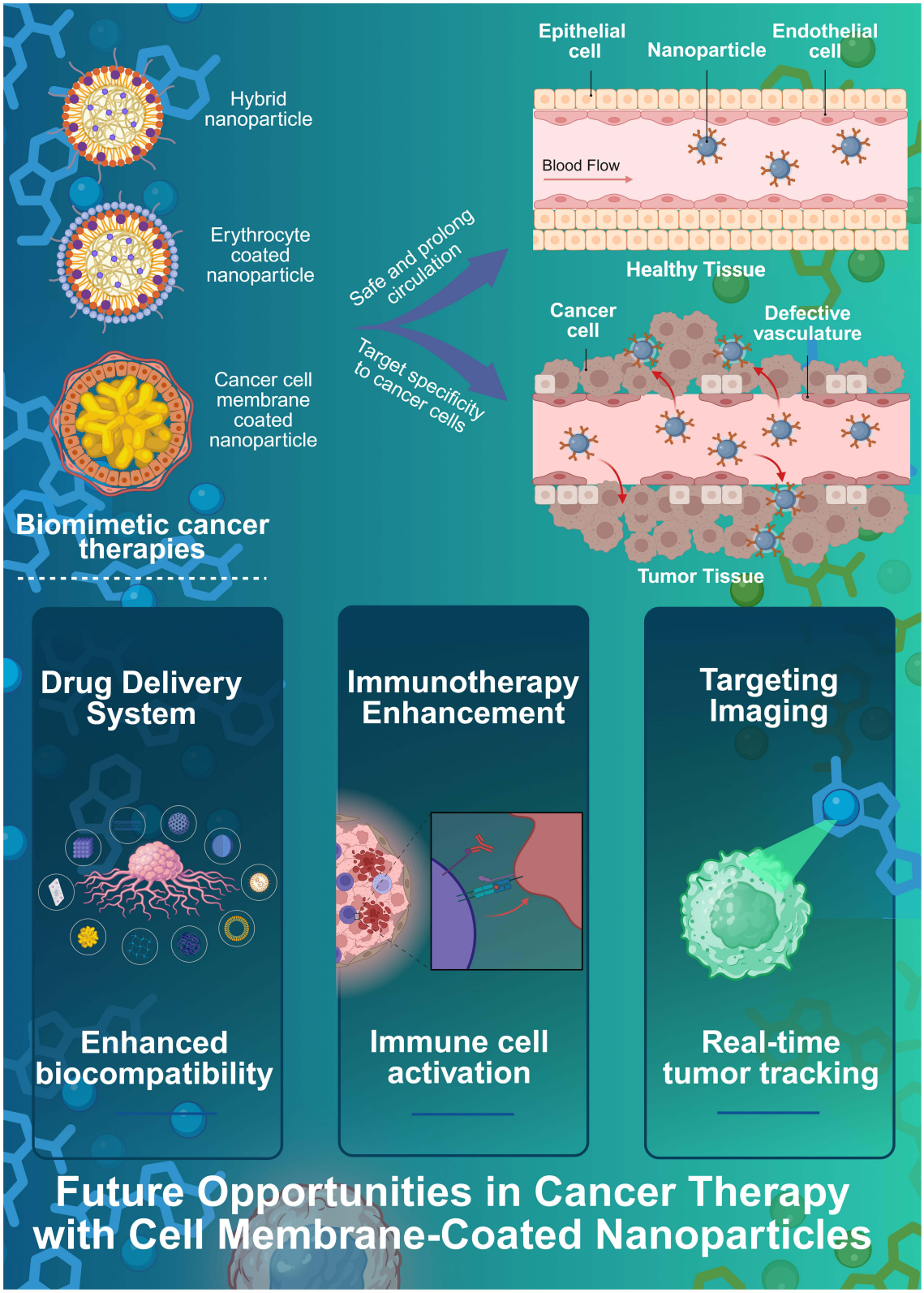

Figure 10 Illustration of the effects of biomimetic nanoparticles on normal and cancer cells and their future opportunities in biomimetic cancer therapies.

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By addressing these critical aspects of biosafety and regulatory approval, researchers and healthcare professionals can unlock the full therapeutic potential of these innovative nanomaterials and potentially contribute to more efficient and targeted cancer treatments with improved patient outcomes (Figure 9). As the field of nanomedicine continues to evolve, it is imperative to remain dedicated to the rigorous assessment and responsible translation of these novel technologies to advance cancer care.

Conclusion and Future Perspectives

Despite established treatments such as surgery, radiation, chemotherapy, and immunotherapy, clinical limitations, including narrow therapeutic windows, poor drug penetration, immunosuppression, and rapid systemic clearance, continue to be a focus of research for advanced delivery platforms. Many factors contribute to the development and progression of cancer in day-to-day life, some of which are well understood, such as environmental factors, unhealthy eating habits, and a sedentary lifestyle, as well as genetic mutations and exposure to chemicals or carcinogenic agents. Advances in medical science provide various treatment options, including surgery, radiation therapy, chemotherapy, and immunotherapy. Despite such advancements in the medical field, researchers, doctors, and scientists continue their search for a reliable and safer cancer treatment. Ultimately, a multi-faceted approach involving awareness, early detection, effective treatment, and palliative care is essential to fight against cancer. Continued research is necessary to develop more effective therapies and improved early detection methods to find a cure for cancer. Biomimetic nanoparticle-based drug delivery system increased the drug solubility for hydrophobic chemotherapeutics, extended circulation, tumor targeting, and enhanced permeability and retention effect. Due to their small size and drug-carrying ability, nanoparticles are a promising technology in minimizing harm to healthy tissues and reducing side effects, helping overcome limitations of conventional approaches, diagnosis, and treatments (Figure 10). Biomimetic nanoparticles overcome these limitations by membrane coating with the cell membrane for passive immune evasion and homotypic active targeting. Their ability to escape the immune system and their enhanced targeting made them a suitable candidate for cancer treatment. Different cell membranes provide unique abilities to conquer the cancer cell within the body, like red blood cell membranes for prolonged circulation and cancer cell membranes for targeted delivery.

Hybrid membrane-coated nanoparticles are another approach for producing a dual effect of two different cell membranes for improved efficacy with specific targeting. Cell membrane coating mimics the natural cell surface, making nanoparticles biocompatible and less recognizable as a foreign substance by the immune system. Despite these mechanistic advantages, biomimetic nanoparticles have critical barriers in clinical applications, such as manufacturing and scalability challenges, a mechanistic and clinical translation gap. In summary, biomimetic nanoparticles offer a versatile platform for biomedical applications by leveraging the unique properties of different cell membranes, especially in targeted cancer therapy. The cell membrane type and nanoparticle core design are critical factors in achieving desired therapeutic outcomes. Therefore, further research is needed to optimize nanoparticle design, improve targeting strategies, and evaluate safety and efficacy in clinical trials.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there is no conflict of interest.

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