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REVIEW

Engineered cell-biomimetic nanosystems for anti-inflammatory therapy: Targeting, neutralization and immunomodulation

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Abstract Inflammation is a complex and dynamic immune response triggered by tissue injury or pathogen invasion, playing a critical role in restoring tissue homeostasis. However, excessive inflammation can lead to tissue damage and exacerbate the progression of various diseases. Issues such as off-target effects and insufficient dynamic regulation pose key challenges to precise modulation of complex inflammatory processes, thereby enhancing efficacy while minimizing adverse effects. Engineered cell-biomimetic nanosystems (ECNs), including membrane-coated nanoparticles, extracellular vesicles (ECVs), and cell-nanoparticle hybrids, are highly adaptable biomimetic platforms with tunable physicochemical properties. Beyond carrier functions, ECNs are capable of actively responding to inflammation-related targets and interacting with the immune microenvironment, thereby promoting the dynamic regulation of inflammation. This review summarizes recent advances in ECNs, with an emphasis on targeting mechanisms and key strategies for inflammatory intervention. These include precise targeting of inflamed tissues, biological neutralization of toxins and overexpressed inflammatory factors to interrupt the inflammatory cascade, and immunomodulatory functions that balance immune responses to achieve activation or suppression. Physical, chemical, and biological engineering strategies for modifying cells and cell membranes for inflammation targeting are also discussed. As an emerging platform for targeted drug delivery and immune regulation, ECNs provide innovative technological approaches for inflammation therapy.

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1. Introduction

Inflammation is a protective response triggered in biological tissues under conditions such as injury or infection, initiating a complex regulatory network to defend against pathogen infection, tissue damage, or to modulate autoimmune signaling[1]. Through the recruitment of immune cells, clearance of pathogens and harmful substances, and subsequent tissue repair, inflammation restores immune homeostasis. In the early inflammatory process, damaged cells or pathogens release danger signals, such as damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), which activate resident immune cells to secrete cytokines, chemokines, growth factors, and reactive oxygen species[2]. Subsequently, circulating immune cells adhere to endothelial cells and home to the inflamed microenvironment, further amplifying the inflammatory response[3]. This coordinated immune response ultimately contributes to the reestablishment of homeostasis. However, when immune responses are inadequate or excessive, disrupting the balance between innate and adaptive immunity, or due to the persistent presence of proinflammatory factors, inflammation can become uncontrolled or transition to a chronic state, leading to organ pathology or systemic inflammatory response syndrome, and even death[4].

Low targeting efficiency and rapid clearance by the immune system limit the ability of anti-inflammatory drugs to maintain effective concentrations at inflamed sites, while promoting off-target distribution and side effects[5]. In addition, many anti-inflammatory agents exhibit poor bioavailability, further increasing the risk of dose-dependent toxicity[6]. Prolonged or high-dose administration can further lead to adverse events such as gastrointestinal injury and immunosuppression[7]. To address these challenges, nanodrug delivery systems have been actively investigated. However, as exogenous materials, nanoparticles face immune recognition and clearance, and may even trigger immune responses. Furthermore, the limited ability of nanocarriers to traverse biological barriers remains a major obstacle to their efficacy. To overcome these issues, ECNs harness a diverse array of receptors and signaling molecules present on natural cell membranes, enabling them to actively localize and recognize sites of inflammation, as well as coordinate with immune cells to evade clearance by macrophages. In addition, ECNs are capable of interacting with the immune microenvironment, integrating functions ranging from targeted delivery to toxin clearance and immune modulation. More importantly, through engineering strategies, ECNs can achieve scalability, modularity, and functional customization while maintaining high bioactivity, thereby offering innovative and precise therapeutic approaches for complex and refractory inflammatory diseases.

Here, we defined ECNs broadly to include three principal formats: (1) membrane-coated nanoparticles, (2) extracellular vesicles, and (3) cell-nanoparticle hybrids that adhere drug depots to living cells ("backpacks"). As demonstrated in Fig. 1, this review summarizes diverse engineering strategies applied to cells, including physical, chemical, and biological modifications aimed at optimizing their functionality. We provided an overview of recent advances in the application of ECNs in inflammation-related therapeutic mechanisms, such as inflammation targeting, biological neutralization, and immunomodulation. The review further discussed the biomimetic properties of ECNs, drug delivery efficiency, and the influence of various types of cells on the applicability of ECNs to diverse inflammatory mechanisms. Finally, we discussed current progress in the clinical translation of ECNs and highlighted the remaining challenges to be addressed.

2. Inflammatory microenvironment involved in targeting and therapy strategies

2.1. Danger signals

The innate immune system is capable of recognizing damaged, dying, and defective cells that contribute to disease onset, thereby initiating protective responses. This recognition relies on a group of germline-encoded pattern recognition receptors (PRRs), which detect PAMPs representing exogenous threats, as well as DAMPs indicating endogenous damage signals.

The sources of PAMPs and DAMPs are diverse. PAMPs may originate from bacterial, viral, fungal, or protozoan pathogens. In contrast, DAMPs come from the host itself and are released during cellular damage or abnormalities. These include endogenous molecules such as extracellular adenosine triphosphate, uric acid crystals, calcium pyrophosphate dihydrate, cholesterol crystals, and glucose, all of which can be recognized by PRRs as danger signals and subsequently promote inflammatory and immune responses[8]. Upon binding with PAMPs or DAMPs, nucleotide-binding domain leucine-rich repeat containing receptors initiate the assembly of inflammasomes[9], activating caspase-1, which in turn mediates the processing and secretion of IL-1β and IL-18, thereby triggering inflammatory responses. Besides nucleotide-binding domain leucine-rich repeat containing receptors, the innate immune system also comprises Toll-like receptors (TLRs) expressed on the surface of immune cells. When TLRs bind to extracellular DAMPs and PAMPs, they can activate cytoplasmic adapter molecules, initiating a series of signaling pathways involving nuclear factor-κB (NF-κB), interferon regulatory factors, and the mitogen-activated protein kinase pathway. These processes generate proinflammatory cytokines (such as TNF, IL-1, and IL-6) and chemokines through transcriptional and post-transcriptional regulation[10]. In addition, PRRs encompass C-type lectin receptors, a class of transmembrane pattern recognition receptors predominantly expressed by myeloid cells. C-type lectin receptors are capable of identifying both pathogens and DAMPs released from dying cells, thereby regulating downstream NF-κB signaling, type I interferon production, and inflammasome formation[11].

However, persistent stimulation by PAMPs and DAMPs can lead to uncontrolled chronic inflammation. Therefore, directly clearing or competitively blocking PAMPs and DAMPs at the pathological source to inhibit danger signal transmission can effectively terminate the cascade amplification of inflammation. This approach provides a clinically meaningful research direction

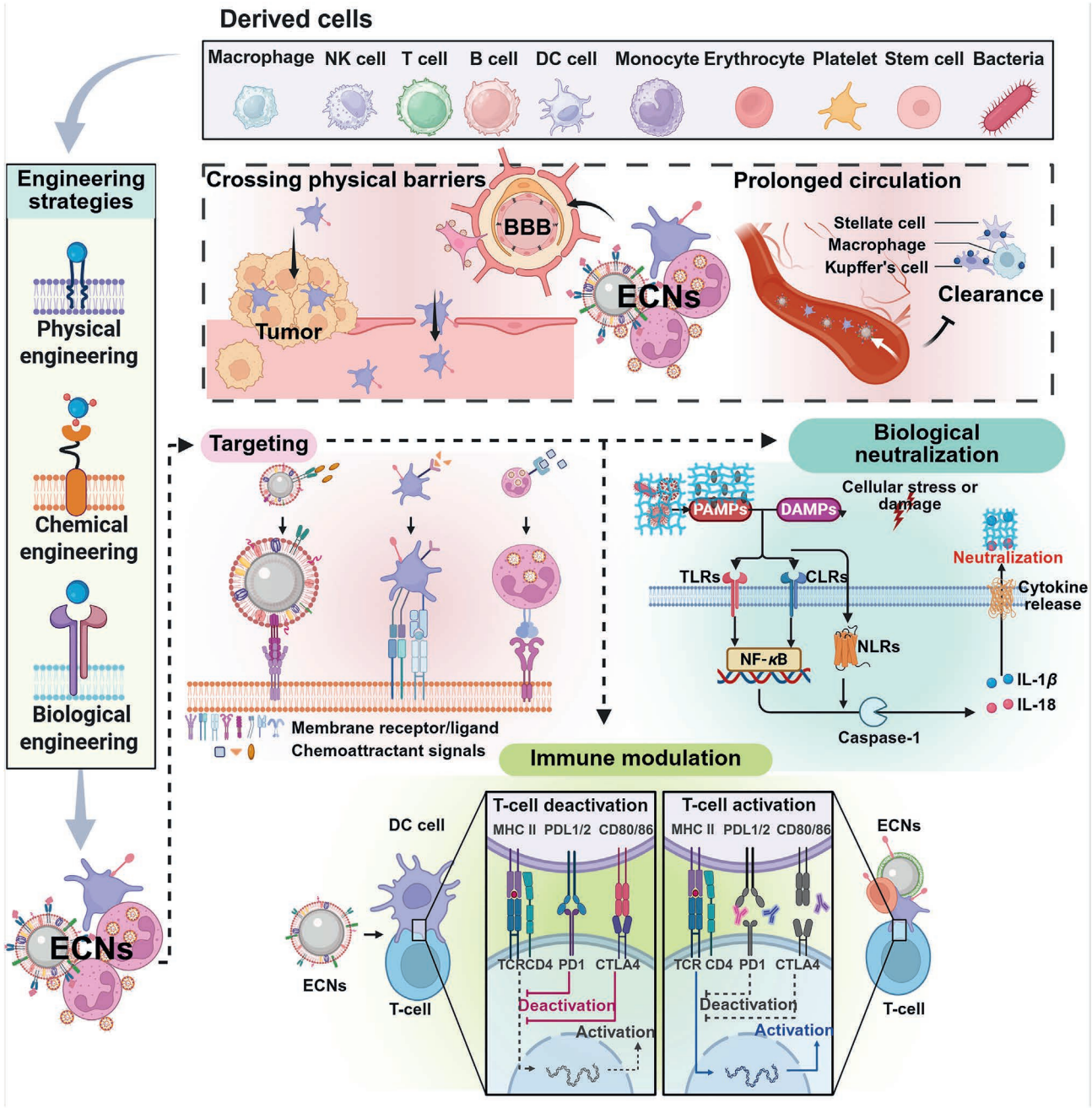

Figure 1 Schematic of preparation, advantage and therapeutic mechanism of ECNs. ECNs facilitate active or passive transport across biological barriers *via* surface-anchored biomarkers. By mimicking the "self" signals of natural cell membranes, these carriers prolong systemic circulation time. Furthermore, they achieve targeted delivery to inflammatory sites through specific receptor-ligand recognition within the inflammatory microenvironment. High-affinity adsorption or competitive receptor binding enables the biological neutralization of inflammatory mediators, while phenotypic modulation of immune cells and regulation of signaling pathways contribute to immunomodulatory effects. Created with BioRender.com.

for mechanistic intervention and precise treatment of inflammatory diseases.

2.2. *The effector cells recruited to the inflammatory site*

Inflammatory cells, including neutrophils, macrophages, lymphocytes, platelets, and stem cells, regulate immune responses and tissue healing during inflammation or injury through highly coordinated actions involving specific surface receptors and secreted factors. These cells, which are demonstrated in Table 1, serve as the molecular basis for designing the targeting and functionality of ECNs.

The recruitment of macrophages to inflammatory sites relies on membrane-expressed chemokine receptors (*e.g.*, C−C chemokine receptor type 2, C-C chemokine receptor type 7, and C−X−C motif chemokine receptor 1) and adhesion molecules (*e.g.*, P-selectin glycoprotein ligand-1 (PSGL-1) and L-selectin), which determine the targeting and homing efficiency of the ECNs[12].

Table 1 The functions, membrane receptors, and targeting ligands of the effector cells recruited to the inflammatory site.

Type	Function	Membrane receptor	Targeting ligand
Neutrophils	Participation in innate and adaptive immune responses Phagocytosis, destruction, and clearance of microorganisms and apoptotic cells Antigen processing and presentation	CCR2, CCR6, CCR7, CCR8, CXCR1, CXCR2, CXCR4	P-selectin, PSGL-1
Macrophages	Recognize and phagocytose pathogens Antigen presentation Produce ROS and release the contents of cytotoxic granules Mediate tissue and cartilage destruction	CXCR1, CXCR2, L-selectin, VLA-4, PSGL-1, LFA-1, β2 integrin, $\alpha4\beta1$ integrin	VCAM-1, ICAM-1, CSF-1, ET-2
Lymphocytes	Antibody production Killing of infected cells or tumor cells Regulation of immune functions	CXCR3, CXCR5, CCR1, CCR4, CCR5, CCR6, CCR7, CCR10, CX3CR1, LFA-1, L-selectin, CLA, $\alpha4\beta7$ integrin, PSGL-1	VCAM-1, ICAM-1, GPCRs, CCL21, MAdCAM-1, E-selectin
Platelets	Thrombus formation and hemostasis Recruitment of immune cells to sites of inflammation Activation of or adhesion to cells at inflammatory sites	TLR family, PSGL-1, PF4, CCL5, αIIbβ3, RANTES	P-selectin, PSGL-1, CD11b/CD18, αMβ2, TREM-1
Stem cells (MSCs)	Regulation of immune homeostasis and remodeling Differentiation Homing to injured tissues Modulation of immune responses	CXCR1, CXCR2, CCR1, CCR2, CXCR4, CX3CR1/fractalkine, CCR7/CCL21, integrin	VCAM-1

Macrophages exhibit M1/M2 phenotypic plasticity, and engineered modulation of their polarization state can dynamically regulate the inflammatory process, enabling personalized anti-inflammatory or pro-repair functions[13].

Neutrophils possess the ability to respond to inflammatory signals *via* membrane surface receptors such as C−X−C motif chemokine receptor 4 (CXCR4) and C−X−C motif chemokine receptor 2, making them ideal candidates for early inflammation targeting[14]. During infiltration, adhesion, and activation, neutrophils release various pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemoattractants, and dominate acute immune responses through reactive oxygen species production, neutrophil extracellular traps release, and phagocytosis. Their high expression of homing molecules enables ECNs to traverse endothelial barriers and achieve precise localization.

T cells and B cells mediate anti-inflammatory or pro-inflammatory processes through antibody production, cell-mediated cytotoxicity, and immune response regulation. The inflammatory homing of lymphocytes depends on interactions involving G protein-coupled receptor responsive to chemokines (including CC, CXC, C, and CX3C ligand families), T-cell receptors, and co-stimulatory molecules. T cell subsets secrete various cytokines (*e.g.*, IFN-γ, IL-10, TGF-β) that regulate inflammation, and can be utilized in the design of ECNs either to activate immunity or to modulate the local immune microenvironment[15,16].

Beyond their roles in hemostasis and thrombosis, platelets participate in inflammatory immune responses by releasing cytokines such as platelet factor 4 and RANTES/CCL5, thereby recruiting inflammatory cells to facilitate wound healing and inflammation resolution. Platelets exhibit unique advantages in inflammatory adhesion and delivery platform construction through molecules such as TLRs and P-selectin[17]. As a source of biomimetic materials, platelet membranes not only confer excellent circulatory stability to ECNs but also enable targeting of activated endothelium and inflammatory sites, enhancing local drug delivery efficiency.

Stem cells, such as mesenchymal stem cells, provide an ideal engineering platform for the development of ECNs in tissue repair and immunomodulatory therapy, owing to homing receptors like CXCR4 and $\alpha4\beta1$ integrin and their broad immunoregulatory functions[18]. Their low immunogenicity and paracrine regulatory capabilities have been demonstrated to contribute to inflammation resolution and tissue regeneration.

The inflammatory microenvironment constitutes a highly coupled dynamic network involving multiple cells, factors, and signaling pathways. Dysregulation of any single cell or signaling pathway may be compensated for by redundant mechanisms of other components, leading to persistent or exacerbated inflammation. Consequently, single-target agents often fail to effectively intervene in complex inflammatory responses due to pathway substitution or immune rebound. ECNs can replicate the multi-level synergistic regulation of inflammatory networks by their source cells, enabling simultaneous intervention at multiple targets for more precise and comprehensive modulation of inflammation. Various effector cells play indispensable roles in inflammatory responses through their unique biological functions, homing capacities, and immunomodulatory mechanisms. These cells not only serve as direct "target cells" for therapy but also provide a rich "material library" for ECNs.

2.3. Inflammatory mediators

Inflammatory cells release various acute inflammatory mediators, including vasoactive amines, peptides, chemokines, cytokines, proteases, as well as reactive oxygen and nitrogen species (RONS)[19]. Vasoactive amines and peptides can induce vasodilation and increase vascular permeability[20]. This vascular response

facilitates the infiltration of plasma rich in chemokines and cytokines in sites of inflammation, amplifying local inflammatory reactions[21]. Cytokines, as key signaling molecules, are generally categorized into pro-inflammatory and anti-inflammatory types. IL-1β, IL-6, TNF, and IFN-γ participate in various phases of the inflammatory response and activate core inflammatory signaling pathways such as the NF-κB pathway and JAKs−STAT pathway to amplify inflammatory effects, further triggering the continuous activation of endothelial cells, neutrophils, lymphocytes, and leukocytes, and promoting the expansion of inflammation. On the other hand, IL-4, IL-10, and TGF-β inhibit inflammation and maintain immune balance through multiple mechanisms[22]. RONS, an important component of pro-inflammatory signaling, include oxygen and nitrogen free radicals such as superoxide (O_2^-), hydroxyl (OH), and nitric oxide (NO)[23,24]. These molecules initiate lipid peroxidation and contribute to oxidative stress and tissue injury. When RONS are overproduced, uncontrolled oxidative stress occurs, causing further cellular and tissue damage. Additionally, proteases mediate extracellular matrix (ECM) remodeling by degrading ECM constituents and regulate the release of pro-inflammatory factors such as TNF-α and IL-1β, thereby directly participating in and promoting the inflammatory response. The interactions and cascade effects among various acute inflammatory mediators collectively regulate the initiation and progression of inflammation. Therefore, the direct elimination or competitive sequestration of excessive inflammatory mediators to inhibit their pathological effects constitutes a mechanistic therapeutic strategy that guides the inflammatory microenvironment toward resolution and restoration of homeostasis.

ECVs are membranous vesicles secreted by cells that carry various bioactive molecules, including proteins, lipids, nucleic acids, and polysaccharides, and mediate intercellular signaling[25]. Not only do they directly clear and sequester excessive inflammatory factors through mechanisms such as receptor neutralization and adsorption, thereby inhibiting the inflammatory amplification cascade, but ECVs also effectively alleviate oxidative stress, reduce excessive immune cell infiltration, induce macrophage polarization toward the M2 phenotype, and enhance the immunosuppressive function of Tregs. Consequently, they facilitate wound regeneration and tissue healing (*e.g.*, by stimulating collagen production and suppressing fibrosis), comprehensively enhancing the self-regulatory and injury-repair capabilities of the body. Furthermore, ECVs can precisely modulate inflammation-related signaling pathways, enabling multidimensional remodeling of the immune microenvironment[26]. As a result, ECVs are regarded as a unique class of inflammatory mediators with considerable clinical translation potential: they can act both as "decoy" molecules that adsorb and neutralize pathological inflammatory factors, and as dynamic regulators that participate in and orchestrate complex inflammatory and immune responses[27]. In the design of systemic inflammation interventions and precision therapeutic strategies, the application of ECVs for efficient clearance of inflammatory mediators, precise regulation of signaling pathways, and synergistic functional optimization with key immune cells such as macrophages and regulatory T cells (Tregs) holds promise for providing new theoretical foundations and technological breakthroughs in the management of major inflammatory diseases.

In summary, the inflammatory microenvironment constitutes a complex and dynamic process encompassing the cascade release of danger signals (*e.g.*, PAMPs, DAMPs), the synergistic regulation of diverse inflammatory cells, and the secretion of various mediators and extracellular vesicles. These precisely regulated biological processes not only drive the initiation and progression of inflammation but also establish specific physiological barriers that limit the efficacy of conventional therapeutic strategies. For instance, during acute inflammation, the overexpression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) on the vascular endothelial surface leads to the massive non-specific recruitment of immune cells, including neutrophils and monocytes. This subsequently alters local blood flow and tissue permeability, thereby affecting drug delivery and distribution[28]. The excessive and fluctuating release of cytokines, including TNF-α and IL-6, forms a complex and dynamic cytokine network, which may trigger systemic inflammatory responses or cytokine storms, making precise regulation challenging. Furthermore, chronic inflammation is often accompanied by aberrant vascular permeability, which not only exacerbates local edema but also impedes the effective accumulation and retention of therapeutic agents at target sites[29]. More importantly, nanocarriers or drugs in circulation are susceptible to rapid clearance by phagocytic cells of the mononuclear phagocyte system, significantly reducing drug bioavailability and therapeutic efficacy[30]. Collectively, a series of challenges, ranging from dynamic abnormalities of immune cells, alterations in tissue barriers, to enhanced immune clearance, highlight the necessity of developing advanced delivery systems capable of actively adapting to and modulating the complex inflammatory microenvironment.

In this context, there is an urgent need to develop advanced drug delivery platforms that can specifically recognize pathological components of inflammation, dynamically respond to local biochemical signals, and precisely regulate cell−cell and cell−matrix interactions. Engineered cell-mimetic nanoplatforms, by mimicking the surface markers, receptor−ligand recognition mechanisms, and functional attributes of natural cells, offer a promising strategy to address the aforementioned challenges. In the following sections, the rational construction and optimization of ECNs through cutting-edge cell/cell membrane engineering technologies will be elaborated in detail, aiming to overcome the unique barriers within the inflammatory microenvironment and ultimately achieve precise therapy for inflammation-related diseases.

3. Engineered cell/cell membrane modification strategies for inflammation

Therapeutic platforms derived from cells or cell membranes have opened new avenues for the design of targeted nanotherapeutics against inflammation. Central to this progress is the ability to modulate not only the structure and function of cell membranes, but also the intrinsic biological properties and phenotypic behaviors of whole cells through various engineering strategies. Such approaches can confer novel cellular surface properties to achieve targeting or immune evasion, while directly regulating cellular activities, such as sustained macrophage polarization or programmed cytokine release. As illustrated in Fig. 2 and Table 2, physical engineering leverages the fluidity of the natural lipid bilayer to enable flexible and rapid modifications while largely preserving membrane integrity and bioactivity. Chemical engineering, on the other hand, facilitates specific conjugation of functional molecules—including therapeutic carriers and targeting ligands—*via* stable covalent bonds or selective affinity

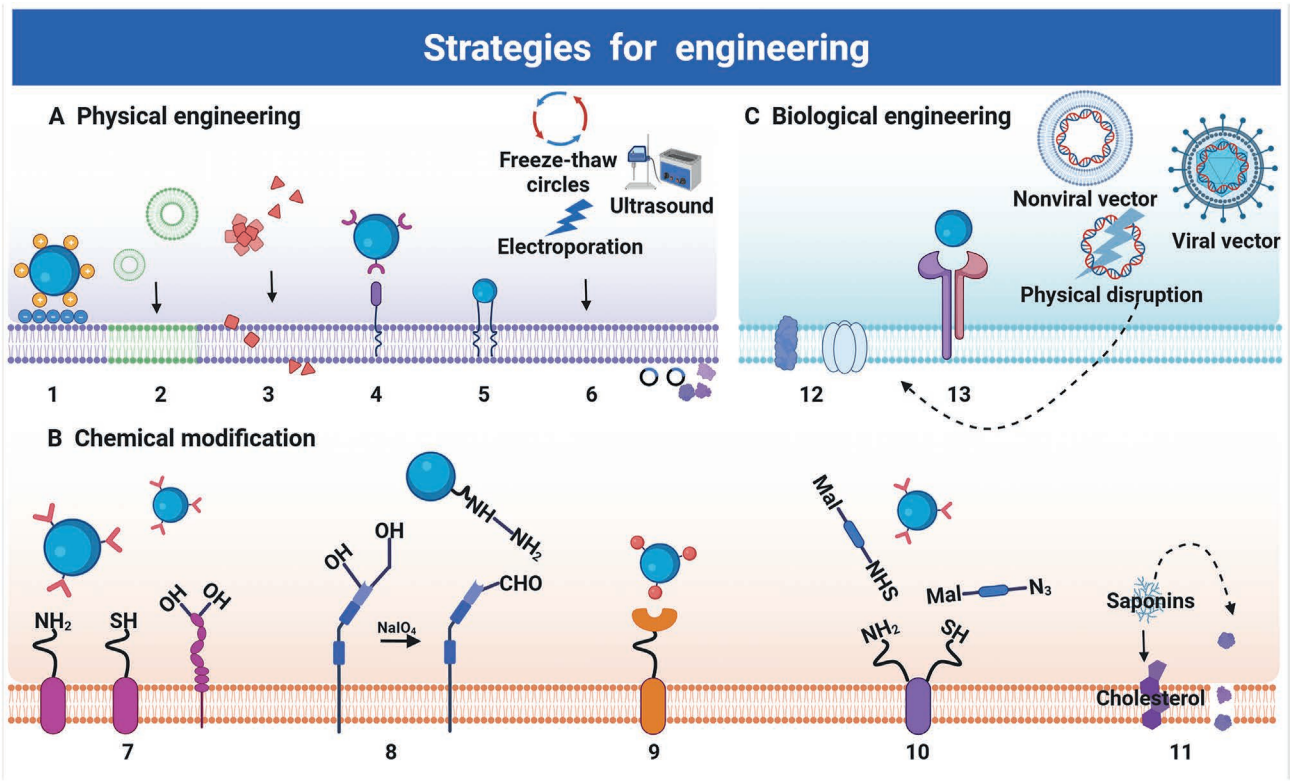

Figure 2 Strategies for cell and cell membrane engineering. The main modification strategies include (A) physical, (B) chemical, and (C) biological engineering. (1) Electrostatic interaction. (2) Membrane fusion. (3) Active encapsulation methods. (4) Insertion of exogenous groups/receptors into cell membranes followed by binding with ligand-conjugated molecules. (5) Aliphatic chain and hydrophobic molecule insertion. (6) Passive encapsulation methods. (7) Direct covalent conjugation of molecules with primary amine, thiol residues, and hydroxyl on cell membranes. (8) With the help of sodium periodate, the abundant sialic acid residues on the cell membrane are converted into aldehyde groups, coupling the amino groups on the surface of the molecule. (9) Introduction of biotin/antigen/receptor reactive groups onto cell membranes and binding with streptavidin/antibody/ligand protein functionalized molecules. (10) The bifunctional linker is introduced to the surface of the cell membrane and binds to the molecule. (11) Saponin can interact with membrane cholesterol, selectively removing it and leaving holes in the membrane to load cargo. (12) Direct genetic introduction of transgene protein expression on the cell membranes. (13) Genetic introduction of "bio-orthogonal" reactive groups/receptors onto cell membranes followed by binding with molecules. Created with BioRender.com.

interactions, allowing precise control over payload loading and surface functionality. Biological engineering, encompassing genetic modification and bioorthogonal chemistry, enables the introduction of novel functions and programmable features while retaining the intrinsic activity of cells or membrane structures. These complementary strategies significantly expand the functionality of ECNs, empowering them in disease targeting, drug delivery, and immune modulation. Accordingly, the following sections will systematically discuss these engineering modalities, elucidating their mechanisms of action, innovative features, and translational potential for next-generation anti-inflammatory therapy.

3.1. Physical engineering

The physical engineering methods for cells and cell membranes are primarily based on the fluidity and lipid structure of the phospholipid bilayer of cell membranes. These methods encompass electrostatic interactions, cell surface anchoring techniques, and cell membrane hybridization technologies[61].

The sialic acid residues of glycoproteins on the cell membrane surface endow the membrane with a negative charge[62], making electrostatic interactions a viable cell membrane modification strategy. This approach is mild and causes minimal side effects to the cells, thus helping to preserve the biofunctions of living cells. For example, polyphenol-functionalized nanocomposites can be linked to the cell membrane surface through electrostatic interactions between the hydroxyl groups of polyphenols and the polar head groups of membrane lipids, as well as hydrophobic interactions between the aromatic structures of phenolic hydroxyl and the fatty acid chains of lipids[31]. Similarly, cationic poly(-diallyldimethylammonium chloride)[32] and poly-L-lysine[33] can also be electrostatically adsorbed onto the cell surface.

Cell membrane anchoring strategies utilize hydrophobic and other non-covalent interactions to anchor lipid molecules onto the cell membrane surface. This method relies on the unique fluidity and phospholipid bilayer structure of the cell membrane[63]. In practice, lipid-anchoring molecules are inserted into the outer layer of the phospholipid bilayer and are conjugated with functional molecules that possess therapeutic or targeting abilities, thereby decorating the cell membrane. This approach is characterized by not affecting membrane protein function or interfering with normal cellular physiological activities, and the modification process is mild and rapid. Zhang et al.[34] designed biomimetic nanoparticles [MΦ-NP(L&K)] featuring a "lure-and-kill" mechanism to target phospholipase A2 (PLA2), a pathogenic factor in

Table 2 Representative strategies for engineered cell-biomimetic nanosystems.

Strategy	Mechanism	Example	Source
Physical engineering			
Electrostatic adsorption	Electrostatic interaction	Polyphenol-functionalized nanocomplexes/ PDADMAC/nanogel → Cell membranes	31−33
Hydrophobic insertion	Aliphatic chain and hydrophobic molecule insertion	Melittin and MJ-33 → macrophage membranes Functional tetrazine groups → T cell membranes	34,35
Membrane fusion	Membrane fusion	Cell membranes/bacterial membranes/fungal membranes/liposomes → Membrane fusion	36
Membrane coating technology	Cell membrane-coated nanoparticles	Macrophage membrane-coated nanocages/hydrogels	37,38
Active encapsulation methods	The fluidity of the lipid bilayer membrane	Curcumin was loaded into AD-MSCs derived exosomes by co-incubation	39
Passive encapsulation methods	The membrane was opened transiently and reversibly using mechanical techniques to allow compounds to diffuse	Compounds were diffused into the vesicle using sonication, freeze−thaw cycles, or electroporation	40-42
Chemical modification			
Chemical reaction	Amine-based reaction	Carboxyl-functionalized molecules (EDC, NHS, or NHS-sulfo pre-activation) + amino groups of membrane → amidation reaction	43−47
	Thiol-based reaction	Maleimide-functionalized molecules + thiol groups of T cell membrane → Michael addition	47, 48
	Diol-based reaction	Phenylboronic acid-modified nanoparticles + *cis*-diol group of polysaccharide of yeast cells → Boronate ester bonds.	49
	Cholesterol-based reaction	Saponin + membrane cholesterol → removing it and leaving holes in the membrane	50
	Reductive amination	Cell membranes treated with sodium periodate + hydrazide groups of nanoparticle surfaces → hydrazone bonds.	51
Biotin-avidin, receptor-ligand, or antibody-antigen interactions	Biotin-avidin interaction	Biotinylated cells + Neutravidin-modified nanoparticles Biotinylated erythrocytes + avidin-modified tPA	52,53
	IgG + anti-IgG antibodies	IgG-expressing monocytes + anti-IgG antibodies-modified nanodiscs	54
	NK1.1 + anti-NK1.1 antibody	NK1.1-expressing DC + anti-NK1.1 antibody and TRAIL-modified liposomes	55
	Hyaluronan + CD44	B cells-expressing CD44 ligand + hyaluronan modified-polymeric microtubes	56
Biological engineering			
Genetic engineering	Direct genetic introduction of transgene protein expression into the cell	MSCs overexpress membrane proteins such as CXCR4, CCR1, SLeX, and CAM-1. C1498 cells or leukocyte membranes overexpress VLA-4.	57−59
	Enzyme-mediated reaction	Sortase A cleaves the membrane-inserted LPETGG motif and ligates peptides with N-terminal sequences.	60

pancreatitis. In this design, melittin and MJ-33 were anchored into the outer layer of the macrophage membrane, serving as a lure and inhibitor of PLA2, respectively. PLA2 produced by pancreatic acinar cells is a key pathogenic factor of acute pancreatitis. The macrophage membrane, modified by lipid-anchored melittin and MJ-33, not only lured and neutralized PLA2 but also eliminated the toxicity of free melittin and MJ-33, thereby effectively suppressing the inflammatory response. This lipid anchoring strategy of the cell membrane offers a guiding strategy for PLA2-mediated inflammatory diseases.

In addition, the anchored lipid can be further modified with other drug molecules or nanoparticles through chemical conjugation or ligand−receptor biorecognition. Researchers have used cell surface anchoring techniques to construct engineered T-cells[35] by inserting functional tetrazine groups into the cell membrane and then modifying the surface with liposomal Ava containing bicyclo[6.1.0]nonyne groups *via* click chemistry. The liposomal Ava increased the cholesterol content in the T cell membrane, thereby promoting rapid TCR clustering and sustained T cell activation. This strategy demonstrated excellent anti-tumor effects in mouse models of melanoma and glioblastoma. The study validated the feasibility of cell surface anchoring engineering for customized cell therapy and drug/antibody combinations. More importantly, it broadens the application scope of nongenetic T cell engineering strategies, which can be applied to multiple cell types.

To achieve multiple targeting functions or immunoregulatory mechanisms, strategies have been developed to construct multifunctional hybrid membrane carriers by fusing membranes from different cell types[64]. For instance, Dehaini et al.[36] innovatively fused erythrocyte membranes with platelet membranes, not only

endowing the carrier with excellent biocompatibility but also preserving the long-circulating capability properties of erythrocytes and the targeting ability of platelets. This approach also offers a novel method for integrating targeting delivery, immunomodulation, and detoxification functions into a comprehensive system. Besides erythrocyte and platelet membranes, other biological membranes, including those derived from leukocytes, macrophages, T cells, B cells, cancer cells, stem cells, and even bacteria and fungi, have been explored as membrane material sources. Additionally, liposomes have been introduced to fuse with cell membranes, promoting the encapsulation and controlled release of small molecules. The fusion of vesicles derived from erythrocyte membranes with cholesterol enhanced the encapsulation efficiency of the chemotherapy drug doxorubicin and the antibiotic vancomycin, enabling pH-responsive drug release[65]. The combination of NK cell membranes with liposomes formed NKsomes, which inherit the natural immune surveillance and tumor-targeting capabilities of NK cells for targeted delivery of doxorubicin[66]. Cell membrane-coated nanoparticles not only retain the targeting specificity and biocompatibility of the source cells but also combine the advantages of nanoparticles, such as high drug-loading capacity, controlled release, and diverse material options, thereby achieving precise and efficient drug delivery and therapy. The main techniques for membrane coating include: (1) physical extrusion, (2) sonication, (3) microfluidic sonication, (4) electroporation[67]. Macrophage membrane-coated gold-silver nanocages (GSNCs) exploit inherited TLR2/4 for pathogen and endotoxin adsorption. Bacterial preincubation of source macrophages increased the expression of TLR2 and TLR4 on the derived membranes, enhancing binding to Gram-positive/negative ligands and improving lesion accumulation in infected tissues. The macrophage membrane-coated gold-silver nanocages core afforded photothermal effect and unique structure (hollow interiors and porous walls), where antibacterial drugs can also be loaded with an on-demand controlled release under near-infrared light. Importantly, the macrophage-membrane-coated nanocages further have excellent immune evasion[37].

In addition to modifying the surface of ECVs membrane, the efficient loading of drugs (compounds, nucleic acids, peptides, proteins, etc.) into ECVs by engineering methods and the joint delivery of multiple drugs have become a key strategy to improve their therapeutic efficacy. According to the hydrophilic/hydrophobic properties of drugs, engineering loading is mainly divided into two categories: passive encapsulation and active encapsulation.

Passive encapsulation methods primarily include direct co-incubation and donor cell pretreatment. The co-incubation method typically involves incubating the drug to be delivered with ECVs under specific temperature and pH conditions, enabling loading through membrane diffusion of small molecular compounds. This approach is suitable for lipophilic or certain small hydrophilic molecules. For instance, Xu et al.[39] utilized the co-incubation method to load curcumin into adipose-derived mesenchymal stem cell extracellular vesicles, significantly enhancing its synergistic effects. This strategy demonstrated excellent inhibition of oxidative stress in osteoarthritic cartilage and protection against chondrocyte apoptosis, showing great therapeutic potential for repairing articular cartilage defects. Another common strategy involves pretreating donor cells (*e.g.*, with drug incubation or nanoparticle labeling) to enable the embedded cargo to be released into extracellular vesicles *via* exocytosis. For example, umbilical cord mesenchymal stem cells labeled with Fe_3O_4 nanoparticles can release extracellular vesicles containing magnetic nanoparticles. These vesicles accumulate in the injured area under magnetic guidance *in vivo* and effectively promote the expression of skin repair-related proteins, offering a novel therapeutic approach for skin wound healing[68]. However, passive encapsulation generally suffers from low loading efficiency, high risk of drug leakage, and difficulty in effectively delivering macromolecules, which limit its broad application in complex disease treatments.

For hydrophilic macromolecular cargos, more efficient active encapsulation techniques have emerged as mainstream approaches, including physical methods such as sonication, electroporation, and freeze-thaw cycles. These techniques transiently and reversibly disrupt the membrane structure of ECVs, significantly facilitating the entry of macromolecular drugs into the vesicular lumen[69]. Among these, the sonication method is widely employed in drug loading of membrane-coated systems due to its operational simplicity and high drug loading efficiency[40]. However, the sonication process may compromise system stability and result in partial drug attachment only to the ECVs surface rather than internalization, thereby affecting delivery efficiency. Electroporation is suitable for the delivery of biological macromolecules such as RNA, with the advantage of rapid operation; however, it poses potential risks to ECVs membrane integrity and the activity of surface functional proteins, and its reliance on specialized equipment increases implementation and maintenance costs[41]. The freeze-thaw cycle method achieves intrinsic loading of drug molecules through multiple cycles of slow freezing and rapid thawing, thereby reducing sustained damage to the membrane structure. Utilizing this method, Khalid et al.[42] efficiently encapsulated hydroxyurea into human plasma-derived ECVs to improve breast cancer treatment efficacy, demonstrating favorable biocompatibility. Although this method requires no specialized equipment, it is time-consuming, and repeated temperature variations may cause partial structural damage to ECVs. Overall, active encapsulation methods offer higher loading efficiency and broader applicability compared to passive strategies, but they are also associated with limitations such as membrane damage, reduced stability, and potential toxicity. There is an urgent need to optimize operational parameters and standardize the processes. In the future, standardized, efficient, and low-damage active engineering technologies for ECVs will further unlock their delivery potential, laying a solid foundation for the large-scale production and clinical translation of novel EV-based therapeutics.

Overall, physical engineering strategies are characterized by simple, mild, and efficient preparation processes. These techniques do not alter the chemical structure of proteins or glycans on the cell membrane, nor do they interfere with the natural receptor−ligand interactions. As a result, compared with other cell modification methods, physical engineering strategies cause less damage to cell membranes and are highly compatible with a variety of cell types. However, the instability of inserted molecules may limit the long-term efficacy of physical engineering approaches, and standardized, efficient, and minimally damaging engineering techniques remain areas requiring further optimization for future translational research.

3.2. Chemical modification

The chemical engineering strategies are mainly based on the primary amine and thiol residues of membrane-associated proteins, as well as the hydroxyl groups of polysaccharides, which serve as reactive groups for various covalent coupling reactions.

According to the complexity of the reaction steps, these methods can be classified into one-step coupling and multi-step coupling approaches.

Carboxyl group-containing functional molecules activated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) can be covalently conjugated to amino residues on cell membranes *via* amidation reactions[43]. Studies have shown that antigen-presenting cells treated with EDC exhibit unique immunotolerant properties when interacting with T cells[44]. In addition, carboxyl-containing functional molecules can be activated by *N*-hydroxysuccinimide (NHS) or *N*-hydroxysulfosuccinimide (NHS-sulfo), allowing them to bind to amino groups on the cell membrane surface[45]. Giraldo et al.[46] employed an NHS pre-activation method to graft poly(-ethylene glycol) onto cell surfaces, creating a spatial barrier that significantly reduced inflammatory responses and immune recognition, suggesting potential applications in transplantation microenvironment modulation. Beyond amino groups, cell membranes of erythrocytes, monocytes, leukocytes, hematopoietic stem cells, and mesenchymal stem cells are rich in thiol residues, allowing coupling with maleimide-functionalized molecules[48]. For hydroxyl modifications, phenylboronic acid functional molecules can rapidly react (usually within seconds) with *cis*-diol groups on membrane surface polysaccharides to form boronate ester bonds. This reaction proceeds under mild conditions and does not interfere with the structure and function of membrane proteins, minimizing impacts on cell physiology[49].

In addition to membrane-associated proteins, membrane cholesterol also serves as a critical site for engineered modification. Detergents, such as saponins, can specifically bind to membrane cholesterol, selectively deplete cholesterol, and form controllable pores in the membrane structure, thereby enabling precise regulation of membrane permeability[70]. Based on this mechanism, ECVs and engineered hybrid membranes can achieve mild and efficient cargo loading while preserving membrane integrity and bioactivity[50]. However, it should be noted that residual chemical reagents during the loading process may affect subsequent experimental results and biosafety.

However, most functional molecules cannot be directly conjugated to the cell surface *via* a single-step reaction and instead require multi-step reactions. The NHS and maleimide groups of succinimidyl-[(*N*-maleimidopropionamido)-diethyleneglycol] ester facilitate the conjugation between amino-rich cell membranes and thiolated peptides or proteins[71]. Utilizing these functional groups as bioorthogonal handles, recombinant human hyaluronidase PH20 was conjugated to erythrocytes to construct erythrocyte membrane-based carriers possessing both hyaluronidase activity and prolonged systemic circulation[47]. These carriers demonstrated efficient diffusion in hyaluronic acid-rich ECM and exhibited targeting and imaging capabilities toward hyaluronan-enriched inflammatory atherosclerotic plaques. Such bifunctional linkers can also be constructed with alternative functional groups, such as azide, enabling the specific conjugation of two or more protein molecules onto cell membranes to enhance biological effects. Another strategy for introducing chemically reactive groups onto cell membranes is by oxidizing sialic acid residues on the membrane to aldehydes using sodium periodate. These aldehydes can then react with hydrazine groups on nanoparticle surfaces to form Schiff bases, which are subsequently reduced by sodium cyanoborohydride to generate stable secondary amine bonds[51].

The incorporation of biotin into cell membranes *via* chemical reactions enables stable conjugation with functionalized molecules or nanoparticles through the specific recognition between biotin and avidin/streptavidin, demonstrating high specificity and stability[52,53]. In addition to biotin-avidin strategies, receptor-ligand binding and antibody-antigen recognition are also important methods for engineering cells or cell membranes. For example, biotin-conjugated IgG antibodies can specifically recognize and bind to monocytes[54]. Similarly, anti-NK1.1 antibodies modified onto liposomes through maleimide-thiol chemistry can bind NK cells expressing NK1.1, creating "super" natural killer cells that induce apoptosis in cancer cells and effectively inhibit the lymphatic spread of the primary tumor[55]. Furthermore, B cells can be functionally modified by exploiting the high affinity interaction between CD44 receptors on their surfaces and hyaluronic acid (HA)[56]. HA containing multilayers has also been used to interact with other cell types, including macrophages and T-cells[72,73]. The interaction between CD44 on B cells and HA plays a significant role in cell migration, adhesion, and signal transduction. This mechanism enhances the selective targeting capability of HA-modified carriers toward B cells, enabling the delivery of anti-inflammatory drugs or regulatory molecules to modulate B cell-mediated immune responses[56].

Chemical engineering strategies not only provide sustained pseudoautocrine stimulation for engineered cells to achieve targeted drug delivery but may also exert certain effects on cellular function and viability. For instance, thiol modification may induce activation of the apoptosis pathway or alter surface antigens, thereby triggering recognition and clearance by the immune system[74]. Additionally, crosslinkers such as EDC can activate carboxyl groups on the cell membrane and organelle surfaces, posing potential cytotoxicity risks. Chemical engineering approaches often face the following challenges: limited reaction specificity, which may impair the function of endogenous membrane proteins, and difficulty in completely removing residual chemical reagents, thereby interfering with intrinsic physiological activities of cells. Therefore, the selection of chemical modification strategies requires careful consideration of their therapeutic potential and safety profiles. In the future, integrating chemical modifications with physical or biological engineering methods may further enhance the precision and efficacy of cellular engineering, thereby facilitating the clinical translation of cell and cell membrane-based therapeutic platforms.

3.3. Biological engineering

Although membrane fusion technology takes into account the functions of membrane proteins from different cells, it also poses certain potential risks, such as the fusion of non-essential proteins and other molecules that may trigger immune responses. In addition, the efficiency and ratio of cell membrane fusion need to be carefully evaluated and validated. Therefore, biological engineering serves as an effective approach for introducing novel ligands, enabling precise functionalization of cells and cell membranes while maintaining their inherent properties[75]. Since this method does not require chemical reactions, it represents a highly promising strategy for large-scale production[76].

In most cases, cell functionalization primarily utilizes the outer membrane, so the ability to achieve surface expression of transgenes is highly desirable[67]. When overexpressing native membrane proteins, the gene sequence typically contains a transmembrane domain, which anchors the protein to the cell surface[77]. This straightforward approach has been widely applied across multiple fields, including the expression of virus-neutralizing antibodies[78], targeted homing to specific cells[57],

prolonging circulation time[79], and macrophage repolarization[80]. However, many applications require the expression of proteins not naturally bound to the cell surface[81]. To achieve this, the target gene can be fused with a signal peptide and a transmembrane domain derived from other proteins. Within target cells, the signal peptide directs the fusion protein to the cell membrane surface, while the transmembrane domain anchors the construct[82]. This approach enables precise control over the presentation of the desired construct, including its spatial orientation and distance relative to the cell membrane[81]. For instance, it has been employed for the presentation of heterologous antigens in vaccination[83], targeted drug delivery for precision therapy[84], and the modulation of immune response proteins[85]. The vectors involved mainly include viral vectors, non-viral vectors, and physical disruption methods.

Viruses can efficiently invade mammalian cells and integrate their genetic material into the host genome, enabling stable transgene expression. Consequently, viral vectors can directly deliver genes to target cells and achieve sustained high-level protein expression[86]. Furthermore, the use of self-inactivating viral particles enhances transduction safety by eliminating the risk of viral replication in host cells[87]. Retroviruses, which are RNA-based viruses, stably integrate their genetic material into the host cell genome through reverse transcription, providing persistent transgene expression[88]. With a packaging capacity of approximately 8 kb, they are suitable for genetic modification in various cell types, including primary neurons and immune cells[89]. Due to their ability to induce long-term transgene expression, retroviruses have been widely employed in cell transfection and clinical trials[90]. Compared with retroviruses, adenoviruses and adeno-associated viruses only mediate transient expression[91]. Their limited packaging capacity restricts their application in engineered cells and membrane development. Herpes simplex virus, as a neurotropic virus, can be used for the genetic engineering of nerve cells[92]. The safety of herpes simplex virus-based vectors has been improved through the partial deletion of genomic sequences.

Non-viral gene vectors refer to gene delivery systems constructed using nanoparticles, liposomes, and polymers. These systems are characterized by high safety, low immunogenicity, large payload capacity, ease of structural modification, and simple preparation. However, their transfection efficiency is generally lower than that of viral vectors[93]. Cationic reagents interact with nucleic acids to form complexes, enabling transient gene transfection[94]. Common approaches include calcium phosphate co-precipitation, liposome-mediated transfection, and polymer-based transfection. Nevertheless, non-viral vectors may lead to batch-to-batch variability in gene transfection[95], and exhibit certain cytotoxicity owing to their cationic properties. Therefore, safety considerations must be carefully evaluated when applying these systems.

Physical methods for introducing genetic material into cells by disrupting the cell membrane can circumvent certain limitations associated with viral and non-viral vectors[96]. These approaches can create transient pores on the cell membrane, thereby enabling efficient entry of exogenous genetic material into cells. Microinjection is a physical technique that directly delivers DNA or RNA into the cell nucleus[97], offering high efficiency and precision, while also facilitating the integration of genetic material into the host genome. However, this method is time-consuming, costly, and low-throughput[98]. Electroporation utilizes an electrical field to induce membrane poration and is suitable for nearly all cell types with high transfection efficiency. Notable applications include the introduction of chimeric antigen receptor (CAR) or programmed cell death protein 1 (PD-1) into T cells[82,99]. Nevertheless, this method may increase cell mortality and carries risks of exogenous nucleic acid degradation[100].

Bioengineering approaches can also introduce bioorthogonal reactive groups onto the cell membrane surface, providing specific sites for selective cellular engineering[58]. For instance, cell membrane-anchoring peptides with specific amino acid sequences serve as targeting receptors, enabling conjugation with functional molecules through enzymatic catalysis[101]. Pishesha et al.[60] integrated the LPETGG sortase motif onto erythrocyte membranes to generate cells stably expressing the LPETGG motif. Subsequently, sortase A specifically recognized and cleaved the threonine-glycine binding pocket, resulting in the formation of a thioacyl-enzyme intermediate. This intermediate is capable of covalently binding to any molecule, drug, or nanoparticle containing an N-terminal glycine sequence. Furthermore, the N-terminal polyglycine on cell membranes can bind Sortase A-pretreated acyl-enzyme substrate complexes, enabling further modifications. This bioorthogonal strategy provides an efficient and specific method for precise modification of cell membrane surface molecules, supporting applications in drug delivery, molecular labeling, and targeted therapy. By enhancing specificity and integrating with chemical and physical methodologies, bioengineering strategies can achieve precise customization of target cells and their membranes, which demonstrates significant research value in the modulation of inflammatory microenvironments and targeted therapy[102].

Bioengineering enables programmable and highly specific membrane modifications through genetic engineering or enzymatic methods, allowing for the introduction of novel functionalities at the cellular level. However, its translational scalability, efficiency, and biosafety are often constrained by technological throughput and regulatory requirements. The use of transgenic components or heterologous proteins in bioengineering may increase the risk of immune recognition, requiring rigorous evaluation.

As summarized in Table 3, a comparative analysis of existing strategies is briefly presented to comprehensively elucidate the rational selection and future translational prospects of ECNs. The optimal engineering approach should be selected based on the target application scenario, regulatory requirements, production scale, and the need to balance biological functionality with safety. In future developments, the integration of multiple strategies is expected to further enhance the therapeutic efficacy and adaptability of ECNs.

4. ECNs for inflammatory therapy

The effective treatment of such diseases necessitates precisely targeted interventions at multiple pivotal stages of the inflammatory cascade. Therapeutic strategies based on ECNs can be systematically categorized into three interrelated modalities, each addressing a critical aspect of inflammation management. Firstly, inflammation-targeting approaches exploit the surface properties and ligand−receptor interactions of ECNs to enable precise delivery to inflamed sites or activated immune cells, thereby providing a foundation for selective therapeutic intervention. Secondly, biological neutralization strategies achieve upstream control by directly sequestering or competitively binding inflammatory triggers and potentiators (such as PAMPs and excessive cytokines), thereby inhibiting the initial transmission of danger signals and halting the propagation of inflammation. Finally,

Table 3 Comparative analysis of engineering strategies.

Strategy	Advantages	Limitations	Typical Applications	Immunogenicity Potential
Physical engineering	Mild, preserves membrane structure, rapid, suitable for large-scale standardized production	Lower long-term stability, possible ligand loss, and relatively low drug loading efficiency	Delivery systems requiring rapid, large-scale production and high membrane integrity	Low
Chemical modification	Versatile, allows precise functionalization	Risk of residual reactants may alter protein function, requiring complex optimization to ensure clinical safety	Therapy demanding high targeting precision (tumor targeting, immunomodulation)	Moderate
Biological engineering	Allows programmable expression, high specificity, and introduction of novel functionalities at the cellular stage	Efficiency and safety may be limited, as it has high regulatory barriers and immunogenicity risks	Personalized treatments requiring long-term, stable expression of specific targeting molecules or signaling pathways	Variable (species/ source dependent)

immune modulation strategies leverage the ability of ECNs to interact with, reprogram, or restore the functional balance of key immune cell populations, ultimately steering the inflammatory microenvironment toward resolution and homeostasis. Collectively, these three therapeutic modalities constitute a rational, progressive, and mutually reinforcing framework-from targeted delivery and mechanistic neutralization to the recalibration of immune axes-that addresses distinct yet closely interconnected steps within the inflammatory network. In this section, we systematically discuss how the rational design of ECNs can be matched to specific mechanistic targets within the inflammatory microenvironment, thus advancing the paradigm from symptomatic relief to mechanism-driven precision therapy for inflammatory diseases.

4.1. ECNs for inflammatory targeting

Nanodrug delivery systems have been extensively studied for anti-inflammatory therapy[103]. However, significant challenges remain in overcoming biological barriers and achieving precise targeting and responsiveness to complex inflammatory microenvironments[104]. Inflammation-associated cells, such as neutrophils, macrophages, lymphocytes, platelets, and stem cells, can be recruited to inflammatory sites and regulate inflammation through multiple pathways. Engineered cells or cell membranes derived from these cells exhibit "self-recognition" properties. By loading drugs or nanoparticles into cells, conjugating them onto cell surfaces, or coating exogenous particles with cell membranes to form hybrid particles, biomimetic nano-delivery systems can be constructed. As detailed in Table 4, these systems endow drug delivery platforms with the inherent functions of their source cells, such as reducing monocyte phagocytosis, enhancing penetration across biological barriers, and achieving targeting at specific tissues, microenvironments, or even intracellular locations[119]. Such strategies may optimize drug distribution, metabolism, and clearance while minimizing off-target effects[120].

4.1.1. Targeting bacteria

Bacterial infections can lead to a wide range of respiratory, cutaneous, and systemic tissue infections, with severe infections by various bacteria potentially progressing to sepsis and septicemia[121]. However, the overuse of antibiotics has accelerated the emergence and spread of resistant bacterial strains[122]. Persistent bacterial infections and repeated antibiotic treatments further increase the risk of resistance and may induce systemic toxicity[123]. Therefore, the development of biomimetic nanodrug delivery systems with enhanced targeting capabilities and delivery efficiency has become a research priority, aiming to reduce systemic toxicity, improve the effective concentration of antimicrobial agents, and mitigate the occurrence of drug resistance.

Macrophages express PRRs, especially TLRs, which recognize PAMPs derived from exogenous microorganisms. As illustrated in Fig. 3[38], macrophage membranes pretreated with bacteria and used to coat nanocages or hydrogels have been shown to significantly enhance bacterial recognition[37,38]. Bacterial pretreatment facilitated the formation of TLR2−lipid A complexes and TLR4−LPS complexes, upregulating the expression of TLR2 and TLR4 on the macrophage membranes, thereby strengthening recognition of Gram-positive and Gram-negative bacteria, respectively. Furthermore, the zeta potential of macrophage membranes increases, reducing electrostatic repulsion against bacteria and markedly enhancing their affinity for bacterial cells and endotoxins. Differential TLR expression profiles induced by distinct bacterial stimuli enable macrophages to achieve highly efficient recognition of specific pathogens at infection sites, thereby providing a pathway for targeted therapy. The cationic antimicrobial peptide polymyxin B (PMB) not only binds to the cell membranes of Gram-negative bacteria through electrostatic interactions but also neutralizes LPS. PMB-modified erythrocyte-mimicking liposomes (P-RL) are selectively anchored to *Escherichia coli* and have demonstrated excellent therapeutic efficacy in the treatment of mixed-toxin infection induced by *E. coli*[105].

Bacteria employ various innate mechanisms to evade immune responses and counteract the effects of antibiotics. Even macrophages, which internalize bacteria, may fail to eliminate them and instead disseminate the pathogens systemically *via* the bloodstream, leading to more extensive infections. Many pathogenic bacteria have evolved immune evasion strategies by exploiting macrophages. Therefore, eradicating bacteria concealed within macrophages and preventing infection dissemination represents an effective therapeutic approach. Me-ANPs were developed by coating the membranes of J774A.1 macrophages onto nanoparticle cores loaded with the antimicrobial agents triclosan and ciprofloxacin[106]. Studies have shown that macrophage membranes from cells internalizing *Staphylococcus aureus* form positively charged, lysozyme-rich scar-like structures on their surfaces, whereas such structures are scarcely found on uninfected macrophage membranes. The negatively charged nature of Me-ANPs

Table 4 Summary of representative engineered cell-biomimetic nanosystems for inflammation targeting.

Therapeutic platform	Carrier cell	Engineering strategy	Targeting mechanism	Disease	Source
Targeting bacteria					
GSNCs	Macrophage	*S. aureus* pretreated macrophage	Bacterial pre-treatment → the expression of TLR2 and TLR4 ↑	*S. aureus* infections	37
P-RL	Erythrocyte	Fusion of erythrocyte membranes with PMB-modified lipids	Amino groups of PMB + phosphate groups of gram-negative bacteria	*E. coli* infections	105
Me-ANPS	Macrophage	Cell membrane-coated technology	Macrophages internalized *S. aureus* → positively charged scar regions + Me-ANPs	*Staphylococcus aureus* infection	106
Targeting inflammatory tissue					
VLA-DEX-NP	Wild-type C1498 cells	The plasma membrane-expressing VLA-4-coated technology	VLA-4 of C1498 cell + VCAM-1 of inflamed endothelial cells	Lung inflammation	57
MM-CEP/NLCs	Macrophage	Cell membrane-coated technology	CD11b/CD44 of macrophage + ICAM-1/P-selectin of inflamed endothelial cells	Acute lung injury	107
Macrophages with cellular backpacks	Macrophage	Discoidal microparticles adhere to the macrophages *via* binding of anti-CD11b antibodies to CD11b	CD11b/CD44 of macrophage + ICAM-1/P-selectin of inflamed endothelial cells	Brain inflammation	108
MPBzyme @ NCM	Neutrophil	HL60 cell membranes-coated technology	Macrophage-1 antigen/LFA-1 + ICAM-1	Ischemic stroke	109
PNV-CSCs	Cardiac stem cells and platelets	PEG mediated the fusion of platelet vesicles and cardiac stem cells	PNV-CSCs-expressing platelet recognition molecules + collagen-coated surfaces and endothelium-denuded rat arteries	Heart injury	110
Targeting tumor					
Nanoparticle-carrying T cells	T cells	Lipid nanocapsules were attached to T cells *via* click chemistry	CD62L/CCR7 of T cell + lymphoid tissues CXCR4 + chemokines released by tumor cells.	Lymphomas	111
NNPs	Neutrophil	Neutrophil membrane-coated nanoparticles	P-/E-selectin + PSGL-1 and integrin	Pancreatic carcinoma	112
Mø@bac	Macrophage	Chitosan-coated bacteria adhered to the macrophages	ICAM-1/VCAM-1 of tumor vasculature and stromal cells + α4 integrin	Subcutaneous 4T1 tumors	113
D-exo	HT1080 and HeLa	Exosomes were isolated from two cancer cell lines, and Doxil was loaded using passive encapsulation methods	The surface ligands + cognate adhesion molecules (such as CD44, galectin-3, and E-cadherin) of TCMs	Cancer	114
Nano BEADS	*S. Typhimurium* VNP20009	Nanoparticles were assembled onto *S. Typhimurium* VNP20009 *via* streptavidin-biotin interaction	Bacteria translocation and proliferation could be exploited to autonomously deliver nanotherapeutics to poorly vascularized and hypoxic tumor tissue	Breast cancer	115
N + R@PLTs	Platelets	Naphthalene diimide-bithiophene derivative was used to synthesize photothermal nanoparticles (N). N and R were introduced into platelets (PLTs)	Platelets + vascular endothelial damage areas at tumor sites.	Cancer	116
Dibenzocyclooctyne (DBCO)-cargo	Cancer cell	The DBCO−doxorubicin conjugate bound to azide-labeled cancer cells	The tetraacetyl-N-azidoacetylmannosamine of cancer cells was enzymatically cleaved to generate azide groups. The DBCO-doxorubicin + azide groups of cancer cells→ click chemistry	LS174T colon cancer, MDAMB-231 triple-negative breast cancer, and 4T1 metastatic breast cancer	117
Dox-MPK @ MDL	Macrophage	Dox-MPK@MDL was prepared by the extrusion method	α4 integrin + VCAM-1 of cancer cells	Lung metastasis of breast cancer	118

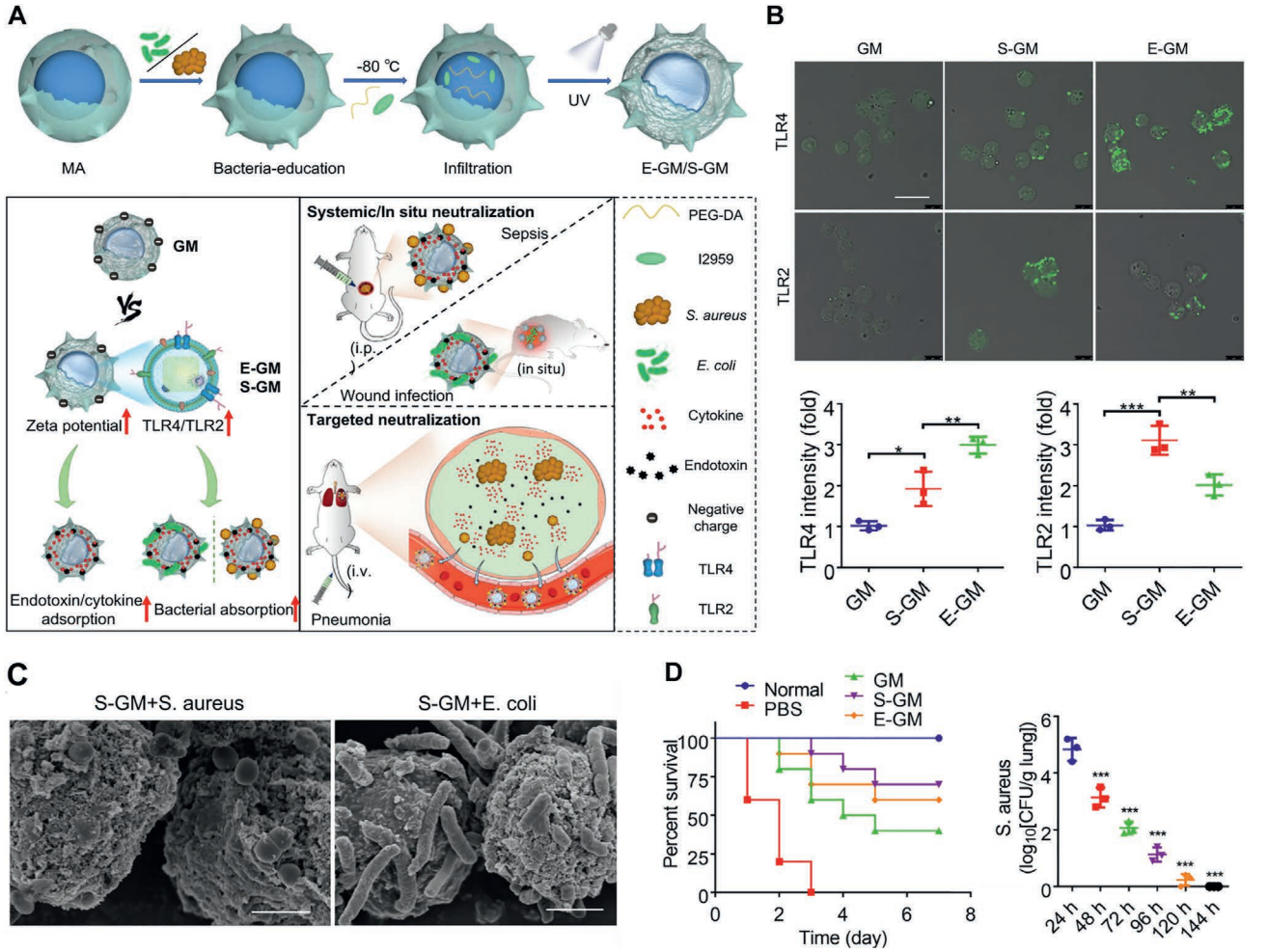

Figure 3 (A) Schematic representation of E−GM/S−GM designed to strengthen bacterium and endotoxin binding. (B) Fluorescence imaging and quantitative analysis of TLR2 and TLR4 production in GMs, S−GMs, and E−GMs. (C) Scanning electron microscopy images of *S. aureus* adsorption by S−GMs and *E. coli* adsorption by S−GMs. (D) The survival rate in 7 days and the changes in *S. aureus* numbers per gram of lung from S−GM-treated mice. Reproduced with permission from Ref. 38. Copyright 2023 Elsevier Inc.

enabled them to efficiently target these infected macrophages, where they were internalized and subsequently eliminated intracellular bacteria. This strategy, combining engineered cell membrane-based nanosystems with the antimicrobial biological characteristics of monocytes, provides a valuable reference for the clearance of intracellular pathogens.

4.1.2. Targeting inflammatory tissue

Oxidative stress and excessive inflammatory responses are common pathological features in the progression of numerous diseases. Inflammatory stimuli induce the overexpression of chemokines and cytokines, such as IL and TNF-α, leading to the upregulated expression of receptors, including VCAM-1, ICAM-1, and P-selectin on vascular endothelial cells. These molecules can be specifically recognized by ligands present on the surface of inflammation-associated cells, such as $\alpha4\beta1$ integrin and $\beta2$ integrin, thereby promoting the recruitment of inflammatory cells to the inflamed sites and regulating the inflammatory response through a series of downstream events[124]. For instance, macrophages accumulate at inflammatory sites *via* the specific binding of their surface ligands (*e.g.*, CD11b and CD44) to ICAM-1 and P-selectin expressed on inflamed endothelial cells. As illustrated in Fig. 4A−D, Lu et al.[107] constructed a macrophage membrane (MM)-coated nanostructured lipid carrier (NLC) loaded with cepharanthine (CEP), termed MM-CEP/NLC, which significantly enhanced the accumulation of CEP in pulmonary inflammatory regions. M2 macrophage-derived exosomes, by virtue of their retained source cell-specific surface ligands, can be targeted and accumulated in the lesion area[125], effectively delivering DNase 1 to clear neutrophil extracellular traps, thereby suppressing the release of inflammatory factors. Furthermore, M2 macrophage-derived exosomes induce the polarization of M1 microglia toward the M2 phenotype and significantly alleviate neuroinflammation by promoting the production of anti-inflammatory cytokines. This strategy demonstrates excellent therapeutic efficacy in reducing cerebral infarct volume, improving long-term neurological functional outcomes, and promoting blood−brain barrier (BBB) remodeling[126]. Additionally, C1498 cells that were genetically engineered to stably express $\alpha4\beta1$ integrin could specifically recognize VCAM-1 on inflamed endothelial cells, thereby improving homing to the inflammatory sites[57].

In addition, central nervous system targeted drug delivery across the BBB remains one of the major challenges in the

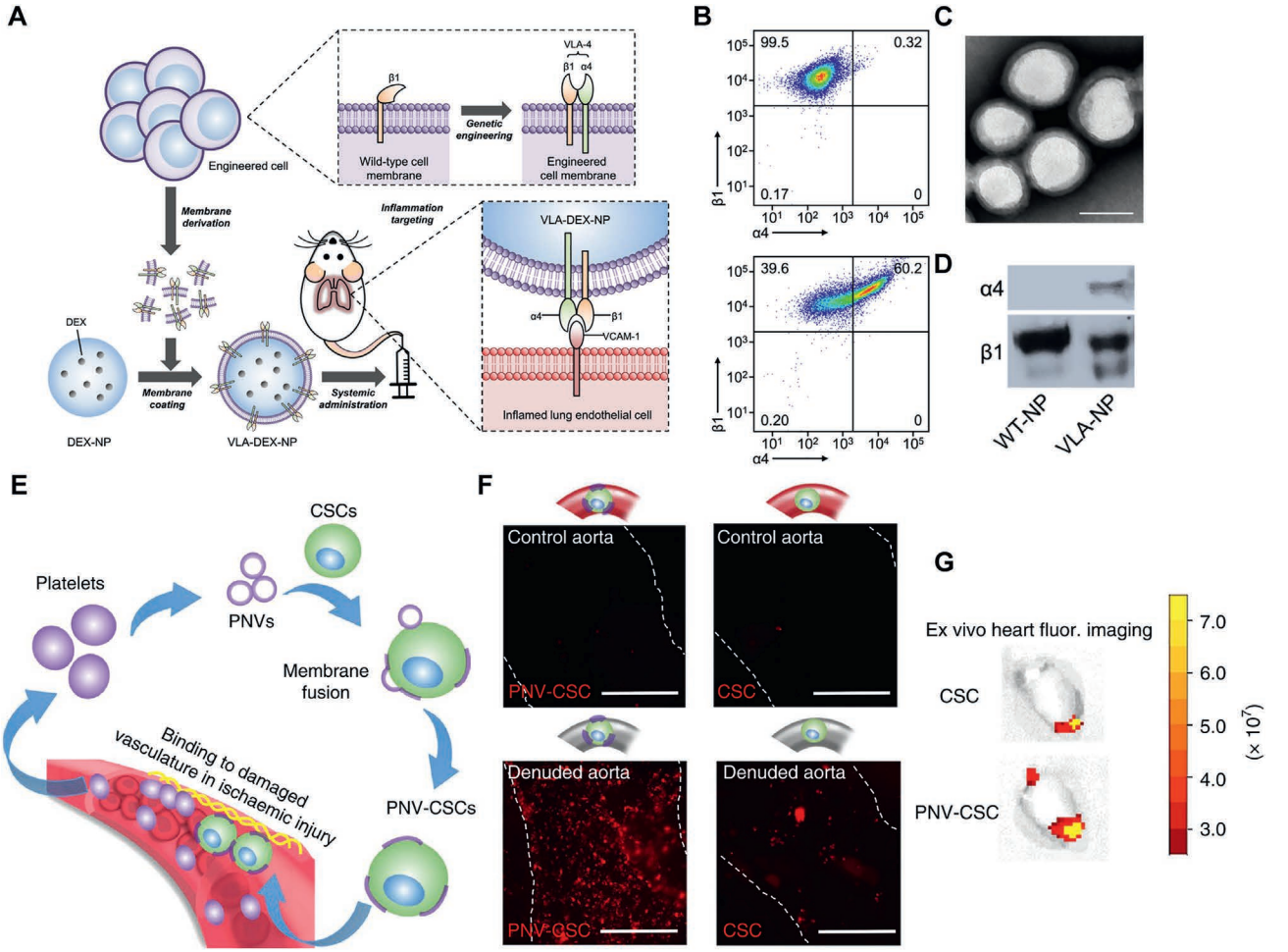

Figure 4 (A) Schematic representation of VLA-DEX-NP for targeted drug delivery to inflamed lungs. (B) Expression of integrins $\alpha 4$ and $\beta 1$ on C1498-WT and C1498-VLA cells. (C) Representative TEM image of VLA-NP. (D) Western blots for integrins $\alpha 4$ and $\beta 1$ on WT-NP and VLA-NP. Reproduced under the CC BY license (http://creativecommons.org/licenses/by/4.0/)[107]. Copyright 2021 the Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. (E) Schematic representation of PNV-CSCs designed to bind to damaged vasculature in ischaemic injury. (F) Representative fluorescent micrographs showing the adherence of DiI-labelled CSCs and PNV-CSCs on control or denuded aortas. (G) Representative fluorescent imaging of rat hearts after infusion of DiI-labelled PNV-CSCs or CSCs. Reproduced with permission from Ref. 110. Copyright 2018 Macmillan Publishers Limited, part of Springer Nature.

treatment of brain diseases. During inflammation, leukocytes are naturally recruited to the BBB and can transmigrate across the endothelium *via* extravasation and chemotactic processes. Researchers designed a polymer patch only a few hundred nanometers thick serving as a reservoir for the antioxidant enzyme catalase, which was electrostatically adsorbed onto the surface of macrophages to form a "backpack". In murine models of traumatic brain injury, intravenous injection of these macrophage "backpacks" enabled targeted delivery to inflamed brain tissues, where catalase was released, helping to maintain the M2 phenotype of macrophages and scavenge free radicals released by activated microglia, thus alleviating neuroinflammation[108]. In another study, Feng et al.[127] reported a neutrophil membrane-coated mesoporous Prussian blue nanozyme (MPBzyme@NCM) for ischemic brain injury therapy and neural functional recovery. Post-ischemic stroke, the expression of endothelial adhesion molecules such as ICAM-1 on inflamed cerebral microvasculature is significantly upregulated[109]. $\beta 2$ integrins (such as macrophage-1 antigen and lymphocyte function-associated antigen-1) on neutrophil membranes interact with these adhesion molecules, enabling targeted delivery to brain inflammatory regions[128]. MSCs are capable of homing to inflamed regions and exerting immunomodulatory effects[129]. Genetic engineering of MSCs to overexpress membrane proteins such as CXCR4, CCR1, PSGL-1, and SLeX can further enhance their homing to sites of inflammation[130]. For example, MSCs engineered to overexpress ICAM-1 display greater adhesion to activated endothelial cells *in vitro* and augmented homing efficiency in models of inflammatory bowel disease[59].

In addition, multiple molecules on the platelet surface (*e.g.*, GPVI, GPIV, GPIb, GPIX, GPV, and GPIIb/IIIa) play critical roles in the recruitment of platelets to inflammatory sites, enabling platelets to directly bind to damaged vascular endothelial cells. As illustrated in Fig. 4E–G, Tang et al.[110] fused platelet-derived vesicles with cardiac stem cells (CSCs) to generate modified CSCs expressing molecules associated with platelet adhesion and recognition functions. These engineered CSCs demonstrated selective binding to endothelium-denuded rat aortas, enhanced cardiac retention efficiency, and significantly reduced myocardial infarction size.

4.1.3. Targeting tumor

During the development of tumors, inflammation-associated cells such as macrophages and neutrophils play crucial roles[131]. Designing drug delivery carriers based on inflammation-associated cells to achieve targeted delivery of anticancer therapeutics holds significant promise for precision tumor therapy. For instance, T cells and monocytes can be recruited by specific tumor-associated chemokines, cytokines, and growth factors[132]. Researchers have developed T cell backpacking. The backpacks were lipid nanocapsules encapsulating SN-38, a version of irinotecan. Leveraging CD62L and C-C chemokine receptor type 7 on T cells for recognition of lymphoid tissue, and CXCR4 for sensing tumor-secreted chemokines, the T cells transported 63 times more SN-38 to tumor-bearing lymph nodes compared to administration of free nanocapsules not associated with T cells[111]. Additionally, neutrophil membrane-coated nanoparticles (NNPs) can utilize interactions between P-/E-selectin and their glycosylated ligands such as PSGL-1, as well as integrin-mediated adhesion, to cross the blood pancreas barrier and selectively accumulate at tumor sites[112]. Macrophages can be efficiently recruited to tumors through α4 integrin-mediated specific binding to ICAM-1 and VCAM-1 expressed on tumor vasculature and stromal cells. As illustrated in Fig. 5A and B a variety of macrophage-associated carriers have been designed, such as Dox-MPK@MDL and Mø@bac, to achieve precise targeted delivery to tumors[133,113]. Notably, tumor cell-derived exosomes and membrane-hybridized carriers possess ideal "homologous targeting" properties, as their surface ligands can specifically bind to receptors on the surface of homologous tumor cells[134,135]. Qiao et al.[114] demonstrated that cancer cell-derived exosomes can not only efficiently target parental cells *in vitro* but also home to primary tumor tissues *in vivo*, highlighting their broad application potential in precise tumor drug delivery. Furthermore, Wu et al.[136] developed tumor cell membrane-biomimetic liposomes capable of specifically targeting homologous tumor foci, thereby achieving efficient delivery of oncolytic viruses and inducing oncolytic effects. These innovative delivery platforms, based on engineered exosomes or membrane-hybridized structures derived from inflammatory and tumor cells, open new avenues for achieving efficient and precise tumor therapy.

Moreover, specific conditions within the tumor microenvironment, such as hypoxia, attract bacterial species, including *Bifidobacterium*, *Clostridium*, and *Salmonella,* to migrate along chemotactic gradients surrounding tumors[137]. Utilizing bioconjugation strategies based on streptavidin-biotin interactions, researchers assembled poly(lactide-*co*-glycolide) (PLGA) nanoparticles onto the outer membrane of tumor-targeting *Salmonella typhimurium* VNP20009 to construct the NanoBEADS system[115]. Nano BEADS exploited bacterial translocation and proliferation to autonomously deliver nanotherapeutics to poorly vascularized and hypoxic tumor regions, significantly enhancing the retention and distribution of nanoparticles in solid tumors (Fig. 5C and D) Given the defective endothelial cell junctions and disrupted tight junctions of tumor blood vessels, platelets (PLTs) serve as efficient drug delivery vehicles to deliver drugs to tumor areas by naturally adhering to these compromised vascular sites. Ma et al. designed a photoresponsive block copolymer, naphthalene diimide-bithiophene derivative (NDI-BT), synthesized photothermal nanoparticles, and co-loaded them with the immunostimulant R837 hydrochloride (R) into PLTs to construct engineered platelets (N + R@PLTs)[116]. Following intravenous administration, N + R@PLTs responded to vascular damage and targeted tumor regions. Near-infrared irradiation triggered localized photothermal effects, inducing acute vascular injury and massive recruitment of platelets *via* a feedback-dependent mechanism, which in turn promotes efficient accumulation of both drugs and nanoparticles at the tumor site. Furthermore, activated platelet plasma membranes generated nanoscale proplatelet particles (nPLTs), which delivered therapeutics into deeper tumor tissues, expanding the coverage and efficacy of the treatment.

Another distinct strategy involves introducing unique chemical functional groups onto the cell surface to mimic the functions of cell membrane proteins, enabling exogenous substances to bind *via* specific chemical reactions. For example, researchers have metabolically labeled tumor cells with tetraacetyl-*N*-azidoacetylmannosamine, resulting in the overexpression of azide groups on the cancer cell surface following selective enzymatic cleavage. By leveraging click chemistry, the accumulation of dibenzocyclooctyne-doxorubicin conjugates was enhanced in tumors, enabling targeted treatment of LS174T colon cancer, MDA-MB-231 triple-negative breast cancer, and 4T1 metastatic breast cancer[117]. This approach, termed Active Tissue Targeting *via* Anchored Click Chemistry, represents a robust small-molecule targeting technology with the potential for extension to the design of other glycoconjugates. These derivatives can be selectively metabolized under the induction of inflammatory factors in various inflammatory diseases, enabling cell-specific azide labeling and consequently precise intervention of inflammatory cells. This strategy opens new avenues for tumor-targeted therapy and interventions for diverse inflammatory disorders, offering a more effective means of achieving precise drug delivery.

The homologous targeting mechanism not only enables ECNs to actively traverse multiple physiological barriers and preferentially home to inflammatory lesions, but also significantly enhances the selectivity of drug delivery and local drug concentration, thereby minimizing systemic side effects and off-target damage. Most drugs (*e.g.*, chemical drugs) predominantly rely on passive diffusion to enter systemic circulation and lack tissue specificity. These drugs are widely distributed in non-target tissues and are prone to causing systemic adverse effects (such as gastrointestinal injury, hepatic and renal impairment, etc.)[138]. Although nanocarriers (*e.g.*, liposomes and polymeric nanoparticles) can achieve a certain degree of accumulation at inflammatory or tumor sites *via* the enhanced permeability and retention effect, their accumulation levels in inflammatory regions remain limited. More importantly, such nanoparticles are readily recognized and rapidly cleared by the mononuclear phagocyte system in the blood, resulting in shortened retention time at pathological sites and limited therapeutic efficacy. Therefore, ECNs have achieved significant breakthroughs in active targeting and deep penetration capabilities within inflammatory regions, laying a crucial foundation for advancing precision therapeutic strategies.

However, current targeting strategies still require improvements in specificity, targeting efficiency, and *in vivo* stability. For instance, the heterogeneity of the inflammatory microenvironment, dynamic changes in receptor expression, and the conformational variability of membrane proteins may all reduce targeting accuracy. Future development should focus on: (1) Utilizing single-cell and spatial multi-omics to untangle the protein profiles of different cell subpopulations in lesion areas, thereby optimizing molecular targets for heterogeneous inflammatory tissues. For example, combining Cre-LoxP technology with single-cell RNA sequencing can enable real-time tracking of

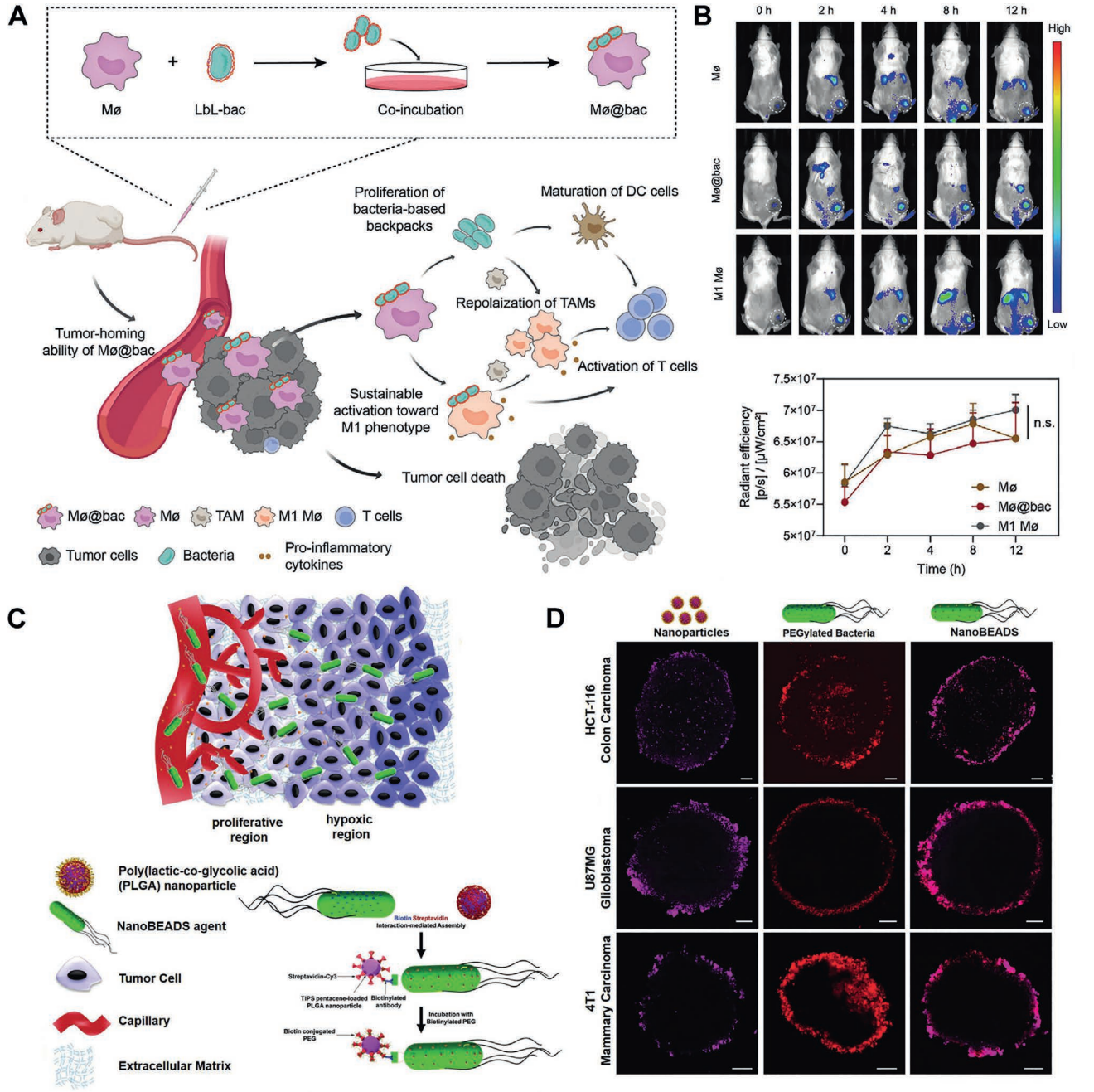

Figure 5 (A) Schematic representation of Mø@bac for regulation of tumor immunosuppressive microenvironment. (B) Migration ability of Mø@bac to tumor cells. Reproduced with permission from Ref. 113. Copyright 2023 Wiley-VCH GmbH. (C) Schematic representation of NanoBEADS for enhanced penetration in poorly vascularized tumor tissue compared with the passively diffusing nanoparticles. (D) Intratumoral distribution of therapeutic agents. Reproduced with permission from Ref. 115. Copyright 2018 the Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

which cell subpopulations take up ECVs *in vivo*, thereby refining targeting design[139,140]. (2) Employing multi-target synergistic modifications and membrane protein engineering to enhance adaptability and stability in complex *in vivo* environments. (3) Integrating molecular dynamics simulations and machine learning to predict the orientation, stability, and target affinity of membrane proteins on biomimetic membranes, facilitating rational design rather than screening. Furthermore, advancing real-time imaging and *in vivo* tracking of ECN targeting mechanisms will provide more intuitive insights into their tissue homing and metabolic pathways, thereby offering theoretical foundations and technical support for the development of highly efficient and precise inflammatory treatment platforms.

4.2. ECNs for biological neutralization

The biological neutralization strategies achieve therapeutic effects by targeting and neutralizing pathological substances or modulating their biological activity, and are evolving from passive neutralization toward active and dynamic regulation. Although

monoclonal antibodies and small-molecule inhibitors have shown remarkable progress in targeted therapy, their "single-target, static intervention" paradigm struggles to address complex diseases such as sepsis, which are driven by multifactorial and dynamic interactions. Therapeutic systems based on ECNs offer innovative solutions by integrating biomimetic carrier engineering strategies with dynamic pharmacological strategies. In addition to mimicking the topological structure and surface proteome of cell membranes to enhance biodistribution properties and targeted delivery efficiency, ECNs can serve as decoys that intercept and neutralize pathological substances through their intrinsic affinity for pathogenic factors, thus preventing damage to normal cells. On this basis, drug conjugation can be adopted as an auxiliary strategy to further augment the therapeutic functions of the cellular carriers. This "bioinspired engineering" approach enables ECNs to evolve from passive delivery vehicles into therapeutic systems with active responsive and precise targeting capabilities.

4.2.1. Toxin neutralization

Bacterial toxins are major pathogenic factors in infectious diseases. Through direct interactions with host cell membranes, bacterial toxins can compromise membrane integrity or trigger complex immune cascades, ultimately leading to cellular damage, tissue pathology, or even multi-organ dysfunction. During bacterial infections, exotoxins (such as hemolysins) and endotoxins (such as LPS) act synergistically, further increasing the complexity of the infection. Exotoxins damage host cells by lysing cell membranes, while endotoxins activate the innate immune response, leading to systemic inflammatory response syndrome, a key mechanism underlying septic shock and high mortality rates.

ECNs combine the highly selective recognition capability of cell membranes with the multifunctional design potential of artificial carriers. For example, by mimicking the binding mechanisms of natural cell membranes, ECNs can adsorb and neutralize a variety of exotoxins and endotoxins. Hemolysins, such as pore-forming toxins (PFTs), are bacterial exotoxins that form pores in host cell membranes, disrupting membrane integrity and resulting in cell lysis. Based on this mechanism, Chen et al.[141] proposed a biomimetic nanosponge coated with erythrocyte membranes, which leverages the natural toxin-binding properties and prolonged blood circulation of the erythrocyte membrane and the high stability conferred by the PLGA nanoparticle core, resulting in highly efficient neutralization of PFTs such as α-toxin, streptolysin-O, and melittin. However, the erythrocyte membrane coating process and structural or locational alterations of membrane proteins may reduce toxin-neutralization efficiency. Since the recognition and binding of PFTs depend on specific domains of the cell membrane, the hybridization of artificial lipid membranes with cell membranes can expand the adsorption capacity for toxins, while simplifying preparation methods. He et al.[142] developed erythrocyte membrane-artificial lipid hybrid nanoparticles (RM-PL), which demonstrated 139-fold higher antitoxin efficiency compared to nanosponge.

Endotoxins (*e.g.*, LPS) are essential components of bacterial cell walls that can induce severe inflammatory responses such as systemic inflammatory response syndrome and septic shock. The multiple epitope targeting of endotoxin contributes to its high toxicity and therapeutic complexity. However, PRRs on immune cell surfaces-such as TLR4, CD14, and cytokine receptors (including CD126, CD120a/b, and CD119)-play crucial roles in the recognition and binding of inflammatory mediators (such as TNF-α and IL-6) as well as LPS. These molecular interactions provide a foundation for engineered carriers of toxin neutralization[143]. Researchers have developed macrophage membrane-coated nanoparticles (MΦ-NPs)[144]. The LPS-binding proteins on the source cell membrane not only efficiently capture and neutralize endotoxins but also sequester proinflammatory cytokines, thereby suppressing LPS-mediated inflammatory cascades. In contrast, nanoparticles modified with red blood cell membranes do not exhibit comparable endotoxin-neutralizing capacities, highlighting the unique ability of macrophage membranes to neutralize both endotoxins and pro-inflammatory mediators. MΦ-NPs significantly mitigate inflammatory immune responses through endotoxin binding, achieving effective toxin neutralization. Furthermore, bioengineering approaches to improve the expression of PRRs (*e.g.*, TLR4, CD14) on macrophage membranes markedly enhance their toxin-binding affinity and anti-inflammatory efficacy.

The coexistence of exotoxins and endotoxins in complex infections significantly exacerbates the challenge of detoxification. Jiang et al.[105] proposed liposomes hybridized with erythrocyte membrane incorporating PMB. P-RL can adhere to and anchor on the bacterial surface *via* strong interactions between PMB and the *E. coli* membrane. Leveraging the natural affinity between erythrocyte membranes and toxins, as well as the electrostatic interactions between PMB and LPS, P-RL demonstrated simultaneous high-efficiency neutralization of both exotoxins (*e.g.*, hemolysins) and endotoxins (*e.g.*, LPS). Furthermore, P-RL anchored to *E. coli* exhibits potential for targeted antibiotic delivery, thereby enhancing therapeutic efficacy. From the precise adsorption and clearance of both exotoxins and endotoxins to targeted delivery of antimicrobial agents, ECNs provide novel strategies for broad-spectrum toxin neutralization. This approach offers promising possibilities for the precision treatment of infectious diseases and opens new avenues to address global challenges such as antibiotic resistance.

4.2.2. Virus neutralization

During viral infection, viruses attach to host cells by binding to specific receptors on the cell membrane and then invade the cells to complete replication. For instance, human immunodeficiency virus (HIV) infection is initiated by the binding of viral envelope glycoproteins (such as gp120) to the CD4 receptor on the surface of T cells, followed by interaction with coreceptors CCR5 or CXCR4 to facilitate viral entry.

As illustrated in Fig. 6A, the researchers proposed a virus decoy strategy based on cell membrane biomimetics. $CD4^+$ T cell membranes were extracted and used to encapsulate nanoparticles, constructing highly biomimetic virus decoy carriers (TNPs). TNPs retained key molecules required for HIV binding, such as the CD4 receptors and CCR5 or CXCR4 co-receptors[145]. Acting as T cell decoys, TNPs bind to gp120, thereby blocking HIV from invading normal T cells and reducing HIV-mediated $CD4^+$ T cell depletion. This decoy-neutralization approach does not impose strong selective pressure directly on the virus, thus avoiding the emergence of resistance mutations while significantly reducing viral infectivity and pathogenicity. Although TNPs can neutralize circulating viruses in the bloodstream, their efficacy against latent viral reservoirs within the host remains limited. HIV reservoirs are widely distributed among immune cells such as memory T cells and macrophages, where the viruses can be reactivated under specific stimuli and release new viral particles, leading to a new round of infection. This characteristic not only poses a major challenge to the long-term efficacy of ART but also limits the overall

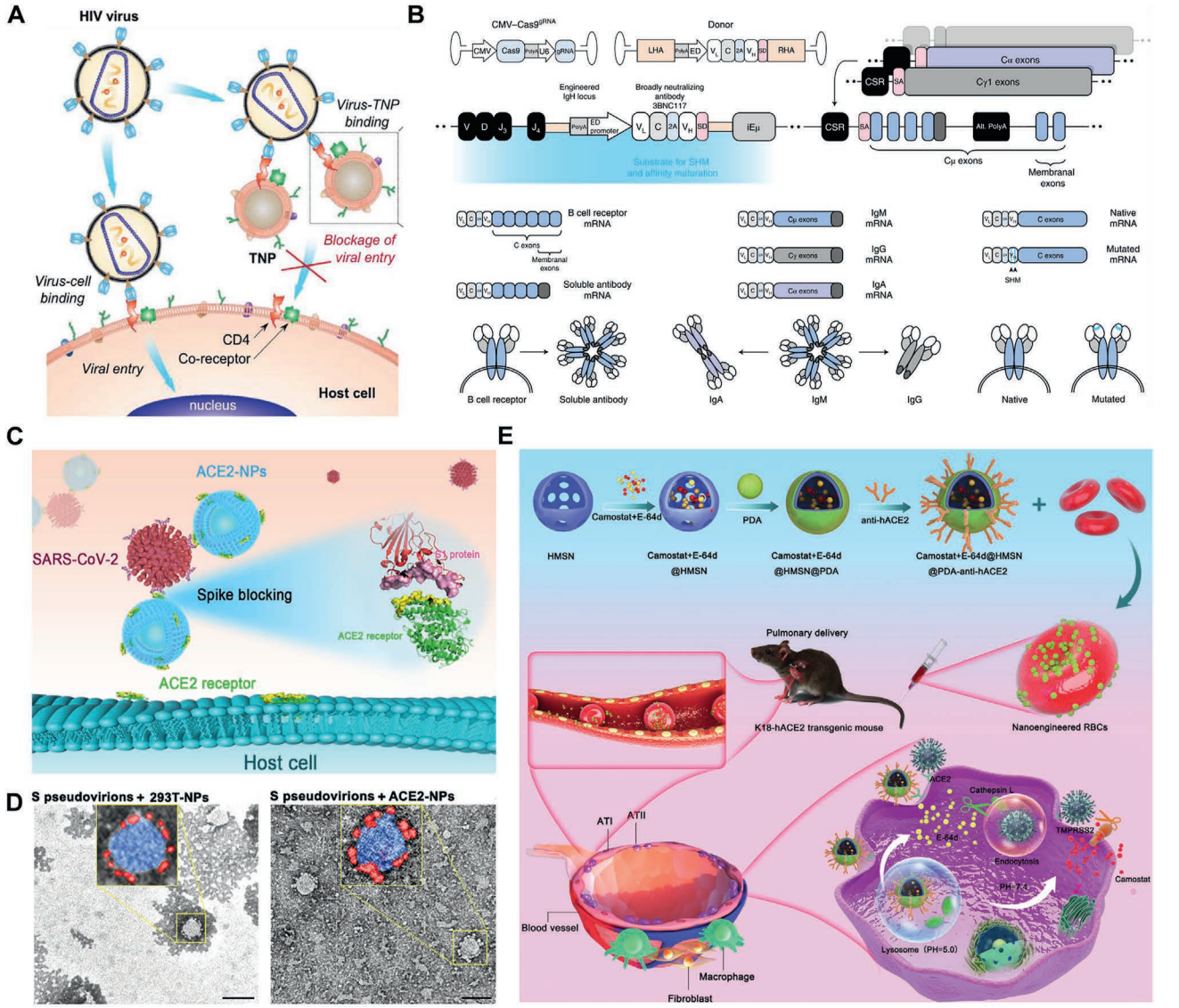

Figure 6 (A) Schematic representation of TNPs designed for attenuating HIV infectivity by acting as decoys to bind with T cell-targeted viruses and subsequently blocking viral entry into and infection of the target cells. Reproduced with permission from Ref. 145. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) The strategy of promoting *in vivo* B cell engineering. Reproduced with permission [146]. Copyright the Author(s), under exclusive licence to Springer Nature America, Inc. 2022. (C) Schematic representation of ACE2-NPs designed for blocking SARS-CoV-2 infection. Reproduced with permission from Ref. 149. Copyright 2021 American Chemical Society. (D) TEM images of NPs absorbing S pseudovirions. (E) Schematic representation of nanoengineered RBCs designed for blocking SARS-CoV-2 cell entry. Reproduced with permission from Ref. 150. Copyright 2024 the Authors. Advanced Materials published by Wiley-VCH GmbH.

neutralizing capacity of TNPs. As illustrated in Fig. 6B, Nahmad et al.[146] developed a gene editing approach in which an adenoviral vector-mediated CRISPR-Cas9 system was used to integrate genes encoding broadly neutralizing anti-HIV antibodies into the immunoglobulin heavy chain locus of B cells. The engineered B cells can be activated by antigens *in vivo*, differentiating into memory B cells and plasma cells that secrete broadly neutralizing anti-HIV antibodies to neutralize HIV. Additionally, the memory B cells can persist long-term in the body and rapidly respond upon re-exposure to HIV, producing large quantities of neutralizing antibodies to provide sustained protection. Through this dual mechanism (active antibody production and durable immune memory), the technology offers a novel therapeutic solution for HIV infection.

ECNs also provide a design framework for combating emerging viral infections such as SARS-CoV-2. The COVID-19 pandemic caused by SARS-CoV-2 continues to pose a serious threat to global public health. Its infection mechanism relies on multi-factor coordination, involving interactions between viral particles and host proteins including Furin, transmembrane serine protease 2 (TMPRSS2), cathepsin L (CTSL), and angiotensin-converting enzyme 2 (ACE2)[147]. Based on this concept, ACE2-expressing exosomes derived from human lung spheroid cells were developed as pathogen "decoys" to neutralize SARS-CoV-2 and effectively protect the host from infection[148]. As illustrated in Fig. 6C and D, Wang et al.[149] utilized engineered cell membrane technology to construct nanoparticles coated with T cell membranes highly expressing ACE2 (ACE2-NPs). These ACE2-NPs

competitively bind to the SARS-CoV-2 spike (S) protein, effectively blocking viral entry into host cells and reducing infection efficiency. In addition, ACE2-NPs alleviate S1 protein-induced apoptosis by upregulating OPA1 expression and inhibiting cytochrome *c* release. Building upon this foundation, antiviral strategies have progressively evolved from merely blocking virus−host receptor interactions to implementing multi-target synergistic interventions. During viral invasion, the enzymatic activities of key proteases such as TMPRSS2 and CTSL are essential for S protein maturation and fusion of the viral and host cell membranes. As illustrated in Fig. 6E, Yang et al.[150] developed a dual-drug nanocarrier conjugated with anti-human ACE2 antibodies, loaded with the TMPRSS2 inhibitor camostat and the CTSL inhibitor E−64d. Through hydrogen bonding and electrostatic interactions, this construct attaches to erythrocytes (RBCs), forming "nanoengineered RBCs". Leveraging the long-circulating capability of erythrocytes, these carriers were targeted to $ACE2^{+}$ lung cells in pulmonary capillaries. Upon endocytosis, the nanocarriers enter lysosomes, where the polydopamine (PDA) degrades in the acidic lysosomal environment (pH 5.0), triggering the precise release of both drugs. These agents inhibit TMPRSS2 activity and block CTSL function, thereby preventing S protein maturation and viral internalization, effectively blocking the viral entry pathway. This multi-targeted, synergistic strategy not only effectively circumvents therapeutic inefficacy caused by viral mutations but also provides a broad-spectrum neutralization approach for the treatment of complex viral infections.

Currently, cell membrane-based biomimetic nanotechnology has advanced the effectiveness of viral neutralization strategies. From HIV to SARS-CoV-2, researchers have achieved efficient viral decoy and blocking mechanisms by integrating the characteristics of host cell membranes with nanoparticle engineering. However, overcoming the limitations of single-target approaches, achieving multi-mechanism synergy, and comprehensively suppressing latent viruses remain critical challenges for future biomimetic neutralization technologies. Through optimization of cell membrane functionality, precision drug delivery, and multi-target intervention, this systemic approach holds promise for providing more comprehensive solutions for broad-spectrum antiviral therapy.

4.2.3. Regulation of inflammatory factors

Inflammation is a critical dynamic process through which the immune system responds to tissue injury and infection. It is characterized by the secretion of inflammatory cytokines by immune cells to modulate the immune responses, eliminate pathogens and damaged cells, and initiate tissue healing to restore homeostasis. However, when the inflammatory response becomes dysregulated or there is excessive release of inflammatory mediators, a range of inflammatory diseases can develop, such as rheumatoid arthritis and ankylosing spondylitis[151].

During inflammatory processes, various immune cells (*e.g.*, neutrophils, macrophages, lymphocytes, platelets) are recruited to sites of infection or tissue injury to participate in the regulation of local inflammatory responses. The cell membranes of these effector cells have been utilized to construct biomimetic nanocarriers[152−154], leveraging their native biological functions to develop dual-functional therapeutic systems capable of both efficient proinflammatory cytokine capture and targeted drug delivery. For instance, macrophage membranes express receptors (such as CD126, CD130, CD120a, etc.) that bind to proinflammatory cytokines[143]. Nanocarriers coated with macrophage membranes not only capture inflammatory mediators but also effectively disrupt disease-associated inflammatory cascades, and have been widely applied in the treatment of sepsis, bone tissue repair, and ankylosing spondylitis[155−157]. Similarly, neutrophil membrane-coated nanoparticles (Neutrophil-NPs) exhibit broad applicability in inflammatory diseases. By neutralizing specific cytokines such as TNF-α and IL-1β, Neutrophil-NPs not only suppress inflammatory responses in myocardial ischemia−reperfusion injury and rheumatoid arthritis, but also promote the repair of damaged tissues[158,159]. However, membrane protein disintegration, loss, and spatial disorganization during nanocarrier fabrication remain unavoidable challenges[160,161], which impair the specific adsorption and binding capacity of nanocarriers for inflammatory cytokines, ultimately reducing cytokine neutralization efficiency[162,163]. To address this limitation, researchers have developed an innovative intracellular gelation technique as illustrated in Fig. 7. Macrophages were infused with phenylalanine-grafted chitosan (Phe-CS) after freeze-thaw cycling, followed by crosslinking with cucurbit[8]uril (CB[8]) to construct gelated macrophages (GMs). These GMs maintained intact membrane architecture, including preserved protein content, structural integrity, membrane fluidity, and lipid ordering, significantly enhancing the inflammatory cytokine neutralization capacity of GMs. In animal models of rheumatoid arthritis and acute pneumonia, GMs demonstrated superior anti-inflammatory effects and can be lyophilized for improved transport stability[164]. Compared to conventional anticytokine drugs, these engineered cells membrane-based biomimetic nanoparticles achieve broad-spectrum inflammation suppression through functional modulation, eliminating dependence on single molecular targets and thereby mitigating multiple inflammatory cascades. Furthermore, these nanoparticles based on effector cell membranes directly utilize their high binding affinity to proinflammatory cytokines, eliminating the need for complex chemical modifications to target specific molecules. This approach simplifies the design and manufacturing of therapeutic carriers, thereby enhancing their translational potential[159].

Moreover, engineered cellular carriers with higher bioactivity demonstrate more precise and sustained therapeutic advantages in the dynamic regulation of inflammatory cytokines, owing to their long-term effects and multi-factor synergistic mechanisms. Li et al.[165] prepared platelet membrane (PM)-decorated M0 microglia (PM-MG) through membrane fusion. Liposomes containing IL-4 were conjugated to PM-MG *via* bioorthogonal click chemistry to obtain PM-MG-CPIL4. Under ultrasound guidance, PM-MG-CPIL4 released IL-4 from hybrid liposomes, inducing anti-inflammatory polarization of microglia. M2-type microglia secrete TGF-β and arginase 1, attenuating inflammation and promoting neuroprotection and cerebrovascular repair. Researchers have also developed engineered neutrophils to mitigate cytokine storms induced by macrophages. Mannose-modified liposomes (M-Lip@TH) containing the NF-κB inhibitor TPCA-1 and the STING inhibitor H-151 were encapsulated within live neutrophils to construct a "Biorobot". This Biorobot specifically targeted macrophages for liposomal delivery, effectively suppressing both NF-κB and STING signaling pathways. This dual inhibition significantly reduced excessive production of TNF-α, IL-6, and other proinflammatory cytokines, thereby neutralizing cytokine storms, ameliorating inflammatory conditions in pneumonia models, and improving survival rates[166]. In response to the complex inflammatory microenvironments of certain diseases (such as low pH, glutathione, or specific enzyme activities),

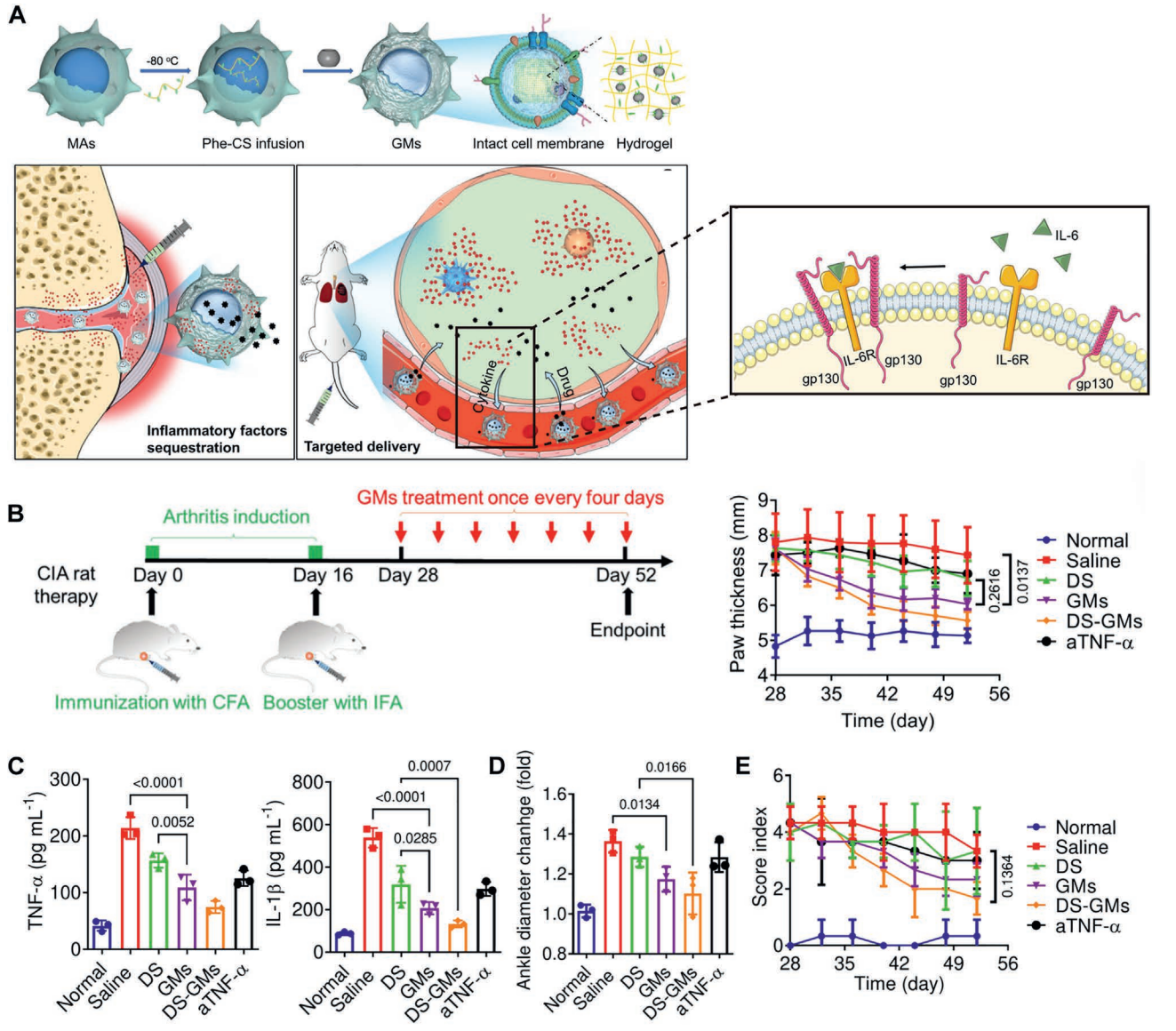

Figure 7 (A) Schematic representation of GMs construction for targeted anti-inflammatory treatment and IL-6 *trans*-signalling pathway. (B) After receiving different treatments, the changes of paw thickness of CIA rats. (C) The concentrations of serum TNF-α and IL-1β after receiving different treatments. (D and E) The ankle diameter changes and the overall arthritis score after receiving different treatments. Reproduced under the CC BY license, Copyright the Author(s) 2024 (http://creativecommons.org/licenses/by/4.0/), Ref. 164.

researchers have further developed responsive nanocarriers to optimize pharmacokinetic profiles. These systems enable both precision drug release and target-independent capture of pro-inflammatory factors[167]. This "top-down" carrier design approach significantly simplifies production processes while achieving broad-spectrum anti-inflammatory mechanisms.

As summarized in Table 5 and illustrated in Fig. 8, engineered cells and cell membrane-based technologies offer precise and broad-spectrum therapeutic strategies for inflammatory diseases by efficiently neutralizing inflammatory cytokines, overcoming single-target dependency, and enhancing drug targeting. This approach, which integrates the innate functions of cells with nanotechnology, not only intervenes in multi-level inflammatory responses but also provides novel insights into improving therapeutic selectivity and minimizing side effects in the treatment of complex inflammatory disorders.

Conventional antitoxin strategies, which rely on specific binding between drugs and toxins, are generally suited to neutralizing individual toxin types and therefore have limited efficiency and spectrum. In complex infections, prolonged toxin release and high dispersion further diminish toxin neutralization efficiency. Thus, broad-spectrum toxin adsorption and neutralization strategies are essential for counteracting deleterious effects of toxins induced by complex infections. Antiretroviral therapy (ART) employs a combination of reverse transcriptase inhibitors, protease inhibitors, and other agents to suppress viral replication, thereby delaying the progression of HIV infection. However, due to the high genetic diversity and frequent mutations of the virus, along with the limitation that most ART regimens primarily block replication without directly eliminating the virus, existing therapies exhibit limited efficacy in the face of drug resistance and the persistent replication of the virus *in vivo*. Cytokine-targeting

Table 5 Summary of representative engineered cell-biomimetic nanosystems for biological neutralization.

Therapeutic	Therapeutic platform	Carrier cell	Engineering strategy	Neutralization mechanism	Disease	Source
Toxin	P-RL	Erythrocyte	Fusion of RBC membranes and PMB-modified lipids	Natural erythrocyte membranes of P-RL + hemolysin, PMB + LPS	*E. coli* infections	105
	hRBC nanosponge	Erythrocyte	Cell membrane-coated technology	Mimicking natural erythrocyte → neutralize toxins	Hla, LLO, and SLO infections	141
	RM-PL	Erythrocyte	Fusion of the RBC membrane and lipid membrane	Hla receptor proteins from erythrocyte membranes of RM-PLs + Hla	Hla	142
	MΦ-NPs	Macrophage	Cell membrane-coated technology	LPS-binding proteins of MΦ-NPs + LPS/pro-inflammatory factors	Sepsis	144
Virus	TNPs	$CD4^+$ T cell	$CD4^+$ T cell membrane-coated technology	The $CD4^+$ T cell membrane of TNPs + gp120 protein of HIV	HIV	145
	Engineered B cells	B cell	The broadly neutralizing anti-HIV antibodies genes were integrated into B cells *via* the CRISPR-Cas9 gene editing system	The broadly neutralizing anti-HIV antibodies secreted by antigen-activated engineered B cells + HIV virions	HIV	146
	ACE2-NPs	Human embryonic kidney-239T cells highly expressing ACE2	Cell membrane-coated technology	ACE2-NPs + S1 subunit of SARS-CoV-2	SARS-CoV-2	149
	Nanoengineered RBCs	Erythrocyte	Based on PDA and anti-human ACE2 antibodies, NCs were combined with erythrocytes *via* hydrogen bonding and electrostatic interactions	NCs targeted alveolar cell lysosomes, and released camostat and E−64d → inhibit TMPRSS2 activity and block CTSL function	SARS-CoV-2	150
Inflammation cytokine	MΦ-NP	Macrophage	Cell membrane-coated technology	CD126, CD130, and CD120a + inflammatory cytokines	Sepsis, ankylosing spondylitis and bone tissue repair	155−157
	Neutrophil-NP	Centriole organelles	Cell membrane-coated technology	Neutrophil-NPs + TNF-α and IL-1β	Myocardial ischemia −reperfusion and rheumatoid arthritis	158,159
	GMs	Macrophage	Macrophages were infused with Phe-CS after a freeze-thaw cycle, and CB[8] was subsequently added as a crosslinker to construct GMs	The macrophage membrane of GMs + inflammatory cytokines	Rheumatoid arthritis and acute pneumonia	164
	PM-MG-CPIL4	Microglia	PM-MG was prepared by membrane fusion, and liposomes loaded with IL-4 were conjugated to PM-MG *via* bioorthogonal click reactions	IL-4 induced microglia → M2 phenotype → the secretion of TGF-β and arginase 1 → modulate inflammation	Stroke	165
	Biorobot	Centriole organelles	Liposomes loaded with TPCA-1 and H-151 were taken up by neutrophils to form a biorobot	Biorobots → NF-κB and STING signaling pathways↓, the production of TNF-α and IL-6↓	Pneumonia	166

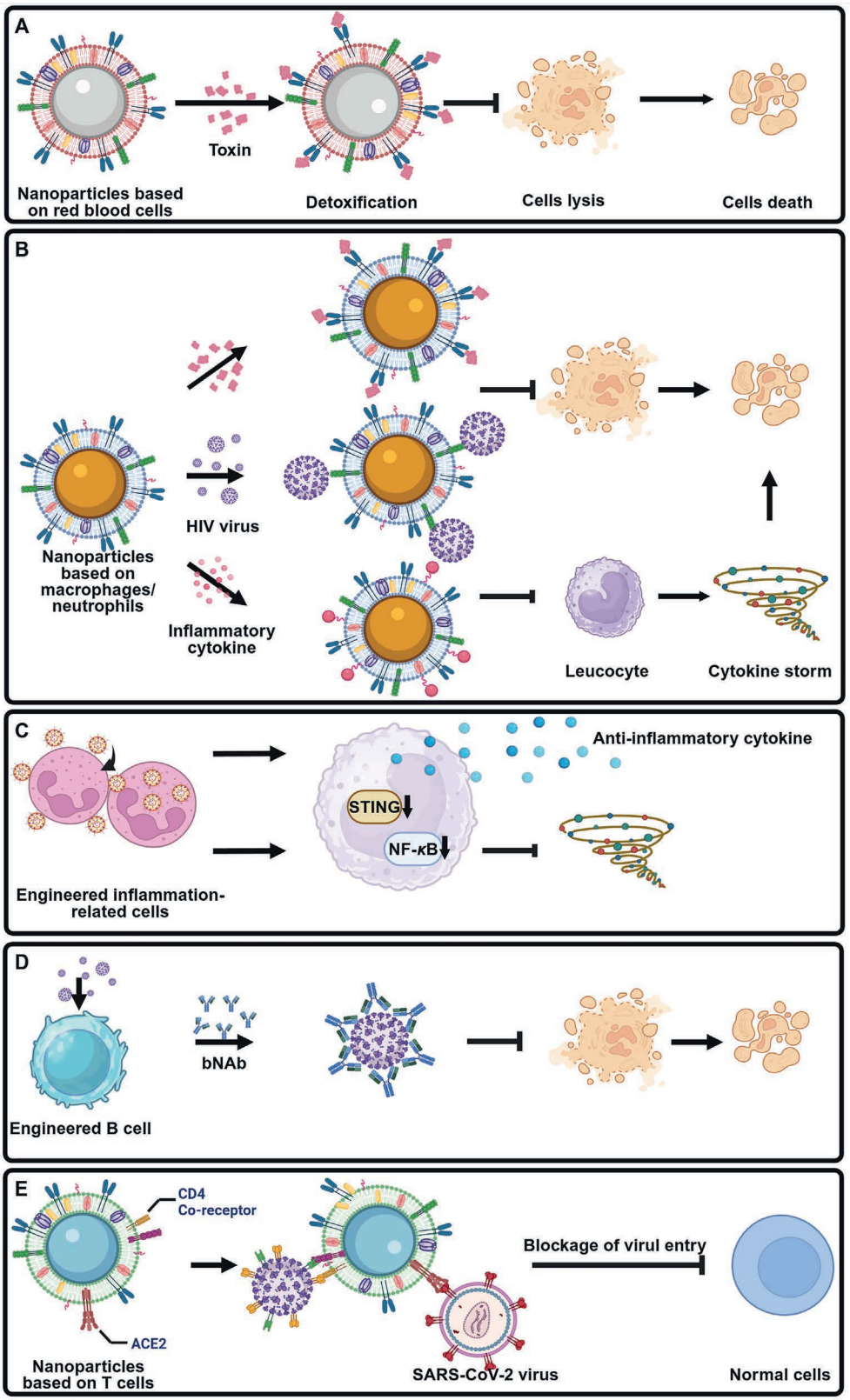

Figure 8 ECNs for the biological neutralization. Schematics of ECNs used in biological neutralization, including (A) red blood cell-based ECNs, (B) macrophage/neutrophil-based ECNs, (C) inflammation-related cell-based ECNs, (D) B cell-based ECNs, (E) T cell-based ECNs. Created with BioRender.com.

antibodies, commonly used for the treatment of inflammatory disorders, typically lack selectivity and focus on single inflammatory mediators, which readily leads to compensatory inflammatory reactions and is often accompanied by severe side effects. Therefore, therapeutic strategies that capture and neutralize multiple toxins, viruses, inflammatory cytokines, and coordinately modulate multiple inflammatory pathways have become an area of active research[168].

ECNs leverage their highly biomimetic membrane surfaces presenting multivalent, high-affinity receptors and domains to actively adsorb, capture, and eliminate various inflammation-related exogenous toxins (*e.g.*, bacterial exotoxins, endotoxins/PAMPs), viruses, and excessive endogenous inflammatory factors, thereby functioning as "molecular decoys". ECNs provide novel therapeutic strategies for critical conditions such as severe infection outbreaks and cytokine storms by intercepting upstream danger signals, disrupting the inflammatory cascade, and restoring immune homeostasis in the microenvironment. Furthermore, ECNs can mimic the immunomodulatory functions of their parent cells, thereby avoiding compensatory inflammatory responses triggered by the suppression of a single pathway and achieving broader-spectrum and more dynamic control of inflammation. Compared to single-antibody or small-molecule inhibitors, ECNs exhibit advantages in broad-spectrum activity, synergistic effects, and dynamic neutralization. Their membranes can be further engineered to enhance neutralization affinity and selectivity toward specific pathogens or inflammatory molecules. However, membrane proteins are prone to degradation *in vivo*, which also imposes limitations on the structural stability and long-term functional maintenance of ECNs. Currently, there remains room for improvement in technologies such as membrane protein modification efficiency, loading control, precise quantification of functional proteins, and real-time monitoring of *in situ* activity.

Future efforts should focus on the following directions: first, developing hybrid biomimetic membrane materials (*e.g.*, combining artificial liposomes and protein) with high stability and controllable functionality to address issues such as membrane degradation; second, constructing dynamically responsive ECNs capable of switching neutralization functions based on inflammatory/infectious microenvironmental signals, thereby improving treatment precision; third, integrating high-throughput screening and proteomics to directionally optimize the enrichment and arrangement of key receptors, enhancing personalized therapeutic capabilities. Ultimately, this will lead to the establishment of a broad-spectrum, highly efficient, and personalized system for neutralizing inflammatory pathologies.

4.3. ECNs for immune modulation

Immunoregulation is central to inflammatory control, with the key being the maintenance of immune homeostasis to balance pro-inflammatory and anti-inflammatory responses. However, conventional drugs or therapeutic strategies exhibit limited specificity and precision in modulating the immune system, often leading to immunosuppression, inflammatory exacerbation, or other adverse effects. ECNs can mimic cellular interaction mechanisms, such as cell surface marker recognition, immune evasion, or immune regulation capabilities. While delivering therapeutic agents, ECNs can modulate the immune response, making them applicable in treating infectious diseases, managing autoimmune diseases, and enhancing tumor immunotherapy. For instance, ECN-based vaccines neutralizing bacterial toxins can activate mucosal immunity through efficient antigen delivery. Engineered immune cell carriers can specifically induce phenotypic shifts of macrophages or T cells to promote inflammation resolution. Additionally, ECNs conjugated with antitumor immune molecules can significantly improve the presentation efficiency of tumor-associated antigens and enhance immune system recognition of tumors.

4.3.1. Immune activation

When the body is confronted by pathogens (such as bacteria or viruses) or self-generated mutative cells (such as tumor cells), the immune system mounts a rapid defense through the coordinated actions of innate and adaptive immunity. Insufficient or suppressed immunoregulatory functions may lead to immunodeficiency or immune dysregulation, ultimately resulting in opportunistic infections or tumorigenesis. This issue is further complicated by the emergence of antibiotic resistance and the side effects associated with cancer therapy. Immunotherapy achieves effective clearance of pathogens or tumor cells by activating or modulating the immune system of the host, while simultaneously establishing durable immune memory to reduce the risk of recurrence and minimize damage to normal tissues[169]. ECNs exert therapeutic effects against infections and cancer or other inflammatory diseases through mechanisms including antigen presentation, immune response amplification, and regulation of inflammation.

Toxoid vaccines are generally prepared from bacterial toxins with low toxicity but retained immunogenicity, enabling stimulation of the immune system to produce antibodies and prevent bacterial infections[170]. However, existing toxoid vaccines face limitations such as limited antigen diversity and insufficient immunogenicity[171]. The cell membrane coating technology can leverage the interaction between bacterial toxins and the host immune system to deliver antigens and modulate the immune microenvironment, thereby activating potent immune responses[67]. As illustrated in Fig. 9D−F, Wei et al.[172] developed MΦ-toxoids by coating PLGA nanoparticles with macrophage membranes and co-incubating them with *Pseudomonas aeruginosa* secretions. After vaccination, the levels of PaS-1/2-specific secretory IgA and IgG in the bronchoalveolar lavage fluid of mice were significantly increased, indicating that the vaccine induced mucosal immunity to prevent bacterial lung infections. For *Acinetobacter baumannii* infections, vaccines prepared by coating nanoparticles with neutrophil membranes and adsorbing toxin factors stimulated rapid maturation of dendritic cells and B cells, promoting germinal center formation and inducing robust humoral immune responses[173]. The advantages of cell membrane coating technology lie not only in its inherent immunological properties but also in its potential *via* functional optimization to enhance the targeting and efficacy of vaccines[174]. For example, selecting highly specific cell subpopulations, such as alveolar macrophages as membrane coating can endow the vaccine with stronger antigen capture and binding capabilities. Hybrid carriers combining cell membranes with bacterial-derived vesicles (such as outer membrane vesicles) further enhance immune activation. As illustrated in Fig. 9A−C, researchers fabricated hybrid nanovesicles ($mBMSC_{CXCR4}$@OMV) by extruding CXCR4-overexpressing bone marrow mesenchymal stem cell membranes ($mBMSC_{CXCR4}$) with outer membrane vesicles[175]. This system retained abundant PAMPs from *E. coli* while enhancing bone marrow-targeting accumulation *via* CXCR4-mediated homing. Experimental results demonstrated that this carrier not only comprehensively activated dendritic cells and macrophages, enhancing antigen presentation and promoting T-cell and B-cell activation, but also suppressed the infiltration of immunosuppressive cells,

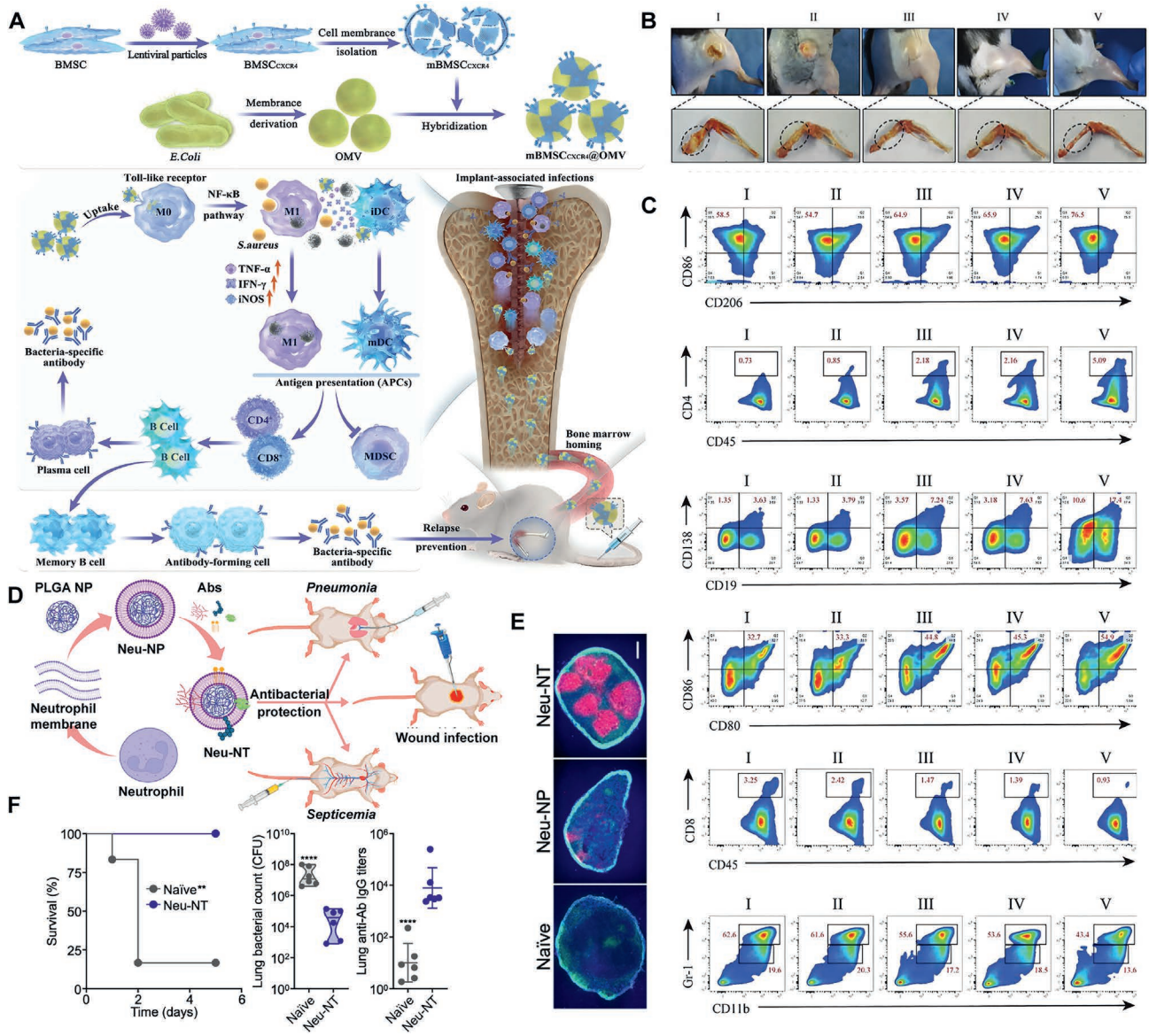

Figure 9 (A) Schematic representation of mBMSC$_{CXCR4}$@OMV nanovesicles construction and their immunotherapeutic effect to eradicate complicated IAIs and prevent relapse. (B) Digital photos of the infected femur after treatment. (C) The representative flow cytometry plots of mBMSC$_{CXCR4}$@OMV boost innate and adaptive immune response. Reproduced with permission from Ref. 175. Copyright 2025 The Author(s). Advanced Science published by Wiley-VCH GmbH. (D) Schematic representation of Neu-NT designed for formulation protects animals in models of pneumonia, septicemia, and superficial wound infection. (E) The representative histological sections of the dLN (blue, CD19; green, IgD; red, GL7). (F) The survival of mice over time after subcutaneous injection of Neu-NT, followed by challenge with 10^8 CFU of *A. baumannii*, the bacterial burden in the lungs of mice and anti-Ab IgG titers in the lungs. Reproduced with permission from Ref. 173. Copyright American Chemical Society.

effectively improving the lesion microenvironment. In primary implant-associated infections (IAIs) models and relapse IAIs models, the vaccine exhibited significant protective effects, suppressing IAIs and preventing disease recurrence.

4.3.2. Immune suppression

Autoimmune diseases (AIDs) affect approximately 5% to 8% of the global population, causing substantial suffering to patients[176]. AIDs are characterized by abnormal immune responses directed against self-components and include conditions such as rheumatoid arthritis, ulcerative colitis, and sepsis. These diseases are frequently associated with uncontrolled inflammatory cascades, ultimately leading to tissue damage and organ dysfunction[177]. Although immunosuppressive strategies can alleviate symptoms, their systemic effects often result in immunodeficiency, thereby increasing the risk of infections and tumorigenesis[178]. ECNs represent a breakthrough in immunosuppressive therapy. Through targeted modulation and multifunctional immunoregulation, these carriers open new avenues for the treatment of AIDs, hypersensitivity reactions, and transplant rejection, as well as other inflammation-related disorders.

Excessive activation of T cells and the overproduction of pro-inflammatory cytokines form a self-amplifying signaling loop, continually exacerbating dysfunctional inflammatory responses

and promoting the progression of AIDs[179]. PD-1 and its ligand PD-L1 constitute a crucial pathway for the maintenance of immune tolerance[180]. In the pathological state of AIDs, excessive soluble PD-1 competitively binds to PD-L1, weakening the inhibitory effect of PD-L1 on T cell activation. This results in T cell overactivation, enhanced release of pro-inflammatory cytokines, and further exacerbation of inflammation[71]. To address this, Gan et al.[181] induced PD-L1 overexpression on RAW 264.7 cell membranes (PRM) *via* IFN-γ stimulation, which were then coated onto PLGA particles to construct PD-L1-enriched nanodecoys (PRM ND). PRM ND binds directly or indirectly to PD-1 or soluble PD-1, inhibiting PD-1 activation and restoring the PD-1/PD-L1 inhibitory signaling axis to regulate inflammatory responses. This technology significantly reduced irreversible bone destruction and tissue damage in a mouse model of rheumatoid arthritis, demonstrating the therapeutic potential of PD-L1-functionalized nanocarriers for AIDs. Furthermore, the expression of immunosuppressive proteins such as PD-L1 on the surface of stem cells[182], *E. coli* Nissle 1917[183], or platelets[184] by genetic engineering has also shown potential for inducing T cell exhaustion and enabling precise inflammation regulation[185]. Notably, the innate inflammation-targeting capability of these cells further promotes the effective accumulation of PD-L1 at inflamed sites, such as lesions in the pancreas, paving the way for precision therapy.

Due to their susceptibility to splenic capture, RBCs can be engineered as highly efficient antigen delivery vehicles[186]. Leveraging the natural antigen regulatory mechanisms of apoptotic cells, antigens can be conjugated to the surface of red blood cells, thereby inducing immune tolerance in both $CD4^+$ and $CD8^+$ T cells[187−189]. Red blood cells modified with specific antigens (*e.g.*, thyroglobulin and insulin) or antigenic peptides (*e.g.*, myelin oligodendrocyte glycoprotein (MOG_{35-55}) and insulin B-chain peptide 9−23) can establish immune tolerance *via* the PD-1/PD-L1 signaling pathway and ameliorate the pathological progression of diseases such as multiple sclerosis and type 1 diabetes[99,190−192]. Additionally, conjugating specific antigens to the surface of monocytes before reinfusion into patients has also been shown to effectively reduce the activity of antigen-specific T cells and induce a tolerogenic response. For example, in a clinical trial (NCT01414634), reinfusion of monocytes conjugated with myelin peptide into patients with multiple sclerosis significantly diminished antigen-specific T cell responses, thereby inducing antigen-specific tolerance[51]. This not only further validates the critical role of immune checkpoint regulation in the resolution of inflammation but also lays the foundation for the clinical translation of ECNs.

Platelets possess inherent biological properties such as inflammation-targeted chemotaxis, interaction with T cells, and rapid clearance, making them promising candidates for engineering as immune checkpoint delivery platforms. As demonstrated in Fig. 10, by using lentiviral transduction to induce sustained overexpression of PD-L1 in the megakaryocyte progenitor cell line L8057, we generated PD-L1 platelets through *in vitro* differentiation. These PD-L1 platelets retained canonical platelet markers such as CD41a and CD42a, and were capable of homing to inflamed pancreatic tissue. In newly diabetic NOD mice, a single intravenous administration of PD-L1 platelets significantly reduced the infiltration of effector T cells in the islets, reversed β-cell destruction, and enabled long-term maintenance of normoglycemia. Compared with hematopoietic stem cell-based vectors, PD-L1 platelets offer controlled sourcing, an appropriate circulatory half-life, and the ability to shed $\sim$100 nm microparticles, further enhancing local PD-L1 exposure. This strategy provides a novel and precise cell engineering platform for adjustable immune tolerance therapy in type 1 diabetes and other autoimmune diseases[184].

Tregs are essential for maintaining immune homeostasis and suppressing excessive inflammatory responses[193,194]. Tregs effectively inhibit aberrant activation of NK cells and T cells through multiple mechanisms, including the secretion of inhibitory cytokines such as IL-10 and TGF-β, induction of metabolic exhaustion, and suppression of dendritic cell maturation[195]. However, the functional maintenance of Tregs requires continuous exogenous IL-2 support. Systemic IL-2 administration, however, is often associated with widespread toxicity and side effects. To address this limitation, Eskandari et al.[196] developed a nanogel system (IL-2/Fc NGs) that anchors IL-2/Fc-loaded carriers to the surface of Treg *via* receptor−ligand interactions. In a reductive environment, this system enables the slow release of IL-2, thereby continuously promoting the proliferation and functional activity of Tregs. This innovative approach has significantly improved the survival of allogeneic grafts and offers a promising therapeutic strategy for AIDs such as type 1 diabetes.

Macrophages possess dual roles in immune regulation, making the modulation of macrophage phenotypes an important strategy for immune regulation and inflammation control[197]. In tissue healing, the topological properties of biomaterials can be directionally utilized to regulate macrophage polarization, thereby promoting the resolution of inflammation. For example, Nakkala et al.[198] developed an M2 macrophage membrane-based composite material (M2-PCL), in which M2 macrophage membranes were coated onto the surface of poly-ε-caprolactone (PCL) nanofibers to effectively induce *in vivo* M2 polarization of macrophages. The results showed that M2-PCL reduced the expression of pro-inflammatory chemokines and simultaneously upregulated the secretion of Arg-1, IL-10, and TGF-β, thus enhancing anti-inflammatory effects. This strategy leverages the intercellular communication capability of macrophage membranes to precisely target immune regulation to lesion sites, modulating immune cell phenotypes for anti-inflammatory purposes. It provides a novel approach for tissue healing and inflammation management. Pei et al.[199] achieved enrichment in myocardial tissue by loading viral macrophage inflammatory protein-II (vMIP-II) into engineered exosomes fused with a cardiac-targeting peptide and platelet membrane. Following uptake by macrophages *via* clathrin-dependent endocytosis, vMIP-II synergized with M2 macrophage-derived miRNAs (*e.g.*, miR-99a-5p) to promote phosphorylation of the STAT6/STAT3 signaling pathway, thereby driving macrophage polarization toward a reparative phenotype. This process improved the cardiac immune microenvironment and facilitated tissue repair. This approach provides a clinically meaningful research direction for mechanistic intervention and precise treatment of inflammatory diseases.

The single-target immunosuppressants or agonists often exhibit limited specificity, which can lead to an imbalance in the immune response, resulting in systemic side effects (such as infections and organ toxicity) and the development of drug resistance following long-term administration. ECNs employ a biomimetic design to achieve dual mechanisms of targeted delivery and active immune remodeling. They leverage natural signaling molecules on the membrane (such as CD47, adhesion factors, etc.) to interact with immune cells (*e.g.*, macrophages, dendritic cells, T cells), thereby actively modulating their phenotype and function. As demonstrated

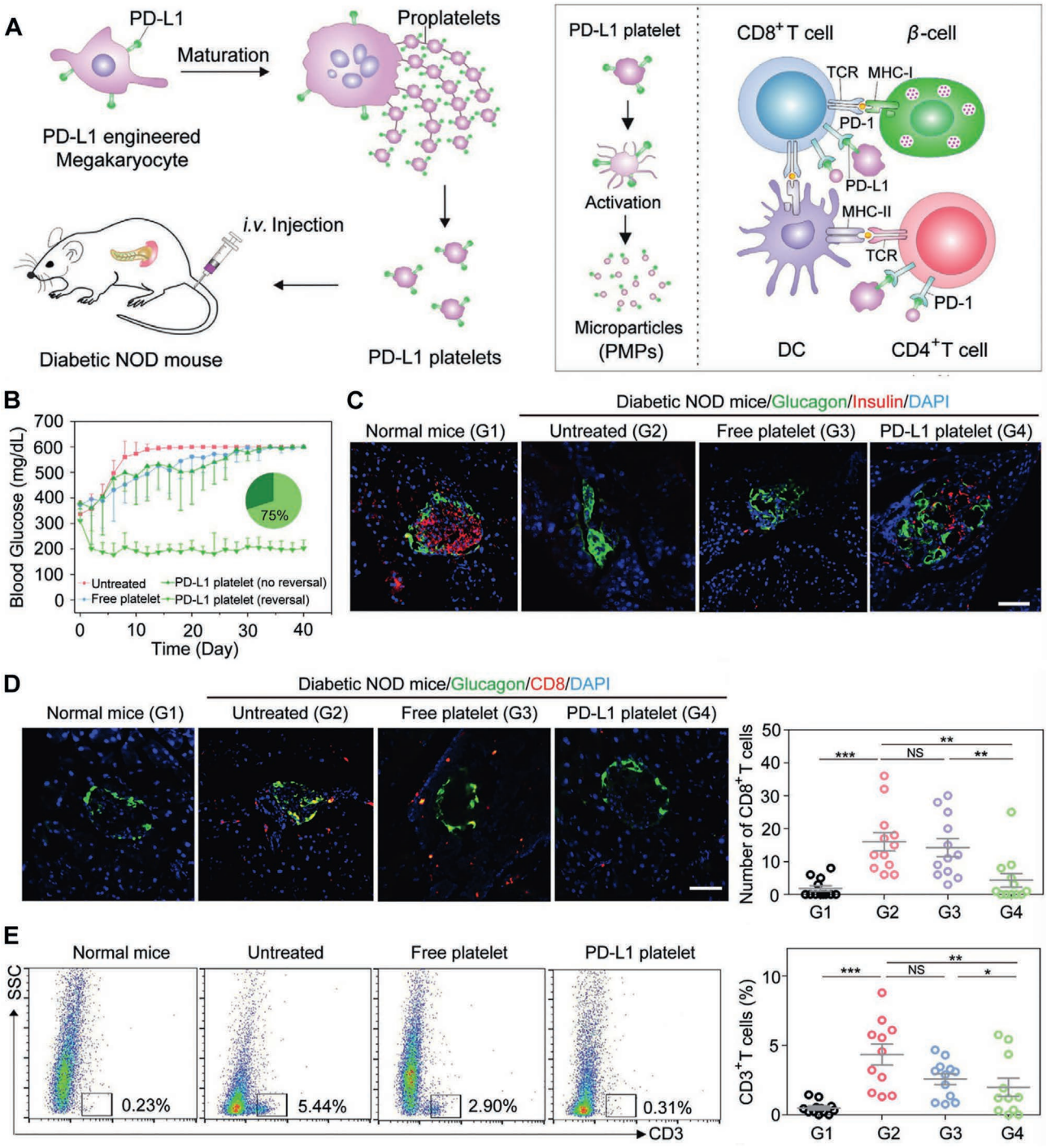

Figure 10 (A) Diagram illustrating the use of platelets engineered to overexpress PD-L1, aiming to suppress activated $CD8^+$ T cells and thereby protect β-cells. (B) Mean blood glucose measurements in diabetic NOD mice subjected to various treatment regimens. (C) Representative confocal microscopy images showing insulin-positive β-cells within pancreatic tissue sections. (D, E) Assessment of T cell profiles in the pancreas of treated diabetic NOD mice, determined by flow cytometry and immunofluorescence analysis. Reproduced with permission from Ref. 184. Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

in Fig. 11, compared to single-target immunosuppressants or agonists, ECNs enable stratified and precise regulation of the immune response during the dynamic progression of inflammation, achieving a synergistic effect of "inhibition-modulation-repair", which significantly reduces immune-related adverse effects and the risk of long-term drug resistance. However, current ECN-based immune regulation platforms face three major challenges: (1) The release of immunomodulatory molecules from ECNs often lacks precise spatiotemporal control, leading to risks of "over-activation" or "insufficient regulation", which may compromise long-term treatment safety; (2) The high spatial and temporal heterogeneity of tumor or inflammatory microenvironments results

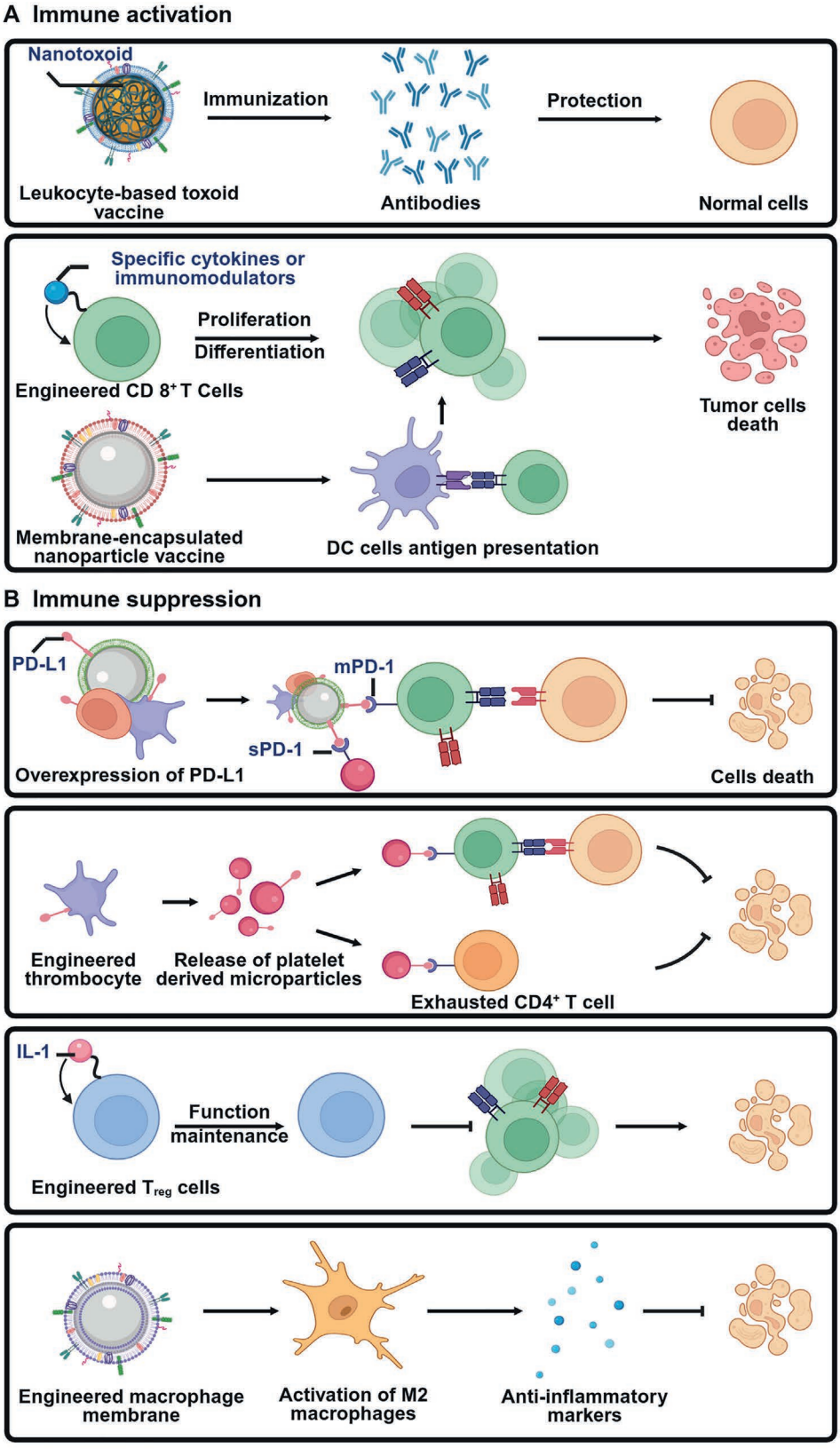

Figure 11 ECNs for immunomodulation. (A) Schematic of ECNs immunosuppression. (B) Schematic of ECNs immune activation. Created with BioRender.com.

in significantly variable interventional efficacy across different regions and disease stages, making stratified and precise intervention difficult to achieve; (3) The long-term host immune tolerance and potential immunogenicity following ECN delivery require comprehensive evaluation. An ideal ECN-mediated immune regulation strategy should: (1) enable on-demand release and spatiotemporal modulation through programmable bioengineering; (2) integrate nanomaterials, targeting systems, and gene editing technologies to construct multi-signal immune regulatory networks that synergistically overcome microenvironmental heterogeneity; and (3) systematically evaluate safety, tolerability, and immune memory formation in personalized and stratified therapeutic contexts. ECNs are evolving from "passive modification" toward "intelligent regulation", holding promise for comprehensive, multidimensional, and full-cycle precision intervention in inflammatory diseases. With the deepening integration of immunological insights, this platform is poised to play a profound role in precision immunotherapy.

In summary, ECNs integrate the triple advantages of active targeting, dynamic neutralization, and precise immune regulation. By overcoming the limitations of conventional drugs and synthetic materials, ECNs provide both theoretical and technical support for multi-dimensional intervention in complex inflammatory diseases. In the future, leveraging these core functions of ECNs in combination with small-molecule drugs, biologics, gene editing, and other therapeutic strategies is expected to further improve the treatment for refractory inflammatory diseases.

5. Challenges in the clinical application of ECNs

Insufficient understanding of cellular pathophysiology hinders the design of effective ECNs for specific disease treatments: (1) Cells of the same type derived from different tissues display heterogeneity, which is further influenced by the complexity of the inflammatory microenvironment. However, current cell classification systems remain inadequate in capturing the diversity of inflammatory microenvironments, thereby limiting the precision of ECN design. Therefore, a clearer understanding of the interactions between cells and lesions, as well as the characteristics of various inflammatory microenvironments, is needed to provide a theoretical foundation for targeted therapies. (2) Limitations of animal models in recapitulating inflammatory disease progression. Many inflammatory diseases, such as lobar pneumonia, exhibit distinct progression stages and pathological subtypes. However, existing experimental animal models fail to accurately simulate the full developmental trajectory of inflammatory diseases, leading to most ECN studies focusing on only a single stage of inflammation. For instance, immune responses differ significantly between acute and chronic inflammation, highlighting the need to further optimize ECNs to suit distinct phases of disease progression. (3) The dynamic nature of inflammation and the complexity of the immune system demand ECNs with adaptable immunomodulatory capabilities. Incorporating both immune activation and suppression-"dual regulation"-into ECN design can help meet the needs of different phases of inflammation. For example, activating pro-inflammatory responses in the early-stage inflammation can combat infection, while regulating anti-inflammatory responses in the later stage can promote tissue repair. Such approaches may even require the synergistic application of multiple types of ECNs to comprehensively address diverse inflammatory stages and phenotypes.

The establishment of large-scale cell expansion and Good Manufacturing Practices production systems is fundamental. A major challenge in scaling up production is the instability of the immune phenotype during *ex vivo* cell expansion and operational processes. This issue has been widely reported for various cell therapy products. For instance, commercial chimeric antigen receptor T cell products such as Kymriah demonstrate batch failure rates as high as 10%−15% during large-scale manufacturing, primarily attributed to the loss of essential surface markers, cell activation, and functional heterogeneity. CAR-macrophage therapy (*e.g.*, CT-0508) shows downregulation of key homing receptors (such as C-C chemokine receptor type 2 and CXCR4) after prolonged culture; MSC products (*e.g.*, CardiALLO, darvadstrocel) exhibit significant phenotypic and secretome alterations over multiple passages. Therefore, there is an urgent need for standardized, systematic production and quality monitoring processes, as well as the refinement of Good Manufacturing Practices systems to ensure product safety and consistency.

Regulatory approval and quality control systems require further improvement. In recent reviews by the Food and Drug Administration and European Medicines Agency, incomplete pharmacokinetic/pharmacodynamic (PK/PD) data, insufficient long-term safety evidence, and the absence of standardized potency evaluation criteria were identified as major obstacles. In Phase I/II clinical trials of exosome-based therapy, the circulating half-life varies considerably, reflecting inter-patient PK/PD variability and the complexity of immune clearance mechanisms. Thus, advancing PK/PD evaluation and establishing unified quality standards are crucial for accelerating clinical translation.

Safety and immunogenicity are also key considerations. Particularly for allogeneic, xenogeneic, or synthetically modified ECNs, animal studies indicate that approximately 15% of models develop anti-drug antibodies and complement activation after repeated administration[200]. CAR-natural killer products have improved production consistency, yet certain off-target cytotoxicity has still been observed in early trials. Although the incidence of adverse events in exosome-related clinical studies is low (<5%), delayed immune events underscore the necessity for long-term follow-up[201]. Therefore, long-term and systematic immunological safety monitoring remains crucial for advancing the clinical application of these novel therapeutic approaches.

6. Conclusions

ECNs can inherit the biomolecular signatures and functions derived from cells or cell membranes. They not only possess receptor-mediated homing ability to inflammatory sites but also engage in dynamic communication with immune cells *in vivo* and achieve spatiotemporal responses to inflammatory signals. Through precise modifications integrating physical, chemical, and genetic engineering approaches, ECNs significantly improve targeted delivery and *in vivo* pharmacokinetic properties, while enabling real-time sensing and reprogramming of the inflammatory microenvironment. These advantages far exceed those of traditional drugs and nanomaterial platforms.

Future research should focus on two highly promising yet underexplored directions: (1) Targeting inflammation-resolution mediators, such as resolvins, lipoxins, protectins, and maresins. These pro-resolving lipid mediators are currently underutilized in ECN design. If these molecules can be effectively integrated with ECNs through engineering strategies, it may enable selective

regulation of endogenous inflammation-resolution pathways, potentially shifting chronic inflammation treatment from suppression to active resolution and tissue healing. (2) Development of rational combination therapy strategies, which involve the systematic integration of ECNs with anti-inflammatory drugs, immune checkpoint modulators, tissue repair factors, and gene-editing tools. Such approaches aim to achieve synergistic multi-target enhancement and personalized precision intervention, effectively addressing the multifactorial nature and ecological heterogeneity of inflammatory diseases. At the translational medicine level, advances such as cryo-electron microscopy for membrane protein topology analysis and microfluidic single-cell encapsulation technology have enabled a closed-loop approach to ECNs development, encompassing structural elucidation through to functional assembly[202]. Integration of organ-on-a-chip platforms for dynamic simulation of inflammatory microenvironments, together with systems biology and synthetic biology, is expected to facilitate the transition of ECNs from passive anti-inflammatory agents to active mediators of immune repair. The interdisciplinary collaboration among nanotechnology, medicine, materials science, bioengineering, and pharmacy is anticipated to reduce development costs, bridge the gap between preclinical research and clinical application, and ultimately deliver more effective ECN-based therapy to patients.

In summary, ECNs integrate major advantages-biomimetic ultra-precise targeting, dynamic immune regulation, and efficient delivery-representing a new generation of therapeutic strategies for complex inflammatory diseases. They introduce new intervention strategies for inflammatory diseases that may offer patients more precise and durable therapeutic benefits.

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Author contributions

Ruiyao Liu: Formal analysis, Investigation, Data curation, Methodology, Writing − original draft. Wuting Dai: Formal analysis, Investigation, Data curation, Methodology. Wenbo Zhou: Methodology, Resources. Weilin Li: Methodology, Resources. Yuan Yu: Conceptualization, Methodology, Resources, Writing − review & editing, Supervision, Funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

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