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Biomimetic Cell Membrane-Coated Scaffolds for Enhanced Tissue Regeneration

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Cell membranes are emerging as valuable models for regulating scaffold-cell interactions in tissue engineering. Their unique structure and function provide an ideal template for creating biomimetic surfaces that support cell adhesion, proliferation, and differentiation. This has led to the development of cell membrane-coated scaffolds (CMCSs), a new class of biomaterials designed to mimic native cellular interfaces and improve therapeutic outcomes. This review begins with an overview of cell–extracellular matrix (ECM) interactions, highlighting their key roles in tissue remodeling and healing. It then introduces ECM-inspired coatings before focusing on CMCSs. A detailed analysis of scaffolds coated with specific membrane components or entire cell membranes is presented, with applications in skin and wound healing, bone regeneration, neural repair, and vascular grafts. Techniques for membrane extraction, surface functionalization, and preservation of membrane integrity and orientation are analyzed. CMCSs demonstrate advantages over traditional scaffolds, including improved homotypic cell attraction, immune modulation, and resistance to non-specific protein and bacterial adhesion. However, several challenges persist, such as standardizing membrane isolation methods, optimizing coating density, and evaluating the stability and reproducibility of coatings, especially when using hybrid membranes from multiple cell types. Overcoming these barriers could significantly advance scaffold technologies for regenerative medicine.

1. Introduction

1.1. Bioinspired Tissue Regeneration: An Urgent Unmet Clinical Need

While global life expectancy continues to rise, concerns about the quality of extended life are growing.[1,2] Diseases once considered acutely fatal—such as cancer, cardiovascular conditions, and infections—are increasingly manageable due to advances in safe, effective, and personalized medicines.[3] However, the ability to maintain tissue integrity and repair damage remains a major unmet challenge. Addressing specific diseases through biochemical pathways is often more straightforward than managing the complex cellular interactions required to restore functional tissues. Despite decades of breakthroughs in regenerative medicine, clinical applications remain limited.[4,5] The field faces persistent issues, including efficient tissue integration, cell viability, vascularization of scaffolds, and prevention of immune responses or infections.[6,7] These scientific and technical hurdles are compounded by

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regulatory and commercial challenges. Many regenerative therapies must be tailored to individual patients, necessitating lengthy and costly clinical trials and complicating widespread accessibility.[8,9] Bridging the gap between laboratory research and clinical implementation requires highly multidisciplinary teams—including experts in biology, pharmaceutical technology, biochemical engineering, and medicine—as well as educational reform to prepare the next generation of clinicians and researchers.[10,11] Progress in this field also relies on the development of bioactive materials and strategies that promote endogenous tissue repair.

A major advancement in biomedical sciences has been the decoding of the human genome, unlocking new therapeutic approaches through advanced therapy medicinal products (ATMPs). According to the European Medicines Agency, ATMPs include gene therapies, somatic-cell therapies, and tissue-engineered medicines.[12] These therapies often integrate cells, genes, and medical devices—such as scaffolds—into single, multifunctional treatments. Some are known as combined ATMPs because the medical device and the biological component are physically and functionally integrated. A detailed list of already approved cell-based medicines can be found elsewhere.[13]

In tissue-engineered therapies, incorporating living cells into or onto synthetic scaffolds remains particularly challenging from both technological and regulatory perspectives.[14] Preserving cell viability during scaffold fabrication is difficult due to exposure to harsh physical and chemical conditions such as high temperatures, pressures, or reactive agents. Human cells, especially in isolation, are very sensitive to environmental changes, unlike when they are embedded in organized tissues. Even minor cellular damage can trigger immune responses or reduce scaffold effectiveness. Additional concerns include identifying reliable cell sources, maintaining required cell densities, preventing tumorigenesis, and ensuring long-term therapeutic efficacy.[15,16]

Given these challenges, simpler and bioinspired strategies are gaining attention. These approaches aim to emulate natural tissue organization and healing mechanisms.[17] Instead of merely serving as structural supports, scaffolds are now designed to be biologically active. They must provide biocompatibility, functionality, and bioactivity, directly participating in tissue regeneration.

A particularly promising direction involves mimicking cell membranes, which serve as essential models for scaffold design. Cell membranes are not just passive barriers; they actively mediate critical biological processes such as signal transduction, energy exchange, and cellular communication.[18,19] Their unique structure—comprising lipids, proteins, and carbohydrates—enables precise control over how cells interact with their environment. Bioinspired scaffolds increasingly incorporate surface modifications that replicate membrane-like behaviors. For example, topographical cues (e.g., nanoscale ridges or grooves) and chemical modifications (e.g., functional groups or ions) on scaffold surfaces can profoundly influence how cells adhere, grow, and differentiate. These cues mimic natural extracellular matrix (ECM) interactions mediated by cell membranes. Techniques such as coating scaffolds with bioinorganic ions that engage with transmembrane proteins or applying surface polymers that alter membrane potential have shown success in modulating cellular responses.

The membrane model is particularly useful for enhancing interfacial processes—the initial and critical stages of interaction between cells and synthetic scaffolds. Efficient adhesion, communication, and proliferation at this interface are essential for successful tissue regeneration. By replicating the biological roles of membranes, scaffold surfaces can be designed to foster more natural cell behaviors, reduce immunogenic risks, and accelerate healing. Moreover, scaffold surfaces that mimic membrane composition can support more selective and effective interactions, enabling the recruitment of specific cell types or the activation of desired signaling pathways.[20] Although still insufficiently explored, this targeted approach can improve tissue regeneration outcomes and aligns with the principles of personalized medicine.

In summary, while regenerative medicine faces ongoing challenges in both science and regulation, cell membranes have emerged as a critical model for next-generation tissue engineering. Their ability to guide biological activity makes them invaluable in the design of biomimetic scaffolds. Leveraging their structural and functional complexity allows for the creation of synthetic environments that closely replicate natural tissues, offering improved cell survival, integration, and regenerative potential. As the field advances, cell membrane-inspired strategies are poised to play a central role in the successful development and translation of tissue-engineered therapies.

1.2. Applying Cell Membrane Coatings to Drug Delivery Systems

In the drug delivery field, coating drug nanocarriers with cell membranes has already received considerable attention as it can provide homotypic targeting.[21,22] Active targeting of the nanomedicines to specific tissues or cells relies on the decoration of the nanoparticles with ligands capable of recognizing receptors that are overexpressed in the membrane of target cells. An increasing knowledge of genomic disorders and disease-related genes allows today to classify diseases according to a genetics-based taxonomy, which is a key achievement, particularly in the case of cancer.[23] Changes in the surface of cells affected by a certain pathology can now be identified, which in turn facilitates the design of ligands capable of simultaneously recognizing two or three of the over-expressed receptors in the membrane of target cells with respect to healthy cells. The ligands should be fixed on the surface of the nanoparticles in an adequate configuration and density. However, the dilemma that arises is which receptor or set of receptors in the cell membrane is best for the nanoparticles to recognize. Very diverse results have been obtained depending on whether the ligands recognize the membrane of endothelial cells, so that when circulating in the blood, they recognize the tumor vasculature, or whether they recognize only the tumor cells.[24] The reality is very complex, and only a very small percentage of the administered nanoparticles effectively reach the target tissue or cells. A step forward in this goal is to decorate nanocarriers with components of cell membranes to provide them with the functionalities that allow cells to recognize different environments using their natural tropism to move in our body to specific places.[25]

Cell membrane coatings provide nanoparticles with lipids, carbohydrates, and proteins that can delay clearance by the immune

system and offer an additional level of surface functionality like that of certain cells. Coatings with red blood cell (RBC) membranes have been shown to help nanoparticles evade the immune system, prolonging the circulation in the bloodstream.[26] Differently, coating the wall of bacteria strongly stimulates innate immunity, enhances biofilm penetration, and facilitates targeted delivery through homotypic binding, improving overall therapeutic efficacy.[27,28] The membrane of platelets, immune system cells, and mesenchymal stem cells can endow nanoparticles with targeting capabilities towards inflamed areas and tumor tissues.[29,30] In the last decade, coating nanocarriers with tumor cell membranes has shown remarkable advantages. Homotypic vectorization, or homologous identification, aims at the self-recognition of tumor cells and metastases to enhance selective drug accumulation in the target cells. This biomimetic approach exploits the affinity between tumor cells, mediated by specific membrane proteins, and is based on the natural capacity of tumor cells to recognize other identical tumor cells and develop strong contacts and adhesive interactions through membrane receptors.[31,32]

Various techniques have been described to obtain tumor cell samples, extract the membranes, and cloak the nanoparticles in the cell-derived membranes.[33,34] The procedures are very diverse and must be optimized for each cell membrane-nanoparticle pair, but despite the technological challenges, the use of natural cell membranes significantly circumvents the difficulties of synthetically replicating their structure and composition.[35] Combining cell membranes of different characteristics on the surface of the nanocarriers is opening a new scenario in drug targeting.[36]

In the field of regenerative medicine, stem cell nanovesicles loaded with miR-181a-5p and coated with platelet membrane have been shown to improve targeting to damaged myocardium.[37] The coated nanovesicles enhanced myocardial cell viability, angiogenic response, and anti-inflammatory macrophage polarization, facilitating postmyocardial infarction cardiac repair. Homotypic targeting has only recently been tested as a way of delivering antimicrobial agents-loaded nanoparticles to infected implants. Levofloxacin-loaded silica nanoparticles coated with a hybrid membrane from *Escherichia coli* and RBC membranes were shown to activate innate immune response, target the antibiotic to the bacterial cells, and modulate the inflammation, eradicating the biofilm from the implant (**Figure 1**).[38]

1.3. Bioinspired Inverted Targeting

A completely different targeting strategy seeks to stimulate the cells to move towards the treatment, instead of developing the magic bullets (drug nanocarriers) that target the cells. The hypothesis behind this "reverse" or "inverted" targeting is that some cells can cover large distances in our body (e.g. tumor cells can form metastases far away from primary tumors), and under adequate signals, their movement can be tuned to accumulate in preimplanted scaffolds. For cell attraction to be efficient, the scaffold should recreate the best possible niche for the cells of interest. In the field of cancer, there are already some examples of scaffolds that perform as ecological traps, attracting and confining tumor cells in a specific place by making use of chemotaxis and haptotaxis. Once confined in the trap, the treatment, either pharmacological or physical, is locally applied, notably enhancing the efficiency and the selectivity of the therapy.[39,40]

An alternative strategy to guide cell movement towards specific tissues involves modifying the cell surface. For instance, mesenchymal stem cells (MSCs) were modified on their membrane with palmitated protein G (PPG), which was then conjugated with a type II collagen antibody. These modifications did not alter cell behavior but significantly increased the affinity of the modified cells for osteochondral surfaces, demonstrating tissue-specific targeting potential. This approach could be valuable for managing cartilage defects and osteoarthritis.[15] In parallel, MSCs spheroids wrapped in polyamidoamine (PAMAM) dendrimers conjugated with the oligopeptide IKVAV and hyaluronic acid (HA) were shown to modify cytokines and miRNA secretion in extracellular vesicles. These changes may impact the behavior of other cells during tissue repair, as demonstrated in a rat myocardial infarction model.[41]

In the regenerative medicine field, preparation of scaffolds capable of attracting cells and regulating their distribution and differentiation for tissue reconstruction has so far relied mostly on single chemical and physical clues emitted from the scaffold.[42–44] Only very recently has the coating of scaffolds with homotypic cell membranes started to be explored as a way of enhancing cell-substrate interactions and the subsequent cell differentiation.

1.4. Aims Of the Review

This review aims to compile information on scaffolds coated with either complete cell membranes or specific membrane components and analyze their advantages and disadvantages compared to non-coated scaffolds. First, an overview of the importance of the interactions between the cells and the ECM is provided, emphasizing the mutual role they play in tissue remodeling and healing. ECM-based coatings have been widely studied.[45,46] In contrast, there is limited research on coatings made from their counterparts—cell membranes—and a comprehensive analysis of the emerging literature may offer insights into the potential of this approach.

2. Coatings Bioinspired in Cell-Extracellular Matrix Interactions

Tissue-inspired interfacial coatings have attracted attention during the last decade as a way to improve the performance of scaffolds in tissue reconstruction.[47] Most efforts have focused on how to mimic the components of the ECM in order to provide a friendly environment that can attract the right cells of the host and regulate their phenotype and functions.

The composition and mechanical properties of ECM are different for each tissue, but all ECMs basically consist of a network of glycoproteins, proteoglycans, and glycosaminoglycans, also comprising enzymes that can degrade such a network and their inhibitors.[48] The ECM dictates how cells organize to form a tissue and provides the required structural support. Each tissue-specific component of the ECM plays a key role in the adhesion

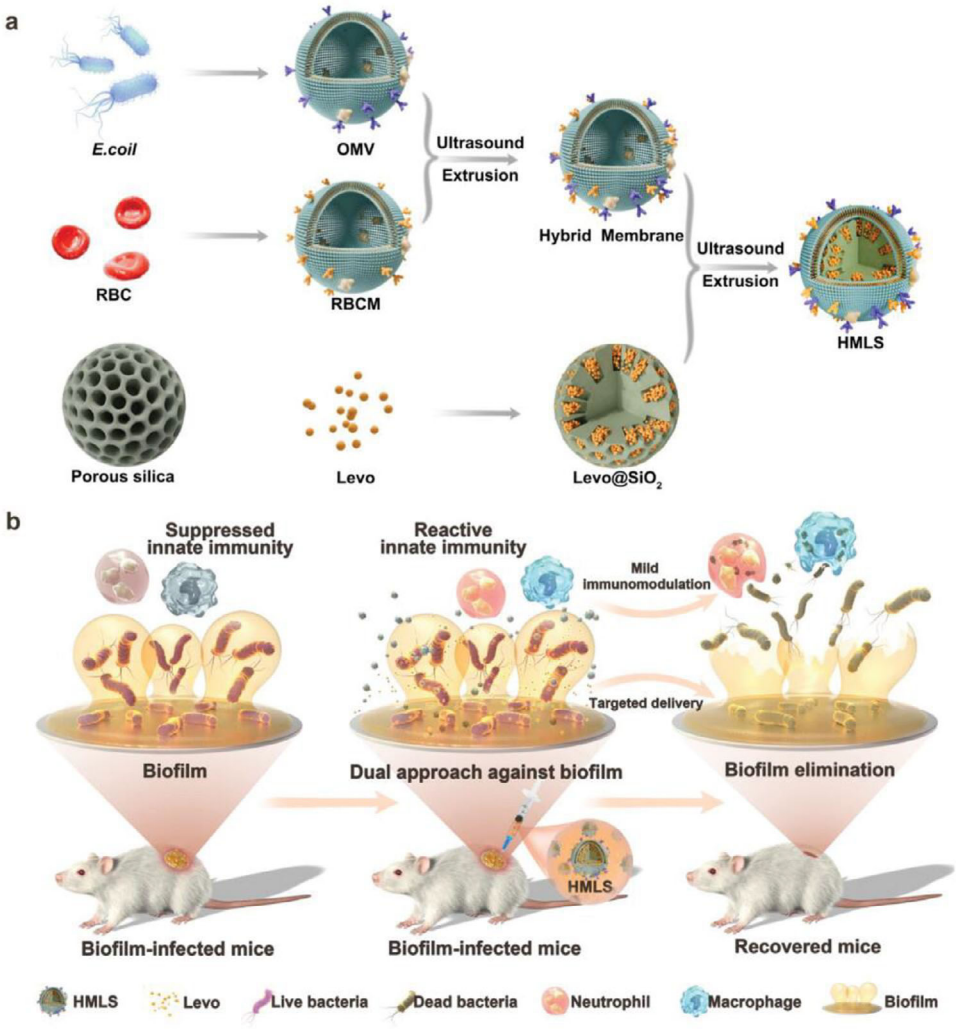

Figure 1. a) Extraction of the outer membrane vesicles (OMVs) of *Escherichia coli* and red blood cell (RBC) membranes and subsequent cloaking of levofloxacin-loaded silica nanoparticles to obtain Hybrid Membrane@Levo@SiO_2 (HMLS); and b) changes induced by the HMLS in the immune response and bacterial targeted delivery of the antibiotic for the treatment of implant-related infections. Reproduced with permission.[38] Copyright 2023, John Wiley and Sons.

and organization of the cells; for example, there are 24 subtypes of collagen that are expressed by different cell types, and the interactions of a cell with each collagen subtype are specific and determine the behavior of the cell. Collagen type I is required to form bones, while a mixture of collagen type I, III, IV, XV, and XVII is needed to form vascular tissue. Elastin in the ECM of the vascular wall regulates the phenotype of vascular smooth muscle cells and the elasticity of blood vessels, while fibrinogen and fibronectin are required to facilitate the adhesion and differentiation of endothelial cells.[49]

ECM is under continuous remodeling by secreting cells to facilitate their movement, proliferation, and differentiation, and in turn, ECM remodeling modifies cell-signaling pathways. The interactions between the cells and the ECM can occur directly or indirectly through cooperative molecules. Direct interaction is mediated via integrins and other cell surface receptors (**Figure 2**). Integrins are categorized according to their ligands in four groups: leukocyte cell-adhesion integrins, Arg–Gly–Asp (RGD)-binding integrins, collagen (GFOGER)-binding integrins, and laminin-binding integrins.[50] Other cell receptors for ECM components comprise the discoidin domain receptor (DDR) family for collagens, the CD44 receptor for hyaluronan (HA), the receptor for HA-mediated motility (RHAMM), and the heparan sulfate proteoglycan (HSPG) receptor for ECM macromolecules and diverse cytokines.[51,52] Alternatively, indirect interactions involve the participation of cooperative molecules such as growth factors (GFs) and cytokines, including chemokines, released by the cells in the tissue or by other cells.[51] Many ECM macromolecules bind GFs and chemokines, creating compositional gradients that regulate chemotaxis and cell differentiation.

The turnover of the ECM components and the release of bound substances from ECM degradation matrix components make the environment of the cells to be highly dynamic. Such a dynamic environment is sensed by the cells through multiple-point interactions with the surrounding molecules. Any imbalance in the external signals causes changes in the intracellular signaling

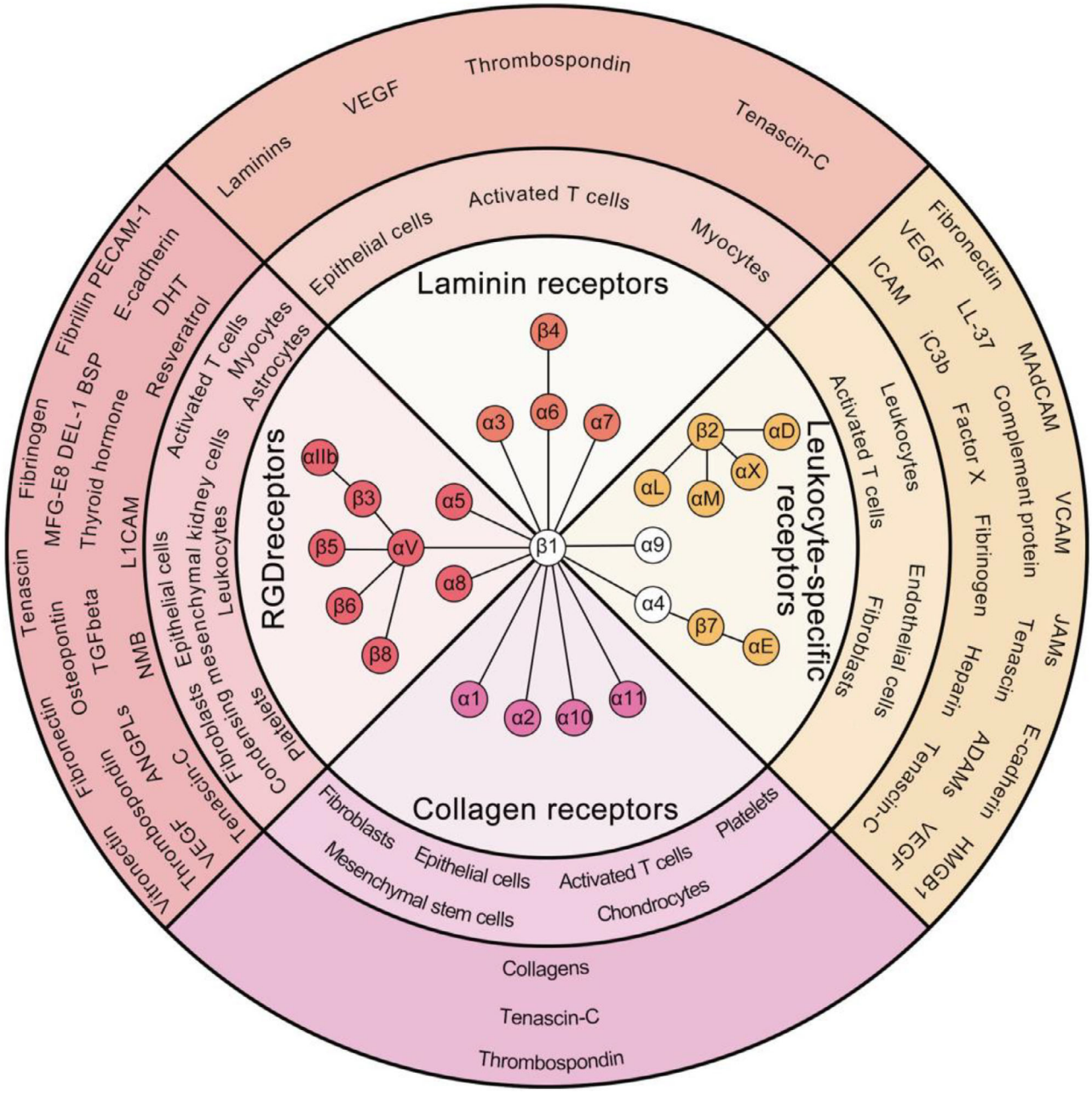

Figure 2. The classification, distribution, and ligands of integrins are illustrated in a three-ring model. The inner ring represents the 24 integrins, composed of 17 α subunits and 8 β subunits, categorized into four groups based on their distribution, ligand specificity, and functions: RGD-binding integrins, leukocyte cell-adhesion integrins, collagen-binding integrins, and laminin-binding integrins. The middle ring depicts the distribution of these integrins across various cell types, while the outer ring highlights the ligands that different integrin types bind to. Reproduced under terms of the CC-BY license.[50] Copyright 2023, The Authors, published by Springer Nature.

pathways, which can initiate a pathological process or can be beneficial for the recovery of the tissue from damage.

The reciprocal interaction between the ECM components and the cells is the basis of ontogenesis, wound healing, and tissue homeostasis.[53] Thus, in a tissue, both the ECM and the cells can be considered from the double perspective of matter and information.[54] Indeed, as many diseases are associated with changes in the ECM (e.g., glycation in diabetes and cancer) or in the ECM-cell signaling, ECM components are being evaluated as potential targets in pharmacotherapy.[55–57] Also, in parallel, water-insoluble decellularized ECM networks are being widely explored as main components of tissue scaffolds, as they retain the biocompatibility and bioinductivity properties of the native ECM.[58]

Coating scaffolds with ECM components has been tested as a way to immobilize a variety of growth factors and to

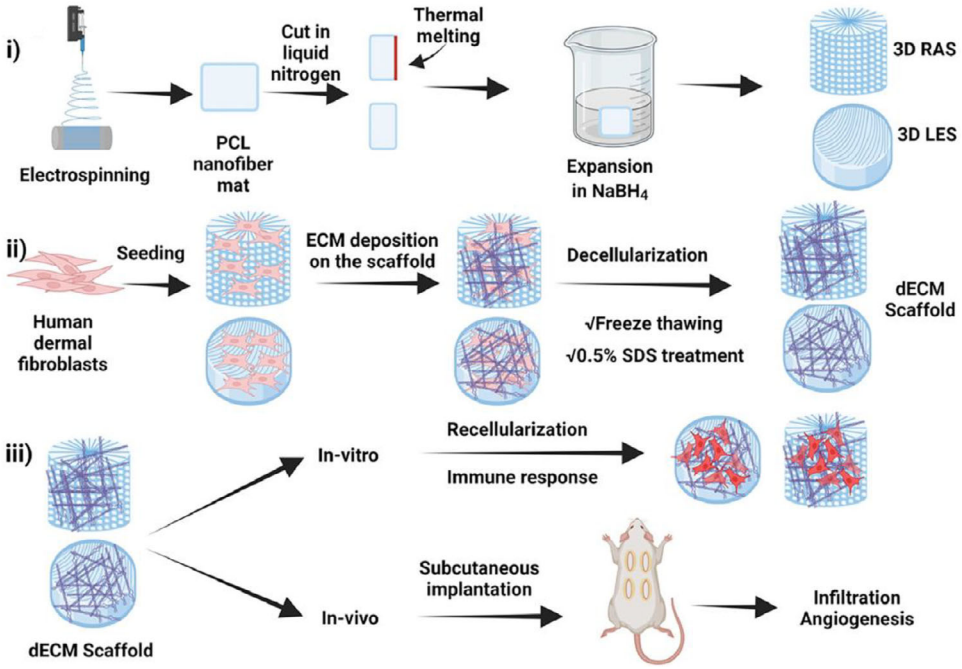

Figure 3. Development of decellularized extracellular matrix (dECM)-decorated 3D expanded nanofiber scaffolds. i) Fabrication of radially aligned (RAS) and laterally expanded (LES) scaffolds by transforming 2D nanofiber mats into 3D scaffolds using a gas-foaming expansion technology; ii) Seeding of fibroblasts on the scaffolds, cell growth, ECM deposition, and subsequent decellularization to generate dECM-decorated RAS and LES; and iii) In vitro and in vivo assessment of dECM-decorated RAS and LES through recellularization and subcutaneous implantation. Reproduced with permission.[65] Copyright 2024, Elsevier.

regulate their activity through a controlled release from the scaffold surface or by creating concentration gradients. Interested readers are referred elsewhere.[45,47,59–61] Just to highlight a few examples, one of the first in vivo demonstrations of the capability of ECM components to improve the survival and performance of transplanted pancreatic islets was made with poly(lactic-co-glycolic) acid (PLGA) porous scaffolds coated with collagen IV, fibronectin, laminin-332, or serum proteins.[62] Pancreatic islets seeded on the collagen IV-coated scaffolds were shown to be able to restore glucose levels in streptozotocin-induced diabetic mice in less than 4 days after implantation. Differently, the graft functionality of serum-coated scaffolds became apparent after 36 days, showing disruption of the islet architecture and presence of individual cells. Scaffolds coated with fibronectin or laminin-332 showed intermediate performance, highlighting the critical role of ECM components in the development of functional tissues.

Biphasic calcium phosphate scaffolds coated with the ECM produced by MSCs have also been shown to improve cell adhesion and bone formation both in vitro and in vivo, compared to non-coated counterparts.[63] More recently, electrospun mats of poly-L-lactic acid (PLLA) and silk fibroin coated with decellularized ECM from osteoblast cells cultured on the scaffold notably enhanced osteogenic differentiation.[64] In this same line, decellularized ECM of human dermal fibroblasts that were grown on poly(ϵ-caprolactone) (PCL) nanofiber scaffolds promoted cell infiltration and neovascularization once subcutaneously implanted (**Figure 3**).[65] Literature on ECM-decorated scaffolds is exponentially increasing as the tests in in vivo models evidence their advantages compared to pristine scaffolds.

Although ECM-based scaffolds are attracting growing attention and hold significant promise for replicating the architecture of entire organs, several critical challenges remain. To meet the safety standards for allogeneic or xenogeneic ECM scaffolds, complete removal of cells and immunogenic antigens is essential to prevent adverse immune responses. At the same time, a deeper understanding is needed of how to effectively recruit, orient, and differentiate the cells necessary for tissue reconstruction, including those involved in vascularization.[66] While these challenges are being addressed, the (bio)functionalization of scaffolds through decoration or encapsulation with cell membranes is gaining increasing attention[67,68] as discussed in the following sections.

3. Cell Membrane-Coated Scaffolds: A Field to Explore

3.1. Literature Search

Information was collected from December 2024 to February 2025 in the Web of Science Core Collection database (Clarivate). The search was also repeated in PubMed and Embase in May 2025 to check for additional contributions. No restrictions were applied regarding the publication date or the date of inclusion in the databases. The search of "cell membrane" AND coating NOT particles NOT nanoparticle NOT nanoparticles NOT fuel NOT catalys* NOT electrochromatography NOT ultrafiltration NOT cancer rendered 1221 outcomes. These 1221 were refined, in separate, by "regenerati*" (39 documents), "wound" (15 documents),

Table 1. Examples of scaffolds coated with cell membrane-mimicking components, with indication of the preparation procedure and main outcomes. Abbreviations: MPC: 2-methacryloyloxyethyl phosphorylcholine; PLLA: poly(L-lactic acid).

Entry	Components mimicking cell-membrane	Scaffold	Preparation procedure	Outcomes	Refs.
1	Zwitterionic interface made of MPC and heparin	Blood-contacting device	Precoating of the device with polydopamine, immobilization of polyMPC using carbodiimide chemistry, and subsequent immobilization of heparin	Lower adsorption of albumin, fibrinogen, and platelets. Higher thrombosis resistance	[81]
2	Zwitterionic interface made of heparin and a copolymer of 2-(N-3-sulfopropyl-N, N-dimethyl ammonium)ethyl methacrylate and 2-methacryloyloxyethyl succinic acid	Blood-contacting device	Precoating of the device with polydopamine, immobilization of the zwitterionic copolymer, and grafting of heparin	Prolonged anticoagulant-free extracorporeal circulation in a beagle dog model without thrombus formation, avoiding the need for systemic administration of heparin.	[82]
3	Zwitterionic interface of MPC	Stainless-steel implant	Chemical grafting of MPC	Lower *Staphylococcus aureus adhesion* and good compatibility with pre-osteoblast cells	[83]
4	Zwitterionic MPC reversible 3D networks	3D hydrogel of MPC copolymers bearing benzoxaborole and catechol	Reversible hydrogel formation through pH and sugar-sensitive boronic esters	Preservation of cell viability of encapsulated cells for 24 h	[85]
5	Zwitterionic poly(MPC-co-n-butyl methacrylate)	Blend of poly(MPC-co-n-butyl methacrylate) and PLLA	Tubes made with the blends and showing a high density of phosphorylcholine groups on the inner surface	Adequate mechanical properties, good hemocompatibility, and slow biodegradation.	[86]
6	Zwitterionic conductive ethylenedioxythiophene (EDOT) monomers with MPC	Bioelectronic device	EDOT-based materials with grafted MPC and also peptide ligands to mimic integrin-ECM interactions	Prevention of non-specific binding of proteins and cells, and electrical stimulation of neural cells	[87]
7	Zwitterionic MPC network combined with collagen network.	Implant for corneal substitution	Cross-linked porcine collagen interpenetrated by MPC hydrogel	Implantation into the cornea of mini-pigs revealed no adverse reactions. 12 months after operation, the implants were populated with corneal epithelial and stromal cells and nerves.	[88]
8	Membrane-like lipidic bilayers	Electrospun scaffold	Immobilization of silk fibroin onto polystyrene scaffold and subsequent covalent immobilization of liposomes	Subcutaneous implantation in a mice model evidenced lower foreign-body reaction and better tissue integration through macrophage polarization toward a pro-regenerative phenotype.	[89]
9	Phospholipid-based large unilamellar vesicles (LUVs)	Glass supports for in vitro studies	LUVs were fused onto hydrophilic glass supports and then modified with RGD ligands	Cell adhesion, morphology, and differentiation strongly depended on RGD ligand density and mobility.	[90]

"healing" (17 documents), "fouling" (14 documents), and "scaffold" (21 documents). All documents were manually screened to identify those dealing with cell membranes or their components used to coat medical devices for regenerative medicine. A summary of the original papers that were finally analyzed is provided in **Tables 1** and **2**. Reviews and book chapters covering these topics were only used to elaborate on the general context. No clinical trials were found when searching in the ClinicalTrials.gov database.

3.2. Cell Membrane Structure and Composition

The plasma membrane of mammalian cells plays a key role in the correct functioning of the cells. It not only regulates the exchange of substances between the inside and the outside of the cell but also participates in critical physiological functions and signaling.

The plasma membrane (7.5–9.0 nm thick) is composed of approximately 50% lipids, mainly glycerophospholipids and cholesterol, and 50% proteins, mostly transmembrane proteins embedded in the lipid bilayer (5 mm thick) and protruding on both sides of the membrane or proteins anchored to the outer leaflet. Lipids and proteins are engaged in a highly regulated way. In addition to their role in the control of the transport of substances and the anchoring to ECM, some lipids and transmembrane proteins are actively involved in communication (cell signaling) and generation of bioactive metabolites, which can act as second messengers or as communication signals to regulate other cells.[69] Recognition and binding of specific external substances cause a conformational change in the lipid/protein that triggers a signal to intracellular messenger molecules. Moreover, the plasma membrane is part of the endomembrane system, which also includes all membranes surrounding intracellular organelles (endoplasmic reticulum, nuclear membrane, the Golgi apparatus, mitochondria, lysosomes...), and may interchange some components

Table 2. Examples of cell membrane-coated scaffolds, with indication of the preparation procedure and main outcomes.

Entry	Cell-membrane source	Scaffold	Preparation procedure	Outcomes	Refs.
1	MIN6 mouse pancreatic beta cells.	Electrospun polycaprolactone (PCL):poly-D-lysine 10:1 nanofibers	Cell membranes were isolated from MIN6 cells, PCL and poly-D-lysine nanofibers were fabricated by electrospinning, and then the nanofibers were coated with the cell membranes by a fusion process. The fusion was confirmed by microscopy and the presence of proteins by SDS-PAGE and Western blotting.	Cell membrane-coated nanofibers (CM-fibers) improved cell proliferation, function (insulin secretion), and cell aggregate formation compared to uncoated nanofibers, demonstrating a successful and functional coating.	[103]
2	Blebs obtained from BHK cells (baby hamster kidney)	Poly(3,4-ethylenedioxythiophene): poly(styrene sulfonate) (PEDOT:PSS) electronic device	BHK cell blebs were generated, adsorbed on PEDOT:PSS, and liposomes and PEG were added to form bilayers and characterized with FRAP and EIS.	The platform demonstrated native protein mobility and targeting, detection of P2 × 2 ion channel activity with ATP, and dual optical and electrical monitoring capabilities.	[104]
3	M1 macrophages (proinflammatory phenotype)	PLGA electrospun nanofibers	PLGA nanofibers were grafted with 1,2-distearoyl-sn-glycero-3-hosphoethanolamine-polyethylene glycol-amine and coated with the membranes of M1 macrophages.	M1 macrophage membrane-coated scaffolds showed a high capability to adsorb inflammatory cytokines, protecting tenocytes from apoptosis in cell culture tests. Wrapping a tendon injury with this scaffold prevented scarring formation.	[106]
4	3T3 fibroblasts and red blood cells.	Electrospun polycaprolactone (PCL) fibers.	Membranes were isolated from 3T3 fibroblasts and RBCs. Electrospun PCL fibers were coated with membranes by dropping the cell membrane dispersion on the fibers. HaCaT keratinocytes were seeded, and growth was evaluated.	Higher HaCaT growth was observed on scaffolds with 3T3 membrane versus non-coated and RBC-coated scaffolds. Coating efficiency was not affected by fibers diameter or charge.	[107]
5	Neuroblastoma (N2a)	Near infrared radiation (NIR)-sensitive MOF nanoparticles	Neuroblastoma cell membrane and cytoplasm were extracted. MOFs were loaded with proteins, coated with the cell membrane, and incorporated into a hydrogel scaffold.	The scaffold with coated MOFs promoted skin regeneration, sensory recovery, and hair follicle neogenesis. Also, it modulated inflammation and released proteins in burns and injuries in an in vivo model.	[108]
6	LPS/INF-y activated mouse RAW264.7 cell and human THP-1cells	Electrospun polylactic-co-glycolic acid (PLGA) nanofibers	Macrophages were activated with LPS/IFN-γ, and cell membranes were isolated. PLGA nanofibers were coated with the membranes by soaking, loaded with MSCs, and evaluated both in vitro and in vivo.	MSCs proliferation and keratinocyte migration were enhanced. Accelerated healing, reduced inflammation, promoted angiogenesis, and collagen remodeling in diabetic wounds by CD200-CD200R interaction.	[111]
7	M2 macrophages (proregenerative phenotype)	PLGA microspheres	Microspheres were loaded with M2 macrophages-derived lysate proteins and then coated with M2 membrane. Release of anti-inflammatory and pro-regenerative components was investigated in detail.	M2 membrane-coated microspheres released anti-inflammatory cytokines and growth factors and regulate cell migration and proliferation in a mice model of pressure ulcer.	[112]
8	Macrophages RAW 264.7	Nanocomplex NC composed of with α-helical polypeptide and siRNA.	Macrophage membrane was extracted, core formed with polypeptide and siRNA, coated with catalase and membrane, and sSDF-1α peptide was anchored for controlled release.	Accelerated bone regeneration, MSC recruitment, enhanced osteogenic differentiation, bone callus formation and excellent biocompatibility were observed in mouse fracture models.	[114]
9	Hybrid cell membrane from anti-inflammatory phenotype macrophages (M2-Macs) and osteoinductive mesenchymal stem cells (oi-MSCs)	Electrospun polylactone (PCL) fibers	Hybrid membranes from anti-inflammatory macrophages (M2-Macs) and osteoinductive mesenchymal stem cells (oi-MSCs). Hybrid membranes and PCL fibers were modified, in separate, with biotin, and then incubated together in the presence of streptavidin to create the functionalized matrix.	Enhanced macrophage anti-inflammatory phenotype, alkaline phosphatase secretion, and mineralization deposition of MSCs in vitro. Facilitated bone regeneration in rat calvarial critical-size defect.	[115]
10	Hybrid cell membrane from M2-Macs and oi-MSCs	Electrospun polylactone (PCL) fibers	siRNA against sFlt-1 and p75NTR were synthesized and encapsulated in hybrid membranes (M2-Macs and ol-MSCs). The hybrid membranes and the PCL fibers were modified, in separate, with biotin, and then incubated together in the presence of streptavidin to create the functionalized matrix (GFM).	GFM promoted angiogenesis, neurogenesis, and osteogenesis in vitro and in vivo, enhancing bone regeneration, vascularization and innervation in a rat skull bone defect model.	[116]

(*Continued*)

Table 2. (Continued)

Entry	Cell-membrane source	Scaffold	Preparation procedure	Outcomes	Refs.
11	MSC (naive and IFN-γ primed)	Gelatin microribbon scaffolds	Microribbon scaffold was modified with poly-lysine and then coated with MSC membrane. Alternatively, nanoparticles containing BMP-2 were immobilized on the scaffold surface before the coating.	MSC (IFN-γ primed) membrane-coated scaffolds promoted the regenerative phenotype of macrophages and T cells. Delivery of low doses of BMP-2 from the membrane-coated scaffolds promoted mineralized bone since week 2.	[117]
12	Red blood cells	Titanium	Titanium was layered coated with tannic acid, black phosphorous, and RBC membranes.	Coated implants showed higher increase I temperature when irradiated with NIR light, and slower cooling when light was switched off. Enhanced antibacterial and osteoinductive outcomes in a *Staphylococcus aureus*-infected bone defect model.	[118]
13	Bone marrow mesenchymal stem cells	PLGA microspheres	Microspheres were loaded with paracrine factors and then coated with MSC membrane.	Coated microspheres showed enhanced proliferation and migration capability of OA chondrocytes, counteracting IL-1β-induced cartilage damage. Micro-CT scanning and X-ray imaging confirmed that after 8 weeks treatment the cartilage of the group treated with the coated microspheres was significantly healed, resembling the sham group.	[125]
14	Chondrocyte cell membrane vesicles	3D printed scaffolds prepared with a bioink made of polymerizable punicalagin-loaded vesicles and sericin	3D bioprinted hydrogels were obtained by irradiation with 405 nm light. The vesicles released from the hydrogels in the presence of elevated ROS levels were readily internalized by chondrocytes.	In vivo test in cartilage defects confirmed antioxidant and antibacterial activities, contributing to faster healing compared to scaffolds prepared without the vesicles.	[126]
15	Chondrocyte cell membrane extracts	Type 2 collagen hydrogels (decellularized hyaline cartilage graft)	3D Col2 scaffolds were prepared either without (Col2S) or with (antCol2S) coatings of chondrocyte membrane extracts.	The membranes shielded Col2, and antCol2S caused upregulation of Wnt/β-catenin signaling pathway, which is an opponent to maintenance of the hyaline cartilaginous phenotype. Consequently, in contact with antCol2S the cells lost the hyaline cartilaginous phenotype.	[127]
16	P12 cells	Titanium	Titanium was modified with APTES and DOPE. Membranes were extracted from NGF-differentiated PC12 cells. Vesicles were fused to form PM-TLB.	PM-TLB reduced protein and bacterial adhesion, inhibited astrocyte and macrophage activation, and promoted neuronal adhesion and growth with neurite elongation.	[129]
17	Red blood cells	Electrospun polycaprolactone (PCL) 10%:poly-D-lysine 0–2% nanofibers	Nanofibers were incubated with the red blood cell membrane vesicles at 4 °C for 12 h. Tubes were prepared by rolling and glued with fibrin and tested as replacement of carotid artery of rabbits.	The membrane-coated tubes decreased the risk of thrombosis and allowed for smooth, laminar blood flow after 21 days implantation.	[133]
18	Red blood cells	PCL electrospun fibers collected on a hydrogel film of collagen and RBC membranes cross-linked with genipin, and rolled to form a tubular graft.	The tubes had the PCL electrospun fibers as external layer and the collagen-RBC membrane lining the inner surface. They were tested as replacement of carotid artery of rabbits.	The tubes promoted rapid vascular regeneration within 31 days, with a complete recovery of the ECM and the smooth muscle cells.	[134]
19	Vascular endothelial cell membranes (BEND.3)	Interpenetrating network of type II and type IV collagen	Cell membrane vesicles were directly mixed with the collagen components. Cell membrane stability was verified after immersion in physiological saline for 1, 7, and 14 days. DiI-stained membranes were observed under a fluorescence microscope.	In vitro studies revealed that the scaffold retained the cell membrane for one week. After in vivo implantation, the scaffold adhered to spleen tissue, decreased oxidative stress, recruited cells, and promoted vascular regeneration.	[135]

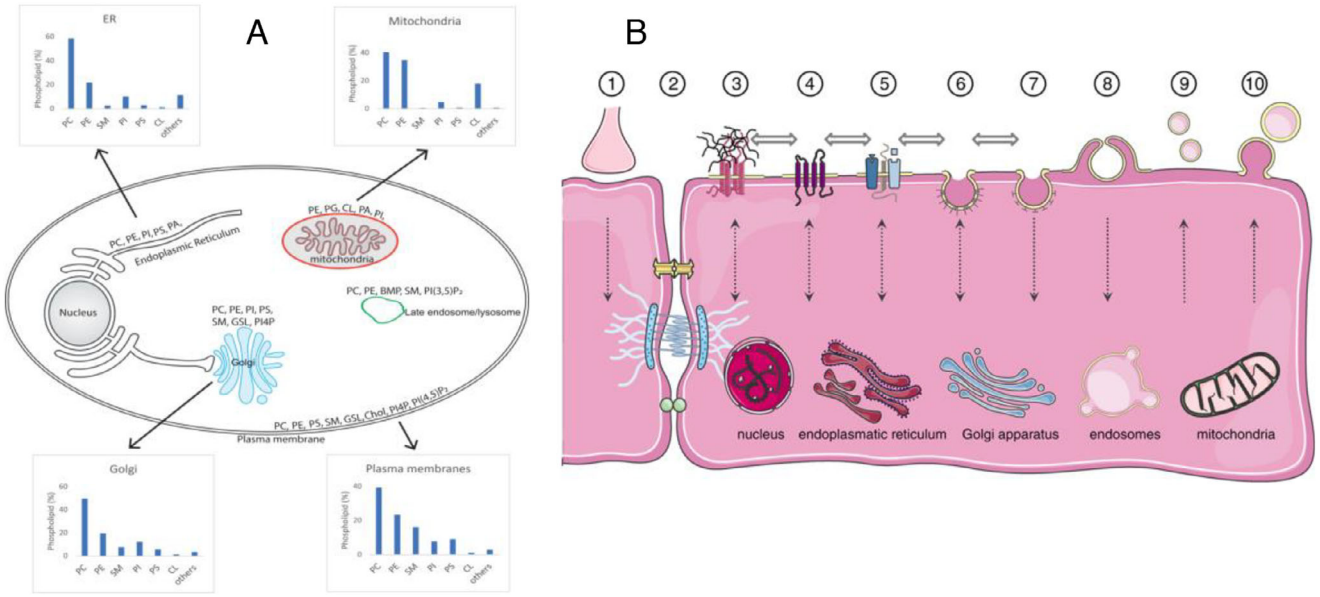

Figure 4. A) Lipid composition of different membrane compartments of a mammalian cell. The bar plots show the percentage of the main phospholipids in a specific membrane compartment. Abbreviations: PC, phosphatidylcholine; PE, phosphatidylethanolamine; SM, sphingomyelin; PI, phosphatidylinositol; PS, phosphatidylserine; CL, cardiolipin; Chol, cholesterol; GSL, glycosphingolipid; PI4P, phosphatidylinositol-4-phosphate; PI(4,5)P2, phosphatidylinositol 4,5 bisphosphate. Reproduced under terms of the CC-BY license.[69] Copyright 2022, The Authors, published by Portland Press. B) Overview of the organization of plasma membrane into various well-defined protein-specific domains, such as (1) synapses, (2) cell–cell junctions, (3) focal adhesions, and membrane invaginations such as (6) caveolae and (7) clathrin-coated pits. Morphologically less-defined structures include (4) tetraspannin microdomains and (5) lipid raft microdomains. Feasibility of lateral movement of protein components between certain domains is indicated by horizontal arrows. The plasma membrane can interact with the extracellular environment, including other cells, through excretion vesicles such as exosomes (9) and microvesicles (10). Internalization of external components or proteins localized in the plasma membrane can, respectively, be accomplished by phagocytosis (8) or mediated by (7) clathrin-coated pits, (6) caveolae, and possibly (5) lipid rafts. As indicated by vertical arrows, membrane subdomains and excretion/internalization systems are also in dynamic interaction with intracellular organelles, including endosomes, endoplasmatic reticulum, Golgi apparatus, mitochondria, and the nucleus. Reproduced with permission.[75] Copyright 2010, John Wiley and Sons.

among themselves (**Figure** 4A). Specific functions of each lipid in the plasma membrane have recently been reported.[69]

More than 7,000 membrane protein structures are available in the Protein Data Bank.[70] Despite this richness and heterogeneity, it is still unclear how many of these structures do really occur in the plasma membrane of human cells; some authors have estimated that between 10% and 20%.[71] Uncertainties in protein composition and conformation come from instability problems when proteins are attempted to be removed from the complex structural and compositional (mostly lipidic) environment of the cell membrane, and from the poor expression of mammalian proteins in the most used expression systems (bacteria, yeasts, insect cells). Re-folding into the functional state of the protein as it was in the cell membrane is, in many cases, difficult as most transmembrane proteins are unusually hydrophobic compared to other proteins and, therefore, unstable in an aqueous environment. Although several ways of addressing these problems are being implemented as new high-resolution techniques appear,[72] in vitro mimicking the "functional paralipidome", i.e., the mutual regulation between membrane proteins and the surrounding lipids, is a challenge.[73] In any case, the information already available evidences that the functionality of plasma membrane proteins is so relevant in the preservation of the health state that they already represent 2 out of 3 protein targets of existing drugs and drug candidates.[74] Indeed, changes in membrane proteins readily occur under pathological conditions, and those changes could be used as prognostic and diagnostic biomarkers as well as to develop antibodies and other drugs that can bind to receptors or enzymes at the membrane and tune their function.[50] That is the case of integrins, one of the main transmembrane receptors, playing key roles as linkers to ECM components and transducers of signals between cells and their environment, as mentioned above (Figure 2). There are already seven commercially available drugs (abciximab, eptifibatide, tirofiban, natalizumab, vedolizumab, lifitegrast, and carotegrast) and nearly a hundred new drug candidates under clinical trials that target integrins.[75]

It is known that cells from different organs differ in the organization of their plasma membranes. Moreover, each plasma membrane is not homogeneous in structure and composition, but it is organized in morphological and functional domains that should be preserved for the correct functioning (Figure 4B). Each plasma membrane domain may contain different proteins and lipids.[75] Furthermore, it has been shown that activation of one of these domains may have positive or negative effects on tissue repair depending on the tissue and the repair process, as reported for, for example, caveolin-1 proteins in caveolae lipid rafts of stem cell membranes.[76]

3.3. Cell Membrane-Mimicking Coats

All mammalian cell membranes are characterized by two main features: (a) the presence of zwitterionic choline phosphate (phosphatidylcholine) in the phospholipid bilayer, which provides anti-fouling and anti-thrombogenic properties, and (b) the glycocalyx formed by the saccharide chains of the glycolipids and glycoproteins of the cell membrane protruding to the outer surface. The glycocalyx is a highly hydrated carbohydrate-based network wrapping the cell membrane, which hinders unspecific protein adsorption and participates in specific molecular recognition. Therefore, bioinspired zwitterionization and glycosylation of the scaffolds' surfaces have been widely investigated to create anti-fouling surfaces, avoid foreign-body reactions, and promote specific cell interactions.[17] Some relevant examples of scaffolds endowed with zwitterionic or glycosylated surfaces are given below (Table 1). Previous works can be found in reviews published elsewhere.[77,78]

3.3.1. Phospholipid-Based Coatings

A variety of (meth-)acrylate monomers with diverse functional moieties have been tested as components of synthetic scaffolds. Ammonium methacrylate copolymers (Eudragit RL) have been shown to promote MSCs adhesion due to opposite charge interactions, but it was also shown that only when the cationic copolymer was combined with polyethylene glycol 400 (PEG400) could the cells also proliferate and differentiate. PEG400 formed pores that created the adequate topography for the cells to spread.[79]

One of the most investigated monomers is 2-methacryloyloxyethyl phosphorylcholine (MPC), which contains the phosphorylcholine group found in membrane phospholipids. MPC has been extensively studied as a component of neutral, hydrophilic coatings for various medical devices. Its zwitterionic properties allow the coating to retain a high amount of free water molecules. This results in the device having a low friction coefficient, making it highly slippery during implantation or use, reducing the likelihood of protein and bacteria adhesion, and preventing thrombosis. As a result, MPC-modified materials are ideal for use in anti-fouling applications, such as blood-contact medical devices, contact lenses, stents, and removable catheters.[80]

MPC-based endothelium membrane-mimetic coating has been investigated to prevent thrombosis and bleeding associated with the use of blood-contacting medical device therapies (Table 1, entry 1). The surface of the device (polyvinylchloride, PVC, tube) was preconditioned with polydopamine, and then a layer of polyMPC bearing carboxylic acid groups was applied to generate amide linkages. The single layer of polyMPC showed small pores through which heparin bonded to the polydopamine substrate through one end link, preserving its functionality. The resulting MPC-heparin hybrid bioinspired coating reduced protein adsorption and platelet adhesion by 50% and 90%, respectively, compared to the heparin-only coating. It also showed superior anticoagulation activity on the device surface while the overall blood coagulation function remained well-preserved.[81] This MPC-heparin hybrid bioinspired coating, as well as coatings that replace MPC with polymers bearing zwitterionic sulfobetaine and carboxyl side-chains (Table 1, entry 2), have been shown to be suitable for improving the in vivo performance of extracorporeal circuits (including hemodialyzers).[82]

MPC has also been shown to be suitable for inhibiting bacterial growth on metallic implants. Grafting of MPC on stainless-steel implants significantly reduced *Staphylococcus aureus* binding while preserving the adhesion of pre-osteoblast cells (Table 1, entry 3).[83] Also, for non-biomedical industrial applications, coating of stainless-steel mesh surfaces was revealed to be critical to avoid premature corrosion of the material by bacteria in wet environments.[84]

MPC hydrogels made of reversible cross-linking points based on benzoxaborole and catechol pendant groups have been explored for cell encapsulation in 3D networks. These hydrogels showed self-healing behavior and dual pH- and sugar-responsiveness due to the boronic esters (Table 1, entry 4). In a short-term study, cells were shown to remain viable inside the hydrogel, probably because the porosity of the hydrogel facilitated the exchange of nutrients.[85]

Since MPC typically inhibits cell-scaffold interactions, for it to be effective in tissue regeneration, MPC-containing coatings must either be temporary, namely MPC disappears as tissue grows, or be combined with other components that can establish specific interactions with the cells of interest. Blends of poly(MPC-co-n-butyl methacrylate) (PMB30W) with poly(L-lactic acid) (PLLA) have been tested as temporary scaffolds of damaged vessels until sufficient vascular healing (Table 1, entry 5). Tubes made with these blends and having a high density of phosphorylcholine groups protruding toward the inner surface showed strong mechanical properties and excellent hemocompatibility.[86]

Modification of the highly conductive ethylenedioxythiophene (EDOT) monomers with MPC leads to novel polymers suitable for bioelectronic devices that exhibit better electrical interfacing with neural cells and tissue (Table 1, entry 6). Bioelectronic devices that combine EDOT-MPC monomers and EDOT conjugated with peptidic ligands were shown to inhibit non-specific binding of proteins and cells, preventing immunogenic scar formation, while facilitating the adhesion of neural cells and their electric stimulation.[87]

Corneal repair has been shown to improve with the use of interpenetrating networks of cross-linked collagen and cross-linked MPC hydrogels (Table 1, entry 7). Compared to collagen-only networks, the MPC hydrogel enhanced the resistance of the scaffold to enzymatic and UV degradation, while preserving corneal cell and nerve in-growth. Evaluation in a mini-pig model of corneal injury confirmed the complete regeneration of the epithelium, stroma, and sensory nerves.[88]

Coatings designed to mimic the lipidic bilayers of cell membranes have been explored to reduce foreign body reactions. For instance, covalent immobilization of liposomes on polystyrene-based electrospun scaffolds functionalized with silk fibroin created a biomimetic lipidic film that attenuated fibrotic tissue formation and inflammatory cell aggregation (Table 1, entry 8). Notably, after subcutaneous implantation, the lipidic coating facilitated macrophage polarization toward a pro-regenerative phenotype, which, in turn, enhanced angiogenesis and tissue integration.[89]

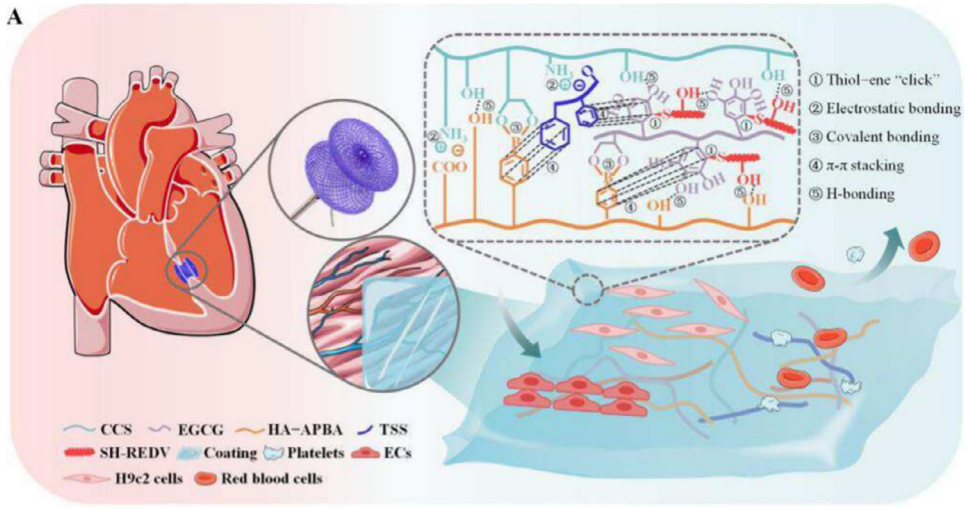

Figure 5. Heart occluder was coated with a glycocalyx-like coating containing carboxylated chitosan (CCS), hyaluronic acid grafted with 3-aminophenylboronic acid (HA-APBA), epigallocatechin-3-gallate (EGCG), tanshinone IIA sulfonic sodium (TSS), and mercaptopropionic acid-GGGGG-Arg-Glu-Asp-Val peptide, showing the capability to attract endothelial cells (ECs) and inhibit the apoptosis of cardiomyocytes (H9c2 cells). Reproduced with permission.[96] Copyright 2024, American Chemical Society.

Supported lipid bilayers (SLBs) modified with Arg-Gly-Asp (RGD) ligands have been shown to regulate the adhesion and differentiation of MSCs to osteoblasts in vitro (Table 1, entry 9). In general, increasing the density of RGD ligands led to greater cells spreading and enhanced differentiation capacity.[90] Additionally, it was found that the relative mobility of RGD ligands, which can be controlled through the transition temperature of the lipids, can impact the interaction of the ligand with the cell receptors and, consequently, influence cell signaling pathways. These findings open new avenues for instructing cells at the nanoscale, enabling precise tissue reconstruction on synthetic implants. Indeed, SLBs formed on conductive polymers are receiving increasing attention in the bioelectronic field to generate cell-friendly interfaces that can promote tissue integration and electrical coupling. Interested readers are referred elsewhere.[91]

3.3.2. Glycocalyx-Based Coatings

Glycocalyx-mimicking strategies also offer anti-fouling properties[92,93] but, more relevantly, specific recognition of molecules and cells. Very diverse physical, chemical, and biochemical methods have been reported for the glycosylation of surfaces.[17,94,95]

A glycocalyx-like coating has been designed to improve the performance of cardiovascular implants and facilitate myocardial repair (**Figure 5**).[96] The coating was applied on a heart occluder and consisted of carboxylated chitosan (CCS) and hyaluronic acid grafted with 3-aminophenylboronic acid (HA-APBA). It also contained epigallocatechin-3-gallate (EGCG; antioxidant), tanshinone IIA sulfonic sodium (TSS; antiaggregant and anti-inflammatory drug), and mercaptopropionic acid-GGGGG-Arg-Glu-Asp-Val (SH-REDV) peptide that has high affinity for endothelial cells. When implanted in a rabbit carotid artery model, the coating reduced inflammation and thrombosis. Moreover, it modified the gene expression in H9c2 cells (cardiomyocytes model), inhibiting apoptosis.

Titanium alloy has recently been coated with aminated polyethylene glycol (PEG), Arg-Glu-Asp-Val (REDV) peptide, and heparin, showing enhanced hydrophilicity, adsorption of bovine serum albumin, and repulsion of fibrinogen. The coating promoted endothelial cell adhesion and proliferation, facilitating rapid endothelization, while inhibiting smooth muscle cells proliferation.[97]

Poly(sulfopropyl methacrylate) (PSPMA) brushes have been shown to be an alternative to glycosaminoglycans, such as heparin, for the specific binding and controlled release of bone morphogenetic proteins (BMPs). Relevantly, the loading of BMP-2 by PSPMA brushes was demonstrated to facilitate the adhesion of fibroblasts and their spreading on the scaffold surface, forming a mature extracellular matrix.[98]

Glycosylation has also been useful to improve the surface properties of decellularized tissue-engineered vascular grafts (TEVGs), which are very prone to thrombosis events. The coating of TEVGs with hyaluronic acid to recreate the glycocalyx of endothelial cells, hindering the collagen of TEVGs, notably attenuated the risk of thrombogenicity in both rat and canine models.[99]

3.4. Cell Membrane-Coated Scaffolds

Since the isolation of specific domains and components from the plasma membrane is difficult and the risk of losing the functional conformation is high,[72] most research on cell membrane-coated medical devices has been carried out with the complete, isolated plasma membrane. It is highly relevant that, as plasma membrane composition and functionality vary between cells, the selection of the cell membrane source will determine the performance of the coating and, therefore, its role in assisting the scaffold in tissue regeneration.

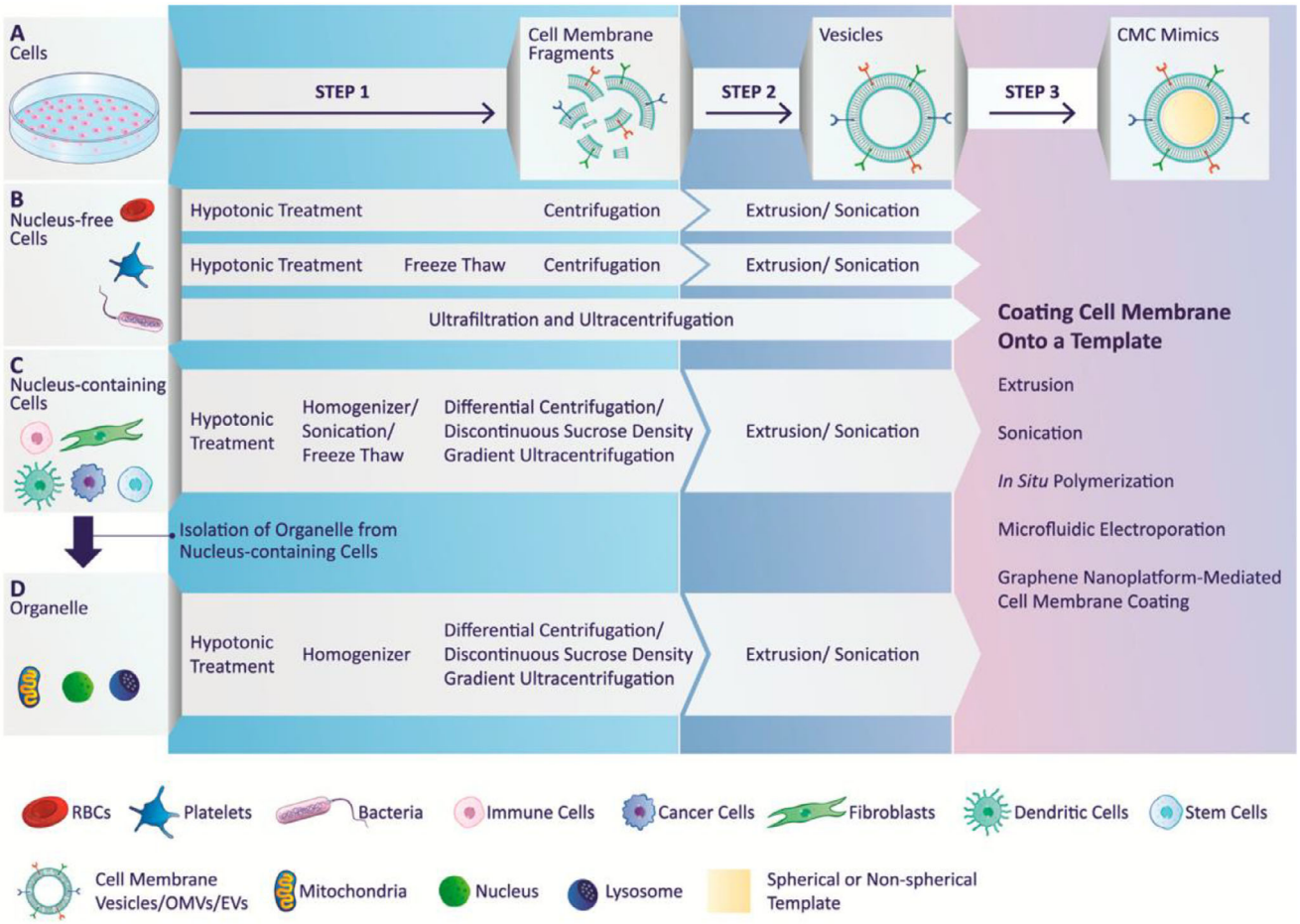

Figure 6. A schematic diagram illustrating the isolation and preparation of membrane vesicles from nucleus-free, nucleus-containing cells, and organelles before coating: A) The process consists of two main stages: extracting cell membrane fragments (step 1) and preparing the cell membrane vesicles (step 2). The methods for steps 1 and 2 vary depending on whether the cells are B) nucleus-free or C) nucleus-containing, as well as the D) organelles to be isolated. Finally, the coating of the cell membrane onto a template (step 3) can be carried out using any of the listed techniques after careful adaptation. Abbreviations: RBCs, red blood cells; OMVs, outer membrane vesicles; EVs, extracellular vesicles. Reproduced under terms of the CC-BY license.[101] Copyright 2021, The Authors, published by American Chemical Society.

A wide variety of techniques and procedures have been reported to isolate the plasma membrane from specific cells. The techniques also depend on whether the isolated membranes are intended for proteomic analysis or their structure should be preserved for the coating. Reviews on the isolation of plasma membranes for proteomic analysis can be found elsewhere.[72] Plasma membrane extraction for subsequent coating of drug nanocarriers has been evaluated in detail because homotypic targeting requires the pristine structure and composition of the cell membrane to be maintained in the coated nanocarrier.[100]

The process of isolating the cell membrane typically involves two main steps, which depend on the type of cell (**Figure 6**): 1) Gentle cell lysis achieved through detergent-free hypotonic treatment (osmotic imbalance) or a combination of hypotonic treatment and mechanical disruption, and 2) Extraction and purification of the cell membrane from intracellular components using centrifugation steps, which may involve differential and sucrose density gradient centrifugation. During membrane isolation, essential components such as transmembrane proteins, receptors, or structural elements like cholesterol may be lost. Cholesterol plays a key role in maintaining the rigidity of the cell membrane, and its depletion can compromise the membrane's mechanical stability. To minimize protein loss and preserve membrane integrity, hypotonic buffers containing divalent ions (e.g., $MgCl_2$) or the supplementation of cholesterol can be beneficial. Additionally, using mild lysis buffers, gentle mechanical forces, optimal pH, and ice-cold conditions is crucial to minimizing the degradation of transmembrane proteins and receptors during membrane isolation.[101] Once the cell membrane vesicle suspension is ready, the coating can be carried out and monitored using a variety of techniques.[68,102] Some relevant examples of scaffolds coated with cell membranes are described below (Table 2).

3.4.1. Cell Membrane Coatings for Tissue Engineering

Advances in tissue engineering and biomedicine have demonstrated the potential of using cell-specific membranes as coatings

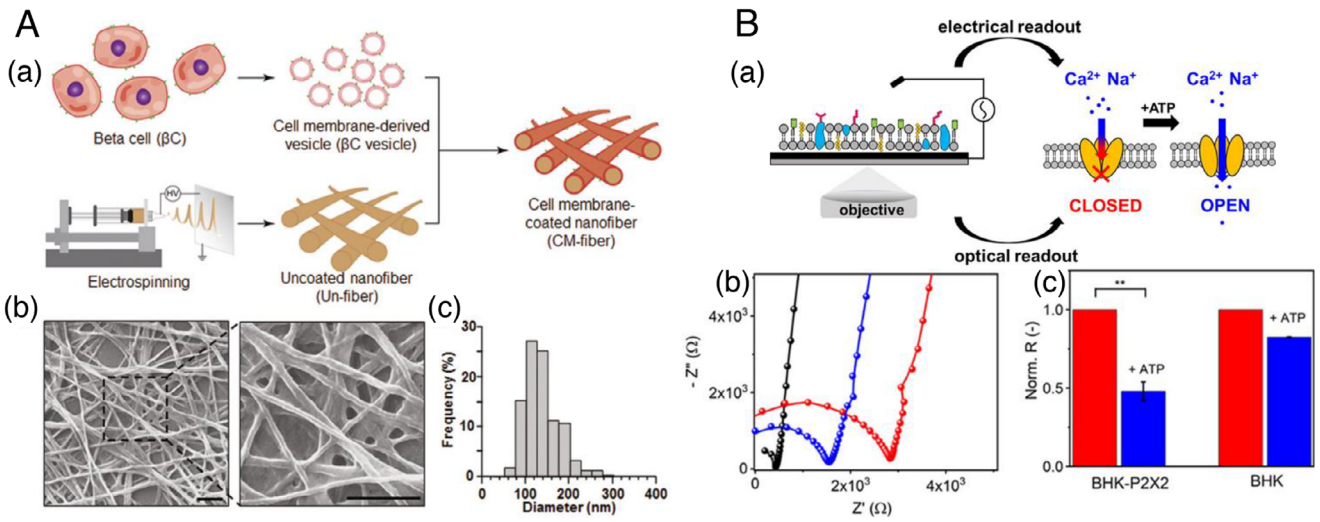

Figure 7. A) Preparation of beta-cell membrane-coated nanofibers (CM-fiber) by obtaining the membrane vesicles (βC vesicles) and subsequent fusion of the vesicles on the nanofiber surface (Un-fiber) a); SEM images b) and size distribution c) of CM-fibers. Reproduced with permission.[103] Copyright 2016, Royal Society of Chemistry. B) Coating of poly(3,4-ethylenedioxythiophene):poly(styrene sulphonate) (PEDOT:PSS) films with mammalian cell membranes containing functional ATP-activated P2 × 2 ion channels allowed electrical and optical monitoring of the effect of ATP binding on channel opening and ion flux a); b) Nyquist plot of the electrode before (black) and after (red) the coating as well as after treatment with ATP (blue), and c) membrane resistance of the P2 × 2-rich coating before (red) and after (blue) ATP (10 μM) treatment, and the corresponding values for a membrane coating not expressing any P2 × 2 ($n = 3$, $p = 0.009$). Reproduced with permission.[104] Copyright 2020, American Chemical Society.

for nanofibers and other materials, offering promising applications across various fields. For example, MIN6 mouse pancreatic beta cell membranes[103] and blebs from baby hamster kidney (BHK) cells[104] have been tested.

Pancreatic beta cells depend on direct cell–cell interactions to sustain their survival and function. It was, therefore, hypothesized that polymeric nanofibers coated with membranes derived from MIN6 pancreatic beta cells could enhance the proliferation and functionality of these cells when cultured on the scaffold. With an antigenic exterior that mimics that of the source cells, the scaffold may replicate the interactions that occur among beta cells in the pancreas (Table 2, entry 1).[103] The coating procedure involved multiple stages. Initially, beta cell membrane vesicles (βC vesicles) were obtained from MIN6 cells via sonication, which allowed for the isolation of cell membranes while preserving their composition and functionality. In parallel, polycaprolactone (PCL):poly-D-lysine 10:1 nanofibers were prepared using electrospinning to generate nanometric-scale fibrous structures ideal for cell adhesion. Subsequently, the nanofibers were immersed in a βC vesicle suspension for 30 min at room temperature to facilitate the fusion of the membranes with the surface of the nanofibers, resulting in a complete coating (**Figure** 7A).

The coating efficiency was verified using various techniques. Scanning electron microscopy (SEM) provided insights into the morphology of the coated nanofibers, confirming the presence of the cell membrane on their surface. Fluorescent markers were used to visualize membrane vesicle fusion with the nanofibers, while protein analysis through SDS-PAGE and Western Blot confirmed the presence of key cell membrane proteins like E-cadherin and Na^+/K^+-ATPase, ensuring that the coating maintained the membrane functionality. MIN6 cells were cultured on the membrane-coated nanofibers (CM-fiber), uncoated nanofibers, and uncoated glass coverslips. In a glucose-stimulated insulin secretion assay, the cells cultured on CM-fibers exhibited increased cell aggregation and higher proliferation rates compared to the controls. Additionally, glucose-stimulated insulin secretion in these cells was five times greater than in those cultured on non-coated nanofibers, indicating that beta cell membrane coating significantly enhanced the survival and functioning of pancreatic beta cells by recreating their natural environment. The preservation of essential membrane proteins, such as E-cadherin and Na^+/K^+-ATPase, in the coating was considered crucial for cell communication and homeostasis.

In another study, bioelectronic devices were coated with mammalian cell membranes containing functional transmembrane proteins, specifically ATP-activated P2 × 2 ion channels (Table 2, entry 2).[104] The goal was to gain an insight into the gatekeeper role of the transmembrane proteins when used as a coating of electrically conducting devices; more specifically, changes in ion flux due to ATP exposure were investigated (Figure 7B). The coating procedure involved obtaining plasma membrane vesicles (blebs) from transfected baby hamster kidney (BHK) cells, preparation of poly(3,4-ethylenedioxythiophene):poly(styrene sulphonate) (PEDOT:PSS) films on glass substrates via spin-coating, and incubation of the blebs on the PEDOT:PSS surface for 15 min. Subsequently, liposomes were added and incubated for 30 minutes to promote lipid bilayer formation, followed by the addition of polyethylene glycol (PEG8k) to improve the bilayer quality. Coating efficiency was assessed using fluorescence recovery after photobleaching (FRAP), total internal reflection fluorescence (TIRF) microscopy, and protease assays, confirming the formation of a fluid lipid bilayer with mobile and properly oriented proteins. The coated system was evaluated with an ion channel activity assay using

electrical impedance spectroscopy, comparing it to devices without membrane coating and devices coated with a lipid bilayer lacking P2 × 2 channels. The results demonstrated that the addition of ATP led to detectable changes in impedance in the membrane-coated device containing P2 × 2 channels, indicating channel opening and ion flux, and the response was ATP concentration-dependent. No significant changes were observed in controls, confirming channel-specific activation. The developed devices coated with transmembrane proteins may be useful for monitoring specific interactions occurring on cell membrane surface and also for the screening of drugs that can regulate dysfunctional ion channels.[104]

Immunomodulation plays a vital role in the mammalian response to injury and is a key factor in tissue regeneration and regenerative medicine. Macrophages, as central regulators of the immune response, exhibit a spectrum of activation states ranging from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes. Poly-ϵ-caprolactone (PCL) nanofibers coated with membranes derived from macrophages of various phenotypes—M0 (non-activated), M1, and M2— preserved the surface antigens and membrane functionalities characteristic of their source cells. In vitro analyses demonstrated that these membrane-coated nanofibers, particularly M2-PCL, suppressed pro-inflammatory markers such as TNF-α and IL-1β, while upregulating anti-inflammatory markers Arg-1, IL-10, and TGF-β. The M2 macrophage membrane-coated nanofibers also demonstrated potent immunomodulatory properties after in vivo implantation, significantly reducing cellular infiltration and collagen deposition. This anti-inflammatory effect is likely attributed to the abundant expression of surface receptors on the M2 membranes, which enable efficient sequestration of inflammatory cytokines and chemokines in the local microenvironment. This interaction dampens toll-like receptor (TLR) activation, thereby inhibiting downstream signaling pathways involving NF-κB and IRF-5 and their associated target genes, such as IFN-β, IL-6, and iNOS.[105] Overall, M2 macrophage membrane-coated nanofibers closely mimic the immunological functions of their parent cells, modulating macrophage behavior, mitigating inflammatory responses, and promoting a regenerative microenvironment.

In line with this study, but applying a different perspective, electrospun PLGA nanofibers were grafted with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol–amine (DSPE-PEG-NH_2) and coated with membranes derived from activated M1 macrophages (proinflammatory phenotype). The aim was to evaluate their ability to preserve tenocyte viability under inflammatory conditions and to prevent scarring during tendon healing. In vitro, tenocytes exposed to TNF-α or IL-1β to induce apoptosis showed significantly higher survival rates when pre-incubated with the macrophage membrane-coated scaffolds compared to those cultured with non-coated scaffolds or scaffolds coated with RBC membranes. This protective effect was attributed to the macrophage membrane's ability to adsorb proinflammatory cytokines, thereby reducing their local concentration around the tenocytes. In a murine model of flexor tendon injury, wrapping the injury with the M1 macrophage membrane-coated scaffolds enhanced both structural and functional tendon recovery and prevented scar formation (Table 2, entry 3).[106]

3.4.2. Cell Membrane Coatings for Skin and Wound Healing

Scaffolds coated with cell-specific membranes can offer numerous advantages for skin regeneration, as observed when 3T3 fibroblast membranes, N2a neuroblastoma membranes, or macrophage membranes (from mouse RAW264.7 and human THP-1 cells) were used.

Aligned PCL electrospun nanofibers were coated with 3T3 fibroblast cell membranes to contribute with surface antigens and topography cues to wound healing (Table 2, entry 4).[107] This study provided interesting results on the effects that the fiber diameters and surface charges have on the efficiency of the cell membrane coating and, subsequently, on the growth and proliferation of keratinocytes (HaCaT cells) on the scaffold. For the coating procedure, cell membranes from 3T3 fibroblasts were obtained while maintaining their composition and functionality. PCL nanofibers were coated with different amounts of 3T3 fibroblast cell membranes by incubation with pre-sonicated cell membrane solutions (covering a wide range of concentrations) for 30 min at room temperature, and then washed with phosphate-buffered saline (PBS). It was shown that 1 µg membrane per cm^2 of scaffold provided a uniform coating on the fiber surface. To assess coating efficiency, various techniques were employed. Wheat germ agglutinin conjugated with AF555 (WGA-AF555) was used to visualize the presence of the cell membrane on the nanofibers. Water contact angle measurements were taken to study changes in hydrophilicity, while Raman spectroscopy detected alterations in molecular vibrational modes, confirming the integration of the cell membranes. SEM was used to examine the morphology of the fibers and validate the uniformity of the coating. Interestingly, minor changes in the coating were recorded for PCL electrospun nanofibers that were pre-coated with poly(D-lysine) as well as for PCL nanofibers having different diameters (from 220 to 2087 nm).

In cell growth tests, HaCaT keratinocytes cultured on 3T3 fibroblast membrane-coated fibers covered a significantly larger area than in controls prepared with non-coated fibers (NT) or RBC membrane-coated fibers (**Figure** 8A). From day 3 onward, HaCaT cells exhibited faster growth and greater coverage on 3T3-coated fibers, with increases of 6.1-fold on day 3, 2.4-fold on day 7, and 1.4-fold on day 14. These cells reached confluence more rapidly on these fibers than on control fibers, suggesting a specific interaction between fibroblast membranes and keratinocytes.[107] Although the underlying mechanism for enhanced HaCaT cell proliferation on 3T3-coated fibers remains unclear, the results pointed out that proteins unique to the 3T3 cell membrane (not in RBC membrane), such as E-cadherin, may play a crucial role in modulating cell–cell interactions. This point should be further explored by testing coatings from different cell sources.

N2a neuroblastoma cell membranes were used to coat metal-organic frameworks (MOFs), creating a neuroinspired biomimetic microreactor (neuro-MOF microreactor) designed to promote peripheral nerve regeneration and hair follicle neogenesis for deep skin burn treatment (Table 2, entry 5). Deep burns cause first severe pain, followed by a loss of sensation. While sensory nerves are known to aid skin healing, current burn therapies do not specifically target sensory nerves. This study hypothesized that MOFs coated with neuroblastoma cell membranes and

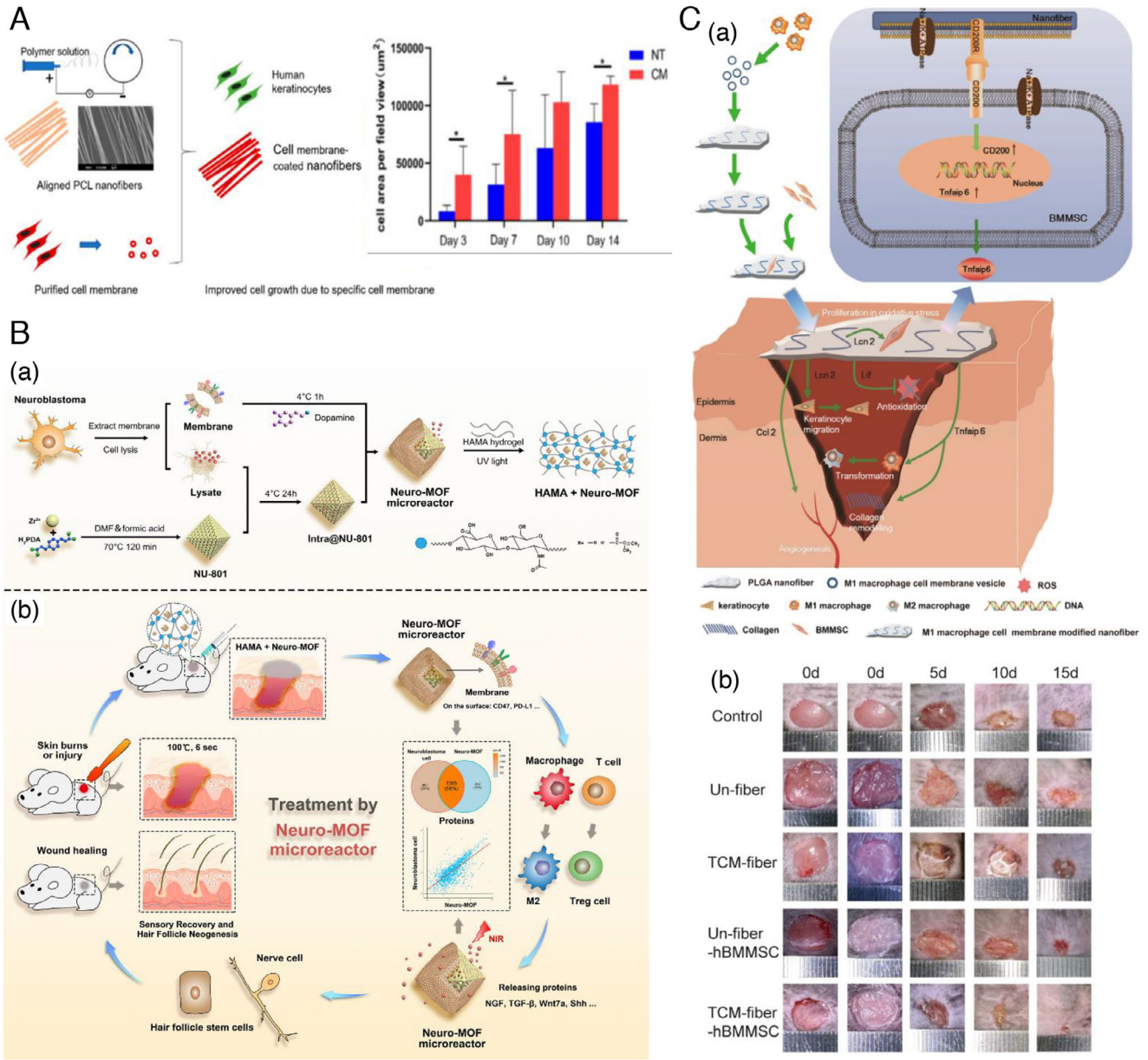

Figure 8. A) Aligned PCL nanofibers coated with 3T3 fibroblast cell membranes (3T3) showed improved growth of human keratinocytes compared to non-coated (NT) and red blood cells (RBC)-membrane-coated nanofibers. Reproduced with permission.[107] Copyright 2021, American Chemical Society. B) a) Neuro-MOF microreactor nanoparticles were loaded with the cytoplasmic content of neuroblastoma cells, coated with the cell membranes, and then dispersed in a hydrogel scaffold. b) Once applied to skin burns, the neuro-MOF microreactor reduced the inflammation through M2 macrophage polarization and Treg cell differentiation, while the release of cytoplasmic proteins promoted sensory recovery and hair follicle regeneration. Reproduced with permission.[108] Copyright 2023, American Chemical Society. C) Schematic depiction of the performance of PLGA nanofibers that were coated with LPS/IFN-γ activated macrophage cell membranes and then cultured with mesenchymal stem cells (MSCs). a) The recognition of CD200R receptors in the macrophage membrane by the MSCs caused the upregulation of *Lcn2, TNFAIP6, Lif*, and *Ccl2* genes in MSCs. b) Such an increased activity of MSCs make the RCM-fibers (TCM-fiber-hBMMSC) facilitate the healing of wounds in an animal model of diabetes compared to the control (non-treated) wounds and to wounds treated with non-coated fibers (Un-fiber), fibers coated with activated-macrophage cell membranes without MSCs (TCM-fiber), and non-coated fibers that were cultured with MSCs (Un-fiber-hBMMSC). Reproduced under terms of the CC-BY license.[111] Copyright 2022, The Authors, published by Springer Nature.

loaded with neural-associated intracellular proteins could evade immune recognition of the MOF while supplying the wound with key cues for peripheral nerve regeneration.[108] To fabricate the microreactor, near-infrared (NIR)-sensitive MOF nanoparticles were first loaded with the cytoplasm content of the neuroblastoma cells and then coated with cell membranes in the presence of dopamine under stirring at 4 °C for 1 h. The cell membrane-coated MOFs were then encapsulated in a hydrogel scaffold. Various analytical techniques confirmed the uniformity and stability of the coating. These neuroblastoma-derived coatings

prevented phagocytosis and modulated inflammation by promoting M2 macrophage polarization and Treg differentiation. Pulsed application of NIR radiation on the MOFs enabled on-demand release of the loaded growth factors essential for triggering hair follicle neogenesis (Figure 8B). In a mouse model of deep skin burns, the coated scaffolds significantly enhanced skin regeneration, underscoring their potential for regenerative medicine.[108]

Healing diabetic wounds is even more challenging than treating deep burns. Persistent oxidative stress and chronic inflammation create significant barriers to normal healing, often leading to chronic, non-healing wounds that can extend to underlying muscles and bones.[109,110] As an alternative to cell therapies that involve the external delivery of free MSCs to the wound, electrospun nanofibers coated with macrophage cell membranes may provide a suitable platform to preserve MSCs viability and even attract the patient´s own MSCs in situ, leveraging their natural ability to target inflamed tissues (Table 2, entry 6).[111] Macrophages (RAW264.7 cells) were activated with lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), and their membranes used to electrospun poly(lactic-co-glycolic acid) (PLGA) nanofibers through soaking for 30 min. The obtained RCM-fibers were confirmed to have a homogeneous coating by using fluorescent staining, Western blot analysis for membrane proteins (Na^+/K^+-ATPase and CD11c), SDS-PAGE electrophoresis, and SEM for morphology examination. In vitro assays showed that MSCs cultured on RCM-fibers exhibited enhanced proliferation and oxidative stress resistance, and upregulation of genes related to wound healing, compared to MSCs cultured on non-coated fibers (Figure 8C-a). In in vivo assays, diabetic wounds treated with MSCs-loaded RCM-fibers healed more rapidly, showing enhanced re-epithelialization, collagen remodeling, and angiogenesis. Similar positive outcomes were found when RAW264.7 cells were replaced with human-derived THP-1 cells as the membrane source for the coating of the fibers (Figure 8C-b). The ability of activated macrophage membrane coatings to in situ immunostimulate MSC activity may be attributed to the significant upregulation of *CD200* in the MSCs. This strengthens the CD200-CD200R interaction between MSCs and macrophage membrane), ultimately accelerating tissue regeneration in diabetic wounds when treated with the RCM-fibers.

PLGA microspheres loaded with lysate proteins derived from M2 macrophages and coated with macrophage cell membranes have demonstrated the ability to modulate the inflammatory response in vivo in pressure ulcers while promoting angiogenesis and the regeneration of skin appendages (Table 2, entry 7).[112] These microspheres functioned as synthetic M2 macrophages, providing sustained release of bioactive factors that neutralized proinflammatory cytokines and endotoxins within the pressure ulcer microenvironment, while enhancing fibroblast proliferation, keratinocyte migration, and endothelial cell migration. Notably, the bioactivity of the M2 macrophage membrane-coated microspheres was preserved even after 28 days of cryostorage at −80 °C, representing a significant advantage over conventional cell-based therapies.

Coating scaffolds with dendritic cell membranes has proven to be particularly effective for expanding T cells ex vivo. THP-1 cells were differentiated into dendritic cells (DCs) and incubated with 1-azidoethyl-choline (0.1 mM) before extracting the cell membranes to obtain membranes enriched with azide groups. Microfibril scaffolds were prepared from fragmented PCL electrospun mats. Simple incubation of the scaffolds with the azide-modified DC membranes allowed uniform coating, while the azide groups were later used in a second step for grafting activated antibodies, CD3 and CD28, to the cell membrane. The controlled release of interleukin-2 enabled the scaffolds to function as antigen-presenting cells, promoting a higher polyclonal expansion of primary human T cells compared to simply grafting the antibodies onto inorganic particles.[113]

3.4.3. Cell Membrane Coatings for Bone and Cartilage Regeneration

Bone regeneration has recently seen significant advancements through the use of different cell membrane sources. One approach utilized specific macrophage membranes, particularly from RAW264.7 cells, to accelerate fracture healing by promoting the recruitment and osteogenic differentiation of MSCs (Table 2, entry 8).[114] The primary aim of this research was to design nanocomplexes (NCs) reversibly coated with macrophage membranes (MM) for targeted co-delivery of a stromal factor-derived peptide (sSDF-1α) and a small interfering RNA targeting Ckip-1 (siCkip-1), enhancing bone repair by stimulating MSC recruitment and osteogenic differentiation. The structure of the NCs was hierarchical and multifunctional. The core consisted of a membrane-penetrating polypeptide (PG) and siCkip-1 complex, surrounded by a catalase (CAT) layer. The outer layer was composed of MM anchored with sSDF-1α (**Figure 9**A-a).

To evaluate the efficacy of the NCs, a mouse femur fracture model was used. The NCs were intravenously injected and effectively accumulated at the fracture site due to the macrophage membrane's ability to localize inflammation. In the inflammatory microenvironment, CAT decomposed H_2O_2, generating oxygen bubbles that detached the macrophage membranes, releasing sSDF-1α to recruit MSCs and delivering siCkip-1 for osteogenic differentiation, accelerating fracture healing. The results showed that mice treated with macrophage membrane-coated NCs had significantly accelerated bone callus formation and mineralization compared to control groups. Micro-CT and X-ray studies confirmed improved fracture union and increased bone mineral density (Figure 9A-b–e). Additionally, the NCs were biocompatible, with no significant toxic effects on major organs or hematological and biochemical parameters.[114]

Another approach using electrospun bone scaffolds involved hybrid membranes derived from anti-inflammatory macrophages (M2-Macs) and osteoinductive mesenchymal stem cells (oi-MSCs). This strategy aimed to regulate inflammation and to promote bone regeneration in critical-size defects (Table 2, entry 9).[115] Biotin-functionalized PCL electrospun scaffolds were coated with biotin-modified M2-Macs membranes, oi-MSCs membranes, or the hybrid membranes, in the presence of streptavidin. Hybrid membranes were shown to strongly inhibit the pro-inflammatory genes, while oi-MSC and hybrid membranes promoted the anti-inflammatory and osteogenic genes. In in vitro tests, cell membrane-coated PCL nanofibers triggered enhanced proliferation and osteogenic differentiation of MSCs, compared to a non-coated scaffold. Relevantly, in vivo studies evidenced the outstanding immunomodulatory and osseointegration

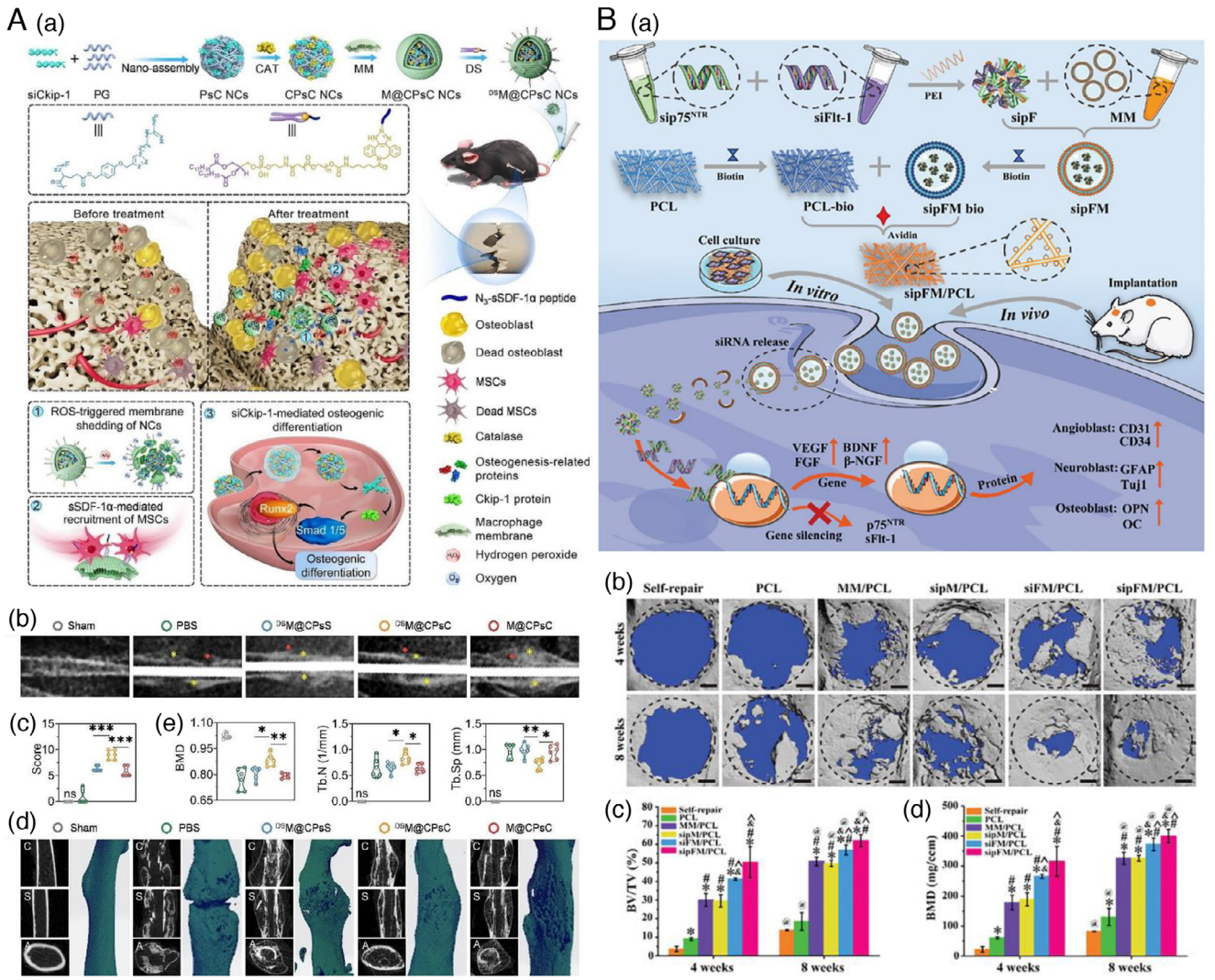

Figure 9. (A) (a) Macrophage membrane-coated NCs were designed to deliver siCkip-1 and sSDF-1α to fracture sites, where catalase (CAT) decomposed H_2O_2 to O_2 bubbles, which detached the coating. sSDF-1α attracted MSCs, while the membrane-penetrating polypeptide (PG) and siCkip-1 complex penetrated into the cells to trigger osteogenic differentiation. These combined effects accelerated bone healing. (b) Representative X-ray images and (c) corresponding total scores based on opacity, cortical remodeling, and bridging, and periosteal and endosteal reactions at day 28 post-fracture ($n = 6$). Yellow stars and red arrows mark the callus and fracture sites, respectively. (d) Representative 2D (left) and 3D (right) reconstructed micro-CT images, along with (e) mineralization-related parameters, also assessed on day 28 post-fracture. "C" and "S" denote coronal and sagittal planes, respectively. Reproduced under terms of the CC-BY license.[114] Copyright 2024, The Authors, published by Springer Nature. (B) (a) Preparation of hybrid membranes loaded with dual small interfering RNA (siRNA)-polyvinylimide (PEI) (siRP) complexes that knock down soluble vascular endothelial growth factor receptor 1 (sFlt-1) and p75 neurotrophic factor receptor (p75NTR), and subsequent coating of PCL electrospun scaffolds (GFMs). These GFMs modulated the expression of vascular- and nerve-related genes, enhanced the paracrine function of vascular and neural factors, and promoted bone regeneration in a skull defect model at 4 and 8 weeks post-implantation. (b) Micro-CT images (scale bar: 1 mm), (c) bone volume to total volume ratio (BV/TV), and (d) bone mineral density (BMD). Data are presented as mean ± SE ($n = 3$). $^{*}p < 0.05$ significant difference compared with the self-repair group at the same time point. # $p < 0.05$ significant difference compared with the PCL group at the same time point. & $p < 0.05$ significant difference compared with the MM/PCL group at the same time point. ^ $p < 0.05$ significant difference compared with the sipM/PCL group at the same time point. @ $p < 0.05$ significant difference compared with the same group at different time point. Reproduced with permission.[116] Copyright 2024, John Wiley and Sons.

capabilities of the hybrid membrane-coated scaffolds, showing enhanced bone repair in four weeks after implantation.

In a subsequent study, this approach was further improved to enhance MSC osteogenic differentiation while promoting vascularization and neurogenesis in bone defects. The hybrid membranes were loaded via extrusion through a polycarbonate membrane with dual small interfering RNA (siRNA)-polyethylenimine (PEI) (siRP) complexes, which locally silenced soluble vascular endothelial growth factor receptor 1 (sFlt-1) and p75 neurotrophic factor receptor ($p75^{NTR}$). These siRNA-loaded hybrid membranes were then applied as a coating onto a PCL electrospun scaffold using biotin-streptavidin interactions (Table 2, entry 10).[116] Microscopic analysis confirmed successful encapsulation of siRNA-PEI complexes within the hybrid

membranes, while transfection assays demonstrated increased siRNA accumulation in MSCs (Figure 9B-a). In vitro studies with human umbilical vein endothelial cells (HUVECs) demonstrated that the siRNA-loaded hybrid membranes enhanced tube formation, branching, and total length compared to non-coated scaffolds and hybrid membranes without siRNA. In in vivo rat bone defect models, the siRNA-loaded hybrid membrane-coated scaffolds reduced inflammation and improved osteointegration by regulating the coupling between vascularization and innervation (Figure 9B-b–d). Overall, these scaffolds created a more favorable microenvironment for bone regeneration by promoting blood vessel and neural network formation.

Notably, a single coating of IFN-γ–primed MSC membranes has been shown to exert significant immunomodulatory effects in in vivo models of critical-size bone defects by promoting macrophage polarization toward a regenerative phenotype.[117] To enhance electrostatic interactions with the MSC membrane, gelatin-based microribbon scaffolds were functionalized with poly-lysine. Coated and uncoated scaffolds were then suspended in phosphate buffer at a final concentration of 10%, mixed with 0.1% LAP photoinitiator, and cross-linked under UV light using cylindrical molds. The resulting hydrogels preserved elevated expression levels of PD-L1 and TNFL6 from the MSC membrane coating, effectively modulating macrophage and T cell responses. When combined with the sustained release of bone morphogenetic protein 2 (BMP-2), these scaffolds significantly accelerated bone regeneration (Table 2, entry 11).

Recent studies have revealed that cell membrane coatings can impart an additional, often overlooked, functional property to bone implants—one linked to the membranes' low thermal conductivity and phase-change behavior.[118] The phospholipid bilayer of cell membranes can store and release energy, making them particularly effective in enhancing photothermal therapy. Photothermal-enabled implants have shown significant promise in promoting angiogenesis and preventing local infections by generating localized heat capable of killing bacteria and disrupting biofilms.[119,120] Upon exposure to near-infrared (NIR) light, heat is generated precisely at the implant surface, raising the temperature within a few microns of the scaffold—enough to eliminate pathogens without damaging surrounding tissues.[121,122] The thermal effect is tightly controlled: temperature increases during irradiation and rapidly dissipates once the light source is removed. To ensure effective bacterial eradication, light intensity and exposure time must be carefully balanced to maximize antimicrobial efficacy while preserving host tissue integrity.

A bioinspired approach to optimizing photothermal performance draws from how cell membranes respond to temperature fluctuations in living organisms—a process known as homeoviscous adaptation (HVA).[123] This adaptive mechanism allows membranes to modulate their viscosity by altering lipid composition and phase behavior, thereby maintaining thermal stability through controlled energy absorption and release.[124] Incorporating this thermoregulatory capability into photothermal therapy systems offers precise heat control and opens new avenues for advanced biomedical applications.

In a practical application of this concept, commercial titanium implants were modified with tannic acid to bind a photothermal black phosphorus (BP) layer, followed by coating with red blood cell (RBC) membranes (Table 2, entry 12).[118] The thermal response of both coated and uncoated implants was tested under 808 nm NIR light in dry and aqueous environments for 10 minutes. The RBC-coated implants exhibited a more sustained and elevated surface temperature, enhancing the photothermal effect. This improvement translated into superior antibacterial and osteoinductive outcomes in a *Staphylococcus aureus*-infected bone defect model. Cylindrical defects were created in the proximal tibia of female rats, and NIR irradiation (1.0 W/cm^2 for 10 minutes) was applied to the right leg for three consecutive days post-surgery, followed by weekly sessions for eight weeks. The group treated with RBC-coated implants showed near-complete bacterial clearance and minimal inflammation, alongside significantly accelerated bone regeneration. These findings underscore the dual role of RBC membranes in enhancing both biocompatibility and the antimicrobial efficacy of photothermal therapy, ultimately contributing to improved healing outcomes.

Coatings with membranes of bone marrow MSCs has been explored to alleviate osteoarthritis (OA).[125] PLGA microparticles loaded with paracrine factors and coated with bone marrow MSCs (BMSCs-CF@M-PLGA) have been shown to significantly enhance chondrocyte proliferation, migration, and ECM synthesis (Table 2, entry 13). In a rat model of osteoarthritis, BMSCs-CF@M-PLGA reduced proinflammatory cytokines and increased anti-inflammatory cytokines, which resulted in amelioration of the joint morphology and cartilage structure. The coated microspheres enhanced the proliferation and migration of OA chondrocytes, effectively counteracting IL-1β-induced cartilage damage. Micro-CT scanning and X-ray imaging demonstrated that, after 8 weeks of treatment, the cartilage in the group treated with coated microspheres exhibited significant healing, closely resembling that of the sham group. These improvements were attributed to the combined effects of the sustained release of paracrine factors and the presence of cell membrane components on the microparticles.

Chondrocyte cell membrane vesicles, retaining chondrocyte-specific membrane proteins and loaded with the polyphenolic drug punicalagin, have been explored as components of 3D bioprinted scaffolds for cartilage defect repair (Table 2, entry 14).[126] The vesicles were functionalized with polymerizable double bonds, combined with cross-linkable sericin, and formulated into a bioink suitable for 3D bioprinting of cartilage scaffolds. The resulting scaffolds released the punicalagin-loaded vesicles in response to elevated ROS levels at the implantation site. Both in vitro and in vivo studies revealed the ability of the scaffolds to promote cartilage repair by scavenging ROS, eliminating bacteria, and enhancing cartilage tissue regeneration.

The role of chondrocyte membranes in promoting the recovery of hyaline cartilaginous phenotype in dedifferentiated chondrocytes has been investigated using collagen II (Col2) scaffolds (Table 2, entry 15).[127] Three-dimensional Col2 scaffolds (from a decellularized hyaline cartilage graft) were prepared either without (Col2S) or with (antCol2) coatings of chondrocyte membrane extracts. After six weeks chondrocytes cultured in Col2S scaffolds exhibited a rejuvenation of the hyaline phenotype, whereas this redifferentiation effect was attenuated in antCol2S, as confirmed by transcriptomic and proteomic analyses. Because chondrocytes naturally reside in an extracellular matrix rich in Col2, their membranes express numerous receptors that interact with

Col2. The coated scaffolds (antCol2S) inherited these surface characteristics, creating antagonistic and shielding effects against Col2. Specifically, in antCol2S, the chondrocyte membrane nanoaggregates preoccupied and saturated Col2 ligand sites, limiting their availability to the seeded chondrocytes. Consequently, the interaction between Col2 ligands and integrin α5 receptors on the chondrocyte surface was antagonized by the membrane coating, promoting activation of the Wnt/β-catenin signaling pathway and contributing to the loss of the hyaline cartilaginous phenotype. These findings highlight the critical role of Col2 in maintaining and restoring the hyaline phenotype in chondrocytes and demonstrate that chondrocyte membranes retain the functional properties of their cells of origin.

3.4.4. Cell Membrane Coatings for Neural Regeneration

Information on the role of cell membrane coatings in neural regeneration is still very incipient. Neural interfacing devices, particularly brain-machine interface (BMI) biomaterials, are increasingly explored for monitoring and stimulating brain function in degenerative diseases and post-injury recovery. However, long-term implantation poses challenges associated with deleterious effects in both the neural tissue (inflammation) and the sensitive electrodes (coating by interfering proteins and cells). Surface chemistry plays a crucial role in these interactions.[128]

To address these challenges, a neuron-specific lipid bilayer derived from PC12 cells (a cell line from a transplantable rat pheochromocytoma) was recently tested as a coating of neural interfaces with the aim of promoting neural adhesion while minimizing immune responses (Table 2, entry 16).[129] The central hypothesis was that this biomimetic coating, derived from PC12 cells differentiated with nerve growth factor (NGF) and expressing the neuronal adhesion molecule L1CAM, would promote better neuronal integration and reduce inflammation in the central nervous system. The transmembrane protein L1CAM is ubiquitously present in the nervous system and plays a key role in neuronal expression, selectivity in binding patterns, and promotion of neurite outgrowth during the progression of the nervous system. To carry out the coating, titanium scaffolds were first modified with phospholipids typical of cell membranes, such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), while in parallel cell membranes were extracted from PC12 cells and used to prepare cell membrane-derived liposomes (**Figure 10**a,b). The DOPE-modified titanium was then incubated in the cell membrane-derived liposomes dispersion at room temperature for 30 min to generate the tethered lipid bilayer (TLB) on the scaffold, which was designed as PM-TLB.

The coating was verified through confocal microscopy, FT-IR spectroscopy, and SDS-PAGE electrophoresis, confirming the presence and functionality of neuronal membrane proteins, including L1CAM. Biological assays demonstrated that PM-TLB resisted protein and bacterial adhesion while favoring neuronal cell attachment over astrocytes and macrophages, even in inflammatory conditions (Figure 10c–g). Compared to poly(L-lysine) (PLL), PM-TLB more effectively promoted neurite outgrowth, enhanced neuronal activation, and reduced gliosis and inflammation. These findings support PM-TLB as a promising biomaterial for chronic neural interfaces, offering improved neuronal integration and long-term stability for implantable devices such as BMIs and neural prostheses.[129]

3.4.5. Cell Membrane Coatings for Vascular Grafts and Spleen Scaffolds

Vascular grafts are widely used to replace narrowed or blocked blood vessels in ischemic diseases. Small-diameter vascular grafts (SDVGs), typically defined by an inner diameter of less than 6 mm, are commonly employed in coronary and peripheral artery bypass procedures. However, synthetic SDVGs are prone to immune recognition as foreign materials, often resulting in chronic inflammation, thrombosis, and intimal hyperplasia—factors that significantly compromise their long-term patency.[130,131] To address these limitations, various strategies have been developed, including surface functionalization with natural cell membranes.

Membranes derived from mature RBCs have demonstrated anti-inflammatory and anti-thrombotic properties when used to coat SDVGs. Key membrane proteins such as CD47 reduce platelet and immune cell adhesion and activation, while others like C8 binding protein, membrane cofactor protein, homologous restriction protein, and complement receptor 1 help suppress complement system activation and immune responses.[132] In one such approach, electrospun mats composed of PCL and poly-lysine were incubated with RBC membrane vesicles and rolled into tubular structures, ensuring that membrane components lined the luminal surface (Table 2, entry 17).[133] These membrane-coated grafts demonstrated mechanical stability under arterial flow conditions and significantly reduced platelet and macrophage adhesion compared to non-coated controls. In a rabbit carotid artery model, membrane-coated grafts supported laminar blood flow and remained open 21 days post-implantation, while non-coated grafts exhibited early turbulent flow and were completely occluded by fibrotic tissue within the same period. Furthermore, the coated grafts promoted recruitment of smooth muscle cells (SMCs), vascular tissue regeneration, and polarization of macrophages toward the anti-inflammatory M2 phenotype.[133]

Similarly, positive results were achieved with SDVGs prepared as collagen hydrogel tubes coated with RBC membranes and reinforced by PCL electrospun nanofibers (Table 2, entry 18).[134] Following implantation in rabbit carotid arteries, these grafts exhibited rapid endothelialization, regeneration of smooth muscle cell layers, and effective prevention of stenosis. Notably, they outperformed ECM-based vascular grafts and offered a significant practical advantage, as their preparation required only a few hours, in contrast to the 4–18 weeks needed for conventional ECM-based vascular grafts.

Vascular endothelial cell membranes have been utilized as scaffold components to enhance spleen repair and vascular regeneration. The spleen's vascular system is essential for nutrient transport and waste clearance, yet its stromal framework—primarily composed of reticular and fibrillar collagen—has limited regenerative capacity. A bioinspired scaffold, consisting of an

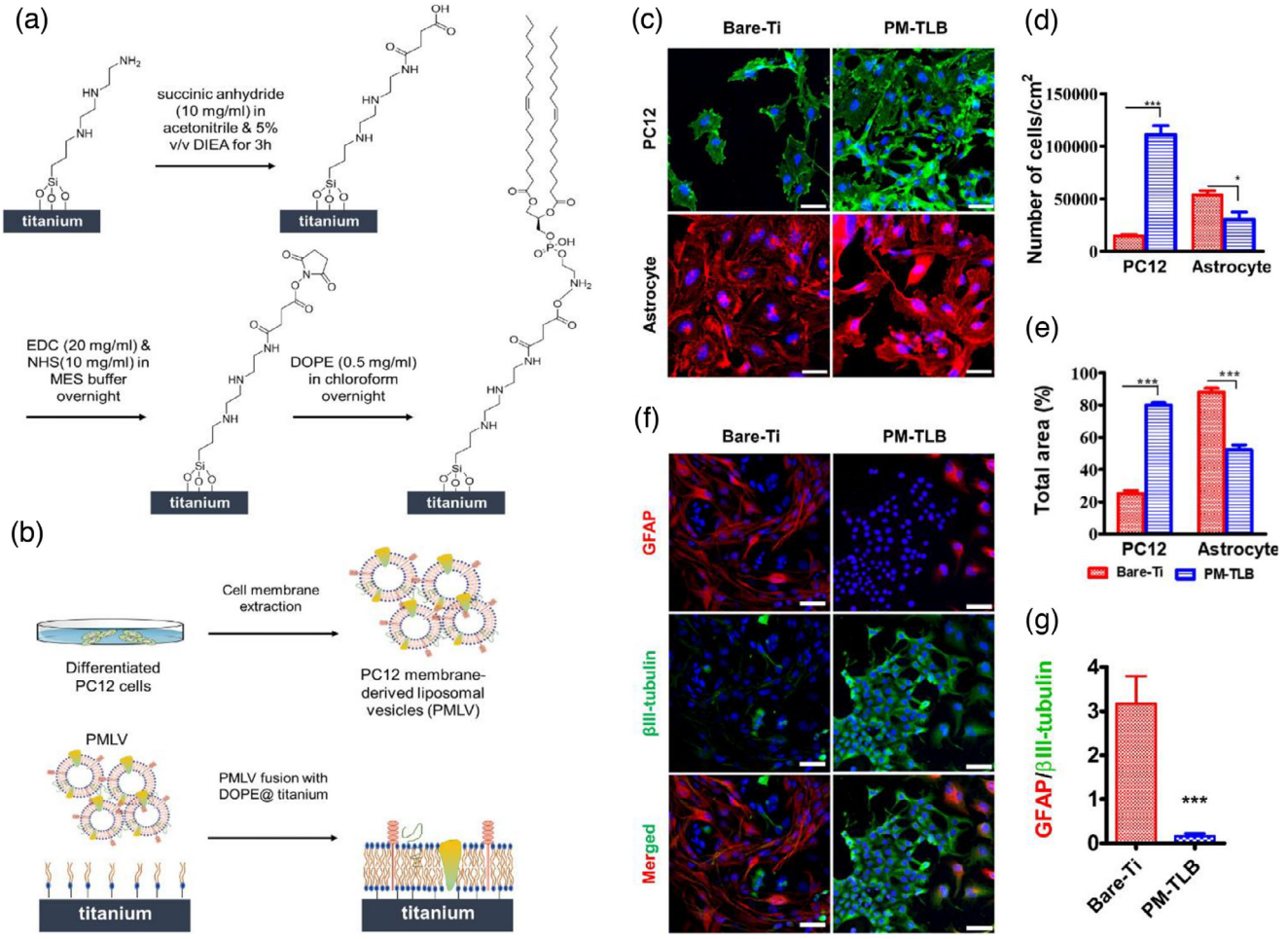

Figure 10. Preparation of titanium scaffolds modified with PC12 cell membrane-derived liposomes. (a) Protocol for the surface modification of titanium with DOPE; and (b) extraction of PC12 cell membranes to prepare vesicles, and subsequent tethering of the vesicles on the titanium surface. (c–g) Co-culture of PC12 cells and astrocytes on modified substrates. (c) immunofluorescence images, (d) cell counts, and (e) total cell area in monocultures. Scale bars: 50 µm. (f) Representative immunostaining of co-cultured PC12 cells and astrocytes, with astrocytes labeled in red (GFAP), PC12 cells in green (βIII-tubulin), and nuclei in blue (DAPI). (g) Quantification of GFAP/βIII-tubulin signal ratios. Scale bars: 50 µm. Reproduced under terms of the CC-BY license.[129] Copyright 2023, The Authors, published by Elsevier.

interpenetrating network of type II and type IV collagen coated with vascular endothelial cell membranes, has demonstrated improved integration with spleen tissue (Table 2, entry 19).[135] This scaffold promoted adhesion to spleen tissue, reduced oxidative stress, recruited cells, and activated key pathways (including Wnt signaling, Statin, and amino acid metabolism) that stimulated splenic cell metabolism, enhanced immune cell function, and supported ECM remodeling. Additionally, the inclusion of vascular endothelial cell membranes promoted vascular regeneration by upregulating neural crest cell differentiation pathways. The regenerated spleen exhibited critical native features, such as red and white pulp and a dense vascular network. Functionally, it maintained blood component homeostasis, reduced abnormal red blood cells, and preserved normal platelet levels. A key finding of the study was that the stability of the cell membrane remained intact for up to one week after immersion in physiological saline, as confirmed by fluorescence microscopy. In summary, this multifunctional scaffold provides a promising approach for in situ spleen regeneration.

3.4.6. Cell Membrane Coatings for Tissue Xenografts

RBC membranes have recently been explored as a strategy to reduce immune rejection of xenogeneic extracellular matrix-based tissue grafts. Xenografts derived from non-human sources offer a potential solution to the shortage of autografts and allografts; however, differences in proteoglycans and collagen composition compared to human tissues often lead to rapid immune recognition and rejection.[136] To address this, coating xenografts with RBC membranes—leveraging their known anti-inflammatory and immune-evasive properties—has shown promise.[137] The proposed clinical approach involves collecting a patient's blood prior to surgery, isolating and lysing RBCs to extract membranes, which are then used to coat the xenografts before implantation.

To test this concept, porcine-derived Living Hyaline Cartilage Graft (LhCG) and its decellularized counterpart (dLhCG), designed for cartilage tissue engineering, were selected as model grafts. These were coated with autologous RBC membranes to serve as a biological camouflage, allowing the xenografts to

be perceived by the immune system as self-tissue. The membrane coating remained stable on the grafts for at least four weeks. In vivo evaluation using an omentum implantation model in female rats—a site highly reactive to foreign materials—demonstrated that xenografts coated with autologous RBC membranes significantly outperformed both uncoated and allogeneic RBC membrane-coated grafts in reducing inflammation over a 14-day period. Overall, the study suggests that autologous RBC membrane-coated xenografts can effectively evade immune detection and represent a promising strategy for minimizing immune and inflammatory responses in tissue engineering applications.[137]

Valvular heart disease affects millions worldwide, with the majority of patients eventually requiring heart valve replacement. However, existing mechanical and bioprosthetic heart valves face significant limitations, including susceptibility to thrombosis, limited durability, and an inability to grow with pediatric patients. Commercially available decellularized heart valve (DHV) xenografts, currently under clinical evaluation, aim to support valve repair, remodeling, and regeneration. Despite their promise, their clinical utility is hampered by strong immune responses and suboptimal recellularization. To address these challenges, a layer-by-layer assembly technique was used to coat DHVs with RBC membranes.[138] This coating substantially enhanced the hemocompatibility of DHVs by reducing plasma protein adsorption, inhibiting platelet activation and erythrocyte aggregation, and promoting macrophage polarization toward the anti-inflammatory M2 phenotype. Additionally, the RBC membrane coating improved the mechanical strength and enzymatic stability of DHVs. In vivo studies using rat models—both subcutaneous embedding and abdominal aorta implantation—demonstrated that the coated scaffolds effectively supported early-stage endothelialization and ECM remodeling and exhibited no signs of thrombosis or calcification.

4. Conclusion and Future Trends

The field of regenerative medicine has advanced rapidly in recent years as research has deepened our understanding of natural tissue repair mechanisms and the physiological response to scaffold materials. The more closely a scaffold mimics natural healing processes, the greater its efficacy and safety. Ideally, cells and the ECM should drive regeneration, but the external administration of these components raises concerns regarding availability, safety (avoiding adverse reactions), and long-term efficacy. Until these challenges are fully addressed to meet the stringent standards of the biomedical industry, bioinspired strategies offer a promising alternative. These approaches aim to replicate key aspects of tissue repair, such as targeted cell recruitment and bio-stimulation, to promote desired tissue formation.

In addition to the bulk properties of scaffolds, surface characteristics significantly influence performance. Cell membranes are not merely protective barriers; they also mediate communication by collecting signals that regulate cell growth, differentiation, and immune interactions. Biomimetic coatings that replicate cell membrane phospholipids and glycocalyx structures have already demonstrated enhanced anti-fouling, anti-thrombogenic, and selective molecular recognition properties. As a result, bioinspired zwitterionization and glycosylation of scaffold surfaces are being widely explored to reduce foreign-body reactions and promote specific cell interactions.

A more advanced approach involves coating scaffolds with membranes from the target cell type. While synthetic replication of membrane components remains challenging due to limited knowledge of their precise spatial organization, it is clear that both composition and structure are critical for proper function. Although research on cell membrane-coated scaffolds is still in its early stages, existing studies highlight their advantages over non-coated scaffolds. These include homotypic cell attraction, immune modulation, and reduced non-specific protein and bacterial adhesion. Despite these benefits, the field remains largely unexplored, with many open questions yet to be addressed.

Key challenges include developing standardized, reproducible methods for isolating plasma membranes from specific cells while preserving their integrity. Current protocols vary widely between laboratories, underscoring the need for systematic optimization. Additionally, critical questions remain regarding the required membrane coating density for different cell types and applications, the factors influencing coating reproducibility and stability, and the potential benefits and risks of using hybrid membranes from multiple cell sources. Addressing these scientific gaps could significantly advance scaffold technology, making them more functional and effective in tissue regeneration. It is worth noting that membrane-coated drug nanocarriers are also emerging as effective tools for targeted delivery of growth factors, antimicrobial agents, genetic material, and other therapeutic molecules to damaged tissues. When applied to scaffolds, cell membrane coatings integrate the benefits of localized drug delivery with the structural support and bioactive surface needed to guide cell behavior and tissue regeneration more effectively over time.

The functionality of the cell membranes and the stability of their binding to the scaffold can be fine-tuned through physical, chemical, or biological engineering approaches, as demonstrated in the development of membrane-cloaked drug nanocarriers[67] and stem cell therapies.[139] Dilution of the cell membranes with tailored liposomes or leveraging the numerous amine or thiol groups within the membrane as reactive binding points may strengthen the binding of the membrane to the scaffold biomaterial through covalent bonds. Furthermore, the cell membranes used for the coating can be engineered to optimize their composition by applying biological tools, including metabolic glycoengineering to modify the glycosylation (via incubation of cells with specific monosaccharides) and genetic engineering to modulate the proteins expressed on the cell membrane. This may not only enable more efficient scaffold coating but also enhance surface selectivity for specific cell types, potentially creating selective binding patterns for various cells and for the most suitable ECM components to guide tissue regeneration.

Relevantly, studies have shown that the addition of external helper phospholipids increases cell membrane fluidity, enabling membrane fragments or vesicles to spread more uniformly over scaffold surfaces, resulting in complete coverage.[140] Computational modeling and experimental analysis have revealed that the key steps of adsorption, deformation in contact with the substrate, rupture of cell membrane vesicles, and fusion again of the membrane to form the continuous coating are highly dependent on membrane fluidity. Conventional extrusion or sonication may

be insufficient to break cell membrane vesicles, which are stiffer than conventional liposomes, due to the presence of proteins. Therefore, hybrid membranes that combine cell membranes and polyunsaturated phospholipids exhibit greater fluidity and coverage while preserving the homotypic interaction ability. The design of cell membrane-coated scaffolds thus requires optimization across multiple variables. As with membrane-cloaked drug nanocarriers, computational modeling and Design of Experiments (DoE) methodologies can be invaluable in identifying critical quality attributes and guiding the rational development of cell membrane-coated biomaterials.[141,142]

Alongside these scientific challenges, the translation of membrane-coated scaffolds to clinical use must address issues related to scalability, cell source availability, and compliance with good manufacturing practices (GMP). Among various tissue sources, blood appears to be the most feasible source of standardized membranes from its cellular components. A variety of blood-based products are already on the market under a well-defined regulatory pathway,[143] and the implementation of RBC and platelet membrane coatings could be relatively straightforward. Additionally, the shelf-life of cell membrane-coated products must also be rigorously assessed, not only through chemical stability under accelerated conditions, but also from a biological standpoint, as minor conformational changes can significantly affect in vivo outcomes. So far, cryopreservation at –80 °C been shown to maintain the stability of macrophage membrane-coated scaffolds for at least one month.[112] The experience gained with cellular components of blood could be translated to membranes from specialized cells, paving the way for the clinical testing of cell membrane-coated scaffolds in the near future.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI-Assisted Technologies in the Writing Process

AI-assisted technologies (chat-GPT) were used in the writing process before submission, but only to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article.

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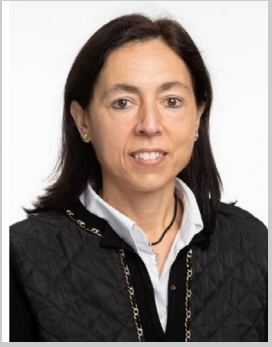

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