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Review

Membranes for the life sciences and their future roles in medicine

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ABSTRACT

Since the global outbreak of COVID-19, membrane technology for clinical treatments, including extracorporeal membrane oxygenation (ECMO) and protective masks and clothing, has attracted intense research attention for its irreplaceable abilities. Membrane research and applications are now playing an increasingly important role in various fields of life science. In addition to intrinsic properties such as size sieving, dissolution and diffusion, membranes are often endowed with additional functions as cell scaffolds, catalysts or sensors to satisfy the specific requirements of different clinical applications. In this review, we will introduce and discuss state-of-the-art membranes and their respective functions in four typical areas of life science: artificial organs, tissue engineering, *in vitro* blood diagnosis and medical support. Emphasis will be given to the description of certain specific functions required of membranes in each field to provide guidance for the selection and fabrication of the membrane material. The advantages and disadvantages of these membranes have been compared to indicate further development directions for different clinical applications. Finally, we propose challenges and outlooks for future development.

1. Introduction

In nature, membranes originate from organisms and occur widely in plants and animals as part of their basic metabolism for living. However, the process of understanding, utilizing and synthesizing membranes has been long and tortuous. In the history of membrane science, a microfiltration membrane was first proposed, and then reverse osmosis and ion-selective membranes were gradually synthesized with the development of polymer materials. The earliest use of membranes in life science was artificial kidneys. In 1943, Kolff, the father of artificial organs, produced his third kidney dialysis device but failed to cure patients using this device [1]. This technology is still continuing to mature with the progress of clinical medicine. However, as in the case of the dialysis membrane, research to develop membrane materials and separation techniques is always time consuming and expensive, resulting in much slower industrialization production and development for clinical applications than for waste treatment, gas separation and energy recovery. In 1999, dialysis membranes accounted for the largest market share of 43.1%, but in 2010, the share was no more than 14% [2]. In 2020, the COVID-19 virus broke out globally, and extracorporeal membrane oxygenation (ECMO) membranes exhibited unique life-saving ability in critical patients who lost partial or total pulmonary function. Clinical membranes are once again attracting increasing general attention worldwide. Membranes have a long history of use in artificial organs, but there are still many deficiencies because membranes cannot fully substitute for the physiological functions of organs. Recently, membranes have been widely used in tissue engineering for tissue reconstruction to compensate for physiological deficiencies. In addition, due to the impact of the epidemic, rapid diagnosis and efficient physical protection requirements have expanded the application of membranes. At present, the main research directions of membranes in life science can be divided into artificial organs (lung, liver, kidney, *etc.*), tissue engineering, *in vitro* diagnosis and medical support. Statistics show that the global research funding in life and health industry reached 16.1 billion USD in 2020, which is continuously increasing [3]. The life and health industry has played an important role in leading global economic development and social progress in the 21st century. The use of membranes in the life sciences is expected to show increasing importance and a necessarily expanding market for the future.

To date, few reviews have summarized and discussed state-of-the-art membrane technique in life sciences for advancing clinical treatment. Therefore, in this review, based on the intrinsic properties, such as the size sieving, dissolution, diffusion and mechanical strength of the membrane, we will mainly introduce various typical membranes used in artificial organs, tissue engineering, *in vitro* blood diagnosis and medical support (shown in Fig. 1). Focusing on

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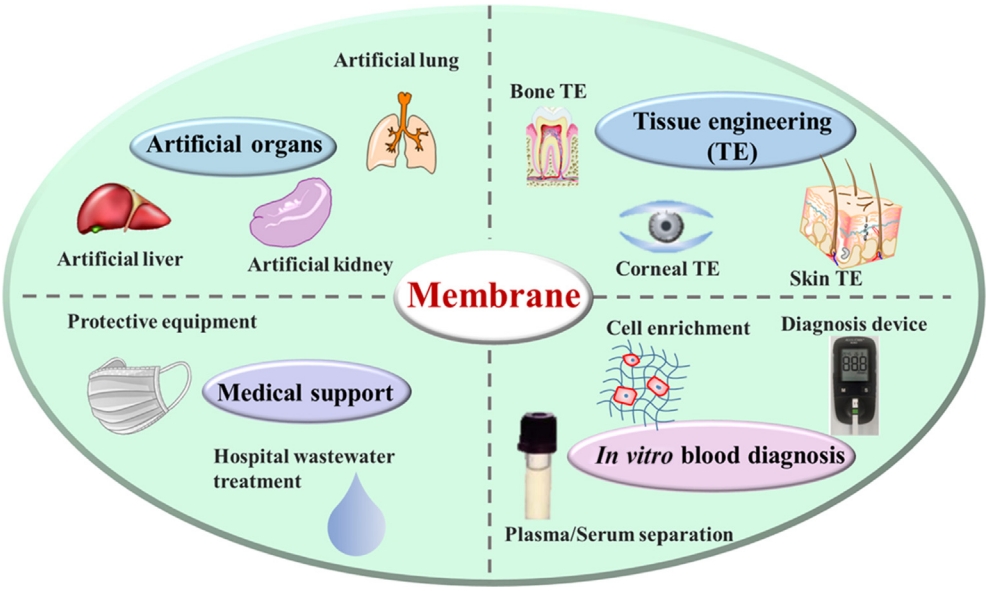

Fig. 1. Schematic of the four aspects of membrane applications in life science.

the different requirements of the above four areas, specific functions derived from different membranes will be emphasized to provide guidance for the selection of optimal membrane materials and their fabrication methods. For example, membranes used for artificial kidneys often need size-sieving ability, while artificial lungs are produced with gas exchange ability; in contrast, corneal tissue engineering pays more attention to transparency and mechanical intensity. In addition, the advantages and disadvantages of the previously mentioned membrane materials will be compared to exhibit possible extensive applications with performance improvement. Finally, prospective future research directions for membranes in life science will be addressed to describe a new but advanced interdisciplinary field for humanity.

2. Membrane Functions Applicable to Life Science

In traditional applications, the main discussed functions of membranes are selectivity and permeability [4–6]. However, due to the specific environment in the body, membranes must possess additional abilities for medical applications. For example, artificial organs take advantage of membranes to mimic the natural functions of human organs, mainly the removal of toxic substances from blood based on the size-sieving function of the membrane. In addition to the above native ability, hemocompatibility is also essential to protect the blood, preventing hemolysis and coagulation behaviors during long-term treatment. In the tissue engineering field, the membrane acts not only as a barrier to resist external destruction but also as a scaffold to provide a microenvironment for cell proliferation and differentiation. To achieve these functions, the membrane should have high mechanical strength and satisfactory biocompatibility (hydrophilicity, electronegativity, hypotoxicity and anti-inflammatory effects). For *in vitro* blood diagnosis, the most important role of membranes used to be sample purification based on the size-sieving function, but recently, sensing functions were successfully integrated into the membrane to achieve the in-situ and online analysis of blood indices. In medical support, membranes are utilized as guards against dusts and pathogens, and novel catalysis functions have been integrated to kill bacteria that may cause infections in humans. The following sections will summarize these properties with typical examples for a better understanding of the different roles of membranes in various clinical applications.

3. Membranes for Artificial Organs

The structure and function of human organs are highly complex, as they maintain human metabolism to balance and stabilize the internal body environment. Generally, the cells in organs can have a certain repair ability except for cardiomyocytes, but once irreversible damage has occurred, losing most of the function of an organ, artificial medicine or surgical repair is the only method. Current treatments mainly include stem cell transplants [7], organ transplants [8] and artificial organs. However, stem cell and organ transplants always face the major challenge that there is usually a serious mismatch between the donor and the recipient after transplantation. The use of artificial organs has become a preferred and safer curing method. Especially in the treatment of COVID-19, ECMO membranes (artificial lungs) have become the most effective method for the treatment of severe cases [9,10].

3.1. Artificial lung

The lungs are the part of the respiratory system that exchange oxygen and carbon dioxide during blood circulation. The structural unit is an alveolar with a diameter of approximately 0.3 mm^2. The total alveolar area is extremely large, approximately 50–100 m^2, providing an average exchange rate of oxygen and carbon dioxide in a normal adult human ranging from 200–250 $ml \cdot min^{-1}$ to 6 $L \cdot min^{-1}$. When the body undergoes gas exchange, oxygen from the outside enters the blood through the alveoli and binds to hemoglobin, while CO_2 is discharged through the opposite route. Artificial lungs rely on artificial membranes to replace alveoli at the interface between air and blood to realize the gas exchange function; therefore, gas exchange efficiency and blood compatibility are the most important membrane properties in determining the clinical performance (shown in Fig. 2(a))[10].

The artificial lung, or ECMO, is an extension of cardiopulmonary bypass, invented by John Gill and first used in human surgery in 1955 [13]. In the early stage of artificial lungs, a bubble oxygenator was adopted [14–16], which is still in use today because of its rapid, simple and inexpensive operation. However, its direct

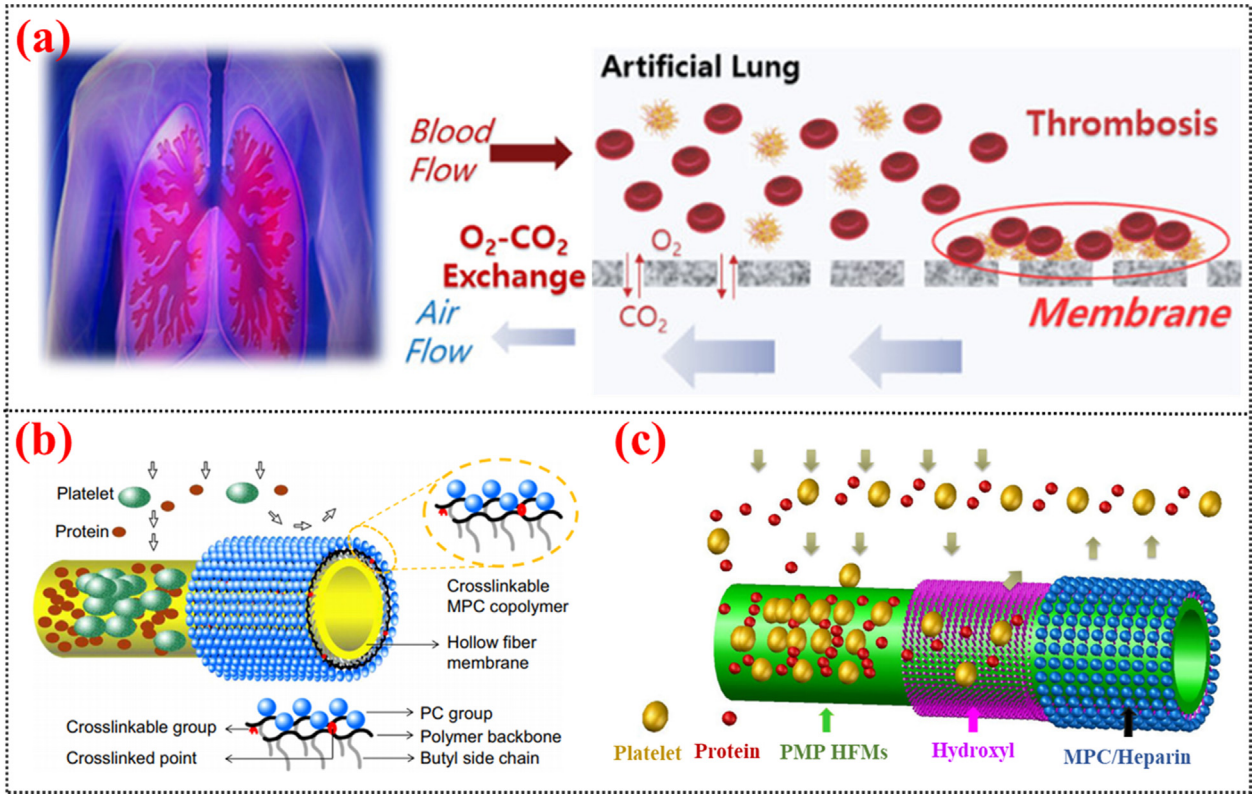

Fig. 2. (a) Diagram of the membrane separation mechanism and biocompatible modification strategies of (b) polypropylene (PP) hollow fiber membrane with amphiphilic phospholipid polymer coating and (c) polymethyl pentene (PMP) hollow fiber membranes by grafting 2-methacryloyloxyethyl phosphorylcholine (MPC) or heparin. Reproduced from Refs. [10,11] and [12] with permission from Elsevier, respectively.

contact between blood and gas will destroy blood components such as red blood cells, platelets and plasma proteins, resulting in hemolysis, thrombocytopenia and the degeneration of plasma proteins [17]. In 1960 and 1970, membrane oxygenators were introduced to separate blood and gas with a semipermeable membrane, enabling the safe use of ECMO for a long time [18,19]. Its form derives from the original drum-shaped, flat membranes folded into hollow fibers. The unique hollow fiber structure of the membrane results in a large exchange area, enabling a cross-flow blood gas exchange method with less frequent thrombosis. To date, hollow fiber membranes still dominate as the best choice for ECMO fabrication. For example, Wang *et al.* [11] adopted a polypropylene (PP) hollow fiber membrane and improved its hemocompatibility with phospholipid copolymer coating. The poly(MPC-*co*-BMA-*co*-TSMA)(PMBT) coated hollow fiber membrane showed good stability in water and ethanol solution without hindering the gas permeability (shown in Fig. 2(b)). In another study, as the polymethyl pentene (PMP) hollow fiber membranes exhibit 12 times higher gas permeability, Huang *et al.* [12] chose PMP hollow fiber membranes for the fa brication of membrane oxygenators. Plasma treatment, chemical reduction and phosphorylcholine (MPC)/heparin coating methods were used to acquire a desirable hemocompatibility (shown in Fig. 2(c)) [10]. From 1965 to 1975, anticoagulation technology began to be employed in membrane preparation due to clinical requirements during surgery [20–22]. After that, the ECMO technique gradually matured for use in long-term adjuvant therapy as a last resort for patients with cardiopulmonary failure. It has performed an outstanding role in the treatment of critical pneumonia patients during the outbreak of COVID-19 in 2020.

ECMO has a very high requirement for the membrane material. To date, there have been three generations of membrane materials for ECMO fabrication with the development of polymer science. The first generation is polydimethylsiloxane, which possesses good blood compatibility and small plasma leakage but weak CO_2 flux [23]. The second generation of ECMO membranes often uses polyethylene, polypropylene and similar materials, which are hydrophobic surfaces with more uniform porous structure [11,24]. Although these materials are beneficial for gas exchange, they also have obvious disadvantages. For example, their microporous structures increase the risk of plasma leakage, and the service life is usually short, within 6 h. This is because with prolonged working time, plasma protein easily adsorbs on the porous surface, which increases the membrane surface energy, resulting in blood leakage [25,26]. At present, PMP serves as the third generation of artificial lungs due to its excellent oxygen flux (approximately 10 times that of polyethylene), good biocompatibility and low dissolution of the molecular segment, which significantly enhance the service life to 2–4 weeks. Although PMP is hydrophobic, it is insoluble in organic solvents, allowing the formation of a thin dense layer (thickness less than 1 μm, pore size less than 100 nm) during the preparation process, thus effectively preventing plasma leakage. Although many countries have realized the importance of the ECMO membrane, the difficulty of preparation restricts its independent production. Especially for PMP, the raw material and preparation technology are monopolistic. In addition to the above three generations of membrane materials, in the latest research, fluoropolymers have been reported to significantly improve the service life by reducing the surface energy during gas exchange and are expected to become a new research direction for the preparation of ECMO membranes [9,10]. In Park's work, the as-prepared poly(vinylidene-co-hexafluoropropylene) membrane was coated with Hyflon AD60X (which is a typical fluoropolymer with an extremely low surface energy), displaying a repulsion for

both water and blood without hemolysis in a long term. This work suggests the fluoropolymers may be a good candidate for the ECMO membranes [7].

In improving clinical performance, blood compatibility is always a main challenge. Blood compatibility is needed to maintain chemical and physical stability during long-term blood contact. Currently, three modification methods of the membrane surface have been most widely applied to improve blood compatibility. (1) The first is heparinization. Heparin acts as an anticoagulant by inhibiting the activation of clotting factors. Owing to this mechanism, membrane surfaces serving as the interface in direct contact with blood have been modified with heparin, which reduces the clotting behavior to decrease cell damage and stabilize the separation performance. Huang *et al.* [12] modified the surface of PMP with specific hydroxyl functional groups by oxygen plasma treatment and sodium borohydride reduction and then grafted on heparin molecules to form an anticoagulant layer, resulting in good blood compatibility (shown in Fig. 2(b)). Although the exchange rate of O_2 and CO_2 was decreased by 5% after modification, the leakage of plasma was greatly reduced. Moreover, the adsorptions of protein and platelets were decreased by 60%–70% and 25%–30%, respectively, greatly increasing the usage life of the ECMO membrane. (2) The second is zwitterionic surface modification. In this process, a zwitterion containing equal amounts of anions and cations was grafted to a membrane surface to achieve electric neutrality. Owing to the strong hydration ability of the modified membrane, a hydration layer is created to reduce the occurrence of thrombosis by preventing the adsorption of nonspecific proteins. Malkin *et al.* [27] aminated or hydroxylated a PMP hollow fiber surface by plasma-enhanced chemical vapor deposition to graft on a sulfobetaine block copolymer. With sheep blood as the target sample, the membrane enabled remarkable rejection of platelet adsorption after modification. Importantly, this method can be generally extended to other membrane materials to reduce cell or protein adsorption, such as modifying the polyvinyl chloride membrane to reduce its platelet adsorption by 95%. (3) The third is surface endothelialization. Endothelial cells regulate the expression of specific proteins through tissue factors, which play an important role in initiating and adjusting the coagulation cascade reaction. Therefore, surface endothelialization is considered to be an effective way to improve the blood compatibility of the membrane surface. Hess *et al.* [28] cultured endothelial cells on the surface of PMP treated with albumin/heparin surface deposition, achieving a reduction in platelet adsorption to 10% without any effect on its gas permeability. Pflaum *et al.* [29] formed a monolayer of endothelial cells on the surface of TiO_2-coated PMP, which could effectively prevent inflammation and thrombosis formation.

3.2. Artificial kidney

The kidney, a bean-shaped organ on either side of the spine, is the main part of the urinary system. The basic unit of its function is the nephron, which participates in filtering wastewater and toxins in the blood and maintaining the balance of body fluid and electrolytes. An artificial kidney, also known as a dialyzer [30], applies membrane technology to replace the kidney for the removal of toxins [31]. It was first proposed in the mid-19th century and was first realized for the clinical treatment of patients in 1945. However, due to the complexity and long period of clinical trials, this technique has not undergone obvious development over a long time until recent years.

Currently, according to the operation mode, artificial kidneys can be divided into three types, hemodialysis (HD), hemofiltration (HF) and hemodiafiltration (HDF), which differ in basic principles and the types of substances removed. The basic mechanism by which HD removes micromolecular urotoxins is the dispersion effect with the help of a semipermeable membrane (shown in Fig. 3(a)) [31]. Micromolecular urotoxins with higher concentrations in the blood side will disperse into the substitute liquid side. The pore diameter of the semipermeable membrane is 3 nm, which allows the removal of small and medium molecules while blood cells and proteins are intercepted. HF removes medium molecules by the convection effect. Under the given transmembrane pressure, the medium molecules permeate through the membrane from the blood side to the dialysate side [33]. HDF combines the principle of HD and HF, serving as an effective way to remove macromolecules.

Since the few attempts of hemodialyzer in human at 20th century [34], the dialysis membrane has undergone many technical improvements. In terms of morphology, the plate-type dialyzer used in the early stage produced much residual blood, and the closed coil-type dialyzer was therefore used more often in the late stage. Currently, hollow fiber membranes, which have better performance, are the most widely applied. In addition to the dialyzer structure, the development of the membrane material also determines the medical effects and has undergone three main milestones with the progress in material science. The first stage was the cellulose membrane. Because of its excellent mechanical properties, good permeability and low price, this membrane dominated the market and research in hemodialyzers from 1970 to 1990. However, it easily triggers inflammatory reactions and has a low clearance rate of medium molecular substances. In 1985, Henderson published an article discussing the biocompatibility of cellulose for artificial kidneys, attracting research attention to the exploration of other materials with better biocompatibility. The second-stage material was the modified cellulose membrane, with different substituent groups grafted onto the main chain of cellulose. The cellulose acetate membrane has become the typical material to reduce inflammation and enhance biocompatibility. In the last decade, various third-stage polymer materials, including polysulfone, polyether sulfone, polyacrylonitrile and polymethyl methacrylate [35–37], have been gradually proposed for dialysis membrane fabrication. These materials present great improvements in membrane preparation and modification techniques, widely promoting market transfer. More importantly, these membranes cause minimal inflammatory reaction, so they are gradually overtaking the market.

Due to the hydrophobicity of the widely applied polysulfone, polyether sulfone and polylactic acid membranes, which cannot satisfy clinical requirements, they are often improved by modification with certain functional molecules. In addition to the plasma treatment method, two main modification strategies (blending with hydrophilic molecules and grafting with anticoagulant molecules) are commonly adopted to address the above deficiency.

(1) Blending hydrophilic additives. Owing to its facile and low-cost operation, this method can be applied in large-scale production. Heilmann *et al.* [36] mixed different polyvinyl pyrrolidones (PVPs) of various molecular weights into polysulfones to prepare membranes. The results showed that PVP with a low molecular weight was easily eluted, while PVP with a high molecular weight could remain stable in the membrane. This study suggests that the amount of introduced PVP should be appropriate because excessive PVP can easily cause complement activation and thrombosis. Omichi *et al.* [38] also mixed PVP with polyether sulfone for membrane preparation, and soluble human thromboregulatory protein (hTM) was applied to test the physical adsorption ability of the membrane surface. In this comparison, the adsorption volume of hTM was confirmed to show little change with as the PVP content increased to 10%(mass). Moreover, the simulative blood experiment verified that the adsorption of the protein improves the blood compatibility of the dialyzer surface.

(2) Anticoagulant molecular modification. Heparin, sulfobetaine methacrylate and hirudin are most commonly applied for surface

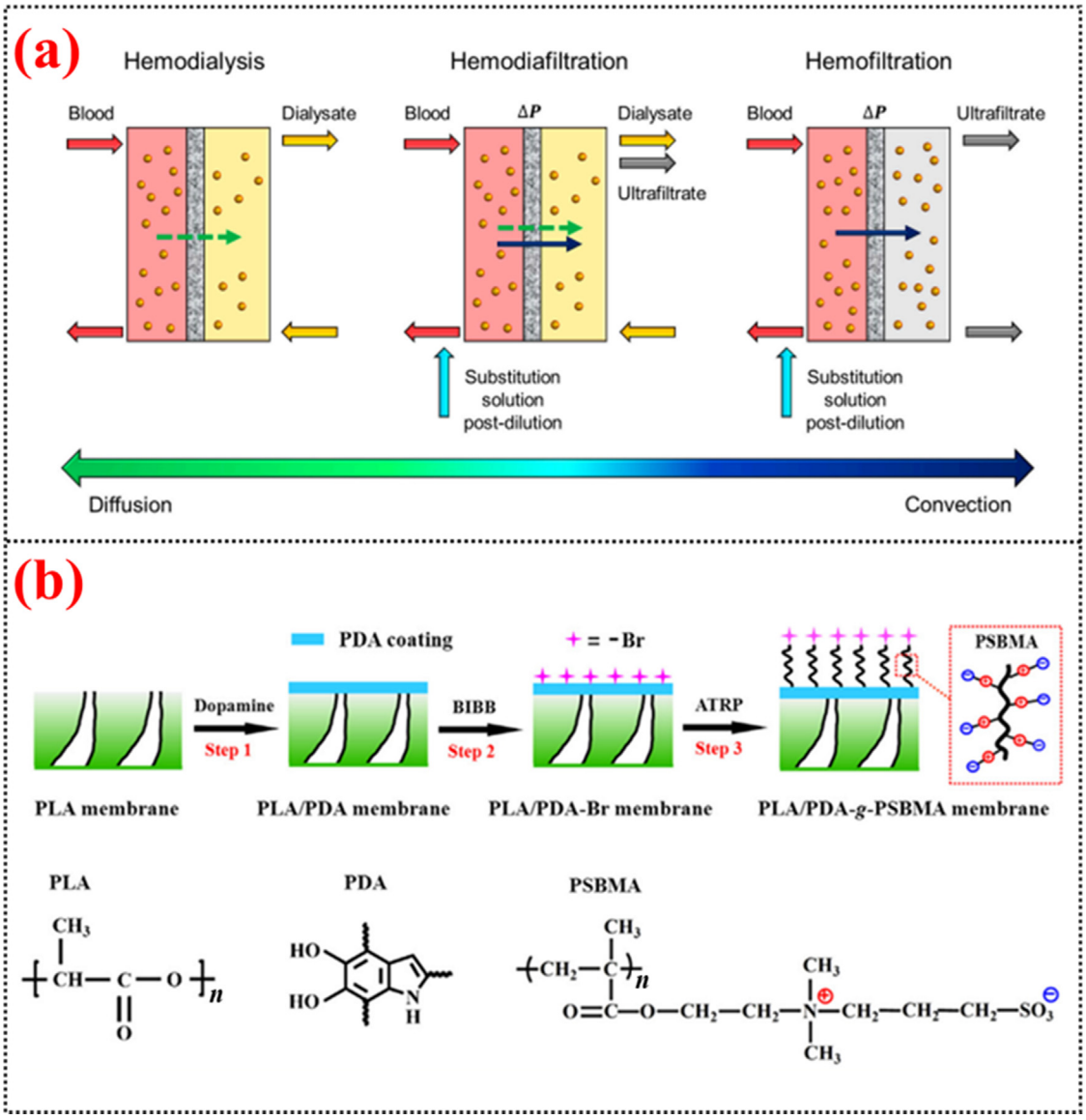

Fig. 3. (a) Diagram of the operation mode of artificial kidney and (b) the preparation of membranes with improved biocompatibility. Reproduced from Ref. [31] and [32] with permission from Elsevier.

modification of dialysis membranes to improve the anticoagulant ability during blood contact. Chen *et al.* [39] modified polysulfone hollow fiber membranes with multilayer components of tannic acid, heparin and poly(2-ethyl-2-oxazoline) brushes for their ability to remove reactive oxygen species and exert anticoagulative effects. Then, in the simulated dialysis experiment, the as-prepared membrane showed good scavenging ability of specific small-molecule (urea) and medium-molecule (lysozyme) toxins while preserving most of the macromolecular protein. Using polydopamine, Gao *et al.* [40] modified the polylactic acid membrane surface with heparin to prolong the time of blood recalcification, thereby inhibiting the formation of thrombosis and effectively improving the blood compatibility of the membrane. Similarly, Zhu *et al.* [32] used polydopamine to modify the surface of a polycaprolactone membrane with amphoteric ion polymethacrylate sulfobetaine (shown in Fig. 3(b)). After modification, the hydrophilicity and electronegativity of the membrane were greatly improved, making it easy to form a hydration layer through electrostatic interactions and hydrogen bonding, thereby endowing the membrane with strong repulsion to proteins and platelets and improved anticoagulant performance. To improve the anticoagulant ability, Li *et al.* [30] modified a PVP membrane surface with hirudin because of the hydrogen bonding interaction between the carbonyl groups on PVP and the carboxyl groups on hirudin. More importantly, the binding was so stable that the modified membrane still showed good anticoagulant performance after 12 h of culture in normal saline.

At present, four types of new artificial kidneys are being studied worldwide: wearable artificial kidneys, 3D-printed kidneys, synthetic kidneys from artificial stem cells, and microchipped artificial kidneys [41–43]. Among them, wearable artificial kidneys are the closest to the clinical stage. Artificial kidneys require large amounts of dialysate to remove toxins, but wearable artificial kidneys cannot contain a large volume of dialysate and remain portable. Currently, the most effective solution is to develop efficient adsorbents that can recycle dialysate. Tijink *et al.* [44] fabricated a dual-layer hollow fiber mixed matrix membrane with a porous macrovoid-free inner membrane layer and active carbon particles containing an outer layer for the removal of creatinine and uremic toxins. Ding *et al.* [45] fabricated a bifunctional membrane that

consists of a polyvinyl alcohol hydrogel as a separation layer and a polyacrylonitrile nanofibrous membrane with UiO-66-$(COOH)_2$ (U-66) nanoparticles as an adsorption layer. In a model of the dialysis process, polyvinyl alcohol/polylactic acid-U-60 composite membranes enabled good removal of toxins from the blood with ultrahigh protein retention. Furthermore, the volume of dialysate required for the polyvinyl alcohol/polylactic acid-U-60 membrane was only one tenth of that required for the polyvinyl alcohol-polylactic acid membrane, confirming the advantages of U-66 in promoting the exchange efficiency. This strategy employing an adsorbent has been adopted by the AWAK company to develop a wearable artificial kidney, and it is now moving into clinical trials. Currently, we believe that with the rapid development of interdisciplinary technology, more comfortable, portable and user-friendly artificial kidneys will soon be available as products that can greatly improve the quality of life of uremic patients.

3.3. Artificial liver

The liver is a multifunctional organ with an especially vital detoxifying ability that decomposes toxins to nontoxic and soluble substances. Normally, small soluble toxins can be excreted by the kidneys or by dialysis membranes, but hydrophobic and insoluble toxins in plasma, such as bilirubin and endotoxin, can be removed only by the liver after combining with albumin (molecular mass of 69 kDa). Liver damage will lead to various diseases, including hyperbilirubinemia, coagulopathy, and detoxification dysfunction. Although the liver has a unique regenerative function, severe damage still requires medical intervention. Due to the shortage of organs and the inflammatory response to transplantation, increasing attention has been given to developing artificial livers in recent years.

According to their composition and properties, artificial livers can be divided into three categories: nonbiological artificial livers, biological artificial livers and hybrid artificial livers. Both biological artificial livers and hybrid artificial liver systems contain liver cells to mimic the physiological functions of the liver while avoiding allograft rejection, but they are still constrained by the lack of effective cell sources and some immune rejections. Therefore, a nonbiological artificial liver is the most practical method for liver replacement. The nonbiological artificial liver can be seen as a blood purification system involving a series of blood purification methods, including plasma exchange, blood perfusion, plasma adsorption, hemofiltration and hemodialysis. Plasma exchange is the most widely used among these approaches.

Plasma exchange is a therapy that separates plasma from whole blood by centrifugation or membrane separation methods and then returns normal plasma without toxins to the body. The membrane technique was first introduced for plasma separation in 1978 as an alternative to the existing centrifugal technique. Compared to the centrifugal method, the membrane separation method has the advantages of online operation, selectivity and low cost. The membrane material and structure have a great influence on the sieving effect. Materials with good hemocompatibility, including cellulose acetates, polyvinyl alcohol, polyethersulfone, polyolefins such as polyethylene and polypropylene, polymethylmethacrylate, polycarbonate, and polyvinyl chloride, are commonly used [46–52]. The membrane must be have appropriate hydrophilicity and mechanical strength, a suitable pore size (usually 0.3–0.5 μm) to prevent the passage of blood cells (erythrocytes, leukocytes and platelets are 7–8 μm, 7–25 μm and 1–4 μm in diameter, respectively), and a suitable pore distribution to maximize the plasma flux [53]. Many studies have been performed for plasma separation. For example, Wang *et al.* [54] developed a zwitterionic polyurethane-modified cellulose acetate membrane with enhanced anti-adsorption ability for rapid and continuous plasma separation. The membrane can obtain 0.5–0.7 ml of plasma from 10 ml of whole blood within 10 min. To solve the problem of toxins in the separated plasma, Liu *et al.* [55] grafted β-cyclodextrin onto the external surface of a polyvinylidene fluoride plasma separation membrane to construct a bilirubin adsorption layer. This bifunctional membrane can remove bilirubin safely *via* one-step "filtration-adsorption" with low hemolysis and blood cell adsorption, providing a new mode for plasma exchange. As some small molecular toxins are always bound to albumins, membranes and adsorbents that are more selective for toxin-bound albumins in plasma should be exploited to prevent the removal of useful albumins in the future.

Although the nonbiological artificial liver system is maturely used for treating patients with liver damage, it provides a much shorter duration of support for patients than the artificial kidney. Patients with renal failure can survive for decades, while patients with liver failure can hardly live for 7 days. This enormous difference is because of the different complexity between the kidney and liver, and some physiological properties are of vital importance for the body. Therefore, the development of biological artificial liver systems provides increased hope for the future.

3.4. Main challenges of artificial organ membranes in the future

Although membrane technology has been widely applied in many devices that are in close contact with blood, including cardiopulmonary bypass devices, indwelling medical devices, and implanted devices, the problem of blood compatibility is still a main challenge during long-term treatment. In particular, most synthetic polymer materials have low surface energy and poor hydrophilicity, which easily cause cell damage and clotting activation, leading to severe hemolysis and coagulation. According to the internationally standardized definition, hemocompatibility requires limiting the reactions of blood to exogenous materials, including resistance to the adsorption of proteins (especially fibrinogen) and cells and the prevention of thrombosis formation, hemolysis and inflammatory reactions. Up to now, there are mainly three strategies to achieve excellent hemocompatibility: performing hydrophilic modification, constructing biomimetic membranes and creating a super liquid-repellent surface. Hydrophilic modification is performed mainly by methods such as plasma etching, blending hydrophilic additives or anticoagulant molecules. Biomimetic membranes are constructed by using phospholipids to mimic the highly oriented structure of biofilms. The super liquid-repellent surface is created by fabricating nanostructures on the membrane by spray particle coating or etching methods (plasma, laser, chemical, and electrochemical etching) to create an air gap between the blood and the material surface. Moreover, inspired by the blood vessels, the liquid gating membrane may be a new kind of membraned to be used in artificial organs [56,57].

The above research developments have greatly improved the survival rates of patients in many areas; however, the high cost and time consumption of current commercial devices still constrain their daily application for each patient. Therefore, minimized and portable artificial organs are arousing increasing research attention to benefit nonhospital patients in the future. Recent new fabrication techniques, such as 3D printing, stem cell culture, and wearable and microfluidic devices, have provided inspiration for future research on artificial organs and their industrial production. For instance, the wearable artificial kidney developed by a team in Singapore has already entered the clinical trial stage. It is believed that an increasing number of household artificial organs with convenient operation and easy replacement will greatly reduce the expense of medical treatment with little influence on the daily life of patients.

4. Tissue Engineering

Although the rapid development of artificial organ technology has significantly improved the physiological status of patients at the beginning of treatment, the mortality in the late stage is still high. This is attributed to the complexity of organs. For example, artificial kidneys can remove toxins but cannot regulate blood pressure and produce enzymes, which are also of vital importance to maintain normal metabolism. Therefore, "tissue engineering" was officially proposed by the National Foundation of the United States in 1987. Tissue engineering is a new subject that combines cell biology and material science to reconstruct tissues or organs *in vitro* or *in vivo*. Due to the blooming of both cell technology and material science, tissue engineering has undergone rapid development since its birth. Three major elements are scaffolds, cells, and signaling factors, which are key to helping damaged tissue repair a wound or to reconstructing the main function [58–60]. Normally, the operation process is as follows [61]: first, seed cells are separated from tissues for proliferation in *in vitro* culture, and then the cells are adhered to a scaffold surface with good biocompatibility, degradability and absorbability. Second, the cell-adhered scaffold is implanted into the damaged tissue, and the scaffold is gradually degraded and absorbed while the cells continuously proliferate and secrete extracellular matrix *in vivo*. Third, the repair or reconstruction of the corresponding tissues or organs are completed in the body. During this process, the scaffold plays an important role in providing a friendly microenvironment for cell growth [62]. Membranes can be ideal for the construction of scaffolds due to their gas or liquid exchange ability and high strength [63,64]. An appropriate membrane material for scaffold application should have advantageous physical properties (intensity, biodegradability, structure, *etc.*) and biochemical characteristics (the ability to carry or release specific signaling factors such as proteins and small molecules) for tissue regeneration [64,65]. Recent progress in membrane applications in different tissues will be summarized in the following section.

The widely used membranes can be divided into natural membranes and synthetic polymer membranes based on the source of materials. Natural membranes are made from animal or plant tissue extracts, such as amniotic membrane, collagen, gelatin, hyaluronic acid, silk and chitosan [66]. They have outstanding biocompatibility and biodegradability but low mechanical strength, and some tissue extracts, such as amniotic materials, also present infection risks and donor limitations. Synthetic membranes are usually prepared from polymer materials such as polymethyl methacrylate, polylactic acid, polycaprolactone, polyvinylidene fluoride, poly(*N*-isopropylacrylamide), and polyethylene glycol [67–69]. These materials possess the characteristic advantages of high mechanical strength, high optical clarity, easy optimization and easy preparation in large quantities but poor biocompatibility and anti-inflammatory properties. Therefore, the combination of the above two kinds of materials is becoming increasingly popular in the preparation of membrane substrates. Clinical applications ranging from bone to skin substitutions have different requirements for membrane function. The following sections will discuss these differences and typical membrane materials for bone, skin and corneal tissue engineering.

4.1. Bone tissue engineering

Bone has a strong self-healing ability, but some severe bone defects need additional medical treatment. Traditionally, there are several strategies for bone repair, including autologous bone grafts, allografts and bone filling. However, limited donors, a lack of integration into the host tissue and immunogenicity problems heavily restrict these methods. A tissue engineering strategy is an emerging new method that can be used for bone reconstruction without the abovementioned problems, where membranes are widely used due to their excellent and controllable properties. Membranes can act as a physical barrier to protect the defect site and prevent soft tissue from reaching the injured area. In addition, the membrane serves as a substrate for the loading of bioactive substances, which can guide bone regeneration (shown in Fig. 4(-a)-(c)). For practical applications, a suitable membrane should possess adequate biocompatibility, mechanical strength, permeability, porosity, osteoinductive properties and osteogenic ability [70,73,74]. Although there are various methods for membrane fabrication, the electrostatic spinning method is the most widely discussed because of the advantages of the prepared nanofiber membranes which have high porosity and a large surface-to-volume ratio, a structure similar to that of the extracellular matrix, and easily optimizable properties [71,75–78].

To mimic the toughness and elasticity of bone tissue, membranes are usually made of composite materials or loaded with bioactive materials, such as hydroxyapatite, β-tricalcium phosphate and bioactive glasses. For example, Ren *et al.* [79] improved the tensile properties of polycaprolactone/gelatin composite membranes with an adjusted ratio of polycaprolactone and gelatin. Sabouri *et al.* [80] developed a mineralized amniotic membrane by depositing calcium and phosphate ions on the human amniotic membrane. Wang *et al.* [81] used biological mineralization technology with calcium phosphate and obtained a collagen-hyaluronic acid membrane with clearly enhanced mechanical strength. Moreover, to improve cell behavior to benefit bone regeneration, modification of the membrane surface by inorganic nanoparticles or bioactive elements is an efficient strategy. Nanoparticles such as silica [82], niobium pentoxide, and ZnO [72] have been loaded onto poly(L-lactic acid) fibrous membranes, polycaprolactone/gelatin electrospun membranes and polycaprolactone membranes, achieving enhanced cell adhesion and proliferation. In addition, bioactive substances such as heparins [83,84], bioactive glass [85], hydroxyapatite [86,87], polydopamine [88] and peptide [89,90] have been widely studied for membrane modification and resulted in higher affinity to cells during culturing. For some specific bone tissues (especially periodontal tissue), the antibacterial and anti-inflammatory properties of the applied membrane should be specifically considered. The most common strategy is the immobilization of bacteria-resistant inorganic nanoparticles such as Au [91,92], Ag [93–95], ZnO [96] and magnesium oxide (MgO) on the membrane. As shown in Fig. 4(d), ZnO was doped in the polycaprolactone membrane for not only increased antibacterial activity but also improved osteoconductivity [72]. Liu *et al.* [97] incorporated MgO into the polylactic acid/gelatin membrane to achieve high antibacterial activity. Moreover, the resulting membrane can be fully resorbed in the body. As heavy metal nanoparticles can easily cause the accumulation of heavy metals in the body, oxides, especially magnesium oxide, have broad application potential due to their easy degradation.

Clear progress has been made in the selection of biological materials for membranes for use in bone substitution; nevertheless, there are still many challenges in obtaining functional mimics of human bone for clinical surgery. One challenge lies in the porous structure. As reported, suitable porous structures that exhibit large size, and high orientation and connection play a critical role in bone growth. However, the existing pore sizes are much lower than the accessible minimum value of 100 μm. Another critical challenge is vascularization on the skeleton of the artificial membrane. This is because the formation of thick tissue will reduce the diffusion of oxygen and nutrients. Furthermore, the lack of proper bioactive material and growth factors also limits transplantation in the body. Hence, research is being encouraged for the

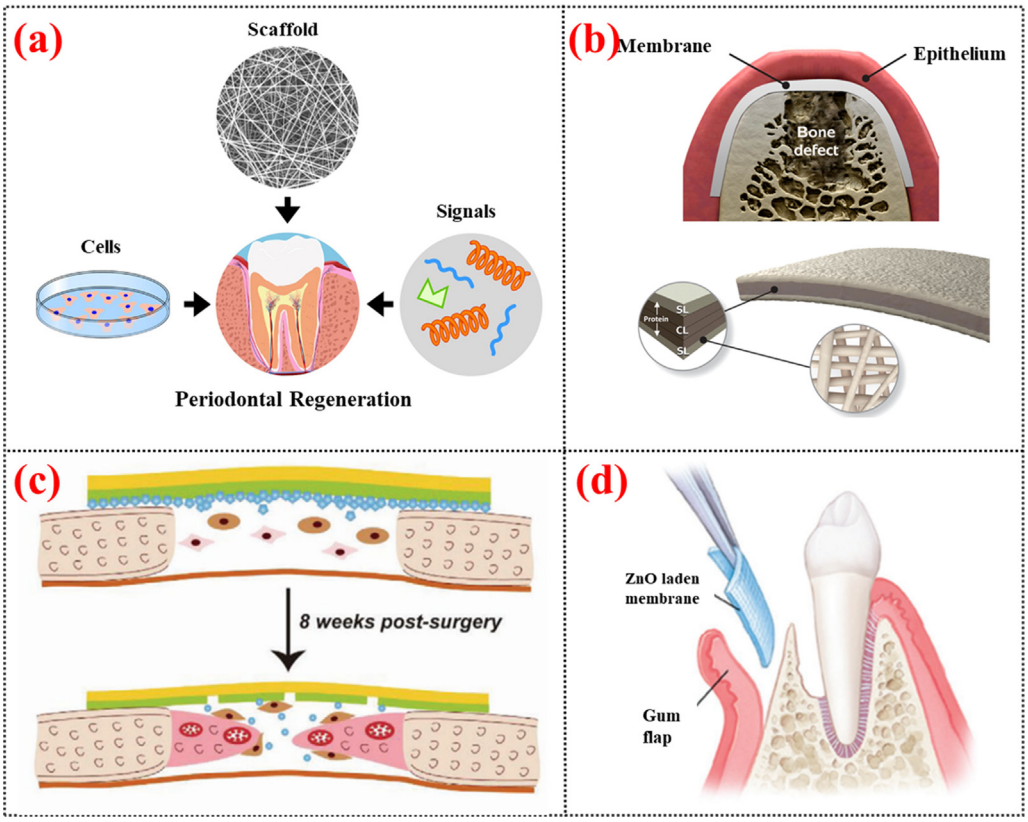

Fig. 4. (a)The schematic of the three major components and (b-d) membrane involved in periodontal tissue engineering. Reproduced from Ref. [70–72] with permission from Elsevier and Wiley Materials, respectively.

development of more novel strategies to provide a more stable structure and better osteogenesis and angiogenesis in addition to adding bioactive materials to the membrane.

4.2. Skin tissue engineering

The skin is the largest organ of the human body and has important functions in protection and metabolism. Therefore, the loss of skin tissue will result in metabolic disorders and an increased risk of infection. Although a small area of skin damage skin can be repaired by the body itself, medical intervention is required when extensive burns occur. Recently, skin tissue engineering has emerged as an alternative to traditional skin grafting because it requires no secondary surgery and the necessary materials are abundant.

In skin tissue engineering, membranes with specific properties are widely used to imitate certain abilities of skin. Porosity is beneficial for both gas exchange and nutrient supply [98]; therefore, fibrous membranes with intrinsic porous structures are commonly constructed by various fabrication methods, such as electrospinning, solution blowing spinning, microfluidic spinning and microfluidic blow-spinning [99]. In addition, the nanofibers of the membrane often possess a high surface-to-volume ratio and an extracellular matrix-like structure, which can promote cell adhesion and proliferation. Cui *et al.* [99] found that the microfluidic blow-spinning method can greatly reduce the minimum diameter of functional fibers. These fibers presented the smallest diameter of 44 nm compared with those prepared through electrospinning, blowing spinning and microfluidic spinning, which were 164, 150 and 800 nm, respectively. Then, this nanofiber-based membrane was cultured with fibroblasts to confirm its facilitation of cell attachment, proliferation and growth because of the large specific surface area. Moreover, the average pore diameter of the membrane was approximately 2.5 μm, and its nitrogen permeance was 164.635 $m^3 \cdot m^{-2} \cdot h^{-1} \cdot kPa^{-1}$, which ensured the smooth exchange of gas and nutrients.

The reconstruction process of skin can be divided into four stages: hemostasis, inflammation, proliferation and remodeling (shown in Fig. 5(a)) [100]. For the hemostasis and inflammation processes, the addition of hemostatic and anti-inflammatory agents is helpful. Materials with antibacterial properties can prevent an overly extended inflammatory response and thereby accelerate wound healing [101–103]. During the proliferation stage, wettability is necessary for cell adhesion, proliferation and differentiation [104]. Mechanical strength is of vital importance in the whole process, serving as a barrier to prevent cell damage from external forces [105–107].

As mentioned above, membranes act as a physical barrier against the invasion of pathogens and destruction caused by external force or movement. Therefore, membranes should have good mechanical strength and flexibility. In this case, polymer materials such as polycaprolactone, polylactic acid, silk fibrin, cellulose and chitosan are widely preferred. Zulkifli *et al.* [107] doped polyvinyl alcohol with hydroxyethyl cellulose to improve spinnability and mechanical abilities such as elasticity and elongation and further cross-linked polyvinyl alcohol with glutaraldehyde to change the water solubility. At the best blending ratio, the calculated Young's modulus shown in the elastic region was measured to be approximately 125.7 MPa. This value is comparable to the tensile modulus of human skin, which lies in the range of 15–150 MPa. Jiang *et al.* [106] mixed poly(L-lactic acid) with tannin-grafted poly(e-caprolactone) to produce a fibrous membrane. The best elongation at the break point was (121.14 ± 12.13)% at 15% (mass)blending, and the Young's modulus values increased almost twofold with

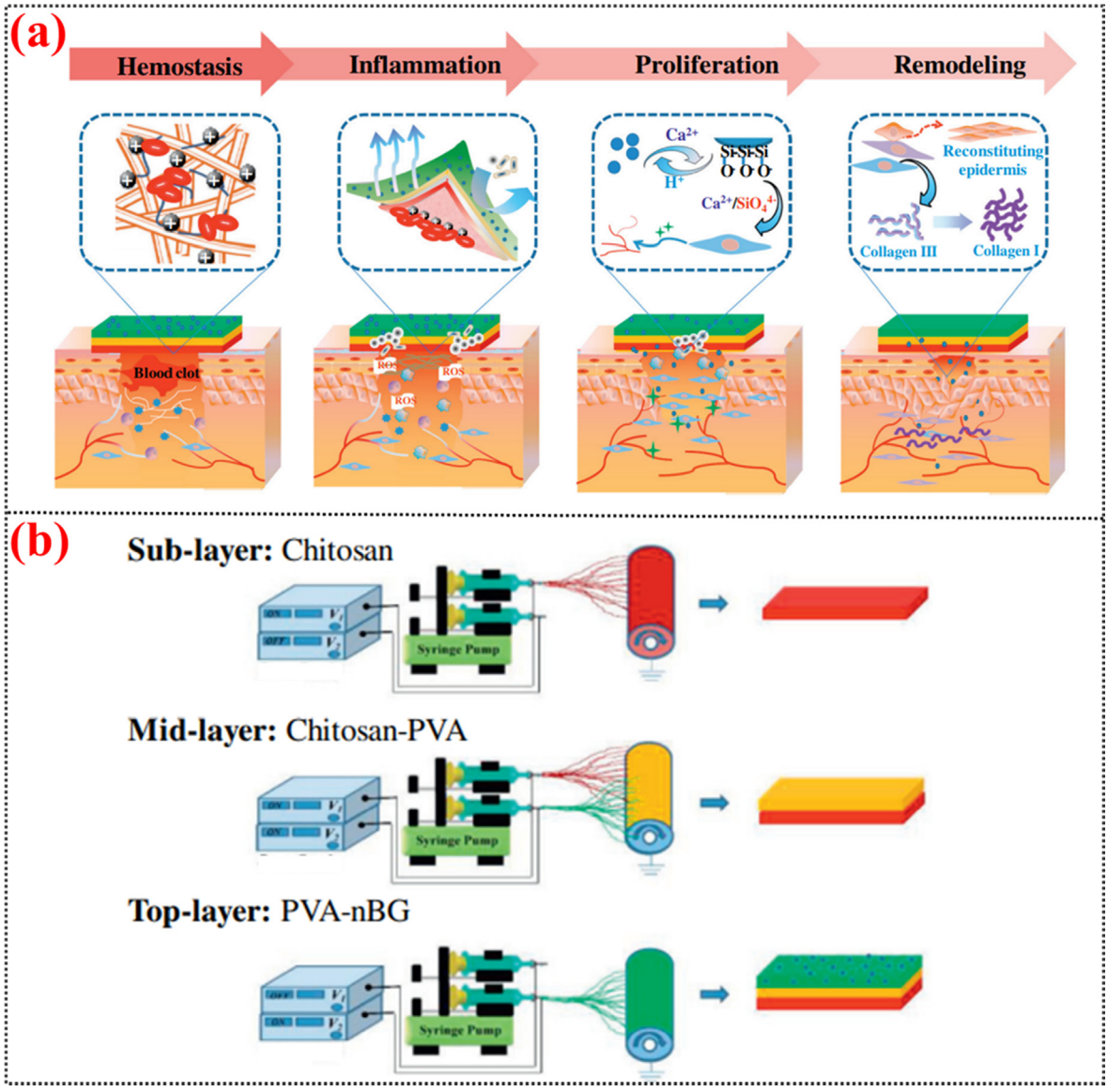

Fig. 5. (a) Schematic illustration of the four stages of skin reconstruction and (b) the fabrication process for multi-functional membrane. Reproduced from Ref. [100] with permission from Elsevier.

the addition of tannin-g- poly(L-lactic acid) to the poly(L-lactic acid) matrix. In another study, glycerol and polyethylene glycol were added to strengthen the fragile chitosan–vitamin C–lactic acid membrane [105]. The introduction of polyethylene glycol alone showed improved integrity but poor frangibility, while the membranes with the addition of glycerol possessed good strength but were breakable. The application of the two additives together enabled the preparation of a membrane that could serve as a satisfactory skin substitute for clinical transplant.

Wettability is also necessary for water retention by the membrane to provide a moist environment for cell adhesion and skin regeneration. Many studies have demonstrated that the contact angle of biomaterials in the range of 40°–80° can efficiently facilitate cell adhesion. In addition, membranes can absorb exudates from the wound to reduce infection. As most polymers are hydrophobic, various hydrophilic modification methods, including plasma treatment, UV crosslinking, alkaline etching and blending of hydrophilic materials such as polydopamine [108], PF108 [106] and quaternized silicone, have been widely used. Although hydrophilic modification or the direct use of a hydrophilic substrate could improve exudate adsorption of the wound dressing, it simultaneously accelerates the evaporation of water from the wound surface to the outside, and the consequent fast wound drying can hinder tissue repair. To solve this problem, Feng *et al.* [104] developed a gradient wetting membrane with poly-(sulfobetaine methacrylate) nanofibers on the inner side to fully absorb the wound exudate and hydrophobic polycaprolactone nanofibers on the external side to block the evaporation of water. Chen *et al.* [100] prepared a multifunctional three-layer nanofiber membrane using polyvinyl alcohol, nanobioglass and chitosan (from the outer to inner layer) by an electrostatic spinning method (shown in Fig. 5 (b)). The sublayer of chitosan has hemostatic and antibacterial effects; the middle layer of chitosan-polyvinyl alcohol can moisturize and absorb exudates; and the top layer of polyvinyl alcohol/-nanobioglass can promote tissue regeneration.

The antibacterial ability of membranes applied to wound healing is essential for patient health because various bacteria easily breed surrounding the wound area. Wahid *et al.* [103] coated a bacterial cellulose membrane with dopamine to bind ε-polylysine, which is a cationic polypeptide with broad-spectrum antimicrobial

ability. *In vivo* experiments showed that this membrane can achieve an antibacterial activity of 99.83%. Moreover, the addition of inorganic nanomaterials is a common strategy for the inhibition of bacterial growth. Zn^{2+} and Cu^{2+} are widely used as antibacterial agents due to their low toxicity; however, poor long-term durability, heat resistance and stability have hindered their practical applications. Recently, CuO and ZnO nanoparticles with photothermal conversion ability have been doped into membranes to effectively produce reactive oxygen species that can kill bacteria as a result of protein denaturation [101,109–112].

For complete skin tissue regeneration, membranes should exhibit bioactivity for cell recruitment to induce collagen deposition, blood vessel formation and even hair follicle formation [99,113–115]. Because most synthetic polymer-based membranes have weak bioactivity, additional substances such as fibrin [116,117], ascorbic acid and tannin or natural polymers including gelatin are often incorporated during membrane fabrication. Although much progress has been achieved in membranes used in skin tissue engineering, there is still a wide gap between tissue-engineered skin and autologous skin. Most such membranes are merely temporary skin tissue substitutes that cannot fully meet the structural and functional requirements for wound repair. Some major characteristics are still being improved. For example, the reconstruction of nerves and blood vessels is still difficult, as tissue engineering still cannot mimic the complex spatial distribution of cells and extracellular matrix; therefore, it cannot replace the sensing and sweat functions of real skin. However, with the rapid progress in biomaterials, tissue engineering and cell engineering, tissue-engineered skin is sure to provide burned patients with skin tissues comparable with human skin.

4.3. Corneal tissue engineering

The cornea is a totally transparent and vascularless tissue that serves as a barrier to protect the intraocular structure and microenvironment while refracting light onto the retina (shown in Fig. 6(a)). Corneal damage is a major cause of blindness, and the cure often depends on the replacement of the cornea. In recent years, the replaced cornea has always been derived from allogeneic donation [118]. However, the availability of donor corneas is very limited. Only one in seventy people has the chance. Studies have shown that corneal epithelial cells determine vision maintenance; therefore, researchers are devoting their main efforts to tissue engineering method to create a transportable artificial corneal [121]. The artificial cornea consists of a membrane with scaffold and cell carrier functions. Unlike other engineered tissues, the artificial cornea must have excellent optical transparency to admit light [119,122,123]. The human amniotic membrane is most widely used because it contains growth factors with low immunogenicity [120,125,126], but its transparency is poor due to its thick seroma layer (shown in Fig. 6(b)). To solve this problem, Zhang *et al.* [122] used a collagenase digestion method to prepare an ultrathin amniotic membrane (30 μm). This membrane was proven to possess improved optical transmittance and a denser cell layer resulting from better nutrient absorption. However, the high cost and potential pathogenic risk from the donor block the widespread application of amniotic membrane in the clinical treatment of eye diseases. Accordingly, researchers are continuously seeking to design artificial membranes with similar functions to amniotic membranes to enable an increasing number of corneal transplantation surgeries (shown in Fig. 6(c)). Generally, there are two categories of artificial membrane materials suitable for corneal construction: natural polymers (collagen, chitosan, silk fibrin, gelatin, *etc.*) [127,128] and synthetic polymers (polycaprolactone, polylactic acid, poly(D-lactic acid), polyethylene glycol and polyvinyl alcohol, *etc.*) [129,130]. Among these materials, some (collagen, gelatin, *etc.*) have inadequate mechanical strength to act as scaffolds for the growth of corneal cells, and they often serve as additives during membrane formation.

Chitosan has high tensile strength, permeability and biocompatibility for the preparation of a corneal membrane; however, it has poor water solubility, and its degradation products can easily cause an inflammatory response. Fortunately, this can be improved by chemical modification or physical blending. Liang *et al.* [131] fabricated a membrane based on grafting hydroxyethyl groups to chitosan for the construction of corneal endothelia. The results showed that this membrane could establish 81.32% water content, which is comparable to that of the human cornea (72%–82%). NaCl

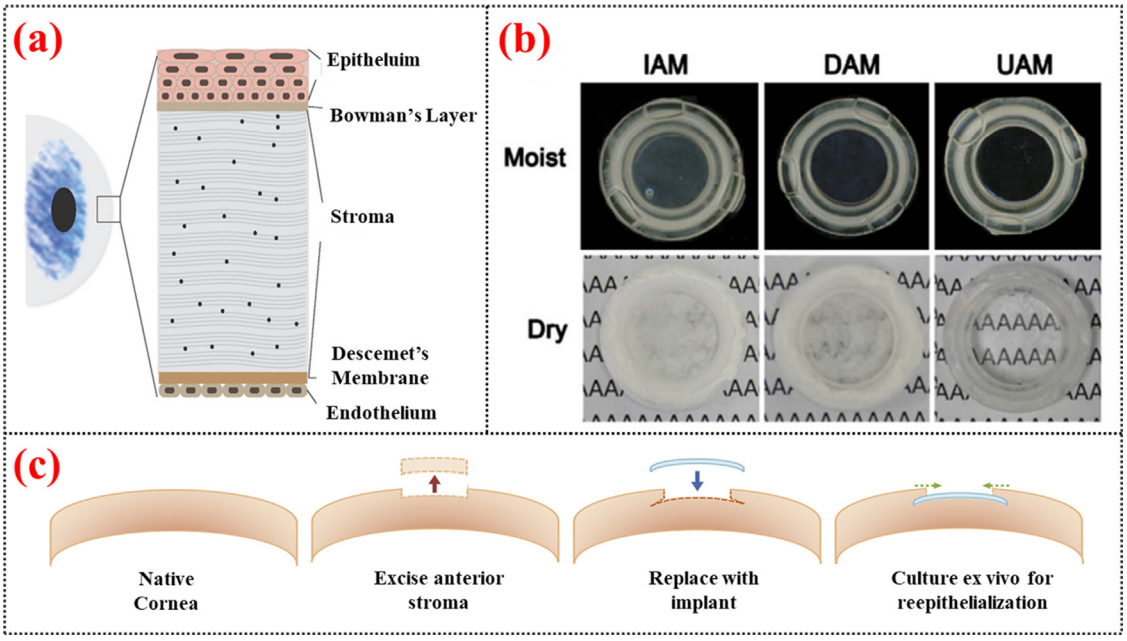

Fig. 6. (a) Diagram of the corneal tissue engineering, (b) the ultra-thin amniotic membranes in moist and dry environment and (c) the corneal tissue engineering model. Reproduced from Ref. [118–120] and with permission from Wiley and Elsevier, respectively.

ions can steadily pass through the membrane with a permeability coefficient of 1.93×10^{-5} cm·s^{-1}, which is better than that of the human cornea (between 10^{-6} and 10^{-7} cm·s^{-1}) for providing nutrients to cells. Importantly, the membrane showed over 90% optical transmittance at light wavelengths ranging from 400 to 800 nm, which is more transparent than the best human cornea, with 75% optical transmittance. In addition to the above chemical modification, physical blending using the crosslinking method is also an effective way to change the membrane properties. Grolik *et al.* [127] first chose a more biocompatible crosslinking agent, genipin, for composite membrane fabrication because genipin can react with the free amino groups on chitosan. Three membranes, chitosan-hydroxypropyl cellulose, chitosan-collagen and chitosan-elastin, were successfully fabricated and characterized. Although collagen and elastin are hydrophobic, the contact angles of the composite membranes range from 55° to 62°, showing moderate hydrophilicity, which is considered to be beneficial for cell adhesion. According to the surface morphology images, the three composite membranes show fibrous, flat and droplet-like structures. Thus, the surface morphology of the chitosan membrane can be easily adjusted by crosslinking with another biopolymer using genipin. Further research conducted by Li *et al.* [119] revealed that the pure genipin crosslinking method could greatly improve the mechanical strength and antidegradation properties of the chitosan membrane.

Silk fibrin can be easily extracted from silkworm cocoons and possesses good biocompatibility, transparency, tunable mechanical strength and low immunogenicity [124,132,133]. Nevertheless, it is also brittle and unstable in moist environments, which makes it difficult to suture during surgery and leads to unstable transparency. To obtain stable transparency, Zhang *et al.* [134] used propionamide crosslinking agents to turn soluble silk fibrin films into insoluble films, which can exist stably in water for 9 weeks. This can be attributed to the crosslinking changing crystalline regions into amorphous regions, which can prevent fibroin molecules from binding with water molecules. The breaking strength of 32 MPa is much higher than that of the human cornea.

Polycaprolactone is a polymer material with high mechanical strength and biocompatibility but poor cell adhesion due to its hydrophobicity. This can be changed by plasma etching or the introduction of hydrophilic components. Sharma *et al.* [135] used helium–oxygen (He/O_2) plasma to pretreat an electrospun polycaprolactone membrane. The results indicated that plasma treatment can increase the light transmittance of the untreated wet membrane from 13% to 47%. Nevertheless, this value does not approach the optical transmittance of the human cornea. Therefore, blending hydrophilic materials is probably a better choice. Salehi *et al.* [136] fabricated a composite membrane using hydrophilic silk fibrin. The membrane showed light transmittance of 90% at 750 nm, a water uptake over 400% and a high tensile strength of 4.67 MPa when the blending ratio was 50:50). Chen *et al.* [137] combined the good mechanical strength of poly(l-lactic acid-*co*-ε-caprolactone) and the hydrophilicity of silk fibrin to fabricate a nanofibrous membrane. The membrane shows both an optical transmittance of 90%, comparable to a glass coverslip, and an improved tensile strength of 9.39 MPa. More importantly, this study shows the successful growth of human corneal endothelial cells for the first time. Moreover, it has been confirmed that if the fibers in the membrane can be aligned, the performance will be markedly enhanced compared with that of a random stack of fibers. Yan *et al.* [138] designed a copper wire-framed rotating drum collector for obtaining aligned nanofibers, achieving a much higher tensile modulus and break strength together with a lower elongation. This membrane enabled greater protein expression than the randomly arrayed fibers. The authors explained that the aligned structure was capable of mimicking natural tissue to guide orderly cell growth, confirming the importance of physical adjustment to the membrane structure.

Intensive efforts have already been devoted to corneal tissue engineering in pursuit of better transparency, mechanical strength, and cell proliferation. In the future, the form of membranes can be extended, for example, liquid gating membranes may be a good candidate due to its excellent transparency and antifouling properties when transporting small molecules [139,140]. However, the corneal curvature of these artificial membranes is rarely considered, although it is important for clinical application. It is believed that with the rapid development of medical materials and synthesis methods, the challenge of producing membranes with a satisfactory corneal curvature similar to that of the autologous cornea will be achieved. Such membranes are expected to efficiently cure blind patients, returning them to a colorful life.

4.4. Main challenges of tissue engineering membranes in the future

As a new interdisciplinary field, tissue engineering has gradually become a major technique in the clinical reconstruction of inactivated and damaged body tissues. Current studies are continuously trying to fully mimic the properties and behaviors of various natural tissues using membrane technology. Although skin and cornea substitutes have achieved several successes in human or animal experiments, the main reconstruction mechanism is still unclear, illustrating difficulties in the parameter control of membrane materials. There is still much room for further research in membrane design, methodology optimization and clinical experiments requiring joint efforts in materials science, chemistry, basic medicine, clinical medicine and biomedical engineering.

5. *In Vitro* Blood Diagnosis

Blood samples contain various biological substances (such as glucose, lactate, glutamate, *etc.*) and biomarkers (such as circulating tumor cells (CTCs)), which are the major detection targets for *in vitro* blood diagnosis (IVBD). Due to the complexity of whole blood, a pretreatment process is required for the removal of interfering substances and enrichment of targets before detection. The complete IVBD process usually used in hospitals requires three processes: anticoagulant collection of blood, centrifugal extraction of serum or plasma, and pathological examination, which are complex and time-consuming. Among the above three steps, centrifugal separation of whole blood is essential for ensuring detection accuracy by preventing hemolysis and coagulation. However, this centrifugal technique normally requires half an hour to finish the separation of serum from whole blood, which makes it difficult to achieve real-time analysis. On-site and dynamic diagnosis of blood contents is always desired by doctors for precise and timely guidance of clinical surgery and emergency treatment. Therefore, it is urgent to develop a new method for rapid and continuous blood separation. Membrane separation technology can realize the precise and dynamic separation of different components with little damage using the size-sieving mechanism. Recently, an increasing number of researchers have gradually examined the application of membranes in the separation of blood components for IVBD.

5.1. Plasma or serum extraction for IVBD

Plasma or serum provides basic nutrients (such as glucose, lactate, and glutamate), hormones, proteins and growth factors. Before diagnosis, plasma extraction from whole blood is necessary to eliminate detection interference from blood cells. Compared with the centrifugal method, membrane separation provides more possibilities for online and point-of-care diagnosis without damage

to blood components. Initially, a flat type of membrane was usually applied to separate plasma from whole blood. Songjaroen *et al.* [141] integrated a paper-like membrane filter into a microfluidic device for serum separation. In that study, a blood separation membrane was combined with traditional filter paper for the first time by the wax dipping method. Using this device, plasma can penetrate through the paper by capillary force without external pumping, while particles greater than 2–3 μm were removed. Due to the hydrophilic nature of the membrane surface, blood flowed over the membrane surface in a horizontal direction and reduced vertical penetration. For quick plasma separation, Zhang *et al.* [142] first fabricated a hydroxyapatite-mineralized polyvinylidene fluoride Janus membrane by diffusion-controlled chemical precipitation (shown in Fig. 7(a)). Prepared with Ca $(NO_3)_2$ and Na_3PO_4 as reactants, needle-like hydroxyapatite nanocrystals were distributed across the membrane, endowing it with asymmetric wettability. Tests showed that 13 μl of blood permeated the membrane within 20 s with successful rejection of blood cells. This membrane was confirmed to be integrable with a blood glucometer for sensitive detection [145]. Although the abovementioned membranes enable dynamic blood separation, the analysis step still requires extra instruments for content detection. Recently, a hollow fiber membrane has aroused great attention for the introduction of analytical functions to membranes due to its hollow structure, which facilitates the construction of a signal circuit. Our group first proposed a separation-sensing membrane to integrate the separation process and electrochemical biosensing process into a single hollow fiber membrane that can extract serum *in situ* and simultaneously recognize the target biomolecules during blood drawing [144]. The heterogeneous nanostructure of this membrane exhibited separation ability on the porous surface layer and biosensing functions in the inner membrane channel (shown in Fig. 7(b)), achieving continuous serum separation and dynamic monitoring of blood glucose, laccase and glutamic acid. Similarly, Wu *et al.* [146] fabricated a gradient hollow fiber membrane with polyaniline and Pt nanoparticles for selective blood separation and point-of-care assays of glucose and cholesterol.

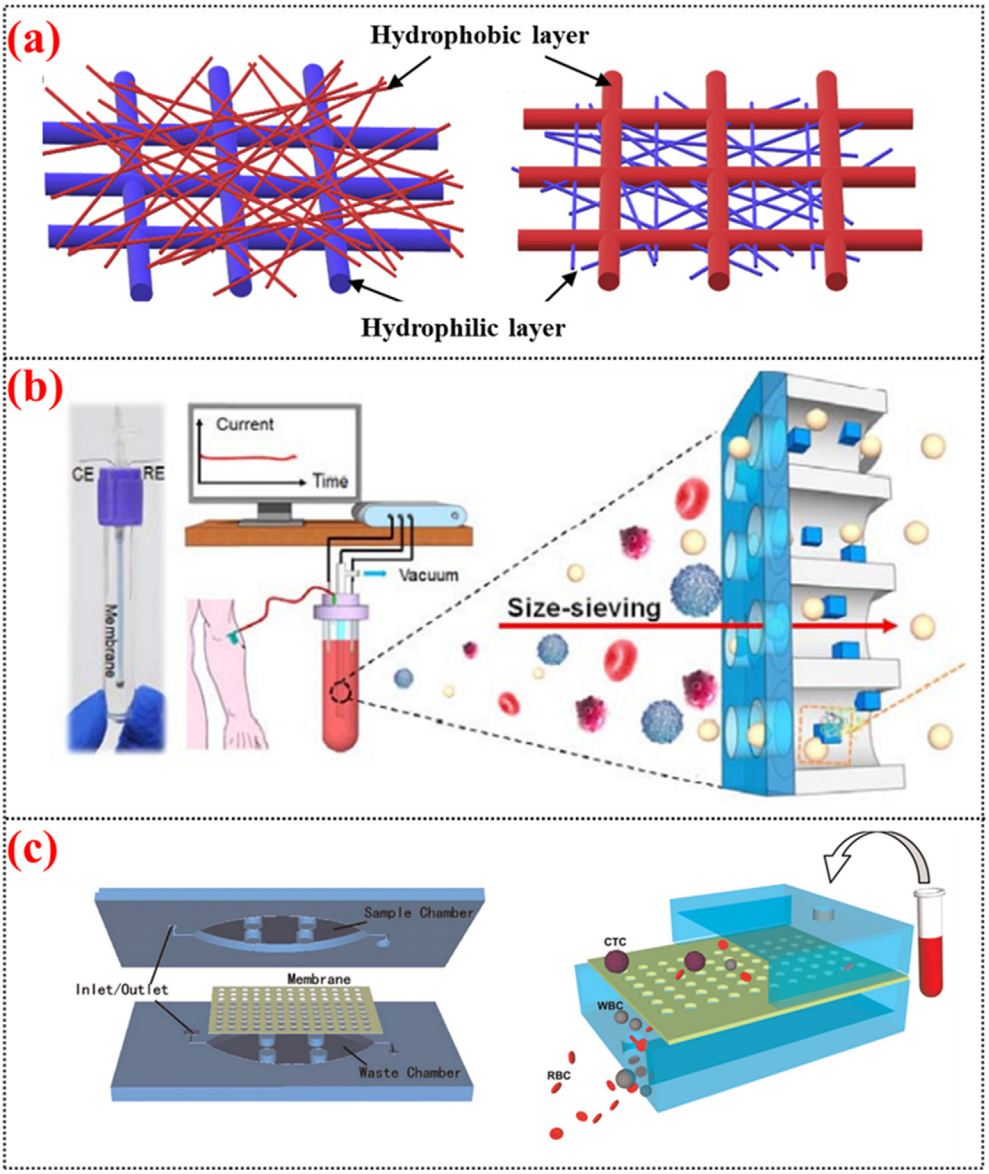

Fig. 7. (a) Diagram of the Jenus membrane used for the pretreatment of blood test, (b) the multifunctional separation-sensing membrane and (c) the enrichment of CTC. Reproduced from Ref. [142–144] with permission from Elsevier and Wiley Materials, respectively.

Overall, membrane technology is playing an increasingly important role in precise point-of-care diagnosis, saving time in IVBD and even dynamically reporting blood indices. Nevertheless, this new research direction faces many challenges from the laboratory to the hospital. The blood processing capacity of membranes still has difficulty matching that of traditional centrifugal instruments, which increases the risk of damage to blood components. Moreover, the integration of the separation and sensing abilities will be encouraged to enable universal response to a larger number of blood analytes, which holds promise for replacing the test ability of the commercial biochemical analyzer. Finally, a much smaller and more portable device must be specifically designed with satisfactory membrane characteristics to be easily and intelligently operated by doctors during clinical treatment.

5.2. Tumor cell enrichment for IVBD

Cancer is the second leading cause of death worldwide. According to statistical data from the World Health Organization (WHO), one death in six is due to cancer [147]. Circulating tumor cells (CTCs) are important biomarkers of tumors and can be used for early diagnosis and rapid evaluation of treatment effects in cancer patients. Although the detection of CTCs helps to improve our understanding of tumors, precise detection is still challenging due to the extremely low concentration of CTCs in the peripheral blood and to the nonspecific binding of blood cells. Therefore, the effective capture of CTCs with high purity is necessary. There are two main types of methods for CTC collection: biochemical and physical methods.

Antibody-based biochemical methods are beneficial for the adhesion of CTCs; however, they often have unstable capture efficiency because blood cells, such as white blood cells, may also be trapped [148–150]. Moreover, this method has difficulty maintaining the viability of CTCs due to irreversible antibody binding. Although some studies have shown progress in maintaining viability after capture, the process of enzymatic treatment may cause viability loss.

The physical method for capturing CTCs relies mainly on differences in size, weight or charge between CTCs and other cells [151,152]. Traditionally, centrifugation was the only method to obtain CTCs for a long time. However, it is disruptive to CTCs and inconvenient for on-site observation. Therefore, membrane separation based on size sieving has been developed as a substitute strategy because it is nondisruptive, inexpensive and quick. Overall, there are three routes for the fabrication of a microporous membrane: track etching, photolithography and thermal nanoimprinting [143,153–156]. Track etching method needs a highly accelerated heavy ion. The track etching method requires a highly accelerated heavy ion. Track etching membranes composed of polycarbonate material have been maturely incorporated with filter devices (such as ScreenCell® devices) for CTC separation [157]. The membrane thickness is 18 μm with a pore size of (7.5 ± 0.36) μm or (6.5 ± 0.33) μm and a hydrophilic surface. However, the pores are randomly distributed and overlap with low density. Photolithography is an alternative method that can be used to obtain through-holes with high density in thin, photosensitive, and heat-resistant polymer materials, which originates from the chip manufacturing technique. Before experiments, the membranes are sandwiched between Si wafer and photoresist. Then with the help of photomask, UV lights that can pass through will soften the photoresist in these areas. In the following process, the areas uncovered by photoresist will be etched through by chemical agents or plasma. By designing the size and shape of photomask, the membranes with specific structure can be fabricated. In a recent work, Kihara *et al.* [158] fabricated a microporous polyethyleneterephthalate (PET) membrane with 380,000 precisely aligned holes. The membrane diameter was adjustable (from 4 to 12 μm) with a precision of ± 0.2 μm. To address the difficult peeling-off problem that may induce pore deformation, they placed weak adhesive tape between the optical PET membrane and Si wafer to strengthen the interaction with high stability. However, this method is not applicable for thicker membranes because it is difficult to etch through-holes. For such cases, thermal nanoimprints have been developed to address these deficiencies. In the work of Tang *et al.* [156], a polyethylene membrane was sandwiched between a Ni mold and a glass substrate. Then, this sandwiched stack was pressed by a nanoimprint machine to obtain a microporous membrane. Subsequently, the O_2-reactive ion etching treatment was incorporated to remove the residual layers to obtain through-holes. The test results revealed that the as-prepared membrane with a uniform pore size of 10 μm showed a high capture efficiency of 84% for PC-9 cells.

In addition, microporous membranes can be easily incorporated with other devices, especially microfluidic devices. For example, Fan *et al.* [143] incorporated a polydimethylsiloxane microfiltration membrane into a simple microfluidic system with an inlet and outlet, and a syringe pump was used to provide negative pressure for sample injection. After injection, CTCs were captured by the membrane with over 90% efficiency (shown in Fig. 7(c)). Sun *et al.* [155] combined a polycarbonate membrane with a low-cost size-based microfluidic chip for separating CTCs from blood. In addition, modified microbeads were introduced to bind onto the target cells, which enlarged the size of smaller CTCs to increase the capture efficiency. Yee-de León *et al.* [154] developed a novel membrane-based microfiltration device comprising a fully automated sample processing unit and a machine-vision-enabled imaging system that allowed the efficient isolation and rapid analysis of CTCs from blood, obtaining a capture efficiency greater than 93%.

5.3. Receptors immobilization for IVBD

For the *in vitro* diagnosis, membranes also have wide applications in the immobilization of receptors acting as functionalized substrates. For example, Yuan *et al.* [159] introduced $-NH_2$ groups on the porous alumina membrane for Pt deposition, realizing a detection of glucose with wide linear range in blood. Darder *et al.* [160] functionalized alumina porous membrane with chitosan matrix for glucose oxide immobilization, and the membrane exhibited a detection range of 4–8 $mmol \cdot L^{-1}$ of blood glucose. More importantly, the work found that the enzyme kinetic is related to the pore diameter of membrane. Ekanayake *et al.* [161] immobilized glucose oxide on alumina membrane by physical adsorption, the remarkably enhanced loading amount brings higher sensitivity and response time than the commercial sensors. In another work, Jain *et al.* [162] functionlized the alumina membrane with polymer brushes, which shows a rapid and strong retention for proteins.".

5.4. Main challenges of membranes applied in IVBD in the future

Membrane separation technology has wide applications in IVBD for serum separation and CTC enrichment relying on size sieving. For the transformation of these studies from the laboratory to commercial devices, there are two main challenges for further research. First, the detection method for serum or CTCs should be integrated with the separation process to achieve on-site and real-time analysis of various blood indices. Second, if the membrane is to be directly applied in clinical diagnosis, it should be further designed as a complete analytical device, including automatic sampling, detection and cleaning, to simplify the assay procedure during surgery or emergency. It is believed that in the future, more convenient instruments will be developed for early screening and

nonhospital disease testing for the dynamic monitoring of physiological status.

6. Membranes for Medical Support

Chemical reagents and pathogenic microorganisms are a great threat to human health in daily life and medical treatment. In particular, in the last two decades, an increasing number of severe infectious diseases caused by viruses or bacteria, such as COVID-19 and Ebola, have been demonstrated to easily contaminate water and air. Therefore, the need for medical protection technology and products, including protective equipment (masks, cloths, *etc.*) and medical wastewater treatment, is increasing each year. In such techniques, the membrane is always the core component in the rejection of pathogens from air or water. Focusing on different application scenarios, membranes with adjustable pore sizes and surface characteristics and controllable separation performance have exhibited advances in the clinical treatment of complicated medical environments compared with traditional methods, such as adsorption and UV.

6.1. Membranes for the protective equipment

Although almost all pathogens can be decomposed by hydrolysis or incineration at a high temperature, these methods are not suitable for the real-time protection of human bodies, especially for medical workers and soldiers. Activated charcoal has been widely used in protective clothing and facial masks to safeguard the wearer from the invasion of hazardous substances, but it is too heavy and retains too much moisture to be comfortable [163–165]. Moreover, the harmful substances are physically absorbed not decomposed by using this method, resulting in the disposal of protective equipment after usage. Therefore, researchers are seeking for more effective and multifunctional substitutes for the fabrication of protective equipment. In 1983, William [166] has pointed that the membrane filter technology can be used for the separations of particles, bacteria, viruses, macromolecules and ions ranging from 0.1 to 10 μm in liquids. With the rapid growth of market demand, membranes especially the nanofiber membranes have been widely used in textiles industry due to their porous structure and large surface to volume ratio, which can both filter particles and absorb chemical contaminants [167–171]. From 2019 to present, these products effectively prevent the plague transmission of COVID-19 which have posed a severe threat to human life.

As shown in Fig. 8(a), a protective mask is normally composed of three membranes: inner, middle and outer layers [172]. The middle layer is the core filter layer. The number of filter layers varies according to different protection levels. Compared with ordinary woven gauze and melt-blown cloth, nanofiber membranes prepared by electrostatic spinning exhibit a stronger ability to filter nanoparticles and absorb pollutants because of their larger surface area to volume ratio and adjustable surface characteristic [174–176]. Usually, the finer the fiber is, the better the filtration but poorer the air flux. However, electrospun membranes usually suffer from poorer mechanical strength than textiles because the fibers are randomly distributed. In addition to the effects of the chemical structure and molecular weight of polymers, fiber alignment has a great impact [177]. Although studies have shown that physical stretching can adjust the orientation of fibers, it is not practical for the electrospinning process. To obtain aligned fibers, Huang *et al.* [178] developed a high-temperature curing method to produce ordered and parallel fibers with the collector at a high

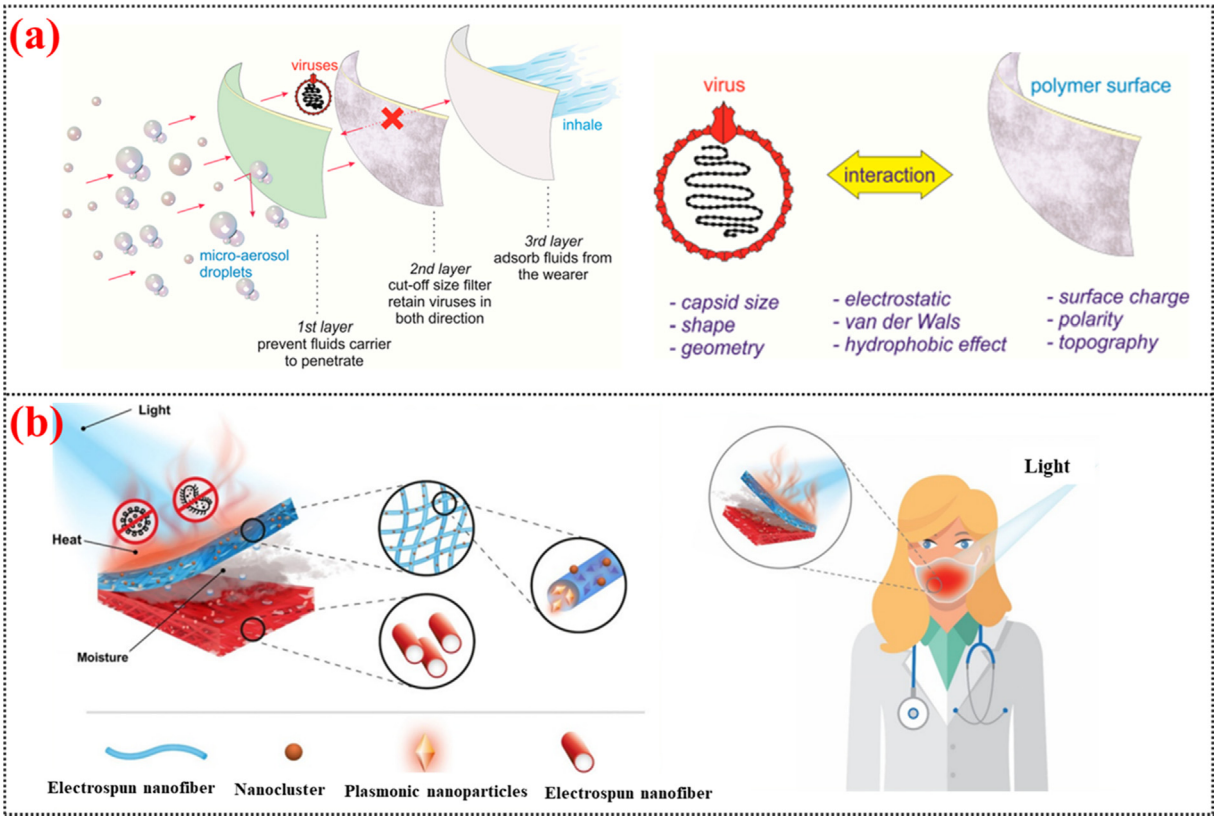

Fig. 8. (a) Illustration of the structure and the protective mechanism of facial mask and (b) the property of the new multifunctional membrane. Reproduced from Ref. [172,173] with permission from Wiley.

rotating speed. According to the tests, the as-fabricated membrane shows a tensile strength of 664 MPa and a tensile modulus of 15.3 GPa, which greatly surpasses the performance of the nonaligned nanofiber membrane (tensile strength of 241 MPa and tensile modulus of 5.8 GPa). The remarkable improvement of the aligned fiber membrane is because it allows each fiber to share the external strength.

Because bacteria penetrating through the membrane filter may cause respiratory disease, antimicrobial ability is usually conferred on the membrane through the introduction of inorganic nanoparticles, including noble metals and metal oxides, to the polymer nanofiber [173,179,180]. The proposed mechanism is that these nanoparticles can damage the cell membrane of pathogens through the generation of reactive oxygen species [181,182]. Overall, there are three kinds of methods to composite nanoparticles with nanofibers: physical blending of the nanoparticles with polymers before electrospinning, electrospraying of the nanoparticles onto polymers during electrospinning, and *in situ* reduction of nanoparticles onto polymers after electrospinning. Sundarrajan *et al.* [183] synthesized MgO nanoparticles first and then mixed them with polymers before electrospinning; however, this route easily caused the aggregation of nanoparticles, resulting in nonuniformity of the membrane. Roso *et al.* [184] fabricated a multilayer membrane based on electrospun polymer nanofibers and electrosprayed TiO_2 nanoparticles. This work innovatively introduced a ring electrode during the electrospraying process to produce a uniform electric field for the even dispersion of TiO_2 nanoparticles on membranes. Lala *et al.* [185] used a polymerization reduction method to reduce Ag^+ to Ag nanoparticles *in situ* on a polylactic acid membrane by UV irradiation. As a result, the nanoparticles dispersed uniformly on the membrane fibers with few aggregations to endow the membrane with good antibacterial properties toward *E. coli* and *P. aeruginosa*.

Currently, membrane-based protection equipment works mainly by size sieving and electrostatic separation mechanisms. The incorporation of inorganic nanoparticles endows the membrane with antimicrobial function and reusability. In the future, membrane-based protection equipment is expected to possess more convenient functions with the integration of multiple technologies. First, the application of electrocatalysis and thermal catalysis technologies will make the membrane capable of faster, more efficient self-cleaning. Second, biosensing technology can be incorporated for real-time detection of the concentration of pathogens captured by protective equipment to provide the wearer with timely information on when to change the equipment.

6.2. Membranes for hospital wastewater treatment

Pharmaceuticals and personal care products have recently been recognized as potentially severe pollutants due to their toxic effects on human health and aquatic organisms at very low concentrations, and they are difficult to clean up (especially antibiotics) in medical wastewater. If untreated, they will pollute the urban water system and cause accumulation in organisms. There are many methods to treat medical wastewater, including adsorption [186,187], advanced oxidation processes (AOP) [188–192] and membrane filtration [193–195]. Traditionally, activated carbon and sludge are the adsorption materials most commonly applied to remove drug molecules, and they rely on porous structures and biodegradation, respectively. Nevertheless, this adsorption strategy is inefficient, and recycling is difficult. AOP using UV irradiation [196,197], electrooxidation [198] or reagents [199–201] can remove refractory pollutants effectively. however, it is limited in terms of range and on-site treatment and is expensive. Therefore, membrane filtration is a novel and effective technique to dynamically treat medical wastewater due to its low energy consumption, high separation efficiency and easy scale-up ability. Although membrane fouling is an unavoidable issue, it can be solved by either physical (backwashing the membrane with air and/or water) or chemical (using chemicals such as caustic soda and hydrogen peroxide) methods to refresh the used membrane. The most widely applied techniques are membrane filtration and membrane bioreactors (MBRs) [193,202]. The former depends only on the size-sieving functions of nanofiltration, microfiltration and ultrafiltration membranes. The latter introduces the bioreactor principle into the membrane process, performing wastewater separation and microbial degradation simultaneously.

Because the membrane separation in the MBR can intensify the function of the bioreactor by rejecting the activated sludge and increasing the residence time of wastewater, the MBR shows a high removal efficiency for various personal care products. For example, Radjenovic *et al.* [203] removed most pharmaceutical products at an efficiency of 80% with an MBR, and the long-term stability of two months provided a guideline for the scaling-up of a biological pilot plant. Oota *et al.* [204] used MBR for the effective removal of coliphage and norovirus, and the high removal efficiency of 96% was ascribed to the activated sludge particles, which can effectively adsorb virus. Further interesting studies were conducted to improve the performance. Song *et al.* [205] used a biofilm-MBR to improve the removal efficiency of total phosphorous, and the advantages of the biofilm-MBR over the conventional MBR in total phosphorous removal might be attributable mainly to the presence of the biofilm, which established a hypoxic/anaerobic environment. Yang *et al.* [206] conducted two parallel experiments on a conventional MBR and an MBR with the addition of rice straw. The removal of trimethoprim increased from 40.82% to 82.10% after the addition of rice straw, which was achieved by the cometabolism of nitrification and denitrification.

MBRs are also capable of combining other water treatment methods to further improve the removal performance. The integration of RO, NF and AOP is commonly adopted. Wang *et al.* [207] and his group revealed that the incorporation of RO membranes can double the removal efficiency of some medicines, such as metoprolol. Ouarda *et al.* [208] combined MBR with ozone to remove carbamazepine, ibuprofen, estradiol and some other drugs in medical wastewater at a rate of 10 $\mu g \cdot L^{-1}$, and the removal efficiency reached 90%. Köhler *et al.* [209] oxidized the wastewater with UV light and hydrogen peroxide after pretreatment with MBR, and the oxidation treatment produced hydroxyl radicals for the effective degradation of reductant drugs in the wastewater.

MBRs have been successfully used in wastewater treatment incorporating AOP and extra RO/NF membranes. However, the AOP technique always requires an ultraviolet source or an external power source, which is inconvenient for movable water treatment. Therefore, the development of alternative irradiation sources such as solar energy or visible light is a future research direction, which could greatly reduce the cost and improve the convenience for users.

6.3. Main challenges of medical supporting membranes in the future

Membranes have been widely applied in the medical supporting areas such as protective equipment fabrication and hospital wastewater treatment relying on the size sieving and adsorption mechanism. The toxic substances absorbed can be decomposed by external power such as ultraviolet source, which is power consuming and inconvenient. Thereby in the future, inorganic nanoparticles with excellent photo-thermal properties can be introduced to achieve a sterilization and disinfection effect. In this way, the toxic substances can be inactivated under natural light at any time. On the other hand, sensing part is suggested to be combined for a real-time monitoring of the toxic substance

concentration to provide early warnings. Moreover, the liquid based porous membranes can be applied for body protection due to its self-cleaning, anti-fouling abilities and pressure driven detection ability [139,210–212]. With the fusion of different technologies, more intelligent membranes are sure to be developed in the future to safeguard the health of human beings.

7. Conclusion and Prospects

Overall, membrane technology has already been confirmed to present novel and broad applications in the life sciences, including artificial organs, tissue engineering, medical support and *in vitro* blood diagnosis. Membranes show a unique and irreplaceable ability to provide humans with a healthier life due to their various functions. Initially, the dissolution and diffusion functions of membranes dominated the scope of their use to construct artificial organs for the replacement of damaged organs (artificial lung, kidney, liver, *etc.*). With the rapid development of medical and material sciences, the applications of membranes have extended to a scaffold function, and they have proven to be capable of providing cell culture and a biocompatible microenvironment in the tissue engineering and medical support fields. In addition, there is a trend for the incorporation of different technologies into a device for rapid diagnosis. The separation and biosensing functions of membranes can be integrated to enable the dynamic monitoring of fluctuations in vital blood components, which cannot be obtained by state-of-the-art commercial instruments in hospitals. Although membrane technology has been confirmed to contribute essential functions in various aspects of life science, there are still many limitations in practical applications. For example, membranes cannot substitute the physiological functions and three-dimensional structure of human organs and tissues, which may still cause a series of complications after treatment. In addition, the fouling of membrane is always a restriction for its long-term use. More importantly, the physical sieving mechanism makes the membrane unable to separate the similar substances with similar size and property. In the future, more intelligent products containing membrane are expected to be developed:

1. A miniaturized and portable household device with convenient operation and easy replacement is still desired ability to decrease the disruption of the normal life of patients during treatment.
2. The mechanism of tissue reconstruction must be clarified to optimize the methodology of membrane design, which can better mimic the properties of human tissue to reduce the exclusion phenomenon and inflammatory reaction.
3. More sensing technologies should be employed in the medical support field to achieve both high rejection efficiency and real-time detection of hazardous substances during pathogen separation and waste purification.
4. The dynamic and online detection of various clinical blood indices is always eagerly desired in not only surgical operation and emergency treatment but also physiological monitoring for nonhospital patients.

Overall, membrane technology is integrating into medical science with rapid development and increasing interdisciplinary knowledge. This integration will accelerate the fabrication of new clinical instruments for facilitating disease diagnosis and treatment. Although clinical transformation and application will still require a long process of safety evaluation and clinical trials, we believe that this field will inevitably receive increasing attention in future research due to the outbreak of global epidemics in recent years.

Declaration of Competing Interest

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

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