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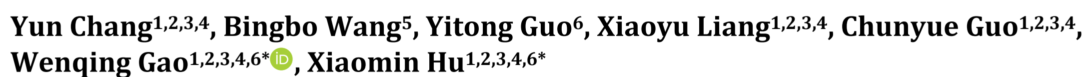
Clinical Translation Challenges and Future Paradigms of Advanced ECMO Coatings: Scalability, Hemocompatibility, and Regulatory Barriers



Yun Chang[1,2,3,4], Bingbo Wang[5], Yitong Guo[6], Xiaoyu Liang[1,2,3,4], Chunyue Guo[1,2,3,4], Wenqing Gao[1,2,3,4,6*], Xiaomin Hu[1,2,3,4,6*]

[1]Central Hospital, Tianjin University/Tianjin Third Central Hospital, Tianjin, China
[2]Tianjin Key Laboratory of Extracorporeal Life Support for Critical Diseases, Tianjin, China
[3]Tianjin Artificial Cell Engineering Technology Research Center, Tianjin, China
[4]Tianjin Institute of Hepatobiliary Disease, Tianjin, China
[5]Tianjin University of Traditional Chinese Medicine, Tianjin, China
[6]Medical School of Tianjin University, Tianjin, China
Email: *gaowq_1224@tju.edu.cn, *hydtheing@hotmail.com

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Abstract

Extracorporeal membrane oxygenation (ECMO) triggers severe thromboinflammatory responses upon prolonged blood contact with synthetic interfaces. While advanced surface modifications aim to actively remodel the local immune microenvironment to surpass the limitations of conventional heparin coatings, their clinical translation remains constrained. This narrative review systematically evaluates the technical and regulatory barriers impeding the commercialization of next-generation ECMO coatings. It analyzes the distinct engineering requirements for primary blood-contacting components: achieving long-term mechanical stability against extreme hemodynamic shear stress in polyvinyl chloride tubing, and resolving the mass transfer paradox to maintain high gas permeability in hollow fiber membrane oxygenators. Furthermore, the review examines critical industrial hurdles, including the degradation of bioactive molecules during mandatory sterilization, complex regulatory pathways for drug-device combination products, and the lack of standardized multi-scale dynamic preclinical evaluation models. Overcoming these multidimensional challenges necessitates rigorous interdisciplinary collaboration among materials engineering, clinical medicine, and regulatory science.

Keywords

Extracorporeal Membrane Oxygenation, Surface Modification, Polyvinyl Chloride Tubing, Hollow Fiber Membrane, Thromboinflammation, Immune Modulation

1. Introduction

Extracorporeal membrane oxygenation (ECMO) has established itself as the ultimate life-saving modality for patients presenting with refractory cardiopulmonary failure [1]. Its clinical application has expanded significantly, particularly in managing acute respiratory distress syndrome and cardiogenic shock, and in serving as a critical transition for organ functional recovery. Despite continuous refinements in device engineering, the survival benefits of ECMO are frequently compromised by severe circuit-induced complications. Recent evidence from the ECLS-SHOCK multicenter randomized trial indicates that the 30-day mortality rate for patients with infarct-related cardiogenic shock receiving veno-arterial ECMO remains between 47.8% and 52.8% [2]. These unfavorable clinical outcomes are primarily attributed to severe vascular complications, hemorrhage, and secondary multiorgan dysfunction rather than mechanical device failure [3].

The fundamental etiology of these complications resides in the suboptimal hemocompatibility of existing synthetic interfaces. The continuous contact between whole blood and non-endothelialized polymer surfaces under extreme fluid shear stress triggers an immediate and aggressive thromboinflammatory response [4]. This pathological process is characterized by the reciprocal amplification of the coagulation cascade and innate immune activation. Specifically, high shear forces combined with foreign surface exposure drive pathological remodeling of platelets, manifested by dense granule defects and the significant proteolytic shedding of Glycoprotein V (GPV). While soluble GPV represents a compensatory antithrombotic marker, the resultant structural depletion and functional exhaustion of platelets contribute to the development of ECMO-associated acquired coagulopathy, characterized by simultaneous risks of thrombosis and bleeding [5].

Furthermore, persistent interfacial stimulus activates the complement system, leading to systemic inflammatory response syndrome and the subsequent release of pro-inflammatory cytokines, which exacerbate immune-mediated organ injury [6]. To maintain circuit patency, the requisite systemic administration of high-dose anticoagulants, predominantly heparin, inevitably disrupts the hemostatic equilibrium of patients. This creates a critical clinical paradox where the intervention required to prevent fatal circuit thrombosis directly precipitates uncontrollable systemic hemorrhage. Therefore, overcoming the intrinsic thromboinflammatory response triggered at the biomaterial interface remains the most urgent unmet need in advancing extracorporeal life support technologies [3] [6].

The ECMO circulatory circuit is primarily composed of two blood-contacting modules with distinct physical properties and physiological roles: the transport tubing and the hollow fiber membrane oxygenator [7]. Medical-grade polyvinyl chloride (PVC) remains the predominant material for circulatory tubing due to its superior flexibility, transparency, and mechanical durability required for extracorporeal blood transport [8]. However, as the primary conduit for large-volume blood flow, the high surface-to-volume ratio and inherent hydrophobicity of PVC surfaces initiate a significant protein adsorption cascade immediately upon contact with whole blood. This phenomenon leads to the formation of a biological layer that facilitates subsequent platelet adhesion and activation [9].

In contrast, the oxygenator represents the most critical functional component for gas exchange, typically utilizing microporous or non-porous hollow fiber membranes [10]. Modern oxygenators predominantly employ poly-4-methyl-1-pentene (PMP) fibers, which offer optimized gas permeability and superior resistance to plasma leakage compared to early polypropylene-based designs [11]. These fibers are arranged in a dense, multi-layered architecture to provide an extensive interfacial area, typically ranging from 1.5 to 2.5 m^2, for efficient oxygenation and carbon dioxide removal. However, this high surface area, combined with the complex geometric arrangement of the fibers, creates a unique microenvironment characterized by stagnant flow zones and localized high-shear regions. Such unfavorable hemodynamic conditions significantly exacerbate the risk of circuit-induced thrombosis and systemic thromboinflammation [12].

The inherent incompatibility between synthetic polymers and the human circulatory system necessitates sophisticated surface engineering to achieve long-term hemocompatibility [13]. While conventional heparin-bonded coatings remain the industry standard for mitigating circuit-induced thrombosis, prolonged clinical application reveals that immobilized heparin is highly susceptible to progressive leaching and denaturation under continuous high-shear flow, resulting in an irreversible decline in antithrombotic efficacy and a failure to prevent complex thromboinflammatory responses [14]. Concurrently, despite the proliferation of thousands of advanced biomimetic interfaces in academic research—such as nitric oxide-releasing materials and peptide networks—the clinical translation of these technologies into commercial extracorporeal devices remains stagnant [15]. This profound discrepancy between thriving foundational research and the scarcity of clinical application is primarily attributed to the multifaceted obstacles encountered when scaling laboratory prototypes to large-scale, strictly regulated medical manufacturing [16]. Therefore, this review aims to critically evaluate the core challenges impeding the clinical translation of advanced ECMO coatings, systematically analyzing the impacts of scalable manufacturing, lagging evaluation standards, and stringent regulatory barriers on the adoption of next-generation bioactive interfaces, while exploring future paradigms for technological breakthroughs.

2. Methods

This narrative literature review primarily utilized original research articles, authoritative review papers, clinical trial reports, and official guidance documents from major regulatory agencies to evaluate the translational barriers and advancements of next-generation ECMO coatings. The search strategy employed principal scientific and medical databases, specifically PubMed, Web of Science, Scopus, and Embase. Keywords utilized in the search algorithms encompassed combinations of Extracorporeal membrane oxygenation, ECMO, surface modification, bioactive coating, hemocompatibility, thromboinflammation, macrophage polarization, scalable manufacturing, and regulatory barriers, combined using Boolean operators. Eligible resources were strictly restricted to peer-reviewed English-language publications from January 2015 to May 2026. Articles were excluded if they focused on non-blood-contacting biomaterials, pertained to early-stage exploratory coatings lacking translational potential, or consisted of non-peer-reviewed preprints and conference abstracts. Following an independent screening, the full texts of relevant articles were critically appraised to address interfacial mechanical stability, multi-scale biological evaluation, and industrial regulatory challenges.

3. Paradigm Shift in Hemocompatibility Evaluation

3.1. Limitations of Traditional Hemocompatibility Evaluation Systems

Traditional hemocompatibility assessment for extracorporeal circuits has historically relied on single-dimensional coagulation metrics, such as activated clotting time (ACT), prothrombin time (PT), and activated partial thromboplastin time (APTT) [17]. These standardized assays, primarily conducted under static or low-shear conditions as defined by ISO 10993 standards, are increasingly recognized as inadequate for predicting the clinical performance of advanced ECMO coatings. The fundamental limitation lies in their failure to replicate the complex hemodynamic environment characterized by extreme shear stress and high-velocity blood flow [18]. Static assays overlook the dynamic evolution of the protein-material interface and the subsequent cellular responses, particularly the rapid consumption of coagulation factors and the progressive activation of platelets and leukocytes. Consequently, there is a profound disconnect between successful laboratory results based on traditional clotting times and the persistent high incidence of thrombotic and hemorrhagic complications in clinical ECMO support [19].

3.2. Molecular Mechanisms of Thromboinflammatory Coupling Activation

The interaction between whole blood and the non-endothelialized synthetic surfaces triggers an aggressive thromboinflammatory response, characterized by the pathological remodeling of platelets and systemic inflammation [20]. Under extreme fluid shear stress, platelets undergo profound structural and functional alterations,

notably including dense granule defects and the significant proteolytic shedding of Glycoprotein V (GPV) [21]. The loss of platelet receptors and the depletion of bioactive cargo within granules not only impair the primary hemostatic function but also facilitate the release of pro-inflammatory mediators. This mechanical and biochemical activation leads to the development of ECMO-associated acquired coagulopathy [22]. Simultaneously, the circuit interface initiates the complement cascade and activates innate immune pathways, resulting in systemic inflammatory response syndrome (SIRS) (**Figure 1**). The reciprocal amplification between thrombin generation and the release of inflammatory cytokines (e.g., IL-6, TNF-*α*) constitutes a vicious cycle of thromboinflammation, which exacerbates both circuit thrombosis and immune-mediated end-organ damage [23].

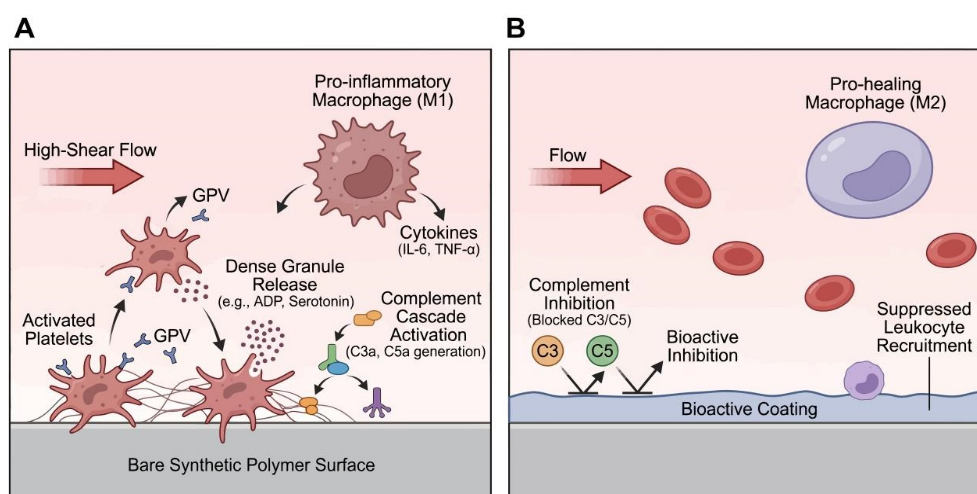

Figure 1. Schematic illustration of the thromboinflammatory cascade and active immune microenvironment remodeling on ECMO interfaces. (A) Pathological activation on bare surfaces under high-shear flow, featuring platelet activation (GPV shedding, granule release) and pro-inflammatory M1 macrophage polarization with cytokine (IL-6, TNF-*α*) secretion. (B) Microenvironment remodeling via bioactive coatings, which inhibit C3/C5 cascades, suppress leukocyte recruitment, and promote a pro-healing M2 macrophage phenotype.

3.3. Active Intervention and Immune Microenvironment Remodeling

To break the thromboinflammatory cycle, next-generation ECMO coatings are shifting from passive antifouling to active modulation of the local immune microenvironment. Advanced surface engineering strategies focus on the simultaneous inhibition of the complement system and the specific guidance of macrophage polarization [24]. By incorporating biomimetic peptide networks or bioactive molecules capable of blocking the C3/C5 cascade, coatings can effectively suppress the recruitment and hyperactivation of leukocytes [25]. Furthermore, research has demonstrated that functionalized surfaces can drive macrophage polarization from a pro-inflammatory M1 phenotype toward a pro-healing M2 phenotype, thereby quelling the excessive inflammatory response triggered by the artificial interface. This transition from simple anticoagulation to comprehensive immune

microenvironment remodeling represents a promising paradigm for enhancing the long-term safety and efficacy of extracorporeal life support devices [26].

4. Engineering Obstacles in Scaled Manufacturing

4.1. Interfacial Mechanical Stability of Polyvinyl Chloride Tubing

In the extracorporeal circuit, the polyvinyl chloride (PVC) tubing serves as the primary conduit for prolonged, high-velocity blood flow, subjecting the luminal surface to continuous and extreme hydrodynamic shear stress [27]. In laboratory settings, many advanced hemocompatible coatings, such as physically adsorbed hydrogels or electrostatic layer-by-layer assemblies, demonstrate excellent antithrombotic properties under static or low-flow conditions. However, when applied to the luminal surface of long PVC tubing under physiological ECMO flow rates, these non-covalently bound coatings rapidly undergo mechanical degradation, delamination, and subsequent systemic embolization [28]. To address this interfacial instability, scalable engineering strategies must integrate robust anchoring mechanisms. Current translational research emphasizes covalent grafting techniques, bio-inspired polydopamine adhesive underlayers, and in situ photocrosslinking. These approaches aim to establish an irreversible mechanical interlock between the compliant PVC substrate and the functional outer layer, ensuring long-term architectural integrity without shedding bioactive components during extended extracorporeal support [27].

4.2. Modification Balance of Hollow Fiber Membranes

The oxygenator module, predominantly constructed from polymethylpentene (PMP) hollow fiber membranes, presents a fundamentally different engineering paradigm. The primary physiological function of the PMP membrane is to facilitate highly efficient gas exchange (oxygenation and decarboxylation) through its complex microporous or asymmetric dense skin layer [29]. A critical paradox arises during the surface modification of these gas-permeable fibers: the incorporation of thick hydration layers, macromolecular hydrogels, or bulky peptide networks simultaneously introduces a substantial mass transfer resistance, despite significantly enhancing hemocompatibility [30]. This physical barrier severely attenuates the diffusion coefficients of oxygen and carbon dioxide, compromising the fundamental life-support capacity of the device. Consequently, the modification of oxygenator membranes requires a precise equilibrium. Engineering efforts must focus on achieving ultra-thin, conformal, and highly permeable nanocoatings. Techniques such as molecular-level surface functionalization, plasma-induced graft polymerization, or nanoscale biomimetic deposition are essential to construct an immune-modulatory interface without occluding the microscopic gas transport channels of the PMP fibers.

4.3. Consistency Challenges of Large-Area Uniform Coating

The transition from small-scale laboratory validation to clinical-scale manufacturing

introduces profound challenges in quality control and coating consistency. Academic proof-of-concept studies typically evaluate novel biomaterials on two-dimensional flat sheets or short tubing segments with surface areas of only a few square centimeters. In contrast, a commercial adult ECMO oxygenator entails a complex three-dimensional topological architecture comprising thousands of tightly woven hollow fibers, yielding a total blood-contacting surface area of 1.5 to 2.5 square meters [31]. Achieving a homogenous, defect-free coating across this immense and intricately packed geometry represents a formidable industrial hurdle. Conventional liquid-phase immersion or spray coating methods frequently result in uneven thickness distribution, pooling at fiber intersections, and the capillary-driven bridging effect, which occludes the inter-fiber blood pathways and drastically increases fluidic resistance. Scaling up requires the development of advanced dynamic deposition technologies, such as continuous roll-to-roll processing for individual fibers prior to weaving, or precisely controlled chemical vapor deposition systems. These industrial strategies are mandatory to ensure absolute coating uniformity, eliminate stagnant flow zones, and guarantee the reproducible clinical efficacy of the modified macroscopic devices [28] [31].

5. Regulatory and Industrial Evaluation Barriers

5.1. Impact of Industrial Sterilization Processes on Coating Activity

Mandatory industrial sterilization techniques for medical devices, such as ethylene oxide exposure and gamma irradiation, pose a severe threat to the structural integrity of next-generation bioactive coatings [32]. For biomaterials aimed at clinical translation, achieving a sterility assurance level of 10^{-6} is a strict regulatory requirement. However, ethylene oxide sterilization frequently induces chemical alkylation of amino acid residues, irreversibly destroying the spatial conformation of biomimetic peptides and natural bioactive monomers. Similarly, gamma irradiation generates reactive oxygen species that trigger oxidative cleavage of polymer backbones and complete denaturation of incorporated biological factors [33]. Consequently, a profound engineering contradiction emerges in extracorporeal life support devices: the obligatory sterilization process essential for patient safety simultaneously eradicates the delicate immune-modulatory functions of the advanced interface, rendering many highly active laboratory coatings non-viable during clinical translation.

5.2. Legal Qualification and Approval Pathways for Combination Products

The incorporation of biological components with active modulatory functions, such as specific antibodies, functional peptides, or natural pharmacological monomers, into the extracorporeal circuit fundamentally alters the regulatory classification of the device. Under the regulatory frameworks of the US Food and Drug Administration and the China National Medical Products Administration, these

advanced ECMO circuits are no longer considered standard Class III medical devices but are reclassified as highly regulated drug-device combination products [34]. This reclassification triggers a complex and time-consuming dual-track evaluation pathway, demanding not only stringent mechanical durability testing but also extensive pharmacological, pharmacokinetic, and toxicological validation [35]. The current absence of unified international guidelines specifically tailored for combination products modulating thromboinflammatory networks introduces significant regulatory uncertainty. This exponentially increases research costs and prolongs the clinical trial phase, thereby severely impeding the market access of novel coatings.

5.3. Absence of Multi-Scale Dynamic Evaluation Models

A core technical bottleneck in the translation of advanced ECMO coatings is the critical absence of standardized, multi-scale dynamic evaluation models. Current preclinical assessments often rely heavily on fragmented *in vitro* static standard tests (such as ISO 10993-based assays) or miniaturized microfluidic thrombosis-on-a-chip platforms. These systems fail to recapitulate the systemic thromboinflammatory cascade of a complete living organism under prolonged high-shear stress [36]. To bridge this translational gap, it is imperative to establish a hierarchical, multi-scale evaluation paradigm. This system must mandate sequential validation: initiating with ex vivo high-shear blood recirculation loops, progressing to small-animal arteriovenous bypass models to assess initial systemic immune responses, and culminating in large-animal long-term veno-arterial ECMO models [37]. Only through such comprehensive and continuous dynamic in vivo modeling can the true long-term hemocompatibility and end-organ protection efficacy of novel bio-interfaces be reliably determined prior to human clinical trials.

6. Conclusions and Future Perspectives

The clinical translation of advanced coatings for extracorporeal membrane oxygenation (ECMO) is governed by a complex matrix of interlocking constraints across material design, scalable manufacturing, and regulatory compliance (**Figure 2**) [38]. A fundamental contradiction exists between the academic pursuit of chemical complexity and the industrial requirement for structural reproducibility. While laboratory research prioritizes multi-component, highly responsive biomimetic interfaces to achieve precise immune-modulatory control, these intricate architectures often fail to maintain long-term interfacial stability under extreme hemodynamic shear stress. Furthermore, the mandatory requirements for large-area uniform deposition across complex three-dimensional topologies and resistance to aggressive industrial sterilization processes frequently compromise the viability and structural configuration of bioactive ligands. When interfacing with regulatory bodies, the introduction of active pharmacological or biological agents elevates the device classification to drug-device combination products, triggering

exhaustive, dual-track approval pathways that drastically extend the timeline and cost of commercial development. Consequently, the field faces a significant translational barrier where optimization in one dimension often precipitates critical failure in another [38] [39].

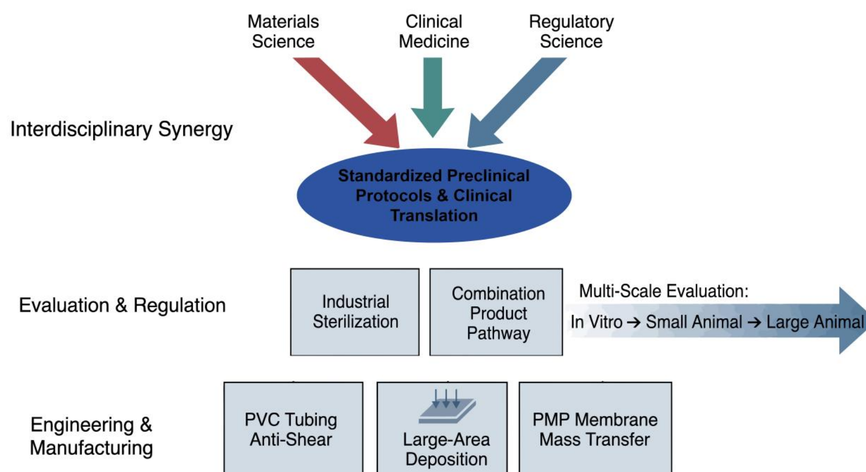

Figure 2. Multidimensional constraints and the interdisciplinary synergistic framework for the clinical translation of next-generation ECMO coatings.

To dismantle the technological barriers hindering next-generation ECMO circuits, a paradigm shift toward deeply integrated, interdisciplinary collaboration is mandatory [39]. The historical insularity between polymer chemistry, fluid mechanics, clinical medicine, and regulatory science must be replaced by a cohesive, synchronized developmental pipeline. Clinical insights are essential to define the precise, dynamic thromboinflammatory pathological endpoints that materials must address in vivo. Concurrently, materials scientists and mechanical engineers must co-design surfaces from the inception with a focus on scalable automation and fluidic durability, ensuring that blood-contacting interfaces can withstand realistic clinical flow regimes without degradation. Most critically, regulatory experts must be engaged early to establish updated, standardized preclinical evaluation protocols—such as standardized long-term large-animal models and dynamic immune metrics—that accurately reflect the dual nature of active interfaces. Only through this comprehensive, cross-sector convergence can the medical device industry reduce trial-and-error costs, accelerate the validation of high-end lifesupport consumables, and successfully transition advanced interfacial concepts into reproducible clinical realities.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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