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Review

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Advances in hemostatic biomaterials: biomimetic strategies, nanotechnology, and smart therapeutics

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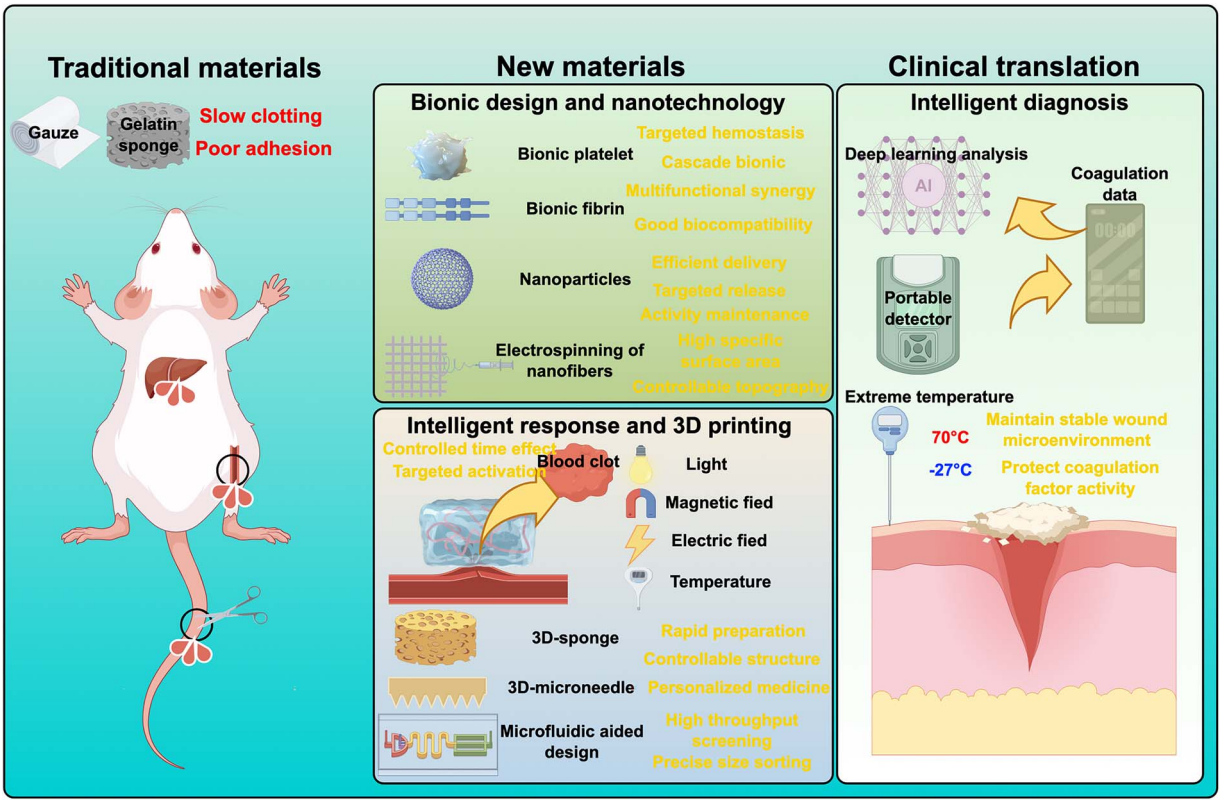
Abstract

Bleeding, a critical complication in trauma, surgery, and conditions such as hemophilia, liver cirrhosis, and thrombocytopenia, often leads to shock or death. The limitations of traditional hemostatic methods—such as compression, suturing, and electrocautery—have prompted the development of advanced biomaterials. In modern research, intelligent, multi-mechanism systems have supplanted basic physical or chemical approaches. Biomimetic designs, such as platelet- and fibrin-inspired materials, alongside nanotechnology (e.g. nanoparticle carriers and electrospun fibers) and stimuli-responsive polymers (e.g. light- or temperature-triggered), enable targeted clotting, controlled drug release, and enhanced wound adhesion. Additionally, 3D printing and microfluidics allow precise material modification, further boosting hemostatic efficiency. Despite these advances, clinical translation faces challenges related to biocompatibility, mass production, and patient-specific customization. Future progress is likely to integrate multidisciplinary technologies, such as artificial intelligence, genetic engineering, smart regulation, and personalized therapies, to improve hemorrhage management. These innovations aim to bridge the gap between laboratory research and clinical application, offering safer, more effective solutions for trauma and surgical interventions.

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Graphical abstract



Keywords Hemostatic biomaterials, Bionic design, Intelligent response, Bleeding, Nanotechology

Highlights

- **Emerging hemostatic biomaterials have progressed from simple occlusion to intelligent, multi-mechanism systems.**
- **Bionic designs and nanotechnology enable targeted clotting through platelet-mimicking structures and responsive materials.**
- **Clinical translation faces hurdles in biocompatibility, mass production, and patient-specific adaptation.**
- **Future integration of artificial intelligence and biomanufacturing promises precision-controlled hemostatic solutions.**

Background

Bleeding is a common complication associated with trauma, surgery, and various conditions, including thrombocytopenia, liver cirrhosis, and hemophilia [1, 2]. In severe cases, it can lead to shock or death. Global statistics indicate that over 5 million people die from trauma annually, with excessive bleeding responsible for 30%–40% of these fatalities [3, 4]. Rapid and effective hemostasis is particularly critical in high-risk environments such as combat zones, natural disasters, or emergency medical rescues. Traditional hemostatic methods, including electrocoagulation, suturing, and compression, often fail to meet the complex clinical demands in these settings [5, 6]. Consequently, the development of advanced hemostatic biomaterials aimed at enhancing hemostatic efficiency and minimizing complications has become a key focus in materials science and biomedical engineering.

The limitations of conventional methods are evident in high-risk clinical scenarios. Noncompressible truncal hemorrhage is a significant challenge, where bleeding from solid organs like the liver or spleen, or deep pelvic injuries, cannot be controlled by external compression and remains a leading cause of preventable death [7, 8]. Similarly, hemorrhage associated with coagulopathies—whether congenital, pharmacologically induced, or trauma-related—renders passive hemostatic agents ineffective, as they depend on an intact clotting cascade that may be compromised or absent [9–11]. High-pressure arterial bleeding further complicates hemostasis, often dislodging conventional agents before a stable clot can form. Additionally, achieving hemostasis on complex anatomical surfaces—such as the wet, dynamic environments of the heart or major blood vessels—requires materials with exceptional adhesive strength and mechanical compliance [12, 13]. The extreme conditions found in military and space medicine demand materials that can perform reliably in weightlessness, extreme temperatures, or high radiation, challenging the limits of material science [14].

Conventional hemostatic agents, such as gelatin sponges, oxidized regenerated cellulose, and fibrin sealants, have proven valuable by providing passive physical barriers or scaffolds for clot formation [15, 16]. However, their reliance on the body's intrinsic hemostatic mechanisms represents a significant

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limitation in the scenarios outlined earlier. These agents fail to address the pathophysiology of bleeding actively, are prone to failure in high-flow environments or coagulopathic conditions, and lack secondary functionalities, such as antimicrobial properties or proregenerative signaling [17–19]. Additionally, some widely used inorganic agents, like zeolites, can cause adverse effects, including exothermic reactions leading to thermal tissue injury or triggering undesirable foreign body responses [20, 21].

In response to these challenges, the field is undergoing a transformative shift from passive materials to active, intelligent systems [22]. This review examines this evolution through three interconnected design paradigms that define the forefront of hemostatic biomaterial research. First, Biomimetic Strategies form the foundational blueprint, replicating core aspects of natural hemostasis—from the targeted, signal-responsive adhesion of platelets to the enzyme-driven polymerization of fibrin [23, 24]. Second, nanotechnology serves as an essential enabler, offering precise engineering tools to realize these biomimetic designs at a biologically relevant scale [22, 25]. It facilitates the creation of platelet-mimetic nanoparticles for targeted drug delivery and electrospun nanofibrous scaffolds that mimic the extracellular matrix (ECM), enhancing properties like ultra-high surface area for faster clotting. The integration of these first two paradigms culminates in the third: Smart Therapeutics. These systems are context-aware and dynamically responsive, capable of sensing microenvironmental cues—such as pH, enzyme activity, or light—and executing programmed actions, such as morphological changes, on-demand therapeutic release, or real-time thrombin activity reporting, offering a new level of precision in hemorrhage control and wound management [26]. This article provides a comprehensive analysis of these paradigms, addresses ongoing challenges in translating these advanced materials from the lab to clinical settings, and explores the future of the field, increasingly influenced by artificial intelligence (AI), genetic engineering, and advanced biomanufacturing.

Review

Bionic design and nanotechnology

Bionic design

Bionic platelets Bioengineered platelets are modified through bioengineering technologies to simulate or enhance the functions of natural platelets. Their primary applications include: (i) internal drug loading, utilizing their natural delivery systems for targeted release [27, 28]; (ii) surface modification to increase binding affinity to specific cells or tissues via ligand modification or antibody conjugation [28]; and (iii) modification of megakaryocytes to produce platelets capable of transporting exogenous proteins, such as anti-inflammatory or antitumor drugs [29–31]. Recent advances in multifunctional hemostatic materials modeled after bioengineered platelets have significantly surpassed the limitations of conventional hemostatic methods.

Bioengineered platelets represent a groundbreaking development in biomimetic hemostatic strategies, designed to replicate the multifaceted roles of their natural counterparts [32]. These synthetic systems have evolved through a clear developmental trajectory, beginning with structural mimicry and progressing toward the emulation of complex, dynamic biological functions. Early research focused on mastering the physical characteristics of platelets, precisely engineering their 1–3 μm size and surface charge to control margination and adhesion behaviors. Shuai *et al.*'s bioengineered platelets Silk Fibroin microspheres (SFMPs) illustrate this approach, achieving a morphological and electrostatic profile resembling natural platelets while incorporating targeting peptides LPCDYYGTCLD/TRYLRIHPQSQVHQI (LD/TI) to enhance their function. This resulted in a 74% improvement in hemostatic efficacy (Figure 1a) [33]. This foundational work demonstrated that even basic physical mimicry could offer substantial therapeutic benefits, overcoming key limitations of natural platelets, including short storage life and immunological concerns.

Building on this structural foundation, the field quickly integrated biochemical intelligence, aiming to replicate the molecular interactions that underpin hemostasis. This involved functionalizing synthetic carriers with bioactive motifs, such as the fibrin-specific LD peptide, the von Willebrand factor (vWF)–targeting TI peptide, and the RD peptide that modulates glycoprotein IIb/IIIa receptors. The combination of multiple biomimetic signals was showcased by Feng *et al.*, who integrated phosphatidylserine (DSPS) to enhance prothrombin activation, a platelet adhesion peptide (PAP), and a cross-linking peptide (PCP) into a unified sprayable hydrogel using peptide-modified lipid nanoparticles (PLNs) (Figure 1b) [34]. This system reduced blood loss by 86% in a rat liver injury model, mimicking the collaborative synergy of natural platelets by engaging multiple coagulation pathways simultaneously, marking a significant advancement from simple to multi-modal mimicry.

The frontier of bionics is advancing toward systems capable of dynamic, system-level behaviors that surpass static imitation. Zeng *et al.*'s artificial platelet microparticles exemplify this cutting-edge paradigm (Figure 1c) [35]. Utilizing catechol-alkyl-modified glycans for supramolecular self-assembly, their constructs form a dynamic, self-healing hemostatic network *in vivo* through rapid, nonspecific interactions, completing the process within 45 s under high-pressure conditions. This adaptive, emergent structuring mirrors the self-organizing intelligence of a natural platelet plug. Moving beyond hemostasis, Yang *et al.* developed self-assembled peptide-based nanoparticles (pNPs) designed for oncological therapy [36]. These pNPs are engineered to transform into activated nanofibers (apNFs) upon targeting CD105 on tumor vasculature, recruiting additional pNPs to form artificial thrombi that occlude the tumor's blood supply. This represents a significant shift in bionic application, extending from restoring hemostasis to orchestrating pathological processes for therapeutic benefit, achieving a remarkable 53% tumor growth inhibition and outperforming established clinical agents.

Despite these groundbreaking advancements, the path toward the ideal synthetic platelet remains fraught with biological complexity. A key challenge lies in moving beyond preprogrammed functionality to achieve true dynamic, multistage responsiveness. Natural platelets possess a sophisticated capacity for progressive activation, adaptively modifying their receptor presentation and secretory profile in response to biochemical gradients—contextual intelligence that current bionic designs have yet to fully replicate. This limitation is closely tied to safety concerns, as the potent pro-adhesive nature

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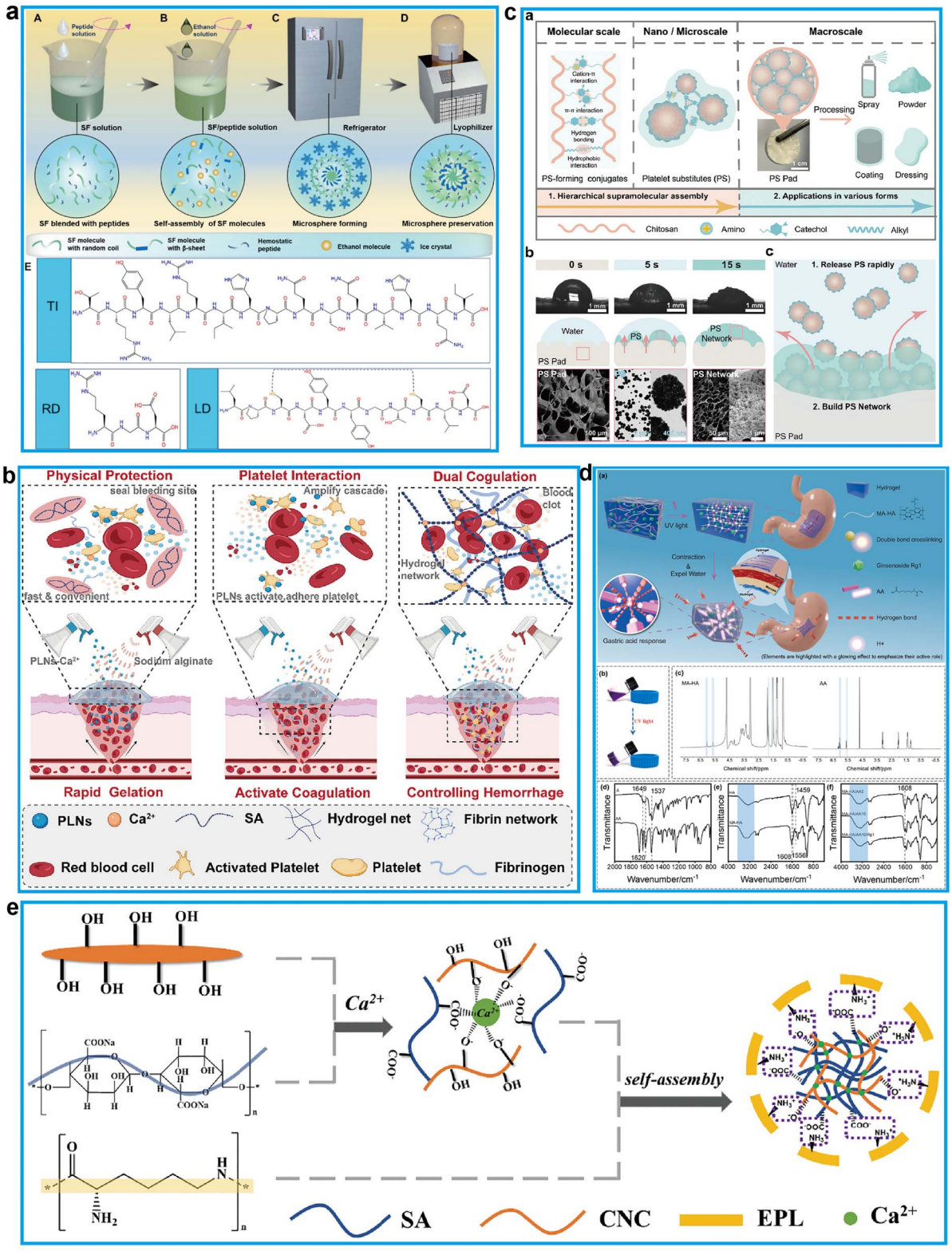


Figure 1 The progression of biomimetic design in hemostatic materials. Panels (**a**–**c**) illustrate the increasing sophistication of platelet mimicry, progressing from structural imitation (a) to multi-functional synergy (b), and finally to dynamic self-organization (c). Panels (**d**) and (**e**) expand the biomimetic concept to microenvironment-adaptive materials, mimicking the body's strategies for gastric acidity (d) and porous tissue architecture (e). (a) Schematic of the preparation of SF-based hemostatic microspheres. Reproduced with permission [33]. Copyright 2025, BioMed Central. (b) Design of a Ca^{2+}-sodium alginate (SA) sprayable hydrogel, based on biomimetic polypeptide–modified lipid nanoparticles (PLNs). Reproduced with permission [34]. Copyright 2025, John Wiley & Sons. (c) Construction of a supramolecular material featuring a hierarchical platelet-substitute (PS) network with water-triggered PS-release capability. Reproduced with permission [35]. Copyright 2025, John Wiley & Sons. (d) Schematic of the preparation and application of the MA-HA/AA hydrogel loaded with ginsenoside Rg1. Reproduced with permission [45]. Copyright 2025, Elsevier. (e) Schematic diagram of the fabrication and action mechanism of PSLMs. Reproduced with permission [50]. Copyright 2022, Elsevier. *TI* TRYLRIHPQSQVHQI, *PLNs* peptide-modified lipid nanoparticles, *SA* sodium alginate, *PS* platelet microparticles, *CNC* cellulose nanocrystal porous microspheres

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of these materials, without carefully calibrated deactivation mechanisms, raises the risk of off-target thrombosis, particularly with systemic administration. Furthermore, the functional scope of most bionic platelets is currently confined to the coagulation cascade [27]. For these agents to become clinically indispensable, future iterations must adopt a more comprehensive design approach, integrating additional functionalities such as antimicrobial properties or controlled release of pro-regenerative factors to address the full spectrum of tissue repair pathophysiology [37]. The field is steadily progressing toward the creation of autonomous, information-rich systems capable of processing multiple environmental cues to execute temporally controlled, sequential actions, ultimately blurring the line between advanced biomaterials and synthetic cellular entities [38].

Biomimetic adaptation to wound microenvironments The pursuit of biomimicry in hemostatic materials extends beyond replicating cellular components like platelets to addressing the critical challenge of wound microenvironment adaptation [39]. The human body demonstrates remarkable sophistication in achieving hemostasis across diverse physiological conditions—from the acidic gastric lumen to the high-flow dynamics of vascular injury and the fragile, porous architecture of parenchymal organs [40–42]. Each of these microenvironments presents unique challenges, and evolution has refined specific biological solutions to meet them. Advanced hemostatic materials are now being designed to emulate these natural strategies, transitioning from generic functionality to targeted, context-dependent actions that mirror the body's inherent logic. This represents a higher level of biomimicry, wherein the material's behavior is driven by the biological constraints of the injury site [43, 44].

A prime example of this adaptation is the development of biomimetic strategies for gastric bleeding. The stomach's highly acidic environment (pH 1.5–3.5) inactivates many biologics and destabilizes conventional hydrogels. Li *et al.*'s methacryloyl hyaluronic acid/acryloyl-6-aminocaproic acid (MA-HA/AA) hydrogel provides a biomimetic solution to this challenge, drawing inspiration from the stomach's mucosal defense mechanisms (Figure 1d) [45]. Rather than merely resisting degradation, the hydrogel utilizes low pH as a biological trigger for activation. Protonation of carboxyl groups on 6-aminohexanoic acid enhances hydrogen bonding, leading to rapid contraction and expulsion of water [46]. This behavior mirrors the body's natural response to seal breaches, emulating a physico-chemical sealing process. Moreover, the hydrogel's robust, photocross-linked adhesion under acidic conditions mimics the persistent attachment of the gastric mucosa, ensuring that the biomimetic seal remains intact against peristaltic forces and fluid flow, enabling rapid hemostasis in under 30 s. Beyond morphological sealing, a more advanced form of biomimicry involves replicating the body's use of ionic signaling to orchestrate complex wound healing processes. The HEMO-IONIC material exemplifies this approach by serving as a biomimetic source of essential ionic messengers [47]. Its core mechanism—the release of Ca^{2+} and Zn^{2+} upon contact with blood—mirrors the endogenous ionic signaling that amplifies the coagulation cascade at natural injury sites. The Ca^{2+} release mimics the body's method of potentiating platelet activation and prothrombin complex assembly, while Zn^{2+} supports fibrin stabilization and cellular signaling. Importantly, the material's biological activity extends beyond hemostasis: the released ions actively promote endothelial cell migration and polarize macrophages toward a prorepair ($CD206^{+}$) phenotype via the ERK pathway. This sophisticated biomimicry mirrors the natural healing sequence, where the same signals initiating clotting also guide subsequent tissue repair and regeneration stages. For injuries to highly vascularized, noncompressible organs like the liver, biomimicry must address the challenge of diffuse hemorrhage through a porous tissue structure. The body's solution involves the infiltration and *in situ* formation of a 3D fibrin network that mechanically integrates with the parenchymal architecture [48, 49]. Yang *et al.*'s porous microspheres sodium alginate/cellulose nanocrystals@ε-polylysine (PSLMs) were designed to emulate a specific biological strategy for hemostasis (Figure 1e) [50]. With a high porosity (>65%) and extensive specific surface area, these microspheres go beyond mere physical attributes, embodying architectural biomimicry by creating a synthetic, interposable analog of the native tissue scaffold. This design allows the microspheres to fulfill a dual biomimetic role: first, as synthetic blood components, they rapidly absorb plasma and concentrate coagulation factors within their porous network, accelerating clot formation; second, the Ca^{2+}-cross-linked alginate network forms a biomimetic ECM that stabilizes the initial platelet plug, mirroring the body's fibrin mesh that provides structural integrity to the hemostatic clot [51]. This multi-mechanistic approach effectively replicates the body's strategy for achieving hemostasis in complex, porous tissue environments.

In conclusion, the development of microenvironment-responsive hemostatic materials is fundamentally grounded in biomimicry principles. The most advanced materials are those that go beyond simple environmental responsiveness; they are engineered to decode and execute the biological programs inherent to specific wound sites. By mimicking the body's solutions—ranging from mucosal sealing and ionic signaling to architectural integration—these materials achieve an unprecedented level of precision and efficacy [17, 52, 53]. The future of this paradigm lies in advancing dynamic systems capable of adapting their biomimetic functions sequentially in response to the evolving wound environment, seamlessly integrating with the full spectrum of the natural healing cascade [54, 55].

Nanotechnology

Nanotechnology has emerged as the essential tool bridging the gap between conceptual biomimetic designs and their functional, intelligent implementation [56, 57]. Operating at the same scale as biological molecules and cellular components, nanotechnology provides a level of precision and control unattainable with conventional materials [58]. This section explores how nanoscale engineering is transforming hemostasis by enabling targeted molecular delivery, creating biomimetic nanostructures, and introducing real-time diagnostic capabilities, laying the foundation for advanced smart therapeutics.

Nanoparticle-based systems for targeted molecular delivery In the field of hemostasis therapy, nanoparticle-based delivery systems have demonstrated significant potential [59, 60]. These systems offer innovative solutions to key challenges faced by traditional hemostatic treatments, such as low delivery efficiency [5, 61], poor targeting [61, 62], and limited stability [63, 64]. Researchers have developed a variety of nanoparticle systems

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that can precisely target bleeding sites, release coagulation factors in a controlled manner, and maintain their activity by fine-tuning the physicochemical properties and surface functionalization of the nanoparticles. These advanced delivery systems not only enhance hemostatic effectiveness but also reduce systemic side effects, opening new pathways for clinical bleeding control therapy.

Shi *et al.* introduced the "artificial platelet" ($CaCO_3$@CSF/Ca^{2+}), a biomimetic design that mimics the phosphatidylserine/calcium ion (PS/Ca^{2+}) structure of natural platelets via the silk fibroin/calcium ion (SF/Ca^{2+}) interface (Figure 2a) [65]. This innovative system enables effective thrombin production and targeted release at the site of injury. The system can function for up to 90 days at 37°C by assembling prothrombin complexes in plasma and stabilizing thrombin activity with a protein crown. Additionally, it mitigates the negative impact of the acidic stomach environment on enzyme activity, making oral administration feasible. This design offers a novel approach to targeted hemostasis, overcoming the limitations of conventional thrombin delivery systems, such as cold chain dependency and acid instability. The Girish group's thrombin-targeted lipid nanoparticles (t-TLNPs) employ von Willebrand factor-binding peptide/collagen-binding peptide (VBP/CBP) to selectively bind to collagen and vWF exposed at the site of vascular injury, enriching the nanoparticles at the bleeding site (Figure 2b) [59]. Through passive diffusion and upregulation of secretory phospholipase A2 (sPLA2) at the injury site, the nanoparticle core encapsulates thrombin, initiating local release and enhancing fibrin formation. *In vitro* studies demonstrated that t-TLNPs successfully restored coagulation function and fibrin production in anticoagulant- or platelet-deficient plasma. In a mouse model of liver damage and tail-tip injury, intravenous administration of t-TLNPs significantly reduced blood loss without increasing the risk of systemic thrombosis. This approach overcomes the limitations of conventional thrombin, which cannot be administered intravenously. To address the challenge of medication-induced coagulopathy, Liu *et al.* developed a mesoporous silica-based nanocapture agent (SiO_2-Mal) that reverses the active metabolites of antiplatelet drugs like clopidogrel and prasugrel (Figure 2c) [66]. By incorporating maleimide groups into the channels of mesoporous silica, these nanoparticles efficiently capture active metabolites containing sulfhydryl groups, thereby restoring normal platelet activity. Experimental results showed that SiO_2-Mal nanoparticles significantly reduced bleeding time in mouse, rabbit, and pig models of liver damage and tail hemorrhage.

These nanoparticle systems successfully address the shortcomings of traditional hemostatic techniques by enabling the effective delivery, targeted release, and sustained action of coagulation factors through innovative material design and functional enhancements. Notably, improvements in intravenous safety, drug reversal specificity, and resistance to gastric acid provide breakthrough solutions to clinical challenges such as traumatic hemorrhage, medication-induced coagulopathy, and gastrointestinal bleeding. As nanotechnology continues to advance and extensive clinical research progresses, these delivery systems hold the potential to usher in a new era of precision and personalized hemostatic therapy.

Electrospinning of nanofibers Electrospinning technology has demonstrated significant technological advantages and promising applications in the development of hemostatic materials, particularly in the preparation of nanofibers. This technique enables the production of nanofibrous materials with customizable topography [67, 68], high specific surface area [69, 70], and 3D porous structures [71, 72] by controlling spinning parameters and material formulations. These attributes make electrospun nanofibers ideal platforms for innovative hemostatic agents. Specifically, electrospinning allows for the creation of hierarchical structures with gradient functions and precise control over fiber diameters at the nanometer to micrometer scale, facilitating solutions that address various needs such as infection resistance, mechanical support, and rapid coagulation.

Lee *et al.* developed a double-sided nanofiber hemostatic dressing (Figure 3a) [17], comprising an inner layer made from silk fibroin (SF) and mussel adhesion protein (MAP), both containing dihydroxyphenylalanine (DOPA). The electrospun homogeneous nanofiber structure encourages platelet aggregation and accelerates coagulation. The outer layer, fabricated from hydrophobic SF and treated with methanol, forms a robust barrier with high mechanical strength that prevents bacterial penetration. Electrospinning's ability to produce a layered, functional structure in a single step, achieving both effective hemostasis and material anti-infection properties, offers distinct advantages. Parhi's work further advances the field by creating an ultra-fine, highly porous nanofiber hemostatic material (Figure 3b). The key innovation lies in the use of a low-molecular-weight polycaprolactone (PCL)/keratin blend system, enabling the fabrication of nanofibers with a 3D porous network structure, an average diameter of just 50 nm, and exceptionally high surface area [73]. This unique structure significantly increases the contact area with blood components, accelerating platelet adhesion. The material also efficiently absorbs coagulation factors and red blood cells, promoting rapid clot formation. The incorporation of keratin improves the fibers' mechanical stability and optimizes the rheological properties of the solution during electrospinning, addressing the challenge of bead formation in ultrafine fibers. Animal studies have demonstrated that this high-porosity nanofiber gauze offers >50% higher hemostatic efficiency compared to conventional materials.

By meticulously managing the electrospinning process, researchers have successfully optimized the material's microstructure, including the distribution of functional components, porosity, and fiber diameter. These nanofiber-based hemostatic materials exhibit excellent hemostatic performance and biocompatibility, particularly when tailored with specific topologies. As electrospinning technology continues to advance, these materials are expected to see broader applications in trauma emergency care and surgery, offering safer and more efficient clinical bleeding control options. Future research may explore the integration of electrospinning with other advanced manufacturing technologies to develop hemostatic material systems with more complex functions and enhanced performance.

Labeling with quantum dots and real-time monitoring Quantum dot–based nanoprobes have shown significant promise in real-time monitoring of the hemostasis process [74, 75]. Key advantages of quantum dot labeling technology, such as high fluorescence intensity, exceptional light stability, and tunable emission wavelengths, distinguish it from conventional detection

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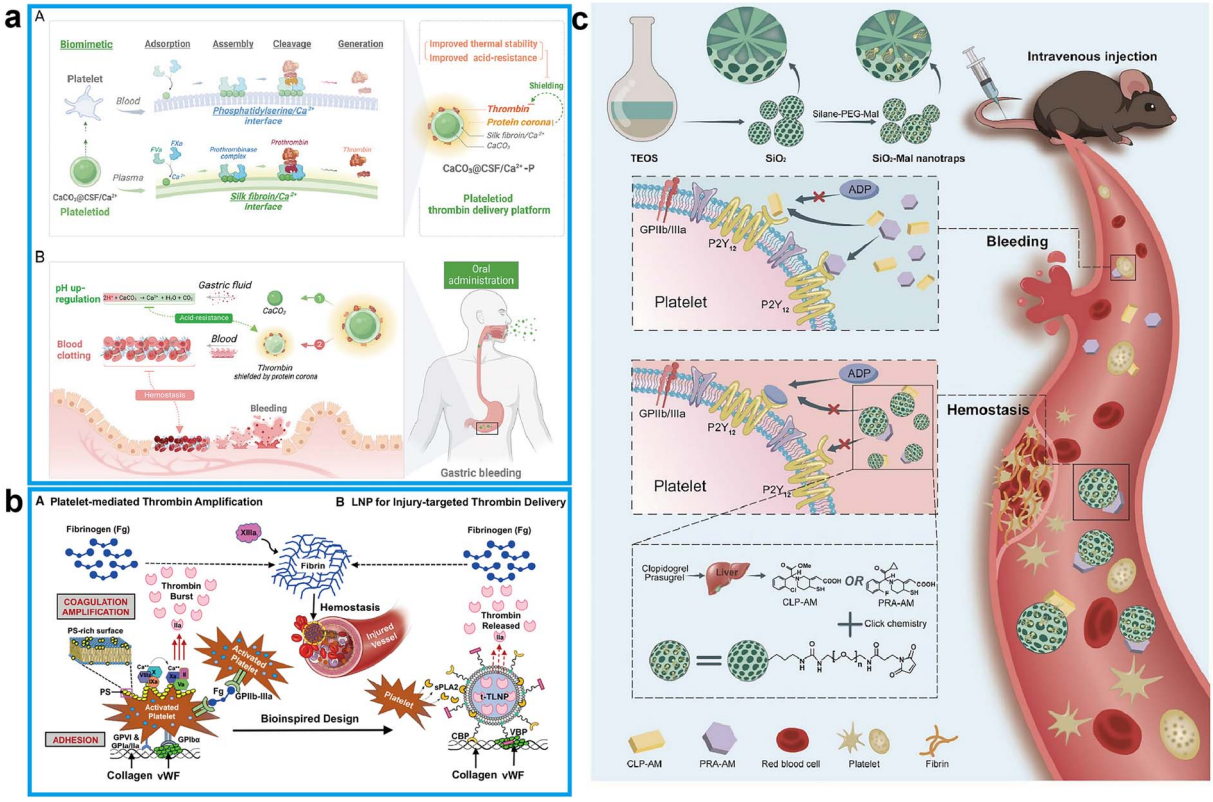


Figure 2 Schematic design and application of nanoparticle-based delivery systems. (**a**) Mechanism of action for the plateletoid ($CaCO_3$@CSF/Ca^{2+}) and its thrombin delivery platform ($CaCO_3$@CSF/Ca^{2+}-P). Reproduced with permission [65]. Copyright 2024, John Wiley & Sons. (**b**) Platelet-mediated hemostatic mechanism and design of platelet-inspired t-TLNP. Reproduced with permission [59]. Copyright 2022, American Chemical Society. (**c**) Synthesis and working model of SiO_2-Mal nanotraps. Reproduced with permission [66]. Copyright 2025, John Wiley & Sons. *t-TLNP* thrombin-targeted lipid nanoparticles, *vWF* von Willebrand factor, *CBP* collagen via collagen-binding peptide, *VBP* vWF-binding peptide

methods. These features enable highly specific and sensitive detection of thrombin activity [76].

Zhang *et al.* developed HPG-TSP-MERHO, a hyperbranched polyglycerol (HPG)–based nanoprobe that selectively detects and responds to thrombin activity through the inclusion of a thrombin-sensitive peptide (TSP). This nanoprobe offers a detection limit of 0.17 ng/ml and rapid response times of under 2 min, facilitating the release of fluorescent groups (MeRho) for enhanced sensitivity (Figure 3c) [77]. Using HPG-TSP-PFPA breath tests, the probe successfully monitored thrombin activity in a living thrombus model, providing a noninvasive monitoring approach. It meets all requirements for fluorescent nanoprobe tracers in hemostatic evaluations, with a long half-life of 22.5 h, excellent biocompatibility, and multimodal detection capabilities, including gas chromatography–mass spectrometry (GC–MS) and fluorescence imaging. Consequently, this nanoprobe is ideal for dynamic, real-time monitoring of the hemostasis process.

As quantum dot surface modification technology advances and multimodal detection platforms are enhanced, quantum dot-labeled nanoprobes are expected to play a more prominent role in diagnosing thrombotic diseases, monitoring anticoagulation therapy, and related fields [77, 78]. The continued development of this technology will facilitate the shift from static evaluations to dynamic tracking in hemostasis monitoring, offering critical support for precision medicine in hemostasis treatment.

Intelligent response and biomanufacturing

Intelligent responsive materials

Intelligent responsive hemostatic materials have become a key focus in trauma treatment research due to their ability to enable precise intervention at bleeding sites through various reaction mechanisms. The development of intelligent systems—such as light-responsive [79], temperature-responsive [80], liquid-responsive [81, 82], electric field-responsive, and cascade-response technologies [7, 83]—has significantly enhanced the controllability and environmental adaptability of hemostatic materials. These advanced materials offer distinct advantages in complex clinical situations by dynamically adjusting their hemostatic properties in response to external stimuli (such as wavelength-specific light, temperature variations, or fluid contact) or internal microenvironmental changes (such as coagulation factor activation).

Liu introduced a novel photoresponsive intelligent hemostatic material, PA-azo-SDS, which combines protamine (PA) with an azobenzene-containing surfactant (AZO-SDS) to provide light-controlled dynamic hemostatic function (Figure 4a) [84]. Upon exposure to ultraviolet (UV) light, azobenzene undergoes reversible photoisomerization, transitioning from its *trans* to *cis* configuration and inducing a phase change from an ordered crystalline form to an isotropic liquid state. This process accelerates

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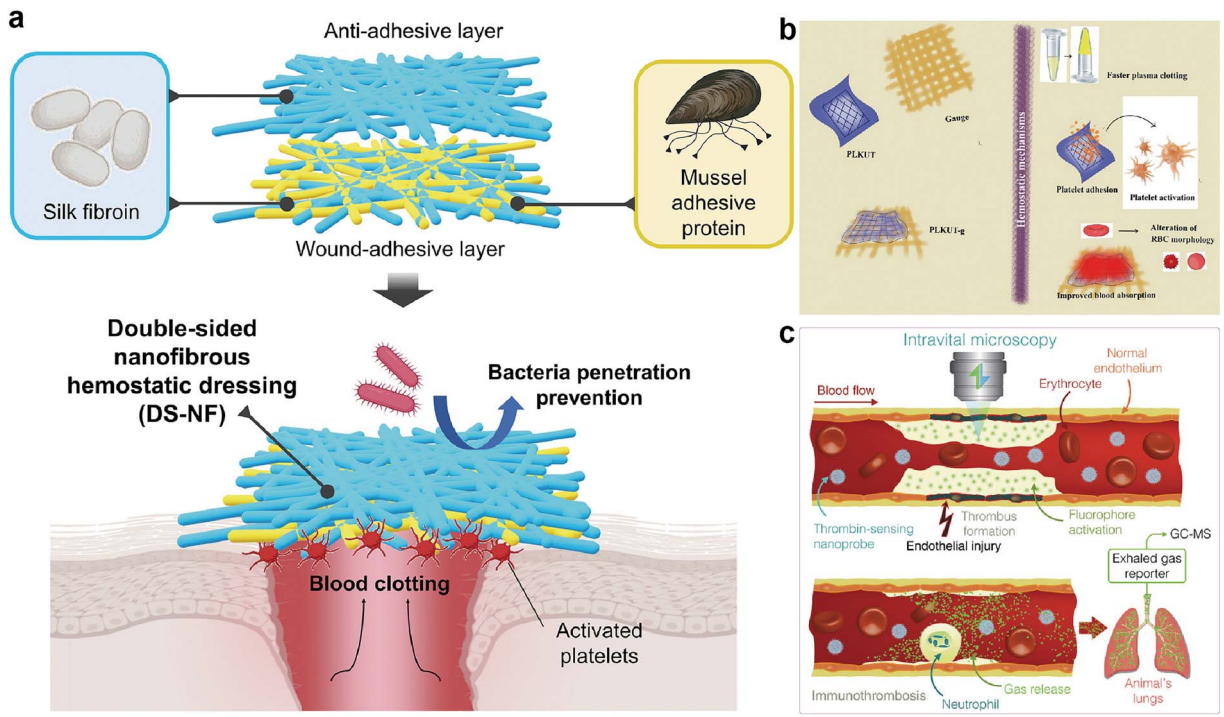


Figure 3 Schematic design and application of electrospun nanofibers and quantum dot labeling for real-time monitoring. (**a**) Application of a dual-sided nanofibrous hemostatic dressing (DS-NF) with wound-adhesive hemostatic inner MAP/SF-based layers and anti-adhesive outer SF-based layers at the bleeding site. Reproduced with permission [17]. Copyright 2024, John Wiley & Sons. (**b**) Proposed mechanism of hemostasis using ultrathin nanofiber composite on gauze. Reproduced with permission [73]. Copyright 2025, John Wiley & Sons. (**c**) Mechanism of nanoprobe detection of thrombin activity *in vivo*. Reproduced with permission [77]. Copyright 2023, John Wiley & Sons

the neutralization of heparin's anticoagulant effect by promoting the release of free PA molecules. Conversely, visible light (Vis) irradiation reverses this transition, re-binding the PA molecules and enabling on-demand control of hemostatic activity. *In vitro* experiments showed that, compared to conventional PA powder, UV-activated PA-Azo-SDS reduced bleeding volume by 37.9% and the coagulation index (BCI) by 21% in a rat tail amputation model. Additionally, the material demonstrated excellent reusability and biocompatibility, with a hemolysis rate under 5% and a cell survival rate exceeding 95%. The release of PA could be modulated through alternating UV/Vis irradiation cycles, providing a precise, light-controlled solution for managing heparin overdose-related hemorrhage. Building on this approach, Wang *et al.* developed thermosensitive gels (F127-PLPS) and multifunctional hemostatic powders (PLPS) based on smart responsive materials (Figure 4b) [85]. PLPS is synthesized by grafting cationic polylysine onto porous starch granules, while F127-PLPS is created by mixing the PLPS with the commercially available thermosensitive polymer F127. PLPS demonstrated effective hemostatic action by preferentially adsorbing fibrinogen, thereby enhancing platelet adhesion and activation. In addition to maintaining the procoagulant properties inherent to PLPS, the F127-PLPS gel exhibits a temperature-sensitive response, transitioning to a gel at physiological temperatures. This feature makes it suitable for various clinical applications, such as hemostasis in femoral artery injuries and renal artery embolism. The design of this material highlights its potential for precision medicine and offers new insights into the development of intelligent, responsive hemostatic agents. Shang *et al.* introduced a water-sensitive collagen/tannic acid (CoITA) hemostatic powder, also based on smart responsive materials (Figure 4c) [86]. Through noncovalent cross-linking, this material can quickly self-gel in liquid environments, forming a hemostatic agent with enhanced adhesive properties. The interaction between collagen (Col) and tannic acid (TA) facilitates the immediate gelation of the CoITA powder, while its unique electrostatic interactions enhance binding to red blood cells, significantly improving hemostatic efficacy. Experimental results demonstrate that CoITA effectively closes complex bleeding wounds in rat models, including those in the liver, heart, and femoral artery. Ravishankar developed a cross-linked urea–chitosan hemostatic material using microwave technology (Figure 4d) [87]. The material's hemostatic properties and environmental stability are significantly enhanced by incorporating hydrophilic urea groups (NH_2-CO-NH-) into the chitosan chain and forming a carbamate bridge (-NH-COO-) cross-linked structure. In an arterial puncture model, this modified chitosan promoted rapid platelet aggregation, achieving hemostasis within 15 s and a remarkably low hemolysis rate of 0.15%. Its hydrophilic, cross-linked architecture improves interaction with blood components while maintaining stability across a broad range of pH and temperature conditions, making it suitable for rapid hemostasis in complex environments.

Wang *et al.* described a kaolinite–zeolite composite hemostatic gauze (KZG) with a cascade response mechanism at its core (Figure 4e) [88]. This innovative material combines the complementary effects of kaolin and zeolite at different stages of coagulation, mimicking the physiological coagulation cascade. Zeolite amplifies and assembles FXa and FVa to form a highly active prothrombin complex during the amplification and propagation stages, while kaolin rapidly activates coagulation

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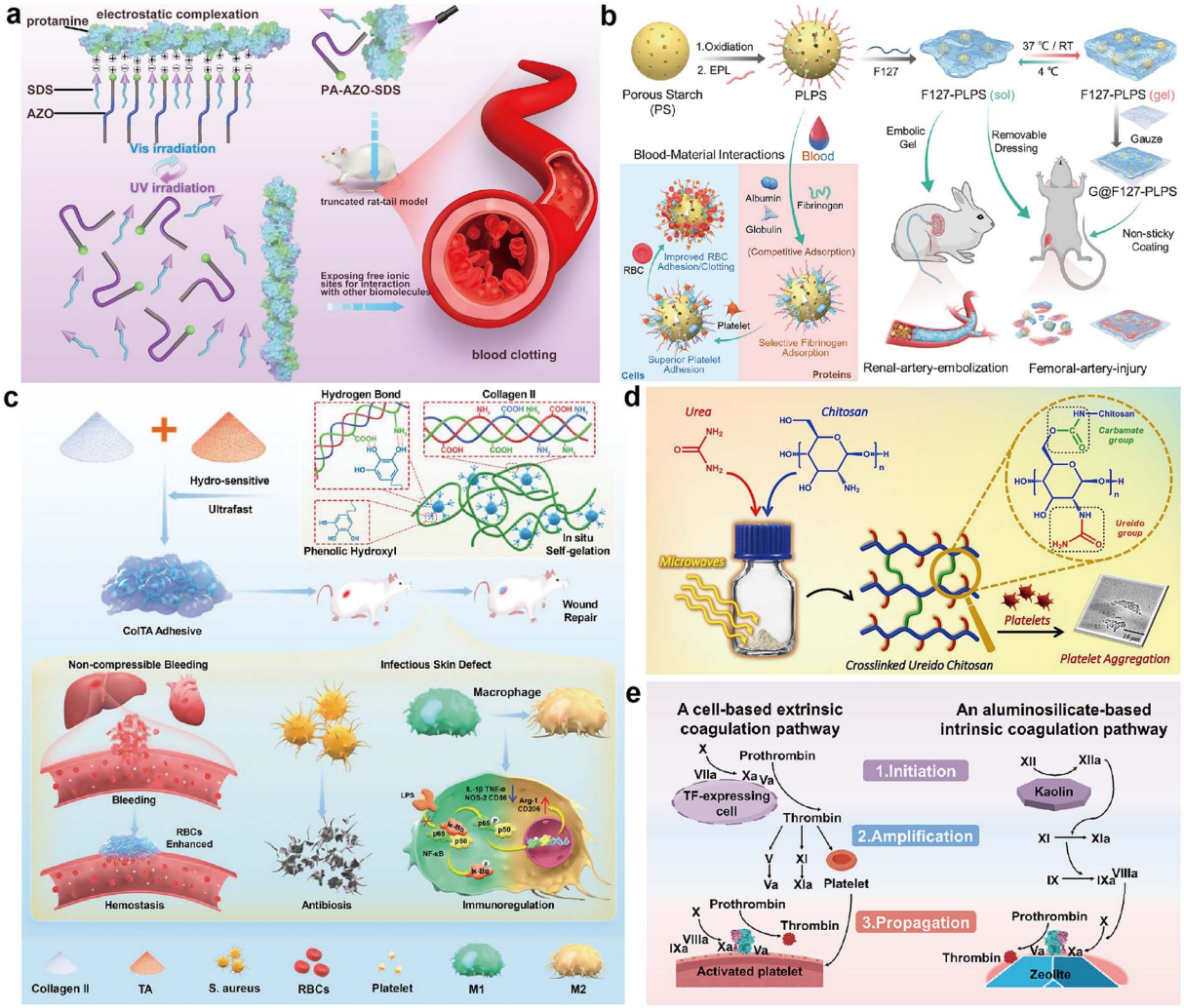


Figure 4 Schematic design and application of intelligent responsive materials. (**a**) Schematic illustration of the generic methodology for fabricating protamine-releasing material PA-AZO-SDS for rapid hemostasis. Reproduced with permission [84]. Copyright 2024, Elsevier. (**b**) Schematic illustration of the preparation of hemostatic PLPS particles (mechanism of procoagulant surfaces) and thermoresponsive F127-PLPS gels for versatile hemostatic applications. Reproduced with permission [85]. Copyright 2023, John Wiley & Sons. (**c**) Schematics of the hydro-sensitive, *in situ* ultrafast physical self-gelatinizing, red blood cell–strengthened ColTA hemostatic adhesive with antibiosis and immunoregulation properties for wound repair. Reproduced with permission [86]. Copyright 2023, John Wiley & Sons. (**d**) Schematic illustration of the microwave-assisted synthesis of crosslinked ureido chitosan. Reproduced with permission [87]. Copyright 2024, Elsevier. (**e**) Extrinsic coagulation system based on the cell surface and intrinsic coagulation pathway based on the inorganic material surface. Reproduced with permission [88]. Copyright 2024, American Chemical Society.
PA-AZO-SDS protamine with an azobenzene-containing surfactant, *TA* tannic acid

factor FXII via its negatively charged surface during the priming stage. This process significantly elevates FXIIa and FXa levels, boosting thrombin activity. In a rabbit femoral artery injury model, KZG reduced blood loss by 75% and shortened hemostasis time by 33% compared to Combat Gauze. Moreover, KZG effectively addressed issues of heat release and particle shedding that often arise with conventional inorganic hemostatic materials. The cascade response mechanism underlying this design offers valuable insights for developing safe and effective hemostatic agents.

By precisely regulating these reaction mechanisms, the hemostatic efficacy and functional capabilities of materials are greatly enhanced. Intelligent, responsive hemostatic materials are poised to evolve toward multi-modal responses [84, 86, 89], precise triggering [87, 90], and dynamic control [64], driven by the interdisciplinary integration of materials science and biomedicine. This progress will lead to safer and more efficient clinical bleeding treatments. Future research should focus on the collaborative integration of diverse response mechanisms to create the next generation of intelligent, flexible hemostasis systems.

Biomanufacturing and structural innovation

The development of intelligent hemostatic materials is closely intertwined with advances in fabrication technologies. Traditional manufacturing methods, which typically produce materials with homogeneous structures and uniform functionality, are inherently limited in their ability to replicate the complex, multi-scale hierarchy of native tissues or to encode the spatiotemporal complexity necessary for smart therapeutics. The advent of advanced biomanufacturing technologies has begun to overcome these

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limitations, marking a shift from passive material production to the active design of bio-instructive structures. This section examines how 3D printing, microfluidic-assisted design, and their emerging convergence are driving a new frontier in hemostatic material innovation, offering unparalleled control over form and function from the macro- to the nanoscale [26].

3D printing technology has evolved from being a prototyping tool to a critical platform for producing hemostatic devices with biomimetic complexity and personalized geometries. Its key strength lies in the digital control of material deposition, enabling the creation of structures that actively manage the biological processes of clotting and healing. Zhang *et al.* demonstrated this potential by 3D-printing a cuttlefish bone elastomeric sponge (CBES) (Figure 5a) [91]. This method allowed for the precise integration of bioactive cuttlefish bone powder (CBp) and the design of a porous network that mimics the rapid wicking action of natural extracellular matrices. As a result, the material achieved complete liquid absorption in 4 s and reduced clotting time by 60% in a rat liver model. Moving beyond static scaffolds, Wu *et al.* developed a dynamic, liquid-impregnated 3D-printed patch by infusing a porous polymer mesh with a hydrophobic liquid (Figure 5b) [92]. This design exemplifies structural intelligence: upon application to a bleeding site, mechanical pressure expels the liquid, displacing blood and moisture to allow a tissue adhesive to form a rapid, robust bond (within 10 s) with the wound bed. This mechanism effectively mirrors nature's strategy for achieving adhesion in wet, dynamic environments, making it suitable for sealing challenging injuries such as femoral artery transections. The pinnacle of architectural control in hemostatic materials is demonstrated by Zhou *et al.*, who 3D-printed a Gel-Okra@PNS hemostatic sponge with meticulously engineered fiber arrangements and a multi-scale porosity gradient (Figure 5c) [93]. This structure functions as an active, instructive scaffold, not just a passive dressing. Its optimized pores concentrate coagulation factors to accelerate clotting, while its mechanical flexibility allows for conformal contact with deep wounds. Additionally, the controlled architecture facilitates the spatially guided release of both hemostatic (okra mucus) and regenerative (PNS) agents, orchestrating a sequential healing program that integrates rapid hemostasis with tissue repair.

While 3D printing governs the macroscopic domain, microfluidic technology dominates the microscopic world of hemostasis. This platform offers two significant advantages: the precise engineering of material components and the replication of physiological microenvironments for predictive testing, bridging essential gaps in material design. Li *et al.* leveraged the first advantage by developing a double-layer microfluidic filtration system for high-throughput, size-based sorting of kaolin micro/-nanosheets [94]. This approach addresses the issue of batch-to-batch variability in natural clays by generating monodisperse fractions. Notably, it demonstrated that smaller kaolin particles (e.g. Kaol-3 at $\sim$0.377 μm), with their increased surface area and charge density, exhibit significantly enhanced hemostatic efficacy. This work emphasizes that precise control over a material's physical parameters directly optimizes its biological performance. Microfluidics also excels as a biomimetic testing platform. Yin *et al.* used a microfluidic chip to replicate vascular flow conditions and optimize a gelatin–tannic acid (Gel-TA) hydrogel for arterial puncture hemostasis [95]. This *in vitro* optimization produced a hydrogel with outstanding mechanical strength (>86.0 kPa) and underwater adhesion (>4.9 kPa), which translated into successful hemostasis *in vivo* with a Gel-TA-coated needle. This paradigm illustrates how microfluidics can streamline development by providing physiologically relevant performance data before costly animal studies, enhancing the efficiency and predictability of the bench-to-bedside translation process.

The true frontier of biomanufacturing lies not in isolated applications of these technologies but in their integration [96]. The future envisions hybrid manufacturing platforms where microfluidics is used to engineer sophisticated, multi-component bio-inks—such as hydrogels loaded with growth factors or nanoparticle assemblies—whose properties are validated on-chip [97, 98]. These optimized bio-inks would then be seamlessly processed by 3D printers to create macroscopic devices with spatially organized biochemical and mechanical cues. This multi-scale manufacturing approach would enable the creation of holistic hemostatic solutions that can, for example, replicate the layered structure of a blood vessel wall or develop bandages that simultaneously control bleeding, release antibiotics, and recruit regenerative cells to underlying tissue layers. Although challenges in scalability, processing speed, and material compatibility remain, the trajectory is clear: the integration of biomanufacturing technologies is poised to unlock a new generation of intelligent, adaptive hemostatic materials, personalized to the patient's anatomy and the specific pathophysiology of their wound [99, 100].

Biological hybridization and interdisciplinary applications

Genetically engineered biological materials

Recent advancements in genetic engineering have significantly accelerated the functional design of biomaterials. Traditional hemostatic materials generally rely on passive mechanisms, such as the activation of coagulation pathways or physical occlusion. However, in complex scenarios like anticoagulant therapy, their efficacy is often limited.

Through genetic engineering, Lee *et al.* developed a hemostatic material with a biomimetic porous structure [49]. They replicated the efficient material exchange properties of alveoli by optimizing the pore architecture using molecular simulation techniques. For the first time, mechanistic research at the genetic level demonstrated that chitosan could selectively activate the platelet TLR2 receptor, triggering the Ca^{2+} signaling pathway and initiating a hemostatic mechanism independent of traditional coagulation pathways. This novel design, targeting genetically modified receptors, enabled sustained hemostatic activity even under anticoagulant conditions. Animal studies showed that the material could halt severe bleeding within 3 min, and clinical trials indicated a reduced hemostasis time following radial artery puncture, averaging 5.56 ± 1.36 min. These findings highlight the advantages of genetic engineering in biomaterial functional design, particularly in precisely controlling material–biomolecule interactions to achieve desired therapeutic outcomes. Beyond modifying natural polymers like chitosan, genetic engineering facilitates the creation of entirely new protein biomaterials with bespoke functions. A groundbreaking 2025 study highlighted this potential by designing a recombinant fusion protein (rhCR) that combines human-derived collagen with the self-assembling peptide RADA-16 [101]. Under physiological conditions, this

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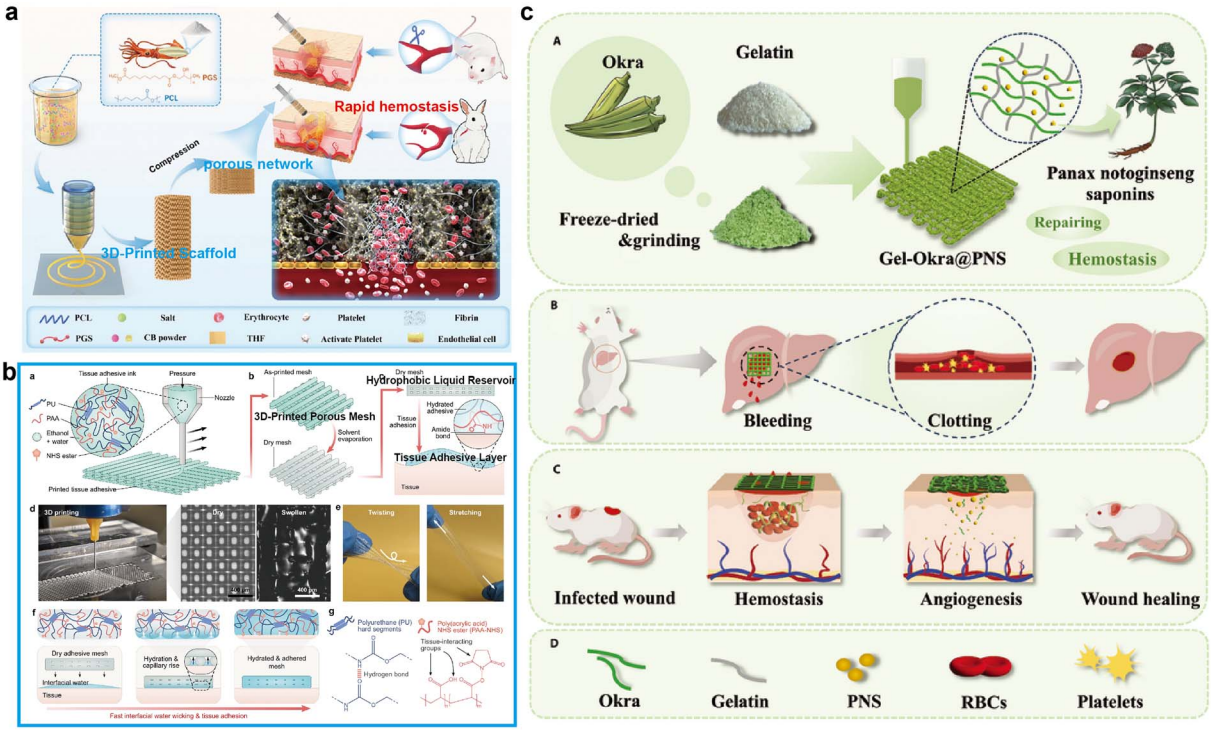


Figure 5 Schematic design and application of 3D printing technology. (**a**) Schematic diagram showing the preparation and application of cuttlefish bone elastomeric sponges. Reproduced with permission [91]. Copyright 2023, John Wiley & Sons. (**b**) Fabrication and adhesion of 3D-printable tissue adhesive. Reproduced with permission [92]. Copyright 2024, Springer Nature. (**c**) Schematic illustration of the preparation of PNS-loaded okra-gelatin gel scaffold (Gel-Okra@PNS) by 3D printing for liver hemostasis and skin wound repair. Reproduced with permission [93]. Copyright 2024, American Association for the Advancement of Science. *PCL* polycaprolactone, *PGS* poly-(glycerolse-bacate), *THF* tetrahydrofuran, *PNS* panax notoginseng saponins

engineered protein spontaneously assembles into a 3D nanofibrous network, structurally mimicking the native ECM. The resulting scaffold demonstrated superior hemostatic properties and significantly accelerated wound healing by providing an optimal biomimetic interface for cell adhesion, proliferation, and migration. This represents a powerful strategy for developing multifunctional hemostatic agents at the molecular level.

In biomedical engineering, the rise of genetically modified biomaterials marks a paradigm shift from "passive adaptation" to "active regulation." In the near future, the integration of synthetic biology and computer simulation technologies is expected to enhance the precision of functional programming in areas like drug delivery, tissue regeneration, and hemostasis [102, 103]. This development is anticipated to drive significant progress in regenerative and personalized medicine.

Artificial intelligence and military medicine

Coagulation function testing has undergone significant breakthroughs with the integration of biomedical engineering and AI technology [104, 105]. Traditional coagulation analysis methods, which rely on large laboratory equipment, are steadily being replaced by more intelligent and compact solutions [106, 107].

Chen *et al.* introduced an AI-assisted diagnostic approach for coagulation function based on optical coagulation biophysics (OCB) feature recognition (Figure 6a) [105]. This innovative method utilizes a customized, ultra-portable optical flow imaging system, smartphone, and cloud computing to continuously capture coagulation images and spatial-temporally adjust OCB characteristic analysis. Deep learning models enable high-precision coagulation function diagnosis by eliminating initial discrepancies through image difference computations. In a prospective clinical trial involving 41 patients, the accuracy of this method in identifying coagulation factors, fibrinogen function, and complete coagulation function was found to be 97.6%, 95.1%, and 100%, respectively. This approach represents a promising new method for diagnosing coagulation functions due to its low cost, portability, and broad clinical applicability.

The development of intelligent coagulation detection technologies marks a key step toward achieving both accuracy and mobility in medical diagnostics. By combining AI with optical biophysics, this technology not only improves detection precision and efficiency but also overcomes the time and location limitations inherent in traditional diagnostic techniques. As mobile health technologies continue to evolve and integrate with the Internet of Things, they are expected to play an increasingly pivotal role in emergency treatment, home health monitoring, and healthcare delivery in remote locations. This advancement promises to provide innovative technical support for the equitable distribution of medical resources globally [105, 108].

In the fields of space and military medicine, treating trauma in extreme environments has long been a significant challenge. These conditions place considerable strain on conventional hemostatic methods, whether in the complex climates of battlefields or the harsh environments of space, including radiation and weightlessness. There is an urgent need for hemostatic materials that can overcome technical limitations such as inadequate temperature tolerance, difficulty accessing deep wounds, and the potential for secondary harm. Addressing these issues is critical to meet the medical rescue needs of deep space exploration and future conflicts [109]. The development

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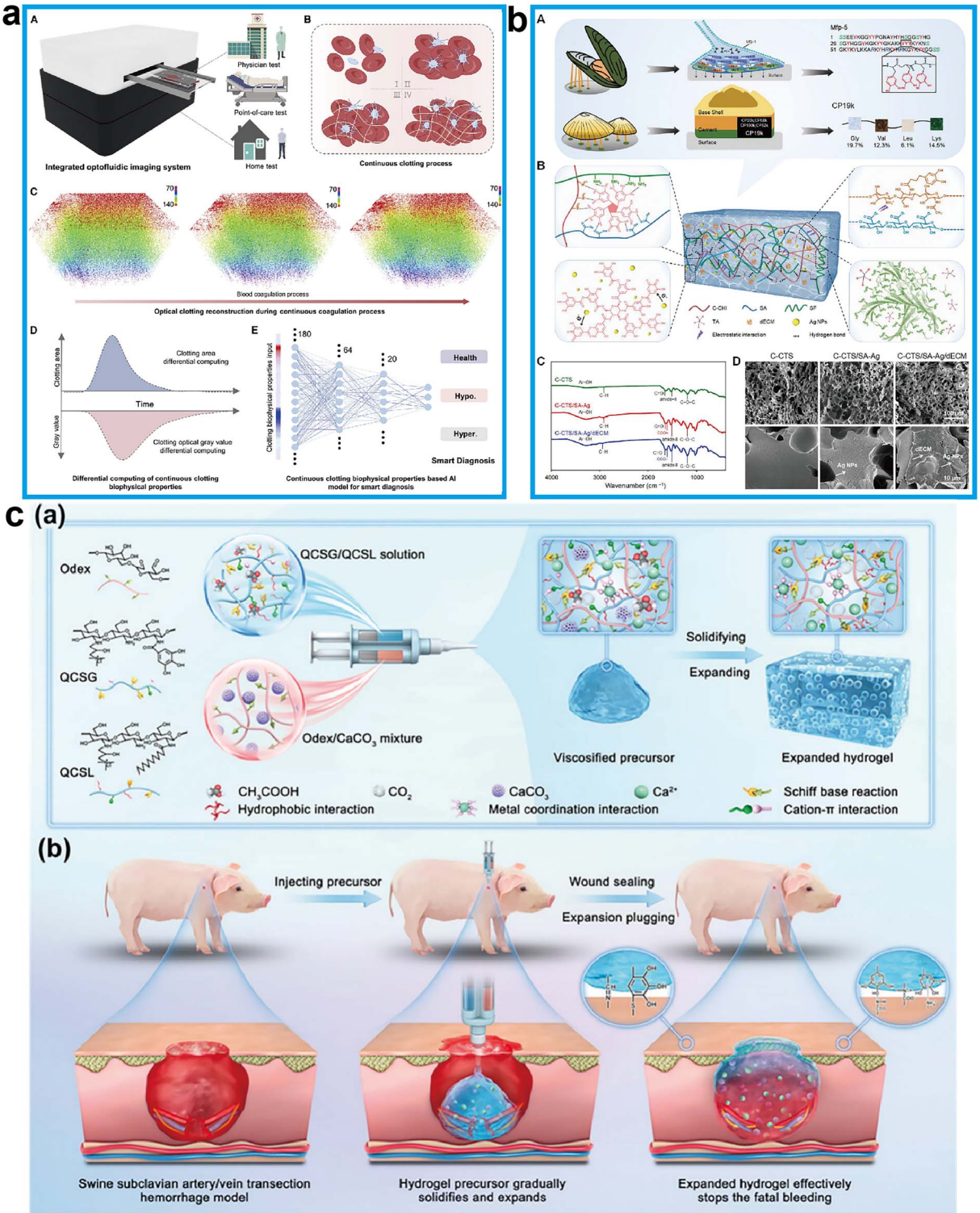


Figure 6 Schematic design and application of AI and military medicine. (**a**) Working principle and application scenarios of the system. Reproduced with permission [105]. Copyright 2022, Elsevier. (**b**) Structural and physical properties of hydrogels composed of different components. Reproduced with permission [110]. Copyright 2022, John Wiley & Sons. (**c**) Schematic illustration of the preparation of an injectable, self-expanding, and self-propelling hydrogel adhesive. Reproduced with permission [111]. Copyright 2024, John Wiley & Sons. *QCSG* gallic acid-modified quaternized chitosan, *QCSL* lauric acid-modified quaternized chitosan

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of hemostatic materials tailored to these specific applications is advancing rapidly, enhancing both environmental adaptability and functional intelligence.

Extreme temperature fluctuations in battlefield and polar environments directly threaten the stability of coagulation factors and the viability of hemostatic materials. To address this challenge, Jia *et al.* developed a hierarchical bilayer gauze (AWNSA@G) that integrates temperature management with hemostatic function [14]. The material features an aerogel layer for thermal insulation and a phase-change material layer that buffers against both high (70°C) and low (−27°C) temperature extremes. This design not only offers passive protection but also maintains a permissive microclimate at the wound site, preserving the activity of endogenous coagulation factors that are typically inactivated under such conditions. Tested in controlled laboratory environments simulating these temperature extremes, the material's ability to stabilize the wound microenvironment represents a significant step toward real-world deployment in arctic or desert warfare scenarios. Inspired by the adhesive proteins in barnacles and mussels, Pan developed a multifunctional bionic hydrogel [C-CTS/SA-Ag/decellularized ECM (dECM)] that combines the water-removal properties of barnacle glue proteins (SF/SA) with the wet adhesion mechanism of catechol groups (C-CHI/TA) (Figure 6b) [110]. This hydrogel demonstrated impressive performance with a wet tissue adhesion strength of 151.40 kPa and rapid self-healing, recovering within just 1 min. In animal models of arterial and visceral hemorrhage, including pig and rabbit models, the hydrogel showed notable hemostatic efficacy, achieving hemostasis within 14.29 s after heart puncture in rabbits. By promoting platelet aggregation and creating a mechanical barrier at the injury site, it achieved noncompressive hemostasis. Additionally, when combined with dECM, the hydrogel significantly improved wound healing outcomes. It was also demonstrated to stop bleeding quickly in deep trauma cases, such as the porcine clavicular artery, where bleeding was controlled in just 32.67 s, suggesting its potential for both clinical severe hemorrhage management and battlefield first aid. To address potentially fatal massive hemorrhages, Zhao *et al.* developed an injectable, self-expanding, and self-propelling hydrogel adhesive (OD-C/QGQL-A30) (Figure 6c) [111]. This hydrogel features rapid gelation, antibacterial properties, antioxidant effects, and procoagulant activity. Through spontaneous gas foaming and rapid Schiff base cross-linking, the hydrogel expands and propels quickly, allowing it to efficiently reach deep bleeding sites and form a strong bond with wounds. In various animal models of bleeding—such as rat liver and femoral artery hemorrhages, rabbit liver major bleeding, and pig subclavian artery and vein transection injuries—this hydrogel outperformed standard hemostatic materials. Furthermore, it demonstrated biocompatibility and biodegradability. These results point to a novel approach for treating lethal bleeding in both civilian and combat situations.

The development of hemostatic materials is being reshaped by the unique demands of space and military medicine. Future advancements must incorporate precise delivery systems, multifunctional integration, and intelligent response mechanisms, alongside ensuring stability in extreme environments [112]. These innovations will significantly enhance emergency response capabilities in both space healthcare and battlefield medical settings. Furthermore, they will pave the way for a new generation of intelligent medical systems that will support human exploration of deep space and provide essential medical assistance in safeguarding national security. In this context, the integration of interdisciplinary technologies is poised to drive key advancements in space and military medicine.

Clinical challenges and future perspectives

Hemostatic materials have evolved through three generations, each marked by distinct advancements. To assess the clinical relevance of these developments, their performance has been compared to commercially available hemostatic materials across various rat models, illustrating a clear trajectory of improvement (Figure 7A–c) (Table 1). The first generation, developed prior to the mid-twentieth century, relied on physical compression and passive hemostasis mechanisms. Examples like cotton pads and conventional gauze were simple to use but offered limited efficacy [112]. The second generation, emerging in the late twentieth and early twenty-first centuries, introduced bioactive agents such as fibrin glue and chitosan-based compounds [6], significantly enhancing hemostatic efficiency through chemical coagulation processes. Since 2010, the third generation of hemostatic materials has been characterized by multi-mechanism cooperation and intelligent reactivity [113]. Innovations like thermostatic hydrogels and nano-hemostatic agents allow for precise control of hemostasis, dynamically adapting to specific bleeding conditions. To further explore the progress in this field, VOS-Viewer was utilized to create visualization and analysis charts based on over 1000 papers from Web of Science published in the last 3 years. These charts confirmed the strong research and application momentum in hydrogels, nanoparticle technologies, and platelet-related materials (Figure 7d and e).

The clinical translation of hemostatic biomaterials remains a prolonged and high-risk process. Quantitative data from related fields offer a sobering perspective: the path from laboratory discovery to clinical approval typically spans 10–15 years, with an overall success rate of $<$10% for investigational agents entering clinical trials [114, 115]. Although many advanced hemostatic materials are still in preclinical or early clinical trial phases, some representative studies highlight their potential clinical application, albeit with associated risks. For instance, a study of the chitosan-based hemostatic dressing Axiostat® in 120 patients undergoing endovascular procedures reported a primary technical success rate of 91.7% and a mean time-to-hemostasis of 8.9 ± 3.9 min. However, bleeding-related vascular access complications occurred in 5.8% of patients [116]. Another systematic review and meta-analysis of topical hemostatic agents in liver surgery, involving 22 studies with over 1200 patients, found that while carrier-bound fibrin sealants significantly reduced time to hemostasis, they did not decrease the risk of blood transfusions, postoperative collections, or bile leaks [117]. These findings highlight an important clinical reality: while advanced hemostatic materials may improve surrogate endpoints like time to hemostasis, they do not necessarily translate into improvements in more critical clinical outcomes such as transfusion needs or postoperative complications.

This stark reality indicates the specific and interconnected challenges that must be addressed. Hemostatic materials intended for systemic administration or long-term implantation must precisely manage the risks of thrombosis, inflammatory responses, and

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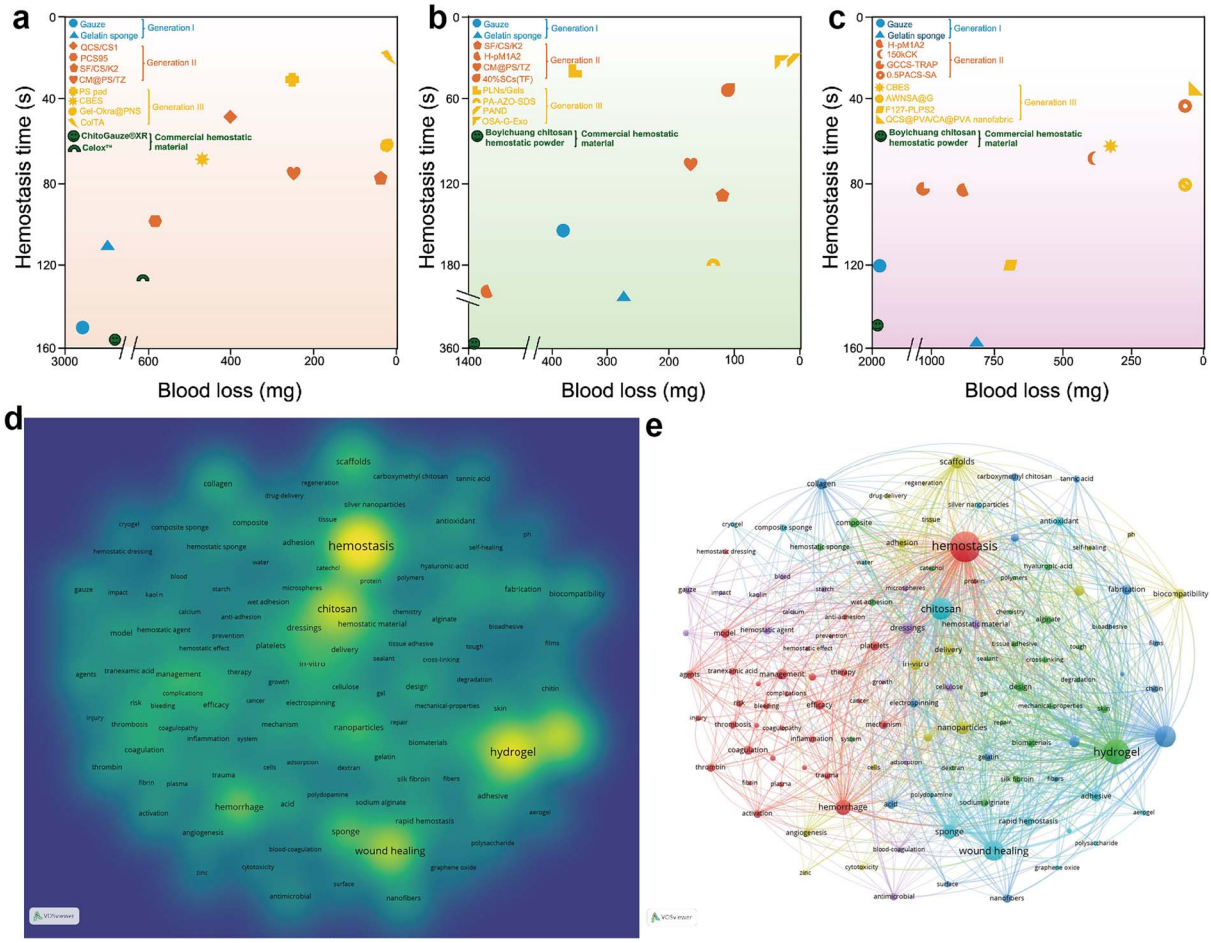


Figure 7 Ashby diagrams of different rat models of hemostasis and visual analysis of literature on hemostatic materials. (**a**-**c**) Ashby plots comparing time to hemostasis (*x*-axis) and blood loss (*y*-axis) for various hemostatic materials in rat liver puncture (a), tail amputation (b), and femoral artery injury (C) models. (**d**, **e**) Density visualization (d) and network visualization (e) analyses of over 1000 publications on hemostatic materials from Web of Science, generated using VOSviewer

immunological rejection to ensure biocompatibility and safety [118, 119]. For example, nanoparticles or bionic platelets used in third-generation materials may accumulate in the body due to incomplete metabolic processes, potentially leading to persistent toxicity [120, 121]. Similarly, the degradation performance and biocompatibility of inorganic hemostatic agents, such as zeolite or kaolin, must be urgently improved to prevent tissue damage caused by particle shedding or local heating effects. The production of complex materials like bionic platelets and smart hydrogels at a large scale typically involves precision techniques, such as electrospinning and 3D printing, or multi-step chemical processes [122]. The stability and cost-effectiveness of their industrial manufacturing processes remain key challenges, with factors such as drug loading efficiency and nanoparticle size distribution complicating the replication of laboratory results in large-scale production [99, 123]. These challenges affect all advanced material platforms, but their manifestations vary depending on the underlying technology. As summarized in Table 2, bionic designs face risks related to thrombosis and immunogenicity, nanotechnology platforms encounter difficulties in scalable manufacturing and long-term biosafety, while intelligent materials struggle with undefined regulatory pathways for their smart functions. The following sections will explore these interrelated challenges in greater detail.

Another notable challenge is clinical adaptation. Patients with conditions such as coagulation disorders or those undergoing anticoagulant therapy often exhibit distinct bleeding mechanisms. Current materials are frequently insufficient in meeting these specific needs. For instance, hemophiliac patients require coagulation factor supplements, while individuals receiving heparin therapy require specialized antagonistic materials [124, 125]. The demand for adaptable hemostasis solutions is further emphasized by the extreme environmental conditions, such as weightlessness in space or high temperatures on the battlefield, which challenge material stability. Additionally, frameworks for standards and regulations are still in their nascent stages. There is a lack of unified clinical evaluation standards for new smart materials that incorporate optical or magnetic responses [99], and the absence of long-term safety data could delay the regulatory approval process [5]. Furthermore, notable discrepancies exist between human coagulation mechanisms and those of animal models, such as rodents.

Regulatory considerations

The clinical translation of advanced hemostatic materials involves navigating a complex regulatory landscape, which extends beyond scientific and technical challenges [112].

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Table 1 Evaluation of the efficacy of various generations of hemostatic materials in distinct rat hemostatic models

Model	Generation	Materials	Hemostasis time (s)	Blood loss (mg)	Reference
Rat liver	I	Gauze	150.44 ± 8.22	2380 ± 200	[34]
		Gelatin sponge	113.44 ± 8.22	1710 ± 160	[34]
	II	QCS/CS1	48 ± 10.23	400 ± 90	[127]
		PCS95	104 ± 11	600 ± 100	[18]
		SF/CS/K2	79.33 ± 5.44	53.33 ± 12.47	[128]
		CM@PS/TZ	75.42 ± 6	250 ± 110	[129]
	III	PS pad	≈30	≈250	[35]
		CBES	67 ± 0.6	460 ± 60	[91]
		Gel-Okra@PNS	≈60	≈37.5	[93]
		ColTA	20	30	[86]
	Commercial hemostatic material	ChitoGauze®XR	≈160	≈1300	[18]
		Celox™	≈125	≈900	[18]
Rat rail	I	Gauze	163.43 ± 14.09	390 ± 20	[129]
		Gelatin sponge	215.55 ± 26.84	276.20 ± 23.06	[130]
	II	SF/CS/K2	128.67 ± 15.52	111.67 ± 6.50	[128]
		H-pM1A2	208	1140	[131]
		CM@PS/TZ	103.96 ± 11.12	160 ± 30	[129]
		40%SCs (TF)	≈55	≈100	[132]
	III	PLNs/Gels	35 ± 5.37	370 ± 50	[34]
		PA-AZO-SDS	≈180	≈130	[84]
		PAND	32	16.7	[64]
		OSA-G-Exo	34.6 ± 2.5	40.33 ± 3.06	[133]
	Commercial hemostatic material	Boyichuang chitosan hemostatic powder	≈360	≈1400	[131]
Rat femoral artery	I	Gauze	≈120	≈2000	[91]
		Gelatin sponge	≈162	≈800	[134]
	II	H-pM1A2	82.8	870	[131]
		150kCK	≈66	≈400	[134]
		GCCS-TRAP	81.3	1030	[135]
		0.5PACS-SA	41	65	[136]
	III	CBES	≈60	≈300	[91]
		AWNSA@G	80	65.5	[14]
		F127-PLPS2	≈120	≈700	[85]
		QCS@PVA/CA@PVA nanofabric	38	18.56	[137]
	Commercial hemostatic material	Boyichuang chitosan hemostatic powder	≈150	≈2000	[131]

Regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) classify products based on their primary mode of action—medical devices, biologics, or combination products. This classification process becomes particularly complicated for multifunctional systems like stimulus-responsive hydrogels or nanoparticle-based hemostats, whose hybrid mechanisms may fall into ambiguous regulatory categories, complicating the approval pathway. A major challenge lies in standardizing the evaluation of "smart" functions. For materials designed to respond to specific physiological cues, regulators require robust, reproducible methods to quantify their stimulus-responsive behavior across production batches. In addition, comprehensive safety data—beyond standard biocompatibility tests—are necessary [21]. This includes detailed profiles of material degradation, metabolic clearance pathways, and the long-term fate of components to mitigate risks of chronic toxicity or unintended thrombosis [57]. To address these needs, developers should adopt a "quality-by-design" approach, ensuring product consistency from the early development stages. The use of predictive preclinical models, such as human-relevant organ-on-a-chip systems simulating vascular injury and coagulation, can provide more translatable safety and efficacy data. Ultimately, early and proactive engagement with regulatory bodies is essential to define appropriate pathways and accelerate the clinical adoption of these innovative hemostatic therapies.

Health economics and clinical value

The successful translation of advanced hemostatic materials also requires careful consideration of their economic impact, extending beyond initial production costs. While sophisticated biomaterials like engineered platelets and smart hydrogels entail higher manufacturing costs compared to conventional

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Table 2 Comparative analysis of advanced hemostatic material technology platforms

Aspect	Bionic design	Nanotechnology	Intelligent responsive materials
Core principle	Mimicking the structure and function of natural hemostatic components (e.g. platelets, fibrin)	Leveraging unique nanoscale effects (e.g. high surface area, targeting)	Responding dynamically to external/internal stimuli (e.g. light, temperature, pH, enzymes)
Key advantages	• High biocompatibility • Synergy with physiological mechanisms • Strong targeted affinity	• High drug-loading capacity and protection • Ability to penetrate complex biological barriers • Precise spatiotemporal control	• On-demand activation/termination of function • Reduced off-target effects, enhanced safety • Multi-functional integration (hemostasis, antibacterial, healing)
Major limitations	• Relatively static functionality and limited dynamic responsiveness • Risk of thrombosis from over-simulation • Storage and immunogenicity concerns for live cell–derived materials	• Unclear long-term biosafety and *in vivo* metabolic pathways • Difficult large-scale manufacturing, batch-to-batch variability • Potential nanotoxicity	• Response logic may be too simplistic for complex *in vivo* environments • Complex material design and control systems • Lack of regulatory standards and long-term safety data
Representative technologies	Bionic platelets, microenvironment-responsive hydrogels, peptide self-assembly	Nanoparticle delivery systems, electrospun nanofibers, quantum dot probes	Light/thermal/magnetic-responsive hydrogels, cascade-response materials, self-healing materials
Clinical translation challenges	• Demonstrating significant advantages over conventional products • Rigorous assessment of immunogenicity and thrombotic risk	• Meeting pharmaceutical-grade GMP production and quality control • Comprehensive toxicology and pharmacokinetic studies	• Defining and validating clinical endpoints for “smart” functions • Unclear regulatory pathways, potentially longer approval cycles

agents, their clinical benefits may justify the investment through improved patient outcomes and reduced complications. These advanced systems offer distinct economic advantages by addressing key cost drivers in surgical and trauma care. Targeted hemostatic materials can minimize blood loss, reduce transfusion requirements, and shorten operative time. Smart dressings, which prevent infection and promote healing, may shorten hospital stays and reduce the need for costly reoperations [126]. Additionally, the integration of monitoring capabilities enhances their value by enabling early intervention before complications arise. A comprehensive economic evaluation should consider the entire clinical pathway. While the initial acquisition cost of innovative materials may be higher, savings from avoided complications, reduced resource utilization, and improved long-term recovery could offset these costs. Future studies should include detailed cost-effectiveness analyses to provide robust evidence for healthcare decision-makers, positioning these technologies not as incremental costs but as valuable investments in patient care quality and system efficiency.

Future perspectives

The next phase of hemostatic biomaterials will involve a shift from single-mechanism solutions to integrated theranostic systems. These fourth-generation materials will combine real-time biosensing with autonomous therapeutic responses, creating closed-loop platforms that dynamically manage the wound microenvironment. The convergence of AI and biomanufacturing will enable patient-specific designs tailored to individual coagulation profiles and anatomical needs. Simultaneously, engineered living materials, incorporating synthetic biology circuits, represent a frontier for adaptive, self-renewing hemostatic constructs. Realizing this potential requires simultaneous advancements in standardized evaluation frameworks for intelligent functions and prospective trials that include health economic endpoints. The success of this next generation will ultimately depend on sustained interdisciplinary collaboration—from fundamental materials science to clinical implementation—to ensure these sophisticated technologies lead to measurable improvements in both patient outcomes and healthcare system efficiency.

Conclusions

The field of hemostatic biomaterials is progressing at an exceptional rate, fueled by the integration of biomimetic design, nanotechnology, intelligent responsiveness, and advanced biomanufacturing. Future breakthroughs are expected to arise from the synergy of AI, genetic engineering, and patient-specific diagnostic tools, paving the way for a transition from passive hemostasis to active tissue regeneration and from universal solutions to personalized therapeutic systems. These innovations have the potential to revolutionize trauma and surgical care globally, delivering safer, more efficient, and adaptable hemostatic solutions.

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Author contributions

Minrui Ji (Data curation, Formal analysis [equal], Investigation, Methodology, Writing—original draft [lead]), Zaixin Yuan (Data

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curation, Software, Validation [equal]), Fei Ju (Data curation, Investigation, Methodology [equal]), Jie Sun (Methodology, Validation [supporting]), Yingying Yan (Investigation, Methodology, Validation [supporting]), Qi Ding (Methodology, Validation [supporting]), Jinling Chen (Resources [equal], Software, Validation [supporting], Visualization [lead]), Qian Qian Yang (Methodology, Resources, Validation [supporting], Project administration [lead]), and You Lang Zhou (Conceptualization, Funding acquisition, Supervision, Writing—review & editing [lead], Project administration [equal])

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Conflicts of interest

None declared.

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