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Perspective

Smart Biomaterials in Regenerative and Antimicrobial Medicine: A Forward-Looking Perspective

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Abstract: Biomaterials have progressed from passive structural supports to dynamic therapeutic platforms with multi-functions that actively regulate biological processes. Modern smart biomaterials integrate antimicrobial, immunomodulatory, and regenerative functions to foster optimal healing environments. Innovations such as advanced hydrogels and electrospun nanofibers, enhanced with biological agents, effectively resolve inflammation, promote angiogenesis, and suppress biofilms. Composite scaffolds with controlled stiffness and spatial delivery of growth factors are redefining bone and cartilage repair. Smart biomaterials enhance implanted devices by responding to biological signals and improving tissue integration. They can adapt to body conditions, release drugs when needed, and resist infection—reducing rejection and promoting faster healing. Antimicrobial biomaterials now emphasize infection-triggered activity, reducing cytotoxicity and resistance. Immune coordination is increasingly recognized as essential for clinical success. Addressing challenges in safety, cost, and scalability will enable smart biomaterials to serve as therapeutic systems, accelerating tissue repair in both acute and chronic settings.

Keywords: smart biomaterials; wound healing; antimicrobial biomaterials; bone regeneration; cartilage regeneration; immunomodulation; bioactive scaffolds; infection-responsive materials

1. Introduction

Biomaterials are natural or synthetic substances, which are designed to interact with biological systems for therapeutic or diagnostic purposes. Their applications span tissue replacement, regenerative medicine, drug delivery, biosensing, and antimicrobial therapy. Ideal biomaterials should fulfill multiple criteria, encompassing biocompatibility, biofunctionality, mechanical integrity, sterilizability and manufacturability, and long-term stability in physiological environments. Modern research integrates materials science, cell biology, nanotechnology, and clinical medicine to enable safe and functional interfaces between engineered materials and living tissues. Biomaterials are classified according to their composition and function (Table 1):

Table 1. Classification of biomaterials and their medical applications.

Material Type	Application	Reference
Titanium alloys	Orthopedic implants	[1]
Bioactive glass	Bone coatings	[2]
PLGA	Drug delivery	[3]
GelMA hydrogel	Wound healing	[4]
Polymer-ceramic composites	Bone scaffolds	[5]

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Table 1. *Cont.*

Material Type	Application	Reference
Graphene	Biosensing	[6]
Shape-memory polymer	Smart implants	[7]
Silk fibroin	Tissue scaffolds	[8]

PLGA = poly(lactic-co-glycolic) acid; GelMA = gelatin methacryloyl.

Biomaterials have transitioned from passive structural supports to dynamic therapeutic systems engineered to coordinate tissue repair. Such advancements are indicative of a move towards "smart" materials that interact with the physiological wound site and modulate critical cell processes. For the treatment of diabetic ulcers, musculoskeletal defects and implant-associated infections traditional dressings [9], orthopedic implants [10], and continuously antimicrobial coatings have their inherent limitations [11]. These conditions typically accompany chronic inflammation, vascular deficiency and biofilm overgrowth emphasizing the requirement for adaptive therapy in biomaterials [12]. Antimicrobial therapy, regenerative medicine, and immunomodulation now converged to reshape the future of biomaterials. The design of smart biomaterials aims to modulate immune responses, prevent, or disrupt infection, and facilitate tissue regeneration.

This perspective highlights recent progress and emerging opportunities at the intersection of wound repair, musculoskeletal regeneration, and antimicrobial biomaterials, three pillars of medical applications. Bioactivity, immunomodulation, and infection response, three central requirements for successful tissue repair, will be elaborated. By perusing shared mechanisms across these areas, this article outlines the conceptual and translational directions to define the future endeavors of biomaterials research.

2. Antimicrobial Biomaterials

Persistent infections, particularly those involving biofilms and multidrug-resistant pathogens, remain major barriers to successful tissue repair [13]. Traditional antimicrobial strategies rely on systemic antibiotics or continuous ion release from metallic coatings, which may provide temporary pathogen suppression but often contribute to cytotoxicity, microbiome disruption, and antimicrobial resistance [14]. Smart antimicrobial biomaterials are tailored to activate antibacterial mechanisms only when infection-specific biochemical cues are present, thereby improving safety and efficacy.

2.1. Infection-Responsive Nanomaterials

Metal and metal-oxide nanomaterials such as silver, copper oxide, zinc oxide, and rare-earth oxides demonstrate strong antibacterial properties through membrane disruption, metabolic interference, and reactive oxygen species (ROS) generation [15]. ROS possess strong oxidation potential and target multiple sites in bacteria, causing double stranded breaks in bacterial DNA and peroxidating lipids, and carbonylated proteins. However, uncontrolled ion release may damage host tissues, limiting their clinical acceptance. Infection-responsive functionalization strategies, such as pH- or enzyme-triggered ion release, reduce nonspecific toxicity and allow antimicrobial action only under pathogenic conditions [16]. Based on intrinsic oxidase-like and catalase-like activity and comparatively low cytotoxicity, rare-earth oxide nanoparticles are emerging as promising candidates, making them attractive for chronic wounds and implant coatings.

2.2. Contact-Active and Anti-Adhesive Antimicrobial Polymers

Cationic polymers and polymer networks carrying quaternary ammonium or amine groups can impair bacterial membranes on contact without producing cytotoxic ion concentrations [17]. Cationic polymers and polymer networks incorporating quaternary ammonium or amine groups can rapidly kill pathogens via electrostatic and hydrophobic interactions with negatively charged bacterial membranes. Recent designs incorporate zwitterionic or hydrophilic motifs to minimize nonspecific protein adhesion and decrease biofilm initiation at the implant or wound surface [18]. These systems are particularly relevant for use in catheters, orthopedic implants, and wound dressings.

2.3. Anti-Biofilm Mechanisms

Biofilm formation is a critical clinical challenge because bacterial cells embedded in extracellular polymeric substances (EPS) exhibit reduced susceptibility to antibiotics and immune clearance [19]. Hybrid strategies combining physical disruption (e.g., nanotopography or shear-responsive surfaces) with chemical cues (e.g., nitric

oxide donors, ROS scavengers, or quorum-sensing inhibitors) are emerging to prevent or destabilize biofilms [20]. Stimuli-responsive antimicrobial release triggered by infection biomarkers rather than continuous release is another promising approach. These hybrid mechanisms facilitate localized and temporally controlled antimicrobial activity without disrupting the beneficial commensal microbiota.

2.4. Immunomodulatory Antimicrobial Platforms

Persistent infection and dysregulated inflammation often exhibit reciprocal reinforcement to prolong tissue damage and delay healing. Biomaterials incorporating anti-inflammatory agents or macrophage-regulating signals represent a promising dual-action strategy to control infection while creating a tissue repair-supportive microenvironment [21]. Inflammation control in wound healing and implant integration depends heavily on macrophage behavior, as these cells regulate the transition from inflammation to tissue repair. Biomaterials can influence macrophage activity through two complementary strategies: passive immunomodulation and active targeting [22].

(1) Passive biomaterials rely on their intrinsic physical and chemical properties—including size, shape, stiffness, and surface chemistry—to influence immune responses. For example, surfaces with optimized stiffness or topography can reduce pro-inflammatory cytokine release and encourage macrophage polarization toward the M2 (pro-regenerative) phenotype. Such materials modulate inflammation indirectly, without requiring exogenous bioactive molecules.

(2) Active biomaterials use ligand-specific targeting to engage macrophage receptors and reprogram immune activity.

- Carbohydrates (e.g., mannose, galactose) bind to CD206 and MGL receptors to drive M2 polarization.
- Bioactive peptides such as *mUNO* and *M2pep* selectively target M2-like subsets to promote tissue repair.
- Hyaluronic acid and chondroitin sulfate interact with CD44, regulating cytokine signaling and facilitating migration.
- Folic acid binds FR-β (folate receptor beta) on activated macrophages, while phosphatidylserine signals debris clearance and promotes resolution of inflammation [22].

Traditional implants often fail due to chronic inflammation or foreign body reactions. In contrast, immunomodulatory biomaterials can proactively "train" immune cells to support regeneration rather than sustain inflammation. By promoting a controlled macrophage response, these materials reduce fibrosis, enhance tissue integration, and improve outcomes in diabetic wounds, complex bone fractures, and implant-associated infections.

2.5. Translation Challenges

Despite promising performance in laboratory studies, clinical translation of antimicrobial biomaterials remains limited by scalability, cost, regulatory complexity, and the lack of standardized biofilm testing models due to their complexity [23]. Near-term clinical success will arise from antimicrobial systems that can balance biological sophistication with manufacturing practicality.

3. Wound Healing Biomaterials

The wound healing microenvironment is biologically complex and involves inflammatory signaling, bacterial burden, vascularization, oxygen tension, and extracellular matrix remodeling. Traditional wound dressings such as gauze, polyurethane films, and passive hydrogels provide moisture balance and physical protection but do not directly influence biological processes that determine healing outcomes [24]. Persistent inflammation, impaired angiogenesis, and high bacterial load in chronic wounds, particularly in diabetic tissue, require biomaterials that can dynamically coordinate healing rather than function as static coverings.

3.1. Hydrogels as ECM-Mimetic Platforms

Hydrogels remain foundational in wound management because of their extracellular matrix (ECM)-like structure and high-water content. Composite and dual-network hydrogels combining chitosan, alginate, gelatin, gelatin methacryloyl (GelMA), or hyaluronic acid improve mechanical strength while supporting keratinocyte migration and collagen deposition [25]. Controlled delivery of growth factors such as vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF) from hydrogels can promote angiogenesis and granulation tissue formation [26]. Hydrogels have emerged as essential materials in emergency therapy and this subject was reviewed by subject Chelu et al. [27]. In brief, the review explores advanced smart hydrogels with self-healing and antimicrobial properties for emergency care and increase survival rates. It also highlights the potentials and challenges to adopt hydrogels into emergency medical protocols.

Modern hydrogel dressings incorporate biophysical and biochemical cues that support extracellular matrix (ECM) remodeling, keratinocyte migration, and controlled exudate absorption. Matrix-mimicking hydrogels are based on collagen, hyaluronic acid, PEG-DA, PVA (polyvinyl alcohol), and gelatin optimize moisture balance, oxygen permeability, and cell adhesion (Figure 1).

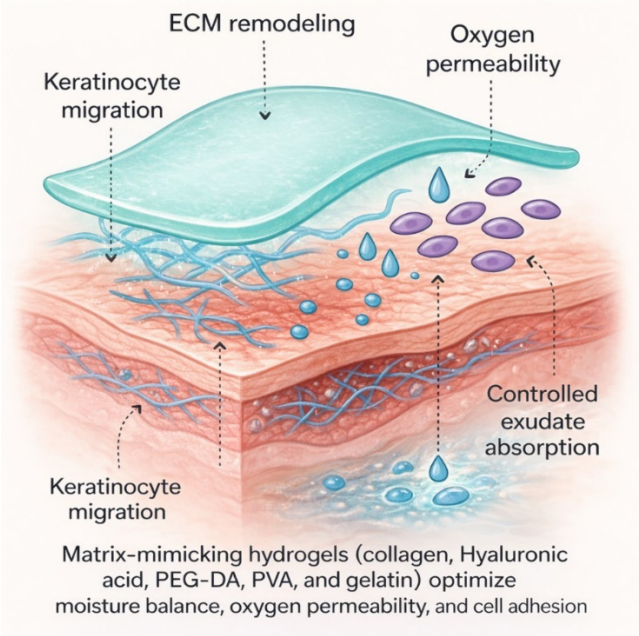

Figure 1. Schematic representation of the role of matrix-mimicking hydrogels (composed of collagen, hyaluronic acid, polyethylene glycol diacrylate (PEG-DA), polyvinyl alcohol (PVA), and gelatin) in enhancing the wound healing process. The hydrogel provides a biomimetic scaffold that maintains moisture balance and supports keratinocyte migration and ECM remodeling. Its oxygen-permeable structure promotes cellular respiration and angiogenesis, while controlled exudate absorption prevents maceration and maintains a favorable healing microenvironment. Together, these properties facilitate optimal tissue regeneration and accelerated wound closure. Illustration created using Microsoft Copilot, an AI companion developed by Microsoft, based on author-provided specifications.

3.2. Electrospun Nanofibers for Sequential Healing

Electrospun nanofibers provide nanoscale topography that mimics collagen fibrils and enhances cell adhesion, migration, and proliferation. Core-shell designs have enabled sequential drug release, where anti-inflammatory agents are delivered early to shorten the inflammatory phase, followed by pro-angiogenic or antimicrobial payloads during the later proliferative phase [28]. This multi-stage release profile is particularly relevant for diabetic ulcers with prolonged inflammatory signaling [29].

3.3. Smart or Responsive Dressings

A breakthrough in wound care is the development of responsive dressings that adjust their function according to biochemical signals at the wound site. Of importance is the design of pH-responsive carriers that release antibiotics under alkaline bacterial conditions. Two other important advances include ROS-scavenging hydrogel matrices that capture or neutralize excess reactive oxygen species to reduce oxidative stress and chronic inflammation, and enzyme-responsive antimicrobial peptide systems that release bactericidal peptides only when bacterial enzymes are present. These systems reduce the need for continuous drug exposure and may limit antimicrobial resistance by providing on-demand therapy only when infection is present [30].

3.4. Electrically and Sensor-Integrated Dressings

Electrically conductive hydrogels can deliver controlled microcurrents to stimulate fibroblast migration, enhance angiogenesis, and accelerate re-epithelialization [31]. Sensor-linked dressings, including electrochemical or colorimetric indicators, permit real-time monitoring of pH, lactate, or bacterial burden while maintaining a closed wound environment. These theranostic dressings (therapy + diagnostics) represent a step toward personalized wound care.

3.5. Immunomodulatory Healing Systems

Persistent inflammation is a defining feature of non-healing wounds. Biomaterials that promote M1→M2 macrophage polarization, reduce inflammatory cytokines (e.g., TNF-α, IL-1β), and modulate neutrophil activity demonstrate improved healing in animal models [32]. Incorporating immunoregulatory peptides, antioxidants, or cerium-based nanomaterials into wound dressings offers a dual benefit of anti-inflammatory and tissue-regenerative support.

3.6. Translation Barriers

Although laboratory progress is rapid, clinical translation remains limited by challenges related to scalability, long-term safety, cost, and regulatory classification for device-drug hybrid systems. The most realistic near-term clinical products are smart hydrogels and nanofiber scaffolds with single or dual biological functions, which balance innovation with manufacturability. There is still an enormous gap between research platforms and commercial products, and the availability of advanced cost-effective wound dressings is a global urgent need [33].

In clinical practice, wound care materials and strategies are selected based on the wound's moisture balance, infection level, and depth.

- Dry or necrotic wounds: Hydrogels help rehydrate and soften necrotic tissue (eschar), promoting autolytic debridement.
- Highly exudative wounds: Alginates and foam dressings absorb excess fluid and protect the surrounding skin from maceration.
- Infected wounds: Antimicrobial dressings containing silver or iodine reduce bacterial load, though hydrocolloids are generally avoided in these cases to prevent bacterial entrapment.
- Superficial or clean wounds: Transparent films or hydrocolloids protect the wound while allowing oxygen exchange and visual inspection.

For deep or chronic wounds, negative pressure wound therapy (NPWT) removes exudate, increases local perfusion, and stimulates granulation tissue formation. Wounds containing devitalized tissue require surgical or enzymatic debridement to remove slough and restart the healing cascade. Sutures provide mechanical closure—non-absorbable for high-tension areas and absorbable for internal layers. While non-healing diabetic ulcers remain among the most challenging cases due to impaired angiogenesis and chronic inflammation, these materials are also vital in treating other wounds such as pressure ulcers, venous leg ulcers, burns, post-surgical wounds, and traumatic injuries. For instance, hydrogels and alginates help maintain moisture and support tissue repair in burns and venous ulcers, whereas NPWT is effective for large traumatic wounds and skin graft stabilization. Antimicrobial and bioactive dressings further reduce infection risk across acute and chronic wound types, underscoring the versatility of these material platforms.

In diabetic wounds specifically, impaired healing is associated with reduced expression of growth-signaling proteins such as VEGF, PDGF, and EGF. VEGF and PDGF stimulate angiogenesis and fibroblast recruitment for tissue regeneration whereas EGF promotes epidermal proliferation and re-epithelialization. However, these growth factors degrade rapidly in the wound environment, requiring sustained delivery systems for effective action.

Nanomaterials and targeted delivery systems address this limitation by stabilizing and gradually releasing therapeutic molecules. Nanofibers and liposomes can encapsulate growth factors for sustained release, while silver nanoparticles (AgNPs) provide antimicrobial protection and nanoceria (CeO_2) act as antioxidants to reduce chronic inflammation stimuli-responsive or 3D-printed hydrogels allow on-demand drug release in response to pH, bacterial load, or oxygen levels—an approach that bridges basic biomaterial science with real-world wound care needs [34,35].

4. Bone and Cartilage Regeneration Biomaterials

Musculoskeletal tissues require biomaterials that provide mechanical integrity while orchestrating biological repair. While bone possesses intrinsic regenerative potential, large defects, load-bearing injuries, and metabolic conditions often require scaffold intervention. Cartilage, being avascular and aneural, is even more challenging because spontaneous regeneration rarely occurs [36].

4.1. Osteoconductive and Osteoinductive Scaffolds

Calcium phosphate ceramics such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) support osteoblast adhesion and matrix mineralization due to their chemical resemblance to native bone [37]. Doping

HA/β-TCP with ions such as Sr^{2+}, Mg^{2+}, Cu^{2+} and Zn^{2+} promotes osteogenic differentiation through activation of signaling pathways including alkaline phosphatase (ALP) and Runt-related transcription factor 2 (RUNX2) [38].

4.2. Polymer Composites with Tunable Mechanics

Biodegradable polymers, including polycaprolactone (PCL), polylactic acid (PLA), poly(lactic-co-glycolic) acid (PLGA), and polyurethane derivatives, are useful for musculoskeletal scaffolds due to customizable stiffness and degradation profiles. Such biopolymers are known for their versatility and applications in various domains with environmental benefits. Composite scaffolds combining polymers with bioactive ceramics or ECM-mimetic biomolecules improve osteogenesis while providing mechanical resilience [39]. Surface patterning (e.g., aligned fibers, microgrooves, and nanoridges) further improves stem cell mechanotransduction and directional growth. Mechanotransduction is the process by which the natural environment of a cell experiences a physical force intracellularly and extracellularly. The exerted force is then converted into biochemical and electrical signals to invoke cellular responses [40].

4.3. Zonal Biomaterials for Osteochondral Repair

Cartilage exhibits depth-dependent variations in mechanical and biochemical features. Multilayer scaffolds consisting of a cartilage-mimetic hydrogel on top and a mineralized, stiffer layer for subchondral bone integration are progressively used to regenerate both tissues simultaneously [41]. Such zonal scaffolds demonstrate improved interface stability and long-term integration compared to single-layer constructs [42].

4.4. D Bioprinting and Cell-Laden Constructs

Additive biomanufacturing enables controlled spatial deposition of cells, signaling molecules, and biomaterial components. Bioinks composed of chondrocytes, mesenchymal stem cells, or osteoblast precursors facilitate region-specific tissue formation in osteochondral constructs [43]. To improve translation, hybrid designs combine 3D-printed polymer frameworks with cell-laden hydrogels to balance mechanical performance and biological activity [44].

4.5. Immune and Vascularization Considerations

Successful bone regeneration depends not only on material design but also on immune coordination and vascular network formation. Persistent inflammation can inhibit osteogenesis and lead to fibrous encapsulation, while insufficient vascularization limits nutrient and oxygen delivery. Biomaterials that promote angiogenesis and regulate macrophage phenotype demonstrate improved long-term implant outcomes [45].

4.6. Translation Barriers

Challenges to clinical adoption include scalability, cost, regulatory classification, reproducibility, and the lack of standardized biomechanical testing models. The most promising near-term clinical candidates are composites with graded stiffness and targeted delivery of osteogenic and angiogenic cues, balancing sophistication, and manufacturability [46]. Smart biomaterials are increasingly pivotal in advanced medical and technological applications, yet their evaluation requires rigorous testing across multiple experimental platforms to ensure safety, efficacy, and functional performance. Biomaterials used in medical devices must undergo ISO 10993 biocompatibility testing and detailed material characterization. This is a crucial international standard series for the biological evaluation and safety testing of medical devices [47]. Regulatory bodies (FDA, CE- Conformité Européenne) require this to demonstrate safety and performance.

5. Implantable Devices and Biomaterial Coatings

Implantable devices such as orthopedic prostheses, cardiovascular stents, dental implants, and catheters remain highly susceptible to infection and adverse immune reactions. Because most implant-associated infections originate from biofilms, modern coatings are shifting from inert surfaces to bioactive, antimicrobial, immune-modulatory, and osseointegrative interfaces.

5.1. Antimicrobial and Antibiofilm Coatings

Traditional antibiotic coatings offer only short-term protection and contribute to resistance. Newer drug-free strategies rely on surface chemistry rather than pharmaceutical release. Zwitterionic and superhydrophilic polymer

brushes prevent protein adsorption and early bacterial attachment [48], while cationic polymers and antimicrobial peptides kill bacteria through membrane disruption. Rare-earth oxides such as CeO_2, La_2O_3, and Nd_2O_3 provide long-term catalytic ROS modulation and antibiofilm activity [15], and graphene-based nanosheets combine physical membrane disruption with osteogenic support [49]. Natural compounds—including curcumin, quercetin, and eugenol—add antimicrobial and anti-inflammatory benefits [50], while hyaluronic acid and chitosan reduce tissue irritation and weaken bacterial cell walls [51]. Drug-eluting coatings remain relevant when controlled release of anti-inflammatory agents such as dexamethasone is needed [52].

5.2. Infection-Responsive Coatings

A major advance is the development of coatings that activate only under pathogenic conditions. pH-responsive materials, such as chitosan-dopamine layers, switch charge and release antimicrobials in the acidic microenvironment of biofilms [53]. ROS-activated nitric-oxide donors release NO during inflammation, and near-infrared-responsive coatings generate heat or ROS for on-demand bacterial killing [54]. Enzyme-triggered systems release drugs only when exposed to bacterial proteases or wound-healing enzymes [55]. These designs minimize cytotoxicity and preserve healthy microbiota.

5.3. Enhancing Osseointegration and Soft-Tissue Sealing

Beyond infection control, coatings increasingly support bone formation and interfacial stability. BMP-2 mimetic peptides activate osteogenic signaling without supraphysiological growth factor doses [56], while integrin-binding motifs such as RGD (Arginine-Glycine-Aspartic acid), PHSRN (Proline-Histidine-Serine-Arginine-Asparagine), and DGEA (Aspartic Acid-Glycine-Glutamic Acid-Alanine) enhance osteoblast adhesion [57]. Silicate- and strontium-doped bioactive glasses promote sustained osteogenic gene expression [58], and TiO_2 nanotube arrays support bone ingrowth while serving as drug-loading platforms [59]. Gallium-doped titanium alloys combine osteogenic support with antibacterial and anti-inflammatory activity [60].

5.4. Immune-Modulatory Interfaces

Immune-informed coatings aim to guide macrophage behavior and reduce fibrosis. IL-4-releasing patches promote M2 polarization [61], CD200-mimetic peptides reduce pro-inflammatory macrophage recruitment, and nanozymes regulate oxidative stress while supporting pro-healing cytokine profiles [62]. These coatings promote immune resolution rather than broad immunosuppression.

5.5. Bioelectronic and Magnetoactive Coatings

Electromechanical signaling is increasingly leveraged in implant design. Piezoelectric layers such as polyvinylidene fluoride (PVDF) and boron nitride nanosheets generate microcurrents during physiological motion [63], while conductive poly(3,4-ethylenedioxythiophene)/polyphenylene sulfide (PEDOT/PPS) coatings deliver controlled electrical stimulation to enhance osteogenesis [64]. Magnetoactive nanoparticles improve mechanotransduction under low magnetic fields [65]. These systems provide both biomechanical and antibacterial advantages and are entering early clinical evaluation.

5.6. Cardiovascular and Dental Applications

In cardiovascular implants, restenosis and thrombosis remain major challenges. Hydrophilic polymer brushes reduce platelet adhesion [66], endothelialization of small-diameter biodegradable polymeric vascular grafts [67], and NO-releasing coatings help maintain vascular homeostasis [68]. In dental implants, peri-implantitis is addressed using catechol-modified chitosan for long-term antibiofilm activity [69], Zn- and Sr-doped hydroxyapatite for combined antibacterial and osteogenic effects [70], and laser-textured zirconia surfaces that improve soft-tissue sealing [71].

5.7. Clinical Translation and Market Landscape

Smart coatings are rapidly entering clinical pipelines. CE-marked surface-modified dental implants such as Osseotite® and MTX® [72], FDA-cleared ClearGuard™ HD antimicrobial barrier caps for catheter protection [73], and FDA-cleared MagnetOs® bone graft substitutes [74] illustrate the breadth of translation. Peptide-based dental biomaterials, including CE-marked P11-4 self-assembling peptide systems, are also progressing toward broader clinical adoption [75]. The global medical device coatings market, valued at USD 13.47 billion in 2024,

is projected to reach USD 21.17 billion by 2030, driven by infection-control needs, chronic disease prevalence, and demand for biocompatible surfaces [76].

6. Future Directions and Outlook

The future research of biomaterials will be shaped by the convergence of immunomodulation, antimicrobial precision, and regenerative medicine. Biomaterials are designed to engage actively with the biological microenvironment, guiding rather than merely tolerating host responses [77]. This shift is supported by advances in materials chemistry, artificial intelligence, additive manufacturing, and cellular bioengineering. One major direction is the development of immunologically informed biomaterials, capable of influencing macrophage polarization, neutrophil recruitment, cytokine expression, and oxidative stress to support balanced local immune activity, rather than broadly suppressing the inflammatory process [12].

Achieving balanced immune activation is central to wound therapy, musculoskeletal repair, and chronic infection management. The movement toward infection-aware biomaterials is a second emerging direction. Instead of continuous drug release, next-generation systems activate antimicrobial mechanisms only when infection-specific biochemical cues, such as acidic pH or elevated ROS, are detected. This precision approach reduces cytotoxicity, supports tissue regeneration, and limits the risk of antimicrobial resistance [78].

The third anticipated trend is AI-driven biomaterial design and personalization of biomaterials. AI emerges as a transformative enabler in the design of smart biomaterials, accelerating discovery by predicting biological interactions, optimizing material properties, and personalizing performance within complex physiological environments. By integrating large datasets from omics, imaging, and clinical outcomes, AI models can identify design rules that would be difficult to capture through conventional experimentation alone. One notable example is the development of AI-engineered hydrogels that dynamically adapt to wound environments [79,80], modulating moisture, pH, and antimicrobial release to promote faster and more effective healing. Beyond hydrogels, AI driven approaches are being applied to scaffold architecture optimization, immune-modulatory coatings, and drug-delivery matrices, pointing toward a future where biomaterials are not only smart but also context-aware and patient-specific. Predictive modeling is beginning to support the selection of material composition, mechanical gradients, pore architecture, and degradation kinetics based on patient-specific biological profiles. Such computational frameworks may accelerate the translation of biomaterials and reduce the time to clinical validation [81]. The field is moving toward immunologically informed, infection-aware, and AI-driven biomaterial design. Precision activation of antimicrobial mechanisms and personalized biomaterial selection are emerging trends. The most impactful solutions will balance biological sophistication with manufacturability and economic viability [82]. Deep learning-guided models have enabled the rational design of smart biosystems, overcoming many of the limitations associated with conventional biomaterial development [83]. Notably, an AI-assisted design and synthesis pipeline has been established for both inorganic and polymeric smart biomaterials, facilitating data-driven prediction of structure-property relationships and performance optimization [84]. AI-driven synthesis routes have further advanced the fabrication of bio-scaffolds with improved mechanical strength, controlled porosity, and enhanced bioactivity [85]. In addition, AI plays an emerging role in implant material optimization—allowing precise tailoring of surface chemistry and nanostructure to promote osseointegration and immune compatibility [86,87]. Overall, AI is not only accelerating hydrogel innovation but also transforming the conceptualization of biocompatible, adaptive, and intelligent materials across regenerative medicine, implant design, and tissue-engineering applications—from initial design and preparation to clinical implementation [88].

From a commercial standpoint, the appeal of AI enabled biomaterials lies in its dual promise of cost reduction and profit generation. By compressing discovery timelines, minimizing trial and error experimentation, and reducing reliance on expensive animal or clinical models, AI can deliver measurable R&D cost savings. At the same time, the ability to market "AI designed" scaffolds, coatings, or hydrogels as differentiated products creates opportunities for premium pricing and competitive positioning in crowded device and biomaterials markets. However, the return on investment is not immediate: upfront expenditures in data infrastructure, algorithm development, and regulatory validation remain substantial. In the near term, AI's greatest commercial value is as a risk mitigation and acceleration tool—helping companies de risk product pipelines and shorten time to market. Over the longer horizon, as predictive accuracy improves and regulatory frameworks adapt, AI driven biomaterials are poised to deliver both lower development costs and higher margins, reshaping the industry. Practicality and clinical acceptance will determine real-world success.

The World Health Organization (WHO) features fifteen families of antibiotic-resistant pathogens with the guidance on the necessary treatments and prevention [89]. This review does not include the potential applications of nanoscale materials respond dynamically to extraneous stimuli like pH/light/temperature, chemical signals, and

magnetic or electric fields. Several reviews of smart nanomaterials such as quantum dots, metal-organic frameworks, metal oxide nanoparticles (NPs), carbon NPs, and nanocomposites [90] as well as potential biomedical applications of smart biomaterials are available elsewhere [91,92].

6. Conclusions

Biomaterials have evolved to become indispensable in modern medicine, with advances in interdisciplinary research enabling the creation of bioactive, immunomodulatory, and stimuli-responsive materials. Natural and synthetic polymers, hydrogels, ceramics, metals, and nanoparticles continue to drive innovation in antimicrobial therapy, tissue engineering, implanted devices, and targeted drug delivery. Smart biomaterials mark a shift from passive implants to active therapeutic systems, where immune coordination is crucial for successful tissue restoration. Integrating antimicrobial, regenerative, and immunomodulatory functions promises major advances in personalized and regenerative medicine, though translation remains challenged by manufacturing, regulatory, and cost barriers. Emerging computational approaches, particularly artificial intelligence, are beginning to enhance material design and predictive modeling. Though still early, AI-guided methods offer powerful support for developing adaptive, clinically relevant biomaterials and accelerating their translation to real-world healthcare.

Author Contributions

A.D.L. (writing: Wound Healing Biomaterials and Bone and Cartilage Regeneration Biomaterials) and J.H.T.L. (writing: Antimicrobial Biomaterials and editing). All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

Given the role as Editor-in-Chief, John H.T. Luong had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal."

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Copilot and Scholar GPT-5 research assistant for language refinement, reference formatting, and structural suggestions during manuscript preparation. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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