

# Smart biomaterials in regenerative medicine

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Smart biomaterials represent a transformative shift in regenerative medicine, functioning not merely as passive scaffolds but as interactive, adaptive, and intelligently responsive systems. These materials are engineered to sense biochemical or mechanical cues such as pH fluctuations, enzymatic activity, oxidative stress, ionic imbalance, or applied strain and subsequently regulate their degradation, drug-release behavior, structural conformation, or immunological signaling. This interactive capacity aligns with foundational analyses of stimuli-responsive biomaterials.<sup>1</sup> Smart biomaterials enable controlled and disease-specific interventions by activating only in pathological environments while remaining inert under normal physiological conditions. This selective responsiveness reduces systemic toxicity, preserves healthy tissues, and allows a higher degree of therapeutic precision compared with that of traditional biomaterials. Moreover, their capacity to adapt in real time to injury-specific microenvironments enhances the stability and long-term efficacy of regenerative treatments. In parallel, the development of eco-friendly and bio-derived adaptive biomaterials has introduced a new dimension of sustainability, allowing clinicians and researchers to integrate environmental considerations into clinical-grade material design without compromising performance.<sup>2</sup> These green and adaptive platforms are increasingly relevant as biomedical manufacturing moves toward lower-waste, resource-efficient methods.

Taken together, these characteristics position smart biomaterials as key components of next-generation regenerative therapies, offering programmable behavior and multi-level biological interaction.

Stimuli-responsive hydrogels constitute one of the most advanced and versatile categories of smart biomaterials. Their hydrated polymeric networks closely resemble the extracellular matrix, supporting cell adhesion and nutrient diffusion while enabling dynamic, precision-controlled responsiveness. Hydrogels can alter their swelling, stiffness, degradation profile, or therapeutic payload release in response to pH, enzymatic activity, temperature, ionic

signaling, or mechanical strain, consistent with earlier mechanistic descriptions in the hydrogel literature.<sup>1</sup>

A specialized review of stimulus-responsive hydrogels for bone tissue engineering has reinforced the scientific foundation for their use,<sup>3</sup> highlighting their relevance in load-bearing tissues and translational bone regeneration strategies. Incorporating this perspective strengthens the conceptual framework for using hydrogels as intelligent therapeutic matrices within orthopedic and musculoskeletal repair workflows.

In musculoskeletal applications, hydrogels facilitate mineralization, angiogenesis, and osteogenic signaling while providing structural compliance compatible with bone marrow niches. Translational studies have documented their ability to guide spatially controlled osteogenesis, regulate ion exchange, and support early vascular ingrowth, underscoring their therapeutic potential in bone repair.<sup>3</sup>

In wound management, hydrogels offer significant advantages for complex and chronic injuries such as diabetic ulcers, which are characterized by elevated reactive oxygen species (ROS), excessive protease activity, persistent inflammation, impaired angiogenesis, and neuropathy. These pathological features make diabetic wound beds well-suited to responsive therapeutic strategies. Stimuli-responsive hydrogels can selectively release antibiotics, antioxidants, or growth factors in response to disease-associated cues such as increased ROS levels, protease activity, or acidic pH. This on-demand delivery ensures that therapeutic agents are administered only when needed, enabling precise and timely treatment while minimizing systemic exposure and reducing overall dosage requirements, thereby enhancing wound-healing efficiency.<sup>4</sup>

Emerging immunomodulatory hydrogel systems that promote macrophage polarization toward the pro-regenerative M2 phenotype have demonstrated improved tissue closure, enhanced epithelialization, and reduced inflammatory burden in diabetic models, highlighting their promise in treating difficult-to-heal wounds.<sup>5</sup>

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**How to cite this article:**

Talniya NC. Smart biomaterials in regenerative medicine. *Biomater Transl.* 2026, 7(1), 174-177.

doi: [10.12336/bmt.25.00073](https://doi.org/10.12336/bmt.25.00073)



Sustainably produced hydrogel formulations have also been developed, combining adaptive performance with reduced environmental impact, an approach that aligns well with modern clinical manufacturing priorities.<sup>2</sup>

Integrating immune-active domains—such as cytokine-binding motifs, controlled macrophage-modulating sequences, or immunoregulatory peptides—further enhances the performance of diabetic wound dressings by promoting balanced immune responses and accelerating granulation tissue formation.<sup>5</sup>

These innovations collectively demonstrate how smart biomaterials can be engineered to target the specific pathological signatures of chronic wounds.

Bone and cartilage regeneration benefit greatly from biomaterials that provide both structural support and dynamic biological activity. In orthopedic applications, smart biomaterials often incorporate osteoconductive ceramics, bioactive glass, biodegradable polymers, or hybrid matrices designed to synchronize degradation kinetics with tissue regrowth.

Calcium phosphate and bioactive glass scaffolds release therapeutic ions that promote osteoblast differentiation and angiogenesis, while polymer-ceramic hybrids combine mechanical strength with controlled biodegradability.

Recent advances in ceramic-hydrogel hybrid scaffolds enriched with bioactive peptides have shown enhanced osteogenic differentiation and controlled immunological signaling, resulting in improved graft acceptance and physiological integration.<sup>6</sup> Similarly, incorporating immunomodulatory elements into bone-repair matrices helps regulate early inflammatory responses, creating a favorable microenvironment for osteogenesis and long-term regeneration.<sup>5</sup>

Stimuli-responsive hydrogels also support bone repair by regulating ion release, modulating mineralization, and facilitating vascular ingrowth through controlled structural adaptation. Their effectiveness has been demonstrated in translational bone regeneration research.<sup>3</sup>

**Table 1** summarizes key categories of smart biomaterials, their regenerative advantages, and the translational challenges associated with scaling them for clinical use.

Additive manufacturing has become a central technology in the evolution of smart biomaterials, enabling the fabrication

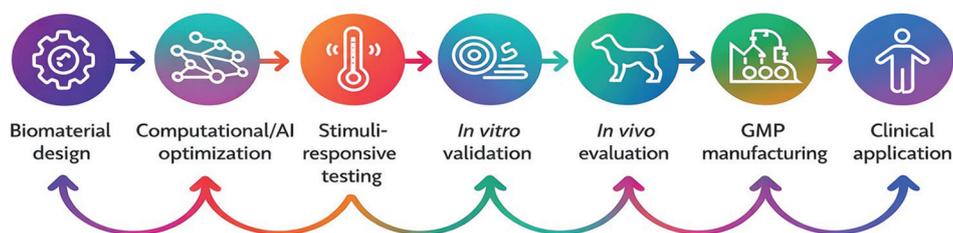
of complex, patient-specific constructs with finely tuned microarchitectures. Traditional three-dimensional printing allows the creation of geometrically precise scaffolds, but these constructs are inherently static. Four-dimensional printing introduces a temporal dimension, enabling printed implants to change shape, stiffness, or functional behavior in response to physiological cues such as moisture, temperature, or biochemical gradients. Building on this, five-dimensional printing employs curved-layer deposition to produce structures with enhanced mechanical strength, superior anatomical conformity, and multi-axial functionality. The integration of nanocomposites into these printing technologies further expands their potential, facilitating the development of constructs capable of embedded signaling, therapeutic release, or mechanical adaptability.<sup>7</sup> These multi-responsive printed systems enable more precise control of the local regenerative environment and support improved integration with surrounding tissues.

In addition, incorporating immune-responsive motifs into the printed matrices promotes favorable early inflammatory responses, facilitating vascularization and tissue regeneration while reducing the risk of fibrotic encapsulation.<sup>6</sup> Such innovations underscore the capacity of advanced fabrication technologies to expand the functional envelope of intelligent biomaterial designs.

As shown in **Figure 1**, the translational pathway for smart biomaterials comprises a series of interconnected phases, beginning with fundamental material design, followed by *in vitro* testing, *in vivo* pre-clinical evaluation, biocompatibility assessment, and scaffold-tissue interaction analysis. The figure illustrates how material composition, structural alignment, immune cell chemotaxis, degradation characteristics, mechanical properties, and therapeutic release behavior collectively influence the progression from the laboratory to the clinic. This sequential representation reinforces the concept that translational success depends not only on functional material innovation but also on the systematic understanding of host-material interactions at each stage of development. The integration of structural architecture, interfacial bonding, immunological adaptation, and controlled release characteristics forms the core of effective translational biomaterial design. Artificial intelligence (AI) has emerged as a powerful tool for accelerating smart biomaterial discovery, enabling researchers to optimize formulations based on extensive datasets encompassing polymer composition, degradation kinetics, immune response patterns, and clinical

**Table 1.** Major classes of smart biomaterials and their translational considerations

Smart biomaterial type	Key advantages	Translational challenges
Stimuli-responsive hydrogels	Mimic hydrated tissue; adaptive swelling; controlled release	Long-term stability; regulatory classification complexity
Immune-instructive polymers	Reduce rejection; macrophage polarization to M2 phenotype	Balancing tolerance versus immunity; long-term signaling
Bioactive ceramics/glass scaffolds	Osteoconductive; strong integration; mechano-responsiveness	Brittleness; limited adaptability in load-bearing areas
Four-dimensional/ five-dimensional-printed constructs	Shape-changing implants; high anatomical accuracy	Scaling complexity; real-time validation requirements
Artificial intelligence-guided hybrid systems	Ultra-rapid discovery; personalized design	Large datasets needed; risk of algorithmic bias



**Figure 1.** Translational pathways for smart biomaterials to clinical applications  
Abbreviations: AI: Artificial intelligence; GMP: Good manufacturing practice.

performance outcomes. Machine-learning systems can evaluate how changes in crosslink density, surface chemistry, or matrix stiffness influence cell adhesion and proliferation, while deep neural networks predict degradation behavior or therapeutic release patterns across diverse biological environments.<sup>8</sup>

Inverse-design frameworks and AI-driven parameter optimization further facilitate the rapid identification of optimal biomaterial configurations without the need for exhaustive experimental trials, thereby reducing resource consumption and shortening development timelines.

The application of AI extends into manufacturing, where quality-control algorithms detect inconsistencies in pore structure, crosslink uniformity, or scaffold density before the final product reaches clinical testing. In addition, AI-supported models have enhanced the precision of spatiotemporal drug release strategies by predicting how therapeutic agents diffuse or degrade under specific physiological conditions.<sup>9</sup> Collectively, these approaches contribute to a more robust and efficient translational pipeline.

The increasing complexity of smart biomaterials—particularly those involving dynamic shape transformation, immune adaptation, or therapeutic release—poses significant challenges in regulatory classification. Many intelligent materials simultaneously exhibit properties of medical devices, pharmaceuticals, and biologics, complicating approval processes and necessitating multidisciplinary evaluation.

Smart biomaterials that can influence epigenetic signaling pathways, stem-cell behavior, or gene expression profiles raise important ethical considerations related to long-term safety and potential unintended biological consequences.<sup>10</sup> Such biomaterials require rigorous characterization of degradation products, sustained release kinetics, and systemic interactions to ensure patient safety.

The need for updated regulatory frameworks and harmonized international guidelines has become increasingly evident, as current classification categories often fail to capture the adaptive nature of emerging smart biomaterial technologies. Establishing these standards will help ensure that innovative materials reach clinical application without undue delay while maintaining rigorous safety requirements.

Translating smart biomaterials from laboratory-scale synthesis to clinical-grade production remains a significant challenge due to their sensitivity to processing conditions. Small variations in temperature, shear forces, reaction timing, or sterilization

methods can greatly affect mechanical properties, degradation behavior, and therapeutic release patterns.

The incorporation of microcarrier-based systems, automated mixing technologies, and continuous bioprocessing provides pathways toward producing consistent, GMP-compliant batches of biomaterials.<sup>11</sup> Real-time analytics and quality-control monitoring are increasingly integrated into manufacturing pipelines to ensure reproducibility, structural precision, and adherence to clinical standards.

Sustainable manufacturing strategies, including the use of bio-derived feedstocks, modular production platforms, and energy-efficient processing, offer additional advantages by reducing environmental impact while maintaining high performance levels.<sup>2</sup> These innovations are expected to play an increasingly important role as translational demand grows and clinical use expands globally.

Long-term success in regenerative medicine depends heavily on orchestrating favorable immune responses. Smart biomaterials now incorporate surface-modified matrices, cytokine-releasing systems, extracellular matrix-mimetic coatings, or adaptive degradation products that guide macrophage, dendritic cell, and T-cell behavior toward pro-regenerative responses.

Immune-instructive biomaterials engineered to promote M2 macrophage activation, modulate inflammatory cytokine release, or enhance dendritic-cell tolerance have demonstrated improved tissue integration and reduced fibrosis in pre-clinical studies.<sup>5</sup> These materials respond dynamically to immune cues, contributing to a microenvironment that supports angiogenesis, extracellular matrix remodeling, and long-term tissue integration.

Hybrid constructs that combine mechanical stability with immune adaptivity—such as peptide-enriched ceramic-hydrogel scaffolds—offer an optimal balance of structural and biological benefits, supporting both early-phase inflammation control and sustained regenerative potential.<sup>6</sup>

Smart biomaterials represent a new generation of adaptive, interactive platforms capable of transforming regenerative medicine. Their ability to sense, respond, and modulate biological environments enables precision therapy across diverse clinical applications, including wound repair, bone regeneration, and immune-guided tissue reconstruction.

The integration of stimuli-responsive behavior, immune compatibility, scalable fabrication, sustainable material development, and AI-driven optimization creates a robust

foundation for the clinical translation of intelligent biomaterials. Future progress will depend on harmonizing scientific innovation with regulatory advancement, manufacturing readiness, and ethical considerations, ultimately expanding access to safe and effective regenerative therapies.

**Acknowledgement**

None.

**Financial support**

None.

**Conflicts of interest statement**

The author declares no conflicts of interest.

**Author contributions**

This is a single-authored article.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data**

Not applicable.

**Open access statement**

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Received: June 26, 2025

Revised: November 27, 2025

Accepted: November 28, 2025

Available online: January 15, 2026