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Perspective

From Biomimetic to Bioadaptive: Next-Generation Titanium Implants for Functional Bone Regeneration

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Abstract: Titanium-based implants are predominantly adopted in orthopedic and dental applications, yet their clinical performance is constrained by enduring challenges such as stress shielding, infection susceptibility, and inadequate osseointegration. To address these hurdles, recent advances have shifted titanium implant design from static biomimetic models toward dynamic, bioadaptive systems capable of actively modifying their architectural, mechanical, and surface properties after implantation. These systems can respond adaptively to specific pathophysiological microenvironments or be activated by external energy sources (e.g., light, ultrasound, electricity, or magnetism), thus providing on-demand biofunctionalities, such as antibacterial, pro-angiogenic, osteogenic, and immune/metabolic regulatory effects, ultimately mitigating complications (e.g., infection, inflammation) while accelerating osteoregeneration and osteointegration. In this Perspective, we propose a strategic framework to guide the design and development of next-generation titanium implants aligned with this trend. It highlights the emerging need to converge a deeper understanding of implant-biology interplays with synergistic advances from materials science (e.g., metamaterial and stimuli-responsive interface design) and cutting-edge bone biology (e.g., immunometabolic and neuro-osseous engineering). This interdisciplinary integration is aimed at enabling expedited, robust, bioadaptive regeneration regimens, particularly for challenging bone defects such as infected, osteoporotic, or diabetic conditions.

Keywords: bioadaptive implants and interfaces; stimuli-responsive designs; antibacterial functionalization; immune/metabolic engineering; osteoregeneration and osteointegration

1. Introduction

Titanium-based implants are widely utilized in orthopedic and dental applications, including but not limited to, artificial joints, dental implants, spinal fusion cages, and bone fixation devices (Table 1), owing to their superior mechanical properties and favorable biocompatibility [1,2]. Nonetheless, the long-term success and clinical performance of these implants remain to be constrained by several key challenges: stress shielding disrupts physiological bone remodeling; the inherent bio-inertness of the implant surface limits chemical bonding with

bone tissue and slows osseointegration; and susceptibility to postoperative infection raises the risk of implant failure [3].

To bypass these hurdles, research endeavors in recent decades have progressed from emphasizing traditional biocompatibility to focusing on bioactive properties, such as antibacterial activity, osteogenesis, and immunomodulation [3]. Over the past ten years or so, a key focus in this regard has been bone-inspired design, enabled by advances in 3D printing and surface/interface engineering [1,4]. By mimicking bone anatomy, mechanical performance, structure, and composition, etc., researchers in this community have created biomimetic implant macro- and interface designs to certain degrees, achieving notable advances in material properties [1]. However, the evolving paradigm of "materiobiology" has revealed that simply replicating bone-like traits in implants is inadequate, especially in an aging population where systemic conditions such as metabolic bone disease, infection, and diabetes compromise the host's intrinsic regenerative capacity [5]. As a core deficit, such static biomimetic designs do not account for the dynamic interplay between implant and biological system. More specifically, they fail to meet the time-sensitive functional demands of the healing process, such as coordinated infection control, anti-inflammatory response, vascularization, and bone formation [6]; In more complex pathological conditions, these designs also lack the capacity to support higher-order regenerative processes, such as metabolic regulation and neuro-osseous coupling [1].

Table 1. Clinical applications of Ti-based medical implants and devices.

Category	Uses	Metal Compositions	Refs.
Dental implants	Braces, bridges, abutments, orthodontics, fixation devices	β-titanium, pure titanium, Ti-6Al-4V, Nitinol	[7–9]
Orthopedic joint implants	Joint components (e.g., stems, cups), meshes, bone substitutes, fixation devices	Ti-6Al-4V, Ti-6Al-7Nb, Ti-15Mo, Ti-13Nb-13Zr, pure titanium, Nitinol	[10–12]
Trauma fixation devices	Plates, screws, rods, nails	Ti-6Al-4V, Ti-6Al-7Nb, and pure titanium	[13–15]
Spinal implants	Cages, discs, fixation devices	Ti-6Al-4V, pure titanium	[16,17]

The concept of "bioadaptability", introduced in 2016 [18], offers insights into and routes for how to design regenerative biomaterials that can meet dynamic biological needs. It marks a shift from the conventional paradigms of biocompatibility and bioactivity toward bioresponsiveness and adaptive functions in biomaterials. This concept has since been widely embraced and extended, giving rise to related ideas such as "precision bioadaptability" [19], "bioadaptive materials" [20], "self-adaptive biomaterials" [21], and "immune-bioadaptive implants" [22]. Guided by these conceptual progresses, the design of titanium implants has evolved from static, bone-mimicking models toward dynamic, bioadaptive systems that can adjust their architectural, mechanical, and surface properties post implantation (Figure 1). These systems are engineered to interplay with the local pathophysiological microenvironments, or to respond to external energy sources (e.g., light, ultrasound, electricity, or magnetism), enabling them to deliver stage-specific biofunctions dynamically—a defining characteristic of next-generation titanium-based bone implants. Key strategies enabling these innovative implants, to our best knowledge, encompass two complementary approaches. On one hand, computationally optimized structural designs are employed, such as origami-inspired deformable scaffolds, metamaterials, and shape-memory implants fabricated via 4D printing [1,23,24]. In parallel, smart stimuli-responsive surface modifications are employed, such as coatings with environmentally adaptive stiffness/wettability [19], sequentially degradable and self-renewing interfaces [6], reconfigurable micro- and nanotopographical structures, drug/ion-doped layers capable of stage-regulated release [25], as well as implant interfaces that enable selective or phase-specific presentation of immobilized biomolecules [26,27].

In this *Perspective*, we delineate potential pathways to transform titanium-based osteoimplants from static, biomimetic devices into intelligent systems capable of dynamically supporting tissue repair. To this end, we underscore design strategies that fuse advances in biomaterials science, such as metamaterial and stimuli-responsive surface/interface design, with insights from cutting-edge bone biology, such as osteoimmunology, osteometabolism, and neuro-osseous coupling. This *Perspective* aims to attract attention to and shed light on this important, emerging field, offering guidance to facilitate the development of next-generation titanium-based implants with more effective bioadaptive bone regeneration and osteointegration, particularly for challenging defects.

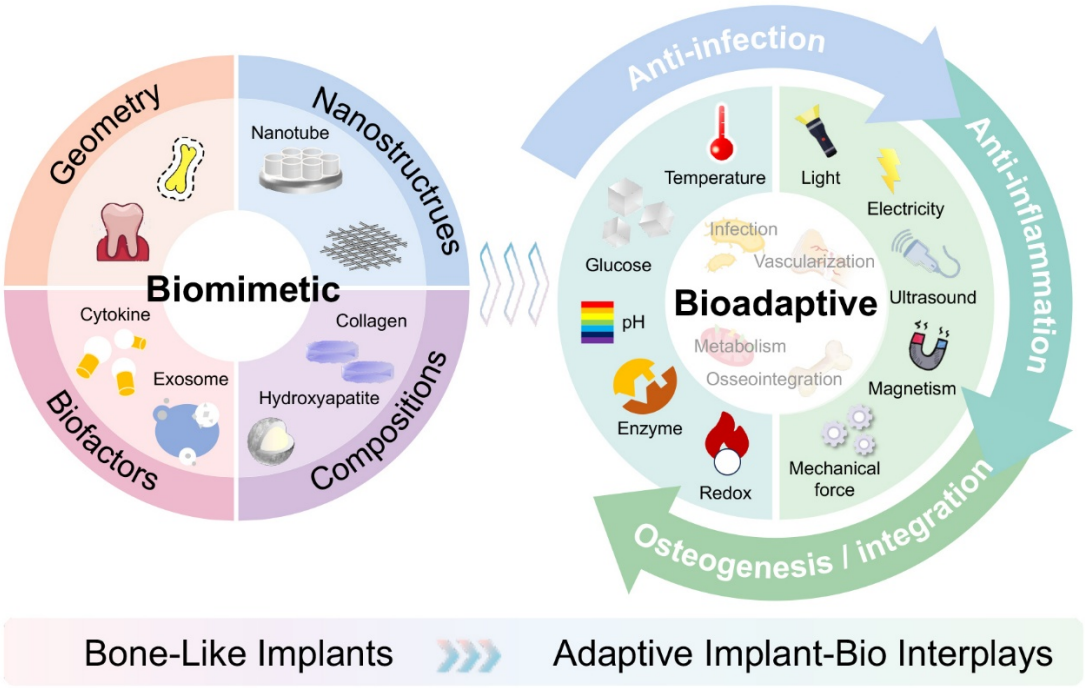

Figure 1. Schematic outline of this review, illustrating the evolution from static, bone-mimetic designs toward adaptive, bio-responsive titanium implant systems, which leverage dynamic microenvironmental interactions or external stimuli to deliver on-demand (e.g., sequential antibacterial, immunomodulatory, pro-osteogenic functions), thereby mitigating complications (e.g., inflammation, infections) and accelerating bone repair.

2. Bioadaptive Strategies in Structural Optimization: Advancing from Structural Biomimetics to Intelligent Functionalization

Bone is a naturally occurring composite material with a multi-level porous structure and complex topological morphology [28]. Precisely mimicking these physical characteristics is recognized a fundamental strategy for constructing an osteoregenerative and bone-repairing microenvironment. In fact, the design of contemporary titanium-based implants has evolved beyond simple morphological replication into a system engineering approach aimed at achieving structural bioadaptability. The core principle lies in actively matching and guiding the host's biological response through multiscale structural optimization. This design framework may be implemented across three levels: (1) bionic architectural design: modulating an implant's macroscopic geometry and internal pore structure to recapitulate the architecture and biomechanical properties of natural bone; (2) surface structure modification: altering the surface topography and features at micro- and nano-scales to actively guide cell behaviors; (3) functional and adaptive structure design: integrating smart materials or responsive elements to endow the implants with the ability to dynamically adapt to changes in local microhabitats. These advances seek to shift titanium implant design from passive imitation to active biomechanical regulation by precisely controlling the implants' pore topology, curvature, and deformation behaviors, etc., thus mitigating stress shielding and directing tissue regeneration through mechanobiology.

2.1. Bionic Architectural Design: from Mechanical Compatibility to Metamaterial Design

With advancements in manufacturing technology, 3D printing can now achieve personalized customization of titanium-based scaffolds with complex internal structures. For instance, Luo et al. [29] successfully designed a highly biomimetic trabecular micro-architecture using the Voronoi algorithm combined with medical imaging data (Figure 2A). Such structures were found not only to achieve good mechanical matching with the host bone, effectively alleviating the stress shielding effect, but also to provide, through their interconnected pore systems, auspicious physiological channels for cell infiltration, nutrient transport, and vascular ingrowth.

Building upon macroscopic structural mimicry, research has progressed to exploit micro- and nanoscale topological cues. Triply periodic minimal surfaces (TPMS) have emerged as particularly promising bioinspired architectures for their structural uniqueness and functional versatility. These structures are characterized by their periodicity and minimal surface areas, which confer them with exceptional mechanical and physical properties [30]. The architectural features of TPMS-based structures, such as their high surface-area-to-volume ratio and interconnected porous architecture, make them amiable for cell adhesion, proliferation, and differentiation (Figure 2B) [31]. It is

noteworthy that these biomimetic scaffold architectures have also been reported to modulate macrophage polarization [31], which in turn favors bone–implant integration. This observation highlights the intrinsic bioadaptive potential embedded within specific biomimetic structures, revealing that biomimetic and bioadaptive strategies are not mutually exclusive but may exist along a functional continuum. Moreover, certain TPMS architectures like the Schwarz Diamond type can effectively mimic the anisotropy of human cortical bone, featuring an asymmetric mechanical response with a compressive modulus of 14–20 GPa and a tensile modulus of 38–55 GPa [32]. These properties are potent to facilitate implant integration by preventing stress shielding and fostering vascularization within the surrounding tissue [33,34].

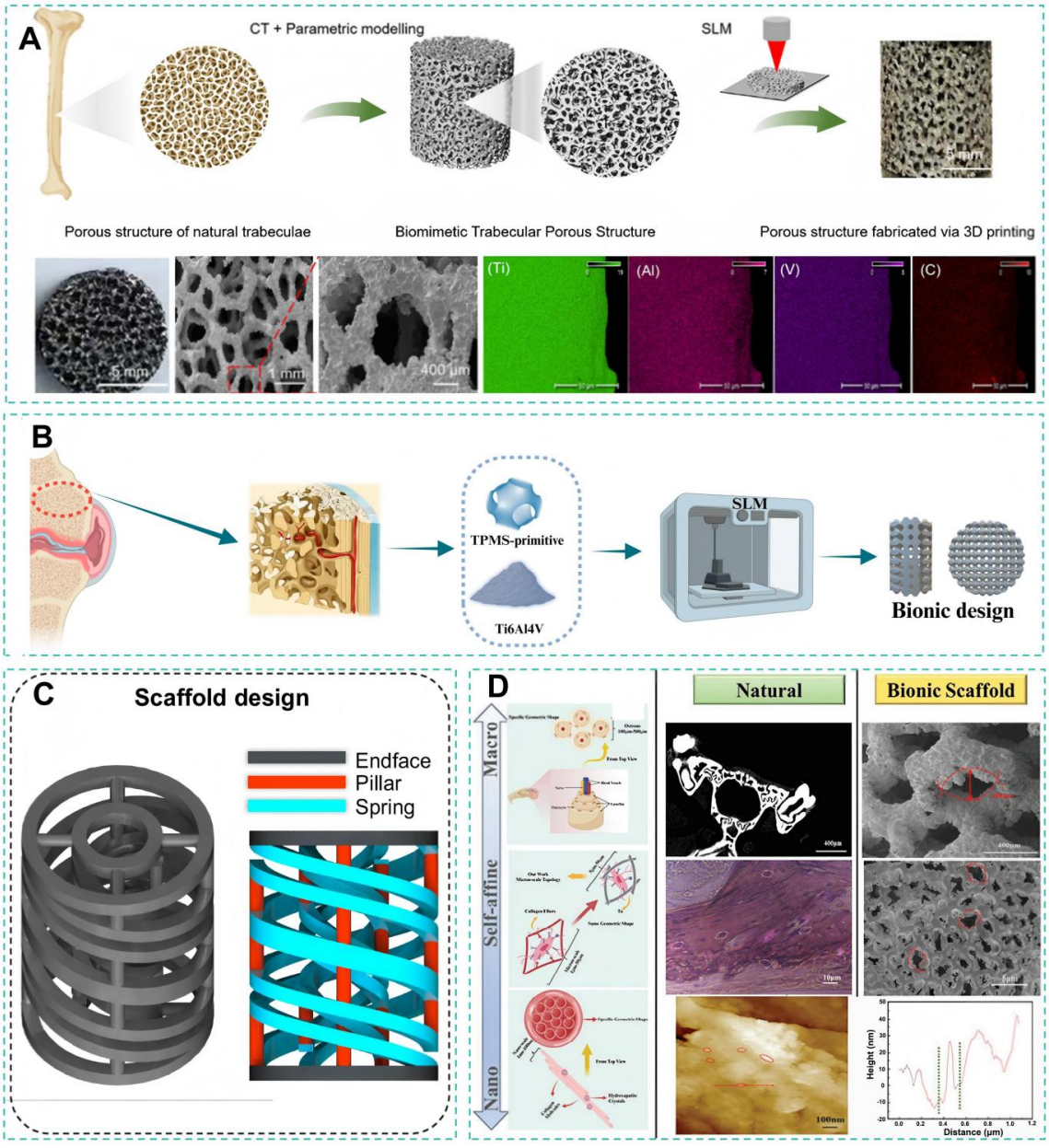

Figure 2. Designing bone implants through structural biomimicry. (**A**) Biomimetic trabecular micro-architecture [29]. Copyright 2025, Wiley. (**B**) 3D-printed scaffolds with TPMS design [31]. Copyright 2025, American Association for the Advancement of Science. (**C**) Design of a two-stage metamaterial scaffold [35]. Copyright 2025, Springer Nature. (**D**) Fractal biomimetic design for a 3D-printed scaffold [23]. Copyright 2025, Wiley.

However, a simple reduction in modulus does not align with the dynamic process of osseointegration. Recent innovations have further expanded the design paradigm beyond static modulus-matching. In a seminal work, Qin et al. introduced metamaterial scaffolds capable of two-stage mechanical behavior (Figure 2C) [35]. By decoupling strength and modulus, these architectures achieved an ultra-low effective modulus (~13 MPa) during initial loading to induce beneficial bone tissue strain (>2%), while providing sufficient strength for meeting load-bearing requirements through a subsequent stiff stage. *In vivo* studies demonstrate that such dynamically-

responsive scaffolds upregulated calcium signaling and HIF-1α expression, enhancing osteogenesis and angiogenesis. After four weeks, new bone formation was increased by 44–498% over classical scaffolds, confirming that bone regeneration can be significantly augmented by engineering scaffolds to elicit optimal strain environments rather than merely matching bone's static modulus [35].

2.2. Surface Structure Modification: Topology-Guided Cell Fate

The implant surface is the primary interface for interaction with host tissue. Surface structure optimization aims to create a microenvironment conducive to cell adhesion, proliferation, and osteogenic differentiation through physical and chemical modifications. The "fractal biomimetics" strategy proposed by Tian's team [23] revealed that natural bone surfaces possess specific fractal dimension characteristics (Figure 2D). By matching natural bone with a precisely designed fractal topology, osteodifferentiation was far more effectively promoted than by conventional randomized roughness, confirming the high sensitivity of cells to nano-scale ordered topological structures. Concurrently, Long and coworkers proposed the innovative concept of "Scaffold Architecture-induced Stress Stimulation (SASS)" in their research on carbon crystalline (e.g., graphene) scaffolds [36]. Their studies indicate that optimized microstructures can guide strain to achieve a more uniform distribution. This not only directly promoted the osteogenic differentiation of mesenchymal stem cells but also coordinated the active balance between osteoblasts and osteoclasts, thereby providing a mechanical basis for long-term maintenance of bone remodeling homeostasis.

Building upon specific topological structures, further biofunctionalization is key to enhancing surface activity [37]. For instance, Wang et al. [38] developed a hydrothermal synthesis method to construct a composite coating on fibrous-grained titanium, which combined microgroove topology with bioactive components (oriented nHA and anatase TiO_2). The topological structure promoted cellular alignment and osteogenic differentiation through contact guidance, while the bioactive components synergistically enhanced surface hydrophilicity, mineralization capacity, and corrosion resistance, and osteoclast inhibition. This synergistic strategy, through the integration of topological structure with chemical/biological modifications, enables precise regulation of cellular responses from both physical and chemical dimensions.

2.3. Functional and Adaptive Structure Design: Achieving Dynamic Bioadaptability

The higher level of structural optimization involves endowing implants with smart functions to actively respond to and modulate the local microenvironment, achieving true dynamic adaptation. Compositing 3D-printed porous titanium alloy scaffolds with functional hydrogel modules is a current research hotspot. The porous metal provides mechanical support, while the hydrogel can mimic the extracellular matrix microenvironment and carry various bioactive factors [39–41]. For example, Che et al. coated a 3D-printed titanium scaffold with an alginate-collagen composite hydrogel loaded with deferoxamine (DFO, a hypoxia-inducing agent) and created a system that simultaneously facilitated angiogenesis and osteogenesis through sustained release of DFO, calcium, and phosphate ions during degradation, significantly enhancing bone-implant interface integration [39]. Additionally, Wang and colleagues developed multifunctional 3D-printed titanium scaffolds decorated with a MXene-PVA composite hydrogel for controlled delivery of engineered extracellular vesicles with a tag of dextran sulfate [41]. This integrated system enhanced wear resistance and interfacial adhesion, offering a promising therapeutic strategy against periprosthetic osteolysis by spurring osseointegration. These composite designs transform the implant from a passive carrier into an active platform capable of dynamically regulating the local biochemical microenvironment for bone regeneration. To attain precise spatiotemporal control, future designs could hybridize 3D-printed titanium scaffolds with stimuli-responsive hydrogels that dynamically release biofunctional (e.g., neurotrophic or angiogenic factors) in response to stage-specific microenvironmental changes (e.g., in pH or ROS levels).

Functionalized smart adaptive structures represent a frontier strategy for optimizing the architecture of titanium implants. Zheng et al. leveraged 3D printing to fabricate a bioadaptive magnesium-titanium (Mg-Ti) composite, aiming at delicately balanced mechanical stability and biological integration during bone defect regeneration [42]. The design accomplished dual functionality: it offered robust, bone-mimetic structural support through its architecture, coupled with progressive mechanical matching to natural bone via the degradation of its Mg component. In addition, this system allowed balanced bone remodeling through dual regulation of bone formation and resorption. By embodying the concept of dynamically-responsive biomaterials through gradual changes in material composition and microstructure upon physiological feedback, such smart adaptive structures represent an emerging focus in titanium implant optimization, paving the way for next-generation orthopedic device designs that offer not only enhanced mechanical compatibility but also superior bioactivity.

3. Adaptive Surface Chemical Modifications: Conferring Proactive Bio-Regulatory Properties

The pursuit of ideal bone-implant integration has driven the evolution of surface engineering from static, bio-inert coatings toward dynamic, "smart" interfaces [43]. Adaptive surface chemical modification represents a paradigm shift in this endeavor. It involves the precise chemical design of titanium surfaces using techniques such as grafting functional molecules, constructing intelligent polymer brushes, or fabricating composite films, so that the surfaces gain environmental responsiveness. Unlike conventional modifications, these engineered surfaces can undergo controlled changes in their chemical properties, topography, or function in direct response to specific physiological or pathological cues within the implantation site. The ultimate goal is to transcend "passive compatibility" and achieve "active regulation", thereby more precisely addressing the multifaceted demands of infection prevention, healing promotion, and inflammation modulation that underpin long-term implant success [44]. Numerous chemical strategies (Table 2, often used in combination) have been developed to enable this adaptive functionality. This section provides a systematic overview of these approaches, elucidating how chemical design could translate into intelligent biological responses.

3.1. Physicochemical Synergistic Modifications

The physicochemical synergistic strategy, building upon previously discussed topographic modifications, aims to create a hierarchically integrated surface where structure and function are unified. While it shares considerable overlap with the intelligent modification of surface structures discussed above, the focus here is placed on the specific role of chemical modifications in enabling intelligent responsiveness to augment the biofunctionality of physical cues. Based on our group's previous experience [6,45], here we exemplify the rationale for its implementation: (1) Micro- or nano-scale features, fabricated through methods such as anodic oxidation [46,47], micro-arc oxidation (MAO) [48,49], or sandblasting and acid etching (SLA) [50,51], serve a mechanical scaffold that promotes initial cell adhesion, spreading, and osteodifferentiation via contact guidance. (2) Subsequently, an adaptive chemical coating can be applied to this textured surface, where the topography offers a dual advantage: its high surface area enhances mechanical interlocking with bone while simultaneously increasing the loading capacity and stability of the chemical coating [44,52]. For instance, through the deposition of Zn-doped hydroxyapatite nanoparticles with polydopamine and Cu^{2+} on alkali-treated titanium, a bionic micro/nano-coating was constructed that achieves sequential Cu^{2+}/Zn^{2+} ion release, thus allowing timed regulation of antibacterial, immune, and osteogenic responses [53]. Thus, through the aforementioned steps, one can obtain a functional coating with dynamic chemical responsiveness on the micro-nano-structured surface, enabling the coordinated regulation of cellular behaviors at the implant interface via the combined action of physical structure and dynamic chemical signaling.

3.2. Biomimetic Multifunctional Composite Coatings

A central challenge in multifunctional bone implant design is addressing the "race for the surface" [45], the critical competition between bacterial colonization and host cell integration. Traditional coatings often favor one function at the expense of another. Biomimetic coatings inspired by mussel adhesion utilize molecules like polydopamine (PDA) to create a versatile, adhesive interface on titanium [54]. This platform can be further functionalized to co-present antagonistic properties. A seminal study demonstrated this by grafting both antibacterial quaternary ammonium compounds and osteogenic phosphate moieties onto a PDA-based interface [55]. The resulting surface achieved contact-active killing of over 99% of bacteria without releasing toxic agents, while simultaneously promoting mesenchymal stem cell adhesion and osteogenic differentiation. Importantly, this surface also fostered an anti-inflammatory immune microenvironment by inducing macrophage polarization toward the regenerative M2 phenotype, thereby unifying anti-infection, pro-osteogenesis, and immunomodulation into a single, coherent surface design. Biomimetic multifunctional composite coatings on porous scaffolds, when further loaded with factors like vascular endothelial growth factor (VEGF) or bone morphogenetic protein (BMP), were shown to enable controllable molecule release [56], thereby significantly promoting early angiogenesis and subsequent bone ingrowth in animal models.

Beyond traditional growth factor delivery, cellular exosomes have garnered widespread attention as an emerging bioactive carrier in recent years. Exosomes are nano-sized vesicles secreted by cells, carrying bioactive components such as proteins and nucleic acids from the parent cell, are an important medium for mediating intercellular communication. Loading exosomes derived from osteoblasts or mesenchymal stem cells onto the implant surface is promising to creating a "biological instruction repository" that can continuously and stably release osteogenic signals [29]. This strategy is not only expected to efficiently guide host cells toward osteogenic

differentiation but also to regulate local inflammatory responses, demonstrating superior osteopromotive capability and regulatory precision compared to single growth factors.

3.3. Catalytically-Active Coatings

Instead of merely releasing pre-loaded antimicrobials, catalytically active coatings generate or modulate therapeutic agents *in situ* in response to specific microenvironmental cues. A prominent example involves nano-ceria (CeO_2), which exhibits both oxidase-like and anti-oxidant enzyme-mimetic (catalase and superoxide dismutase-like) activities [57]. Its catalytic behavior is redox-state-dependent. In an infected, inflammatory microenvironment that is often characterized by mild acidity and elevated H_2O_2 levels, CeO_2 can catalyze the conversion of H_2O_2 into highly bactericidal hydroxyl radicals. Conversely, in later stages should excessive oxidative stress impede healing, such a coating platform can switch to an antioxidant mode given its multifaceted nanozyme activity, scavenging destructive ROS and thereby protecting cells to promote repair [58,59]. This intrinsic, self-regulating "switch" makes catalytic coatings highly promising for managing the dynamic and complex biochemical landscape of the implant site.

3.4. Stimuli-Responsive Polymeric/Molecular Grafting

This approach represents the most straightforward form of smart adaptation, where the coating itself undergoes a physicochemical change triggered by a specific biological signal. Stimuli-responsive polymers (e.g., sensitive to pH, temperature, enzymes, or ROS) or labile molecular linkers are covalently anchored to the implant surface [60,61]. For example, a pH-sensitive platform, fabricated from titania nanotubes integrated with poly-γ-glutamic acid, was shown to allow the efficient loading and microenvironment-responsive release of silver ions (Ag^+) [62]. Upon release, the Ag^+ not only exerted antibacterial effects but also orchestrated a beneficial osteoimmune microenvironment by polarizing macrophages toward the pro-healing M2 phenotype and modulating osteoblast/osteoclast coupling. These coordinated actions collectively enhanced osseointegration under infectious conditions by spatiotemporally matching the bone healing process. In the specific context of bacterial infection, adaptive and on-demand drug release strategies can also be achieved by engineering titanium implant surfaces to release bactericidal agents in response to enzymatic activity [63] or elevated levels of ROS [64].

Moving beyond static biomaterials, adaptive surface chemical modification fosters the development of interactive biointerfaces. By leveraging synergistic topography, biomimetic multifunctionality, intrinsic catalysis, and precise stimulus-responsiveness, these advanced strategies hold the key to developing a new generation of titanium implants capable of actively participating in and guiding the healing process toward successful long-term biointegration and effective antibacterial properties.

Table 2. Key strategies for adaptive surface chemical modification of titanium implants.

Strategy	Mechanism and Functions	Cases of Coatings
Physicochemical synergistic modification	Compositing micro/nano structures with responsive chemical coatings creates a synergistic system, whereby the topography provides mechanical interlocking and contact guidance while the chemistry delivers dynamic bio-signals and active functionality.	• Zinc-doped micro-nano porous layer [52]; • Zinc-doped nHA with PDA and copper ions, deposited onto the alkali treated Ti surface [53]
Biomimetic multifunctional composite coatings	Co-immobilization of multiple functional groups within a single coating via universal adhesives for a multifunctional bioactive interface.	• PDA and AgNPs were coated on TNN [54]; • Quaternary ammonium groups and phosphate groups spatially organized on Ti through polyphenol-amine-mediated covalent modification [55]
Catalytically active coatings	Incorporating nanostructures with enzyme-mimetic activities that catalytically regulate reactive oxygen species (ROS) levels in the local microenvironment.	• Dual-catalysis system consisting of Na_2TiO_3 nanotubes with CeO_2 nanodots and PDA [57]; • Hydrothermal synthesization of different nano-shaped CeO_2 on TC4 [58]
Responsive polymer/molecule grafting	Covalent grafting of smart polymers or functional molecules enables stimulus-responsive conformational changes or cleavage, allowing for spatiotemporally controlled drug release.	• Titania nanotubes and poly-γ-glutamic acid combined with silver ions, achieving pH-sensitive release [62]; • Antimicrobial peptides coupled to carrier peptide and immobilized onto Ti and PCL, achieving enzyme-responsive release [63]

4. Immune and Metabolic Interface Engineering: From Molecular Cues to Systematic Microenvironmental Regulation

In the previous section, we have summarized bioadaptive strategies based on chemical modifications and biomolecular functionalization. These methods regulate the surface chemical composition, immobilize bioactive factors, or enable controlled molecular release, endowing implants with initial microenvironment responsiveness, which helps ameliorate early cell adhesion and osteogenic differentiation. However, as the healing process progresses through different stages with dynamic changes in inflammation, redox states, and energy requirements, relying solely on molecular-level signal functionalization cannot adequately match the biological needs under complex pathological conditions [65]. In pathological conditions like diabetes, osteoporosis, or aging, key factors including immune dysfunction, persistent ROS elevation, and metabolic inefficiency could significantly compromise implant performance [66].

Therefore, to further enhance implant materials' adaptability to the dynamic changes of the host microenvironment, emerging research in this field is gradually expanding from "signal empowerment" to "systematic regulation". This involves actively influencing immune response programs and cellular metabolic states through material design, further reshaping the inflammation–repair transition and energy supply mechanisms [67,68]. These deeper bioadaptive strategies expand the regulatory dimensions of materials in dynamic microenvironments, offering new possibilities for more precise interface regulation under complex pathological conditions and providing a foundation for a more systematic understanding of immune and metabolic mechanisms in bone repair [69].

4.1. Macrophage Polarization Guidance and Dynamic Immunomodulation: Reprogramming the Bone Immune Microenvironment

The critical role of the immune system in determining the long-term stability of implants has been well established [70,71]. Recent research paradigm is shifting from "avoiding immune activation" to "adaptive immune modulation", by harnessing programmable material–environment interactions to actively guide macrophage behaviors and reconstruct immune homeostasis favorable for bone regeneration (Figure 3A) [72], thereby embodying the "microenvironment responsiveness" principle outlined in the Introduction.

Macrophage polarization plays a central role in bone repair and infection control. M1 macrophages are responsible for pathogen clearance and inflammation in the early stages, while M2 macrophages are widely known to promote angiogenesis, matrix deposition, and osteogenic differentiation in later healing stages. Therefore, the M1/M2 balance induced by materials not only influences infection control but also determines the quality and speed of osseointegration [70–72]. Studies have shown that nanoscale topography can serve as a powerful immune-regulating cue. Zhu et al. [67] reported that honeycomb-like TiO_2 structures with an average diameter of 90 nm significantly promoted M2 polarization of adhered macrophages, whereas larger pore sizes of TiO_2 honeycombs tended to induce higher M1 polarization. Specifically, smaller honeycomb diameters stimulated cell adhesion molecules and peroxisome proliferator-activated receptor pathways in attached macrophages, mediating M2-like polarization, while macrophages on larger pores activated MAPK, TNF, NF-κB, and NOD-like receptor signaling pathways and were primarily polarized toward M1-like phenotypes **(**Figure 3B**)**. This finding supports the feasibility of regulating the surface nanostructure of titanium implants to repolarize M1 macrophages to M2, thereby optimizing the peri-implant immune microenvironment. However, static nanoscale topographies, while effective in guiding initial polarization, are unable to dynamically adapt to the evolving immune microenvironment remodeling needs during bone repair. In this context, cutting-edge research is shifting from static regulation to dynamic responses, focusing on how to address different biological response stages and achieve flexible immune modulation through changes in material interfaces. For example, Wang et al. [73] proposed a "bridge-burn" coating strategy, which can dynamically modulate material surface interactions with macrophages to switch macrophage activity at different repair stages, thus optimizing bone repair. This strategy combines adjustable surface charge, hydrophilicity, and bioactive factor delivery, allowing reversible immune modulation at different stages of repair (Figure 3C). Under conditions of disrupted immune homeostasis (e.g., diabetes or osteoporosis), this dynamic regulation strategy could better favor implant–bone integration by enhancing the precision of immune responses, thereby significantly improving implant adaptability and long-term stability in complex physiological environments.

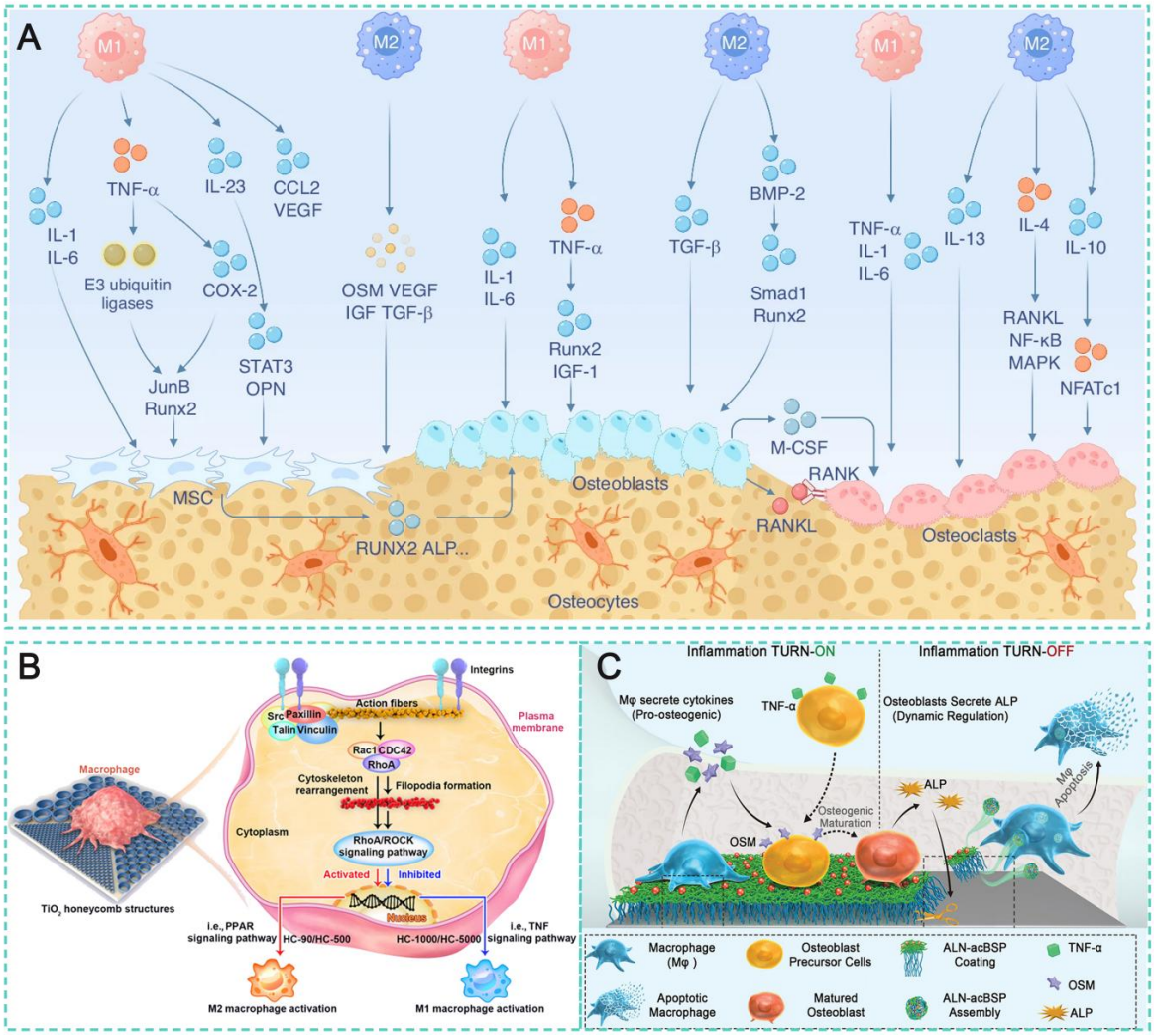

Figure 3. Mechanisms of immune regulation for bone homeostasis and immune-bioadaptive implant interface engineering. (**A**) Immune regulation of bone homeostasis [72]. Copyright 2025, Springer Nature. (**B**) Scheme illustration of the mechanism of macrophage polarization on the nanostructures [67], Copyright 2021, American Association for the Advancement of Science. (**C**) Design of the "bridge-burning" coating (ALN-acBSP) to switch on and off macrophages on implants [73]. Copyright 2020, Wiley.

4.2. Cellular Metabolic Reprogramming and Pathological Microenvironment Remodeling: Restoring Energy Homeostasis for Bone Regeneration

In addition to immune modulation for reconstructing a pro-repair microenvironment, bioadaptive strategies gain deeper insight by directly targeting cellular metabolic states as a complementary core dimension. Bone regeneration is a highly energy-dependent process, and its efficiency is strictly constrained by cellular energy metabolism levels [74]. Bone degeneration is frequently triggered by chronic glucose metabolism disorders or various aging-related pathological factors, all of which share a common physiological basis: skeletal energy metabolism imbalance [75]. Consequently, a pivotal shift in modern bone repair strategies lies in transitioning from merely supplementing cells or bioactive factors to implementing "systemic regulation" of local cellular metabolic networks at the implant interface [76,77]. The core of this strategy is to optimize cellular energy and material distribution by precisely intervening in metabolic pathways, consequently activating suppressed osteogenic programs under pathological conditions and restoring bone metabolic homeostasis.

Within this framework, the surface functionalization of titanium implants is instrumental to enable spatiotemporally precise metabolic reprogramming. Metabolic-regulating materials can be surface engineered to actively adjust the metabolic states of osteogenic-related cells in response to microenvironmental stimuli. For example, osteoporosis creates a disrupted microenvironment characterized by excessive ROS accumulation and decreased pH, leading to mitochondrial dysfunction, impaired osteogenic differentiation, and overactivation of osteoclasts [76,78]. To address this, Guo et al. [76] developed an ROS-responsive titanium implant coating composed of calcium carbonate mineralized nicotinamide mononucleotide (NMN) nanoparticles, lipoic acid-

modified gelatin (LAMG), and sodium alginate (SA). This coating was found to effectively scavenge ROS, restore pH, and regulate the NAD^+/NADH ratio through NMN release, activating the SIRT1 signaling pathway, restoring mitochondrial function, and promoting osteogenic differentiation (Figure 4A,B). This multifunctional coating enhanced biointegration around the implant under osteoporotic conditions by restoring the pathological bone microenvironment, inhibiting osteoclast activity, and promoting osteoblast formation. Additionally, Chen et al. [77] developed a multifunctional metal-organic framework (MOF) coating for treating osteoporotic fractures. The MOF coating gradually degraded in the acidic bone microenvironment of osteoporosis, releasing Ce/Sr ions and p-xylylenebisphosphonate salts (PXBP), which efficiently decomposed hydrogen peroxide and superoxide in the bone interface, restore mesenchymal stem cell (MSC) morphology and metabolic function, and reverse their senescence. PXBP also induced osteoclast apoptosis, reduced bone resorption rates, and synergistically improved the osseointegration of Ti implants, restoring bone homeostasis at osteoporotic fracture sites (Figure 4C,D). These studies suggest that titanium implants can be surface-modified to precisely direct osteogenesis through time-dependent modulation of cellular metabolism and senescence, thus providing a novel regenerative strategy with clinical potential.

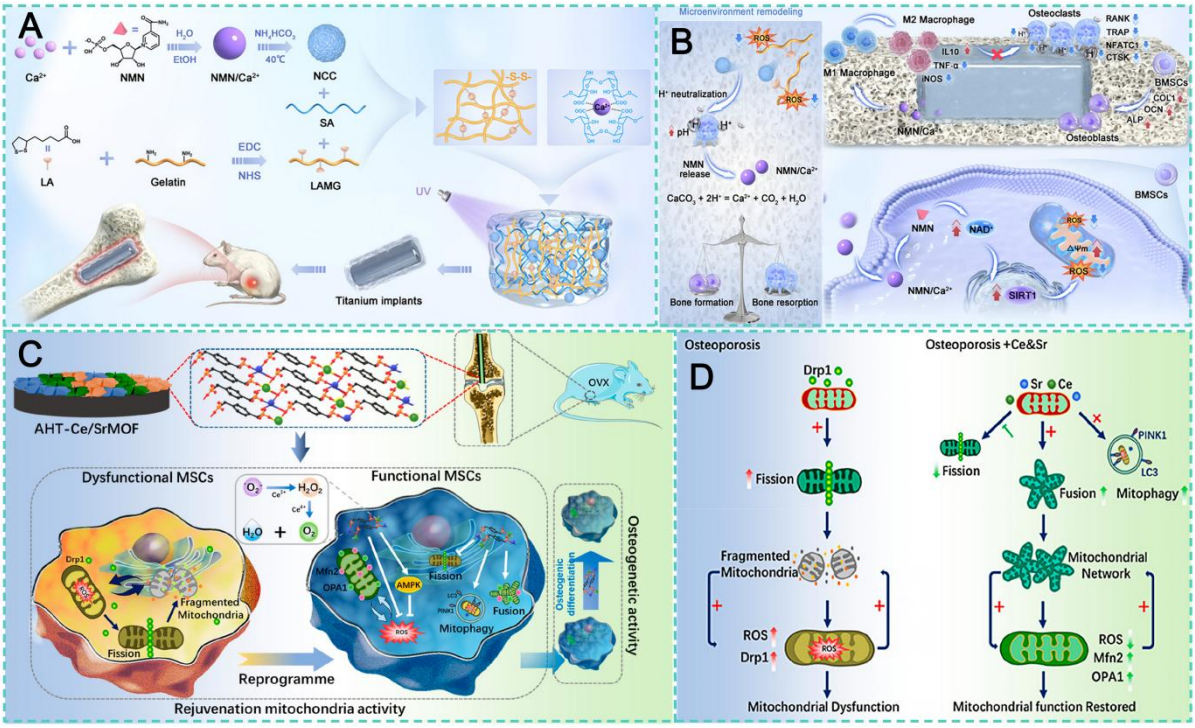

Figure 4. Restoring energy homeostasis for promoting bone regeneration. (**A**,**B**) Schematic illustration of the construction strategy (**A**) and mechanism for enhancing osteoporotic osseointegration (**B**) of ROS-responsive titanium implant coatings [76]. Copyright 2025, Wiley. (**C**) Schematic illustration of the SOD/CAT-like bio-MOFs for normalizing dysfunctional mitochondria in senescent MSCs of osteoporosis-affected bone fractures [77]. Copyright 2025, American Chemical Society. (**D**) The bioMOFs could stimulate AMPK signaling in MSCs to activate mitophagy, thus restoring their mitochondrial functions to reverse the senescent phenotype [77]. Copyright 2025, American Chemical Society.

5. Synergistic Bioadaptive Interface Engineering: From Infection Control to Programmed Bone Regeneration

5.1. Beyond Traditional Antibiotics: The Rise of Stimuli-Responsive Physicochemical Antibacterial Strategies

We have discussed how to enhance the adaptability of implant surfaces to dynamic microenvironments from the perspectives of metabolic regulation strategies and immune modulation engineering, by optimizing cellular energy metabolism to overcome healing barriers under pathological conditions. However, in the real implant microenvironment, the initial challenge faced by the material surface is often not cell adhesion or osteogenic induction, but the rapid adhesion of bacteria and formation of pathogenic biofilms [79,80]. Early infections can quickly disrupt microenvironmental homeostasis, triggering immune imbalances and fundamentally hindering the long-term biointegration of implants [79]. Therefore, surface functionalization for bone repair should not only focus on cellular regulation but also need to possess an active defense capability against infection risks. This requirement has spurred the development of bioadaptive antibacterial interfaces where the material can

dynamically modulate its antibacterial and immune-regulatory functions in response to local pathological shifts, thereby creating a microenvironment conducive to tissue repair (Table 3).

Table 3. Bioadaptive implant interface engineering strategies for multipurpose bone repair [6,80–83].

Category	Strategy Name	Design Features	Multiple Effects	Challenges and Limitations
Dynamic responsive antibacterial strategy	Piezoelectric nanoreactor-titanium scaffold system	Fusing piezoelectric nanostructures with titanium-based materials, with ultrasound stimulation triggering antibacterial reactions	Antibacterial (ROS generation) + immunomodulation (immune activation)	Limitations in ultrasound activation; Control over ROS generation timing and local concentration
Immunomodulatory and synergistic antibacterial strategy	Functional coatings-immunostimulatory molecules	Surface functionalization of materials for targeted release of immunomodulatory molecules	Immunomodulation (immune restoration) + antibacterial (immune activation)	Immune activation may trigger excessive inflammatory responses; Timeliness and control of immune molecule release.
	Quorum sensing interfering nanoparticles	Nanoparticle design for targeting	Antibacterial (virulence disruption) + immunomodulation (enhanced immune sensitivity)	Effective against specific strains, with limited universality; Biocompatibility and long-term stability of nanoparticles need further validation
Multimodal adaptive interface	Piezoelectric polymer/MOF composite film	Polymer/metal-organic framework composite, responsive to mechanical stimuli	Osteogenesis promotion + antibacterial (Mg^{2+} release) + anti-inflammatory (curcumin release)	High dependence on mechanical stimuli; Requires optimization of precise control over antibacterial molecule release.
	Dynamic crosslinked hydrogel adaptive interface	Hydrogel material design for tuning biofunctional substance release based on chemical changes	Antibacterial (TA, tobramycin) + immunomodulation (M2 polarization) + osteogenesis	Precision and timeliness of substance release control; Stability and biocompatibility in complex microenvironments

Traditional antibiotic coatings, due to their passive release modes, limited duration of effectiveness, and potential to induce resistance, fail to meet the long-term adaptation requirements in complex microenvironments [80]. In this context, non-antibiotic physico-chemical antibacterial interfaces, capable of dynamic regulation according to local pathological changes, have gradually become the core of future research direction. These interfaces typically integrate units sensitive to external stimuli (e.g., ultrasound, pH, or ROS), which can be rapidly activated when the microenvironment becomes imbalanced, forming an "early detection and rapid response" antibacterial mode that enables adaptive control of bacterial burdens.

5.2. Antibacterial–Immunomodulatory Synergistic Design: Orchestrating Antibacterial Actions with Host Immunomodulation

It is increasingly recognized that there are interplays between antibacterial effects and host immunity, which can be leveraged in to afford smart bone implants with stage-balanced multifunctionality. A notable example in this regard is the piezoelectric nanoreactor–titanium scaffold system constructed by Zheng et al. Under low-intensity ultrasound, this system generated piezoelectric potentials, driving sono-chemical cascade reactions to continuously produce overwhelming ROS, which, through potent oxidative stress, disrupted bacterial membrane structures and metabolic functions, effectively clearing drug-resistant strains [80]. However, the same system can achieve moderate ROS levels at a later stage to activate beneficial immune responses, thereby shifting the microenvironment from infected to reparative, demonstrating the inherent immune-synergistic properties of such externally-activatable physico-chemical antibacterial strategies. Recognizing this antibacterial–immunomodulatory synergy, the field is witnessing a convergence where bioadaptive interfaces proactively integrate immune modulation, going beyond the limitations of single-mechanism antibacterial approaches [84]. For example, by releasing immunostimulatory agents such as CpG oligonucleotides, functional coatings can reverse the immunosuppressive state induced by biofilms and reactivate macrophage-mediated phagocytosis and bacterial killing [81]. Additionally, quorum sensing-interfering nanoparticles can be explored to reduce bacterial virulence, thereby enhancing immune sensitivity and weakening biofilm formation at its source [82]. Overall, whether via ROS-mediated oxidation, release of immune-stimulants, or quorum-sensing interference, these strategies share a key feature: well-orchestrated antibacterial and immunomodulatory effects. It is this dual-action mechanism (i.e., antibacterial response plus immune regulation) of these non-antibiotic interfaces that defines their bioadaptive nature and pro-repair function.

5.3. Toward Multimodal and Temporally Programmed Interfaces: Sequential Phased Regulation of Tissue Repair Cascade

With the gradual maturation of the "precise bioadaptability" concept, research on next-generation biomaterial implants is advancing toward the development of multimodal adaptive interfaces that integrate antibacterial property,

immune modulation, and tissue repair [85]. For example, piezoelectric polymer/MOF composite films can be harnessed as bioadaptive design elements, serving dually as energy converters that transform mechanical stimuli into osteogenic signals and as reservoirs for the sequential release of antibacterial and anti-inflammatory molecules [83]. Complementing to this, our group's recent work [6] introduced a dynamical hydrogel-based adaptive implant interface that enabled temporally programmed "self-renewing" changes in surface landscape and functionality in response to evolving pathological states (Figure 5). The core design leverages a dynamically-crosslinked therapeutically-active gel toplayer (TDGel), self-assembled from tobramycin, tannic acid and an adaptor molecule 3-formylbenzoylboric acid (3-FPBA), for triggered therapeutic release and conditional exposure of underlying micro/nano-topographies and bioadhesive moieties. This interface can dynamically adapt to meet the evolving biological demands of infectious diabetic tissue repair: first, decomposing the TDGel to release antibacterial gel components (tobramycin/tannic acid) upon pathological pH/ROS cues; then, leveraging the antioxidant/anti-inflammatory action of tannic acid to scavenge excess ROS and drive M2 macrophage polarization for inflammation resolution; and finally, unveiling its micro/nano-structured and catechol-modified titanium substrate to direct cell adhesion, osteogenesis, and biointegration. Such smart, condition-dependent, time-sequenced functional switching epitomizes a precision bioadaptive strategy for complex pathogenic tissue repair.

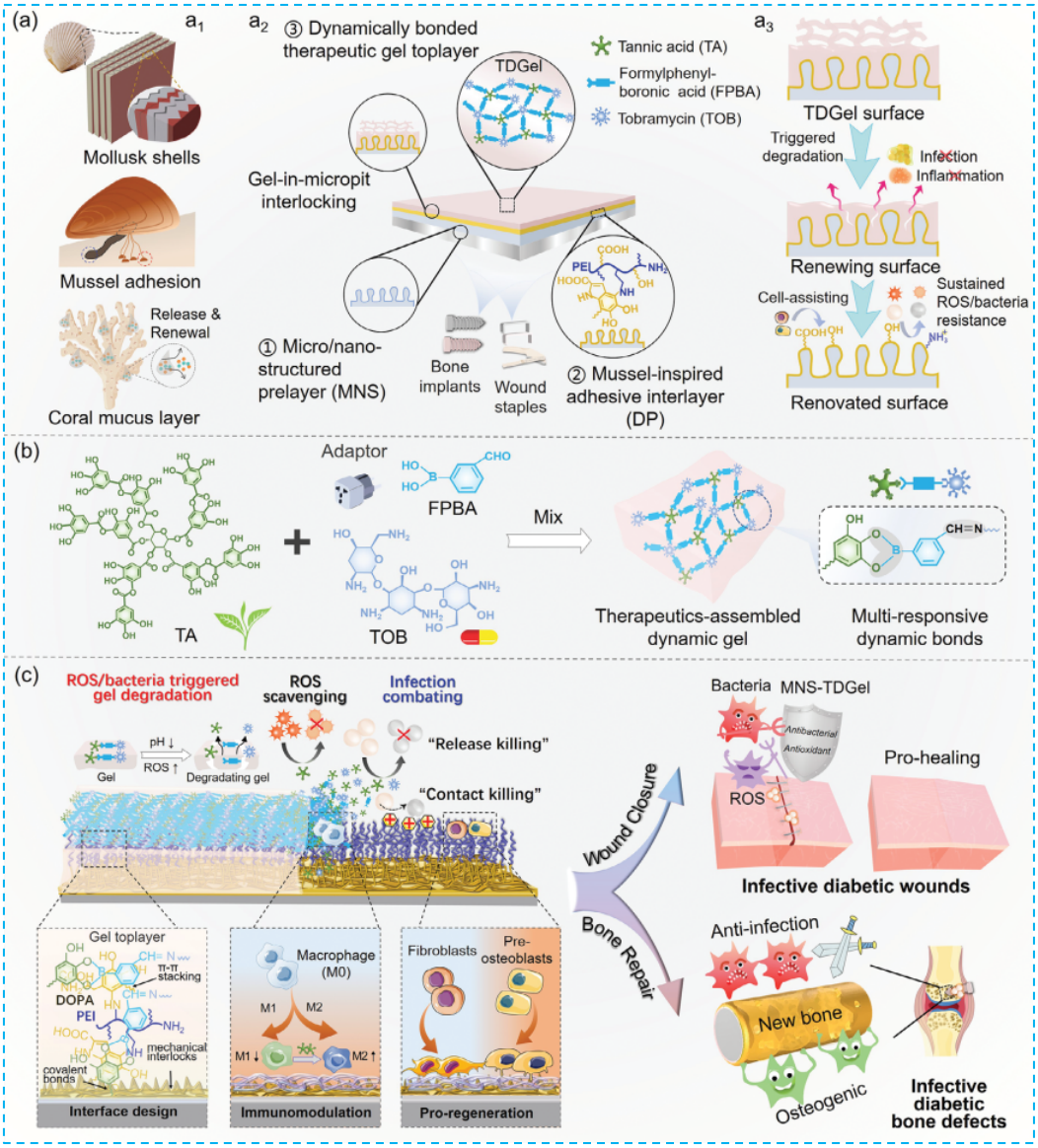

Figure 5. Schematics of the bioinspired temporally-programmed bioadaptive interfacial engineering strategy and its proof-of-concept bioapplications. (**a**) Strategic overview showing: (**a1**) triple bioinspirations, (**a2**) sandwiched architectures, and (**a3**) surface self-renewing mechanism; (**b**) Self-assembly chemistry of TDGel; (**c**) Proposed working mechanism for diabetic tissue repair via sequential phases of anti-infective, immunomodulatory, and pro-healing/regenerative functionalities [6]. Copyright 2024, Wiley.

5.4. Paradigm Shift and System Integration: Shaping Pro-Regenerative Microenvironments through Proactive Synergy

The development of adaptive antibacterial interfaces, over recent five years or so, has vastly advanced implant surface engineering from simple antibacterial or osteogenic functions to miscellaneous systems that can dynamically support the entire bone-healing cascade. By enabling rapid infection-fighting intervention in the early infection phase, maintaining immune homeostasis during the inflammation phase, and promoting tissue regeneration/biointegration in the repair phase, such interfaces are capable of effectively safeguarding key regulatory bioprocesses of osteoregeneration, ultimately providing a decisive advantage for achieving rapid, robust osteointegration [62]. Embracing the trend that antibacterial design is evolving from "passive defense" to "active synergy", adaptive implant functionalization strategies are poised to become a cornerstone in constructing a sterile, pro-healing peri-implant microenvironment, particularly through an ingenious integration of infection defense with immunomodulation and metabolic regulation.

6. From Bench to Bedside: Toward Bioadaptive yet Clinically Translatable Titanium Implants

Bioadaptive titanium implants, as extensively exemplified in preceding sections, are defined by a shift from passive biocompatibility to active, context-aware regulation [43,86]. This paradigm is rooted in the strategic convergence of materials science, bioengineering, and precision medicine, paving the way for implants with truly multifunctional, integrated, and adaptive capabilities. However, realizing their clinical translation requires overcoming major scientific, engineering, and regulatory barriers. Key challenges span from predicting long-term performance of complex materials and ensuring biosafety across pathological states, to establishing scalable manufacturing and evolving regulatory frameworks for dynamic devices.

6.1. Long-Term Stability and Safety of Smart Coatings: Challenges in Bioactive Species Release in Complex Physiological Environments

From the perspective of biomaterials science, ensuring the long-term stability and safety of smart coatings poses a major challenge [87]. Incorporating multiple functional components (e.g., metal ions, immunomodulatory molecules, responsive polymers, or catalytic nanostructures) into hybrid coatings often leads to unpredictable interactions among these components and with the host in complex physiological settings [88]. For example, multilayered ion-releasing coatings, designed for sequential antibacterial and osteogenic functions, may exhibit altered release kinetics due to protein adsorption or disruption of body fluid flow, leading to loss of temporal precision [89]. Similarly, stimuli-responsive systems (e.g., those triggered by pH or ROS) often struggle to capture the highly dynamic yet patient-specific nature of actual pathological signals [90]. Moreover, inadequate responsiveness may result in functional inertia, whereas excessive activation can evoke tissue damage. These issues may arise from a fundamental divergence: our models simplify the implant microenvironment, whereas host integration is in fact governed by an intricate, multidimensional reality encompassing microbial activity, inflammation, metabolism, and neuroimmune responses, and more.

6.2. Manufacturing and Engineering for Translation: Bridging the Gap from Lab-Scale to Industrial-Scale Production

Translating laboratory prototypes into industrial-scale production with structural/functionality consistency and reproducibility represents a major obstacle in implant development, demanding robust and scalable manufacturing strategies. This challenge is particularly pronounced in the fabrication of adaptive medical implants with complex architectures, such as TPMS/fractal/metamaterial architectures, multi-scale porosity, composite coatings, and patterned bioactivity [31]. Emerging production technologies like additive manufacturing, atomic layer deposition, and femtosecond laser micromachining enable the integration of structure and function [91]. Yet, their industrial translation hinges on critical supporting technologies: robust digital twins for design, integrated in-process monitoring, and physics-based quality control frameworks [92,93]. Only by advancing these supporting systems in concert can the controllability and reliability of complex implants be seamlessly ensured from design and manufacturing through to final performance.

6.3. Advancing Regulatory and Evaluation Framework: Customizing Standards for Evaluating Dynamic Bioadaptive Implants

Regulatory complexity represents another arduous challenge. Because bioadaptive implants often exhibit stimulus-dependent changes in surface chemistry, ion release behaviors, or biological activity post implantation, they do not fit well into the conventional device–drug–biologic regulatory framework widely adopted by regulatory agencies [94]. With dynamic and signal-responsive nature, bioadaptive implants fall outside the scope

of conventional regulatory schemas that segregate medical products into distinct device, drug, and biologics. More critically, current biosafety standards like ISO 10993 are not designed to assess the time-dependent functionality, repeated activation, degradation-coupled responses, or evolving benefit-risk profiles of adaptive implant systems. Advancing the field requires establishing a dedicated framework of standards and methods to evaluate device performance across physiological and pathological conditions, assess durability through repeated use, and adequately integrate long-term clinical data to validate efficacy and safety. Defining feasible and predictable approval pathways requires early developer–regulator collaboration, supported by progress in regulatory science and harmonized evaluation standards, to prevent costly delays and resource waste in the translation process [94,95].

7. Concluding Remarks

In this *Perspective*, we propose the paradigm shift in titanium bone implant design from static, biomimetic devices to dynamic, bioadaptive systems. This transition is driven by integrated advances in structural design, manufacturing, and surface engineering, together with microenvironment-responsive strategies. Collectively, these enable implants to deliver precisely timed and spatially controlled biological functions essential for challenging bone repair, particularly in cases requiring balanced antibacterial/osteogenic activity and/or stage-adaptive immunometabolic regulation.

Notably, however, this field is at a nascent stage, with many research directions still being actively explored, yet its developmental momentum is evident. Recalling that the core of "bioadaptability" lies in the dynamic material–bio interplays [18,19], we believe that advancing the field requires a tighter convergence of advanced material innovations and fundamental biological insights. Intelligent structural designs, such as metamaterial scaffolds and 4D-printed shape-memory architectures, warrant continuous, systematic investigation [35,96]. This is especially relevant when employing machine learning and artificial intelligence to predictively devise patient-specific implants, where algorithms can optimize implant geometry, pore topology, and other parameters per individual anatomy and defect characteristics [97–99]. Such computational methods would not only facilitate implant customization but also help reveal complex structure–function relationships that are difficult to elucidate through conventional trial-and-error experimentation [1]. The resulting digitally-optimized implants can then be additively manufactured and functionally coupled with smart surface compositions capable of sensing and responding to pathological signals, for instance, pH variations in infected microenvironments or dynamic mechanical loading [96,100], hence allowing real-time adaptation to host demands throughout the therapeutic/healing stages. Meanwhile, the spatiotemporally-programmed incorporation of immunomodulatory, metabolic, proangiogenic, and even neuromodulatory cues [101–103] directly into the implant interface will prove instrumental for guiding complex cellular and tissue responses in challenging clinical scenarios, noticeably infected or metabolically compromised bone defects.

Albeit for their promise, translating these sophisticated bioadaptive implant systems into clinical practice remains an arduous task that requires a careful balance between functional complexity and practical feasibility. A viable pathway forward, as we see it, may involve modular platforms consisting of certified titanium modular bases paired with interchangeable bioactive coatings (e.g., stimuli-responsive anti-infective/osteogenic multilayers) that can be tailored to individual patient needs [1]. Such an approach could help streamline regulatory approval and scale up manufacturing without compromising therapeutic design flexibility and precision [104]. Despite remaining challenges, advances in bioadaptability, fueled by interdisciplinary collaboration across materials science, chemistry, biology, computational science, manufacturing, and clinical orthopedics, are positioned to foster ongoing innovation and accelerate the clinical translation of next-generation titanium implant systems.

Author Contributions

Y.L. and D.S.: writing—original draft, writing—review & editing, visualization, software, data collection and curation; Y.Z.: visualization, formal analysis, data collection and curation; C.W.: writing—review & editing, methodology, resources; F.Z. and Z.J.: conceptualization, writing—review & editing, methodology, supervision, resources, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare the following potential conflicts of interest: C.W. is an employee of ITI Medical Equipment Co., Ltd. All other authors declare no relevant competing financial or personal interests.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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